Investigation of Naturalistic Sleep/Wake Behaviour in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Abstract

Sleep dysfunction is a prominent feature in the subjective experience of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Although studies using polysomnography have identified at least one abnormal sleep characteristic in individuals with ME/CFS, no standard abnormalities in sleep have been identified. At the time of writing, only one published study had compared actigraphic measures of sleep between ME/CFS and controls, with no differences found. The aim of this study was to compare sleep parameters in people with and without ME/CFS using self-report and actigraphy. The sample consisted of 16 individuals with ME/CFS and 16 healthy controls matched for age and sex who were self-reported good sleepers. Participants wore a wrist actiwatch and kept a sleep diary for 7 days. Participants were asked to give subjective ratings sleep quality and feeling rested each morning. Results showed that individuals with ME/CFS experienced objectively (as measured by actigraphy) longer sleep onset latency and duration of wake after sleep onset, more fragmented sleep, and lower sleep efficiency than controls, with no difference in total sleep time. They also reported longer subjective (as reported in sleep diaries) sleep onset latency and duration of wake after sleep onset, and lower sleep efficiency, with no difference in total sleep time. The ME/CFS group also reported poorer sleep quality and feeling less rested after sleep. Individuals with ME/CFS experienced greater variability over the seven day assessment period in objective (actigraphic) total sleep time, sleep efficiency and duration of wake after sleep onset, and greater variability of subjective sleep efficiency and feeling rested than controls. These results provide objective evidence to support the subjective reports of poor sleep in ME/CFS and suggest possible bases of the non-restorative sleep described in ME/CFS. From a clinical perspective this highlights the

importance of including sleep assessment and the treatment of sleep problems in this population as part of a holistic management plan. The original intention of this study was to include cardiopulmonary coupling (CPC) as an additional measure in the investigation of possible differences between the sleep of ME/CFS and control groups. However, technical difficulties with the SleepImage M1™ devices lead to CPC data only being available from a subgroup of participants, which included both ME/CFS and control participants. The available CPC data (n = 17) offered an opportunity to assess the validity of the M1™ device against actigraphic and subjective assessments. Analyses found mainly weak and non-significant correlations between CPC measures and the other measures of sleep quality. Total sleep time as measured by CPC was also significantly greater than actigraphic sleep time. Further research is needed before the M1™ device may be considered a valid measure of sleep quality.

Doctor of Psychology Declaration

"I, Catherine Stevens, declare that the Doctor of Psychology (Clinical Psychology) thesis entitled Investigation of Naturalistic Sleep/Wake Behaviour in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome is no more than 40,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work".

Signature: Date:

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Chapter 1: Literature Review

1.1. Introduction

Fatigue has been known as a medical symptom since Hippocrates' description of "the disease of the Scythians", whereby men who spent the day on horseback experienced persistent and debilitating tiredness (Wyller, 2007). Descriptions by neurologist Beard and psychiatrist Van Deusen subsequently led to fatigue becoming a core symptom in psychiatry (Wyller). Today, fatigue is a symptom of many medical and psychiatric disorders, including Chronic Fatigue Syndrome (CFS), which is now more widely known in medical circles as Myalgic Encephalomyelitis (ME). The World Health Organisation (WHO) first recognised ME/CFS as a neurological disease in 1969 (Twisk, 2014). The WHO's International Classification of Diseases (ICD-10) currently includes "postviral fatigue syndrome" and "benign myalgic encephalomyelitis" coded as G93.3 (WHO, 2010).

The prevalence of ME/CFS is estimated to be between 0.4% to more than 2% of the general adult population (Van Houdenhove, Pae, & Luyten, 2010). The course and severity of ME/CFS varies greatly from patient to patient. It is estimated that 25% of those with ME/CFS are severely disabled by the illness, and spend most of their time housebound or bedbound (Carrico et al., 2004). Some others are able to lead relatively active lives, within carefully observed limits. A pattern of relapse and remission is common (Carrico et al.). The mean duration of the illness ranges from 3 years to 9 years (Prins, Van der Meer, & Bleijenberg, 2006).

The hallmark symptom of ME/CFS is a severe, incapacitating fatigue that does not improve with rest and may be further exacerbated by physical or mental activity

(Carrico, Jason, Torres-Harding, & Witter, 2004). In fact, post-exertional malaise is a distinguishing feature of ME/CFS, where even modest physical or mental exertion may lead to a worsening of symptoms for days or even weeks. A formal definition of ME/CFS requires that the fatigue cannot be explained by psychiatric or medical conditions, persists for at least 6 months and causes a significant reduction in daily activities (Reeves et al., 2005). However, ME/CFS has multiple debilitating symptoms beyond fatigue. These include joint and muscle pain, headache, sore throat, tender lymph nodes, short-term memory and concentration problems, and sleep difficulties, particularly difficulty initiating sleep, maintaining sleep, and waking feeling unrefreshed (Carrico et al., 2004). The mechanisms underlying poor sleep in ME/CFS are unclear, with studies using polysomnography (PSG) reporting varied and often minimal differences between those with ME/CFS and controls (eg. Majer et al., 2007; Reeves et al., 2006; Togo et al., 2008; Neu et al., 2009). The aim of the current study is to investigate both subjective (using sleep diaries) and objective (using actigraphy) sleep in individuals with ME/CFS and compare these measures with healthy matched controls.

The following literature review will examine research relevant to the issues of sleep in ME/CFS. It will first review what is currently known about ME/CFS, including diagnostic criteria and theories surrounding its etiology and pathophysiology. It will also review current treatments for ME/CFS. The next section will review the research surrounding sleep, with a key section being sleep in ME/CFS. As individuals with ME/CFS frequently report sleep problems and non-restorative sleep, there will also be an emphasis on sleep difficulties and the current research surrounding the definition and impacts of non-restorative sleep. The objective measures of sleep being used in this

study will then be reviewed. As actigraphy is being used extensively in the current study the following topics are explored: clinical and research uses of actigraphy, actigraphy practice parameters, validity of actigraphy, and the use of actigraphy in ME/CFS. Another aim of the study is to investigate the validity of a portable device that utilises cardiopulmonary coupling (CPC) as a measure of sleep quality. The use of such technology is relatively new in sleep research and in this study is being used to explore sleep parameters in a range of sleepers, from self-reported "good" sleepers to "poor" sleepers. The review will describe how CPC is used and its validity as a measure of sleep stability and quality. Lastly, the literature review will provide an introduction to the current study by outlining the rationale, aims and hypotheses.

1.2 Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

1.2.1 Diagnostic criteria

As there are no diagnostic tests or biomarkers to clearly identify ME/CFS, diagnosis can be a challenge for medical professionals. Historically, diagnosis has typically been one of exclusion, whereby alternative medical or psychological causes of the debilitating fatigue are eliminated. With individuals suffering ME/CFS experiencing a wide variation of symptoms and severity, diagnosis is an even more complicated task (McCleary & Vernon, 2010). The goal of researchers and clinicians with expertise in ME/CFS has been to develop a clear set of guidelines in the diagnosis of ME/CFS. These guidelines have been revised and refined over a number of years.

In 1988, the United States Centers for Disease Control (CDC) introduced the first working case definition of chronic fatigue syndrome (Holmes et al., 1988). Researchers recognised that patients diagnosed with chronic Epstein-Barr illness

presented with a complex array of symptoms characterised by incapacitating fatigue and accompanied by a range of other symptoms including headache, myalgia, arthralgias, lymph node pain and sore throat. They noted that chronic Epstein-Barr illness was poorly and inconsistently defined, especially as there was often a lack of correlation between chronic fatigue symptoms and Epstein-Barr virus serology results (Holmes et al.). In an attempt to provide researchers and clinicians with a reliable and consistent set of diagnostic criteria, the CDC changed the name of chronic Epstein-Barr illness to chronic fatigue syndrome and produced a working case definition. Along with eight minor criteria, patients were required to fulfil the two major criteria of new onset debilitating fatigue or easy fatigability of unknown cause, with 50% impairment of premorbid functioning for at least six months (Holmes et al.).

In 1994, the CDC revised their original working case definition and developed a new set of research guidelines to be used in studies of CFS (Fukuda et al., 1994). These guidelines became more widely known as the Fukuda criteria and are the most commonly used criteria used in the research of CFS in adults (Brurberg, Fonhus, Larun, Klottop, & Malterud, 2014). The Fukuda criteria are less stringent than the 1988 criteria, and requires the presence of debilitating fatigue for at least six months, along with four other minor criteria. Treatable sleep disorders such as narcolepsy and obstructive sleep apnoea are excluded. Although medical and a number of psychiatric causes of fatigue are excluded, non-psychotic psychiatric disorders are not and it has been argued that the Fukuda criteria do not adequately distinguish between ME/CFS and conditions such as major depressive disorder (Jason & Richman, 2007). Another concern raised by Reeves et al. (2005) was that ME/CFS research has produced inconsistent and often conflicting results. In an attempt to address these concerns,

Reeves et al. developed an empirical definition of the Fukuda criteria. Although the criteria remained the same, the researchers recommended the use of standardised and validated instruments that assess the key dimensions of ME/CFS be used in order to improve reproducibility across studies.

In 2003, the Canadian Clinical Case definition (also known as the Canadian Consensus Criteria) was developed by an Expert Medical Consensus Panel with vast experience in the clinical management and research of ME/CFS (Carruthers et al., 2003). A primary reason for this development was the increasing demand from the medical fraternity for a clinical case definition that would aid in the diagnosis and treatment of their patients. The Fukuda criteria was intended to be used only in research (Fukuda et al., 1994). Carruthers et al. recognised that having fatigue as the sole compulsory criterion meant that other fundamental symptoms were de-emphasised, making it difficult for clinicians to distinguish between the fatigue of ME/CFS and fatigue from other causes. A key difference between the Canadian Consensus Criteria and the Fukuda criteria is the ability of the Canadian Consensus Criteria to differentiate patients with ME/CFS from those with major depressive disorder (Jason & Richman, 2007). Under Fukuda criteria, patients are able to be given a CFS diagnosis with no physical symptoms apart from fatigue. The Canadian Consensus Criteria selects a more homogenous set of patients and identifies those with greater cognitive and physical impairments and with more physical debility (Jason & Richman). As well as incorporating a larger range of symptoms, the Canadian Consensus Criteria stipulates that patients with ME/CFS will have at least six months of physical and mental fatigue, post-exertional malaise and/or fatigue, sleep dysfunction, and pain, along with four other symptoms (Carruthers et al., 2003).

In 2011, the Canadian Consensus Criteria was used as the starting point for a new case definition, the International Consensus Criteria (ICC) (Carruthers et al., 2011). Emerging research outlining the complex systemic dysfunctions that occur in ME/CFS have formed the basis for the new criteria. The most significant change was the emphasis on fatigability rather than fatigue, with post-exertional neuroimmune exhaustion (resulting in at least a 50% reduction in premorbid activity level) being the only compulsory symptom. Another important change was the removal of the six month waiting period before diagnosis. The ICC is currently used only as a clinical assessment tool and is yet to be used in research.

1.2.2 Etiology and pathophysiology of ME/CFS

While there are now internationally recognised criteria for diagnosing ME/CFS, its etiology and pathophysiology are not fully understood. Early theories focused on an acute viral illness or psychiatric disorder underlying the condition (Afari & Buchwald, 2003). However, increasing research shows that ME/CFS is most likely an illness of multifactorial etiology including impairments of the immune, nervous and endocrine systems, and cellular metabolism and ion transport impairments (Carruthers et al., 2011). It is possible that the abnormalities in these physiological systems are associated with the sleep dysfunction often reported in ME/CFS.

Neuroimaging methods including magnetic resonance imaging (MRI) scans, single-phone emission computed tomography (SPECT) and positron emission tomography (PET) have found evidence of functional and structural abnormalities within the brains of patients with ME/CFS (Chen et al., 2008). These abnormalities suggest dysregulation of the central nervous system, and may provide at least part

explanation of the neurological symptoms and cognitive impairment experienced in ME/CFS. When compared to healthy controls, patients with ME/CFS were found to have significantly reduced grey matter and increased white matter (Chen et al.). Cerebral blood flow has also been studied. Although some studies have found no abnormalities in brain blood flow in patients with ME/CFS, others have found either global hypoperfusion or hypoperfusion in specific brain regions, including the brain stem and anterior cingulate region using SPECT. Reduced blood flow in the bilateral middle cerebral artery territories has also been found in ME/CFS patients using xenon-computed tomography (Chen et al.). However in a monozygotic study of twins, no differences were found in the cerebral perfusion of the patient with ME/CFS when compared with the healthy twin (Lewis et al., 2001).

Dysregulation of the central nervous system and autonomic nervous system is thought to alter the way pain and other senses are processed in ME/CFS (Meeus, Nijs, Huybrechts, & Truijen, 2010). Widespread hyperalgesia, central nervous system hyperresponsiveness and deficient endogenous pain inhibition suggests central sensitisation plays a key role in the pathophysiology of ME/CFS (Nijs et al., 2012). Deficient endogenous pain inhibition has been shown in patients with ME/CFS who have a significantly reduced pain threshold after exercise when compared with controls. This inhibition has been implicated in the post-exertional malaise patients with ME/CFS experience (Nijs et al.). Extreme mental fatigue and cognitive deficits in concentration, attention, working memory and information processing are also common symptoms in patients with ME/CFS. This may be partly due to the increased subcortical and cortical brain activation needed to complete challenging mental tasks, as shown in some functional MRI studies (Ocon, 2013).

It is thought that dysregulation of the central nervous system and deregulation of the immune system in ME/CFS is initiated by an acute infection (Carruthers et al., 2011). Many patients with ME/CFS report an infectious illness immediately prior to the onset of ME/CFS (Salit, 1997; Swanink et al., 1995). Many and varied viruses have been reported in a number of ME/CFS patients, including Epstein-Barr virus (Zang et al., 2010), human herpes virus 6 and 7 (Chapenko et al., 2006), enterovirus (Chia et al., 2010), cytomegalovirus (Beqaj, Lerner, & Fitzgerald, 2008), chlamydia (Chia & Chia, 1999), Coxiella burnetti (Zang et al., 2010), and parvovirus B19 (Kerr et al., 2003). Altered faecal microbial flora with an increase in aerobic gram positive intestinal bacteria (enterococcus and streptococcus) has also been found in a subset of ME/CFS patients (Sheedy et al., 2009). Evidence for immune dysfunction has been shown in studies of cytokine dysregulation in patients with ME/CFS (Bansal et al., 2012). Early studies have shown conflicting results, with the only consistent finding being the reduction in the function and number of natural killer (NK) cells (Bansal et al.). However a recent study of 95 ME/CFS patients and 50 healthy controls by Brenu et al. (2011) showed evidence of chronic low grade inflammation in ME/CFS. Both numbers and cytotoxic activity of NK cells were significantly reduced in ME/CFS patients when compared to controls. ME/CFS patients also had marked increases in the cytokines interleukin-10, interferon-Ɣ and tumour necrosis factor-α, along with significant increases in CD4+CD25+ T cells, and FoxP3 protein (a regulator in the development and function of regulatory T cells) and vasoactive intestinal peptide receptor 2 expression. However it is still unclear whether immune dysregulation is the cause or the result of ME/CFS (Bansal et al., 2012).

Abnormalities of the hypothalamus-pituitary-adrenal (HPA) axis is also a focus of ME/CFS research. There is evidence that psychosocial stress and the subsequent increase in cortisol and increased negative feedback leads to reduced adrenocorticotropic hormone (ACTH) production and HPA axis suppression (Arnett, Alleva, Korossy-Horwood, & Clark, 2011). It is thought that due to reduced ACTH, secretion of glucocorticoid steroids (which act as an immunosuppressant) is depressed, contributing to the increased inflammatory pathology seen in ME/CFS. A significantly lower salivary cortisol awakening response has been found in 108 adolescent ME/CFS patients in comparison to 38 healthy controls (Nijhof et al., 2014). Nater et al. (2008) found evidence of altered diurnal salivary cortisol rhythm in adults with ME/CFS. ME/CFS subjects had lower salivary cortisol concentrations in the morning and higher salivary cortisol concentrations in the evening in comparison to controls. However Cleare (2004) argued that HPA hypofunction is only present once ME/CFS is well established, and is not present before the onset of the illness, nor during its early stages. It is therefore possible that HPA abnormalities are not a cause of ME/CFS, but rather a consequence of ME/CFS. Reduced physical activity, physical deconditioning and sleep disturbances that frequently occur in ME/CFS may result in HPA hypofunction (Cleare).

There is also growing evidence of energy production/transport impairments in ME/CFS. A review by Morris and Maes (2014) revealed significant evidence of mitochondrial dysfunctions in ME/CFS. Mitochondrial damage, impaired oxidative phosphorylation and reduced ATP production have all been shown in patients with ME/CFS. Muscle biopsies have shown mitochondrial structural damage in a number of patients with ME/CFS. Disorders of mitochondrial dysfunction often result in exercise

intolerance, as is seen in ME/CFS. It is suggested that mitochondrial dysfunction in ME/CFS is caused by inflammatory processes and increased levels of oxidative and nitrosative stress (Jason et al., 2009).

1.2.3 Treatment of ME/CFS

Although there is now good evidence showing ME/CFS as a medical illness with a complex biological pathophysiology, evidence for the efficacy of pharmacological treatments is still emerging. A survey of 94 Australian ME/CFS patients showed that these patients took a wide range of both conventional and complementary and alternative medicines (Kreijkamp-Kaspers et al., 2011). Most commonly used conventional medicines (both prescription and over-the-counter) included antidepressants, sedatives, simple analgesics and opiates. However, the evidence for the efficacy of these pharmacological treatments for ME/CFS is limited and inconsistent.

Stubhaug, Lie, Ursin, and Eriksen (2008) found some improvement in ME/CFS symptoms in patients taking the antidepressant mirtazapine. However improvements were only observed in patients who had first received a course of cognitive-behavioural therapy (CBT) before beginning mirtazapine. Several other randomised controlled trials have shown no effect of antidepressant therapy on ME/CFS symptoms (Hickie et al., 2000; Natelson et al., 1996; Vercoulen et al., 1996). Benzodiazepines and opiates may provide short-term relief for symptoms such as insomnia and pain, but patients run the risk of addiction and reduced potency with long-term use (Kreijkamp-Kaspers et al., 2011). Melatonin has shown some promise in reducing subjective fatigue and increasing concentration and activity levels in ME/CFS patients (van Heukelom, Prins, Smits, &

Bleijenberg, 2006). However these patients had Dim Light Melatonin Onset and reported improvements were likely due to advancement in circadian rhythmicity rather than improvements in sleep.

The key to successful pharmacological treatment may lie in targeting the underlying pathological dysfunctions in ME/CFS, although significantly more research is needed. Immunomodulating therapies, such as interferon therapy or anti-viral treatments, may be of benefit in certain subsets of ME/CFS patients (Bansal et al., 2012), as may anti-inflammatory treatments such as anti-tumour necrosis factor biologicals (Arnett et al., 2011). The use of antibiotic and/or alkalinizing agents in ME/CFS patients with D-lactic acidosis may reduce gastrointestinal symptoms (Sheedy et al., 2009). Further research into treatment strategies aimed at desensitising the central nervous system in patients with ME/CFS is also needed (Nijs et al., 2011).

Non-pharmacological treatments such as CBT and graded exercise therapy (GET) have also had mixed success. A meta-analysis by Malouff et al. (2008) showed CBT to be moderately efficacious, with 33% to 73% of ME/CFS patients assigned to CBT reporting fatigue levels in the normal range at follow-up. However dropout was significant in some studies, ranging from 0-42%. A small pilot study of mindfulness-based cognitive therapy (MBCT) for individuals with ME/CFS still experiencing excessive fatigue after CBT has shown some promise as an additional intervention, with MBCT participants reporting greater reduction in fatigue levels than a waitlist group (Rimes & Wingrove, 2013). Improvements were maintained six months post treatment. GET has shown to significantly reduce fatigue and improve physical functioning in a randomised study of 160 ME/CFS patients in comparison with specialist medical care alone (White et al., 2011). However patients with a physical functioning score of greater

than 65/100 on the short form-36 physical function subscale were excluded from this study, with only mild- to moderately-impaired ME/CFS patients included. More severe cases of ME/CFS are physically unable to perform GET. Additionally, GET must be carefully individualised as overexertion in ME/CFS can have deleterious outcomes, with a significant worsening of symptoms (Brown, Khorana, & Jason, 2011).

1.3 Sleep

1.3.1 Classifications of sleep difficulties

Pollak, Thorpy and Yager (2010) distinguish between at least 77 separate sleep disorders, however this number varies according to the classification system being used. Three such classification systems include the *International Classification of Sleep Disorders (ICSD-2)* (American Academy of Sleep Medicine, 2005), the non-organic sleep disorders section of the *International Classification of Disease (ICD-10)* (World Health Organisation, 2010) and the sleep disorders section of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association [APA], 2000). For the purposes of the current study diagnostic criteria as defined by the DSM-IV-TR have been used. A review by Roth et al. (2011) found that DSM criteria captured almost all clinically relevant cases (93.3%), with the ICD-10 capturing only severe cases and the ICSD-2 failing to recognise the decrements in perceived health that co-occur with insomnia. As such, the authors supported the use of the broader DSM criteria. At the time of participant recruitment the DSM-IV-TR was the most current DSM available.

The sleep disorders section of the DSM-IV-TR (APA, 2000) categorises sleep disorders into four major sections: Primary Sleep Disorders, Sleep Disorder Related to

Another Mental Disorder, Sleep Disorders Due to a General Medical Condition, and Substance-Induced Sleep Disorder. The latter three categories include sleep disorders related to another psychiatric or medical disorder, or due to substance use. Primary Sleep Disorders are further categorised into Dyssomnias and Parasomnias. Dyssomnias generally relate to disturbances in the quantity, quality or timing of sleep (APA). These include Primary Insomnia (difficulty initiating or maintaining sleep, or non-restorative sleep), Primary Hypersomnia (excessive sleepiness), Narcolepsy (sudden and irresistible episodes of refreshing sleep), Breathing-Related Sleep Disorder (such as obstructive sleep apnoea) and Circadian Rhythm Sleep Disorder (sleep disruption due to a mismatch between one's circadian sleep-wake pattern and the sleep-wake schedule required by one's environment).

Parasomnias involve abnormal movements, behaviours or dreams occurring during sleep (APA, 2000). These include Nightmare Disorder (repeated awakenings from extremely frightening dreams), Sleep Terror Disorder (abrupt awakening in fear, with no recall of a dream) and Sleep Walking Disorder. Parasomnias are thought to occur due to inappropriate arousal of the autonomic nervous system or motor or cognitive processes during sleep or during transition through sleep stages (Pollak et al., 2010).

1.3.2 Non-restorative sleep

Non-restorative sleep (NRS) is a complex and poorly understood subjective symptom of poor sleep. Individuals experiencing NRS typically describe their sleep as being unrefreshing (Roth, 2010). The concept of NRS arises from restorative theory, in which brain activity in sleep functions to replenish the mind and body for adequate functioning the next day (Stone et al., 2008). It is therefore logical that this

replenishment will be experienced as feeling refreshed upon wakening and a lack of replenishment will be characterised by NRS. “Unrefreshed sleep” or “loss of restorative feelings in the morning” is included as a diagnostic criteria for ME/CFS in the Canadian Clinical Case definition (Carruthers et al., 2003). NRS is frequently reported by patients with ME/CFS. In a study of 37 patients with ME/CFS by Fossey et al. (2004), 89% reported that they woke up feeling unrefreshed. Of 14 patients meeting criteria for ME/CFS in a Japanese community population, 13 (92.9%) indicated they experienced unrefreshing sleep (Hamaguchi, Kawahito, Takeda, Kato, & Kojima, 2011). Nisenbaum, Reyes, Unger, and Reeves (2004) investigated symptoms in 1391 chronically fatigued subjects in the U.S. Of these, 43 subjects had ME/CFS and 93% of the ME/CFS subjects reported unrefreshing sleep. Interestingly, only 53.4% of subjects experiencing chronic fatigue but not meeting criteria for ME/CFS or an ME/CFS-like illness reported unrefreshing sleep. In a reference sample of subjects reporting no fatigue (n = 3007), 10.5% reported experiencing unrefreshing sleep.

Despite sleep being the focus of much research, relatively little attention has been paid to NRS (Ohayon, 2005a). A reason for this seems to lie partly in the lack of a standardised definition of NRS, with considerable variation in how NRS is defined across studies (Stone et al., 2008). A review by Vernon et al. (2010) found that although a number of patient-reported outcome instruments are used in measuring NRS, there are currently no reliable or well-validated instruments. The 26 instruments reviewed varied widely from single item measures such as “overall quality of sleep” or “waking up feeling not refreshed or rested”, to some several-item measures asking about subjective nocturnal or diurnal aspects of NRS. Stone et al. (2008) recommended defining NRS as a feeling of being unrefreshed upon awakening after a normal sleep duration, occurring

at least three times a week for at least one month, with the absence of a sleep disorder. However Wilkinson and Shapiro (2012) argue that there is a lack of evidence supporting the selection of these criteria and that the choice of frequency is arbitrary.

There is also a lack of consensus regarding NRS being either a distinct condition, a symptom of other medical or psychological conditions, or simply another symptom of insomnia (Roth, 2010). Historically, NRS has been seen as primarily a result of inadequate sleep, typically due to the insomnia symptoms of difficulty initiating sleep, difficulty maintaining sleep or early morning awakenings (Sarsour et al., 2010). However several studies have now disputed this assumption. One large-scale epidemiological study (N = 24,600) showed that NRS may or may not be accompanied by other insomnia symptoms and that it also may occur in the presence of normal sleep duration (Ohayon & Roth, 2001). In this study, prevalence of NRS was 4.1% of the sample, with 26.7% of NRS subjects having neither a sleep disorder (including primary insomnia) nor a psychiatric disorder diagnosis. Another study involving 541 subjects with NRS found that 14.8% of NRS subjects did not meet criteria for insomnia based on Insomnia Severity Index scores and 19.3% of NRS subjects did not report difficulty initiating or maintaining sleep or early morning awakenings three times or more per week (Sarsour et al., 2010). Roth et al. (2010) conducted an exploratory study of sleep in subjects reporting NRS with or without insomnia symptoms (difficulty initiating or maintaining sleep). Insomnia symptoms were confirmed as being present or absent by polysomnography. Subjects with potential causes of NRS, including chronic sleep restriction or sleep deprivation, and medical and psychiatric conditions known to be associated with NRS, were excluded. Of the 226 subjects reporting NRS, 115 (50.9%)

had NRS-only, with no insomnia symptoms. These findings provide strong evidence to support the existence of NRS as a distinct condition in some individuals.

Wilkinson and Shapiro (2012) suggest that three broad categories of NRS be created: NRS due to medical illness (such as ME/CFS, fibromyalgia, or pain), NRS due to psychiatric illness (such as a mood disorder), and isolated or "pure" NRS. In addition to ME/CFS and insomnia, NRS is frequently found in a large number of sleep and other health problems, including narcolepsy, periodic limb movement disorder, obstructive sleep apnoea, fibromyalgia, temporomandibular joint disorders, irritable bowel syndrome, rheumatoid arthritis, and systemic lupus erythematosus (Stone et al., 2008). Pain has consistently been shown to be positively associated with the presence of NRS. In a study of almost 19,000 subjects aged 15 years or older from five European countries the prevalence of NRS was 4.5% (Ohayon, 2005b). Of those subjects reporting NRS, 42.3% reported at least one chronic painful physical condition, such as backache, headaches, or joint/articular diseases. This percentage dropped to 15.9% of those not reporting NRS. It has been shown that painful stimuli disrupts slow wave sleep, resulting in an increase in alpha and beta electroencephalogram activity and a decrease in delta and sigma EEG activity (Moldofsky, 2001). This disruption of slow wave sleep subsequently results in unrefreshing sleep.

Several potential physiological markers of NRS have been identified, although causal relationships are yet to be made and significantly more research is needed (Wilkinson & Shapiro, 2012). One promising marker is the pro-inflammatory cytokine interleukin-6, which has been shown to be negatively correlated with slow wave sleep (Burgos et al., 2006). Another potential marker is C-reactive protein (CRP), a biomarker for inflammation. A recent study of 11,000 subjects by Zhang et al. (2013) showed that

serum CRP was higher in those with NRS only (no difficulties initiating or maintaining sleep) when compared to individuals with insomnia symptoms but no NRS. This increased CRP level persisted after controlling for obstructive sleep apnoea and restless legs syndrome. The researchers suggested that increased CRP may be directly linked to the pathophysiology of NRS.

Despite the lack of a clear definition or etiology, there is strong evidence that NRS has a significant impact on daily functioning. Zhang et al. (2013) used the general productivity subscale of the Functional Outcomes of Sleep Questionnaire (FOSQ) to assess functioning in domains such as concentration, memory, sleepiness, and work performance. Lower scores were indicative of greater impairment. It was found that subjects with NRS only (no difficulties initiating or maintaining sleep) reported significantly lower FOSQ scores than subjects with no insomnia symptoms or with insomnia symptoms but no NRS. Similarly, Ohayon (2005a) showed that subjects with NRS only (n = 2756) reported significantly higher levels of physical and mental fatigue, irritability, depressed mood, anxious mood, memory problems, and difficulties staying alert than subjects with insomnia but no NRS (n = 5916). NRS has also been associated with lower subjective cognitive, physical and emotional functioning, independently of other insomnia symptoms and depression (Sarsour et al., 2010).

NRS is a commonly reported symptom of ME/CFS. However, the cause of NRS remains elusive. What is evident, however, is that NRS has a considerable negative impact on daily functioning. In addition to the impact of NRS, individuals with ME/CFS must also cope with a multitude of biological dysfunctions which compound the functional impairments they experience.

1.3.3 Sleep in ME/CFS

Macrostructure of sleep in ME/CFS

Comprehensive reviews by Jackson and Bruck (2012) and Gotts, Ellis, Newton and Deary (2014) found that despite common subjective reports of unrefreshing and disturbed sleep by ME/CFS patients, studies using PSG have typically reported only minimal differences in sleep macrostructure between individuals with ME/CFS and healthy controls. Several researchers have suggested that sleep state misperception may occur in ME/CFS, as poor sleep quality is often reported in the absence of objective markers of sleep pathology.

Hypnograms have generally been unable to discriminate individuals with ME/CFS from healthy controls, with most studies to date showing no differences in stage one (S1) %, stage two (S2) %, slow wave sleep (SWS) %, non-rapid eye movement (NREM) sleep %, or rapid eye movement (REM) sleep % between subjects with ME/CFS and controls (Majer et al., 2007; Neu et al., 2007; Reeves et al., 2006). Reeves et al. (2006) found no differences in total sleep time, sleep onset latency, sleep efficiency percentage or time spent awake after sleep onset between 43 subjects with ME/CFS and 43 controls. Majer et al. (2007) compared PSG sleep parameters of 35 subjects with ME/CFS with 40 controls. Subjective sleep quality was assessed using two items from the CDC Symptom Inventory that assess sleep quality over the preceding month (unrefreshing sleep and problems initiating or maintaining sleep) and perception of sleep quality during the PSG (best possible to worst possible sleep). ME/CFS subjects reported significantly poorer sleep quality than controls despite no differences in PSG-derived total sleep time, sleep onset latency, sleep efficiency

percentage, wake after sleep onset minutes, number of arousals, or arousal index. Neu et al. (2007) used the PSQI to measure subjective sleep quality in 28 'pure' (no primary sleep and no psychiatric disorders) ME/CFS subjects and 28 age- and sex-matched healthy controls. ME/CFS subjects reported significantly poorer subjective sleep quality. However PSG showed no differences in total sleep time, time in bed, sleep onset latency, or wake after sleep onset percentage. In contrast, Togo et al. (2008) found lower total sleep time and lower sleep efficiency in 26 subjects with ME/CFS when compared to 26 healthy controls. Although 12 of Togo et al.'s ME/CFS group also had co-morbid fibromyalgia (FM), there were no differences in sleep parameters between the two subsets of ME/CFS subjects.

Several studies have shown some differences in the sleep architecture of individuals with ME/CFS. Researchers from the University of Washington conducted a monozygotic co-twin control study involving 22 twin pairs discordant for ME/CFS (Ball et al., 2004; Watson et al., 2003). Watson et al. (2003) used the means of sleep measures across two nights of PSG to investigate objective and subjective measures of insomnia. ME/CFS twins more frequently endorsed the eight insomnia-related items on the Sleep Disorders Questionnaire, and reported poorer sleep quality after PSG than their healthy co-twins. No differences were found in PSG measures of total sleep time, sleep efficiency percentage, arousal number, or sleep latency between the two groups. However, they did find increased REM percentage in the ME/CFS twin along with a clinical, although not statistically significant, shortening of REM latency. The researchers suggested that increased REM pressure is associated with ME/CFS, either as a consequence of ME/CFS or as a predisposing factor. In the same twin study, Ball et al. (2004) used just the second night of PSG-derived measures of sleep in their analyses.

In addition to finding increased REM percentage in the ME/CFS twin, the ME/CFS twin also displayed increased percentage of slow wave sleep (SWS).

Le Bon et al. (2007) conducted a retrospective comparison of the NREM distribution between 28 pure ME/CFS subjects, 27 subjects with obstructive sleep apnoea (OSA), and 27 healthy controls. ME/CFS subjects displayed increased NREM sleep and increased ratios of SWS-to-light sleep in comparison to OSA subjects and controls. The researchers noted that the sleep pattern in ME/CFS differed markedly from those with disrupted sleep due to period limb movement, sleep apnoea, or artificial awakenings, with a pattern more closely resembling that seen as a result of infectious or auto-immune processes. They suggested that these observations offer further evidence to ME/CFS being an illness with a physiological etiology, distinct from primary sleep or psychiatric disorders. In a replication of Le Bon et al.'s 2007 study, Neu et al. (2009) compared the sleep of 32 pure ME/CFS subjects, 30 subjects with OSA and 14 healthy controls. As was seen in Le Bon et al.'s study, ME/CFS subjects displayed increased NREM sleep and increased ratios of SWS-to-light sleep in comparison with the other two groups. In contrast, Guilleminault et al. (2006) found SWS percentage to be lower in 14 subjects with ME/CFS in comparison to 14 controls. Therefore, although some differences have been found in sleep architecture in ME/CFS, results are at times contradictory. However the different methods of data collection used (ie. one night, vs night one and night two combined, vs night two only) to examine PSG in ME/CFS may explain these inconsistencies. It is also interesting to note that an increase in SWS would normally be associated with higher subjective sleep quality, something which is not usually reported by ME/CFS patients. This suggests that there is likely to be a more complex underlying pathophysiology in ME/CFS.

Stage shifts and dynamic stage transitions in ME/CFS

Although few differences have been found in sleep architecture in ME/CFS, studies of stage shifts and dynamic stage transitions have shown more promise in offering a possible explanation for the sleep problems reported in ME/CFS (Jackson & Bruck, 2012). Kishi et al. (2008) conducted one night of PSG to explore the global and normed relative frequencies in transitions between sleep stages in 22 females with ME/CFS and 22 healthy controls. Both the global and normed relative frequencies in transitions from NREM sleep to awake were higher in ME/CFS subjects than controls. The normed relative frequency in transition from REM to awake was also greater in ME/CFS than controls. Both the global and normed relative frequencies in transitions from REM to NREM was significantly lower in ME/CFS than controls, with ME/CFS subjects displaying more transitions from REM and S1 to wakefulness. The researchers suggested that these disruptions in sleep continuity and the increased tendency to awaken may explain the subjective reports of poor sleep quality in ME/CFS.

In a more recent study, Kishi et al. (2011) explored transition probabilities and rates between sleep stages (waking, REM, S1, S2, and SWS) and statistical distributions of duration of each sleep stage in 14 subjects with ME/CFS, 12 subjects with ME/CFS and FM, and 26 healthy controls. Interestingly, differences in transition probabilities were found between ME/CFS alone and ME/CFS and FM groups. Both probabilities and rates of transitions from waking, REM, and S1 and S2 were significantly greater in subjects with ME/CFS and FM than controls. Probabilities and rates of transitions from SWS to waking and S1 were also higher in ME/CFS and FM than controls. Probability of transitions from REM to waking was significantly higher in ME/CFS than controls.

The researchers concluded that these results support the notion of ME/CFS and FM being distinct illnesses, each with different dysfunctions in sleep regulation.

Sleep microstructure in ME/CFS

Another technique in sleep research is the utilisation of power spectral analysis in order to quantify and examine the constituent frequency components of the EEG signal (Jackson & Bruck, 2012). Alpha activity is primarily present during wake and after brief awakenings (Berry, 2012). Delta activity is most frequently associated with SWS. Increased delta activity typically occurs after a period of sleep restriction, with attenuation of delta power being associated with impaired sleep homeostasis (Berry). Alpha activity is virtually absent during stage 2 and SWS, except when associated with arousals. However an anomaly known as “alpha-delta sleep” occurs when alpha activity intrudes into SWS (Berry) and has been seen in a number of conditions such as chronic pain syndromes, fibromyalgia and depression. Early studies have shown evidence of alpha-delta sleep in patients with ME/CFS (Manu et al., 1994; Whelton, Salit, & Moldofsky, 1992). However, subsequent researchers have been unable to replicate these findings and delta EEG activity is now considered to provide the best discrimination between those with ME/CFS and healthy controls (Le Bon et al., 2012).

Decker, Tabassum, Lin and Reeves (2009) evaluated overnight PSG in 35 ME/CFS and 40 control subjects. Individual EEG signals were deconstructed into primary frequency bands of alpha, beta, delta, theta and sigma using Fast Fourier Transformation (FFT). In comparison with controls, subjects with ME/CFS displayed reduced delta power during SWS but increased delta power during both S1 and REM sleep. Reduced alpha power was also seen during S2, SWS and REM sleep, with the

greatest reduction occurring during REM sleep. The researchers posited that the reduced spectral power of delta and alpha activity signified impaired sleep homeostasis in ME/CFS and was a possible reason for the subjective non-restorative sleep and excessive fatigue of ME/CFS. In contrast to Decker et al., Armitage et al. (2009) found no differences in any frequency band between 13 female twin pairs discordant for ME/CFS. They concluded that genetic influences on sleep microarchitecture may be stronger than the illness influence of ME/CFS, despite the ME/CFS twins reporting poorer sleep quality. However despite finding no differences on the baseline night, Armitage et al. (2007) had previously found reduced delta power in SWS in response to sleep challenge in ME/CFS twins when compared to their healthy co-twins. They found that the ME/CFS twins experienced a blunted slow wave activity response when bedtime was delayed by four hours. The researchers suggested possible impairments of basic sleep drive and homeostatic response in ME/CFS.

In contrast to other studies, one study has shown *increased* delta power in ME/CFS (Guilleminault et al., 2006). The researchers applied FFT for the delta 1 (slow delta), delta 2, alpha, sigma 1, sigma 2 and beta frequency bands in a comparison between 14 subjects with ME/CFS and 14 controls. A significant increase in delta 1 relative power was found in the ME/CFS group when compared to controls. Where Guilleminault et al. examined slow delta, Le Bon et al. (2012) recognised the lack of research examining delta activity in the very slow end of the delta frequency band in ME/CFS. In a pilot study of 10 subjects with ME/CFS and 10 healthy controls, it was found that ultra-slow delta power was significantly lower in ME/CFS subjects than controls. The researchers suggested a failure in neural recruitment or dysfunction in the

oscillations in membrane potential as a possible reason for reduced ultra-slow wave delta power in ME/CFS.

Cyclic alternating pattern (CAP) is an EEG marker of unstable sleep, and is characterised by transient EEG activity during NREM sleep. CAP was originally considered to be arousal but is now seen to be more closely related to the process of sleep fragmentation and sleep maintenance (Parrino, Ferri, Bruni, & Terzano, 2012). CAP is a reflection of disturbed sleep which is distinct from arousals derived from PSG. Sustained periods of non-CAP sleep are indicative of sleep consolidation. Only one study to date has examined CAP in subjects with ME/CFS. Guilleminault et al.'s 2006 study of 14 ME/CFS subjects and 14 controls showed significantly higher CAP rates (therefore indicating greater NREM sleep instability) in the ME/CFS group. However several of the ME/CFS subjects in this study presented with increased nasal resistance which is suggestive of upper airway resistance syndrome (UARS). Increased CAP has been shown in patients with UARS (Guilleminault, Lopes, Hagen, & da Rosa, 2007) and so it is possible that the increased CAP seen in these ME/CFS subjects was due to the underlying pathology of UARS. What is clear, however, is that further research into the microstructure of sleep in ME/CFS is needed. Such research may be the key to discovering the underlying causes of non-restorative sleep in ME/CFS (Jackson & Bruck, 2012).

Biochemical regulation of sleep and its implications in ME/CFS

HPA axis hypofunction (Arnett et al., 2011) and immune dysfunction, as evidenced by cytokine dysregulation (Bansal et al., 2012) have been shown in individuals with ME/CFS. Both of these abnormalities have potential implications for

the regulation of sleep and may, in part, contribute to the sleep dysfunction reported by those with ME/CFS.

Cytokines such as interleukin-1 (Il-1), interleukin-6 (Il-6) and tumour necrosis factor (TNF) play a vital role in sleep regulation (Motivala & Irwin, 2007). Evidence for the involvement of Il-6 in sleep regulation has been shown in studies of exogenous administration of Il-6 in healthy humans (Spath-Schwalbe et al., 1998). Sleep architecture was significantly altered in these subjects, with decreased SWS in the first half of sleep and increased SWS during the second half. REM sleep was significantly decreased throughout the night. Subjects also reported increased fatigue and poorer concentration after receiving Il-6 in comparison to the placebo night. Plasma levels of Il-6 and TNF's soluble receptor p55 have also been shown to increase with extended periods of sustained wakefulness (Mullington, Hinze-Selch, & Pollmacher, 2001). However it is unclear whether an increase in cytokines leads to reduced sleep, or whether reduced sleep leads to an increase in circulating cytokines. Interestingly, Krueger et al. (2011) found that exogenous administration of TNF-alpha or Il-1 increased time spent in NREM sleep. Therefore increased TNF-alpha may be associated with the increases in SWS seen in ME/CFS. Exogenous TNF-alpha or Il-1 also resulted in increased subjective fatigue, sensitivity to pain, and poor cognition, symptoms which are commonly reported by individuals with ME/CFS.

A review by Buckley and Schatzberg (2005) examined the role of the HPA axis and sleep. They acknowledged that the HPA axis plays considerable roles in modulating sleep and maintaining alertness, with dysfunction of any aspect of the axis potentially leading to disrupted sleep. Low cortisol levels, which are often found in ME/CFS patients, enhances SWS sleep (Buckley & Schatzberg). In normal sleepers, a marked

and rapid rise in cortisol and ACTH occurs in response to final awakening in order to promote wakefulness and alertness (Chapotot et al., 1998). Hypocortisolism and reduced ACTH secretion may therefore also contribute to the unremitting fatigue experienced by ME/CFS patients. Glucocorticoid deficiency has also been associated with malaise, fatigue, somnolence and pain (Clauw & Chrousos, 1997), all symptoms typically reported in ME/CFS.

1.4 Measures of sleep

1.4.1 Actigraphy

Actigraphy has been used in the study of sleep/wake behaviour for many years. It offers significant cost reductions compared to polysomnography and allows portable monitoring and longer monitoring periods (Littner et al., 2003; Morgenthaler et al., 2007; Thorpy et al., 1995). Actigraphy is typically used in conjunction with sleep logs in order to study sleep-wake patterns and circadian rhythms. It is based on assessing movement, most often of the wrist, using an actimetry sensor mounted in a device similar in appearance to a wrist watch (Martin & Hakim, 2001). The actigraph measures and records gross motor activity and the data is downloaded onto a computer for further analysis.

Computer software is used to analyse periods of activity and inactivity, which are then further analysed to estimate a number of variables related to sleep and wake states (Ancoli-Israel et al., 2003). The software uses the activity count within each epoch and the surrounding epochs to compute a Total Activity Count (TAC) (Boyne et al., 2013). The epoch is scored as wake when the TAC surpasses a certain threshold and scored as sleep if below that threshold. The Philips Actiware software used in the

current study has a default sensitivity setting of medium (40 activity counts), but may be manually changed to low (20 activity counts) or high (80 activity counts). The software scores an epoch as mobile if the activity count within that epoch equals or exceeds the number of 15-second intervals within the epoch (Boyne et al.). For example, when the epoch length is set for one minute, the activity count must be greater than or equal to 4 in order to be scored as mobile. Time of lights out and final wakening are manually entered based on sleep diary information. This information and epochs of immobility are then used by the software to distinguish between periods of sleep and wake.

1.4.2 Clinical and research uses of actigraphy

The current study is investigating sleep variables such as sleep efficiency and sleep quality which are commonly associated with sleep disorders. The use of actigraphy in ME/CFS research has focused primarily on investigating sleep disorders such as insomnia and circadian rhythm disorders (particularly delayed sleep phase disorder) for differential diagnosis purposes. Therefore these aspects of sleep will be the main focus of the following section.

Insomnia

Actigraphy is a useful tool to assess sleep parameters both before and after treatment in people with known insomnia (Morgenthaler et al., 2007). The portability, relative ease of use, and lower cost of actigraphy make it an attractive alternative to PSG. As insomnia sufferers tend to have significant variability in sleep parameters from night to night, actigraphy is considered a particularly useful tool in evaluating sleep over an extended period time as it is less resource and cost prohibitive than PSG (Vallieres, Ivers, Bastien, Beaulieu-Bonneau, & Morin, 2005).

In validating actigraphy against PSG in a sample of 57 participants meeting conservative criteria for insomnia, Lichstein et al. (2006) demonstrated that four sleep parameters - number of wakenings, wake time after sleep onset, total sleep time and sleep efficiency percentage – were all acceptable measures for the clinical evaluation of insomnia. Sleep onset latency with actigraphy was only weakly correlated with polysomnography and so not considered a valid measure of this parameter. As actigraphy detects sleep onset from lack of movement, this may be difficult to interpret in insomnia sufferers, particularly those who quietly lay awake in bed for long periods of time while attempting to initiate sleep (Paquet, Kawinska, & Carrier, 2007).

Actigraphy has also been shown to adequately distinguish between insomniacs and normal sleepers. A retrospective study compared sleep parameters between patients with diagnosed primary insomnia (n = 126) and normal sleepers (n = 282) (Natale, Plazzi, & Martoni, 2009). The actigraphic sleep parameters which were analysed included time in bed, sleep onset latency, total sleep time, wake time after sleep onset, sleep efficiency percentage, number of wakenings longer than 5 minutes, and mean motor activity. Of these parameters, all except time in bed significantly differentiated insomnia patients from normal sleepers. Further analysis identified that a combination of sleep onset latency, total sleep time and number of wakenings longer than 5 minutes yielded the best efficacy in distinguishing the insomnia group from the control group. This was not surprising given that these parameters correlate with the commonly reported symptoms of insomnia of difficulty initiating and/or maintaining sleep.

Circadian rhythm sleep disorders

Circadian rhythm sleep disorders typically arise due to the desynchronisation between a person's intrinsic circadian clock and extrinsic environmental time cues such as light/dark (Bittencourt, Santos-Silva, De Mello, Anderson, & Tufik, 2009). Actigraphy has been recognised as a useful tool in the diagnosis of circadian rhythm sleep disorders, including advanced sleep phase syndrome (ASPS), delayed sleep phase syndrome (DSPS) and shift work disorder (Morgenthaler et al., 2007). A review by Ancoli-Israel, Cole, Alessi, Chambers, Moorcroft and Pollak (2003) concluded that actigraphy is useful for distinguishing sleep disturbances due to disruption of circadian rhythms, and characterising sleep improvements after treatments that improve rhythms. They reported that there is good evidence to show that actigraphy may help diagnose DSPS, as the actigraphic detection of circadian rhythm phase delays in people with DSPS corresponds to delays in melatonin secretion. People experiencing DSPS have difficulty initiating sleep at the desired time and so fall asleep late and subsequently have difficulty awakening (Wyatt, 2004). They typically do not fall asleep until after midnight and do not waken until late morning or early afternoon.

Uses in other populations and disorders

Actigraphy is steadily increasing in popularity as a sleep assessment tool in both clinical and research spheres and there are now many published actigraphic studies. It is beyond the scope of this thesis to explore all uses in depth and so these will be listed only briefly. Actigraphy has been shown to be a useful sleep assessment tool in both paediatric and geriatric populations, in whom traditional assessment using polysomnography can be difficult (Morgenthaler et al., 2007). A growing number of

studies have utilised actigraphy with older adults (Blackwell et al., 2012; Cochrane, Robertson, & Coogan, 2012; Rowe et al., 2008; Van den Berg, Miedema, Tulen, Hofman, Knuistingh Neven, & Tiemeier, 2009). Actigraphy has been used to assess sleep in children with attention-deficit/hyperactivity disorder (Corkum, Tannock, Moldofsky, Hogg-Johnson, & Humpries, 2001; Sangal, Owens, Allen, Sutton, Schuh, & Kelsey, 2006; Wiggs, Montgomery, & Stores, 2005) and autism spectrum disorders (Souders et al., 2009; Wiggs & Stores 2004). Actigraphy has also been used to investigate sleep in healthy infants (Muller, Hemmi, Wilhelm, Barr, & Schneider, 2011; So, Adamson, & Horne, 2007) and children (Acebo, Sadeh, Seifer, Tzischinsky, Hafer, & Carskadon, 2005; Holley, Hill, & Stevenson, 2009; Spruyt, Gozal, Dayyat, Roman, & Molfese, 2011).

The use of actigraphy to measure sleep variables in those experiencing a range of medical and psychiatric conditions is also gaining in popularity. Such conditions include sleep apnoea (Hedner, Pillar, Pittman, Zou, Grote, & White, 2004; Nakayama-Ashida et al., 2008;), periodic limb movements in sleep (Allan, 2007; Gschliesser et al., 2009), bipolar disorder (Kaplan, Talbot, Gruber, & Harvey, 2012; Millar, Espie, & Scott, 2004), posttraumatic stress disorder (Kobayashi, Huntley, Lavela, & Mellman, 2012; Westermeyer et al., 2007; Westermeyer et al., 2010), psychotic disorders (Afonso, Brissos, Figueira, & Paiva, 2011; Tahmasian, Khazaie, Golshani, & Avis, 2013), Parkinson's disease (Stavitsky, Saurman, McNamara, & Cronin-Golomb, 2010), Alzheimer's disease (Camargos, 2013), chronic obstructive pulmonary disease (Nunes et al., 2013) and cancer (Ancoli-Israel et al., 2006).

1.4.3 Actigraphy practice parameters

As actigraphy has become more widely used in both clinical and research settings to evaluate sleep disturbances, practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders have been revised and refined over time. The American Academy of Sleep Medicine (AASM) Standards of Practice Committee (SPC) have reviewed published peer-reviewed literature on the use of actigraphy in sleep and circadian rhythm disorders in order to develop these practice parameters (Littner et al., 2003; Morgenthaler et al., 2007; Thorpy et al., 1995).

The original practice parameters published in 1995 concluded that actigraphy should not be used in the routine diagnosis or assessment of severity of any of the sleep disorders (Thorpy et al., 1995). However, they also concluded that actigraphy may be useful when used in conjuction with a detailed history and examination, and a subjective sleep diary, particularly when multiday information was needed, more objective information was needed, or to clarify the effects of treatment. Actigraphic technology improved markedly after the publication of these practice parameters, and the use of actigraphy in research and clinical settings increased considerably, leading to a review of new evidence resulting in revised practice parameters being published in 2003 (Littner et al., 2003).

The most recent practice parameters were published in 2007 (Morgenthaler et al., 2007). These were the result of a review of the considerable amount of research conducted since the previous practice parameters were published. Evidence in the peer-reviewed literature regarding the use of actigraphy in sleep and circadian rhythm disorders was reviewed and graded by experts in the use of actigraphy. From an initial computerised search which yielded 3641 papers, a total of 108 studies were deemed to

meet appropriate inclusion criteria and so formed the basis of the review. The purpose of the project was to define principles of practice to meet the needs of most patients in most situations. A number of recommendations were made regarding the use of actigraphy in clinical practice. The following standards and guidelines reflected moderate to high levels of clinical certainty: actigraphy is to be considered a valid and reliable measure of sleep in normal, healthy adult populations and in patients suspected of certain sleep disorders, including insomnia; actigraphy is able to assist in the assessment of individuals with suspected advanced sleep phase syndrome, delayed sleep phase syndrome and shift work disorder; actigraphy is indicated to estimate total sleep time in individuals with obstructive sleep apnoea when polysomnography is not available; actigraphy is a useful outcome measure in assessing the response to treatment in individuals with circadian rhythm disorders and insomnia; actigraphy is indicated for characterising sleep and circadian rhythm patterns and to assess treatment responses in older adults, including those living in nursing homes; and actigraphy is indicated for delineating sleep patterns and assessing treatment responses in infants and children, including special paediatric populations.

The practice parameters do not clearly address issues such as epoch length, actiwatch placement and optimal length of data collection. However Berger et al. (2008) reviewed twenty-one studies which evaluated sleep/wake patterns in adult patients with cancer in order to explore methodological challenges when using actigraphy in research. Patients with cancer were chosen in order to make comparisons within a single population. A number of observations and recommendations were made. Actigraphs were most commonly reported as being placed on the non-dominant wrist. Data should be collected over at least three, consecutive 24-hour periods. One-minute epoch lengths

are usually sufficient for assessing sleep disorders. Inclusion of the following key sleep variables is recommended: time spent in bed, total sleep time after sleep onset, number of awakenings, minutes spent awake, and wake after sleep onset. Due to variations typically seen in sleep/wake patterns between weekdays and weekends, the days of the week on which monitoring occurs should be kept consistent, if feasible. The use of a sleep diary is essential to determine start and stop times for actigraphy analysis.

1.4.4 Validity of actigraphy

Actigraphy has been validated as a valuable instrument for measuring various sleep parameters in both healthy and some clinical populations and with a range of ages from children to the elderly. It is considered the most appropriate objective measure of sleep in the non-laboratory setting when PSG is not available or is impractical (Van de Water, Holmes & Hurley, 2010). As PSG is considered the "gold standard" of sleep measurement, validation of actigraphy involves measuring concordance between sleep/wake measures obtained by actigraphy with those concurrently obtained by PSG. This is typically done in one of two ways: sleep parameters concordance analysis (for example comparing duration of wake after sleep onset obtained by actigraphy with that obtained by PSG) and epoch-by-epoch analysis (Marino et al., 2013).

Epoch-by-epoch analysis is used to investigate sensitivity (actigraphy identifies sleep when PSG identifies sleep) and specificity (actigraphy identifies wake when PSG identifies wake). Many validation studies have reported high sensitivity but low specificity (Sadeh, 2011). That is, actigraphy is highly accurate when identifying sleep, but less accurate when identifying wake. This is likely due to the scoring algorithm of actigraphy software which uses activity counts to determine sleep. Accuracy tends to

reduce in individuals with poorer sleep quality where lying still, but awake, may be scored as sleep (van de Water, Holmes & Hurley, 2010). Additionally, validation studies vary widely in the period of recording, with many studies comparing one night's data of actigraphy and PSG. Low specificity may therefore be a result of a first night effect of quiet wakefulness (Van de Water et al.).

It is important to note that a broad range of actigraphy devices and scoring algorithms have been used in research. As such, it is problematic to directly compare results obtained from different studies, unless the same device and algorithm was used in each study. In a study by Rupp and Balkin (2011), 29 healthy young adults concurrently wore the Actiwatch-64 (AW) and the Motionlogger Watch (MW) while undergoing two nights of PSG. In comparison to PSG, the AW underestimated sleep efficiency (SE) and total sleep time (TST) and overestimated number of awakenings on both nights, and underestimated sleep onset latency (SOL) on the baseline night. The MW underestimated both SE and TST overall and overestimated SE on the second night. In a similar study by Meltzer, Walsh, Traylor and Westin (2012), 115 children and adolescents concurrently wore the Philips Respironics Mini-Mitter Actiwatch-2 (PRMM) and the Ambulatory Monitoring Inc. Motionlogger Sleep Watch (AMI) while undergoing overnight PSG in a sleep laboratory. Inter-device agreement was poor for TST, duration of wake after sleep onset (WASO) and SE, with the AMI device finding a shorter TST, more WASO and lower SE compared to the PRMM device. Comparisons of different scoring algorithms and sensitivity settings were also made. Results showed varying concordance with PSG measures of TST and SE, with these differences related to age and sleep disordered breathing status. The researchers therefore concluded that caution is needed when comparing results across studies using different actigraphic

devices and that researchers should consider adjusting the scoring algorithm/sensitivity depending on the study population.

However, Meltzer et al. (2012) also found high intra-device correlation, with no significant differences found between devices of the same brand, suggesting that comparable results can be obtained using multiple devices of the same brand and model within a study. In the current study, all participants wore the same brand and model actiwatch and actigraphic data was scored using the same algorithm (using the default sensitivity setting as recommended by the manufacturer). Therefore, despite the concerns regarding generalisation across different studies, valid comparisons can be made across the participant groups in this study.

The sleep parameters measured for the current study included total sleep time (the time in minutes spent asleep from lights out until final wakening), sleep onset latency (the time from lights out until initial sleep onset), wake after sleep onset (the time spent awake between initial onset of sleep and final wakening), sleep efficiency (100 x total sleep time/time in bed) and sleep fragmentation index (a measure of restlessness, or a lack of sleep continuity). The sleep fragmentation index is calculated as 100 x the number of groups of consecutive immobile 60-second epochs/by the total number of immobile epochs (Cambridge Neurotechnology Ltd, as cited in van den Berg, Knvistingh Neven, et al., 2008). Therefore it is important to discuss the validity of actigraphy in measuring each of these parameters, with a focus on both healthy adults, and adults with insomnia and/or major depression, as these disorders may co-occur with ME/CFS (Mariman et al., 2013).

Total sleep time

Paquet, Kawinska, and Carrier (2007) measured three nights of simultaneous PSG and actigraphy in 15 healthy adults (aged 20-60 years). Participants underwent three different sleep conditions: a nocturnal sleep episode followed by two daytime recovery sleeps (one with placebo and one with caffeine). Although actigraphy overestimated total sleep time compared to PSG in both the daytime recovery sleeps, good concordance was obtained with nocturnal sleep, suggesting that actigraphy is a valid measure of total sleep time for nocturnal sleep. McCall and McCall (2012) measured one night of sleep with concurrent actigraphy and PSG in 54 adults diagnosed with a current major depressive episode and chronic insomnia. No significant differences in total sleep time were found between the two measures, indicating that actigraphy is a valid measure of total sleep time in this population. A validation study by Sanchez-Ortuno, Edinger, Means & Almirall (2010) was unique in that it involved measuring concurrent actigraphy and PSG for up to three consecutive nights in the participants' own homes. Both groups of 31 healthy sleepers and 31 primary insomnia patients showed no difference between actigraphic and PSG measures of total sleep time.

Sleep onset latency

Actigraphic sleep onset latency generally has poorer concordance with PSG than other sleep parameters, with most studies reporting that actigraphy underestimates sleep onset latency when compared with PSG. Although this is consistent among different populations, including healthy individuals (Paquet, Kawinska, & Carrier, 2007; Sanchez-Ortuno, Edinger, Means & Almirall, 2010), the difference is more prominent

in individuals with insomnia (Sanchez-Ortuno et al.; Lichstein et al., 2006). Individuals with insomnia are more likely to lie quietly in bed awake before falling asleep than normal sleepers, therefore actigraphic signals may misinterpret the lack of movement as sleep (Van de Water, Holmes & Hurley, 2010). Tyron (2004) suggested that differences in sleep onset latency between actigraphy and PSG are systematic rather than random, due to sleep onset being a gradual process and actigraphy identifying sleep at an earlier stage of the sleep-onset process than PSG.

Duration of wake after sleep onset

Marino et al. (2013) measured concurrent actigraphic and PSG sleep parameters in 77 participants across a mean of 3.2 nights. Participants included young and older adults, normal sleepers and individuals with chronic primary insomnia, and also included the daytime sleep of 23 night shift workers. They found that actigraphy overestimated PSG wake after sleep onset by a mean of five minutes when PSG wake after sleep onset was 30 minutes or less. When PSG wake after sleep onset was greater than 30 minutes, actigraphy underestimated wake after sleep onset, with the difference increasing as PSG wake after sleep onset increased. However in Sanchez-Ortuno et al's (2010) study of primary insomnia patients and normal sleepers, no difference was found between PSG wake after sleep onset and actigraphic wake after sleep onset in either group. Likewise McCall and McCall (2012) found no difference in wake after sleep onset in individuals with depression and chronic insomnia.

Sleep efficiency

Actigraphy has been shown to be a valid measure of sleep efficiency. No differences have been found between PSG and actigraphy in healthy participants

(Sanchez-Ortuno, Edinger, Means & Almirall, 2010), primary insomnia patients (Sanchez-Ortuno et al.; Lichstein et al., 2006), or adults with depression and chronic insomnia (McCall & McCall, 2012). However Rupp and Balkin (2011), in their comparison of two actigraphy devices (Motionlogger Watch and Actiwatch-64) to PSG in 29 young healthy adults, found that both devices underestimated sleep efficiency overall, although there were also significant differences found between the two devices. This highlights the importance of using the same make/model actigraph and scoring algorithm for each comparison group (as in the current study) in order to reduce random error.

Sleep fragmentation index

Validation studies of actigraphy do not seem to investigate the concordance between sleep fragmentation in actigraphy and PSG. The standard for quantifying sleep fragmentation in PSG is the arousal index, which is a measurement of the number of arousals per hour of sleep. Unlike actigraphy which uses mobility data to measure sleep fragmentation, the criteria for electroencephalography (EEG) arousals have been defined by the American Sleep Disorders Association as an abrupt shift of EEG frequency lasting 3 seconds or longer with at least 10 seconds of sleep prior to the shift (Iber, Ancoli-Israel, Chesson, & Quan, 2007). There appears to be no published studies comparing sleep fragmentation in actigraphy and PSG in adults. However a study of 130 children (aged 2-18 years) showed that sleep fragmentation measured by actigraphy is at best a fair index of sleep fragmentation as measured by the PSG arousal index (O'Driscoll, Foster, Davey, Nixon, & Horne, 2009).

For the purposes of the current study, actigraphic sleep fragmentation index is considered an adequate measure of restlessness during sleep. As actigraphy uses mobility data to measure sleep fragmentation, different actigraphy threshold settings would make substantial differences to the measurement obtained. However, as sleep fragmentation is being compared between two groups using the same actiwatches and actigraphy algorithm, the need for concordance with PSG is reduced.

Validity of actigraphy in measuring sleep in ME/CFS

Overall, researchers have concluded that actigraphy is a valid measure of total sleep time, sleep efficiency and duration of wake after sleep onset, with sleep onset latency to be interpreted with caution (Martin & Hakim, 2011). However, to date there appears to be just one published study comparing sleep parameters using PSG and actigraphy in ME/CFS (Creti et al., 2010). This study of 49 participants with ME/CFS found that actigraphy underestimated sleep onset latency (consistent with studies of other populations) and overestimated wake after sleep onset when compared with PSG. No differences were found in total sleep time and sleep efficiency. This study indicates the usefulness of actigraphy as a valid measure of sleep parameters in individuals with ME/CFS.

1.4.5 Comparisons between actigraphy and subjective measures of sleep parameters

Total sleep time

Lauderdale, Knutson, Yan, Liu and Rathouz (2008) examined the concordance between subjective and actigraphic TST in a study involving 615 healthy adults, and found subjective TST to be longer than actigraphic TST. Similar results have been

found in studies of 385 adolescents (Short, Gradisar, Lack, Wright, & Carskadon, 2012), 969 elderly persons (Van den Berg, Van Rooij, et al., 2008), 22 inpatients of an alcoholism treatment program (Brooks, Krumlauf, Whiting, Clark, & Wallen, 2012), and 43 subjects with heart failure (Wang, Hung, & Tsai, 2011). However, Van den Berg, Van Rooij, et al. (2008) also found that subjectively poor sleepers (as assessed by the PSQI) reported shorter TST than that measured by actigraphy. This bias is not uncommon in populations with subjective poor sleep, such as those with insomnia or depression. Fifty-four patients diagnosed with a current major depressive episode and chronic insomnia completed one night of concurrent PSG and actigraphy (and kept a sleep diary) in a sleep laboratory (McCall & McCall, 2012). Although actigraphic total sleep time and subjective total sleep time were moderately correlated, the difference between the two was significant, with participants reporting lower total sleep time than actigraphy. Research examining concordance between subjective and actigraphic measures of traditional sleep parameters in ME/CFS is limited. Creti et al. (2010) found no difference between subjective or actigraphic TST in 49 subjects with ME/CFS. When the subjects were separated into subgroups according to chronic insomnia diagnosis, these lack of differences remained.

Sleep onset latency

Individuals tend to report higher subjective SOL in comparison to actigraphic measures of SOL, regardless of health status. This bias may be greater in those with an insomnia diagnosis, as the lack of movement while lying quietly awake in bed may be misinterpreted by the actigraphy software as sleep (Van de Water et al., 2010). Subjective SOL has shown to be significantly greater than actigraphic SOL in studies of

healthy adults (Kaplan, Talbot, Gruber, & Harvey, 2012; Kobayashi, Huntley, Lavela, & Mellman, 2012; Signal, Gale, & Gander, 2005), bipolar disorder (Kaplan et al., 2012), major depressive disorder and chronic insomnia (McCall & McCall, 2012), post-traumatic stress disorder (PTSD) (Kobayashi et al., 2012), and ME/CFS (both with and without co-morbid chronic insomnia) (Creti et al., 2010). In contrast, Wang et al. (2011) found no significant difference between subjective SOL and actigraphic SOL in patients with heart failure.

Duration of wake after sleep onset

As is frequently found in comparisons of total sleep time, good sleepers are more likely to report subjectively lower duration of WASO than actigraphic WASO, with subjectively poor sleepers reporting higher duration of WASO than actigraphic WASO. Significantly higher actigraphic WASO than subjective WASO estimates have been found in healthy adolescents (Short et al., 2012), healthy adults and PTSD (Kobayashi et al., 2012), and heart failure (Wang et al., 2011). McCall and McCall (2012) found that depressed insomniacs subjectively estimated their WASO to be, on average, 24 minutes greater than that measured by actigraphy. In contrast however, Creti et al. (2010) found that subjects with co-morbid chronic insomnia and ME/CFS reported less WASO than measured by actigraphy.

Sleep efficiency

Although studies comparing subjective and actigraphic SE are few, these studies have shown good agreement between the two. It may be argued that the combination of reported underestimation of WASO and overestimation of SOL in comparison to actigraphy negate each other, resulting in an overall concordance of subjective and

actigraphic SE. No differences in subjective SE and actigraphic SE have been found in ME/CFS patients (either with or without co-morbid chronic insomnia) (Creti et al., 2010), heart failure patients (Wang et al., 2011) or inpatients of an alcoholism treatment program (Brooks et al., 2012).

1.4.6 The use of actigraphy in ME/CFS

Actigraphy in ME/CFS research has primarily been used to investigate diurnal activity. Diurnal physical activity has been shown to be lower in children with ME/CFS than healthy controls (Ohinata et al., 2008). Tyron, Jason, Frankenberry, and Torres-Harding (2004) found a significant reduction in daytime activity measured by actigraphy in adults with ME/CFS when compared with healthy controls. However Rahman, Burton, Galbraith, Lloyd and Vollmer-Conna (2011) found no significant difference in daily actigraphy between 15 subjects with ME/CFS and 15 controls. Van der Werf et al. (2000) found that 75% of their ME/CFS sample had comparable activity levels to controls, with 25% showing significantly lower diurnal activity. Actigraphy has also been found to be a valid measure of daytime activity levels in the assessment of nonpharmacological treatment outcomes for ME/CFS (Brown, Khorana, & Jason, 2011).

There are fewer studies using actigraphy as a measure of nocturnal sleep/wake patterns in ME/CFS. Although Ohinata et al. (2008) examined the sleep of 12 children (12 to 16 years) fulfilling Reeves criteria for ME/CFS and 7 age-matched controls, there was no distinction made between daytime napping and nocturnal sleep in the statistical analyses conducted. Each subject wore a wrist actiwatch and kept a sleep diary for 1-2 weeks. Subjects in the ME/CFS group were further divided into two groups based on

information obtained from the sleep diary and questionnaire. Those who met DSM-IV-TR criteria for Circadian Rhythm Sleep Disorder, Unspecified Type, were placed in the 'irregular sleep type' (IR) group (n = 5) and those who met DSM-IV-TR criteria for Circadian Rhythm Sleep Disorder, Delayed Sleep Phase Type, were placed in the 'delayed sleep phase' (DSP) group (n = 7). Both ME/CFS groups were found to have longer actigraphic total daily sleep time than healthy controls. Actigraphic total daily sleep time was longer in the DSP group than the IR group.

Rahman et al. (2011) investigated circadian rhythms in adults with ME/CFS using actigraphy. Fifteen patients fulfilling Fukuda criteria for ME/CFS were recruited from a tertiary referral clinic, where they were in the second week of a graded-activity oriented cognitive-behavioural therapy program. Fifteen healthy control subjects of similar age, sex, body mass index, and activity levels were recruited from the community. All subjects wore a wrist actiwatch and completed a diary of sleep/wake behaviour for five continuous days, including a weekend. Subjective sleep quality was assessed using the PSQI. Although subjects were asked to record subjective sleep quality each morning in their diaries, no analyses of this variable were reported. Time to bed and wake up times were comparable for both groups. Additionally, no significant differences in actigraphic total sleep time, sleep efficiency or sleep fragmentation were found between the two groups, despite the ME/CFS group rating their sleep quality (as based on global PSQI scores) as being significantly poorer than controls. Based on these findings, the researchers concluded there was a lack of evidence supporting the hypothesis of circadian rhythm disturbance being the key to unrefreshing sleep and debilitating fatigue in ME/CFS.

Creti et al. (2011) used concurrent PSG, actigraphy, and sleep diaries to evaluate the sleep/wake behaviour of 49 subjects meeting Reeves criteria for ME/CFS. Thirty-two of these subjects also had a chronic insomnia diagnosis, with 17 having no chronic insomnia diagnosis. One night of data was collected in a sleep laboratory. Upon wakening, subjective sleep quality was measured by asking subjects to rate 'What was the quality of your sleep last night?' on a Likert-type scale of 1 to 10 (1 = very poor, 10 = very good). Subjective non-refreshing sleep severity was also rated on a scale of 1 to 10 (1 = not refreshed at all, 10 = very refreshed). The researchers found no association between feeling unrefreshed in the morning and actigraphic measures of sleep (sleep onset latency, wake after sleep onset, total sleep time, or sleep efficiency) in either the 'chronic insomnia' group or the 'no chronic insomnia' group. However, moderate to high correlations were found between some actigraphic sleep parameters and subjective sleep quality. In the 'chronic insomnia' group, subjective sleep quality was associated with actigraphic measures of total sleep time (positive correlation), duration of wake after sleep onset (negative correlation), and sleep efficiency (positive correlation). In the 'no chronic insomnia' group, subjective sleep quality was associated with actigraphic measures of duration of wake after sleep onset (negative correlation) and sleep efficiency (positive correlation).

1.4.7 Cardiopulmonary coupling

Cardiopulmonary coupling (CPC) is a relatively new technique which uses the electrocardiogram (ECG) signal to measure sleep stability and quality (Thomas, Mietus, Peng, & Goldberg, 2005). During sleep, autonomic nervous system dynamics such as respiration and heart-rate have distinct variations according to sleep type and depth. The

CPC analysis algorithm uses a Fourier-based technique to generate frequency spectrograms of ECG R-wave amplitude and heart rate variability fluctuations associated with respiration. The frequency at which coupled heart rate-respiratory oscillations occur is used to categorise sleep as stable or unstable. Periods of high-frequency coupling (HFC) occurring at 0.1-0.4 Hz are indicative of stable nonrapid eye movement (NREM) sleep. Periods of low-frequency coupling (LFC) occurring at 0.1-0.01 Hz are indicative of unstable NREM sleep (Schramm, Thomas, Feige, Spiegelhalder, & Riemann, 2012). Very-low-frequency coupling (VLFC) of 0.0039-0.01 Hz occurs during REM and wake states but without the recording of muscle tone distinction between the two states is not possible (Yang et al., 2011).

1.4.8 Validity of cardiopulmonary coupling as a measure of sleep stability and quality

Although measures of CPC are most typically obtained by extracting ECG data from polysomnograms (Thomas et al., 2005), research comparing CPC with PSG variables such as percentage time spent in different sleep stages is limited. A promising study of 19 adults with major depression showed moderate to strong correlations between PSG and CPC variables (Schramm, Poland, & Rao, 2014). HFC was positively correlated with PSG measures of sleep efficiency and % sleep spent in stage N3 sleep, and negatively correlated with % time spent in stage N1 sleep, duration of wake after sleep onset, number of awakenings, and arousal index. LFC was positively correlated with % time spent in N1 sleep, wake after sleep onset, number of awakenings and arousal index, and negatively correlated with sleep efficiency and % time spent in stage N3 sleep.

A study by Schramm et al. (2012) has shown CPC can differentiate between insomniacs and good sleepers. The researchers analysed the CPC variables of 36 good sleepers and 50 patients with primary insomnia and found that individuals with primary insomnia had significantly lower HFC and higher LFC than good sleepers. CPC has also been shown to differentiate between subjects with moderate to severe OSA (*n*=20) and subjects with no OSA (*n*=16) (Harrington, Schramm, Davies, & Lee-Chiong, 2013). Although no difference was found in LFC, subjects with moderate to severe OSA were found to have significantly lower HFC than those with no OSA.

CPC has also been shown to be a valid tool to measure post treatment improvements in sleep. Lee et al. (2014) used CPC to measure improvements in sleep stability in 52 patients with OSA after treatment with a mandibular advancement device. LFC significantly decreased and HFC significantly increased after treatment. Increases in HFC and decreases in LFC have also been shown in a sample of 37 children after having adenotonsillectomy for OSA (Lee et al., 2012).

Although CPC has been able to demonstrate sleep stability/instability and improvements in sleep stability in several populations, studies comparing CPC with subjective measures of sleep quality have been mixed. The study of primary insomnia patients and good sleepers by Schramm et al. (2012) showed no statistically significant correlations between HFC and LFC and global PSQI scores, PSQI estimate of sleep time or PSQI sleep efficiency estimates in either group. Likewise Yang et al. (2011) found no significant correlations between HFC or LFC and global PSQI scores in either depressed patients or healthy controls. Chien et al. (2013) found a weak but significant positive correlation between global PSQI scores and % time spent in unstable sleep in a study of 156 nurses. A weak negative correlation between global PSQI scores and %

time spent in stable sleep was also evident. A study of 155 healthy adults by Yang et al. (2010) found seemingly spurious but significant weak correlations between PSQI estimate of sleep duration and % time spent in stable sleep (positive correlation) and % time spent in unstable sleep (negative correlation). It may be argued that the use of the PSQI, a retrospective measure of sleep quality, is not the ideal measure of sleep quality in this type of study. It seems that there is no published research comparing night-by-night subjective sleep quality with CPC variables.

As an alternative to ECG measured with PSG, small devices that adhere to the chest and use a single lead to measure CPC are now available. One such device is the SleepImage M1™ recorder. There is little published research investigating the validity of the M1™ device. A case study of a 67-year-old female with mild OSA showed that the M1™ device was able to differentiate between nights where OSA therapy was applied (a mandible advancing appliance or sleep position restriction) and where no OSA-specific therapy was applied (Schramm & Thomas, 2012). Sylvia et al. (2014) used the M1™ device to investigate the efficacy of a brief CBT-based intervention for insomnia (CBT-i) and hypersomnia in eight adults with bipolar disorder. The study also explored the level of "acceptability" of the M1™ device, with participants reporting that it was very easy to use and apply, and did not interfere with sleep. Post CBT-i there was no change in HFC, but LFC increased and sleep duration increased. The researchers suggested that one reason for the unexpected increase in unstable sleep was the intervention focus on improving sleep duration rather than sleep quality. However, what is evident is that further research is needed into the validity of the M1™ device.

1.5 The current study

1.5.1 Rationale

STUDY 1: Unrefreshing and disturbed sleep are prominent features in the subjective experience of ME/CFS. However studies using PSG have reported varied and often only minimal differences in sleep parameters between individuals with ME/CFS and controls. A number of researchers have concluded that individuals with ME/CFS do not have abnormal sleep, despite subjective reports to the contrary. Discrepancies between subjective and PSG-measured sleep have led to some researchers suggesting psychosocial factors as a primary reason for negative perceptions of sleep quality. However the underlying cause of unrefreshing sleep reports in ME/CFS remains unclear.

This study aims to compare sleep in participants with ME/CFS with sleep in healthy controls using 7 nights of actigraphy and subjective measures. Although actigraphy has been used in several studies measuring diurnal activity in ME/CFS, few studies have used actigraphy as a measure of nocturnal sleep in this population. Published studies that have used actigraphy focus primarily on circadian rhythm disturbances with less investigation into sleep parameters such as sleep onset latency and wake after sleep onset. This study will compare such actigraphic parameters between participants with ME/CFS and controls.

There appears to be no research comparing self-reported sleep parameters such as sleep latency onset, wake after sleep onset, total sleep time or sleep efficiency between ME/CFS and controls. This study will use sleep diaries to compare such subjective parameters between participants with ME/CFS and healthy controls.

Subjective sleep quality is also an important measure, with previous research consistently showing that individuals with ME/CFS report poorer sleep quality than controls. However most of this research has utilised retrospective reports of non-restorative sleep and measures of subjective sleep quality (such as the PSQI). Some other studies have asked participants to rate sleep quality after a single night of PSG. This study will compare night-by-night subjective sleep quality and ratings of feeling rested after sleep between participants with ME/CFS and controls. The study will use the "feeling rested after sleep" scores as a measure of non-restorative sleep.

Additionally, there appears to be no published research investigating night-to-night variability of sleep in ME/CFS. In order to fill this gap this study will compare night-to-night variability of both actigraphic and subjective sleep parameters (such as total sleep time and sleep efficiency) between ME/CFS and matched controls. It will also compare night-to-night variability of subjective sleep quality ratings and rating of feeling rested after sleep between participants with ME/CFS and controls. Night-to-night sleep variability has been shown in a number of disorders, and its role in the precipitation and maintenance of sleep problems, particularly insomnia, is well documented. It is important to consider night-to-night variability as one possible factor in the poor sleep in ME/CFS.

The original intention of Study 1 was to include cardiopulmonary coupling (CPC) as an additional measure in the investigation of possible differences between the sleep of ME/CFS and control groups. However, a number of technical difficulties, including CPC data recorders failing to collect data on some nights, and difficulties uploading data from the devices, lead to CPC data only being available from a subgroup of participants, which included both ME/CFS and control participants. (For

further details please see Appendix A). However, the available CPC data (n=17) offered an opportunity to assess the validity of the CPC device, against a range of objective and subjective measures, using participants from both participant groups who may vary in their sleep parameters. Thus Study 2 was developed.

STUDY 2: The use of devices that utilise cardiopulmonary coupling as a measure of sleep stability and quality is relatively new, with few published validation studies. Although CPC has been shown to reveal sleep instability and improvements in sleep stability, studies comparing CPC with subjective measures of sleep quality have been mixed. This is possibly due to PSQI scores being typically used as the measure of subjective sleep. This study will replicate and extend this by also exploring the relationship between CPC measures and the night-by-night subjective ratings of sleep quality and ratings of feeling rested after sleep. The participants in Study 2 will include those with and without a diagnosis of ME/CFS and the advantage of this is that we may expect, based on the previous literature, the sample to have a range of different levels of subjective sleep.

A key gap in the literature is the validation of portable CPC devices such as the SleepImage M1™ recorder, with CPC research often using ECG data extracted from polysomnograms. Additionally, there appears to be no published research exploring the relationship between CPC variables and actigraphy. This study will explore correlations between sleep parameters obtained concurrently with the M1™ recorder and actigraphy, and will also compare total sleep time concordance between the two devices. It is common research practice to exclude the first night of a laboratory PSG study due to participants typically sleeping more poorly on the first night. Although considered less invasive than PSG it is unknown if an adaptation effect occurs when using the M1™

recorder in the home setting. As the M1™ device is adhered to the chest with a single lead to measure ECG activity, it may be argued that it would disrupt sleep on the first night while the wearer adjusts. This study will investigate whether an adaptation effect does actually occur.

1.5.2 Aims and hypotheses

Study 1: Comparison of various sleep parameters in people with and without ME/CFS using self-report and actigraphy

The primary aim of Study 1 is to examine the differences between objective and subjective sleep parameters of individuals who have been diagnosed with ME/CFS and matched individuals (controls) without ME/CFS (matched on age and sex variables). These sleep parameters include total sleep time, sleep onset latency, duration of wake after sleep onset, sleep fragmentation index, sleep efficiency and sleep quality and will be measured subjectively using sleep diaries and objectively using actigraphy.

A number of studies have shown differences between sleep on weekdays and weekends in adolescents, with adolescents typically sleeping longer on weekends (eg. Crowley & Carskadon, 2010; Noland, Price, Dake & Telljohan, 2009). However whether differences exist between weekday and weekend sleep in adults is less researched, with the assumption often made that there are no differences. Therefore before undertaking the analyses of hypotheses the data was analysed to confirm no differences between weekday and weekend sleep parameters.

There are four hypotheses for Study 1:

1. There will be a significant difference between individuals with ME/CFS and controls in objective (actigraphic) measures of sleep onset latency, duration of

wake time after sleep onset, sleep fragmentation, and sleep efficiency. It is expected that individuals with ME/CFS will experience longer sleep onset latency, greater duration of wake time after sleep onset, greater sleep fragmentation, and lower sleep efficiency than controls, with no difference in total sleep time.

2. There will be a significant difference between individuals with ME/CFS and controls in subjective (sleep diary) measures of sleep onset latency, duration of wake time after sleep onset, sleep efficiency, sleep quality rating and feeling rested rating. It is expected that individuals with ME/CFS will report longer sleep onset latency, greater duration of wake time after sleep onset, lower sleep efficiency, poorer sleep quality and less refreshing sleep than controls, while reporting the same total sleep time.

3. There will be a significant difference between individuals with ME/CFS and controls in night-to-night variability of objective (actigraphic) measures of total sleep time, sleep onset latency, duration of wake time after sleep onset, sleep fragmentation, and sleep efficiency. It is expected that individuals with ME/CFS will experience greater variability in each of these measures than controls.

4. There will be a significant difference between individuals with ME/CFS and controls in night-to-night variability of subjective (sleep diary) measures of total sleep time, sleep onset latency, duration of wake time after sleep onset, sleep efficiency, sleep quality rating and feeling rested rating. It is expected that

individuals with ME/CFS will experience greater variability in each of these measures than controls.

Study 2: Investigation of the validity of the SleepImage M1™ sleep recorder by comparing CPC-derived sleep parameters with (1) actigraphy and (2) self-report

The primary aim of Study 2 is to examine the validity of CPC as a measure of sleep quality by comparing sleep parameters obtained by the M1™ sleep recorder with those obtained by actigraphy and sleep diaries.

There are four hypotheses for Study 2:

1. There will be a significant difference between first night and third night measures of sleep quality and total sleep time as measured by CPC. It is expected that total sleep time and the percentage of time spent in stable NREM sleep will be lower on night 1 than night 3 and that percentage of time spent in unstable NREM sleep will be higher on night 1 than night 3.

2. There will be a significant correlation between CPC measures of sleep quality (% time spent in stable NREM sleep and % time spent in unstable NREM sleep) and actigraphic measures of sleep quality (sleep efficiency, duration of wake time after sleep onset, and sleep fragmentation index). It is expected that % time spent in stable NREM sleep will be positively correlated with sleep efficiency and negatively correlated with sleep fragmentation index and duration of wake time after sleep onset. It is expected that % time spent in unstable NREM sleep

will be negatively correlated with sleep efficiency and positively correlated with sleep fragmentation index and duration of wake after sleep onset.

3. There will be a significant correlation between CPC measures of sleep quality (% time spent in stable NREM sleep and % time spent in unstable NREM sleep) and subjective measures of sleep quality (sleep efficiency, self-rated perceptions of sleep quality and feeling rested after sleep, and PSQI scores). It is expected that % time spent in stable NREM sleep will be positively correlated with sleep efficiency and subjective ratings of sleep quality and feeling rested after sleep, and negatively correlated with PSQI scores. It is expected that % time spent in unstable NREM sleep will be negatively correlated with sleep efficiency and subjective ratings of sleep quality and feeling rested after sleep, and positively correlated with PSQI scores.

4. There will be no difference between CPC-derived and actigraphic measures of total sleep time.

Chapter 2: Methodology

2.1 Study 1: Comparison of various sleep parameters in people with and without ME/CFS using self-report and actigraphy

2.1.1 Participants

A total of 32 adults (26 females and 6 males) participated in the study. This gender split is consistent with the gender split generally seen in ME/CFS, with 75% or more of patients with ME/CFS being female (Prins et al., 2006). There were two groups of participants: the "ME/CFS" group consisted of participants with diagnosed ME/CFS and the "control" group consisted of self-reported "good sleepers" who were case matched for age and sex with the ME/CFS group.

ME/CFS group participants were required to be patients of the CFS Discovery Centre and have a diagnosis of ME/CFS according to Canadian Consensus Criteria. ME/CFS group participants were recruited via an information sheet that was handed to them by staff at the CFS Discovery Centre (see Appendix B for information sheet). All CFS Discovery patients with a formal ME/CFS diagnosis (whether new or review patients) were given the opportunity to participate in the study. Dr Don Lewis agreed to assist in the recruiting of participants and in confirming the diagnosis of ME/CFS (see Appendix C for supporting letter). In the ME/CFS group there were 16 participants (13 female and 3 male) between the ages of 22 and 61 years (M = 37.06, SD = 11.39). Scores on the Symptom Severity and Symptom Hierarchy Profile indicated a range of severity of ME/CFS symptoms within the ME/CFS group (M = 31.3, SD = 11.3)

In the control group there were 16 participants (13 female and 3 male) between the ages of 23 and 61 years (M = 37.06, SD = 11.14). These participants were friends,

family and colleagues of the researchers and were recruited via word of mouth and a flier posted on social media (see Appendix D). Efforts were made to individually match the control participants with each of the ME/CFS participants by age (+/- 4 years) and sex and this aim was broadly achieved (see Appendix E). Due to interference with the electrocardiograph signal, devices measuring CPC cannot be used in people with atrial fibrillation, ventricular bigeminy, demand ventricular or biventricular pacing and so participants reporting these conditions were excluded from the study. Participants who were taking prescription hypnotics (including melatonin) and those with diagnosed sleep apnoea were also excluded from the study. Participants were required to have a score on the Epworth Sleepiness Scale (ESS) of less than 15 (see Appendix F and section 2.1.2) and have a Multivariable Apnoea Risk Index less than 0.5 (see Appendix G and section 2.1.2). Potential control group participants were also required to NOT meet criteria for a DSM-IV-TR diagnosis of Primary Insomnia as determined by the Sleep Difficulties Checklist (see Appendix H and section 2.1.2) and also by a score of less than 8 on the Insomnia Severity Index (ISI) (see Appendix I and section 2.1.2). The range of ISI scores for the control group was 0-4 (M = 1.6, SD = 1.18). Insomnia was not an exclusion criteria for the ME/CFS group as sleep-related problems are included in the diagnostic criteria for ME/CFS (Carruthers et al., 2003). Eight potential ME/CFS participants were excluded (five due to high ESS scores and three due to reporting diagnosed sleep apnoea). Two potential control participants were excluded (one due to having an ISI score of 8, and one due to reporting diagnosed sleep apnoea).

2.1.2 Materials

Each participant was first sent a screening pack containing four questionnaires and the relevant ethics materials and then sent a full participation pack which included an actiwatch, a SleepImage M1™ sleep recorder, a day/sleep diary and several questionnaires. The following sections describe each measure/questionnaire and the scoring procedure for each.

Epworth Sleepiness Scale (screening questionnaire)

The Epworth Sleepiness Scale (ESS) is a measure of general daytime sleepiness. Individuals are asked to rate his/her chance of dozing in eight different situations (for example, watching television) on a scale of 0 (*would never doze*) to 3 (*high chance of dozing*). Scores greater than 15 are generally only found in individuals with narcolepsy, idiopathic hypersomnia or obstructive sleep apnoea syndrome (Johns, 1991). The reliability and validity of the ESS has been established, with high internal consistency (Cronbach's alpha = 0.88) (Johns, 1993).

Multivariable Apnoea Risk Index (screening questionnaire)

The Multivariable Apnoea Risk Index is a validated measure that uses an individual's body mass index, age, gender and scores on three questions related to sleep apnoea (snorting and gasping, loud snoring, and breathing stops) to calculate probability of sleep apnoea (Maislin et al., 1995). The three sleep apnoea questions have been shown to have a high internal consistency, with a Cronbach alpha statistic of 0.85 to 0.93 (Maislin et al.).

Sleep Difficulties Checklist (screening questionnaire)

The Sleep Difficulties Checklist was a checklist of items that correspond to criteria for a DSM-IV-TR diagnosis of primary insomnia. This checklist is used to aid the exclusion of potential control participants who meet criteria for a primary insomnia diagnosis, or who reported other disorders which may negatively impact on sleep, such as narcolepsy, sleep apnoea, parasomnias, depressive disorder, generalised anxiety disorder, delirium, or sleep problems due to substance use.

Insomnia Severity Index (screening questionnaire)

The ISI is a validated 7-item measure designed to be a screening measure of insomnia, with a score of 0-7 indicating no clinically significant insomnia (Bastien, Vallieres, & Morin, 2001). Severity of insomnia problems, such as difficulty falling asleep, are rated on a scale of 0 (*none*) to 4 (*very severe*). It has been shown to have high internal consistency, with a Cronbach alpha of 0.90 to 0.91 (Morin, Belleville, Belanger, & Ivers, 2011).

General information questionnaire

Participants were given a questionnaire containing questions about demographic details and use of prescription and over-the-counter medications (see Appendix J). Participants were asked to maintain a reasonably consistent intake of any permitted over-the-counter supplements and/or prescription tablets over the entire 7 day period. (See Appendix K for list of prescription medications taken by participants during study 1).

Actigraphy

Activity levels were objectively determined using an actigraph accelerometer (Actiwatch 2, MiniMitter Philips, USA). Participants wore the actiwatch on the non-dominant wrist 24 hours/day across seven days. The actiwatch is similar in appearance to a wrist watch and allows the recording of day and night activity levels for periods of up to 30 days when set to collect data in one minute epochs. It is waterproof, and so can be worn at all times, even when people are showering. Participants received an Actiwatch Information Sheet (see Appendix L). Philips Actiware Software Version 6.0.0 was used to analyse actigraphy data. The Actiware software uses an algorithm that compares individual epochs to a wake threshold value in order to score each epoch as either sleep or wake. For this study the default sensitivity settings (40) were used as recommended by the manufacturer and epoch collection set for one minute. Time of lights out and final wakening time was obtained via sleep diaries and manually entered into the software program. Sleep onset was defined by the Actiware software program as the first epoch of sleep identified after time of lights out followed by at least 10 minutes of immobility.

SleepImage M1™ sleep recorder

CPC was measured using a SleepImage M1™ sleep recorder, which consisted of two small electrodes that adhered to the chest (see Appendix M). These electrodes were connected by a short cable and participants were advised to wear a t-shirt while wearing the device in order to prevent the cable being dislodged during sleep. Participants were advised to attach the recorder just prior to going to bed, and remove it upon getting up in the morning. Participants wore the recorder every night for 7 nights and attached new

electrodes to the device with each use. Participants were given an M1™ Sleep Recorder Information Sheet (see Appendix M). Data was uploaded from the M1™ device onto a computer and the ECG signals automatically processed and analysed by the SleepImage CPC software to generate a sleep spectrogram. Sleep variables including % time spent in stable NREM sleep, % time spent in unstable NREM sleep, and total sleep time were automatically computed by the SleepImage software.

Day/sleep diary

As well as aiding the interpretation of the wrist actigraphy output (eg. time of lights out) the diary also provided subjective assessments of total sleep time, sleep onset latency, duration of wake after sleep onset, sleep quality, and feeling rested after sleep. The sleep diary items are widely used in clinical practice and included items such as time of getting into and out of bed and time taken to fall asleep. Each morning, participants were also asked to rate each of the following on a Likert-type scale of 1 to 10: “I would rate the quality of last night’s sleep as” and “I would rate how well rested I feel on getting up today as”. The “feeling rested” rating was used in the current study as a measure of non-restorative sleep. Also included was a section where participants indicated whether they experienced physical symptoms during the night, such as muscle pain or sweating, the Positive and Negative Affect Schedule (PANAS), Chalder Fatigue Scale, Symptom Severity and Severity Hierarchy Profile, and ME/CFS Ability/Disability Scale. Analysis of these reported symptoms and four scales were beyond the scope of this thesis. The diaries for ME/CFS and control participants can be found in Appendix N.

2.1.3 Procedure

Prior to data collection, ethics approval was obtained from the Victoria University Human Research Ethics Committee (see Appendix O for ethics approval letter). Potential participants were given a plain language statement (see Appendix B for Information to Participants Involved in Research sheet). Those interested contacted the researcher and the initial screening procedure was conducted by either email or phone. Potential participants in the ME/CFS group confirmed their diagnosis had been made by Dr Lewis. Potential participants in the control group confirmed that they considered themselves to be good sleepers. Potential participants who were taking prescription hypnotics (including melatonin) and those with diagnosed sleep apnoea were excluded from the study at this point. A consent form (see Appendix P) and the sleep screening questionnaires were then posted to potential participants in order to exclude those with evidence of a non-permitted sleep disorder as described above.

Once a potential participant returned his/her signed consent form and screening questionnaires confirming their eligibility in the study, the researcher sent the participant a full participation pack. This pack differed between the ME/CFS group and the controls group. The ME/CFS pack included an actiwatch, a SleepImage M1™ sleep recorder, an ME/CFS Day and Sleep Diary, the Symptom Severity and Severity Hierarchy Profile, the ME/CFS Ability/Disability Scale, the Pittsburgh Sleep Quality Index and a general information questionnaire. The control group pack included an actiwatch, a SleepImage M1™ sleep recorder, a Control Group Day and Sleep Diary, the Pittsburgh Sleep Quality Index, and the general information questionnaire. No uniform day of the week was selected as a start day and so participants started the study

on different days of the week. At the conclusion of the seven day study, participants returned the participant pack to the researcher via a post-paid envelope.

2.1.4 Data analysis

All analyses were conducted using PASW Statistics 21.0 (SPSS Statistics). Demographic and descriptive data was obtained using frequency statistics. Prior to analysis, data was screened for outliers and missing data. Unless otherwise specified in the results section, all sleep data were averaged for each participant across nights. As some actiwatches failed to maintain adequate battery charge (despite being recharged immediately prior to use), some nights of actigraphy data was missing from four participants (see Appendix Q). Mean actigraphic data were used in hypothesis testing for this study as follows: over 7 nights for 28 participants, 6 nights for two participants, 5 nights for one participant and 4 nights for one participant. Although complete subjective (sleep diary) data was obtained from each participant, only data from nights with corresponding actigraphic data was used. In sleep studies utilising polysomnography in the laboratory it is common practice to withhold first night data from analyses (eg. Kobayashi, Huntley, Lavela & Mellman, 2012; Gooneratne et al., 2011). However, due to the relatively non-intrusive nature of the actiwatch and the fact that it is generally used with individuals in their natural environment it has been shown that there is no significant adaptation effect with actigraphy (van Hilten et al., 1993). Additionally, the current actigraphy practice parameters do not mention a first night or adaptation night effect (Morgenthaler et al., 2007). Therefore data obtained on the first night is typically retained for analyses and was done so for the present study.

An intra-individual coefficient of variation (I-I CV) was calculated to measure night-to-night variability of sleep parameters (Rowe et al., 2008). The calculation used was the individual standard deviation (across all available nights) of the variable divided by the individual mean (across all available nights) of the variable x100. A higher I-I CV indicates greater variability.

Appropriate assumption testing was performed prior to conducting parametric testing. Normality of the variables was assessed through histograms, normal Q-Q plots, detrended normal Q-Q plots, and the Shapiro-Wilk Test of Normality. Homogeneity of variance was tested using Levene's test for equality of variances in SPSS. Where normality was not evident the data was transformed using a logarithmic transformation. Where normality assumptions were not violated (either before or after a logarithmic transformation), paired-samples and independent-samples t-tests were conducted as appropriate. Where the data used in an analysis had undergone a logarithmic transformation to produce normality, this is explicitly mentioned in the relevant results section. When such a logarithmic transformation was unsuccessful at producing normality, a non-parametric test was used instead. Non-parametric tests are robust against violations of normality (Coakes & Steed, 2007). In this study, Wilcoxon Signed Rank Tests for paired samples and Mann-Whitney U Test for independent samples was used.

As a series of tests were conducted, the issue of alpha inflation was considered. However, as all analyses conducted were pre-designed as part of a set of hypotheses and were considered necessary for the current study, adjustments were deemed unnecessary (Keppel & Wickens, 2004). However, more conservative two-tailed tests were used in all analyses. Unless otherwise stated, alpha level was set at 0.05. Effect sizes for non-

parametric tests were reported using Cohen (1988) criteria of 0.1 to 0.29 = small effect, 0.3 to 0.49 = medium effect, and 0.5 to 1.0 = large effect. For parametric tests, the eta squared statistic was calculated as a measure of effect size, with 0.01 = small effect, 0.06 = moderate effect, and 0.14 = large effect (Cohen).

2.2. Study 2: Investigation of the validity of cardiopulmonary coupling (CPC) in measuring sleep quality

2.2.1 Participants

There were 17 participants (11 female and 6 male) between the ages of 22 and 61 years (M = 38.12, SD = 11.86), of whom 6 had ME/CFS and 11 were from the control group (see also Appendix A). The recruitment of participants and exclusion criteria were the same as in study 1. Confirmation that the sample consisted of participants with a range of subjective sleep quality was obtained by examining global Pittsburgh Sleep Quality Index scores (range 1-10, M = 5.12, SD = 2.76).

2.2.2 Materials

The materials and measures used for this study was the same as those used in Study 1 with the addition of the ***Pittsburgh Sleep Quality Index.*** All participants completed the Pittsburgh Sleep Quality Index (PSQI) once, on day one of the study (see Appendix R). The PSQI is a validated measure of retrospective sleep quality and disturbances (Buysse, Reynold, Monk, Berman and Kupfer, 1989). Nineteen items that relate to one's usual sleep habits over the previous month contribute to the total score. The items are grouped into seven equally-weighted scale scores: 1. Subjective sleep quality, 2. Sleep latency, 3. Sleep duration, 4. Sleep efficiency, 5. Sleep

disturbances, 6. Use of sleeping medication, and 7. Daytime dysfunction. Items 1 to 4 are free entry in order to obtain detail of total sleep time, sleep latency and usual bed and wake up times. Responses to items 5 to 19 are scored on a 4-point Likert scale and include items related to problem frequency and subjective sleep quality. All scale scores range from 0 to 3. The total of each scale score gives a global score, giving a range of 0 to 21. Higher scores indicate poorer sleep, with a recommended cut-off of 5. The PSQI has been shown to have high internal consistency, with an overall Cronbach alpha of 0.83 (Buysse et al.).[1]

2.2.3 Procedure

Prior to data collection, ethics approval was obtained from the Victoria University Human Research Ethics Committee. Ethics approval obtained for study 1 covered data collection and analysis for study 2. Participant procedures were the same in study 2 as for study 1.

2.2.4 Data analysis

All analyses were conducted using PASW Statistics 21.0 (SPSS Statistics). Demographic and descriptive data was obtained using frequency statistics. Prior to analysis data was screened for outliers and missing data. Unless otherwise specified in the results section, all sleep data were averaged for each participant across nights. Due to problems with the CPC devices, CPC data was missing for some nights for some participants (see also Appendix A). Mean CPC data were used in hypothesis testing for this study as follows: over 7 nights for 8 participants, 6 nights for 3 participants, 5

[1] PSQI scores were not analysed in study 1 due to an incomplete data set across the ME/CFS and control groups within that study.

nights for 4 participants, 4 nights for 1 participant and 3 nights for 1 participant. One night of actigraphy was missing for one participant. Complete subjective (sleep diary) data was obtained from each participant. Only data from nights with complete CPC, actigraphy, and sleep diary data was used in analyses.

Appropriate assumption testing was performed prior to conducting parametric testing. Normality of the variables was assessed through histograms, normal Q-Q plots, detrended normal Q-Q plots, and the Shapiro-Wilk Test of Normality. Homogeneity of variance was tested using Levene's test for equality of variances in SPSS. Where normality was not evident the data was transformed using a logarithmic transformation. Where normality assumptions were not violated (either before or after a logarithmic transformation), paired-samples t-tests were conducted. When such a logarithmic transformation was unsuccessful at producing normality, a non-parametric test was used instead. In this study, Spearman's rho correlation was used as it is insensitive to outliers and lack of normality (Tabachnick & Fidell, 2007).

As a series of tests were conducted, the issue of alpha inflation was considered. However, as all analyses conducted were pre-designed as part of a set of hypotheses and were considered necessary for the current study, adjustment were deemed unnecessary (Keppel & Wickens, 2004). Unless otherwise stated, alpha level was set at 0.05. Effect sizes for Spearman's rho tests were reported using Dancey and Reid's (2004) criteria of 0.1 to 0.3 = weak correlation, 0.4 to 0.6 = moderate correlation, 0.7 to 0.9 = strong correlation. For t-tests, the eta-squared statistic was calculated as a measure of effect size, with 0.01 = small effect, 0.06 = moderate effect, and 0.14 = large effect (Cohen, 1988).

Chapter 3: Results

This chapter presents the results for the two studies. Study 1 compares people with and without ME/CFS in terms of their objective and subjective sleep variables, using a matched case-control design. Study 2 investigates the validity of cardiopulmonary coupling (CPC) as a measure of sleep quality.

3.1 Study 1: Comparison of various sleep parameters in people with and without ME/CFS using self-report and actigraphy

3.1.1 Data screening

Sleep diary data was complete for all participants. Some complete nights of actigraphic data was missing from some participants. No evidence of bias was found in scanning the data, with comparable data missing from both ME/CFS and controls groups (see Appendix Q). Inspection of diary data showed all participants but one exhibited regular behavioural sleep timing. One ME/CFS participant exhibited an irregular sleep pattern with time of lights out ranging from 10.15pm to 5am and final wakening time ranging from 6am to 12.30pm, with a total sleep time (by actigraphy) range of 22 minutes to 10 hours 15 minutes.

3.1.2 Hypothesis 1: There will be a significant difference between individuals with ME/CFS and controls in objective (actigraphic) measures of sleep onset latency, duration of wake time after sleep onset, sleep fragmentation, and sleep efficiency. It is expected that individuals with ME/CFS will experience less total sleep time, longer sleep onset latency, greater duration of wake time after sleep onset, greater sleep

fragmentation, and lower sleep efficiency than controls, with no difference in total sleep time.

All variables were found to be either positively or negatively skewed prior to analysis. Logarithmic transformation was unsuccessful at producing normality. The results from Mann-Whitney U Tests showed that individuals with ME/CFS experienced objectively longer sleep onset latency and duration of wake after sleep onset, more fragmented sleep, and lower sleep efficiency than controls (all medium effect size), with no difference in total sleep time (see Table 1).

Table 1

Descriptive statistics and Mann-Whitney U Test results for actigraphic sleep variables for ME/CFS group and controls

	ME/CFS		Controls					
Sleep variable	Median	Mean (*SD*)	Median	Mean (*SD*)	*U*	*Z*	*p*	*r*
% Sleep efficiency	80.61	76.53 (13.15)	86.26	86.01 (5.41)	64.00*	-2.41	.016	.43
Total sleep time (min)	414.50	399.04 (66.98)	412.21	404.00 (42.09)	128.00	0.00	1.00	
Wake after sleep onset (min)	62.50	73.04 (41.78)	43.43	44.04 (13.87)	56.00*	-2.71	.007	.48
Sleep onset latency (min)	19.71	29.63 (23.45)	8.43	14.51 (15.73)	74.00*	-2.04	.042	.36
Sleep fragmentation index	35.35	43.13 (28.84)	24.72	26.10 (8.32)	75.00*	-2.00	.046	.35

Note. * $p < .05$

3.1.3 Hypothesis 2: There will be a significant difference between individuals with ME/CFS and controls in subjective (sleep diary) measures of sleep onset latency, duration of wake time after sleep onset, sleep efficiency, sleep quality, and feeling rested after sleep. It is expected that individuals with ME/CFS will report less total sleep time, longer sleep onset latency, greater duration of wake time after sleep onset, lower sleep efficiency, poorer sleep quality and less refreshing sleep than controls, while reporting the same total sleep time.

Prior to analysis, wake after sleep onset and sleep onset latency were found to be positively skewed, and sleep efficiency negatively skewed. Logarithmic transformation was unsuccessful in producing normality and so Mann-Whitney U tests were used to test for group differences for these variables. Total sleep time, sleep quality rating and feeling rested rating were all normally distributed and met all assumptions for parametric testing. Independent-samples t-tests were used to test for group differences for these variables. (Multivariate Analysis of Variance (MANOVA) was not used due to multicollinearity as evidenced by high correlations between several dependent variables).

The results from Mann-Whitney U Tests showed that individuals with ME/CFS reported longer subjective sleep onset latency and duration of wake after sleep onset (both medium effect size) and lower sleep efficiency (large effect size) than controls (see Table 2). Results of independent-samples t-tests showed that individuals with ME/CFS reported poorer sleep quality and less refreshing sleep than controls (both large effect sizes), while total sleep time did not differ (see Table 3).

Table 2

Descriptive statistics and Mann-Whitney U test results for subjective (sleep diary) sleep variables for ME/CFS group and controls

	ME/CFS		Controls					
Sleep variable	Median	Mean (*SD*)	Median	Mean (*SD*)	*U*	*Z*	*p*	*r*
Subjective % Sleep efficiency	87.86	85.47 (9.23)	95.03	94.35 (3.53)	34.00*	-3.54	<.001	.63
Subjective wake after sleep onset (min)	21.47	38.60 (38.00)	9.86	10.65 (8.19)	55.00*	-2.75	.006	.49
Subjective sleep onset latency (min)	32.50	32.79 (19.96)	12.68	15.74 (10.95)	57.00*	-2.68	.007	.47

Note. * $p < .05$

Table 3

Descriptive statistics and t-test results for subjective (sleep diary) sleep variables for ME/CFS group and controls

	ME/CFS		Controls					
Sleep variable	*M*	*SD*	*M*	*SD*	95% CI	*t*(30)	*p*	*eta squared*
Subjective total sleep time (min)	449.18	57.86	444.90	36.42	[-39.18, 30.64]	-.25	.804	
Subjective sleep quality /10	4.88	1.19	6.70	1.00	[1.02, 2.61]	4.67**	<.001	.42
Subjective feeling rested /10	3.95	1.18	6.67	0.83	[1.98, 3.45]	7.55**	<.001	.66

Note. CI = confidence interval.
** $p < .001$

3.1.4 Hypothesis 3: There will be a significant difference between individuals with ME/CFS and controls in night-to-night variability of objective (actigraphic) measures of total sleep time, sleep onset latency, duration of wake time after sleep onset, sleep fragmentation, and sleep efficiency. It is expected that individuals with ME/CFS will experience greater variability in each of these measures than controls.

Prior to analysis all variables were positively skewed. Logarithmic transformation was successful in producing normality in all variables apart from intra-individual coefficient of variation (I-I CV) for total sleep time. T-tests were used to test for group differences for transformed variables. (MANOVA was not chosen as the parametric test due to multicollinearity).

The results from a Mann-Whitney U Test showed that individuals with ME/CFS experienced greater variability of objective total sleep time than controls, with a medium effect size (see Table 4). Results of independent samples t-tests showed that individuals with ME/CFS experienced greater variability of both objective sleep efficiency and duration of wake after sleep onset than controls (both large effect sizes) (see Table 5).

Table 4

Descriptive statistics and Mann-Whitney U test results for intra-individual coefficient of variation (I-I CV) for actigraphic total sleep time for ME/CFS group and controls

Group	Median	Mean (*SD*)	*U*	*Z*	*p*	*r*
ME/CFS	21.28	25.57 (17.51)				
Controls	11.74	12.31 (4.02)				
			66.00*	-2.337	.019	.41

Note. * $p < .05$

Table 5

Descriptive statistics and t-test results for intra-individual coefficient of variation (I-I CV) for actigraphic sleep variables for ME/CFS group and controls

	ME/CFS		Controls				
I-I CV	*M*	*SD*	*M*	*SD*	*t*(30)	*p*	*eta squared*
Sleep efficiency	17.21	16.93	4.77	4.87	3.70*	.001	.31
Sleep onset latency	119.51	59.18	104.77	37.50	0.47	.645	
Wake after sleep onset	45.43	16.20	30.38	22.93	3.08*	.004	.24
Sleep fragmentation index	35.01	10.47	30.81	17.71	1.38	.177	

Note. * $p < .05$

3.1.5 Hypothesis 4: There will be a significant difference between individuals with ME/CFS and controls in night-to-night variability of subjective (sleep diary) measures of total sleep time, sleep onset latency, duration of wake time after sleep onset, sleep efficiency, sleep quality rating and feeling rested rating. It is expected that individuals with ME/CFS will experience greater variability in each of these measures than controls.

For one control participant the mean of wake after sleep onset was zero, therefore an I-I CV for wake after sleep onset was unable to be calculated. Both the control and corresponding matched ME/CFS participant were excluded from analyses involving I-I CV for wake after sleep onset. Prior to analysis all variables apart from I-I CV for sleep onset latency and I-I CV for wake after sleep onset were positively

skewed. Logarithmic transformation was successful in producing normality in all variables apart from I-I CV for total sleep time. T-tests were used to test for group differences for these variables. (MANOVA was not chosen as the parametric test due to multicollinearity).

The results from a Mann-Whitney U Test showed no difference in variability of subjective total sleep time between individuals with ME/CFS and controls (see Table 6). Results of independent samples t-tests showed that individuals with ME/CFS experienced greater variability of subjective sleep efficiency than controls and greater variability of feeling rested than controls (both large effect size) (see Table 7).

Table 6

Descriptive statistics and Mann-Whitney U test results for intra-individual coefficient of variation (I-I CV) for subjective (sleep diary) total sleep time for ME/CFS group and controls

Group	Median	Mean (*SD*)	*U*	*Z*	*p*	*r*
ME/CFS	13.84	20.15 (15.66)				
Controls	12.20	12.06 (2.87)				
			88.00	-1.508	.132	

Table 7

Descriptive statistics and t-test results for intra-individual coefficient of variation (I-I CV) for subjective (diary) sleep variables for ME/CFS group and controls

	ME/CFS		Controls				
I-I CV	*M*	*SD*	*M*	*SD*	*t*(30)	*p*	*eta squared*
Subjective sleep efficiency	13.24	12.23	4.21	2.85	3.90*	.001	.34
Subjective sleep onset latency	80.50	29.97	76.66	33.43	0.45	.655	
Subjective wake after sleep onset[1]	102.50	43.60	104.91	44.74	-0.15	.882	
Sleep quality	35.95	23.94	25.64	11.46	1.40	.171	
Feeling rested	36.10	19.19	23.11	7.25	2.39*	.024	.16

Note. [1] $n = 30$ and $df = 28$
* $p < .05$

A post hoc exploration was conducted on actigraphic total sleep time, sleep efficiency and duration of wake after sleep onset, and sleep diary sleep efficiency and feeling rested rating for the ME/CFS group (as they were the more variable group) in order to determine whether a weekend effect was present. As work schedule data was not collected, “weekend” variables were operationalised as the means of data taken over Friday and Saturday nights. “Weekday” variables were operationalised as the means of data taken over Tuesday and Wednesday nights.

Prior to analysis, all variables (apart from subjective feeling rested rating) were found to be either positively or negatively skewed. Logarithmic transformation was unsuccessful at producing normality and so Wilcoxon Signed Rank Tests were used to test for weekday-weekend differences for these variables. A paired-samples t-test was used to test for a weekday-weekend difference in feeling rested rating. The paired-samples t-test showed that there was no statistically significant difference in feeling rested rating between weekdays (M = 4.03, SD = 1.18) and weekends (M = 4.09, SD = 1.67), t (16) = 0.196, p = .847 (two-tailed). The results from Wilcoxon Signed Rank Tests showed that individuals with ME/CFS reported significantly higher subjective sleep efficiency on weekends than weekdays, with a medium effect size. However, no differences were found between weekdays and weekends in actigraphic sleep efficiency, total sleep time, or duration of wake after sleep onset (see Table 8).

Table 8

Descriptive statistics and Wilcoxon Signed Rank Test results for sleep variables on weekdays and weekends for ME/CFS group

	Weekday		Weekend				
Sleep variable	Median	Mean (*SD*)	Median	Mean (*SD*)	*Z*	*p*	*r*
Sleep efficiency % – actigraphy	81.71	78.74 (13.75)	80.87	73.74 (19.37)	-0.57	.569	
Total sleep time (min) - actigraphy	418.25	417.19 (87.40)	417.00	396.16 (100.76)	-0.47	.642	
Wake after sleep onset (min) - actigraphy	57.50	68.00 (42.39)	64.75	85.34 (76.67)	-0.93	.352	
Subjective sleep efficiency %	85.56	82.00 (16.15)	93.73	91.03 (6.44)	-2.28*	.023	.40

Note. * $p < .05$

3.2 Study Two: Investigation of the validity of cardiopulmonary coupling (CPC) in measuring sleep quality

3.2.1 Hypothesis 1: There will be a first night effect for the CPC device and this will be shown by a significant difference between night 1 and night 3 measures of sleep quality and total sleep time as measured by CPC. It is expected that total sleep time and the percentage of time spent in stable NREM sleep will be lower on night 1 than night 3 and that percentage of time spent in unstable NREM sleep will be higher on night 1 than night 3.

Night 1 CPC data was missing from three participants (one male and two female) and so these participants were excluded from the analyses. Night 3 CPC data was missing from one participant and so night 4 data was used instead for this participant. All variables were approximately normally distributed. A high correlation between % time spent in stable sleep and % time spent in unstable sleep for both nights indicated multicollinearity. Correlations between total sleep time and % time spent in stable sleep and % time spent in unstable sleep were generally low and non-significant. As MANOVA relies on dependent variables being moderately correlated (Tabachnick & Fidell, 2007) paired-samples t-tests were conducted to test for differences between nights for these variables.

Results showed no differences between night 1 and night 3 in any of the CPC variables and therefore no evidence of a first night/adaptation effect (see Table 9). Therefore the means of data across all available nights were used in subsequent analyses.

Table 9

Descriptive statistics and t-test results for CPC sleep variables on night 1 and night 3

CPC variable	Night 1		Night 3		95% CI	*t*(13)	*p*
	M	*SD*	*M*	*SD*			
% time spent in stable NREM sleep	51.35	12.69	51.86	13.53	[-3.98, 2.96]	-.32	.75
% time spent in unstable NREM sleep	28.28	11.54	30.65	13.44	[-7.84, 3.09]	-.94	.37
Total sleep time (min)	512.15	72.85	472.24	82.72	[-9.14, 88.97]	1.76	.10

3.2.2 Hypothesis 2: There will be significant correlations between CPC measures of sleep quality (% time spent in stable NREM sleep and % time spent in unstable NREM sleep) and actigraphic measures of sleep quality (sleep efficiency, duration of wake time after sleep onset, and sleep fragmentation index). It is expected that % time spent in stable NREM sleep will be positively correlated with sleep efficiency and negatively correlated with sleep fragmentation index and duration of wake time after sleep onset. It is expected that % time spent in unstable NREM sleep will be negatively correlated with sleep efficiency and positively correlated with sleep fragmentation index and duration of wake after sleep onset.

Prior to analysis all actigraphic variables were found to be either positively or negatively skewed. Results of the Spearman's rho correlations showed no significant

correlations between CPC measures of sleep quality and actigraphic measures of sleep quality (see Table 10).

Table 10

Spearman's rho correlations of CPC measures of sleep quality and actigraphic measures of sleep quality

Variable	% time spent in stable NREM sleep	% time spent in unstable NREM sleep
Sleep efficiency %	-.05	.14
Duration of wake after sleep onset	-.03	-.16
Sleep Fragmentation Index	.32	-.33

3.2.3 Hypothesis 3: There will be a significant correlation between CPC measures of sleep quality (% time spent in stable NREM sleep and % time spent in unstable NREM sleep) and subjective measures of sleep quality ((i) sleep diary sleep efficiency, self-rated perceptions of (ii) sleep quality and (iii) feeling rested after sleep, and (iv) PSQI scores). It is expected that % time spent in stable NREM sleep will be positively correlated with measures (i) to (iii), and negatively correlated with PSQI scores. It is expected that % time spent in unstable NREM sleep will be negatively correlated with measures (i) to (iii), and positively correlated with PSQI scores.

Prior to analysis sleep diary sleep quality and all PSQI subscale variables were found to be either positively or negatively skewed. The results of the Spearman's rho correlations showed a number of weak to moderate correlations between CPC measures of sleep quality and subjective measures of sleep quality, and only one of these was statistically significant with this sample size (see Table 11). A positive correlation was found between % time spent in unstable NREM sleep and scores on the PSQI subscale 2, with the strength of this relationship being moderate (0.51). This subscale is a subjective measure of sleep onset latency over the previous month, with higher scores indicating longer sleep onset latency. Thus as PSQI subjective sleep onset latency increased, so did % time spent in unstable NREM sleep, suggesting that individuals who reported generally having more trouble falling asleep also tended to have more unstable sleep. Although not statistically significant, moderate correlations were also found between % time spent in stable NREM sleep and (i) PSQI subscale 7 scores (-.46) and (ii) global PSQI scores (-.40), and between % time spent in unstable NREM sleep and (i) PSQI subscale 7 scores (.43) and (ii) feeling rested rating (-.41).

Table 11

Spearman rho correlations of CPC measures of sleep quality and subjective measures of sleep quality

Variable	% time spent in stable NREM sleep	% time spent in unstable NREM sleep
Subjective sleep efficiency %	.21	-.08
Sleep quality rating	.10	-.09
Feeling rested rating	.30	-.41
PSQI 1	-.34	.39
PSQI 2	-.33	.51*
PSQI 3	-.10	.02
PSQI 4	-.16	.05
PSQI 5	-.14	.12
PSQI 6	-.22	.26
PSQI 7	-.46	.43
Global PSQI	-.40	.21

Note. * $p < .05$

As sleep quality rating and feeling rested rating yielded different correlations with both % time spent in stable NREM sleep and % time spent in unstable NREM sleep (although none were statistically significant), post hoc correlations between subjective sleep quality and feeling rested were conducted. The results of the Spearman's rho correlations showed a strong positive correlation between sleep quality rating and feeling rested rating, $rs(15) = .85$, $p < .001$, and a moderate correlation between sleep quality rating and global PSQI score, $rs(15) = -.67$, $p = .003$.

3.2.4 Hypothesis 4: There will be no difference between CPC-derived and actigraphic measures of total sleep time.

Prior to analysis all variables were found to be approximately normally distributed. A paired-samples t-test showed that there was a statistically significant difference in total sleep time (minutes) as derived by actigraphy (M = 390.89, SD = 47.31) and CPC (M = 482.17, SD = 65.69), t (16) = 6.75, $p < .001$ (two-tailed). On nights where both the M1 recorder and actiwatch were worn, the actiwatch recorded significantly less sleep time on average than the M1 recorder, with a mean difference of 91.28 minutes with a 95% confidence interval ranging from 62.62 to 119.93. The eta squared statistic (0.74) indicated that the magnitude of the difference was large.

3.3 Summary of significant findings

3.3.1 Comparison of various sleep parameters in people with and without ME/CFS using self-report and actigraphy

- Individuals with ME/CFS experienced objectively (as measured by actigraphy) longer sleep onset latency and duration of wake after sleep onset, more fragmented sleep, and lower sleep efficiency than controls, with no difference in total sleep time. Individuals with ME/CFS took longer to fall asleep and spent more time awake during the night than controls.
- Individuals with ME/CFS reported longer subjective (as reported in sleep diaries) sleep onset latency and duration of wake after sleep onset, and lower sleep efficiency than controls, with no difference in total sleep time. Individuals with ME/CFS reported poorer sleep quality and feeling less rested after sleep than controls.

- Individuals with ME/CFS experienced greater variability of objective (as measured by actigraphy) total sleep time, sleep efficiency and duration of wake after sleep onset than controls. Controls experienced a more consistent sleep pattern than individuals with ME/CFS.
- Unlike objective measures, there was no difference in variability of subjective total sleep time or duration of wake after sleep onset between individuals with ME/CFS and controls. There was also no difference in variability of subjective sleep onset latency between individuals with ME/CFS and controls. However, individuals with ME/CFS did report greater variability of subjective sleep efficiency and feeling rested than controls. Individuals with ME/CFS reported greater subjective sleep efficiency on weekends than on weekdays.

3.3.2 Investigation of the validity of cardiopulmonary coupling (CPC) in measuring sleep quality

- There was no evidence of a first night/adaptation effect when using the SleepImage M1™ sleep recorder.
- There were no statistically significant correlations between CPC measures of sleep quality and actigraphic sleep quality.
- Although there were a number of weak to moderate correlations between CPC measures of sleep quality and subjective measures of sleep quality, only one of these was statistically significant in this sample size. A positive correlation was found between % time spent in unstable NREM sleep and scores on the PSQI subscale 2. This subscale is a subjective measure of sleep onset latency over the previous month, with higher scores indicating longer sleep latency. This

indicated that as PSQI subjective sleep onset latency increased, so did % time spent in unstable NREM sleep, suggesting that individuals who reported generally having more trouble falling asleep also tended to have more unstable sleep.

- There was a significant difference in total sleep time between actigraphic measured sleep time and CPC measured sleep time. Actigraphic total sleep time was significantly less than CPC measured sleep time.

Chapter 4: Discussion

This research addressed a significant gap in the literature by examining the subjective and objective sleep of people with ME/CFS in comparison to healthy controls (who were self-reported good sleepers) as experienced in their own home over a one week period. In a separate analysis, it also considered the validity of a relatively new device, the SleepImage M1™ sleep recorder, which measures cardiopulmonary coupling and may hold promise for better understanding and measuring sleep stability and quality. The discussion of the findings of the current study are organised by hypothesis for clarity. The discussion of study 1, the comparison of various sleep parameters in people with and without ME/CFS using self-report and actigraphy, is presented in section 4.1. The discussion of study 2, the investigation of the validity of CPC in measuring sleep quality, is presented in section 4.2. Limitations and directions for future research and conclusions are discussed in parts 4.3 and 4.4 respectively.

4.1 Study 1: Comparison of various sleep parameters in people with and without ME/CFS using self-report and actigraphy

4.1.1 Hypothesis 1: There will be a significant difference between individuals with ME/CFS and controls in objective (actigraphic) measures of sleep onset latency, duration of wake time after sleep onset, sleep fragmentation, and sleep efficiency. It is expected that individuals with ME/CFS will experience longer sleep onset latency, greater duration of wake time after sleep onset, greater sleep fragmentation, and lower sleep efficiency than controls, with no difference in total sleep time.

As hypothesised, results of the current study found that individuals with ME/CFS experienced longer sleep onset latency and duration of wake after sleep onset

time, greater sleep fragmentation, and lower sleep efficiency than controls. This is contradictory to the only published study that has compared actigraphic measures between ME/CFS and control participants (Rahman et al., 2011), which found no differences in sleep efficiency and sleep fragmentation between the two groups. Sleep onset latency and wake after sleep onset was not reported in the Rahman et al. study. Possible explanations for the differing results may be found by considering the characteristics of the ME/CFS samples in the two studies. Both studies involved almost identical sample sizes. Rahman et al. recruited participants who met Fukuda criteria for ME/CFS. Fukuda criteria requires the presence of debilitating fatigue for at least six months, along with four other minor criteria (Fukuda et al., 1994). "Unrefreshing sleep" is included as a possible, but not essential, symptom. In order to meet Canadian Consensus Criteria for an ME/CFS diagnosis, sleep dysfunction (such as unrefreshing sleep, insomnia, hypersomnia, or circadian rhythm disturbances) **must** be present (Carruthers et al., 2003). Therefore, it may be argued that the current study includes a more homogeneous sample of ME/CFS participants, particularly in regards to sleep dysfunction. It is possible that the ME/CFS participants of the current study experienced greater sleep dysfunction than those in the Rahman et al. study and so differences between ME/CFS and control groups were more likely to be found.

Additionally, Rahman et al. (2011) recruited ME/CFS participants who were in the initial stages of a graded-activity oriented cognitive-behavioural therapy program. This suggests that these participants were not severely impaired, as individuals with severe ME/CFS are physically and cognitively unable to participate in such a treatment program. Jason and Richman (2007) have argued that the Canadian Consensus Criteria identifies those with greater cognitive and physical impairments and with more physical

debility than does the Fukuda criteria. Although symptom severity was not quantitatively analysed, it is possible that ME/CFS participants in the current study were more functionally impaired than those in the Rahman et al. study.

Unlike the current study, Rahman et al. excluded potential participants taking tricyclic and/or selective serotonin reuptake inhibitor antidepressants. As outlined in Appendix K, no control participants and four (25%) of ME/CFS participants were taking prescribed antidepressants in the current study. It is possible that these medications have influenced the findings. However, antidepressants taken included amitriptyline, mirtazapine, and escitalopram, all medications which have been shown to increase sleep efficiency, decrease sleep latency and decrease nocturnal awakenings (Holshoe, 2009; Mayers & Baldwin, 2005). Therefore, these medications are unlikely to be contributing factors in the lower sleep efficiency, increased WASO and increased SOL found in ME/CFS in comparison to controls in the current study.

This study is the first to compare actigraphic measures of WASO and SOL between ME/CFS participants and controls. While some studies have suggested actigraphy is a reliable measure of WASO in normal sleepers (Sanchez-Ortuno et al., 2010), others have shown differences in WASO between actigraphy and PSG, the difference of which has been inconsistent across studies. In their study of 49 participants with ME/CFS, Creti et al. (2010) found that actigraphy overestimated WASO in comparison to PSG in this population. Therefore, it is possible that the difference found between the two groups in this study has been overestimated. However, Marino et al. (2013) found that actigraphy underestimated WASO (when compared with PSG) when PSG WASO was greater than 30 minutes in a study of a range of sleepers. As the ME/CFS group experienced a mean WASO of 73.04 minutes

(by actigraphy) it is very possible that actigraphy *underestimated* WASO in this group, suggesting that the difference in WASO between ME/CFS and controls was actually greater than documented in the current study. Actigraphy has been shown to consistently underestimate SOL in comparison to PSG in most populations, including ME/CFS (eg. Creti et al., 2010; Sanchez-Ortuno et al., 2010). However, although the actual time to sleep onset may be invalid, the differences between the two groups would still be valid.

As expected, and consistent with previous research (Rahman et al., 2011), no difference in total sleep time was found between ME/CFS and controls. This finding raises important issues regarding the cause of non-restorative sleep frequently reported in ME/CFS, which to date remains elusive. It would seem that insufficient total sleep time is not responsible for non-restorative sleep in ME/CFS. However, it is possible that disrupted sleep, as evidenced by increased WASO and sleep fragmentation, and decreased sleep efficiency, may be one source of non-restorative sleep that warrants further investigation.

4.1.2 Hypothesis 2: There will be a significant difference between individuals with ME/CFS and controls in subjective (sleep diary) measures of sleep onset latency, duration of wake time after sleep onset, sleep efficiency, sleep quality, and feeling rested after sleep. It is expected that individuals with ME/CFS will report longer sleep onset latency, greater duration of wake time after sleep onset, lower sleep efficiency, poorer sleep quality and less refreshing sleep than controls, while reporting the same total sleep time.

As predicted, individuals with ME/CFS reported subjectively longer sleep onset latency and duration of wake after sleep onset time, lower sleep efficiency, poorer sleep quality and less refreshing sleep than controls. There has previously been no published research comparing self-reported sleep parameters of sleep onset latency, wake after sleep onset, total sleep time or sleep efficiency between ME/CFS and controls and this study fills this gap in the literature. Although no quantitative analyses comparing subjective to actigraphic sleep parameters were conducted, the directions of the differences between the two groups on each of the subjective measures are consistent with the directions of the differences between the groups as shown by the same actigraphic measure, where available.

As previously outlined in the methodology, “feeling rested” was used as a measure of non-restorative sleep (NRS) in the current study. This is the first study to compare subjective ratings of feeling rested after sleep between ME/CFS and controls. This is interesting given that a large majority of ME/CFS patients report NRS (Fossey et al., 2004; Nisenbaum et al., 2004; Hamaguchi et al., 2011). One possible reason for this paucity of previous research is the lack of a standard definition of NRS (Stone et al., 2008). There is also a lack of reliable or well-validated measures of NRS, with some researchers using the term “overall quality” to encompass NRS (Vernon et al., 2010). However the importance of investigating NRS in ME/CFS cannot be overstated, given that NRS has a significant negative impact on daily functioning, even in the absence of insomnia symptoms (Ohaynon et al., 2005a; Sarsour et al., 2010; Zhang et al., 2013). Individuals with ME/CFS have the compounding effects of NRS and multiple biological dysfunctions causing significant impairment and reduction in quality of life.

A number of studies have compared subjective sleep quality between ME/CFS and controls, with ME/CFS participants consistently reporting poorer subjective sleep than controls. However, these studies have typically utilised retrospective measures of sleep quality, such as the CDC Symptom Inventory (Majer et al., 2007) or the PSQI (Neu et al., 2007). Although some studies have asked participants to rate sleep quality after a single night (Watson et al., 2003), the current study is the first to investigate night-by-night comparisons over a week. Using the mean of subjective quality ratings over a week is likely to give a more accurate picture of overall sleep quality, particularly as sleep may vary considerably from night to night, with some nights being subjectively better than others.

4.1.3 Hypothesis 3: There will be a significant difference between individuals with ME/CFS and controls in night-to-night variability of objective (actigraphic) measures of total sleep time, sleep onset latency, duration of wake time after sleep onset, sleep fragmentation, and sleep efficiency. It is expected that individuals with ME/CFS will experience greater variability in each of these measures than controls.

As hypothesised, individuals with ME/CFS experienced greater night-to-night variability of actigraphic measures of total sleep time, sleep efficiency and duration of wake after sleep onset than controls. It was considered that these variations may be due to a weekend effect, however post hoc analyses revealed no differences between weekday and weekend measures of total sleep time, sleep efficiency or wake after sleep onset in the ME/CFS group. Contrary to expectations, no differences in variability of sleep onset latency or sleep fragmentation were found between the groups. This suggests that while those with ME/CFS experienced relatively consistently long sleep

onset latency and high sleep fragmentation night after night, their total sleep time, sleep efficiency and duration of wake after sleep varied considerably from night to night. This variation has significant implications for the use of actigraphy in ME/CFS. Although the latest actigraphy practice parameters by Morgenthaler et al. (2007) do not state optimal length of data collection in actigraphy, a review by Berger et al. (2008) concluded that data collection over three consecutive 24-hour periods is sufficient. However, the results of this study suggest that this length of time may be insufficient for collecting reliable actigraphic data in the ME/CFS population given their variability across seven days, although further research is needed.

Although intra-individual variability of sleep has been well documented in insomnia sufferers (Sanchez-Ortuno & Edinger, 2012), there appears to be no published research investigating night-to-night variability of sleep (either objective or subjective) in ME/CFS, and no published research making comparisons with controls. Of particular interest in the current study is the inconsistency of total sleep time, especially considering there were no differences found in mean total sleep time between ME/CFS and controls. It has been shown that high night-to-night variability in sleep duration, rather than mean sleep duration, is related to poor subjective well-being and poor subjective sleep quality (Lemola, Ledermann, & Friedman, 2013). Therefore, it is important to consider heightened night-to-night variability as just one possible factor in the poor sleep in ME/CFS.

Individuals with ME/CFS have reported variations in diurnal symptoms of ME/CFS from day to day (Anderson, Jason, Hlavaty, Porter, & Cudia, 2012) and it is possible that diurnal and nocturnal variations are related. Additionally, day-to-day waking activity is typically more variable in the ME/CFS population (Gaitanis &

Tooley, 2005) and may also account for the night-to-night variability seen in the current study. These results also suggest possible circadian rhythm dysfunction in the ME/CFS group, with night-to-night variability in sleep being one indicator of impaired circadian function (Berry, 2012). However, this needs further research.

4.1.4 Hypothesis 4: There will be a significant difference between individuals with ME/CFS and controls in night-to-night variability of subjective (sleep diary) measures of total sleep time, sleep onset latency, duration of wake time after sleep onset, sleep efficiency, sleep quality rating and feeling rested rating. It is expected that individuals with ME/CFS will experience greater variability in each of these measures than controls.

As predicted, individuals with ME/CFS experienced greater night-to-night variability of subjective sleep efficiency and feeling rested than controls. Contrary to expectations, no differences in variability of subjective total sleep time, sleep onset latency, wake after sleep onset, or subjective sleep quality were found between the groups. These results are of interest, especially given the lack of published research investigating subjective sleep parameters (apart from subjective sleep quality) and subjective night-to-night variability in CFS/ME.

Given the lack of a standardised definition or measure of NRS and with some researchers asking for reports of subjective sleep *quality* as a measure of NRS, the results pertaining to variability of subjective sleep quality (no difference in amount of variability across the groups) and feeling rested (variability) are particularly noteworthy. It seems that individuals with ME/CFS experienced a consistently poor subjective quality of sleep, whereas feeling rested varied from night to night. This suggests that

NRS and subjective sleep quality are separate entities, and that asking those with ME/CFS about sleep *quality* only may not give a complete picture of the subjective sleep experience.

It was considered that the night-to-night variations shown by the ME/CFS group may be due to a weekend effect, with post hoc analyses revealing the ME/CFS group reporting subjectively higher sleep efficiency on weekends than weekdays. However, the variability the ME/CFS group reported across the different nights in terms of feeling rested did not appear to be related to a weekend effect. There is clearly more to understand in terms of the possible source of night-to-night variations in the sleep of the clinical group.

4.2 Study 2: Investigation of the validity of cardiopulmonary coupling (CPC) in measuring sleep quality

4.2.1 *Hypothesis 1: There will be a first night effect for the CPC device and this will be shown by a significant difference between night 1 and night 3 measures of sleep quality and total sleep time as measured by CPC. It is expected that total sleep time and the percentage of time spent in stable NREM sleep will be lower on night 1 than night 3 and that percentage of time spent in unstable NREM sleep will be higher on night 1 than night 3.*

Contrary to expectations, no differences were found in CPC measures of total sleep time, percentage of time spent in stable NREM sleep, or percentage of time spent in unstable NREM sleep across the two nights. Measures of CPC are most typically obtained by extracting ECG data from polysomnograms (Thomas et al., 2005). PSG is often conducted in sleep laboratories and is prone to a first-night effect, whereby

individuals sleep more poorly on the first night as they adapt to sleeping in a different environment and while connected to equipment with multiple leads. One benefit of the SleepImage M1™ sleep recorder over PSG is that it has the potential to collect multiple nights of sleep data in the person's home environment. Although less invasive than PSG, CPC data collection using the M1™ device does involve the person sleeping with the device adhered to his/her chest and so sleep may be disrupted on the first night while the wearer adjusts. No published studies utilising the M1™ device have investigated the presence or absence of an adaptation effect. The results of this study showed no evidence of a first night/adaptation effect when using the SleepImage M1™ sleep recorder. This is an encouraging outcome, as it suggests that the device may be a valid measure in single night studies.

4.2.2 Hypothesis 2: There will be significant correlations between CPC measures of sleep quality (% time spent in stable NREM sleep and % time spent in unstable NREM sleep) and actigraphic measures of sleep quality (sleep efficiency, duration of wake time after sleep onset, and sleep fragmentation index). It is expected that % time spent in stable NREM sleep will be positively correlated with sleep efficiency and negatively correlated with sleep fragmentation index and duration of wake time after sleep onset. It is expected that % time spent in unstable NREM sleep will be negatively correlated with sleep efficiency and positively correlated with sleep fragmentation index and duration of wake after sleep onset.

Analyses revealed no significant correlations between CPC measures of sleep quality (% time spent in stable NREM sleep and % time spent in unstable NREM sleep) and actigraphic measures of sleep quality (sleep efficiency, duration of wake time after

sleep onset, and sleep fragmentation index). Previous studies investigating CPC as a measure of sleep stability/quality have shown moderate to strong correlations between PSG and CPC variables (Schramm et al., 2014). CPC has also shown promise in differentiating between insomniacs and good sleepers (Schramm et al., 2012), between subjects with moderate to severe OSA and no OSA (Harrington et al., 2013), and in measuring improved sleep as a treatment outcome (Lee et al., 2012; Lee et al., 2014). However, all of these studies utilised ECG measured with PSG and there is little published research investigating the validity of the SleepImage M1™ device. Additionally there is no published research investigating the relationship between CPC variables and actigraphic variables.

Although the findings of the current study would suggest that the M1™ device is not a valid measure of sleep quality, the issue of whether weak to moderate correlations were present but unable to achieve significance due to sample size needs to be considered. The two highest correlations were between % time spent in stable NREM sleep and sleep fragmentation index (where a non-significant correlation of 0.32 was found) and between % time spent in unstable NREM sleep and sleep fragmentation index (where a non-significant correlation of -0.33 was found). These are consistent with the hypothesis, however, the strength of these correlations are not high enough to indicate an important measurement of relationship.

4.2.3 Hypothesis 3: There will be a significant correlation between CPC measures of sleep quality (% time spent in stable NREM sleep and % time spent in unstable NREM sleep) and subjective measures of sleep quality ((i) sleep diary sleep efficiency, self-rated perceptions of (ii) sleep quality and (iii) feeling rested after sleep, and (iv) PSQI scores). It is expected that % time spent in stable NREM sleep will be positively

correlated with measures (i) to (iii), and negatively correlated with PSQI scores. It is expected that % time spent in unstable NREM sleep will be negatively correlated with measures (i) to (iii), and positively correlated with PSQI scores.

Contrary to expectations, only one significant correlation was found. A significant positive correlation was found between % time spent in unstable NREM sleep and scores on the PSQI 2 subscale (a subjective measure of sleep onset latency over the previous month, with higher scores indicating longer sleep onset latency). This result suggests that participants who reported generally taking longer to fall asleep also experienced a greater percentage of unstable NREM sleep once asleep. Contrary to expectations, no other significant correlations were found. However, it is possible that a larger sample size may have produced significant correlations between % time spent in stable NREM sleep and (i) PSQI 7 scores (a measure of daytime dysfunction) and (ii) global PSQI scores, and between % time spent in unstable NREM sleep and (i) PSQI 7 scores and (ii) feeling rested rating, as non-significant correlations of around 0.4 were found in the current study. Although considered to be moderate correlations according to Dancey and Reid (2004) criteria, it is arguable whether such correlations would be clinically meaningful as indicators of a valid measurement relationship, even if they were significant.

Although there are no published studies examining the relationship between PSQI scores and CPC variables using the SleepImage M1™ sleep recorder, several studies have investigated the relationship between PSQI scores and CPC variables extracted from polysomnograms. The current study is also the first study to investigate night-by-night subjective sleep quality and ratings of feeling rested after sleep. Most previous studies have utilised the global PSQI score in analyses, with Schramm et al.

(2012), Yang et al. (2011) and Yang et al. (2010) finding no significant correlations between % time spent in stable NREM sleep and % time spent in unstable NREM sleep and global PSQI scores. Although Chien et al. (2013) found a weak but significant positive correlation (r = 0.22) between global PSQI scores and % time spent in unstable NREM sleep duration and a weak negative correlation (r = -0.17) between global PSQI scores and % time spent in stable NREM sleep, it is arguable that such weak correlations are clinically meaningful.

4.2.4 Hypothesis 4: There will be no difference between CPC-derived and actigraphic measures of total sleep time.

Analyses revealed a large difference between CPC-derived actigraphy-measured total sleep time and CPC-measured total sleep time, with actigraphic total sleep time being less than CPC-measured total sleep time. There has been no published research which has made this comparison using the SleepImage M1™ sleep recorder. The current study included good sleepers and individuals with ME/CFS. Actigraphy has shown good concordance with PSG for total sleep time in healthy individuals (Paquet et al., 2007; Sanchez-Ortuno et al., 2010) and in ME/CFS (Creti et al., 2010). Therefore, these results suggest that the M1™ sleep recorder may overestimate total sleep time. One explanation for this may lie in the different ways actigraphy and CPC determines whether an individual is asleep or awake. Actigraphic software analyses periods of activity and inactivity in order to estimate sleep and wake states (Ancoli-Israel et al., 2003). The CPC analysis algorithm examines the frequency at which coupled heart rate-respiratory oscillations occur in order to determine sleep (Thomas et al., 2005). As the M1™ sleep recorder is unable to record muscle tone, it is unable to distinguish between

REM and wake states (Yang et al., 2011). It is possible that wake is misinterpreted as REM sleep by the device, therefore overestimating total sleep time. However, it is also possible that the reverse may occur, that is, REM sleep may be misinterpreted as wake by the M1™ sleep recorder. In that case, total sleep time would be underestimated by the device. While the reason for the discrepancy between actigraphic and CPC-derived total sleep time remains unclear, there is no evidence from the present study that the M1™ sleep recorder misinterprets REM sleep as wake, and the data suggests the reverse interpretation is a possibility that needs further investigation. It must also be noted that different actigraphic devices and scoring algorithms yield different results, and so further research utilising a range of actiwatch brands and scoring algorithms is needed.

In summary, Study 1 found that there are significant differences in sleep parameters between ME/CFS and healthy controls, both for subjective measures and actigraphic measures. While those with ME/CFS frequently report poor sleep, this study has also provided objective evidence of their subjective experience. In addition to individuals with ME/CFS experiencing both objectively and subjectively poorer sleep, they also experience greater inconsistency in their sleep patterns across multiple nights than normal sleepers. Additionally, Study 2 found that the SleepImage M1™ sleep recorder yielded few important relationships to either actigraphic sleep measures or subjective sleep assessments and the issue of whether the SleepImage M1™ device may possibly be a useful tool for assessing sleep quality in an individual's home environment remains an open question. Considerably more research with larger sample sizes is needed.

4.3 Limitations and directions for future research

As previously outlined in chapter 1, the original intention of this study was to include CPC as an additional measure in the investigation of possible differences between the sleep of ME/CFS participants and controls. Technical difficulties experienced with the SleepImage M1™ sleep recorder resulted in a subset of participants wearing the device during study 1. It may be argued that the wearing of the sleep recorder would impact the results of study 1, with participants who wore the device experiencing poorer quality sleep. Although not quantitatively analysed, this does not appear to be the case, with the ME/CFS group experiencing poorer sleep than the control group, despite more control participants (n = 8) than ME/CFS participants (n = 6) wearing the device. In this regard it is also important to note that no first night effect for the M1™ device was found in Study 2.

Study 1 has numerous strengths, including the matched case-control design. Another significant strength was the use of a single medical centre specialising in the assessment and treatment of ME/CFS for recruitment of ME/CFS participants, therefore ensuring all were correctly diagnosed according to the Canadian Consensus Criteria. Although the recruiting physician was not blinded to the study design or hypotheses, the risk of bias was reduced by giving **all** diagnosed patients the opportunity to participate in the study, with no patients being specifically selected for the study based on certain reported or unreported criteria. The current study also recruited controls who were self-reported good sleepers. Although previous studies have recruited controls in good health (eg. Reeves et al., 2006 Togo et al., 2008; Kishi et al., 2011; Rahman et al., 2011) it seems that these studies have not required that controls consider themselves to be

good sleepers. It is therefore possible that the control group of the current study is a more homogenous sample of subjectively good sleepers than previous studies.

It may be argued that the sample size of the current study is small and so results may be prone to both type I and type II error, but power was sufficient enough to detect medium and large effect sizes. However, future research may benefit from increasing the sample size in order to investigate whether additional differences with low effect sizes not detected by the current study may be occurring. In study 2, several moderate correlations were found between CPC measures of sleep quality and subjective measures of sleep quality. However, only one of these correlations reached statistical significance, and so replicating this study with a larger sample size may increase power enough to detect statistically significant correlations. The SleepImage M1™ sleep recorder has the advantages of portability and absence of a first night/adaptation effect. However, further research utilising larger sample sizes is needed to investigate the validity of the SleepImage M1™ sleep recorder as a measure of sleep quality.

Validation of the use of actigraphy in ME/CFS is limited, with only one published study comparing actigraphy with PSG in ME/CFS (Creti et al., 2010). However, the Creti et al. study involved an adequate sample size (N = 49) and showed actigraphy to be a valid measure of objective sleep in this population, particularly total sleep time and sleep efficiency. Actigraphy also has benefits in being a relatively unobtrusive way to collect sleep data over an extended period of time, a particularly important consideration when investigating sleep with significant night-to-night variability.

Another possible limitation of the current study is that some questionnaires used (ESS, MAPI, and PSQI) have not been validated for specific use in the ME/CFS

population. Further research on the validity of these scales in ME/CFS research would be of interest. Questionnaires and day/sleep diaries were designed to be brief to minimise difficulties arising from possible concentration, short-term memory, and information processing deficits known to occur in ME/CFS (Carruthers et al., 2003).

Presumably, the participants used for the current study were adequately self-motivated to complete all questionnaires and complete a diary twice daily over the 7 day study. It is possible that the individuals with ME/CFS in the current study may represent only those within the clinical population who had less concentration or memory impairments and/or were sufficiently functional to complete the study. However, all ME/CFS participants did meet Canadian Consensus Criteria for ME/CFS and so were likely to have significant functional impairments. Although length of illness data was not collected in the current study, ME/CFS patients typically spend many years unwell, with a mean of 3 to 9 years reported (Prins et al., 2006). With such a protracted and debilitating illness with no definitive explanation or cure, individuals with ME/CFS are possibly more motivated to participate in research than some other unwell populations in an attempt to gain some insight into their suffering. In this regard they are likely to be willing to contribute to increasing the body of knowledge surrounding ME/CFS, despite their functional impairments.

It should be noted that the current study cannot make specific conclusions on the role or effects of medications (such as antidepressants) on sleep, although participants taking prescription hypnotics, including melatonin, were excluded. In study 1, 25% of ME/CFS participants (and no controls) took prescribed antidepressants. In study 2, 17.6% of participants took prescribed antidepressants. The current study did not examine whether these medications were comparable across groups or whether the

specific medications taken had an influence on sleep. Therefore it is unknown whether this may have influenced results. Reviews by Holshoe (2009) and Mayers and Baldwin (2005) have shown that antidepressants have varying effects on sleep, with some improving sleep architecture and others disrupting sleep architecture. It is also unknown whether non-prescription medications taken by participants had an influence on sleep. Future research may benefit from controlling for such medications and supplements. It should also be noted that work schedule and diurnal activity may impact on sleep, with individuals with ME/CFS being more physically active on weekends as opposed to weekdays if they are not in employment. Future research may benefit from analysing work schedule in the ME/CFS population.

Overall, this study has provided a valid and reliable contribution to the research currently available on sleep in individuals with ME/CFS. As there is limited published research using actigraphy to compare sleep parameters and sleep variability in ME/CFS with controls, further research and replication of the current findings are needed. This would aid in building a more comprehensive understanding of the sleep dysfunction seen in ME/CFS, with a key goal being an understanding of the cause(s) of the non-restorative sleep reported in ME/CFS. Such an understanding would assist health professionals in developing appropriate treatment and/or symptom management plans for a population who experience significant debility but for whom evidence-based treatments are few. The results of the current study have important clinical implications in the assessment and management of individuals with ME/CFS. It is recommended that:

- A thorough sleep assessment be included as part of the assessment protocol for individuals with ME/CFS, including a sleep diary (and actigraphy if possible) over a period of at least one week
- Targeted sleep interventions be employed in the treatment of ME/CFS in order to help improve sleep. These interventions may include, but are not limited to, good sleep hygiene practices such as: establishing a regular bedtime routine; scheduling regular sleep and wake times; having wind-down/relaxation time before bed; getting out of bed if spending extended time in bed awake

Further extended areas of research that may be of benefit/interest include further investigation into sleep in ME/CFS, including:

- Development of a valid and reliable measure of non-restorative sleep, validated for use with the ME/CFS population as a tool for both research and as a treatment outcome measure
- Investigation into possible sleep differences in subsets of ME/CFS based upon onset (sudden or gradual), symptom type and severity, age, sex, co-morbidities and duration of illness
- Longitudinal studies to explore any changes or fluctuations in sleep over the course of the illness
- Further investigation of night-to-night variability of sleep parameters over an extended period of time
- Investigation into possible correlations between actigraphic measures of sleep and biological abnormalities (such as hypocortisolism) in ME/CFS
- Exploration of the correlations between mood and/or pain and both actigraphic and subjective measures of sleep quality

- The use of actigraphy to investigate possible correlations between diurnal activity and subsequent nocturnal sleep in ME/CFS
- Evaluation of the role of disordered cognitions and maladaptive behaviours around sleep in the investigation of sleep differences between individuals with ME/CFS and controls

Further, many questions remain unanswered in regard to the etiology and pathophysiology of ME/CFS, including the relationship between sleep and the clinical manifestations of the illness.

4.4 Conclusions

4.4.1 Study 1

This research addressed a number of significant gaps in the literature regarding sleep in ME/CFS. Sleep dysfunction is a requisite criterion for an ME/CFS diagnosis according to the Canadian Clinical Case Definition. However, the clinical features of this dysfunction are imprecise, and meeting this criterion typically relies on self-report. Most previous research has concluded that sleep state misperception occurs in ME/CFS, as poor sleep is often reported in the absence of objective markers of sleep pathology. Of particular interest is the concept of non-restorative sleep (NRS), a common symptom in ME/CFS for which no clear etiology is known. This study adds to the research by providing objective evidence of sleep dysfunction in ME/CFS and suggesting possible explanations for the NRS reported by those with ME/CFS.

This study is the first study to show differences in both subjective and objective sleep between individuals with ME/CFS and healthy controls who are self-reported good sleepers. Despite disrupted sleep being frequently reported by those with ME/CFS,

no published study has compared self-reported sleep variables such as sleep onset latency, duration of wake after sleep onset, total sleep time, and sleep efficiency between ME/CFS and controls. This study found that individuals with ME/CFS reported taking longer to fall asleep and spending more time awake during the night than controls, with no difference in total sleep time. The use of actigraphy in the current study provided objective evidence to validate the subjective experience of poor sleep in ME/CFS. These results suggest that disruptions such as nocturnal awakenings and restlessness in sleep, rather than insufficient sleep, may be a cause of NRS reported in ME/CFS.

Previous research has shown that individuals with ME/CFS consistently report poorer subjective sleep quality than healthy controls. However, retrospective measures of sleep quality such as the PSQI have typically been used. This study adds to that research by comparing night-by-night subjective sleep quality over a week between individuals with ME/CFS and controls. Additionally, the study used night-by-night ratings of feeling rested after sleep as a measure of NRS and made comparisons between ME/CFS and controls. As expected, those with ME/CFS rated their sleep as poorer quality and less refreshing than controls.

This study is also the first to investigate night-to-night variability of sleep in ME/CFS and to show that ME/CFS experience greater night-to-night variability across multiple nights than controls, in a range of actigraphic and subjective sleep parameters. Of particular interest were the significantly higher variations of objective total sleep time and subjective ratings of feeling rested in ME/CFS in comparison to controls. High night-to-night variability in sleep duration has been shown to contribute to poorer subjective wellbeing and so is possibly one additional cause of poor subjective

wellbeing in ME/CFS. Differences in variability of subjective ratings of feeling rested across the groups in the absence of differences in variability of subjective sleep quality ratings suggest that sleep quality and NRS are distinct entities. This is important as it suggests that subjective reports of sleep quality may not be an accurate measure of NRS in ME/CFS.

The findings of this study are of considerable clinical importance. In addition to providing potential clues into the nature of NRS in ME/CFS, it also provides an additional focus on which to develop appropriate treatment plans. This study provides good evidence that poor sleep in ME/CFS is not simply sleep state misperception but objectively measured disrupted sleep with high levels of fragmentation and wakefulness during the night. This poor sleep reality causes significant functional impairment in a population already significantly impaired by multiple physiological, immunological and neurological dysfunctions.

4.4.2 Study 2

A new and emerging technique in sleep research is the analysis of cardiopulmonary coupling (CPC). There is a lack of published research examining the validity of CPC as a measure of sleep stability and sleep quality, particularly the validity of portable devices such as the SleepImage M1™ sleep recorder. This study is the first study to investigate the validity of the SleepImage M1™ sleep recorder in a sample with a wide range of different levels of subjective sleep. Several studies have compared CPC with PSQI measures of subjective sleep quality, with few significant relationships found. This study replicates and extends on this previous research by including night-by-night subjective ratings of sleep quality and ratings of feeling rested after sleep. This

is also the first study to investigate the relationship between CPC variables and actigraphy and to compare total sleep time concordance between the M1™ device and the MiniMitter Philips Actiwatch 2.

The absence of an adaptation effect with the M1™ device found in the current study suggests it may have validity in single night studies. However, this study yielded little evidence to support the SleepImage M1™ sleep recorder being a valid tool for assessing sleep quality, with few significant relationships found between CPC variables and either actigraphic sleep measures or subjective sleep assessments. Additionally, the M1™ device overestimated total sleep time in comparison to actigraphy. Considerable more research, including with larger sample sizes, is needed before the SleepImage M1™ sleep recorder may be considered a useful tool in the assessment of sleep for clinical or research purposes.

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Appendix A: Problems encountered with SleepImage M1™ sleep recorder and the study where each participant was included

Participant ID	Group	Problems with device	In Study 1	In Study 2
E001	ME/CFS	No problems		Yes
E002	ME/CFS	No problems	Yes	Yes
E003	ME/CFS	Device worn for 7 nights but data failed to upload from device – possible software problem	Yes	
E004	ME/CFS	No problems	Yes	Yes
E006	ME/CFS	Device failed to collect data for nights 1, 6 and 7, despite being worn	Yes	Yes
E007	ME/CFS	Device failed to collect data for night 1, despite being worn	Yes	Yes
E008	ME/CFS	Device failed to collect data for nights 4-7, despite being worn	Yes	Yes
C002	Control	No problems	Yes	Yes
C003	Control	No problems		Yes
C004	Control	Lead broke night 3, device failed to collect data nights 5 and 7, despite being worn.	Yes	Yes
C005	Control	Lead broke night 1, device became detached from participant's chest during night 5	Yes	Yes
C006	Control	Device failed to collect data on night 7 – possible flat battery despite new batteries being used for each participant	Yes	Yes
C008	Control	No problems	Yes	Yes
C009	Control	No problems		Yes
C010	Control	No problems		Yes
C011	Control	No problems	Yes	Yes
C016	Control	No problems	Yes	Yes
C017	Control	Device failed to collect data on night 6, despite being worn.	Yes	Yes

Note. An additional 18 subjects (10 ME/CFS and 8 controls) who participated in Study 1 did not wear a SleepImage M1™ sleep recorder

Appendix B: Information to participants

INFORMATION TO PARTICIPANTS INVOLVED IN RESEARCH

You are invited to participate

You are invited to participate in a research project entitled

"Investigation of naturalistic sleep/wake behaviour in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome"

This project is being conducted Professor Dorothy Bruck, Dr Michelle Ball and Dr Melinda Jackson from the School of Social Sciences and Psychology at Victoria University. It will also involve student researcher Cathie Stevens.

Project explanation

Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) is a pervasive disorder that causes considerable discomfort to sufferers. As well as symptoms of extreme fatigue, individuals often report significant sleep disturbance, including difficulties falling asleep, frequent awakenings and unrefreshing sleep. There is a lack of research exploring sleep parameters in these patients in a naturalistic setting, with previous research often conducted in sleep laboratories. This project aims to fill this gap by investigating objective (using actigraphy and cardiopulmonary coupling) and subjective (using sleep diaries) measures of 24-hour sleep patterns in patients with CFS in their everyday environment and comparing these patterns to healthy controls.

What will I be asked to do?

Firstly there will be an initial screening phase which will be conducted over the telephone with one of the researchers. The researcher will ask a series of questions about your sleep, use of sleeping medication, hours of work, and any heart conditions you may have. It is anticipated this will take approximately 15 minutes. Your responses to these questions will determine your eligibility in the study.

If eligible…

1. You will complete a general information questionnaire that includes i) demographics, ii) intake of prescription medication, and iii) use of over-the-counter supplements.

2. You will complete the Pittsburgh Sleep Quality Index (PSQI) once, at day 1 of the study. The PSQI consists of 24 questions that relate to one's usual sleep habits over the past month.

3. CFS group participants will also complete the Symptom Severity and Severity Hierarchy Profile on day 1. The Symptom Severity and Severity Hierarchy Profile consists of a list of 21 common symptoms of CFS, that are rated on a 4 point scale (0 = absent – 3 = severe), and rank in order of severity.

4. CFS group participants will also have their treating doctor/General Practitioner complete the ME/CFS Ability/Disability Scale. It is a short pen-and-paper scale that requires the doctor to circle your level of ability, on a scale of 0-100. It is expected to take only 1 or 2 minutes to complete. This scale is a useful tool for medical practitioners to measure the level of activity and ability of patients with CFS to function.

5. You will wear a wrist Actiwatch which measures activity for a continuous period of 7 days. A wrist Actiwatch is a device that is worn on your non-dominant for the duration of the study. It is similar in appearance and use to a wrist watch. It is waterproof, and so can be worn at all times, even when you are showering.

6. You will complete two short pen-and-paper diaries every day for 7 days, one just prior to going to bed (the "day diary") and one upon waking in the morning (the "sleep diary"). The day diary includes items such as physical symptoms and mood. The sleep diary includes items such as time of lights out and your perception of how well you slept.

7. You will wear an M1 sleep recorder at night while sleeping for a period of 7 nights. The M1 Sleep Recorder consists of two small electrodes which adhere to the chest. These electrodes are connected by a short cable and you will be asked to wear a t-shirt (or similar) while wearing the device in order to prevent the cable being dislodged during sleep. You will attach the recorder just prior to going to bed, and will remove it upon getting up in the morning.

8. You will agree to abstain from prescription sleep medication (with agreement from your doctor) during the 7 day study.

What will I gain from participating?

Although the benefits of this research will not affect you directly, you will be contributing to research that aims to help us to better understand the experience of people living with CFS.

How will the information I give be used?

We will be comparing results between individuals with CFS and healthy controls. We aim to publish the results of this study in an international scientific journal, and the data will also be used by the student researcher to complete the thesis component of the Doctor of Psychology (Clinical Psychology). The data may also be used in conference presentations. Published results will include group data only, and no individuals will be identified in any way. If you wish to have feedback about your assessments over the 7 day period we will be happy to give you, on request, a verbal summary of your individual data.

What are the potential risks of participating in this project?

While it is extremely unlikely that you will experience any irritation or discomfort from wearing the Actiwatch for 7 days, it is a possible risk. An information sheet about wearing the Actiwatch will be provided in the participation package. It is also unlikely that you will experience any irritation or discomfort from wearing the M1 Sleep Recorder electrodes for 7 nights but it is a possible risk. An information sheet about wearing the M1 Sleep Recorder will also be provided in the participation pack.

As participation will require completion of some self-report forms there is an increased risk of experiencing mental fatigue. There is a small possibility this may increase your feelings of irritability, depressed mood, anxiety, and difficulty concentrating. If any of this troubles you to the extent that you wish to obtain psychological help and/or advice you are invited to contact a psychologist who is independent of this research. Associate Professor Gerard Kennedy (phone 9919 2481) is available to discuss treatment options and access to psychological services.

How will this project be conducted?

If you are interested in participating the first step is to call or email Dr Melinda Jackson (details below). She will record your name and phone number and arrange for the student researcher to telephone you at a convenient time to conduct the initial screening process. If, after this process, you are eligible to participate in the study, you will be sent a consent form which you will complete and return to VU by post. Once this form is returned, you will be sent a participation pack which will include a wrist Actiwatch, an M1 Sleep Recorder, a day/sleep diary and questionnaires as outlined above. At the conclusion of the 7 day study, you will return the Actiwatch, M1Sleep Recorder, diaries and questionnaires to VU via a post-paid envelope.

Who is conducting the study?

This research is being conducted at Victoria University, by Chief Investigators Professor Dorothy Bruck, Dr Michelle Ball and Dr Melinda Jackson in conjunction with student investigator Cathie Stevens.

Dr Melinda Jackson

melinda.jackson@vu.edu.au

Phone 9919 9582

Dr Dorothy Bruck

dorothy.bruck@vu.edu.au

Phone 9919 2158

Dr Michelle Ball

michelle.ball@vu.edu.au

Phone 9919 2536

Any queries about your participation in this project may be directed to the Principal Researchers listed above.

If you have any queries or complaints about the way you have been treated, you may contact the Ethics and Biosafety Coordinator, Victoria University Human Research Ethics Committee, Victoria University, PO Box 14428, Melbourne, VIC, 8001 phone (03) 9919 4148.

Appendix C: Supporting letter from CFS Discovery

Dr DP Lewis
MBBS FRACGP DRACOG

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DONVALE Victoria 3111
Tel: (03) 9841 4500 Fax: (03) 9841 5800

dlewis@cfsdiscovery.com.au **www.cfsdiscovery.com.au**

March 22, 2012

Victoria University
Human Ethics Research Committee

Project Title:

Investigation of naturalistic sleep/wake behaviour in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

I, Donald Peter Lewis...

Agree with the outlined recruitment and testing procedure

Confirm that I will not place the patient under any pressure to participate, and my recruitment role will be limited to handing them a leaflet explaining the research

Confirm that the diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is made using the criteria of the Canadian Consensus Criteria for ME/CFS as outlined in the application

Dr D.P. Lewis

Appendix D: Advertisement for control group

Are you interested in learning more about your sleep patterns? Then read on!

Victoria University Research Study

"A naturalistic study of sleep/wake behaviour in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and control participants"

Participants needed

We are looking for volunteers to be involved in a study exploring 24-hour sleep and activity patterns.

The study involves wearing a wrist actiwatch, which records day and night activity levels, wearing an M1 sleep recorder at night, which measures heart rate and respirations while sleeping, and completing a sleep diary, for a duration of 7 days.

We are looking for individuals who:

- are aged 18 years and over
- consider themselves to be good sleepers
- are not currently taking prescription sleep medication
- do not have a sleep disorder, such as sleep apnoea
- are not shift workers working a rotating or night shift schedule of work

If you are interested in finding out more about this study, please contact Dr. Melinda Jackson at Victoria University on 9919 9582, or melinda.jackson@vu.edu.au

This study has been approved by the Victoria University's Human Research Ethics Committee.

Appendix E: Study 1 case matching

Participant ID	Group	Age (years)	Sex
E002	ME/CFS	22	Female
C026	Control	23	Female
130	ME/CFS	23	Male
C004	Control	27	Male
E008	ME/CFS	29	Female
C005	Control	28	Female
105	ME/CFS	29	Female
C015	Control	28	Female
121	ME/CFS	30	Female
C018	Control	28	Female
E004	ME/CFS	32	Female
C024	Control	29	Female
E007	ME/CFS	32	Male
C011	Control	29	Male
118	ME/CFS	34	Female
C022	Control	34	Female

Participant ID	Group	Age (years)	Sex
147	ME/CFS	34	Female
C006	Control	38	Female
E006	ME/CFS	39	Female
C013	Control	38	Female
134	ME/CFS	39	Female
C021	Control	41	Female
163	ME/CFS	39	Male
C017	Control	42	Male
E003	ME/CFS	43	Female
C008	Control	42	Female
112	ME/CFS	46	Female
C016	Control	47	Female
E009	ME/CFS	61	Female
C025	Control	58	Female
120	ME/CFS	61	Female
C002	Control	61	Female

Appendix F: Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

Appendix G: Multivariable Apnoea Risk Index

Now we would like to ask you some questions about your sleep

During the last month, have you had, or have you been told about the following symptoms: (show the frequency by putting a cross in one box)

Symptoms:	(0) never	(1) rarely, less than once a week	(2) 1-2 times a week	(3) 3-4 times a week	(4) 5-7 times a week	(5) don't know
1. snorting or gasping	☐	☐	☐	☐	☐	☐
2. loud snoring	☐	☐	☐	☐	☐	☐
3. breathing stops, choke or struggle for breath	☐	☐	☐	☐	☐	☐
4. frequent awakenings	☐	☐	☐	☐	☐	☐
5. tossing, turning or thrashing	☐	☐	☐	☐	☐	☐
6. difficulty falling asleep	☐	☐	☐	☐	☐	☐
7. legs feel jumpy or jerky	☐	☐	☐	☐	☐	☐
8. morning headaches	☐	☐	☐	☐	☐	☐
9. falling asleep when at work or school	☐	☐	☐	☐	☐	☐
10. falling asleep when driving	☐	☐	☐	☐	☐	☐
11. excessive sleepiness during the day	☐	☐	☐	☐	☐	☐
12. awaken feeling paralysed, unable to move for short periods	☐	☐	☐	☐	☐	☐
13. find yourself in a vivid dreamlike state when falling asleep or awakening even though you know you're awake	☐	☐	☐	☐	☐	☐

Appendix H: Sleep difficulties checklist

SLEEP DIFFICULTIES CHECKLIST

Please answer with regard to the last month

1.) Does it take you more than 30 minutes to fall asleep on most nights (ie 3-7 times a week)?

YES ☐ NO ☐

2.) Do you often wake up during most nights (ie 3-7 times a week)?

YES ☐ NO ☐

3.) Do you CURRENTLY suffer from narcolepsy, sleep apnoea, or parasomnias (such sleepwalking, restless leg disorder or sleep terror disorder)?

YES ☐ NO ☐

4.) Do you CURRENTLY suffer from major clinical depression, generalized anxiety disorder, or delirium?

YES ☐ NO ☐

5.) Is there a possibility that your sleep problem may be due to the intake of drugs OTHER than your normal prescribed medications? (E.g. marijuana use, binge alcohol intake).

YES ☐ NO ☐

Appendix I: Insomnia Severity Index

For each question, please *CIRCLE* the number that best describes your answer.

Please rate the *CURRENT (i.e. LAST 2 WEEKS) SEVERITY* of your insomnia problem(s).

Insomnia problem	None	Mild	Moderate	Severe	Very severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problem waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Appendix J: General information questionnaire

Researcher Use Only
ID.....

Name:_____

Address: _____

_____

Phone number (Home)_____Mobile_____

Email address_____

1. Please list all PRESCRIPTION medication (name and dose per day) that you are currently taking:

_____
_____
_____
_____
_____
_____

2. Please list all OVER-THE-COUNTER supplements you are currently taking:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____*(Please write overleaf if necessary)*

NB: If you are taking any of the above to help with your sleep, please mark these with a #.

Please note that participants in this research are asked to maintain a reasonably consistent intake of any permitted over-the-counter supplements and/or prescription tablets over the entire 7 day period. Should a significant change become necessary participants are asked to obtain prior approval from the researchers.

Appendix K: Prescription medications taken by participants during study 1

Prescription medications taken by ME/CFS group

Participant ID	Prescription medications
E002	Lamotrigine, propranolol, potassium chloride, oral contraceptive
E003	Propranolol
E004	Amitriptyline, venlafaxine, propranolol, potassium chloride, oral contraceptive
E006	Methylphenidate, erythromycin, potassium chloride
E007	Piracetam
E008	Lamotrigine, propranolol, potassium chloride, hydroxychloroquine, trimethoprim, azithromycin, oral contraceptive
E009	Amitriptyline
105	Escitalopram, rhinocort spray
112	Mirtazapine
118	None
120	None
121	None
130	Fluticasone inhaler
134	None
147	None
163	None

Prescription medications taken by control group

Participant ID	Prescription medications
C002	Esomeprazole, rosuvastatin
C004	Albuterol inhaler
C005	Oral contraceptive
C006	None
C008	None
C011	None
C013	None
C015	None
C016	None
C017	Rhinocort spray
C018	Oral contraceptive
C021	None
C022	None
C024	None
C025	Atorvastatin calcium
C026	None

Appendix L: Actiwatch information sheet

An actiwatch provides information on sleep/wake behaviour, daytime activity and light levels

What is it?

A wrist actiwatch is small device, like a watch, which measures the amount of your arm movement and stores it electronically in periods of one minute length. From this information we can obtain information about your sleep/wake patterns, the quality of your night's sleep and how active you have been during the day.

The wrist actiwatch also has a small light sensor on it and this helps us confirm your 'lights out' time at night and also measures how much light you are getting every day.

It can collect activity and light exposure information over periods of four weeks or more.

Wear and care instructions

The actiwatch is normally worn on the non-dominant hand – that is the one NOT used for writing. It is waterproof so it can safely be worn during showering. However, we suggest taking it off if you are going swimming.

As we would also like to measure light exposure levels please try to avoid the small light sensor on the actiwatch from being covered by shirt or blouse cuffs.

It is extremely unlikely that you will experience any irritation or discomfort from the wearing of an actiwatch. It is a good idea to dry beneath the watch band after showering. A small piece of soft cloth or tissue could be inserted beneath the actiwatch if there is any skin sensitivity. Please let us know if you are experiencing any discomfort that concerns you.

Please avoid exposing the actiwatch to any harsh detergents or chemicals. Please be aware that the actiwatch is an expensive and specialised piece of electronic equipment. There is a small button on the side- please ignore this. It does not matter if you press this or not (it is NOT an on/off button).

Instructions for this research

Please put the actiwatch on your non-dominant wrist on the morning that we have nominated as Day 1. Please wear the actiwatch continuously for the 7 day duration of the research – in accordance with the instructions above. When completing the sleep diary it is quite important to be reasonably precise about the time of 'lights out' in bed as this helps us interpret your sleep patterns.

Appendix M: SleepImage M1™ sleep recorder information sheet

What is it?

The M1 Sleep Recorder uses an electrocardiogram (ECG) wave form to derive heart rate and breathing rate. In normal, healthy, stable sleep, the heart beat will slow down and speed up in tune with regular respiration. This is known as “coupling”. During stable sleep this coupling occurs at a high frequency, whereas coupling occurs at a much lower frequency during poor sleep. Comparing the ratio of stable over unstable sleep creates a measure of sleep quality.

Wear and care instructions

See below for a pictorial demonstration of how to apply the M1 Sleep Recorder. There are no on or off buttons that need to be pressed. Once you have applied the electrodes, the device will begin recording automatically. This will be indicated by a green flashing heart signal on the device.

It is unlikely that you will experience any irritation or discomfort from the wearing of the M1 Sleep Recorder electrodes. Ensure the electrodes are applied to clean and dry skin and use new electrodes every night. Please let us know if you are experiencing any discomfort that concerns you.

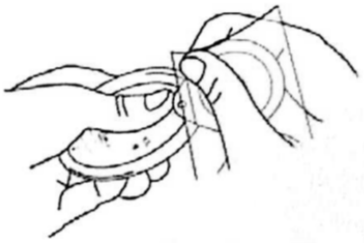
Please avoid exposing the M1 Sleep Recorder to any harsh detergents or chemicals. Please be aware that the M1 Sleep Recorder is an expensive and specialised piece of electronic equipment. There is a small button on the front of the device – you may ignore this. It does not matter if you press this or not (it is NOT an on/off button). This button can be used to check for an ECG signal and you may wish to press it if the heart signal has not turned green yet and you are about to go to sleep.

Instructions for this research

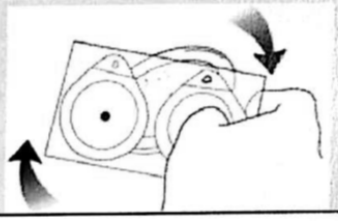
Please apply the M1 Sleep Recorder electrodes according to the instructions below just before going to bed at night and remove upon getting out of bed in the morning. Repeat this process every night for 7 nights. Use new electrodes every night. Please wear a t-shirt or similar while wearing the M1 Sleep Recorder in order to prevent dislodging the leads during sleep.

How to apply the M1™ Recorder

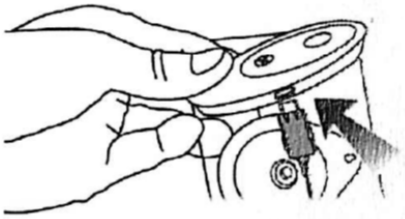
1. Before removing the electrode backing, align the hole at the top of the electrode with the hook at the back of the M1



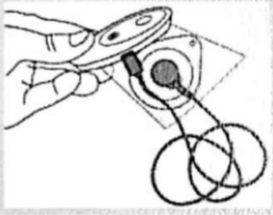
2. Rotate electrode and snap in place.



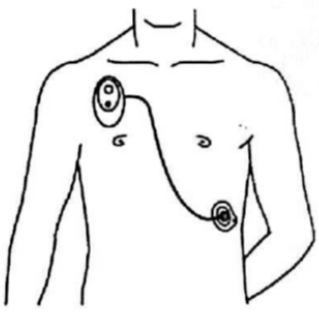
3. Gently insert the end of the blue cable into the side of the M1 with the arrow on the connector facing up



4. Snap the other end of the blue cable onto the second electrode.



5. Apply the electrodes to clean dry skin surface as shown. Body hair may affect signal quality and electrode adhesion. Make sure the cable hangs loose between electrodes to allow for movement. Placement does not have to be exact and will vary by body size.



Appendix N: Sleep/day diaries

Control group diary

Office Use Only
D1

Day Diary

ID_____

COMPLETE EACH EVENING AT BEDTIME.

Today's day and date (eg. Monday 4th April) _____

DAY 1 QUESTION- At what time did you put on the actiwatch today? _____

2. Did you take the Actiwatch off at any time today? Yes/No

If yes, what time did you take it off and what time did you put it back on again?

Took OFF at _____ AM/PM

Put back ON at _____AM/PM

3. Today I napped from _____ _ to _____ (note time of all naps).

Office Use Only

N1

Sleep Diary

ID_____

COMPLETE EACH MORNING.

Today's day and date (eg. Tuesday 5th April) _____

Time of completing this diary _____

1. The Positive and Negative Affect Schedule Questionnaire

This scale consists of 20 words that describe different feelings and emotions. Read each item and then list the number from the scale below next to each word. **Indicate to what extent you feel this way right now, that is, at the present moment**

1	2	3	4	5
Very slightly or not at all	A little	Moderately	Quite a bit	Extremely

_____ 1. Interested

_____ 2. Distressed

_____ 3. Excited

_____ 4. Upset

_____ 5. Strong

_____ 6. Guilty

_____ 7. Scared

_____ 8. Hostile

_____ 9. Enthusiastic

_____ 10. Proud

_____ 11. Irritable

_____ 12. Alert

_____ 13. Ashamed

_____ 14. Inspired

_____ 15. Nervous

_____ 16. Determined

_____ 17. Attentive

_____ 18. Jittery

_____ 19. Active

_____ 20. Afraid

2. Last night I took _____ mg of _____ or _____ of alcohol as a sleep aid (include all prescription and over-the-counter sleep aids).

3. Last night I got in my bed at _____ (AM/PM).

4. Last night I turned off the lights and attempted to fall asleep at _____ (AM/ PM).

5. After turning off the lights it took me about _____ minutes to fall asleep.

6. I woke from sleep _____ times. (Do not count your final awakening here).

7. My awakenings lasted _____ minutes. (List each awakening separately).

8. Today I woke up at _____ (AM/ PM). (NOTE: this is your final awakening).

9. Today I got out of bed for the day at _____ (AM/PM).

10. I would rate the quality of last night's sleep as:

Very Poor				Fair					Excellent
1	2	3	4	5	6	7	8	9	10

11. I would rate how well rested I feel on getting up today as:

Not at all				Somewhat					Well rested
1	2	3	4	5	6	7	8	9	10

12. During the night I experienced the following (tick all that are appropriate):

Restless legs	☐	Headache	☐
Joint pain	☐	Muscle pain	☐
Need to go to toilet more than once	☐	Sweating	☐

ME/CFS group diary

Office Use Only

D1

Day Diary

ID_____

COMPLETE EACH EVENING AT BEDTIME.

Today's day and date (eg. Monday 4th April) _____

DAY 1 QUESTION- At what time did you put on the actiwatch today? _____

We would like to know more about how you felt **TODAY**, compared with how you felt with CFS during the week before starting the VU study. Please answer **ALL** the following questions concerning today by ticking the appropriate boxes.

	Less than usual	*No more than usual*	*More than usual*	*Much more than usual*
1. Did you have problems with tiredness?				
2. Did you need to rest more?				
3. Did you feel sleepy or drowsy?				
4. Did you have problems starting things?				
5. Were you lacking in energy?				
6. Did you have less strength in your muscles?				
7. Did you feel weak?				
8. Did you have difficulty concentrating?				
9. Did you have problems thinking clearly?				
10. Did you make slips of the tongue when speaking?				

	Better than usual	*No worse than usual*	*Worse than usual*	*Much worse than usual*
11. How was your memory?				

12. I would rate my level of pain today to be (circle the appropriate number):

No Pain *Moderate* *Severe*

1 2 3 4 5 6 7 8 9 10

13. We would like to know about your OVERALL EXPERIENCE of symptoms of CFS. When compared with how I felt during the week before starting the VU study, today was (circle appropriate response):

Better than usual	*No worse than usual*	*Worse than usual*	*Much worse than usual*

14. Did you take the Actiwatch off at any time today? Yes/No

If yes, what time did you take it off and what time did you put it back on again?

Took OFF at _____ AM/PM

Put back ON at _____AM/PM

15. Today I napped from _____ _ to _____ (note time of all naps).

Office Use Only

N1

Sleep Diary

ID_____

COMPLETE EACH MORNING.

Today's day and date (eg. Tuesday 5th April) _____

Time of completing this diary _____

1. The Positive and Negative Affect Schedule Questionnaire

This scale consists of 20 words that describe different feelings and emotions. Read each item and then list the number from the scale below next to each word. **Indicate to what extent you feel this way right now, that is, at the present moment**

1	2	3	4	5
Very slightly or not at all	A little	Moderately	Quite a bit	Extremely

_____ 1. Interested _____ 11. Irritable

_____ 2. Distressed _____ 12. Alert

_____ 3. Excited _____ 13. Ashamed

_____ 4. Upset _____ 14. Inspired

_____ 5. Strong _____ 15. Nervous

_____ 6. Guilty _____ 16. Determined

_____ 7. Scared _____ 17. Attentive

_____ 8. Hostile _____ 18. Jittery

_____ 9. Enthusiastic _____ 19. Active

_____ 10. Proud _____ 20. Afraid

2. Last night I took _____ mg of _____ or _____ of alcohol as a sleep aid (include all prescription and over-the-counter sleep aids).

3. Last night I got in my bed at _____ (AM/PM).

4. Last night I turned off the lights and attempted to fall asleep at _____ (AM/ PM).

5. After turning off the lights it took me about _____ minutes to fall asleep.

6. I woke from sleep _____ times. (Do not count your final awakening here).

7. My awakenings lasted _____ minutes. (List each awakening separately).

8. Today I woke up at _____ (AM/ PM). (NOTE: this is your final awakening).

9. Today I got out of bed for the day at _____ (AM/PM).

10. I would rate the quality of last night's sleep as:

Very Poor				Fair					Excellent
1	2	3	4	5	6	7	8	9	10

11. I would rate how well rested I feel on getting up today as:

Not at all				Somewhat					Well rested
1	2	3	4	5	6	7	8	9	10

12. During the night I experienced the following (tick all that are appropriate):

Restless legs	☐	Headache	☐
Joint pain	☐	Muscle pain	☐
Need to go to toilet more than once	☐	Sweating	☐

Appendix O: Letter of ethics approval

VICTORIA UNIVERSITY
MELBOURNE AUSTRALIA

MEMO

TO Professor Dorothy Bruck
Social Sciences and Psychology
Victoria University

DATE 10/09/12

FROM Dr Debra Kerr
Acting Chair
Victoria University Human Research Ethics Committee

SUBJECT Ethics Application – HRETH 12/169

Dear Professor Bruck

Thank you for submitting this application for ethical approval of the project entitled:

HRETH 12/169 Investigation of naturalistic sleep/wake behaviour in Myalgic Encephalomyelitis/chronic Fatigue Syndrome (HREC 12/117)

The proposed research project has been accepted and deemed to meet the requirements of the National Health and Medical Research Council (NHMRC) 'National Statement on Ethical Conduct in Human Research (2007)' by the Victoria University Human Research Ethics Committee. Approval has been granted from 10 September 2012 to 10 September 2014.

Continued approval of this research project by the Victoria University Human Research Ethics Committee (VUHREC) is conditional upon the provision of a report within 12 months of the above approval date (10 September 2013) or upon the completion of the project (if earlier). A report proforma may be downloaded from the VUHREC web site at: http://research.vu.edu.au/hrec.php.

Please note that the Human Research Ethics Committee must be informed of the following: any changes to the approved research protocol, project timelines, any serious events or adverse and/or unforeseen events that may affect continued ethical acceptability of the project. In these unlikely events, researchers must immediately cease all data collection until the Committee has approved the changes. Researchers are also reminded of the need to notify the approving HREC of changes to personnel in research projects via a request for a minor amendment. It should also be noted that it is the Chief Investigators' responsibility to ensure the research project is conducted in line with the recommendations outlined in the National Health and Medical Research Council (NHMRC) 'National Statement on Ethical Conduct in Human Research (2007).'

On behalf of the Committee, I wish you all the best for the conduct of the project.

Kind regards,

Dr Debra Kerr
Acting Chair
Victoria University Human Research Ethics Committee

Appendix P: Consent form

CONSENT FORM

FOR PARTICIPANTS

INVOLVED IN RESEARCH

INFORMATION TO PARTICIPANTS:

You are invited to participate in a research project entitled

"Investigation of naturalistic sleep/wake behaviour in Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome"

Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) is a pervasive disorder that causes considerable discomfort to sufferers. As well as symptoms of extreme fatigue, individuals often report significant sleep disturbance, including difficulties falling asleep, frequent awakenings and unrefreshing sleep. This project aims to investigate objective (using actigraphy and cardiopulmonary coupling) and subjective (using sleep diaries) measures of 24-hour sleep patterns in patients with CFS in their everyday environment and comparing these patterns to healthy controls.

CERTIFICATION BY SUBJECT

I,

of

certify that I am at least 18 years old* and that I am voluntarily giving my consent to participate in the study:

"Investigation of naturalistic sleep/wake behaviour in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome"

being conducted at Victoria University by Professor Dorothy Bruck and Drs Melinda Jackson and Michelle Ball.

I certify that the objectives of the study, together with any risks and safeguards associated with the procedures listed hereunder to be carried out in the research, have been fully explained to me (tick one or both):

☐ via an Information Sheet obtained from my doctor or the researchers

☐ via a phone call with one of the researchers.

and that I freely consent to participation involving the below mentioned procedures:

1. I will complete a general information questionnaire that includes i) demographics, ii) intake of prescription medication, and iii) use of over-the-counter supplements.

2. I will complete the Pittsburgh Sleep Quality Index (PSQI) once, at day 1 of the study.

3. If I am a participant of the CFS group I will complete the Symptom Severity and Severity Hierarchy Profile on day 1 of the study.

4. If I am a participant of the CFS group I will have my treating doctor complete the ME/CFS Ability/Disability Scale.

5. I will a wrist Actiwatch which measures activity for a continuous period of 7 days

6. I will complete a short diary every morning and evening about my sleep, mood and daytime symptoms across 7 days

7. I will wear an M1 sleep recorder at night while sleeping for a period of 7 nights. I will wear a t-shirt (or similar) while wearing the device in order to prevent the cable being dislodged during sleep. I will attach the recorder just prior to going to bed, and will remove it upon getting up in the morning.

8. Across the 7 day assessment period I will agree to abstain from prescription sleep medication (with agreement from my doctor).

I certify that I have had the opportunity to have any questions answered and that I understand that I can withdraw from this study at any time and that this withdrawal will not jeopardise me in any way.

I have been informed that the information I provide will be kept confidential. I further understand that none of the medical (or similar) details on file with my treating doctor, apart from my diagnosis of CFS, will be provided to Victoria University without my written consent.

Signed:

Date:

Any queries about your participation in this project may be directed to the researchers.

Dr Melinda Jackson

melinda.jackson@vu.edu.au

Phone 99199582

Professor Dorothy Bruck

Dorothy.bruck@vu.edu.au

Phone 9919 2158

Dr Michelle Ball

Michelle.ball@vu.edu.au

Phone 9919 2536

If you have any queries or complaints about the way you have been treated, you may contact the Ethics & Biosafety Coordinator, Victoria University Human Research Ethics Committee, Victoria University, PO Box 14428, Melbourne, VIC, 8001 phone (03) 9919 4148.

Appendix Q: Missing actigraphic data for study 1

		Missing actigraphic data	
Participant ID	Group	Night(s) of study	Corresponding night(s) of week
E009	ME/CFS	Night 1	Monday
C022	Control	Night 7	Monday
105	ME/CFS	Nights 6 and 7	Sunday and Monday
C024	Control	Nights 5, 6, and 7	Sunday, Monday and Tuesday

Appendix R: Pittsburgh Sleep Quality Index

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

---

1. During the past month, what time have you usually gone to bed at night?

   BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

f) Feel too cold

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

g) Feel too hot

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

h) Had bad dreams

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

i) Have pain

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

_____

No bed partner or room mate

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____