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Investigation into the Pathophysiology and the Objective Neurophysiological Measurement of Cancer-Related Fatigue in a Pre-Treatment Cancer Cohort

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Declaration

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Abstract

Cancer-related fatigue (CRF) is one of the most common, debilitating, highly prevalent and unrelenting symptom experienced by patients through all stages of the cancer trajectory and often into survivorship (Berger et al., 2015a; Barsevick et al., 2010). Two factors, central and peripheral, can contribute to fatigue in CRF sufferers. Central fatigue involves difficulty in initiating or sustaining voluntary activities (Davis and Walsh, 2010; Gandevia, 2001), due to challenges with self-motivation, perceived demand and internal biochemical cues, without demonstrable cognitive failure or motor weakness (Davis and Walsh, 2010; Finsterer and Mahjoub, 2014). Peripheral fatigue is caused by failure of either muscle excitation-contraction mechanisms or metabolic changes within the muscle which generally manifest at the affected muscle site and can be described as a progressive loss of power or any exercise induced reduction in the ability to exert muscle force or power. (Davis and Walsh, 2010; Edwards, 1981; Gandevia, 2001; Prinsen et al.).

Despite the high prevalence rates, CRF is under-diagnosed and under-treated and perhaps due to its perceived multifactorial nature no universal definition or standard objective measure exists. Current CRF evaluation is based on subjective questionnaires, some of which focus on examining fatigue severity while others address its affective, functional and/or cognitive impact. However, subjective evaluation does not provide insight into the possible underlying aetiologies (cause of CRF) and/or pathophysiology (functional changes as a result of CRF) which remains undetermined and obscured. Therefore, to increase our knowledge and understanding of CRF, a standardised means to objectively assess CRF and its manifestations must be developed.

The primary focus of this research was to build on the literature, design and test an objective measurement method employing neurophysiology, electroencephalography (EEG) and electromyography (EMG), which may enhance assessment and help clarify any possible underlying mechanisms of CRF and to address the gaps in the current knowledge about relative contribution of central and peripheral mechanisms, if any. This was to be achieved by examining independent and combined EEG and EMG signal changes for CRF sufferers and healthy controls during a fatigue inducing motor task in a clinical outpatient setting. In addition, the clinical applicability of the objective method in an outpatient clinic was evaluated. The method was assessed in a pre-treatment cancer cohort, which had not been previously examined.

In this research, which was carried out over a series of studies, all participants performed a fatigue-inducing task consisting of a sustained isometric contraction at 30% of their maximal force until failure due to fatigue. A hand-held dynamometer was employed in the studies and

EEG and EMG were simultaneously recorded during the fatigue-inducing task. The main findings demonstrated that at diagnosis CRF was evident, prior to any fatigue inducing cancer treatment and may suggest a more centrally mediated disorder (i.e. fatigue that originates at the central nervous system (CNS) which decreases the neural drive to the muscle). A metric to objectively evaluate correlates of CRF was developed and its applicability to a routine clinical setting was confirmed.

The studies undertaken also provided comparisons between CRF and chronic fatigue syndrome (CFS), sufferers who share overlapping symptoms, onset, and a decreased quality of life. It was hypothesised that these two patient cohorts would show similar results. However, this was not observed, with CFS sufferers recording higher levels of fatigue. A possible explanation for the CFS results was perhaps due to the diagnostic process, whose symptoms must be evident and recorded for six months minimum prior to a diagnosis being confirmed.

Another element recognised as relevant to the studies undertaken was that results recorded may be impacted by participants' lack of sustained attention to the task or mind wandering. Cancer patients often describe attentional problems, finding it interferes with their cognitive and motor performance, which in turn may affect their ability to complete the task required within this research. Thus, an important question arose as to whether failure during the task was caused by fatigue or inattention. A retrospective analysis of the EEG data obtained during the fatigue inducing motor task in the CRF showed no difference in what may be considered "mind wandering" when compared to healthy controls. However, as this was a retrospective study, no direct inference could be made as to whether the individuals did experience mind wandering or if there was comparability between the two groups. Nevertheless, by considering the impact of sustained attention and mind wandering this work highlights another element to be considered in research and what cognitive changes may occur with CRF.

In conclusion, an objective method employing EEG and EMG was developed and tested which added to existing measurement knowledge of CRF. This was achieved by examining EEG and EMG signal changes for CRF sufferers and healthy controls during a fatigue inducing motor task in a clinical setting with clinical applicability and participant acceptability recorded. Results of this research demonstrated that CRF and CFS had higher subjective fatigue and both CRF and CFS groups exhibited a reduced ability to perform the motor task and perceived physical exhaustion sooner (Lower MVC and endurance time) than healthy controls.

The further development of objective methods of CRF assessment may provide clinicians with objective data which in turn could aid in designing more personalised therapeutic intervention of CRF symptoms and enhance the clinical outcomes of treatment.

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Peer Reviewed International Conference Papers

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International Conference Poster and Oral Presentations

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Table of Contents

List of Figures

List of Tables

GLOSSARY OF ABBREVIATIONS

ASCO	American Society of Clinical Oncology
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BB	Biceps Brachii
BFI	Brief Fatigue Inventory
BR	Biceps Radialis
CBT	Cognitive Behavioural Therapy
CFP	Cancer Fatigue Patient
CFS	Chronic Fatigue Syndrome
CI	Confidence Interval
CMC	Corticomuscular Coherence
CNS	Central Nervous System
CRF	Cancer-Related Fatigue
CSD	Current Source Density
CT	Chemotherapy
ECOG	Eastern Cooperative Oncology Group
EEG	Electroencephalography
EF	Elbow Flexion
EMG	Electromyography
EORTC-QOL	The European Organization for Research and Treatment of Cancer
ET	Endurance Time
FACT-F	The Functional Assessment of Chronic Illness Therapy- Fatigue subscale
FQ	Fatigue Questionnaire
FCR	Flexor Carpi Radialis

FCU	Flexor Carpi Ulnaris
fMRI	Functional Magnetic Resonance Imaging
FSI	Fatigue Symptom Inventory
FSS	Fatigue Severity Scale
HC	Healthy Control
HRT	Half Relaxation Time
IMT	Intermittent Motor Task
MAF	Multidimensional Assessment of Fatigue
ME	Myalgic Encephalomyelitis
MEF	Maximum Elbow Flexion
MEG	Magnetoencephalography
MF	Median (power) Frequency
MFI	Multidimensional Fatigue Inventory
MPF	Mean Power Frequency
MVC	Maximum Voluntary Contraction
MW	Mind Wandering
NCCN	National Comprehensive Cancer Network
NMJ	Neuromuscular Junction
NSCLC	Non-Small Cell Lung Cancer
OLHCC	Our Lady's Hospice & Care Centre
PNS	Peripheral Nervous System
PTF	Peak Twitch Force
RMS	Root Mean square (Voltage)
RT	Radiation Therapy
SC	Sustained Contraction

SJH	St James's University Hospital
SNR	Signal-to-Noise (Ratio)
SVUH	St Vincent's University Hospital
TB	Triceps Brachii
TCD	Trinity College Dublin
TCBE	Trinity Centre for Bioengineering
TF	Twitch Force
TFD	Twitch Force Development
TMS	Transcranial Muscle Stimulation
VAFS	Visual Analogue Fatigue Scale

Chapter 1: INTRODUCTION

1.1 Cancer: An Overview

Cancer is the name given to a collection of related diseases. In all types of cancer, abnormal cell growth occurs and these cells can spread into surrounding tissues. Cancer is a complex and highly prevalent disorder that affects all aspects of the individual's life including normal functioning, social interaction and a decreased quality of life.

The latest statistics show that cancer is one of the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012 (IARC, 2014). By 2030, the number of new cases is expected to increase to 21 million and 13 million deaths per year (IARC, 2014). This is due to a growing ageing population and an increase in established risks from lifestyle including alcohol, diet, obesity, tobacco and lack of physical activity. It is estimated that one in three people will develop cancer in their lifetime (National Cancer Registry, 2014).

1.2 Economic Burden

The economic burden of cancer worldwide is substantial and likely to increase in the future due to expected growth and ageing of the population. Improvements in survival rates as well as better treatment options and associated costs of care following cancer diagnosis will have an impact on this economic burden. Cancer costs are normally reported starting at diagnosis or at the time of a specific event for a group of cancer patients defined by clinical characteristics or for all cancer survivors alive in a specific year (Yabroff et al., 2011). If current cancer incidence, survival and costs of care remain at constant levels, by the year 2020, the costs of cancer care in the US are projected to increase to $157.8 billion dollars from $124.5 billion in 2010. Despite the recent trends of decreasing incidence and improved survival, increasing costs continue, therefore the estimated cost of cancer care in the US will increase to $172.8 billion per year in 2020 (Mariotto et al., 2011; Yabroff et al., 2011).

Cancer costs in the EU were €126 billion in 2009, with health care accounting for €51 billion (40% of overall cancer costs). Productivity losses because of early death cost €42.6 billion, lost working days cost €9.43 billion and informal care cost €23.2 billion. In a study carried out in 2013; lung cancer had the highest economic cost (€18.8 billion, 15% of overall cancer costs), followed by breast cancer (€15.0 billion, 12%), colorectal cancer (€13.1 billion, 10%), and prostate cancer (€8.43 billion, 7%) (Luengo-Fernandez et al., 2013).

There are a myriad of cancer types, symptoms and anti-cancer treatments. In 2016, the five most common cancers were those of the lung, breast, colon, bronchus and prostate. Cancer patients experience many distressing symptoms during the course of their illness, which they commonly describe as moderate or severe. In addition to pain, they commonly suffer from anorexia, constipation, dyspnoea, fatigue, nausea, and vomiting (Donnelly and Walsh, 1995; Shoemaker et al., 2011). Cancer-related fatigue (CRF) is one of the most common and debilitating symptom experienced by cancer patients (Berger et al., 2015a; Barsevick et al., 2010).

1.3 Background of Cancer-Related Fatigue (CRF)

In most healthy people, fatigue is a protective response to physical and psychological stress and is easily alleviated by rest or sleep (Ahlberg et al., 2003; Prue et al., 2006). It is subjective in nature with physical, mental and psychological dimensions (Hauser et al., 2008).

Conversely as stated, CRF is one of the most common and debilitating symptom, experienced through all stages of the cancer trajectory and into survivorship (Barsevick et al., 2010; Berger et al., 2015a; Ryan et al., 2007). Unlike the typical fatigue that healthy people experience, CRF can occur suddenly, is disproportionate to exertion and is not relieved by rest or sleep (Hofman et al., 2007; Ryan et al., 2007; Barsevick et al., 2010; Berger et al., 2015a).

Patients have described CRF as worse than pain or nausea (Butt et al., 2008):

''I couldn't overcome it. I couldn't force myself…the fatigue was overwhelming…there would be times when you might be tired but you can make yourself do it anyway. I couldn't make myself do things anyway during certain phases of it. So it was just overwhelming. And, it did, it kind of took over my life…'' (Wu and McSweeney, 2007).

"…sometimes the fatigue can become so strong you just almost feel like you've been drugged and you need to go lie down and sleep and it can come over you very suddenly" (Wu and McSweeney, 2007).

"*How do you describe it? You just don't want to do anything. All you want to do is just sit. And sometimes you don't want to sit. If you can lie down, that's even better yet. And it's so bad that you don't want to push the button on the remote control. All you do is just sit…"* (Wu and McSweeney, 2007)

The impact of CRF on a patient's ability to function is considerable; hence, this symptom is among the most distressing of all those reported by patients (Hofman et al., 2007). Unfortunately, CRF is under-recognised and under-diagnosed and has a major effect on the quality of life of cancer patients and survivors (Barsevick et al., 2010).

The variable prevalence of CRF is likely due to different definitions, imprecise fatigue criteria, varied assessment methodology, and/or the influence of specific disease sites and anti-cancer treatments (Minton et al., 2013; Berger et al., 2015a; Bower et al., 2014). CRF can occur as part of symptom clusters which include anorexia-cachexia, depression, dry mouth, pain and sleep disorders (Kirkova and Walsh, 2007; Kirkova et al., 2010a; Kirkova et al., 2010b; Lin et al., 2013). The basic mechanisms are not well understood and there may be one predominant cause or several conditions that coexist and contribute to the experience.

1.3.1 Prevalence

CRF is one of the predominant cancer symptoms. As mentioned previously it occurs in the majority of cancer diagnoses and is experienced at all stages of the cancer trajectory and frequently persists into survivorship (Hofman et al., 2007; Minton et al., 2013; Bower et al., 2006). The prevalence rates of CRF can vary from 59% to nearly 100% (Weis, 2011; Hofman et al., 2007; Lawrence et al., 2004; Ryan et al., 2007) depending on cancer population studied i.e. cancer type, stage of the disease, type of treatment and the assessment tool used to assess CRF (Berger et al., 2015a; Bower et al., 2014; Lawrence et al., 2004; Servaes et al., 2001b; Hofman et al., 2007).

CRF may be present at diagnosis and increase while undergoing treatment. Previous published studies have shown that patients undergoing chemotherapy (Wang and Woodruff, 2014; Minton et al., 2010), radiotherapy (Albuquerque et al., 2012; Hojan et al., 2016) and immunotherapy (Phillips et al., 2013) have all reported the occurrence of fatigue (Weis, 2011).

The percentages of prevalence for each therapy and survivors are presented below:

- Chemotherapy = 75-99% (Iop et al., 2004).
- Radiotherapy = 65–93% (Servaes et al., 2001b).
- Palliative care setting = 60%; 15% severe (Servaes et al., 2001b).
- Cancer survivors = 19-82%; they may report fatigue for months post-treatment, with a great impact on quality of life (Stone, 2002).

Patients receiving combination therapies like surgery and chemotherapy or chemotherapy with radiation report the highest incidence of fatigue (Servaes et al., 2001b; Weis, 2011; Lawrence et al., 2004).

Despite the high prevalence rates, CRF is under-diagnosed and under-treated (Mitchell, 2010). The reasons for this may be that patients tolerate their symptoms as an expected side effect of the disease, lack of awareness of possible CRF treatments and a desire to avoid pharmacological treatment of the fatigue (Curt et al., 2000). In addition, clinicians may not understand the impact and distress CRF can cause, and may fail to assess and offer the patient relevant treatment options (for CRF) (Saligan et al., 2015; Rao and Cohen, 2008; Lawrence et al., 2004).

1.3.2 Definition

One of the challenges in reviewing the medical literature concerning CRF is the lack of an agreed definition. The word "fatigue" may describe both an objective decrease in physical or mental performance and a subjective mental state. Research into CRF has been based on various descriptors, including "asthenia", "lethargy" and "tiredness" (Radbruch et al., 2008; Bower et al., 2014). A clear distinction between the terms exhaustion, fatigue, tiredness and weakness has not been made, despite there being conceptual differences. Several definitions of CRF have been proposed; one from The National Comprehensive Cancer Network (NCCN) which has been adopted by the American Society of Clinical Oncology Clinical Practice Guidelines (NCCN/ASCO) and another from The European Association for Palliative Care (EAPC).

The NCCN/ASCO (Bower et al., 2014) has the most comprehensive and commonly used definition:

"Persistent, subjective sense of physical, emotional, and cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity, and significantly interferes with usual functioning."

The European Association for Palliative Care (Radbruch et al., 2008) defines CRF as:

"A subjective feeling of tiredness, weakness or lack of energy"

This latter definition was chosen to reflect The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC-QLQ-C30) fatigue subscale that assesses tiredness, weakness and lack of energy (Radbruch et al., 2008; Seyidova-Khoshknabi et al., 2010). However, the EAPC definition fails to include all aspects of CRF, related symptoms and the impact on quality of life. This highlights the need for a universally agreed definition.

1.3.3 Impact

CRF is one of the most challenging side-effects of cancer and its treatment. It has a huge effect on the individual's quality of life and their ability to function; physically and cognitively. It is problematic to manage as it can exacerbate other symptoms and mood disturbances causing significant distress for patients and their families (Mitchell, 2010; Minton et al., 2013; Curt et al., 2000). In advanced cancer, fatigue can occur as part of a symptom cluster which can also include anxiety, anorexia-cachexia, insomnia, and pain all of which can exacerbate the feeling of fatigue (Barnes and Bruera, 2002).

1.4 Symptom Assessment

Those with cancer suffer from a multitude of symptoms. These symptoms may be caused by the disease itself, anti-cancer treatment and/or other co-morbidities (Temel et al., 2010; Carlson et al., 2012). Symptoms are clinically important as they often cause distress and suffering, and reflect underlying pathophysiology and prognosis (Kirkova et al., 2010a; Kirkova et al., 2010b; Cleeland et al., 2013). A key reason for inadequate symptom relief of CRF is a lack of effective symptom assessment (Naughton and Homsi, 2002). Poor symptom assessment may lead to suboptimal treatment and symptom relief. A comprehensive assessment of symptoms is necessary before any treatment can be undertaken and effective treatment strategies are available for a number of common symptoms (Naughton and Homsi, 2002).

1.4.1 Current CRF Assessment

Fatigue assessment involves characterising the severity, temporal features (onset, course, duration and daily pattern); exacerbating and relieving factors associated distress and impact on life (Barnes and Bruera, 2002). Current clinical approaches to measure fatigue can be distinguished as self-reported ('Subjective') and physiological ('Objective'). Physiological approaches test a patient's capacity such as muscle strength (Seyidova-Khoshknabi et al., 2010). Self-report approaches rely on the patient's perception of fatigue and its consequences and are based on fatigue questionnaires. The available evidence suggests that subjective fatigue questionnaires are the most widely employed fatigue assessment methods in the clinical setting up to date (Minton et al., 2013; Berger et al., 2015a; Seyidova-Khoshknabi et al., 2010).

The NCCN guidelines recommend that all cancer patients should undergo a comprehensive evaluation for fatigue so that early intervention can take place and a decrease in their quality of life can be prevented. (Barnes and Bruera, 2002; Berger et al., 2015a; Bower et al., 2014; Mock et al., 2001).

1.4.2 Subjective Assessment

As mentioned, current evaluation is generally based on subjective questionnaires which can be uni- or multi-dimensional in design. There are over 40 fatigue self-assessment tools which contain different domains and dimensions (Mortimer et al., 2010; Seyidova-Khoshknabi et al., 2010). Some evaluate fatigue severity while others address the affective or functional impact of fatigue and the cognitive effects (Table 1-1) (Seyidova-Khoshknabi et al., 2010; Mortimer et al., 2010).

Unidimensional questionnaires are used to evaluate fatigue severity. Some examples of these questionnaires are the following: the Brief Fatigue Inventory (BFI) assesses the severity of fatigue on a scale of 0-10. The European Organisation for Research and Treatment of Cancer Quality Of Life Questionnaire (EORTC QLQ-C30) assesses severity of fatigue and quality of life. The Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-F) and Piper Fatigue Scale assess behavioural, affective, sensory, and cognitive/mood attributes of fatigue (Mortimer et al., 2010; Seyidova-Khoshknabi et al., 2010).

Table 1-1: Summary of uni- and multi-dimensional fatigue assessment questionnaires for clinical evaluation of CRF

Scale name	Scale	Dimensions of fatigue covered	Group comparison for validation
BFI	Numerical	Physical functioning	Distinguished between CRF and healthy controls
EORTC-QLQ	Likert	Physical functioning	Distinguished between local and regional disease
FSS	Numerical	Physical functioning	Distinguished between CRF and healthy controls
FACIT-F	Numerical	Physical functioning	Distinguished between three known hemoglobin levels (>13, 11-13, <11)
FQ	Likert	Physical and mental	Distinguished between Hodgkin's disease and healthy controls
FSI	Numerical	Physical and mental	Distinguished between pre- and post-treatment fatigue levels
MAF	Numerical	Physical distress , cognitive impairment	Distinguished between patients with arthritis and healthy controls

BFI: Brief Fatigue Inventory; EORTC-QOL: The European Organization for Research and Treatment of Cancer; FSS: Fatigue Severity Scale; FACT-F: The Functional Assessment of Chronic Illness Therapy-Fatigue subscale; FQ: Fatigue Questionnaire; FSI: Fatigue Symptom Inventory; MAF: Multidimensional Assessment of Fatigue

While these questionnaires are standard and are proven to be reliable and validated in measuring self-reported fatigue in adults in an oncology population, they are subjective measures with different domains and dimensions. Assessment of fatigue is therefore challenging as there is no one specific characteristic, tool or laboratory marker for measurement. In addition, there is difficulty in separating disease and treatment-related fatigue (Bruera, 2009) which will be discussed in greater detail in Chapter 2, 2.6.

Medical literature mainly consists of publications employing subjective evaluations of fatigue, and while this method gathers useful information, the biggest limitation is that such qualitative methods do not provide any insight into the likely multifactorial aetiology of CRF nor pathophysiological observations of CRF. However, objective measurements are emerging and they aim to address this limitation.

1.4.3 Objective Assessment

Recent research in the medical literature has shown a number of objective assessment methods have been developed to measure fatigue, these include for example: blood chemistry to check if fatigue is caused by other co-morbidities e.g. anaemia or thyroid dysfunction. The causes of fatigue include factors that reside in the brain (central mechanisms) as well as the muscles themselves (peripheral mechanisms). Some of the methods to assess central and peripheral fatigue are: corticomuscular coherence analysis (CMC), electromyography (EMG, surface or needle), electroencephalography (EEG) (discussed in Chapter 3), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) nerve conduction studies, near-infrared spectroscopy (NIRS), positron emission tomography (PET), and transcranial magnetic stimulation (TMS) (Finsterer and Mahjoub, 2014; Davis and Walsh, 2010; Conway et al., 1995; Filler et al., 2014; Yang et al., 2009; Janssens et al., 2013; Millet et al., 2012; Taelman et al., 2011). These methods can provide information about the underlying pathophysiology of fatigue at the supra-spinal and spinal levels and within muscle function (Finsterer and Mahjoub, 2014; Gandevia, 2001). A comparison to other groups such as healthy controls and those of other chronic illnesses may help further locate the potential cause(s) of CRF (Davis and Walsh, 2010; Finsterer and Mahjoub, 2014).

1.5 Available Interventions for CRF

In accordance with the NCCN practice guidelines in the treatment of CRF, there are a number of interventions that can be tailored to the patient taking account of the stage of treatment and the patient's history (Bower et al., 2014). They can be broken down into general and specific interventions and vary based on clinical status (pre-treatment, active treatment, post-treatment and patients at end of life). The NCCN treatment guidelines for CRF fall into two categories; general interventions which include self-controlled strategies such as self-monitoring fatigue, conserving energy and finding meaning in their current circumstances and specific interventions where the cause of fatigue cannot be identified, non-pharmacologic and pharmacologic treatments are introduced (Berger et al., 2015b; Bower et al., 2014).

1.6 Conclusion

CRF is a highly prevalent and unrelenting symptom of cancer. It is a crucial, but often overlooked aspect of cancer treatment, care and management. The significance of the problem posed by CRF, in terms of its impact on health and on the economy far exceeds the research focus given to the area.

As stated earlier, there is currently no widely accepted definition or gold standard of an objective measure of CRF. Additionally, the multifactorial aetiology and underlying pathophysiology still remain undetermined and obscured. The use of subjective methods of assessment provide relevant information, however it is likely that the treatment of CRF would improve if quantitative data was also available. In Chapter 2 there will be a discussion and literature review of the possible underlying aetiologies and pathophysiology of CRF.

Chapter 1: Summary Points

- Cancer is one of the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012
- Estimated cancer costs: US $172.8 billion per year by 2020; EU: €126 billion in 2009.
- Cancer-Related Fatigue (CRF) is the most common and debilitating symptom for patients and survivors.
- CRF is under-recognised and under-diagnosed and majorly affects quality of life
- Prevalence rates among cancer patients are between59-100%.
- Lack of universally agreed definition as well as inadequate symptom assessment methods.
- Subjective evaluation is predominately used - quantitative data is needed to improve knowledge on underlying aetiologies or pathophysiology.
- Possible interventions are broken down into general and specific interventions and vary based on clinical status, however no specific intervention exists.

Chapter 2: LITERATURE REVIEW

PATHOPHYSIOLOGY OF CANCER-RELATED FATIGUE

The review detailed in this chapter has resulted in a peer-reviewed journal publication and was chosen as paper of the week for the National Cancer Institute (Southwest Oncology Group (SWOG)) (Appendix A)

The Pathophysiology of Cancer-Related Fatigue: Current Controversies

O'Higgins, C.M., Brady, B., O'Connor, B. et al. Support Care Cancer (2018).

https://doi.org/10.1007/s00520-018-4318-7

2.1 Introduction

As discussed in Chapter 1, CRF can be present at diagnosis, increase during treatment and continue even after treatment has been completed. The basic mechanisms of CRF are not well understood. There may be one predominant cause or several conditions that coexist and contribute to the experience. This chapter will discuss the possible underlying aetiology and pathophysiology of CRF and there will be a literature review on the possible central and peripheral hypotheses.

2.2 Search Methods

This literature review is a narrative overview that aims to synthesise the current literature on the underlying aetiology and pathophysiology of CRF.

A search of the electronic databases CINAHL, PubMed, Science Direct, and Scopus from January 1st 1998 to January 31st 2018 was conducted; these dates were chosen as the number of relevant literature papers investigating cancer-related fatigue radically increased over the past 20 years. A subject librarian was consulted in order to identify and assign the appropriate search terms before beginning. Title and abstracts were searched for terms which included:

Table 2-1: Search terms used for Literature Review

Electronic Database	Search Terms	
Medline via PubMed **CINAHL via EbscoHost** **Science Direct** **Scopus**	Medical Subject Headings (MeSH terms): • Anorexia • Assessment • ATP/Metabolism • Biologic Response Modifiers • Cachexia • Central Fatigue • Circadian Rhythm • Chemotherapy • Clinical characteristics • Comorbidity • Cytokines • Cytokine/Metabolism • Depression • Immunotherapy • Incidence • Malnutrition • Mitochondria • Neoplasms/Fatigue • Neoplasm/Physiopathology • Peripheral Fatigue • Radiotherapy • Sarcopenia • Serotonin • Sleep Disorder • Sleep • Surgery • Symptom Cluster • Tumour Burden • Wasting Syndrome	Keywords: • Cancer-Related Fatigue • Cellular Abnormality • Circadian Rhythm Modulation • Emotional Distress • Hypothalamic-Pituitary-Adrenal Axis • HPA Axis • Muscle Wasting • Physiopathology • Proinflammatory Cytokines • Serotonin Dysregulation • Sub-Cellular Abnormality • Vagal Afferent Nerve • Vagal Afferent Hypothesis

Searches were restricted to articles written in English, conducted on humans, in the last twenty years with full text available. Reference lists of relevant articles were also hand-searched. Articles were excluded if they were abstracts only, editorials, or letters to the editor.

2.3 Language of Fatigue

One of the challenges in the literature is the lack of an agreed definition of CRF. The word “fatigue” may describe both an objective decrease in physical or mental performance and a subjective mental state (Stone and Minton, 2008). Research into CRF has been based on various descriptors, including “asthenia”, “lethargy” and “tiredness” (Radbruch et al., 2008). As mentioned in Chapter 1, The National Comprehensive Cancer Network (NCCN) which has been adopted by the American Society of Clinical Oncology Clinical Practice Guidelines (Bower et al., 2014) has the most comprehensive and commonly used definition. It defines CRF as a “persistent subjective sense of physical, emotional, and cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity, and significantly interferes with usual functioning.” Defining fatigue is important for the development of treatment guidelines and research in oncology, supportive care and palliative medicine. The aim of this literature review is to identify and discuss the controversies behind the pathophysiology of CRF.

2.4 Clinical Characteristics

A detailed characterisation of CRF is necessary to improve diagnostic evaluation and management strategies. It is important to identify symptom dimensions like the onset and duration to distinguish between acute and chronic fatigue. Those with chronic fatigue typically require more intensive evaluation, and management focused on both short- and long-term goals. Other important fatigue descriptors or dimensions include severity, daily pattern, frequency, exacerbating and palliative factors, associated distress, interference with daily activities and comorbid symptoms (Hofman et al., 2007).

2.5 Aetiology

Despite the high prevalence, severity and distress associated with fatigue, it is under researched, and little is known about its epidemiology, pathophysiology, and management. It is a complex disorder and is likely to be influenced by several different factors; the disease itself, the treatment and other related co-morbidities.

No specific aetiology of CRF has been identified to date. However, CRF can be directly affected by the cancer itself, cancer treatments and many other factors. Some of the proposed tumour-related factors include abnormalities of energy metabolism, decreased metabolic substrates, production of toxic substances which inhibit normal muscle metabolism, neurophysiologic changes in skeletal muscle, chronic stress responses, and hormonal changes (Gutstein, 2001; Ryan et al., 2007; Wang, 2008; Saligan et al., 2015; Davis and Walsh, 2010; Barsevick et al., 2010; Campos et al., 2011; Lee et al., 2012).

It is difficult to identify consistent correlates of fatigue as CRF often occurs concurrently with other symptoms. These symptoms or symptom clusters often follow the disease trajectory or treatment and can contribute to fatigue (Figure 2-1). However, it is unclear which symptom manifests first.

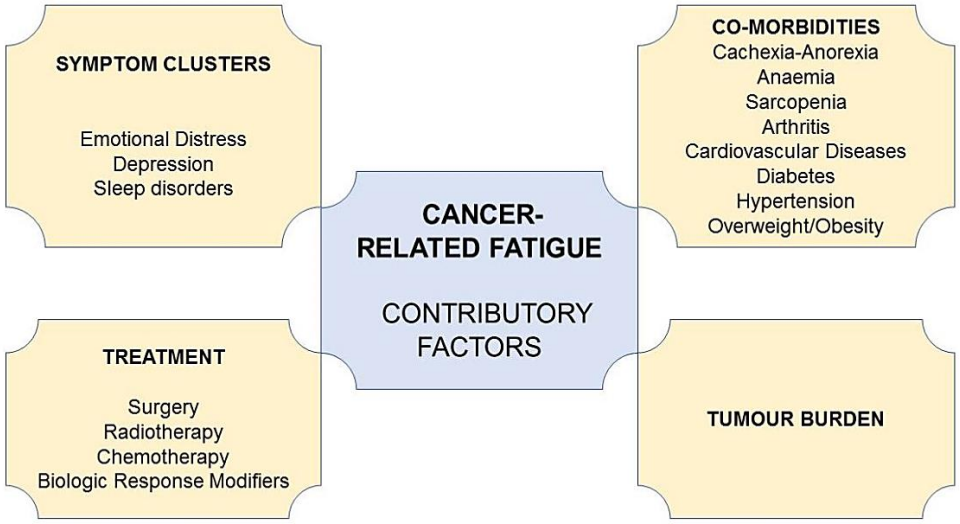


Figure 2-1: Contributory factors to cancer-related fatigue

2.6 Direct Effects of Cancer and It's Treatment

2.6.1 Tumour Burden

The primary site and disease stage may affect the prevalence and severity. Lung, ovarian and melanoma primary sites appear to have the highest prevalence at diagnosis, and

breast and testicular cancer have the lowest (Servaes et al., 2001b). This may be due to the disease stage at presentation, for example, lung cancer is usually at a more advanced stage at diagnosis than breast cancer.

2.6.2 Surgery

Surgery can be used for prevention, diagnosis or definitive cancer treatment. Post-operative fatigue is pervasive and has been attributed to the natural physiological response of the body undergoing recovery rather than the disease itself. Other factors related to surgery, like anaesthesia, analgesics, anxiety, inactivity, infection or pain may also contribute (Rubin et al., 2004). A fatigue study comparing post-surgery to healthy controls may be of great clinical value.

2.6.3 Radiotherapy

For those undergoing radiotherapy, fatigue is the most severe and activity-limiting side effect, with prevalence as high as 65-93%. Combination therapy with chemotherapy and radiotherapy is a high risk factor for persistent chronic fatigue (Dhruva et al., 2010). Fatigue from radiotherapy is not well understood but has been attributed to the destruction of tumour cells and build-up of waste products in the body. In addition, radiotherapy can cause side effects like anaemia, diarrhoea, pain and weight loss which may increase fatigue severity (Berger et al., 2012). Studies in breast and prostate cancer demonstrate that CRF increases throughout treatment, peaks at mid-point; and remains constant until treatment has been completed. CRF improves somewhat in the following months, but not all patients return to pre-treatment energy levels (Gutstein, 2001; Dhruva et al., 2010; Berger et al., 2012). More studies need to be conducted to investigate CRF in radiotherapy patients. One possible study of clinical value may be to compare breast cancer CRF during chemotherapy to prostate CRF during radiotherapy.

2.6.4 Chemotherapy

The prevalence of fatigue during chemotherapy is 75-99% with a steady increase as treatment progresses (Iop et al., 2004). It is not well understood and but it is has been suggested that cell damage and tissue necrosis are the cause (Gutstein, 2001; Iop et al., 2004; Andrykowski et al., 2005). Unlike local radiation, chemotherapy can damage healthy tissue throughout the body (depending on the type and intensity). Chemotherapy can also cause side effects like anaemia, cognitive impairment, diarrhoea, nausea, peripheral neuropathy, vomiting, (or an accumulation of end products from cell destruction) which can cause CRF (Gutstein, 2001). Another theory is that cytotoxic agents have neurotoxic effects when brain metastases interfere with the blood brain barrier which can lead to CRF (Deeken and Loscher, 2007) In a longitudinal study (Berger et al., 2009) fatigue intensified at the midpoint of chemotherapy cycles, but decreased when that was completed. Energy levels did not however, return to the pre-treatment level.

2.6.5 Biologic Response Modifiers (BRM)

These treatments employ exogenous and endogenous cytokines. Interferons (IFN), interleukins-2 (IL-2) and tumour-necrosis factor (TNF) are the most common treatments (Malik et al., 2001). BRM usually precipitate flu-like symptoms which include fatigue, fever, chills, headaches, myalgias, and malaise. Many report intense fatigue, which is a dose-limiting toxicity (Malik et al., 2001). More studies need to investigate BRM and CRF. One possible study may compare those with cancer on BRMs to those on BRMs for other autoimmune diseases where fatigue is also a major problem like hepatitis C and rheumatoid arthritis.

2.6.6 Fatigue and Symptom Clusters

CRF rarely occurs alone, it commonly clusters with multiple common symptoms like emotional distress, mood disorders, pain and/or sleep disturbance (Kirkova and Walsh, 2007; Kirkova et al., 2010b; Lin et al., 2013; Barnes and Bruera, 2002). Such symptoms often exacerbate one another, impair quality of life and can influence the course of the

disease, treatment or prognosis (Lin et al., 2013; Kirkova et al., 2010b; Fiorentino et al., 2011). Other factors that influence symptom clusters include demographic factors; age, gender, personality and performance status (Walsh et al., 2000). While symptom clusters which include CRF may help in diagnosis, treatment, follow-up and prognostication, we require more knowledge of the clinical significance of research into symptom clusters.

2.6.7 Emotional Distress

The relationship between CRF and emotional distress is uncertain. While fatigue can be a symptom of depression and/or anxiety, severe fatigue can itself lead to low mood and emotional distress particularly when important personal roles and daily activities are adversely affected (Conley et al., 2016; Brown and Kroenke, 2009).

2.6.8 Depression

Although depression is much less prevalent than CRF, they may be related. It can be difficult to distinguish between CRF and depressive symptoms (Kirkova and Walsh, 2007; Kirkova et al., 2010b; Fiorentino et al., 2011; Roscoe et al., 2005). Clinical trials in cancer patients with selective serotonin re-uptake inhibitors and serotonin agonists (Bupropion, Paroxetine, Sertraline) have demonstrated improved depression symptoms but without a reduction in fatigue (Alexander et al., 2010; Roscoe et al., 2005; Morrow et al., 2003; Stockler et al., 2007).

2.6.9 Sleep Disorders

Many cancer patients report sleep disturbances such as hypersomnia, insomnia, early awakening, difficulty maintaining sleep, and poor sleep efficiency. Such problems can become chronic and persist for many months or years following cancer therapy (Lin et al., 2013; Wu et al., 2012; Liu et al., 2008). Individuals with cancer spend more time at rest and asleep than those who are healthy. Sleep patterns are often disrupted with

poor sleep quality (Parker et al., 2008). Poor sleep hygiene (such as daytime naps) may also contribute to nocturnal sleep disturbance.

Sleep disorders might also arise from several CRF related conditions. These include changes in cytokine expression, a disrupted or suppressed HPA-axis and altered circadian rhythms, which also have key roles in the regulation of sleep (Ryan et al., 2007) as well as potential roles in CRF.

2.6.10 Comorbid Conditions

CRF often occurs in tandem with other chronic comorbid conditions like hypertension, hypothyroidism and heart disease (Berger et al., 2012). Ogle and colleagues (Ogle et al., 2000), noted that 69% of those with cancer had at least one comorbid condition and 33% had two or more. The most common were arthritis, cardiovascular diseases, diabetes, hypertension, and respiratory diseases and their incidence increased with age. Hypertension, heart disease and diabetes were the most common comorbid conditions reported in breast cancer (Berger et al., 2012). It was noted that heart disease and hypertension predicted long-term survivor fatigue in women with breast cancer 5-10 years post-diagnosis (Bower et al., 2006).

2.6.11 Sarcopenia

Sarcopenia is a multifactorial syndrome (Rosenberg 1989; Cederholm and Morley, 2015; Rolland et al., 2011; Santilli et al., 2014) first proposed in 1989 by Rosenberg (Rosenberg 1989). It has since been characterised by decreased skeletal muscle mass, strength, tissue quality and atrophy and low physical quality (Cruz-Jentoft et al 2019). This usually occurs by replacement of muscle fibres with fat, fibrosis, muscle metabolic dysregulation, oxidative stress and degeneration of the neuromuscular function. Sarcopenia is caused by progressive loss of skeletal muscle mass and function and increased frailty with fatigue, generalised weakness, and decreased quality of life (Ryall et al., 2008; Santilli et al., 2014). Sarcopenia is measured by: the presence of low skeletal muscle mass and either low muscle strength (e.g., handgrip) or low muscle performance

(e.g., walking speed or muscle power); if all three conditions are present, then it may be diagnosed as severe sarcopenia (Santilli et al., 2014; Cruz-Jentoft et al 2019).

Sarcopenia differs from cachexia, as cachexia is defined as a metabolic syndrome with inflammation as the key feature and is usually secondary to another underlying condition like cancer with loss of muscle mass with or without loss of fat mass (Fearon et al., 2011).

Evidence of muscle dysfunction in those with cancer can be found across all diagnoses. However, the cause of cancer-related muscle dysfunction remains poorly described, due to lack of longitudinal and comparative data. The causes of muscle dysfunction are difficult to separate and may vary greatly depending on the clinical setting. However, it is still unclear whether changes in muscle mass and strength are causative or the result of fatigue (Christensen et al., 2014).

Deconditioning from bed rest reduces muscle mass and causes chronic fatigue. It has been found that physical training programmes such as aerobic activity (Dimeo et al., 2008) and resistance training (Segal et al., 2003) reduce CRF. Several measures of muscle function (Kilgour et al., 2011) - handgrip strength, quadriceps strength and skeletal muscle index - correlate with fatigue in advanced cancer. Sarcopenia is a possible predictor of overall survival in metastatic renal cell carcinoma (Sharma et al., 2015).

2.6.12 Cachexia-Anorexia Syndrome

The cachexia-anorexia syndrome is affects about 50% of those with cancer but up to 85% of those with gastric and pancreatic cancers (Nicolini et al., 2013; Fearon et al., 2011). It causes weight loss, lower quality of life, and shorter survival. Anorexia often accompanies cachexia, but it appears not to cause tissue loss, particularly that of lean body mass. Tissue catabolism in cancer cachexia is likely mediated by cytokines, such as TNF-α, IL-6 and CRP (Fearon et al., 2011; Fearon et al., 2013). It may also be caused by tumour metabolism directly, or tumour catabolic by-products, such as lipid-mobilising factor and proteolysis-inducing factor (Fearon et al., 2011). There is a possible link between HPA-axis disruption and the fatigue/cachexia symptom cluster.

Proinflammatory cytokines may also induce the release of corticotrophin-releasing hormone, which is an anorexigenic (Nicolini et al., 2013).

The aetiology of cancer cachexia is complex and multifactorial. It is characterised by severe skeletal muscle wasting and loss of adipose tissue. It cannot be reversed by nutritional support and causes progressive functional impairment (Fearon et al., 2011). It is caused by a combination of low nutrient intake, and tumour-induced metabolic alterations, including protein catabolism and reduced skeletal muscle protein synthesis (Fearon et al., 2011; Ryan et al., 2007). When energy requirements exceed supply, fatigue usually occurs. Energy conservation by decreased activity may lead to deconditioning and further reduction in exercise tolerance.

Although the exact mechanism of the cachexia-anorexia syndrome is poorly understood, cytokines and tumour-related factors are likely play an important role in the pathogenesis. Tumour factors such as proteolysis-inducing factor and host factors like angiotensin II, glucocorticoids, pro-inflammatory cytokines and tumour necrosis factor-α can all induce muscle atrophy. Longitudinal studies would be particularly important to investigate muscle atrophy further.

2.6.13 Anaemia

Anaemia is defined as a deficiency of red blood cells or haemoglobin in the blood. Cancer-related anaemia occurs in approximately 40% of cancer patients (Dicato et al., 2010) and it may be from either the cancer itself or its treatment. The frequency and severity in cancer patients depends on the disease type, stage, and duration and associated treatments.

Cancer anaemia is multifactorial. Bleeding, bone marrow infiltration, impaired erythropoietin production, nutritional deficiencies or the myelosuppressive effect of chemotherapy can all contribute to it (Ryan et al., 2007; Wang, 2008). In addition, overexpression of inflammatory cytokines such as IL-1, IL-6, IFN-α, and TNF-α inhibit erythropoiesis. This decreases erythrocytes production, which results in anaemia and fatigue (Dicato et al., 2010; Jager et al., 2008). The NCCN has identified anaemia as one of the more treatable contributory factors for CRF (Mock, 2001; Mock et al., 2007).

In several studies with darbepoetin alpha (Esquerdo et al., 2011) and epoetin alpha (Bohlius et al., 2006), correction of anaemia significantly improved activity, energy levels and quality of life. However, in a meta-analysis of fifty-three erythropoiesis stimulating agents (ESA) studies (Bohlius et al., 2009) mortality increased with ESAs used during cancer treatment. There were also more thrombotic and thromboembolic events from treatment with ESAs. For this reason, they are no longer recommended.

Many aspects of the pathophysiology of anaemia in cancer are now better understood. While those with anaemia can be fatigued, not every cancer patient with fatigue has anaemia.

2.7 Pathophysiology

Despite the high prevalence, severity and distress associated with fatigue, the pathological mechanisms that cause or contribute to it remain unknown (Davis and Walsh, 2010; Stone and Minton, 2008). The pathogenesis appears complex and multi-factorial, involving the interaction of cognitive, emotional, psychosocial and somatic factors, with highly variable clinical expression. It is likely these co-exist and the main contributors to CRF change as disease and treatment progresses (Ryan et al., 2007; Mortimer et al., 2010; Barsevick et al., 2010; Bower et al., 2014; Saligan et al., 2015).

A variety of biological mechanisms have been hypothesised and investigated in relation to CRF. Several mechanisms may attempt to explain the causation of CRF. These mechanisms could be broadly divided into central or peripheral in origin. Possible central mechanisms include circadian rhythm dysregulation, hypothalamic-pituitary-adrenal-axis dysregulation, increased proinflammatory cytokines, serotonin disruption and vagal afferent nerve activity. Possible peripheral mechanisms include muscle dysfunction, adenosine triphosphate dysregulation and impaired contractile properties (Bower et al., 2014; Berger et al., 2012; Campos et al., 2011; Ryan et al., 2007; Saligan et al., 2015; Wang, 2008; Wang and Woodruff, 2014).

The medical literature and patient descriptions of CRF may suggest that there are both central and peripheral contributions, with a dysfunction in communication of the central nervous system and the functioning muscle (Davis and Walsh, 2010; Kisiel-Sajewicz et

al., 2012; Kisiel-Sajewicz et al., 2014; Mitchell, 2010; Mitchell and Berger, 2006). However, in considering the cohorts involved in this research i.e. newly diagnosed, pre-treatment, both central and/or peripheral abnormalities may not be fully evident in assessing CRF. It could be suggested that for example, central contributions may exist perhaps due to depression, anxiety, and pain related to the cancer diagnosis and/or symptoms related to cancer itself. A limited number of previous published studies imply that CRF is of a more central origin (Cai et al., 2014; Davis and Walsh, 2010; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Markicevic, 2015; O'Connor, 2016; Yang et al., 2009; Yavuzsen et al., 2009). The methodology developed for this research and the resultant data may provide us with a perspective about the central and/or peripheral mechanisms, if any, in terms of CRF. The cause of CRF may be associated with central neuropathy and/or peripheral neuropathy which provides some distinctions, which are discussed in Chapter 3, section 3.2. A better understanding of the possible causative mechanisms is necessary in order to improve diagnosis, develop targeted treatments and thus, improve the patient's quality of life.

The next section includes a discussion on muscle anatomy and the factors influencing muscle fatigue.

2.7.1 Muscle Physiology

Muscle is a tissue surrounded by a membrane called the sarcolemma. The sarcolemma is the cell membrane of muscle fibres. The sarcolemma acts as a conductor for electrochemical signals that stimulate muscle cells. Connected to the sarcolemma are transverse tubules, known as t-tubules. These run along the length of the muscle fibre connecting other t-tubules and the sarcoplasmic reticulum network (Figure 2-2). T-tubules help carry electrochemical signals into the middle of the muscle fibres to activate muscle contraction (Kamen and Gabriel, 2010; Enoka and Stuart, 1992). The sarcoplasmic reticulum serves as a storage facility for calcium ions (Ca2+) that are vital to muscle contraction. Mitochondria, the "power houses" of the cell, are abundant in muscle cells to break down sugars and provide energy in the form of ATP to active muscles (Enoka and Duchateau, 2007; Enoka and Stuart, 1992). Most of the muscle fibre's structure is made up of myofibrils, which are the contractile structures of the cell.

Myofibrils are made up of many proteins fibres arranged into repeating subunits called sarcomeres. The sarcomere is the functional unit of muscle fibres (Kamen and Gabriel, 2010).

The generation of a muscle contraction begins with the central drive which activates the motor neurons that lead to tension in the muscle. Each muscle is made of many fibres and these fibres are innervated by motor neurons. They are attached to the central nervous system via the spinal cord at the synaptic junction. Each motor neuron and the group of fibres it controls are known as a motor unit. A motor unit may consist of anywhere between 3 and 2,000 fibres depending on the muscle. Action potentials propagate along these motor units from the central nervous system to the muscular plate, which results in a contraction or movement in the muscle. Movement by muscles is determined by the number of motor units recruited and the firing rate of these units (Kamen and Gabriel, 2010; Winter, 2009b). The normal firing rate of the motor units is around 6 to 35 Hz, increasing to 50 Hz during strong and fast contractions (Mima and Hallett, 1999b), with presynaptic processes contributing to the firing rates (Farmer et al., 1993). Muscles fibres are classified into two types based on conduction ability. Type I muscle fibres are slow twitch fibres and deliberate in their contractions. They are resistant to fatigue because they use aerobic respiration to produce energy from sugar. We find Type I fibres in muscles throughout the body for stamina and posture i.e. spine and neck regions (Winter, 2009b; Martini et al., 2011).

Type II are fast twitch fibres. Type II fibres are broken down into two subgroups: Type II A and Type II B. Type II A fibres are stronger and faster than Type I fibres, but have less endurance. Type II A fibres have more endurance and are found throughout the body, especially in the legs where they support your body throughout a long day of walking and standing (Davis and Walsh, 2010; Martini et al., 2011; Winter, 2009b). Type II B fibres are stronger and faster than Type II A, but have even less endurance. Type II B fibres are also considerably lighter in colour than Type I and Type II A due to lack of myoglobin, an oxygen-storing pigment. Type II B fibres are found throughout the body, but particularly in the upper body where they give speed and strength to the arms and chest at the expense of stamina, thus fatiguing fast (Davis and Walsh, 2010; Martini et al., 2011; Winter, 2009b).

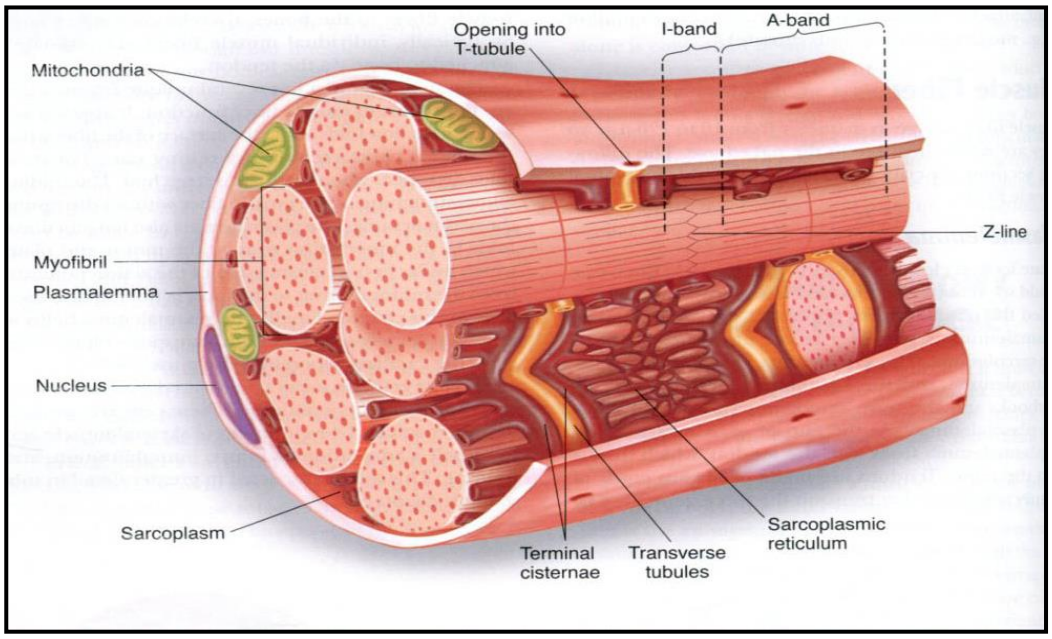


Figure 2-2: Structure of a single muscle fibre.

Muscle is comprised of fibres surrounds by a membrane called the sarcolemma, and comprised of transverse tubules (t-tubules) these run along the length of the muscle and connect to other t-tubules and the sarcoplasmic reticulum network. Electrical signals are transmitted through the t-tubules to promote muscle fibre tension.

[Adapted from (Kenney, 2011)]

2.7.2 The Size Principle

Under the Henneman size principle motor units are recruited in an arranged manner (Henneman et al., 1965). The smallest motor units are recruited first, at a low firing rate which gradually increases with tension to a maximum, with larger motor units being recruited later with increasing firing rates as the muscle moves towards maximal voluntary contraction (De Luca et al., 1982; Gandevia, 2001; Henneman et al., 1965; Mendell, 2005). This generally holds true in isometric contractions and under non-fatigued conditions. The fast twitch fibres are recruited last, but fail first under fatigued conditions, or drop out first when muscle tension is being reduced (De Luca et al., 1982; Gandevia, 2001; Henneman et al., 1965; Winter, 2009b).

2.7.3 Neuromuscular Pathway

The neuromuscular system links the Central Nervous System (CNS) to the peripheral nervous system (PNS) and is composed of a neural circuit including motor neurons in the spinal cord, sensory neurons in the dorsal root ganglion, and skeletal muscle fibres (Ko, 2001). The primary motor pathway is also called the corticospinal pathway. These pathways originate in the brain or brainstem and descend down the spinal cord to control the alpha-motor neurons (Gandevia, 2001; Ko, 2001). There are two types of motor neurons in the spinal cord ventral horn, alpha and gamma. These ventral horn neurons send their axons out through the ventral roots to innervate individual muscle fibres through the neuromuscular junction (Boyas and Guevel, 2011) to directly control the muscles. The motor pathways can control posture, reflexes and muscle tone, as well as voluntary movements. The basic motor pathway and regions involved are schematically represented in Figure 2-3, and the neuromuscular junction is represented in Figure 2-4.

The “pyramidal system” pathway begins with the signals originating in the large pyramidal neurons of the motor cortex, descends through the pyramids of the brainstem, and finally ends on or near the alpha-motor neurons. This system is extremely important to understand clinically, as it is affected by various pathologies including stroke, dystonia, Parkinson’s disease and CRF (Gandevia, 2001; Reece, 2016).

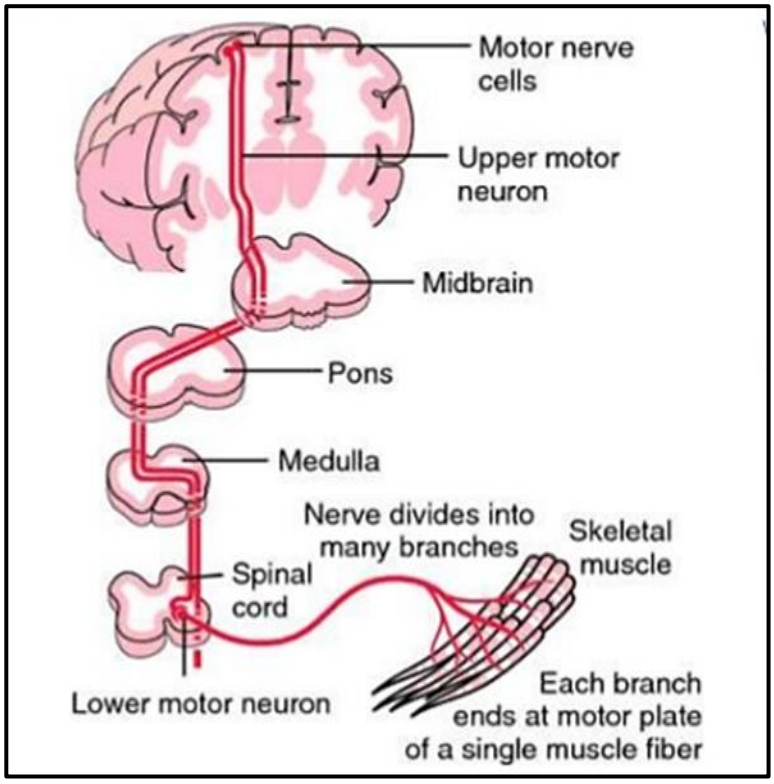


Figure 2-3: Schematic of basic motor pathway from the motor cortex to the affecter muscles.

[Adapted from (Damjanov, 2012)]

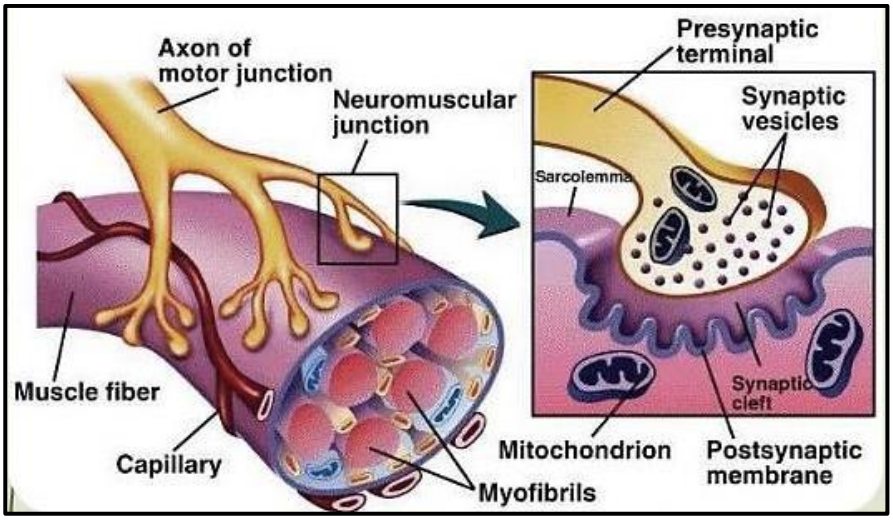


Figure 2-4: Schematic drawing of Neuromuscular Junction

Neuromuscular junction is a chemical synapse formed by the contact between the presynaptic terminal of a motor neuron and the postsynaptic membrane of a muscle fibre.

[Adapted from (Stanfield, 2012)]

2.7.4 Neuromuscular Fatigue

The CNS is responsible for generating signals that control voluntary contraction. Physiological or neuromuscular fatigue can be defined as the loss of force generation during a task, or a progressive loss of the ability to generate maximal force during repeated or sustained muscle contractions, or reduced endurance (Davis and Walsh, 2010; Finsterer and Mahjoub, 2014; Prinsen et al.; Vollestad, 1997). The mechanisms that are responsible for CRF can originate at any part of the pathway, from the cerebral cortex to the muscle fibre (Davis and Walsh, 2010; Prinsen et al.), thus suggesting that CRF may be either central or peripheral in origin or it may be a combination of both (Davis and Walsh, 2010; Finsterer and Mahjoub, 2014; Prinsen et al.).

To better define fatigue, the concept of central and peripheral fatigue are introduced in the next section.

2.8 Central and Peripheral Components of Fatigue

2.8.1 Central Fatigue

Central fatigue involves difficulty in initiating or sustaining voluntary activities (Davis and Walsh, 2010; Gandevia, 2001), due to discord in self-motivation, perceived demand and internal biochemical cues, without demonstrable cognitive failure or motor weakness (Davis and Walsh, 2010; Finsterer and Mahjoub, 2014).

It can present as impaired muscle performance but it is caused by issues within the CNS (Finsterer and Mahjoub, 2014; Gandevia, 2001). It can be a loss of voluntary muscle activation which derives from progressive failure to transmit motor neuron impulses proximal to the neuromuscular junction (NMJ), which occurs at spinal or supra-spinal levels (Cai et al., 2014; Davis and Walsh, 2010; Finsterer and Mahjoub, 2014; Gandevia, 2001; Yavuzsen et al., 2009). Supra-spinal regulation is based on the combination of both primary motor cortex activity and the function of structures involved in planning and controlling movement throughout motor control network. Spinal regulation mediated through Alpha and Gamma motor neuron activities which includes feedback inhibition (Figure 2-5) (Cai et al., 2014). Feedback inhibition is where the firing of motor

neuron is dampened. Psychological factors like attitude, endurance and motivation (Finsterer and Mahjoub, 2014) also influence central fatigue.

As mentioned in Section 2.7, there are numerous central mechanisms which may possibly result in reduced somatosensory drive and a reduced physical capacity for work i.e. central fatigue (Berger et al., 2012; Bower et al., 2014; Campos et al., 2011; Ryan et al., 2007; Saligan et al., 2015; Wang, 2008). Possible mechanisms of peripheral fatigue will now be discussed in Section 2.8.2.

2.8.2 Peripheral Fatigue

Patients often describe fatigue as feelings of weakness and/or a constant lack of energy (Davis and Walsh, 2010; Finsterer and Mahjoub, 2014). Peripheral fatigue is caused by failure of either muscle excitation-contraction mechanisms, metabolic changes within the muscle or NMJ dysfunction that generally manifests at the affected muscle site. This can be defined as a progressive loss of output or any exercise induced reduction in the ability to exert muscle force or power regardless of whether or not the task can be sustained or an inability to perform a motor task in response to central stimulation (Davis and Walsh, 2010; Edwards, 1981; Gandevia, 2001; Prinsen et al., 2015). Issues related to skeletal muscle like atrophy of muscle, altered muscle metabolism, electrolyte disturbance (calcium, magnesium), fatigability and soreness are prominent in CRF (Yavuzsen et al., 2009). Again, CRF can originate in any part of the pathway (Davis and Walsh, 2010; Yavuzsen et al., 2009).

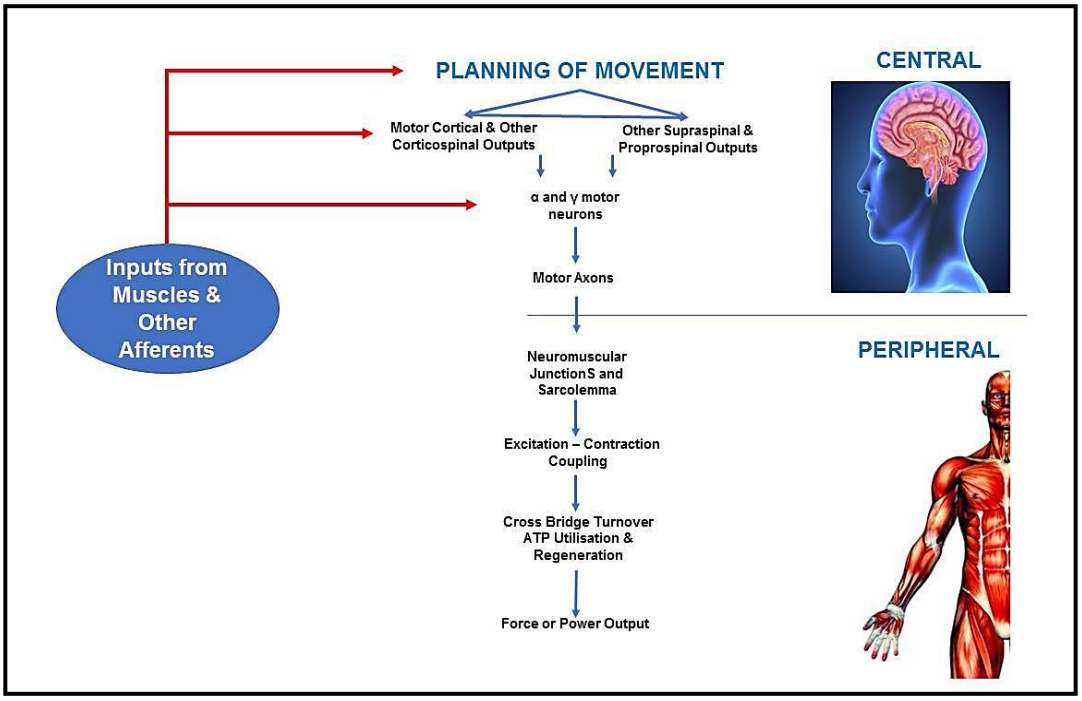


Figure 2-5: Illustration of potential fatigue sites along the neuromuscular pathway [Adapted from (Kisiel-Sajewicz et al., 2012)].

As discussed, the specific aetiology and contributing factors for CRF are unclear; there are several hypotheses for both central and peripheral contribution to fatigue, each of which will now be introduced in Section 2.9

2.9 Review of Current Central and Peripheral CRF Hypotheses

From examining the literature, the hypotheses for possible central and peripheral contribution to CRF which will now be explored in detail are listed in approximate order of significance. Cytokines are first as there is mounting evidence of their importance as they are a common factor running through all hypotheses discussed. These hypotheses are derived from some animal models, limited CRF human studies, and other clinical conditions where fatigue is typical like chronic fatigue syndrome (CFS), exercise-induced fatigue or rheumatoid arthritis (RA) (Table 2-2; Table 2-3).

Table 2-2: Fatigue Hypotheses in Various Conditions.

Various conditions that share fatigue hypotheses with CRF. CFS and CRF are two fatigue syndromes, with overlapping characteristics in terms of: (1) symptoms, (2) potential mechanisms of onset/exacerbation; (3) involvement of both the Central and Peripheral Nervous System, (4) a negative impact on Quality of Life (QOL) of those affected.

Hypotheses	Cancer-Related Fatigue	Chronic Fatigue Syndrome	Diabetes Mellitus	Exercise	Rheumatoid Arthritis
Cytokine Response Dysregulaton	X	X	X	X	X
Hypothalamic-Pituitary-Adrenal Axis Disruption	X	X			X
Circadian Rhythm Dysregulation	X	X			
Serotonin Dysregulation	X	X		X	
Vagal Afferent Theory	X				
Muscle Metabolism/ATP Dysregulation	X	X	X		

2.9.1 Central Hypotheses

2.9.1.1 Cytokine Dysregulation Hypothesis

There is growing evidence from studies that ongoing inflammation may play some crucial role in CRF. Cytokine signalling changes behaviour, neural activity and psychological processes (Kelley et al., 2003; Kurzrock, 2001; Dantzer, 2001). Cytokines and mediators causing "peripheral" effects may also have prominent actions in the central nervous system (CNS). Cytokines convey to the brain that an infection has occurred in the periphery; this can occur via the traditional endocrine route from the blood or direct neural transmission through the afferent vagus nerve (Jager et al., 2008). These changes resemble animal model characteristics with cytokine-induced "sickness behaviour" (Kelley et al., 2003; Kurzrock, 2001; Dantzer, 2001; Dantzer et al., 2008). Sickness behaviour refers to adaptive behavioural changes such as depression, fatigue, lethargy, and loss of appetite (Barsevick et al., 2010; Bower et al., 2014; Bower et al., 2002; Dantzer, 2001; Dantzer et al., 2008; Kelley et al., 2003; Kurzrock, 2001). These changes are due to the release of inflammatory mediators that act on the brain to induce feelings of "sickness". Fatigued cancer patients and survivors have significantly higher serum levels of proinflammatory cytokine markers compared to non-fatigued survivors and healthy controls (Schubert et al., 2006). Cytokines like c-reactive protein (CRP), interleukin-1 receptor antagonist (IL-1ra), interleukin-1 Beta (IL-1β), interleukin-6 (IL-6), interferons (IFNs), neopterin, soluble tumour necrosis factor receptor 2 (sTNF-RII), and tumour necrosis factor-alpha (TNFα) may induce central fatigue through mechanisms which include anaemia, cachexia, and depression, and peripheral fatigue through mitochondrial impairment (Barsevick et al., 2010; Bower et al., 2002; Bower and Lamkin, 2012; Coussens and Werb, 2002; Kurzrock, 2001; Schubert et al., 2006). The underlying mechanism with the most significance for CRF still remains unclear.

Increased cytokine activity may occur in response to tissue damage from chemotherapy, radiation or both. It is unclear whether cytokine activity produces or exacerbates CRF. Overall, studies of the link between inflammation and fatigue largely support this hypothesis (Barsevick et al., 2010; Bower et al., 2002; Bower and Lamkin, 2012; Coussens and Werb, 2002; Gandevia, 2001; Kurzrock, 2001; Schubert et al., 2006; Bower et al., 2009; Bower et al., 2013)

Importantly, the literature indicates that enhanced proinflammatory cytokine signalling dysregulation represents a significant basis for subjective symptoms in CRF and also intersects with several other hypotheses. These include direct influence on HPA-axis dysregulation, altered serotonin metabolism and possibly vagal afferent activation which links together several hypotheses of CRF. Therefore, enhanced pro-inflammatory cytokine activity could possibly play an etiological role in CRF.

It has been suggested that proinflammatory cytokines may play a role throughout all the CRF hypotheses proposed. Detailed insight in the central role of increased activities of proinflammatory cytokines in CRF could offer an effective approach in the treatment of CRF by affecting an array of proposed causative factors e.g. anaemia, disturbances of the hypothalamic pituitary adrenal axis, and altered brain serotonin (Barsevick et al., 2010; Bower et al., 2014; Bower et al., 2002; Dantzer, 2001; Dantzer et al., 2008; Kelley et al., 2003; Kurzrock, 2001; Jager et al., 2008).

Previously published studies that assessed the association between inflammatory markers and treatment induced fatigue reported conflicting results. Perhaps this was due to the data collection procedures and/or use of non-standard and/or low-sensitive assays (Bower et al., 2013; Schubert et al., 2006; Ryan et al., 2007; Wang, 2008). Another consideration is that perhaps the results are inconsistent due to the fact that no association exists. An important research question is, if pharmaceutical agents (e.g. Infliximab, Etanercept Glucocorticoids) that may block proinflammatory markers (e.g. TNF-α, IL-1B) were investigated, would it broaden our understanding of cytokine dysregulation in CRF?

2.9.1.2 Hypothalamic-Pituitary-Adrenal Axis Disruption Hypothesis

This hypothesis proposes that cancer (or its treatment) disrupts the normal HPA axis either directly or indirectly causing endocrine changes that induce CRF. Physical and/or psychological stresses *increase* hypothalamic CRH expression, while chronic inflammation (i.e. biological stress) *reduces* central CRH synthesis and release (Saligan

et al., 2015; Davis and Walsh, 2010; Ryan et al., 2007). The HPA axis normally regulates the release of the stress hormone cortisol in response to physical or psychological stress (Figure 2-6). In addition, cortisol has important biological effects, which include the regulation of, blood pressure, the cardiovascular system, immune system function and metabolism. Cortisol inhibits cytokine production (Ryan et al., 2007) and this together with immune response suppression helps protect the individual from a lethal over activation of the immune system, and minimizes tissue damage from inflammation.

The HPA-axis also plays a key role in regulation of cytokine production and has potent anti-inflammatory effects via a negative feedback control loop. Proinflammatory cytokines (e.g., IL-1, IL-6, TNF-α), serotonin levels and sleep disturbances may disrupt the HPA-axis. Sleeplessness and fatigue can affect the HPA by causing a 24 hour increase of ACTH and cortisol secretion. Serotonin affects the HPA by impairing ACTH release.

An acute release of pro-inflammatory cytokines, like IL-1, IL-6 and TNF-α, stimulates the HPA axis with an increase of cortisol levels. In contrast, chronic cytokine exposure decreases HPA axis stimulation with lower cortisol activity and blunted circadian rhythm. Elevated cytokine levels causing HPA axis and circadian disruption lead to CRF. This connects to the cytokine hypothesis of CRF and suggests that decreased cortisol levels may increase cytokine production. Hypocortisolemia has been observed in cancer, RA and CFS (Fries et al., 2005).

Previous studies suggest that CRF may be due to low cortisol output (Bower et al., 2005; Morrow et al., 2002; Schrepf et al., 2012). When compared with non-fatigued breast cancer survivors, the cortisol stressor response in fatigued survivors is significantly blunted. They also have lower morning serum cortisol levels and a flattened diurnal cortisol cycle, (with elevated cortisol in the evening) (Bower et al., 2005; LaVoy et al., 2016; Morrow et al., 2002; Schrepf et al., 2012). Certain cancer treatments such as glucocorticoids, radiotherapy and some chemotherapy drugs can also suppress the HPA-axis and the consequent blunted stress response may reduce energy levels (Bower et al., 2014; Bower and Lamkin, 2012; Morrow et al., 2002). Increased circulating cytokines and cortisol is somewhat of a paradox as glucocorticoids are known to suppress cortisol and inflammatory cytokine production.

At present the relationship between cancer, CRF and HPA dysregulation is unknown. The changes in the HPA-axis in cancer may be secondary to various disease-related factors like anti-cancer treatment, the excess proinflammatory cytokines (IL-1, IL-6, and TNF-α) or comorbid conditions like sleep disturbance. Considering the influence of the HPA axis on fatigue, cytokine production in the hypothalamus is particularly significant (Wang, 2008). The role of the HPA-axis in CRF can only be better understood through more frequent longitudinal measures of cortisol and glucocorticoid levels, before, during and after treatment. To date no such study has been reported in the literature.

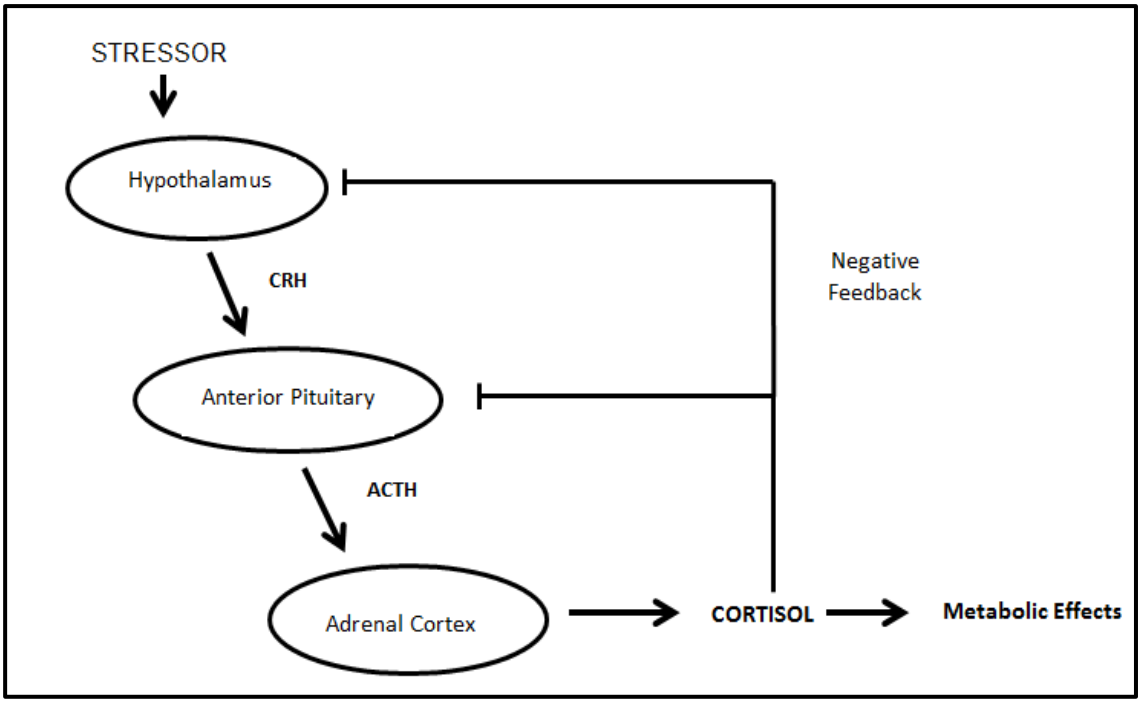


Figure 2-6: Schematic diagram of the HPA-Axis.

The HPA axis normally regulates the release of the stress hormone cortisol in response to physical or psychological stress. Stress stimulates corticotrophin releasing hormone (CRH) from the hypothalamus. CRH acts with arginine vasopressin to release adrenocorticotropic hormone (ACTH) from the pituitary. ACTH in turn increases cortisol release from the adrenal glands. Cortisol then exerts a negative feedback on the HPA axis.

2.9.1.3 Circadian Rhythm Dysregulation Hypothesis

Circadian rhythms are physical, mental and behavioural changes that follow a 24-hour cycle. They are sensitive to environmental changes like light and dark, stress or illness,

and alter with age. The central circadian system regulates various behaviours which include arousal, body temperature regulation, hormone secretion and sleep. In addition to these behaviours, circadian rhythms regulate daily rhythms of the immune system, which may disrupt /increase cytokine production or tumour associated cytokines (IL-6, TNF-α, TGF-α).

Circadian rhythms and quality of life are considered by some to be important predictors of survival for cancer patients (Sultan et al., 2017). In healthy individuals, cortisol levels display a diurnal pattern corresponding to the rest-activity cycle (Wang, 2008; Neefjes et al., 2013). Cortisol provides energy during the stress response. Acute elevations occur in response to brief stressors.

Altered diurnal cortisol secretion and disrupted circadian rhythms are both indicative of HPA-axis dysfunction which in turn has been linked to increased cytokine signalling and fatigue in a variety of clinical conditions. For example, a flattened circadian cortisol cycle is observed in chronic fatigue syndrome. With chronic stressors, the negative feedback system that regulates cortisol becomes impaired, with chronically elevated cortisol levels, (particularly at night) due to the loss of diurnal rhythm.

Cancer or its treatment certainly affects this system and may disrupts an individual's arousal or sleep patterns by altering cortisol rest-activity levels. CRF subjects have significantly altered cortisol circadian levels i.e. greater fatigue is associated with flatter diurnal slopes and a slower decline of evening cortisol (Bower et al., 2005; Bower et al., 2004; Schmidt et al., 2016; Weinrib et al., 2010). One study in advanced lung cancer reported 24-hour urine cortisol level increased during treatment. Higher overall values were found across the 24-hour cycle, but with erratic peaks and troughs (Sephton et al., 2012).

Another study observed higher evening cortisol levels and a significantly flatter slope among 130 breast cancer patients compared to non-fatigued participants (Tell et al., 2014). Cancer patients often report poor sleep quality and insomnia leading to an examination of rest-activity patterns. A recent study (Sultan et al., 2017) which examined rest-activity cycles in cancer chemotherapy reported worsening of both rest-activity rhythms and quality of life.

Actigraphy studies and polysomnography (an objective measure) have reported that circadian rhythm differed significantly in fatigued participants compared to controls (Levin et al., 2005; Parker et al., 2008; Roscoe et al., 2011). Those with CRF showed abnormal sleep patterns, with higher than expected wakefulness during normal sleep times and extensive sleep periods during normal activity times (Parker et al., 2008; Roscoe et al., 2011). Limitations to these studies include small recruitment numbers, and short-term measurements over one or two days, rather than continuous assessment over several weeks. The current evidence therefore suggests that circadian rhythm disruption, accompanied by abnormal cortisol levels, reflected in altered rest-activity patterns may contribute to CRF.

However, the higher cortisol levels in CRF may be secondary to stress or disrupted rest/activity cycles from fatigue. Alternatively, the higher cortisol pattern and fatigue may not be directly linked but instead triggered by a primary HPA axis disruption as cortisol is closely linked to energy production and regulation, along with many other vital behaviours and bodily functions (Bower et al., 2005).

2.9.1.4 Serotonin Dysregulation Hypothesis

High brain serotonin (5HT) levels or upregulation of serotonin receptors may be involved in CRF. It is suggested that fatigue may be caused by either a high or low level of brain 5-HT throughout the brain i.e. there may be an optimal 5-HT level without fatigue (whereas lower or higher levels are causative), which in turn lowers cortisol output (Jager et al., 2008).

This supports the hypocortisolemia and proinflammatory cytokine theories described above. 5HT and its receptors influence each other and the HPA axis. This occurs by regulation of upstream corticotrophin releasing hormone (CRH) via activation of serotonin receptor in the paraventricular nucleus of the hypothalamus which in turn affects cortisol and cytokine levels (by increasing their levels), decreases somatomotor drive, alters HPA function and lowers physical work capacity (Barsevick et al., 2010; Gandevia, 2001; Jager et al., 2008; Ryan et al., 2007; Wang, 2008).

5HT has well-known effects, that include causing drowsiness, helping regulate eating and digestion, causing lethargy, muscle contraction and regulating sleep and waking depending on which 5HT receptor and brain area is activated (Meeusen and Watson, 2007; Meeusen et al., 2006). Low levels are related to sleep disturbances and mood disorders, which are common in cancer.

There is controversy on how 5HT may be involved. One hypothesis is that *low 5HT levels* decrease both the stimulation and responsiveness of the hypothalamic 5HT receptors (5HT-1A). This may occur due to elevated pro-inflammatory cytokines like IL-2, INF-γ, or TNF-α activating the tryptophan- and 5-HT-degrading enzyme indoleamine 2,3-dioxygenase (IDO). This in turn, may lower HPA-axis activity and impair cortisol production.

Another theory is that chronically *increased 5HT levels* may disrupt the HPA-axis lowering cortisol production; it is thought that these persistently high 5HT levels may be from high proinflammatory cytokines (Jager et al., 2008).

Serotonin neurotransmission can also be impaired from inflammation by cytokine-induced activation of indoleamine 2,3-dioxygenase. This metabolizes the serotonin precursor tryptophan into kynurenine, which lowers 5HT levels due to enhanced 5HT reuptake. Kynurenine is further metabolized into neurotoxic kynurenine metabolites that may play a role in depression and are associated with fatigue in lung cancer patients (Dantzer et al., 2014; LaVoy et al., 2016).

The known relationship between depression and fatigue raises another proposed mechanism of 5-HT dysregulation in CRF. Yet, clinical trials of Paroxetine (Morrow et al., 2003; Roscoe et al., 2005) and Buspirone (Alexander et al., 2010) a selective serotonin reuptake inhibitor and selective serotonin agonist respectively, to treat chemotherapy fatigue did not show benefit for fatigue, although 5-HT levels should have increased. This suggests that fatigue is unaffected by brain 5-HT levels correction, and that either the psychomotor retardation evident in depression differs from CRF or the changes have already occurred before treatment.

The complexity of the 5-HT hypothesis is that brain neurotransmission activity cannot be directly measured and 5-HT levels are not readily available, therefore direct evidence is lacking. However, while there have only been a few studies with the use of anti-depressants as treatment for fatigue, these show that serotonin is not the main causative factor. This hypothesis is mainly derived from animal or non-cancer studies but even then with conflicting results. However, it seems the evidence again leans towards cytokines as important. Further research is needed into 5-HT dysregulation and its influence on CRF.

Research to further elucidate the role of 5-HT includes longitudinal testing of 24-hour urine test of 5-HT, cerebral spinal fluid (CSF) levels or imaging methodologies such as positron emission tomography (PET). For PET scanning, a specialized radioligand would measure serotonin e.g. 3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile, labelled with carbon 11 (C-DASB) binds to the serotonin transporter. This would allow relatively direct inferences to be made about serotonin levels.

2.9.1.5 Vagal Afferent Nerve Activity

In addition to supplying several visceral organs with parasympathetic efferents, the vagal nerve contains 80-90% afferent fibres that convey visceral autonomic, motor and sensory functions to the brain stem (Barsevick et al., 2010; LaVoy et al., 2016; Ryan et al., 2007; Wang, 2008).

Vagal afferents can be activated by peripheral neurotransmitter release (interleukin cytokines, prostaglandins and serotonin) caused by cancer or its treatment. These afferents reduce somatic motor activity, modulate somatic muscle tone and also cause continuous plastic changes in brain areas associated with fatigue such as the hypothalamus.

Vagal afferents may also cause “sickness behaviour” from the release of peripheral cytokines like IL-1β (Barsevick et al., 2010; LaVoy et al., 2016; Ryan et al., 2007; Wang, 2008; Dantzer, 2001). Animal studies reveal “sickness behaviour” from administration of intraperitoneal IL-1β which causes vagal nerve activation, this induces IL-1β

production in the brain stem, hippocampus and hypothalamus (Barsevick et al., 2010; Ryan et al., 2007; Wang, 2008). This response was decreased or eliminated completely by abdominal vagotomy (Hansen et al., 1998). Other animal studies suggest that vagal nerve afferents activated by proinflammatory cytokines or 5-HT cause reflex inhibition of somatomotor activity in muscles and this contributes to CRF and the feeling of weakness (Barsevick et al., 2010; Dantzer, 2001; Hansen et al., 1998; Ryan et al., 2007; Wang, 2008).

This links the cytokine, HPA axis, muscle activity and serotonin hypotheses of CRF. Again, with the HPA axis role in fatigue, cytokine production in the hypothalamus is significant. However, to date no human studies have been reported to support this. Human studies to clarify the role of vagal afferents in CRF are required. They should also include examination of reflex mediated changes, blood pressure variation, and heart rate variability (LaVoy et al., 2016). These are known methods of assessing vagal nerve activity.

Considering the involvement of the HPA axis in fatigue and CRF, the role of the vagus nerve in stimulating cytokine production in the hypothalamus is an important research area to be considered.

2.9.2 Peripheral Hypotheses

2.9.2.1 Muscle Metabolism

It has been reported that fatigue is associated with abnormalities in skeletal muscle structure and function (Davis and Walsh, 2010; Saligan et al., 2015). Muscle fatigue is defined as: “any exercise induced reduction in the ability to exert muscle force or power regardless of whether or not the task can be sustained” (Vollestad, 1997; Gandevia, 2001). Patients often describe fatigue as “feelings of weakness” and/or a “constant lack of energy”. It is possible that this subjective feeling may be attributed to more peripheral rather than central fatigue (Davis and Walsh, 2010; Prinsen et al., 2014). For possible peripheral hypotheses of CRF, two particular mechanisms have been proposed.

2.9.2.2 Adenosine Triphosphate

The ATP dysregulation hypothesis proposes that cancer or its treatment damages the sarcoplasmic reticulum with increased intracellular calcium levels and/or impaired mitochondrial mechanisms for regeneration of skeletal muscle (ATP) (Prinsen et al., 2014) (Cai et al., 2014; Davis and Walsh, 2010; Kisiel-Sajewicz et al., 2012; Yavuzsen et al., 2009). Sarcoplasmic reticulum dysregulation may cause CRF due to lower protein synthesis or metabolite accumulation (ATP, chloride, inorganic phosphate, lactic acid, magnesium, potassium, and reactive oxygen species).

Accumulation of metabolites can directly or indirectly produce metabolic fatigue within the neuromuscular junction or muscle fibres through:

1. Interference with the release of calcium (Ca^{2+}) from the sarcoplasmic reticulum
2. Reduction of the sensitivity of contractile molecules actin and myosin to calcium or ATP dysregulation (Davis and Walsh, 2010; Yavuzsen et al., 2009; Prinsen et al., 2014; Cai et al., 2014; Kisiel-Sajewicz et al., 2012).

ATP is a major source of energy for skeletal muscle contraction. Normally, it is quickly replenished with cellular ATP formed in the mitochondria by oxidative phosphorylation. Failure to replenish ATP will compromise muscle function and decrease ability for physical work with subjective fatigue. In addition, anaemia and nutritional deficiencies in cancer can affect ATP generation (Davis and Walsh, 2010). Individuals with cancer anorexia/cachexia have altered muscle protein metabolism which may produce peripheral CRF. This is manifested by increased muscle protein catabolism leading to loss of muscle mass. This may reduce ATP regeneration and precipitate fatigue.

Evidence of ATP dysregulation in cancer is limited (Agteresch et al., 2000a; Agteresch et al., 2000b; Agteresch et al., 2000c). One study (Agteresch et al., 2000b) investigated ATP infusion in non-small cell lung cancer (NSCLC), while another (Forsyth et al., 1999) investigated the efficacy of Nicotinamide Adenine Dinucleotide + Hydrogen (NADH) for chronic fatigue syndrome symptoms. NADH is the reduced form of the coenzyme nicotinamide adenine dinucleotide (NAD), a key coenzyme of oxidative phosphorylation. NAD triggers energy production through ATP generation. Both of these studies

demonstrated improved fatigue, muscle strength, quality of life and weight gain. These effects were short lived. An active research question is to investigate the potential use of ATP/NADH as treatment agents in CRF.

2.9.2.3 Contractile Properties

Two studies in CRF (Kisiel-Sajewicz et al., 2012; Yavuzsen et al., 2009) and one in chronic fatigue syndrome (Siemionow et al., 2004) compared muscle contractile properties to healthy volunteers. Kisiel-Sajewicz et al., 2012 and Yavuzsen et al., 2009 had CRF participants and healthy controls perform a sustained isometric elbow flexion contraction of the right arm at 30% maximal level until self-perceived exhaustion. EMG signals of the elbow flexor and extensor muscles were recorded during this sustained contraction and these studies showed that CRF patients experienced less myoelectrical manifestation of muscle fatigue at exhaustion and that these results suggested that central nervous system fatigue plays a more important role in limiting endurance-type of motor performance in patients with CRF. A recent study (Serra et al., 2018) showed that resistance training reduced the effects of fatigue and improved physical and behavioural function in addition to reduction of inflammation in breast cancer survivors with fatigue; this inflammatory change as a result, may demonstrate a link to the cytokine hypothesis of CRF. These studies demonstrated that those with CRF and chronic fatigue syndrome fatigued earlier in motor tasks, but contractile property did not change when measured by twitch force stimulation. This may be interpreted as a central activation failure in CRF.

Limitations in these studies included the different cancer populations employed in their analysis (e.g. breast, lung, thyroid, ovarian, liver, stomach), a single assessment, small study samples and not taking central nervous system stimulants or depressant medications into account. Longitudinal objective investigations with larger sample sizes are needed to help further knowledge of CRF and its natural trajectory as well as the development of CRF in other cancer populations. The development of objective measures may then help distinguish and provide further evidence on the central and peripheral contributions to CRF. These investigations may include longitudinal

assessment with electrical muscle stimulation, fatiguing motor tasks while recording both electromyography (EMG) and electroencephalography (EEG) simultaneously to assess muscle and neural activity to assess possible central and peripheral contributions to fatigue. How EMG and EEG can be employed independently of each other or in combination to assess fatigue is further discussed in Chapter 3, Section 3.2.

Table 2-3: Fatigue hypotheses and their impact on functioning

List of hypotheses proposed and the possible impact and result they may have on an individual

HYPOTHESIS AFFECTED BY CANCER AND/OR ANTI-CANCER TREATMENT:	IMPACT ON:	MAY RESULT IN:
CYTOKINES DYSREGULATION	Circadian Rhythm Comorbidities HPA Axis Neurotransmitters (5-HT) Vagal Nerve	Anorexia Anaemia Cachexia Increased Fatigue Increased or Decreased HPA-Function Increased Inflammation Sarcopenia Sleep Disorders
HYPOTHALAMIC PITUITARY ADRENAL AXIS DISRUPTION	Circadian Rhythm Cytokines Comorbidities Neurotransmitters (5-HT)	Comorbidities Depression Increased Fatigue Increased Inflammation Sleep Disorders
CIRCADIAN RHYTHM DYSREGULATION	Cytokines HPA Axis Comorbidities Neurotransmitters (5-HT)	Depression Increased Fatigue Increased Inflammation Rest-Activity Cycle Disruption Sleep Disorders
SEROTONIN DYSREGULATION	Circadian Rhythm HPA Axis Cytokines Vagal Nerve Motor Drive	Anorexia-Cachexia Circadian Rhythm Disruption Decreased capacity to work HPA function Increased Fatigue Increased Inflammation Pain Vagal Nerves activation
VAGAL AFFERENT ACTIVITIES	Cytokines HPA Axis Stomach muscle activity Neurotransmitters (5-HT)	Increased Fatigue Increased Inflammation Sickness behaviour Sleep disorders
MUSCLE METABOLISM DYSREGULATION	ATP Regeneration Comorbidities Protein Metabolism Physical performance (Skeletal muscle)	Anorexia Cachexia Decreased ATP regeneration Decreased Protein Decreased Muscle Performance Increased Fatigue Increased Inflammation Sarcopenia

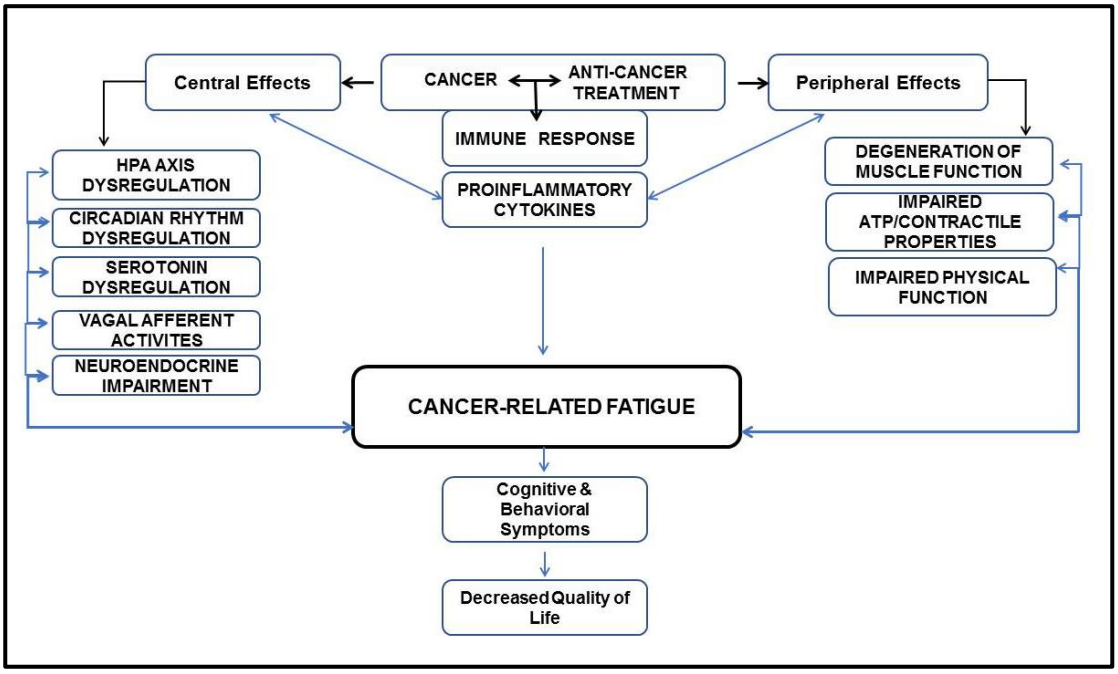


Figure 2-7: Summary Diagram of Cancer-Related Fatigue

Cancer and/or its treatment result in simultaneous complex biochemical, physiological and psychological dysregulation of important biological systems in an individual. This cascade of events, in both the central and peripheral nervous system results in cancer-related fatigue which is manifested with cognitive and behavioural symptoms, and a decreased quality of life.

2.10 Conclusion

The most comprehensive and commonly used definition of CRF is by the NCCN [Bower 2014]. It defines CRF as a "persistent subjective sense of physical, emotional, and cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity, and significantly interferes with usual functioning."

Fatigue presentation may be influenced by the interaction of cognitive, emotional, psychosocial and somatic factors with a highly variable pattern of clinical expression. In an attempt to explain CRF, several hypotheses have been proposed Figure 2.7 (Saligan et al., 2015) (Figure 2-7). While biochemical and physiological abnormalities related to fatigue are identified, it is not clear whether these mechanisms are the underlying cause or just linked to CRF and its associated symptoms. In addition, it is challenging to separate one hypothesis from another due to their inter-dependence (Figure 2-7).

While they are not the only common feature throughout all the proposed hypotheses, there is evolving evidence that proposes cytokines may play an important role. Cytokines have a key role in normal CNS function, including the modulation of neuronal and glial cell functioning and neural repair and the metabolism of dopamine and serotonin. IL-1B, IL-6, TNF-a influence nearly every step of the signalling pathway and several feedback loops, with proinflammatory cytokine mediators active in the HPA axis, circadian rhythm, serotonin metabolism and vagal afferent activation. Cytokines may also be indirectly involved in CRF related issues like anaemia, anorexia, cachexia, depression and sarcopenia.

The HPA axis is an important regulator of cortisol and cytokine production and has potent anti-inflammatory effects. Serotonin influences the HPA axis and potentially also plays a role in the anorexia-cachexia syndrome. Serotonin release can also be triggered by pain, which is another extremely common cancer symptom.

Circadian rhythm, regulated by the hypothalamus, is known to be affected by cortisol, cytokine and serotonin levels. Distorted circadian rhythms can also affect the HPA axis.

CRF patients often report feelings of weakness and lack of energy, and often have a decreased ability to do physical work; this is typically referred to as peripheral fatigue. This may be due to ATP dysregulation or build-up of metabolic by-products in the neuromuscular junction or muscle. However, studies examining muscle dysfunction and

ATP have not drawn definitive conclusions and those looking at contractile properties have suggested a more central origin of CRF.

A limited numbers of studies to date have investigated the hypotheses discussed. They have not yet been conducted in all the relevant patient groups or for all aspects of fatigue (e.g. severity vs duration, pre- and post- treatment). Our knowledge of the factors that cause or contribute to CRF continues to evolve. A neuroendocrine cause of CRF is especially attractive as it may facilitate direct and simple therapeutic interventions. However, additional research is required to elucidate the specific cause(s), as well as more research into cytokine dysregulation, where evidence seems to be the strongest.

CRF is a serious problem that impairs patients physically, psychologically and socially. While it has been referred to as a decrease in performance (i.e. peripheral fatigue) there are also behavioural and central manifestations that occur (i.e. central fatigue).

In this chapter, the definition of CRF and possible central and peripheral hypotheses of its underlying aetiologies and pathophysiology have been discussed. Chapter 3 will now introduce a literature review of recent research into objective assessment of CRF.

Chapter 2: Summary Points

- NCCN is the most commonly and comprehensive definition used of CRF.
- Several hypotheses suggest that simultaneous complex biochemical, physiological and psychological dysregulation of important biological systems contribute to CRF.
- There have been a limited number of published studies to date on possible aetiologies and pathophysiology.
- CRF is broadly divided into two categories; central and peripheral hypotheses.
- Possible Central hypotheses: Cytokine dysregulation, Hypothalamic-Pituitary-Adrenal Axis disruption, Circadian Rhythm disruption, Serotonin dysregulation, Vagal Afferent activities.
- Possible Peripheral Hypotheses: Muscle Metabolism, Adenosine Triphosphate, Contractile dysregulation.
- Increased evidence that cytokines play a crucial role as they are evident throughout all hypotheses.
- A comprehensive clinical assessment of the relationship between CRF and other cancer-related symptoms and co-morbid conditions (like depression, pain and sleep disorders) is important to advance our understanding of the complex pathophysiology behind CRF.

Chapter 3: OBJECTIVE ASSESSMENT OF CANCER-RELATED FATIGUE

LITERATURE REVIEW

3.1 Introduction

This chapter is a literature review evaluating studies that attempt to assess CRF through the use of electroencephalography (EEG) and electromyography (EMG). This research will investigate the correlation of these two measurements to determine the corticomuscular coherence. Corticomuscular coherence (CMC) is the synchronisation of EEG and EMG signals in the frequency domain. The analysis of such signals will also be examined to link together the possible central and peripheral mechanisms.

In Section 2.8, it was hypothesised that CRF had both central and peripheral manifestations. Fatigue is difficult to define (Chapter 1, Section 1.3.2) but even more challenging to measure (Finsterer and Mahjoub, 2014). The majority of the published research on CRF subjectively examines symptoms and biological markers to understand the aetiology of CRF. However, it is also possible to assess fatigue using neurophysiological and neuroimaging methods e.g. EMG, EEG or functional magnetic resonance imaging (fMRI). There is an abundance of published studies (1453 papers and abstracts (Seyidova-Khoshknabi et al., 2010)) that investigate CRF through the current assessment methods summarised in Chapter 2, which are predominantly subjective. However, these studies tend to focus on qualitative data of fatigue on a simple Likert scale, rather than determining the underlying mechanisms surrounding CRF.

In order to appropriately assess fatigue experienced by clinical populations, it is critical to use a valid task as well as a valid measure of fatigability (Finsterer and Mahjoub, 2014; Kluger et al., 2013; Seyidova-Khoshknabi et al., 2010). The selection of the task may be made on the basis of current knowledge of the neurophysiology in the illness of interest and data derived from tasks in previous published studies and from healthy individuals. A general overview of neurophysiological methods as a means to quantify fatigue will

be presented (Sections 3.3.1, 3.3.2 and 3.3.3), in addition to a literature review of emerging objective (neurophysiological) methods to assess CRF (Section 3.2).

It is widely accepted that an increase in voluntary effort during prolonged performance of a submaximal motor task is indirectly indicated by an increase in electromyographic (EMG) signals (such as EMG amplitude, EMG power, median frequency) recorded from the performing muscles (Liu et al., 2003), with respect to force generating capacity. Where the state of the skeletal muscle is not known, it is possible EMG recordings may not necessarily provide a reliable indicator of variations in voluntary effort (discussed in chapter 9). With electroencephalography (EEG) signals, it is expected that activity would increase with increasing effort and fatigue during a motor task. However, recording the neural activity during prolonged submaximal motor task has not been routinely assessed to the same extent in CRF. Knowing how the brain modulates muscle fatigue may help explain why fatigue is so prevalent in patients with neurological disorders and CRF (Gandevia, 2001; Davis and Walsh, 2010; Chaudhuri and Behan, 2004). It may also help understand the neuropathology of CRF, as it is believed that underlying mechanisms may be central in origin (as detailed in Chapter 2).

In terms of assessing fatigue through neural signals both EEG (a method employed to measure neural electrical activity using surface electrodes placed on the scalp detailed in Section 3.3.2 (Halliday et al., 1998)) and magnetoencephalography (MEG) (Conway et al., 1995) have been used in conjunction with EMG (detailed in 3.3.1). MEG provides excellent spatial and temporal resolution; however, it is expensive to implement and is not widely clinically available. Examining brain activity through fMRI has been employed to investigate fatigue (Ancoli-Israel et al., 2005; Liu et al., 2007; Liu et al., 2003; Liu et al., 2005a). Both of these methods require a specially shielded room within a clinical environment. Initially, reports on analysis of the correlation between neural oscillations and motor output was limited to MEG (Conway et al., 1995) but Halliday and colleagues reported that EEG is equally effective at assessing neural activity during fatigue (Halliday et al., 1998).

Search Methods

A literature review was carried out in January 2015 and updated in April 2018.

The purpose of this literature review was to provide an up-to-date evaluation of the studies which focussed on assessing CRF that only incorporate EEG and/or EMG and CMC. It included some studies that have used CMC to study fatigue in other chronic illnesses to provide more information. A search of the electronic databases PubMed, Science Direct, and Scopus; accessed through the Trinity College Dublin and Our Lady's Hospice and Care Services network. A search from January 1st 1998 to January 31st 2018 was conducted; these dates were chosen as the number of relevant literature papers investigating cancer-related fatigue radically increased over the past 20 years. Searches were restricted to articles written in English, conducted on humans, in the last twenty years with full text available. Reference lists of relevant articles were also hand-searched. A subject librarian was consulted in order to identify and assign the appropriate search terms before beginning. Title and abstracts were searched for MeSH terms and keywords (Table 3-1) which included:

The databases listed below were used in carrying out this research, accessed through the Trinity College Dublin and Our Lady's Hospice and Care Services network:

- PubMed
- Scopus
- Science Direct

Table 3-1: MeSH terms and keywords used for literature search.

Electronic Database	Search Terms	
Medline via PubMed **Science Direct** **Scopus**	Medical Subject Headings (MeSH terms): • Neoplasm • Tumors • Tumor • Cancer • Cancers • Malignant Neoplasms • Malignant Neoplasm • Neoplasms/Fatigue • Neoplasm/Physiopathology • Central Fatigue • Peripheral Fatigue • Electromyography • Electroencephalography • Beta Rhythm • Lung Neoplasms/Drug therapy • Electroencephalography/methods • Fatigue/diagnosis • Humans • Neurologic Examination/methods • Fatigue/etiology • Fatigue/physiopathology • Neoplasms/complications • Electric Stimulation • Electromyography • Muscle Fatigue/physiology • Isometric Contraction/physiology • Neuromuscular Junction/physiology • Signal Processing	Keywords: • Cancer-Related Fatigue • Electromyography • Electroencephalography • Corticomuscular Coherence • Corticomuscular Coupling • EEG • EMG • CMC • Peripheral Fatigue • Central fatigue

Within the databases, the following search term combinations were used:

1. "Cancer" AND "Related" AND "Fatigue" AND "Central" AND/OR "Peripheral"
2. "Cancer" AND "Related" AND "Fatigue" AND "EMG"
3. "Cancer" AND "Related" AND "Fatigue" AND "EEG"
4. "Cancer" AND "Related" AND "Fatigue" AND "EEG" AND/OR "EMG"
5. "Cancer" AND "Related" AND "Fatigue" AND "Corticomuscular" AND "Coupling"
6. "Cancer" AND "Related" AND "Fatigue" AND "Corticomuscular" AND "Coherence"
7. "Corticomuscular" AND "Coherence"
8. "Corticomuscular" AND "Coupling"

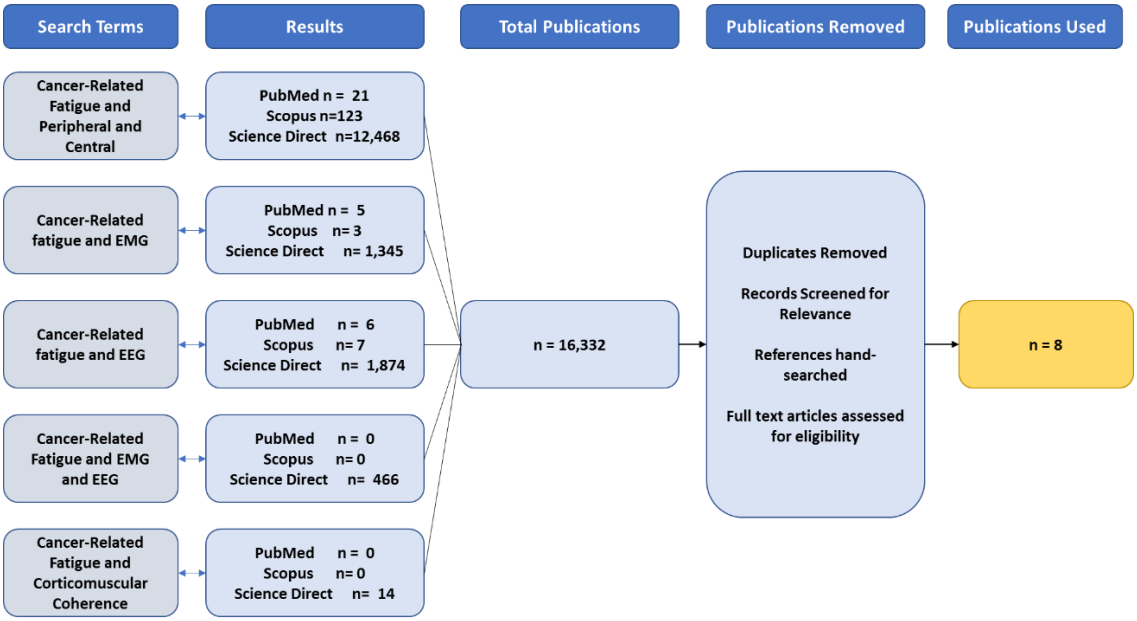


Figure 3-1: Literature review research methods; results of search terms

3.1.1 Results

This literature was to provide an overview of studies that employed an objective approach, of EEG and EMG to study CRF, in addition to outlining studies that employed corticomuscular coherence to study fatigue.

The search term ''cancer-related fatigue'' on its own was not used here as this is a broad term resulting in many publications with no relevance to project-specific questions in this case. The number of results that appeared in the initial search for "cancer-related fatigue" was 5,223 on PubMed, 9,916 on Scopus and 52,491 on Science Direct.

In order to narrow this to find literature that is particularly relevant to this research, other terms were added to the search, including MeSH terms (table 3-1, searches 2-8). No results appeared on Scopus or PubMed for searches 5-8 and while 466 results appeared on Science Direct, just 2 had relevance (two conference abstracts for CMC). The relevance to this study of each of the identified publications was assessed one by one by the author of this thesis. From the initial search for "cancer-related fatigue" AND "electroencephalography" AND/OR "electromyography" AND/OR "corticomuscular coherence", the results of this publication review process generates just eight publications with respect to the inclusion criteria, relevance to CRF only and removals of duplicates (Table 3-1). This includes two conference abstracts (within the one reference (Davis et al., 2011)). The earliest study was published in 2009 (Yavuzsen et al., 2009). Two of the eight publications are from the same research group (Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014) and four of the studies have authors in common (Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Yavuzsen et al., 2009; Cai et al., 2014). The only finding investigating CRF with CMC analysis is a conference abstract (Davis et al., 2011) which reported that CRF patients had significantly lower coherence which may have been caused by a pathophysiological impairment. In response to a query on this abstract, the lead author confirmed that no journal articles were published. Summaries of these papers can be found in Tables 3-2 and 3-3.

3.2 Neurophysiological Methods

Following the literature search, the neurophysiological methods (EMG, EEG, CMC) will be discussed in detail.

3.2.1 Electromyography

EMG is a method of recording and evaluating the electrical activity produced by muscles. This can be accomplished by either surface or needle EMG electrodes placed on or in the desired muscle body (Figure 3-1). EMG detects action potentials generated by muscle cells when these cells are electrically or neurologically activated.

Surface EMG (sEMG) can be recorded by a pair of electrodes or by a more complex multiple array. More than one electrode is needed as recordings display the potential

(voltage difference) between two electrodes with respect to a third ground. sEMG is used to detect both the magnitude of the action potentials and the firing rate or frequency at which they are generated. An increase in EMG amplitude is related to an increase in firing rate of action potentials of motor units, or the additional recruitment of motor units or a combination of both (Winter, 2009b; Kamen and Gabriel, 2010). The signal that is detected by surface EMG is of the order of millivolts, typically 0 to 10mV (peak-to-peak) and the usable energy of the signal is between 0 and 500Hz, in which the range 50-150Hz dominates (Luca, 1997; Luca, 2002). Electromyography (EMG) signals can be used for clinical and/or biomedical applications. In assessing fatigue there are several EMG parameters that are analysed such as the EMG amplitude, time, and a spectrum shift to lower frequencies.

Piper 1912, noticed a progressive ‘‘slowing’’ of the EMG signal during isometric voluntary sustained contractions, which consisted of a shift of the spectral components of the sEMG signals toward lower frequencies. Since then, many authors have used EMG to evaluate muscle fatigue. The amplitude of sEMG signals is influenced by the number of active motor units (Moritani et al., 1986), their discharge rates, and the shape and propagation velocity of the intracellular action potentials (Dimitrova and Dimitrov, 2002). sEMG amplitude has been reported to increase during submaximal isometric contractions and could decrease during maximal, however the relationship between amplitude and maximal force can vary depending on the fatiguing protocol.

Previous studies investigating CRF with EMG attempted to objectively measure the central and peripheral components of CRF. Studies have also reported an increase in EMG amplitude as fatigue progresses during a submaximal contraction task (Cai et al., 2014; Davis et al., 2011; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Yang et al., 2009; Yavuzsen et al., 2009). This may be accompanied by a shift in the mean and median frequencies of the power spectrum towards lower frequencies, arising from decreased firing rates, de-recruitment of motor units or both (Merletti et al., 1990; Vollestad, 1997; Merletti et al., 1984). Spectral analysis to determine the mean or median frequency shifts. The median frequency is thought to shift to lower frequencies as mentioned previously, however there are several different things that could contribute to this and so as mentioned, this should not be used to solely assess muscle fatigue. While the literature reports a power spectrum shift towards lower frequencies

following fatigue this may not always occur. Therefore caution is necessary when evaluating changes in the power spectra (Vollestad, 1997; Kisiel-Sajewicz et al., 2014). When central mechanisms are involved (due to impaired descending drive, reduced motor unit firing, alpha motor cord neuron firing or reduced motivation (Finsterer and Mahjoub, 2014; Davis and Walsh, 2010; Kisiel-Sajewicz et al., 2014) there is a change in the EMG parameters: decreased amplitude, altered spectral frequency and reduced density of interference pattern (interference pattern - where a single motor unit action potential cannot be distinguished from each other). Reduced amplitude at task failure, e.g. motor task indicates either loss of recruitment or synergistic activation of multiple muscles (Davis and Walsh, 2010; Finsterer and Mahjoub, 2014; Kisiel-Sajewicz et al., 2014). MVC (& endurance time); as mentioned previously, muscle fatigue has been defined as ‘‘any exercise-induced reduction in the capacity to generate force or power output’’. Therefore, force, power and torque have been used as direct measurements of muscle fatigue. This is not sensitive enough with sEMG alone and so several different parameters such as the aforemented, including endurance time and twitch force.
All of these parameters have been employed in previous studies and in these studies are have been shown to valid in assessing peripheral components fatiguing tasks.

Limitations of surface EMG are that they are restricted to superficial muscles, influenced by the site subcutaneous tissue depth (varies with body weight), and cannot discriminate between adjacent muscles. Of greater concern is the signal-to-noise (SNR) ratio and distortion of the signal. SNR is the ratio of energy between the signal and noise, where noise includes all electrical signals that are not part of the desired EMG signal. Distortion refers to the alteration of frequency components in the EMG signal. Major advantages of sEMG include providing an inexpensive, safe and non-invasive method that allows quantification of the muscle activity.

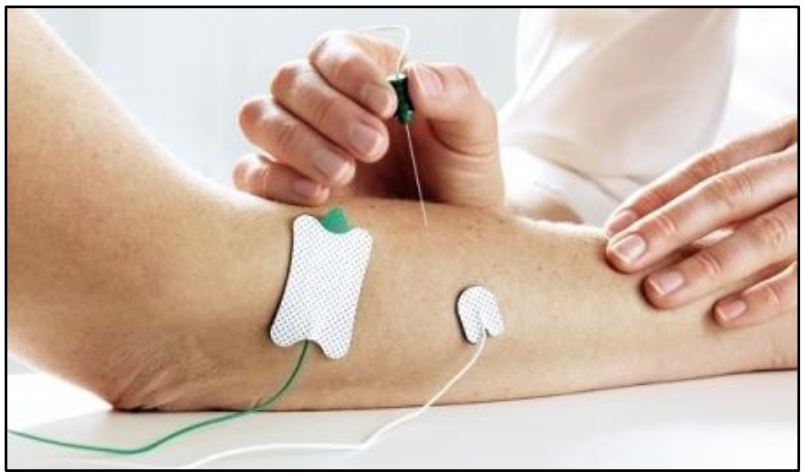


Figure 3-1: Surface and Needle EMG electrode
(Ambu® Neuroline, 2014)

3.2.2 Electroencephalography

Electroencephalography (EEG) is a method that is employed to measure neural electrical activity using surface electrodes placed on the scalp (Figure 3-2). It provides excellent temporal resolution of cortical activity, but poor spatial resolution as the signals detected originate from groups of thousands or even millions of pyramidal neurons (Niedermeyer, 2005; Davidson, 2000). These neurons are arranged perpendicular to the surface of the brain. As action potentials are transmitted along the lengths of the neurons, the signal detected is an average of the activity in that region. Furthermore, current falls off with the square of distance from the source and the signal picked up by the EEG electrode has to penetrate through several layers in the brain, skull and scalp. As a result, EEG is typically described in terms of rhythmic activity and categorised into the following frequency bands:

- Delta (Δ): 1-4Hz
- Theta (θ): 4-8Hz
- Alpha (α): 8-15Hz
- Mu (μ): 8-12Hz
- Beta (β): 15-35Hz
- Gamma (γ): >35Hz

In relation to fatigue, EEG can be used to monitor areas of activation or deactivation in the brain during a fatiguing task. As fatigue progresses, higher cortical activation is expected during a fatiguing task. The effects of CRF have been assessed employing the use of EEG. Moore and colleagues (Moore et al., 2014b) (Table 3-2) employed EEG to assess physical and mental fatigue associated with chemotherapy for breast cancer patients. Moore and colleagues (Moore et al., 2014b) and other previous published studies (Davis et al., 2011; Liu et al., 2007; Liu et al., 2003; Siemionow et al., 2004; Decker et al., 2009; Halliday et al., 1998) that employed EEG and fMRI and investigated other chronic illnesses reported an increase in neural activity and specifically EEG power in the Alpha and Beta bands with increasing fatigue. A disadvantage of employing EEG is that the signals are subject to contamination with artefacts like cardiac artefacts, eye blinks, facial movements, muscle-activation and interference from other electrical devices. However, EEG is an inexpensive, safe and non-invasive method which is less arduous for neural monitoring for the patient.

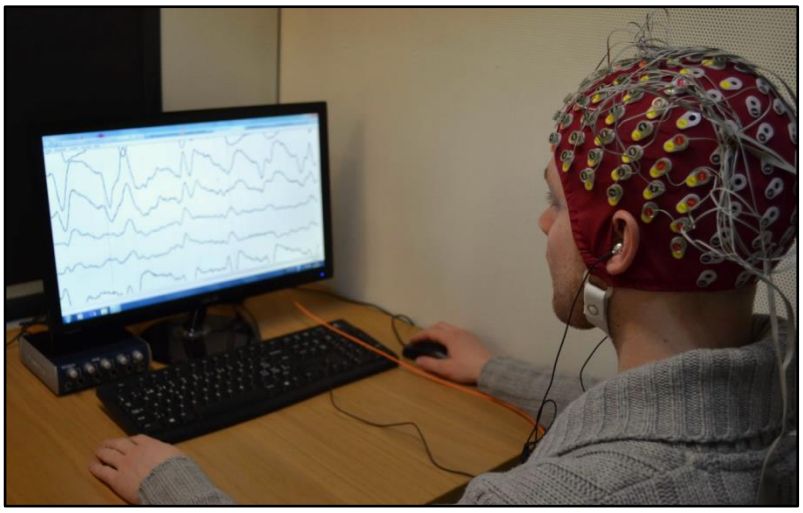


Figure 3-2: EEG 128-electrode Cap with electrical signals displayed on computer screen (Biosemi, 2018).

3.2.3 Corticomuscular Coherence Analysis

Voluntary motor activity is a result of cortical command driving muscle actions. Both neural and muscular malfunctions are believed to be involved in CRF and analysing the interactions between the central and peripheral nervous systems may assist in developing a theory on the underlying mechanisms. CMC is a method employed to study the cortical-muscle function coupling which reflects the interaction between the cerebral cortex and the muscle tissue which represents the correlation of cerebral cortex activity and muscle tissue activity. It is generally accepted that CMC reflects the communication between the brain and muscle which is considered to be related to controlling force and modulating fatigue and thus, reduced CMC may play a role in the cause of fatigue (Feige et al., 2000, Mima and Hallett, 1999, Yang et al., 2009).As mentioned, neuropathological mechanisms contributing to CRF are unknown, and with limited studies and knowledge makes CRF difficult to treat. Recent research has shown dissociation between changes in the brain and muscle signals during voluntary motor performance in cancer survivors with CRF, and this dissociation may be caused by an interruption in functional coupling of the two signals (Jiang et al; 2019; Yavuzsen et al., 2009).

One of the first studies to examine CMC, simultaneously recorded MEG over the sensorimotor cortex and EMG from contralateral hand muscles during sustained voluntary isometric contractions. Statistically significant coherence between the two signals was observed in the Beta frequency range (15-35Hz) (Conway et al., 1995). Measurements of coherence analysis have been employed in other studies with healthy individuals (Gwin and Ferris, 2012, Yang et al., 2010, Yang et al., 2009) and those with movement disorders, like amyotrophic lateral sclerosis (Proudfoot et al., 2018) multiple sclerosis (Tomasevic et al., 2012), Parkinson's disease (Salenius et al., 2002) and stroke (Mima et al., 2001). These studies demonstrated abnormal CMC within the Beta frequency band suggesting impaired communication between the brain and muscle during voluntary motor activity tasks.

Further, during a sustained contraction task, CRF patients reportedly show significantly lower CMC compared to healthy controls during minimal fatigue stage which may be caused by possible pathophysiological impairment in the patients. A study by Yang and

colleagues outlines that muscle fatigue impairs normal neuromuscular coherence, and that cancer patients with fatigue symptoms exhibit substantially weakened CMC, even without the influence of muscle fatigue (Yang et al., 2009).

The limited literature investigating EEG-EMG coherence in CRF demonstrates a reduced CMC and impaired neuromuscular junction propagation (signals from the central nervous system (proximal to NMJ) would undergo transmission difficulties distal to NMJ. This would lead to reduced functional corticomuscular coupling during voluntary muscle contraction. Impairment in NMJ propagation function in CRF contributes to diminished corticomuscular signal coupling during voluntary motor activities), particularly at the Beta frequency band (15-35 Hz) (Davis et al., 2011). While there is some inconsistency in interpreting the Beta and Gamma frequency bands in the literature, the consistent observation is that there is a decrease in the Beta frequency band with muscular fatigue. This Beta frequency band observation indicates reduced communication between the cortical output centres and voluntary activity of the muscles (Yang et al., 2009, Khoshknabi et al., 2008, Davis et al., 2011). CMC in CRF has the potential to be used as a biomarker. Weakening of corticomuscular coherence in those with cancer may be a major neural mechanism that contributes to muscle fatigue and associated performance impairment. Interventions that improve coherence could reduce fatigue, these may then be monitored during fatigue treatment to measure therapeutic efficacy.

3.2.4 Recent Relevant Neurophysiological Studies

Many studies in the literature examining cancer-related fatigue employ subjective measures and biologic measures as discussed in Chapter 2. The general experimental design most relevant to CRF used in the studies reviewed (Table 3-2, Table 3-3) concerning fatiguing tasks is either intermittent submaximal/maximal muscle contraction or sustained submaximal/maximal muscle contraction to exhaustion, with a handgrip or flexion. The common practice in the analysis of the data collected is to detect physiological and muscle output differences between the pre-fatigue and post-fatigue measurements (Tecchio et al., 2006; Yang et al., 2009; Yang et al., 2010; Cai et

al., 2014; Yavuzsen et al., 2009). Alternative analysis aims to compare block results after dividing the whole fatigue data into a number of relevant blocks (Peltier et al., 2005). However, in other neurological conditions fatigue is a progressive process; the ability of a muscle to generate force declines progressively with time during task performance. Therefore, it may be more appropriate to view the progression of fatigue in a sustained muscle contraction as a single trial task (Brown et al., 1999; Salenius et al., 1997; Yang et al., 2010).

The common finding in the studies involving CRF patients is that there is a lack of muscle contractile changes during fatigue by examining the results of EMG amplitude, mean power frequency and twitch interpolations (Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014). There is an initial low baseline for a number of measurements (such as maximal voluntary contraction, twitch force and endurance time for fatiguing tasks) when compared with healthy controls. These observations suggest a greater failure of the central nervous system as opposed to the peripheral nervous system, due to the results from additional force elicited by stimulation and EMG amplitude not increasing to the same extent as the healthy controls during the fatiguing tasks.

Table 3-2 and Table 3-3 show a summary of relevant studies to CRF and have been divided into two groups. The first table is focused on studies assessing fatigue employing EEG and/or EMG, and muscle stimulation within in healthy controls, CRF and chronic fatigue syndrome. The second table is focused on studies that assess fatigue through CMC analysis within healthy controls and CRF, and other neurological disorders. Studies employing CMC analysis with healthy controls and those with other chronic illnesses were reviewed as there is an extremely limited number of studies examining CRF. Reviewing and analysing these studies in terms of experimental set up, analysis of CMC and the type of data of produced can provide insight into how CMC may occur in those with cancer. In addition, it could help us adapt the methodology for CRF research and help us to identify what to expect when examining healthy controls in comparison to CRF, like in this research.

Those studies involving CRF patients were composed of mixed cancer cohorts, at different stages of disease and treatment. Therefore, within the cancer cohorts tested;

the type, stage and treatments may have had varying influences on the results reported.

Table 3-2: Summary of studies investigating fatigue with EEG, EMG, and/or Electrical Stimulation in healthy controls, cancer –related fatigue and chronic fatigue syndrome.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Central & Peripheral Contributions to Muscle Fatigue in Humans during Sustained Maximal Effort Kent-Braun et al 1999	9 Healthy Controls 4 Female 5 Male (30-32 years)	EMG and Electrical Stimulation. Three measures of central activation (central activation ratio (CAR) before and after exercise, MVC, and Changes in iEMG signals with CMAP amplitude). One measure of peripheral activation (compound muscle action potential, CMAP) were made using electromyography (EMG) and electrical stimulation. Foot was held firmly against a foot platform Sustained isometric contraction of *tibialis anterior muscle, Ankle Dorsiflexor* muscles at 30% MVC until subjective exhaustion	1) MVC, Mean Tetanic Force, Mean Twitch Force, and Twitch Contraction Time all decreased significantly. 2)The measures of central activation suggested some central fatigue during exercise. 3) Amplitude of CMAP did not fall significantly, indicating no significant failure of the neuromuscular excitability at the NMJ or muscle membrane during fatigue. 4) A significant decrease in EMG and lack of CMAP amplitude shows that central factors contributed to muscle fatigue during this motor task. Author Conclusion: The results indicated that isometric exercise results in fatigue that is attributable to both central and peripheral factors. Central

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
		tibialis anterior muscle, Ankle Dorsiflexor muscles Fatigue was quantitated as the fall in MVC	factors, which were not associated with altered peripheral excitability, contributed to approximately 20% of muscle fatigue, with the rest being attributable to intramuscular (i.e., metabolic) factors.
Altered Central Nervous System Signal during Motor Performance in Chronic Fatigue Syndrome Siemionow et al. 2004	CFS patients 3 Female 5 Male (43.1 ± 7.6 years) 8 Healthy Controls 3 Female 5 Male (2.3 ± 8.2 Years)	EMG and EEG *First Dorsal Interosseous, Flexor Digitorum Superficialis, Flexor Digitorium Profundus and contralateral Extensor Digitorium* muscles 2 tasks: Intermittent (right) handgrip contractions at 50% MVC (Non-fatigue task) Intermittent contractions (Fatigue task) Custom handgrip device connected to a pressure transducer	1) Motor performance of CFS was poorer than controls. 2) Relative power of EEG theta frequency band during both fatiguing and non fatiguing performances were significantly higher in CFS. 3) Motor activity-related cortical negative potential for combined tasks were higher in the CFS group. 4) Motor activity-related cortical negative potential was greater for the fatigue task than the non-fatigue task in CFS, No difference in controls.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
		Visual feedback was provided on oscilloscope	Results suggest that CFS patients are weaker and more easily fatigued than healthy individuals. Significance: Fatiguing physical activities that induce EEG signal changes may be used as physiological markers for a more objective diagnosis of CFS.
Cancer-Related Fatigue: Central or Peripheral? Yavuzen, et.al. 2009	16 CRF patients (advanced solid cancer) 9 Females 7 Males (48-81 years) 16 age-matched Controls 11 Females 5 Males (36-74 years)	EMG and Twitch Force BFI Questionnaire Sustained submaximal *elbow flexion* contraction at 30% MVC with upper arm *radial nerve* stimulation for twitch force and M-wave measurement Handgrip measured by force transducer Visual feedback was provided on oscilloscope	1) CRF patients exhibited higher BFI score and lower Endurance time. 2) CRF patients had greater TF with SC than controls, indicating central fatigue. 3) CRF group had lower M-wave amplitude indicating impaired neuromuscular junction conduction. Author Conclusion: Data suggested that CRF patients exhibited greater central fatigue, indicated by shorter ET and less voluntary muscle recruitment during a sustained contraction relative to controls.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Muscle Fatigue Changes in Bicep Brachii Muscle Twitch Force Properties in Controls but not in Cancer-Related Fatigue (Abstract Only) Davis, et.al. 2011	10 CRF patients (Advanced Solid Cancers) 12 Healthy Controls (No information on age)	EMG Twitch Force Stimulation Sustained submaximal elbow flexion contraction at 30% MVC of right arm Task terminated if contraction force dropped by 10% or more for longer than 3s *biceps brachii, brachioradialis, and tibialis anterior muscles*	1) Peak force, contract time and relaxation time reduced significantly in healthy controls but minimal in CRF. 2) Task failure caused by central fatigue than peripheral due to insignificant muscle fatigue. As there was no voluntary muscle activation involved with the electrical stimulation evoked muscle contraction, the measured TF parameters were pure muscle responses and their changes after S30 reflect effects of muscle fatigue. Significance: Minimal reductions in peak TF, CT, and HRT in CRF patients suggest task failure in CRF patients is due to central fatigue and less muscle fatigue.
Lack of Muscle Contractile Property Changes at the Time of	10 patients with advanced solid state cancer	EMG and Stimulation BFI Questionnaire	1) CRF patients reported significantly greater fatigue by BFI.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Perceived Physical Exhaustion Suggests Central Mechanisms Contributing to Early Motor Task Failure in Patients with Cancer-Related Fatigue Kisiel-Sajewicz, et al. 2012	(lung, breast, and gastrointestinal cancer); 7 Females 3 Males (59.9±10.6 years) 12 age-matched Controls 9 Females 1 Male (46.6±12.8 years)	Motor fatigue task with force transducer Sustained *elbow flexion* contraction of dominant arm at 30% MVC until exhaustion Visual feedback was provided on oscilloscope Muscle twitch force – electrical stimulation of biceps brachii muscle pre and post task Evaluated mild and severe fatigue *biceps brachii muscle*	2)CRF patients failed task sooner. 3) Muscle contractile parameters changed significantly in controls but not in CRF patients indicating central role for CRF patients. Author Conclusion: Results supports the perception that central fatigue may play a more significant role in limiting motor activities in CRF.
Myoelectrical Manifestation of Fatigue Less Prominent in	12 CRF patients with advanced solid cancer 8 Females	EMG and Stimulation BFI Questionnaire	1) CRF patients reported significantly greater fatigue. 2)CRF patients failed task sooner.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Patients with Cancer-Related Fatigue Kisiel-Sajewicz, et al. 2013	4 Males (48-81 years) 12 age-matched Controls 9 Females 3 Males (46-58 years)	Motor fatigue task with force transducer Sustained isometric *elbow flexion* at 30% MVC until subjective exhaustion. Termination of task if contraction force dropped below 10% for longer than 3s Visual feedback was provided on oscilloscope Muscle twitch force measured with electrical stimulation Evaluated mild and severe fatigue *biceps brachii muscle* *brachioradialis muscle*	2) Muscle contractile parameters changed significantly in controls but not in CRF patients. 3) CRF experience less myoelectrical manifestation of muscle fatigue suggesting a more significant central role. Author Conclusion: The sooner perceived physical exhaustion and the lack of prominent electromyographic changes during a prolonged, submaximal fatiguing motor task those with CRF suggest indirectly that central nervous system fatigue plays a more important role in limiting endurance-type motor performance.
Evidence of Significant Central Fatigue in Patients with CRF During Repetitive Elbow	10 CRF patients (advanced solid cancers) 7 Females 3 Males	EMG and Evoked Twitch Force BFI Questionnaire Motor fatigue task with force transducer	1) Higher subjective fatigue in CRF group than in controls. 2) Pre-IMT MVC lower in CRF group than in controls, MVC decreased for both groups from pre- to post-IMT.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Flexions Till Percieved Exhaustion Cai et al 2014	(48–82 years) 14 Healthy Controls 9 Females 5 Males (26–72 years)	Intermittent Motor Task: Repetitive isometric elbow flexion concentration of right arm at 40% until subjective exhaustion. If not fatigued: Sustained Contraction was carried out. Visual feedback was provided on oscilloscope Twitch force by electrical stimulation for assessment of peripheral fatigue *Biceps Brachii* Muscles	3) Lesser number of trials and shorter duration in CRF group than in controls. 4) TF_{ratio}: higher in CRF group than in controls – inability to recruit muscle fibers. Author Conclusion: Results support that CRF, more specifically, fatigue associated with motor performance is more of central rather than peripheral origin.
Electroencephalogram Power Changes as Correlates of Chemotherapy-Associated Fatigue and Cognitive Dysfunctions	8 CRF patients (breast cancer) (53 ±6 years) 8 age-matched Controls (54 ± 6 years)	EEG BFI Questionnaire BMF Questionnaire	1) Patients reported more subjective fatigue at baseline and increased during chemotherapy and did not entirely resolve by 1 year.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Moore et al 2014		3 Cognitive tests - Symbol Search and Digit Symbol-Coding tests, two nonverbal processing speed subtests of the Wechsler Adult Intelligence Scale-III Motor fatiguing task Sustained contraction of elbow flexion at 30 % MVC until subjective exhaustion Task terminated if force dropped by 10% or more for longer than 2s Fatigability was quantified as endurance time (ET) 3 measurements: After surgery at baseline (clinically cancer free), 3 Chemotherapy cycles in, 1 year recovery Subjects rated perceived effort during motor task (Borg 15-category scale)	2) EEG power increased after a physical task in patients during chemotherapy but not controls. 3) Subjective mental fatigue was similar for patients at baseline and 1 year but worsened during chemotherapy. 4) Patients performed similarly to controls on formal cognitive testing at all time points, but EEG activity after the cognitive task was increased in patients only during chemotherapy. Author Conclusions: The observed increase in EEG power during chemotherapy which also further increases during physical and mental tasks, suggests a more intense activation of neural structures associated with chemotherapy-related mental and physical fatigue.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
			Scalp EEG has potential as a novel and noninvasive means for measuring a correlate of mental and physical fatigue associated with chemotherapy.
Role of Central and Peripheral Muscle fatigue in Post-Cancer fatigue. A randomised controlled trial. Prinsen et al 2015	16 patients to Cognitive Behavioural Therapy (49.1±_ 8.6) 8 patients on waiting list (48.8 ± 10.9)	EMG and Twitch interpolation technique Muscle Fibre Conduction Velocity Check-List Individual Strength for fatigue severity Sustained contraction of *Biceps Brachii* muscle Handheld dynamometer	1) MFVC and CAF were not significantly different, between fatigued and non-fatigued. 2) Change scores of MFCV and CAF were not significantly different between patients in CBT and waiting list groups. 3) Patients in CBT group reported larger decrease in fatigue than waiting list group. Author Conclusion: Postcancer fatigue is neither characterized by abnormally high central muscle fatigue nor by low peripheral muscle fatigue. The results from this study suggest different underlying physiological mechanisms for postcancer fatigue vs. other fatigue syndromes.

Table 3-3: Summaries of studies investigating corticomuscular coherence using EEG-EMG, or MEG-EMG in healthy and cancer-related fatigue, and other neurological disorders.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Cortical Control of Human Motoneuron Firing During Isometric Contraction Salenius et al. 1997	6 Healthy Participants (right-handed) 3 Females 3 Males (22-34 years)	EMG and whole scalp MEG Isometric contraction of *first dorsal interosseous* (hand) muscle, *biceps brachii*, and *flexor halluces revis*(foot) muscle	1) Observed that cortical signals preceded motor unit firing by 12-53 ms. 2) Time lags increase with increasing corticomuscular distance. Results may suggest that the motor cortex, known to be involved in the initiation and alteration of movements, also influences the timing of motor units during maintained contractions. Author Conclusion: suggest that motor cortex drives spinal motoneuronal pool during sustained contractions; and cortical rhythmic activity influences timing of efferent commands
Coherent Cortical and Muscle Discharge in Cortical Myoclonus	8 patients with suspected Cortical Myoclonus	EEG and sEMG	Correlation between EEG and EMG during myoclonic activity indicating synchronization of muscle discharge and cortical activity in patients

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Brown et.al. 1999		(forearm, hand and foot) measurement performed during myoclonic activity to examine coherence	Six patients, significant coherence between contralateral EEG and EMG was observed in ranges similar to previously reported for normal subjects (15–30 and 30–60 Hz). Three out of these six had significant coherence at higher frequencies (up to 175Hz) Author Conclusion: Identified several frequency bands in which there may be coherence between EEG and EMG in those with cortical myoclonus. These activities may represent pathological exaggerations of physiological central rhythmicities related to movement.
Dynamic Synchronization between Multiple Cortical Motor Areas and Muscle	7 Healthy Participants 1 Female 6 Males	EEG and sEMG right flexor digitorum muscle	EEG-EMG synchronization in Beta frequency range (15-35Hz) during movement when attentional demands of motor task were higher.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Activity in Phasic Voluntary Movements Feige et.al. 2000	(29 - 47 years)	Rapid flexion followed by extension of the *right index finger* Participants were asked to pay attention to finish the rapid pulse movement towards end of task	During the movement execution a low-frequency (2–14 Hz) synchronization was found.
Coherence Between Cortical and Muscular Activities After Subcortical Stroke Mima et.al 2001	6 patients 1 Female 5 Males (53 - 72 years) With Chronic Right Hemiparesis (stroke –pure motor paresis after subcortical infarction)	EEG and EMG (earlobe reference) 3 tonic contraction power grip tasks- 1)elbow flexion 2)wrist extension, 3)power grip (20%MVC) using all digits; all on the affected(right) side Patients held a soft sponge ball in their task-performing hand Maximal grip power was measured with a force transducer *Flexor Carpi Radialis*, *Opponents Pollicis* and *First Dorsal Interosseous* muscles	1) EEG-EMG coherence was shown to be localized over the contralateral sensorimotor area with no significant coherence at ipsilateral side. 2) EEG-EMG coherence significantly smaller on the affected side for hand and forearm muscles but not for biceps suggesting that the central motor pathway is necessary for the generation of EEG-EMG coherence during tonic contraction. 3) The different effects of the lesion on the proximal and distal muscles appear to be associated with the strength of the corticospinal pathway.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Effects of attention and precision of exerted force on Beta range EEG-EMG synchronization during a maintained motor contraction task Kristeva-Fiege et.al 2002	10 Healthy Participants (Mean age 25.3 years)	EEG from the contralateral sensorimotor areas and sEMG Sustained motor contraction task at 8% MVC under conditions of 1) high precision 2) high precision, simultaneously performing arithmetic task 3)Low precision Fatiguing task was performed by pressing a force transducer with dominant index finger starting from complete relaxation. *Flexor digitorum superficialis* muscle	1)Amount of EEG-EMG Beta range(15-30Hz) synchronization decreased below 95% confidence level with reduction in attention 2)Frequency of beta range synchronization is higher with a higher level of precision but still lies within the beta frequency range (15–30 Hz).
Defective Cortical Drive to Muscle in Parkinson's Disease and its Improvement with Levodopa Salenius, et.al. 2002	8 Parkinson's Disease Patients 3 Females 5 Males (41-70 years) 8 age- matched ControlS	Whole scalp MEG and sEMG of forearm extensor muscles Moderate (~30% MVC) isometric muscle contraction of worst affected hand-wrist was extended to 30® against a plastic constraint while forearm rested on a flat surface	1) Prior to levodopa treatment, Parkinsonian patients showed a reduction in MEG-EMG coherence at 15-35 Hz compared to healthy subjects. 2) MEG-EMG coherence in patients observed at higher frequencies following levodopa medication.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
		1) before administration of levodopa medication & 2) 1 hour after medication.	
Cortical short-term fatigue effects assessed via rhythmic brain–muscle coherence Tecchio et al 2006	14 medication-free Healthy Participants 7 Females 7 Males (32±9)	Full-scalp MEG and EMG of ECD muscles Voluntary sustained isometric contraction (20-35% MVC) of *extensor communis digitorum* muscles during and post fatigue task. Left and right median nerves stimulation	1) MEG-EMG coherence in Beta band (13-32Hz) was higher after than before fatigue. 2) Reduction in EEG background activity during contraction with respect to rest/cerebral reactivity observed to be less evident after than before fatigue in Gamma (33-45 Hz) and Beta (15-35Hz) bands.
Gamma-Range Corticomuscular Coherence during Dynamic Force Output Omlor et.al. 2007	8 Healthy Participants 4 Female 4 Males (29±13 years)	NeuroscanEEG and EMG Visio-motor task, where subjects exerted a steady-state or periodically modulated isometric force output with their right-index finger to keep a visual cursor within target zone *pars indicis* of right *flexor digitorum superficialis* muscle.	1) In the static condition, significant coherence was confined to Beta-range. 2) During dynamic force corticospinal oscillation mode of the sensorimotor system shifts towards higher (principally gamma) frequencies for rapid integration of visual and somatosensory information required to produce appropriate motor command.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
On the Development of Human Corticospinal Oscillations: Age-Related Changes in EEG–EMG Coherence and Cumulant James et.al. 2008	48 Healthy right handed adults and children (2-59 years)	EEG and EMG Grasping movement and wrist extension of right (dominant) arm (extensor muscle)	1) Increase in EEG-EMG coherence between childhood, adolescence and adulthood. 2) Changes observed in cortical oscillatory drive (~20Hz) to human motoneurone pools during motor development.
Weakening of Functional Corticomuscular Coupling during Muscle Fatigue Yang et.al. 2009	9 Healthy Participants 6 Females 3 Males (26 - 38 years)	EEG and EMG Sustained isometric *elbow flexion* at 30% MVC until subjective exhaustion. Termination of task if contraction force dropped below 10% for longer than 3s 2 stages (minimal and severe fatigue)	1) The power of EEG and EMG separately increased significantly. 2) Coherence decreased in second stage of fatigue
Correlation between EEG-EMG Coherence during Isometric Contraction and its Imaginary Execution	13 Healthy Participants 2 Females	EEG and EMG 1)Motor task execution (ME)-Isometric right *tibialis anterior* muscle contraction	1) Significant EEG-EMG coherence increase during ME and MI within 14-30 Hz band.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Hashimoto et al 2010	11 Males (21–30 years)	2)Imagery of the movement(MI) without overt motor behaviour 3)Rest without MI	Conclusion: ME and MI involve overlapping neural networks.
EEG-EMG Signal Coherence Impaired in Cancer-Related Fatigue (Abstract Only) Davis et al. 2011	14 CRF patients (Advanced solid cancers) 14 age-matched Controls	EEG and EMG Sustained submaximal elbow flexion contraction at 30% MVC of right arm until subjective exhaustion - task ended if contraction force dropped by 10% or more for longer than 3s *biceps brachii musle* *tibialis anterior muscle*	1) Higher subjective fatigue in CRF group 2) Poor motor performance in CRF group 2) Motor fatigue is more central due to shorter endurance and twitch force
Weakening of Corticomuscualr Signal Coupling During Voluntary Motor Action in Aging Bayram et al 2015	28 Older and 28 Younger Individuals.	EEG and EMG *biceps brachii , brachioradialis and tibialis anterior* muscles 3 MVC tasks of *elbow flexion* at 20%, 50% and 80%.	1) Compared to younger subjects the older individuals exhibited significantly weakened at all force levels. 2) Proportional relationship between corticomuscular coherence and force both groups.

Title Author Year	Population involved in study	Measurements & Experimental paradigm	Results
Impaired Corticomuscular and Interhemispheric Cortical Beta Oscillation Coupling in Amyotrophic Lateral Sclerosis Proudfoot et al 2018	17 ALS patients 5 Females 12 Males (46-78 years) 11 Healthy Controls 3 Females 8 Males (41-84 years)	MEG and EMG Sustained contraction at 20% MVC until exhaustion Coherence recorded	During light voluntary muscular contraction, Beta-band corticomuscular coherence was significantly reduced in ALS patients compared to healthy controls Propagation of motoric Beta rhythms across the cortical hemispheres was also shown to be impaired in ALS patients

3.3 Discussion

To date, the underlying pathophysiology of CRF has not been adequately elucidated (Wang, 2008; Cai et al., 2014; Ryan et al., 2007). As discussed comprehensively in Chapter 2, a number of hypotheses regarding pathomechanisms of CRF have been proposed, these hypotheses have been largely based on evidence where fatigue is an intrinsic characteristic, such as in chronic fatigue syndrome and daily activity/exercise (Ryan et al., 2007; Wang, 2008; Wang and Woodruff, 2014; Saligan et al., 2015). While current assessment is mainly subjective, this provides limited insight into pathophysiology underlying fatigue. Objective assessments like surface electromyography (EMG) and electroencephalography (EEG) could enhance our understanding of muscle and cortical function in those with CRF. As demonstrated from this review (Table 3-2, Table 3-3) researching objective measures of CRF, there are very few studies (eight) that have evaluated the possible central and peripheral contributions to CRF induced by a specific task or condition in CRF such as muscle fatigue caused by a prolonged exercise. Previous objective CRF neuromuscular assessment have focused on EMG (Cai et al., 2014; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Yavuzsen et al., 2009;) and few studies incorporated cortical activity through EEG (Yang et al., 2009; Davis et al., 2011). In addition to this, the few previous EMG-EEG studies were confined to specialised hospital laboratories.

The general experimental design used in EEG, EMG and CMC studies of fatigue is either sustained or intermittent submaximal/maximal muscle contraction or sustained submaximal/maximal muscle contraction to exhaustion with handgrip, or flexion tasks, with the majority of studies using 30% MVC (which is representative of daily living activities (Cai et al., 2014)). The common practice in data analysis is to detect neurophysiological and muscle output differences between the pre-fatigue and post-fatigue measurements. It has been reported that altered neuromuscular conditions (including muscle fatigue or impaired endurance) with cancer may contribute to CRF. Table 3-2 is a summary of some relevant fatigue measurement studies (Table 3-2) (Yang, 2008; Yang et al., 2009; Cai et al., 2014; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al.,

2014; Moore et al., 2014a; Yavuzsen et al., 2009; Davis et al., 2011). In addition, employing an isometric contraction exercise is an advantage when using of EMG recordings due to reduced motion artefact in the EMG signal and is easier to standardise and administer within a weak patient group.

The reviewed publications (details can be found in Table 3-2, Table 3-3) demonstrated consistency in terms of concluding that CRF has more of a central rather than peripheral origin. The studies reviewed employed a validated subjective fatigue questionnaire (BFI) as a subjective measure of fatigue in CRF patients (as discussed in Section 1.4.2), with an objective method being EEG and/or EMG (discussed in Section 3.2). While four of the studies listed in Table 3-2 and Table 3-3 that investigated central and peripheral contribution to CRF, analysed the data from the same group of cancer participants (Kisiel-Sajewicz et al., 2014; Yang et al., 2009; Cai et al., 2014; Yavuzsen et al., 2009) which contained mixed, advanced cancers with patients undergoing different treatment regimens (Cai et al., 2014). While the population didn't change for each of these studies mentioned, Cai and colleagues (Cai et al., 2014) proved repeatability of the results, supporting the concept that CRF is more central in origin. In addition, these studies (Yang, 2008; Yang et al., 2009; Cai et al., 2014; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Moore et al., 2014a; Yavuzsen et al., 2009; Davis et al., 2011) employed similar methodology, with use of a motor fatigue task and isometric contractions, to test their hypotheses (refer to Section 3.2.4). The methodology and data analysis was not fully described in the conference abstract by Davis and colleagues (Davis et al., 2011).

Electrical muscle stimulation/twitch force is a brief, contractile response of a skeletal muscle. In the majority of studies examining CRF (as well as healthy and other chronic illness) force generated by electrical stimulation of the muscles was used as an indicator of force generating capability after exhaustion. The results reported from these studies were consistent, demonstrating that the fatigue was of a more central origin despite the mixed populations, muscle types and tasks employed in each study (i.e. sustained isometric elbow flexion, bicep contraction, handgrip) (Table 3-2) (Prinsen et al., 2014; Cai et al., 2014; Yavuzsen et al., 2009; Kent-Braun, 1999; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014). While electrical muscle stimulation/twitch force has an

advantage in terms of providing increased objectivity, by bypassing central mechanisms, it is invasive and may be painful for the patient. Overall, these studies prove that there is merit in this methodology but they should be repeated with larger sample sizes across specific populations to consolidate the findings.

The neural mechanisms behind fatigue and CRF are not well known. Two studies examining CRF employed EEG methodology, however the analysis methods of EEG processing for one of these sources ((Davis et al., 2011) is not reported (first author was contacted; no journal paper was published). However, within this abstract, a sustained elbow flexion contraction was used as the motor fatigue test. As mentioned, Moore and colleagues (Moore et al., 2014b), examined EEG power in those with CRF to investigate the hypothesis of central fatigue. The experimental design is laid out comprehensively, using a sustained elbow flexion contraction to exhaustion as a motor task and cognitive tasks. The results demonstrate statistical significance. This is an isolated study that conforms to the theory that CRF is central in origin. Although both of these studies involved small subject numbers, without EMG and twitch force, the results from both continue to support the central hypothesis.

As discussed, CMC analysis is often employed in research and reported in the literature to examine central and peripheral contributions to muscle fatigue. A summary of literature investigating CMC analysis is included (Table 3-3). No studies examining CRF specifically employing this methodology were encountered during the review in section 3.2.4, Table 3-3, apart from a conference abstract (Davis et al., 2011). This abstract does not contain sufficient information for an in-depth evaluation of the CMC analysis. Due to the lack of studies examining CRF with CMC analysis, reviewing and including other studies that employed CMC analysis provided a means to increase the understanding of the methodologies used in healthy individuals and in those who have fatigue from other illnesses. This in turn may provide us with insight as to how CMC may occur in those with cancer, in addition to helping us adapt methodology for CRF research. These studies demonstrate that CMC analysis may provide additional information on central and peripheral aspects of CRF, it was necessary to summarise other studies that use CMC analysis to evaluate muscle fatigue in healthy individuals and other chronic illnesses

(Table 3-3). These studies used similar methodologies employing EEG and EMG with a sustained or intermittent submaximal isometric contraction and results showed that coherence in those with chronic illnesses was significantly reduced in comparison to healthy individuals, particularly at the Beta frequency band during a 30% MVC motor task. Useful information that arises from the previous studies included, that investigate CMC is that in examining healthy people, corticomuscular coherence weakens with fatigue (Yang et al., 2009). It also reduces with age and increases with contraction strengths (Bayram et al., 2015). As this thesis analyses data over a range of ages, this result should be taken into consideration.

For example, examining CMC in those with stroke demonstrated that EEG-EMG coherence was significantly smaller on the affected side (Mima et al., 2001).

It is evident from studies of other chronic illnesses and healthy individuals that EEG and EMG methods show promising opportunities to objectively evaluate fatigue in CRF patients, with CMC analysis facilitating the investigation of the central and peripheral contributions of CRF and establishing a variation in the pattern of fatigue. There have been reports of larger discrepancy between central and peripheral fatigue and greater impairment in neuromuscular junction transmission function in CRF than controls (Yavuzsen et al., 2009; Davis et al., 2011; Yang, 2008). The methodology used to derive these conclusions were endurance time, twitch force and electrical muscle stimulation. Measuring twitch force during a sustained contraction is a standard physiological method of assessing central fatigue. These demonstrated that CRF patients exhibited greater central fatigue indicated by their shorter ET and less voluntary muscle recruitment due to greater twitch force response in comparison to controls. The impaired NMJ function may explain some of the differences in muscle fatigue between the CRF and healthy groups; central signals would be inefficiently transmitted across the NMJ and thus the muscle would be incompletely recruited, this impairment could have shortened the ET times (Yavuzsen et al., 2009; Davis et al., 2011; Yang, 2008).

Therefore, it could be argued that corticomuscular coherence is weakened in CRF, which may be the result of possible pathophysiological impairment, such an impaired NMJ. Distinguishing the CMC pattern, along with EEG and EMG patterns in CRF patients and

with healthy controls would help develop a better understanding of the CRF pathomechanisms and contribute to identification of neurophysiological markers of CRF. As mentioned previously, weakening of corticomuscular coherence in those with cancer may be a major neural mechanism that contributes to muscle fatigue and associated performance impairment. Understanding this phenomenon would help better elucidate fatigue mechanisms and develop therapies for treating the vast fatigue symptoms in clinical populations. Interventions that improve coherence could reduce fatigue. In addition, as CMC is a non-invasive measure of corticomotorneuronal function, clinical application is likely. The advantage of employing similar methodology and data analysis could lead to the future development of a standard diagnosis and multisite testing protocol for CRF.

As a result of the literature reviews conducted, the majority of studies have been conducted in a research lab and thus, the appropriate task that was envisaged for this research into CRF would be based on clinical utility, and to help investigate fatigue without the confound of treatment induced fatigue in a clinical setting with minimal intrusion. As discussed in Chapter 2.8 it is hypothesised that CRF had both central and peripheral manifestations and it is possible to assess objective correlates of fatigue using neurophysiological methods like EMG, and/or EEG. As EEG measures cortical activity and EMG measures electrical impulses within the muscle; the data provided by recording EEG and EEG simultaneously should provide specific data which in turn can be analysed when examining the central and peripheral hypothesis.

Therefore, the use of portable and non-invasive EMG (to assess muscle activity), EEG (to assess temporal representation of brain activity) and handgrip elements was important in order ease of use, for both patients and clinicians and to reduce patient burden, with a subjective comparison (e.g. BFI). The novelty of this research is that it is going to recruit only non-small cell lung cancer patients, prior to any cancer treatment. It is believed that this is the first attempt to characterise the EEG, EMG and coherence profile in this cohort, and thus characterise the physiological pattern due to the disease alone, without the confounder of treatment.

The discussion of CRF in this literature review considered the challenges of the assessment, measurement and definition of CRF. It is difficult to measure something that is not directly measurable although its existence is inferred by other facts. As previously mentioned, many publications (Radbruch et al., 2008; Bower et al., 2014; Seyidova-Khoshknabi et al., 2010; Stone and Minton, 2008), suggest that there is no universally agreed definition of fatigue. It may be suggested that the concept of fatigue of itself cannot be measured but symptoms, similar to those outlined in 7-1 b, could be regarded as facts from which it can be inferred that fatigue exists.
So, it could be asked as to whether the development of reference fatigue measures employable in examining illnesses according to the specific features of that illness, may contribute to the operationalisation of the fatigue concept. The fatigue concept could be subdivided into variables for instance; health: is there a defined healthy control level of fatigue; age: what elements of healthy control baseline levels of fatigue increase/decrease with age; illness: is there a range of standard methods of measuring fatigue which could be used in whole or in part by clinicians to measure fatigue in line with the particular illness they are treating, in this context cancer and CRF. If this or any other developed approach was considered for fatigue then it's operationalisation may provide a foundation for a standard approach to fatigue research, measurement and treatment.

3.4 Conclusion

Following a thorough review of the literature to date it is clear that there is a lack of objective measures of CRF. This could be due to the multifactorial pathophysiology of CRF. There have been a limited number of studies that have investigated possible measures to assess CRF. A means of quantifying CRF may provide additional data which clinicians could utilise in devising treatments for CRF sufferers' in addition to using subjective questionnaires. For example, use of biological markers (cytokine and cortisol levels) and neuromuscular function by EMG and twitch force stimulation, EEG, and CMC

analysis (Mitchell, 2010; Yavuzsen et al., 2009; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Cai et al., 2014; Saligan et al., 2015; Berger et al., 2015a; Berger et al., 2015b). However, the underlying pathophysiology for CRF is still unknown. As a result, CRF remains an untreated and distressing symptom for the patient. In order to improve the patient's quality of life and treatment of symptoms, an objective measure of CRF needs to be developed. If there is an objective measure developed, it will may allow clinicians to follow the natural trajectory of fatigue and to observe if existing treatment options are improving symptoms and the patient's feelings of fatigue.

In the meantime, the existing knowledge on peripheral and central fatigue during fatiguing motor tasks can be applied to cancer-related fatigue in an effort to discover the aetiologies specific to this disease. This research will focus on designing a task and set up to assess CRF that is portable and can be performed in the outpatient clinical setting, as opposed to requiring already heavily-burdened patients to attend a specialist laboratory.

Chapter 4 will introduce the research hypotheses and outline a number of relevant research questions resulting from this literature review.

Chapter 3 Summary Points

- Cancer-related fatigue is a complex symptom that is associated with activities all along the motor pathway from the brain to the muscle.
- Clinicians and researchers are recognizing that cancer-related fatigue is a significance consequence of cancer and its treatment that requires more clinical attention and intervention.
- A thorough review of the literature to date demonstrates that there is a lack of objective measures of cancer-related fatigue.
- Few studies have evaluated peripheral and central contributions to cancer-related fatigue.
- The general experimental design used in these studies of fatigue is either sustained or intermittent submaximal/maximal muscle contraction or sustained submaximal/maximal muscle contraction with handgrip or elbow flexion to exhaustion.
- The underlying pathophysiology for cancer-related fatigue is still unknown. As a result, cancer-related fatigue remains an untreated and distressing symptom for the patient.
- In order to improve patient's quality of life and treatment of symptoms, an objective measure of cancer-related fatigue needs to be developed.

Chapter 4: THESIS RESEARCH QUESTIONS AND HYPOTHESES

4.1 Introduction

As outlined in Chapter 3, it is possible that neurophysiological measures may be employed in the objective evaluation of Cancer Related Fatigue. In previous studies, neurophysiological assessments were only undertaken in specialised laboratories. This is not practical for longer studies and it would increase the burden on seriously ill cancer patients. An objective assessment of CRF that is easily administered in the routine clinical outpatient setting would eradicate any additional stress.

If an accepted quantifiable measure of CRF is developed, this would further our understanding of the possible underlying aetiology and pathophysiology and aid in the development of a clinical solution for CRF intervention.

4.2 Research Goals

The aim of the research is to objectively assess possible central and peripheral correlates of CRF during a fatigue inducing motor task in a clinical outpatient setting to address gaps in the current knowledge about relative contribution of central and peripheral mechanisms to CRF.

The primary focus of this research is on designing objective methodology employing neurophysiology to assess objective correlates of CRF which can be performed in an outpatient clinic and validated in a cohort of cancer patients. As discussed in Section 3.4, the novelty of this research is to recruit only non-small cell lung cancer patients, prior to any cancer treatment, and to undertake the assessment in a routine outpatient clinic.

It is believed that this is the first attempt to characterise the EEG, EMG and coherence profile in this cohort, and to describe the physiological pattern due to the disease alone, without the confounder of treatment induced fatigue, in order to gather a baseline of CRF manifestation.

4.3 Research Questions

The review of the literature leads to a number of questions that remain to be addressed to understand pathophysiology and lead to an objective measure of CRF.

4.3.1 General Questions

1. Is CRF of central or peripheral origin?
2. Can neurophysiological methods be employed as a robust objective measure of CRF?
3. By removing treatment as a confounder and by focusing on pre-treatment CRF patients, is there a comparison with previous published studies?
4. What are the changes that occur during fatigue and can these be measured by neurophysiology methods?
5. What analytical methods allow us to acquire neurophysiological data?
6. Is employing the BFI as a effective subjective method, an appropriate comparator of the development of an objective measure?
7. Is there an appropriate comparison cohort against which it is possible to analyse the results of CRF cohort?

4.3.2 Specific Questions

8. Is hand dynamometer an adequately reliable device for measurement of force application and force variation for fatigue analysis?
9. Can the hand dynamometer alone assess fatigue?
10. Are the participants providing maximum effort during the hand dynamometer task? Is it possible to assess this objectively?
11. Can participants' sustained focus be objectively measured during a sustained motor contraction task using EEG and EMG?
12. Which muscle groups in the forearm can be used in a clinical setting to obtain EMG signals?
13. Do the endurance time, maximal voluntary contraction, EMG characteristics, and EEG power differ significantly between cancer patients and healthy controls?
14. What is the level of EEG-EMG device acceptability from the patient's perspective?

15. What proportion of CRF is due to insufficient activation of motor drive, as opposed to failure of the contractile muscle properties?
16. What specific frequency bands of the EEG signal generate the most significant relationship with fatigue?
17. Where is the source of the EEG signal activity at the beginning of a motor task and how does it change with the progression of fatigue?
18. Is CMC analysis an appropriate method of objectively quantifying CRF?
19. Can a neurophysiological assessment be drawn between two patient groups?
20. Is there a statistically significant correlation between subjective and objective measures of CRF?

4.4 Research Outline

To address these questions, this research is organised into a number of studies which focus on the development of objective methods to evaluate CRF.

Chapter 5 introduces the development of the experimental methods, its protocol of use and validation of data that was carried out in order to acquire the neurophysiological data for all studies and will attempt to answer questions 21-5, 8, 13, 14, and 16-19. Chapter 6 reports a comparison study in objective measurement of fatigue in cancer and chronic fatigue syndrome patients compared to healthy controls and attempts to answer questions 1-3,7, 12, 13, and 15-19. Chapter 7 examines the use of a handgrip assessment alone against a subjective assessment of CRF and will attempt to answer questions 6-9, and 20. Chapter 8 discusses a retrospective analysis of FrontoMedial Theta for assessment of attentional vigilance during the fatiguing task with an aim to answer questions 7 and 10. Finally, chapter 9 presents the main findings from this research along with a discussion of its clinical impact. In addition, the limitations, followed by recommendations for future research are examined in order to further enhance knowledge and use of objective assessment of CRF.

These studies involved a close collaboration between the Trinity Centre for Bioengineering in Trinity College Dublin, clinicians in Our Lady's Hospice, Harold's Cross, St. Vincent's University Hospital, Dublin and St. James Hospital, Dublin.

Chapter 5: EXPERIMENTAL SET UP, PROTOCOL TESTING & COMPLETION OF STUDY 1

STUDY 1

Validation, Reliability and Quantification of Cancer-Related Fatigue with Neurophysiological Methods in an Outpatient Setting.

This study has been published as an abstract in the Journal of Supportive Care in Cancer (Volume 25, supplement 2, June 2017) and presented at the following international conferences (Appendix B):

Multinational Association of Supportive Care Cancer *(MASCC) June 2017*

(Journal of Supportive Care in Cancer (Volume 25, supplement 2, June 2017)

European Association of Palliative Care Research Network *(EAPC RN) October 2016*

The Annual Irish Association for Palliative Care *(IAPC) 2016*

5.1 Introduction

While various experimental tasks have been employed to study CRF, only a limited number of studies examined CRF employing neurophysiological methods (Chapter 3) with mixed types of advanced cancer in their patient cohorts and at different stages of treatment. In addition, these studies did not exclude aspects like the impact of treatment-induced fatigue (Yavuzsen et al., 2009; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Cai et al., 2014; Moore et al., 2014a; Davis et al., 2011). At diagnosis, the causes of fatigue are reduced to only the effects of the cancer and possible emotional distress, otherwise known as “sixth vital sign” in cancer care (Conley et al., 2016). Therefore to conclusively understand CRF, a standardised task which can provide an objective measure of fatigue must be developed. Thus, the aim of this study was twofold: to design an experimental setup for and to demonstrate the use of neurophysiological methods for fatigue in a clinical setting of an oncology day ward. This chapter develops such a task and validates it on a small cohort of CRF participants and aims to answer research questions 1-8 (Chapter 4, Section 4.3).

5.2 Experimental Design and Set Up

The objective assessment of CRF using neurophysiological methods and a standard motor fatiguing task may provide additional information in the quantification of the role of central and peripheral mechanisms in CRF (Yavuzsen et al., 2009; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Cai et al., 2014; Moore et al., 2014a; Davis et al., 2011). Following the review of available literature and consulting medical professionals (OLHCC & SVUH), a fatigue-inducing motor task was designed for the target patient group (O'Connor, 2016; Markicevic, 2015).

5.2.1 Participant Recruitment

5.2.1.1 Non-Small Cell Lung Cancer Patients

Ten pre-treatment (Chemotherapy/Radiotherapy/Biological Modifiers) and pre-surgery participants with NSCLC were recruited (Table 5-1). Recruitment of newly diagnosed,

pre-treatment patients took place in St James's University Hospital (SJH) and St Vincent's University Hospital Groups (SVUH) between November 2014 and August 2017. All patients recruited were right hand dominant.

All patients were assessed for fatigue by their oncology physician, screened for depression and had an Eastern Cooperative Oncology Group (ECOG) score of less than 2 (Appendix B). In order to be able to perform a motor task, a certain level of physical strength was required. Prior to a treatment decision, the overall physical functioning of the patient was evaluated by their oncology physician (ECOG Score) to ensure patients were strong enough to cope with the possible side-effects of cancer treatment. ECOG of 2 or less was chosen as it is the usual cut-off score for chemotherapy and ensured that patients were well enough for study participation. Informed consent was obtained from all participants prior to testing. Of the 12 CRF participants recruited, 10 participated in the study (Figure 5-1 and Table 5-1) and experimental BFI, EMG and EEG data was obtained.

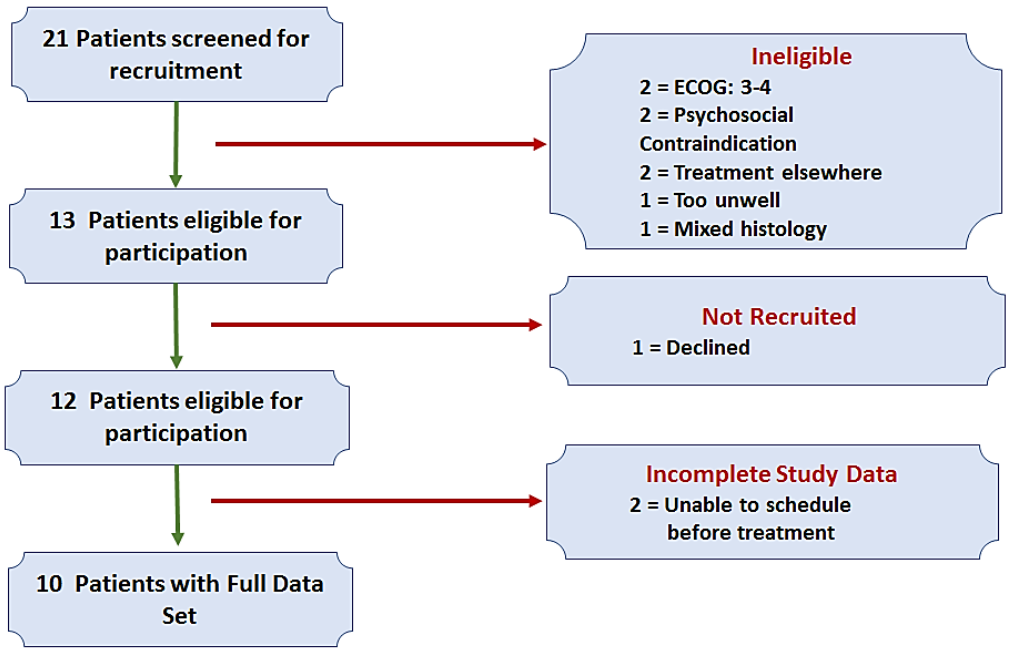


Figure 5-1: Flowchart of recruitment for cancer-related fatigue participants.

Table 5-1: Details of the CRF patients who underwent the testing

Recording took place in St. Vincent's University Hospital and St. James Hospital.

Patient Study Number	Age	Gender	ECOG Score
CFP1	48	F	1
CFP2	78	M	1
CFP3	58	F	1
CFP4	65	M	1
CFP5	77	F	0
CFP6	77	F	1
CFP7	50	F	1
CFP8	60	F	2
CFP9	54	M	1
CFP10	73	M	0

5.2.1.2 Healthy Control Participants

Data from control participants (Table 5-2) for this study were acquired in St. Vincent's University Hospital and the Trinity Centre for Bioengineering, Trinity College Dublin (TCD). Ten healthy controls were recruited to obtain experimental BFI, EMG and EEG data. All data analysis was conducted offline.

It is important to note that participants for this study were not age matched as this was a preliminary study in order to test the set up and protocol. This will be discussed later in this chapter (Section 5.6).

Table 5-2: Details of the healthy control participants
Recording took place in Trinity College Dublin.

Participant Study Number	Age	Gender
CFV26	26	M
CFV27	30	F
CFV28	25	M
CFV29	27	M
CFV30	24	F
CFV31	26	M
CFV32	25	F
CFV33	26	M
CFV34	22	M
CFV35	50	M

5.2.2 Ethical Implications

The possible ethical implications involved in this study were systematically identified and addressed, in consultation with healthcare professionals from Our Lady's Hospice and Care Services, Dublin and St. Vincent's University Hospital, Dublin. Ethics approval was obtained from St. Vincent's Healthcare Group Ethics and Medical Research Committee, St. James' Hospital and Trinity Health Sciences Ethics board. The Ethics approval documents are attached in Appendix B. The main ethical concern was the acquisition of physiological signal data from the study participants. Given the nature of data collection and transmission, protection of participant privacy is essential.

5.2.3 Informed Consent and Privacy

During the recruitment of cancer patients, only participants with the ability to provide informed consent were selected to participate in this study.

The privacy of the data collected and the anonymity of the results were respected throughout the study to ensure that each participant was comfortable with how their information would be managed in accordance with the Data Protection Legislation.
Data from the fatigue questionnaires and physiological measurement data (EEG, EMG and grip force values) were stored anonymously. All hard copies of data were securely stored and locked. All digital data is identifiable only by the study number and stored on a password protected hard drive.

5.3 Assembly and Validation of Measurement Set Up (Hardware and Software Set Up)

5.3.1 Motor Fatiguing Task: Isometric Muscle Contraction

All participants performed a fatigue-inducing motor task consisting of a sustained isometric contraction at 30% of their maximal force using a hand-held dynamometer (Figure 5-3, Figure 5-6), while EMG and EEG were simultaneously recorded (Figure). Therefore, a multi-unit system was developed (Figure 5-2). A crucial requirement in order to allow data analysis was to ensure synchronised recording of EMG and EEG signals.

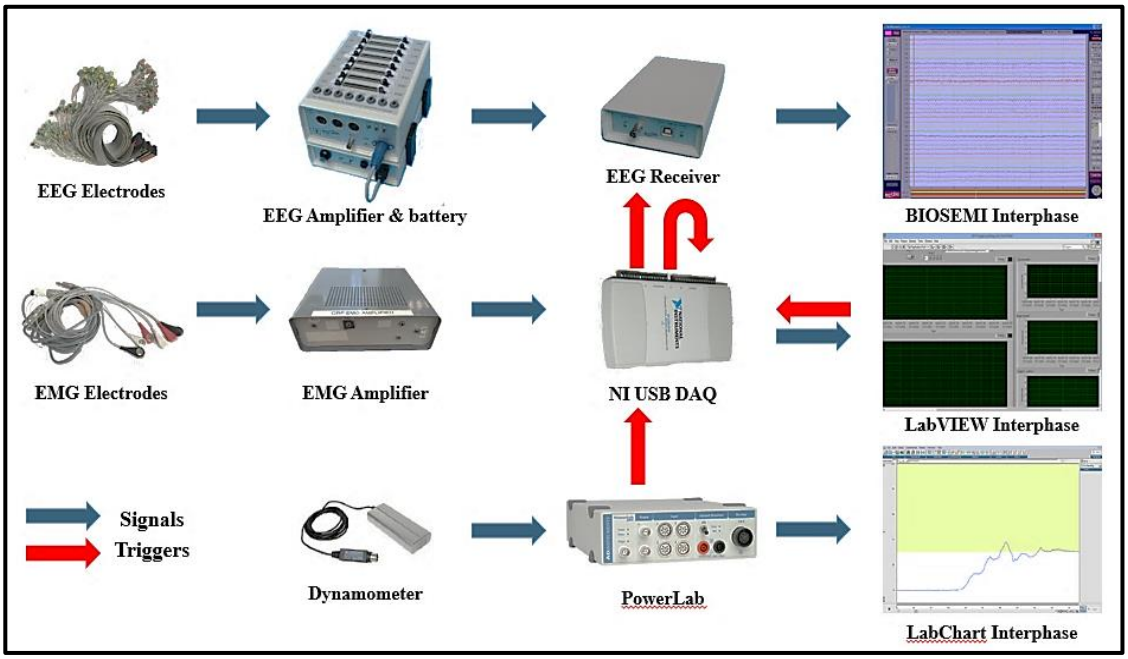


Figure 5-2: Data Acquisition setup for this experiment.

To assist in synchronisation, a series of time-locked pulses were sent from the PowerLab to a National Instruments Data Acquisition (NI DAQ), which then sent time-locked synchronisation pulses to the USB EEG Receiver. Time-locking synchronisation pulses are also looped back from the NI DAQ output terminal to the input terminal to ensure the pulses are saved in the LabVIEW file containing EMG data.

The recording setup comprised of three main steps, which are explained below in the following order:

1. Dynamometer and Force Data Acquisition
2. Arm Restraint
3. EMG acquisition
4. EEG acquisition

5.3.2 Dynamometer and Force Data Acquisition

A strain gauge hand-held dynamometer (MLT004/ST grip force transducer by AD Instruments (ADI)) in conjunction with an ADI Powerlab was employed to record the MVC for each participant (Figure 5-3). The experimental system was designed to provide

real-time feedback of this data (Figure 5-4) to study participants in an intuitive manner. Force data was recorded using ADIs LabChart software. Participants received visual feedback through a Graphic User Interface implemented through the software, which provided them with real-time data to maintain target force.

ADI LabChart and PowerLab software were programmed for the following stages of the fatigue task:

1. Computation of MVC before the task began;
2. Generation of visual feedback, while performing the task (as shown In Figure 5-4), of a reference line for the 30% MVC value was created by a continuous force indication.
3. Detection of changes in the force values during the sustained grip task was used to initiate the time-locking pulses of the simultaneously recorded EMG and EEG data.
4. Generation of pulses sent to the LabVIEW system to synchronize the EEG and EMG acquisition
5. Generation of sound cues (beeps) at two stages: firstly, to prompt the participant to relax after the force value dropped below 10% of the sustained force, then to indicate completion of the test.

   In the design a horizontal line indicated the target force and the area above this line was coloured to account for anyone who may be colour-blind (Figure 5-4).

Figure 5-3: Dynamometer used in conjunction with AD Instruments Powerlab for fatigue task

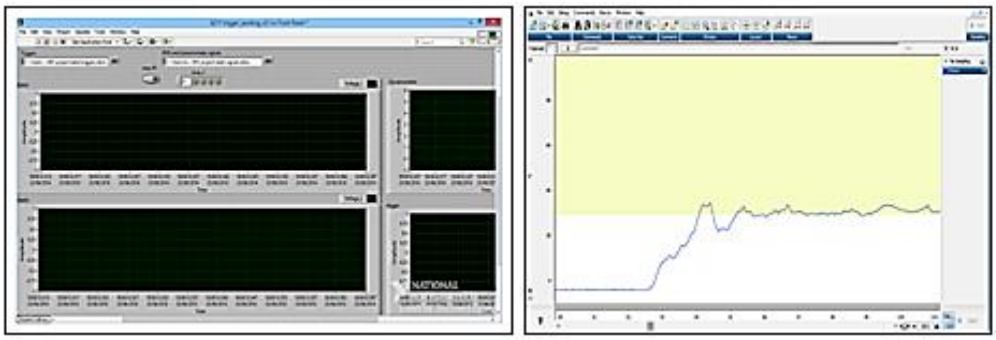


Figure 5-4: LabChart (task screen) and LabVIEW interface.

Real-time output as subject reaches the 30% target force at the beginning of the sustained contraction. Dynamometer output is indicated by the blue points.

In addition to acquiring and digitising grip force readings, the ADI PowerLab was configured to initiate the generation of pulses at various time intervals during the experiment:

1. At the beginning of the experiment, 30 seconds of the data was recorded before initiation of the motor task. During those 30 seconds a 3V analog pulse was generated every second (Figure 5-5).
2. Once 30% force level was reached, a 5V analog pulse was generated every two seconds and sent during the entire length of the motor task (Figure 5-5).
3. At the end of the motor task, when the participant fails to maintain a target force above 27% MVC for longer than three seconds, a 3V analog pulse was generated every five seconds for the next three minutes (Figure 5-5).

These thresholds included instances when the participant first reached 30% MVC and when the participant failed to maintain the target force above 27% MVC for longer than three seconds. The pulses and force data were recorded in the LabChart files and exported to Matlab for offline processing.

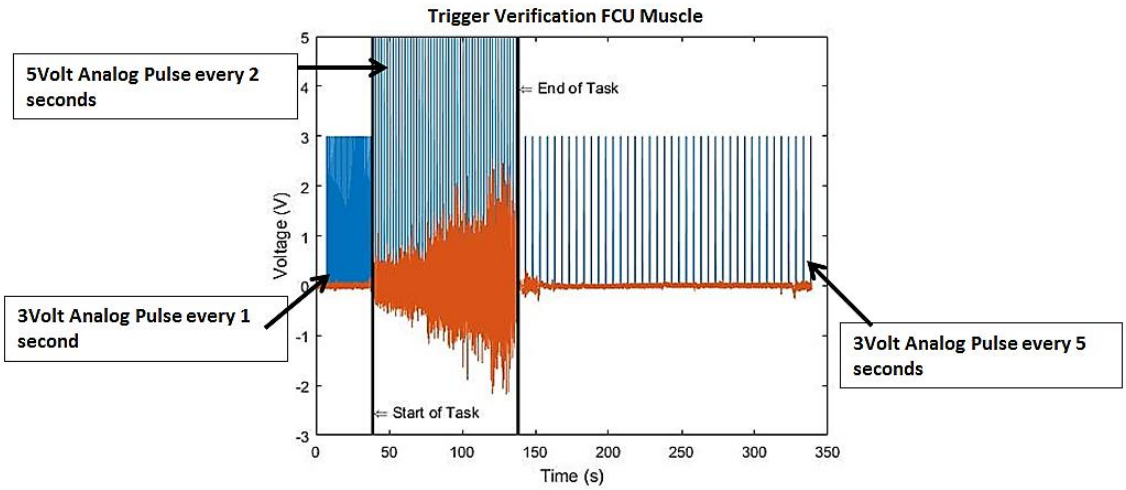


Figure 5-5: Raw EMG signal during task.

Pulses (blue) are 3V before and after the task and 5V during the task. EMG signal (red) amplitude is used to visually verify the start and end times of the task. The pulses of interest (black) are shown (start and end of task).

5.3.3 Arm Restraint

A form of arm restraint was developed for the experiment, which consisted of a gutter arm rest clamped to a height adjustable table (Figure 5-6) and was secured around the wrist and near the elbow joint. The restraint served two purposes:

1. To stabilise the arm and maintain it in the same position throughout the sustained contraction ensuring that the muscles are isometric throughout the test. It was also important to stabilise the wrist in a neutral position as changes in wrist posture can shorten and lengthen the muscles affecting the geometry of forearm muscles and altering the EMG signals (Roman-Liu et al., 2013).
2. Movement of the arm would introduce artefact into the EMG signals due to movement at the electrode site, or of the electrode cables. Localising the arm reduced variation between tests and allowed for repeatability and objectivity.

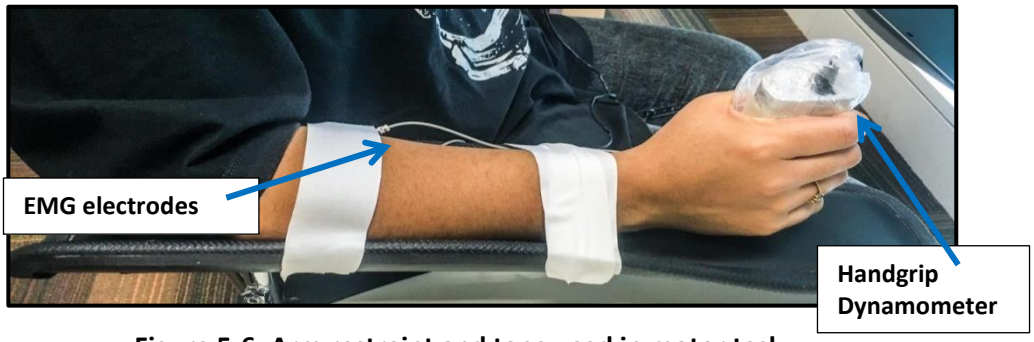


Figure 5-6: Arm restraint and tape used in motor task

5.3.4 EMG Acquisition

Surface EMG was recorded using bipolar surface electrodes. Disposable adhesive surface electrodes containing AgCl electrolyte, were used (25mmx20mm; SDENIS01520, Unimed®). Two channels were placed on the forearm muscles; flexor carpi radialis (FCR) and flexor carpi ulnaris (FCU), which were identified by palpitation of the arm while participants flexed and extended the appropriate fingers (Figure 5-7).

Reviewing available publications it can be suggested that there is little satisfactory research when it comes to the question how to place electrodes in a best way in order to acquire surface EMG signals during grip hand work. (Baranski and Kozupa 2014). The flexor carpi radialis muscle flexes the hand and fingers and the flexor carpi ulnaris muscle flexes and adducts the hand. While the strongest flexor of the hand is flexor digitorum superficialis, it has to be taken under consideration that this muscle lies deeper than the two other strong flexors of the hand: flexor carpi ulnaris muscle and flexor carpi radialis muscle. It is difficult to place and use only sEMG to locate activity of the flexor digitorum superficialis muscle specifically. Thus, it was decided to examine the two muscles that are flexing the hand strongly and at the same time are situated most superficially for ease of sEMG placement for this study, particularly for ease of access in a clinical setting, non-invasiveness in order to reduce patient burden. There is further discussion of the limitations of these muscles in Chapter 9, Section 9.4.3, .

Each channel consisted of three electrodes, two placed over the muscle belly while a third, reference electrode was placed over the bony prominences of the corresponding elbow.

EMG data was sampled at 2048 Hz. The EMG signal was amplified by a gain of 200. LabView acquired the EMG data and provided real-time profiles of the EMG signals from both muscles (Figure 5-8).

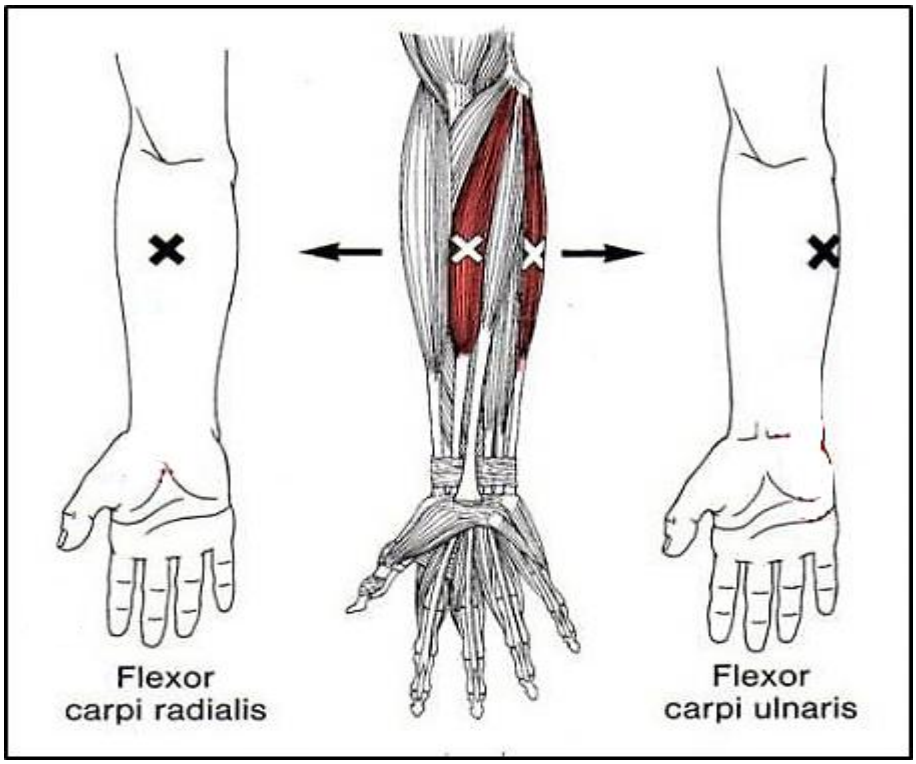


Figure 5-7: Surface EMG Placement

Surface EMG signal is recorded from flexor carpi radialis (FCR) and flexor carpi ulnaris (FCU) muscles. White "X" representing each muscle used and the black X representing electrode placement.

Figure 5-8: Experimenter view of the LabVIEW interface

Screenshot of the experimenters view of two of the four LabVIEW panels displaying time domain signals of recorded electrophysiology data from two electrode recording sites during execution of the experiment.

5.3.5 EEG Acquisition

An ActiveTwo BioSemi system with 128- Ag-AgCl electrodes was employed to obtain EEG data, sampled at 2048Hz. In active electrode systems such as the ActiveTwo system, the DC offset value is an indicator of the electrode impedance. To obtain optimal readings, it was required to have offsets below ±25 mV (Biosemi 2014).

5.4 Experimental Protocol and Data Collection

5.4.1 Equipment Setup and Verification for Participant Testing

Prior to participant recording, the equipment was set up and verified using the following protocol:

- Time-locking data synchronisation pulses were sent correctly from the dynamometer to acquisition platforms.
- Dynamometer was tested by squeezing the hand3grip and observing the response on the feedback screen and display panel as part of the LabVIEW front panel.
- EMG amplifiers were tested by placing them on the researchers' forearm and observing the amplitudes of the EMG acquired data on the display panel as part of the LabVIEW front panel.
- Test files were stored correctly and checked. Anonymity of each participant was preserved.

Table 5-3: Summary of Experimental Protocol

Steps taken for participant recording

Sequence	Steps	Measurements
1.	Complete BFI and ESAS questionnaires	BFI mean score and symptoms
2.	Compute MVC and 30% MVC (Maximal value out of 3 dynamometer tests).	Grip force
3.	30 second recording prior to start of task	Grip force, EEG, EMG
4.	Fatiguing task (Isometric grip force application at 30% MVC value until failure)	Grip force, EEG, EMG
5.	3 minute recording post task	Grip force, EEG, EMG
6.	Acceptability questionnaire administered	Score

5.4.2 Participant's Preparation Prior to the Experiment

The experiment duration was approximately one hour. Subjective symptom evaluation was carried out via Brief Fatigue Inventory (BFI) and Edmonton Symptom Assessment System (ESAS) Questionnaires (Appendix B).

The BFI is a subjective nine-item questionnaire developed to assess fatigue in the last 24 hours and the extent that it interferes with daily activities and work (Seyidova-Khoshknabi et al., 2010). It has a 0 to 10 numeric rating scale where 10 reflects severe fatigue. The BFI was undertaken with both participant groups, in order to perform intergroup comparisons of the results.

The ESAS questionnaire is a tool designed to assess nine common symptoms in cancer patients: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing and shortness of breath (Chang et al., 2000; Johnstone et al., 2017). Symptom severity at the time of assessment is rated from 0 to 10 on a numerical scale, 0 meaning that the symptom is absent and 10 that it is of the worst possible severity. CRF patients were further screened for medications to treat both cancer-related symptoms and for other illnesses.

Participants were then prepared appropriately for both the EEG and EMG recordings. In front of the participants was the task screen (Figure 5-9) which displayed the dynamometer reading along with the signal acquisition equipment.

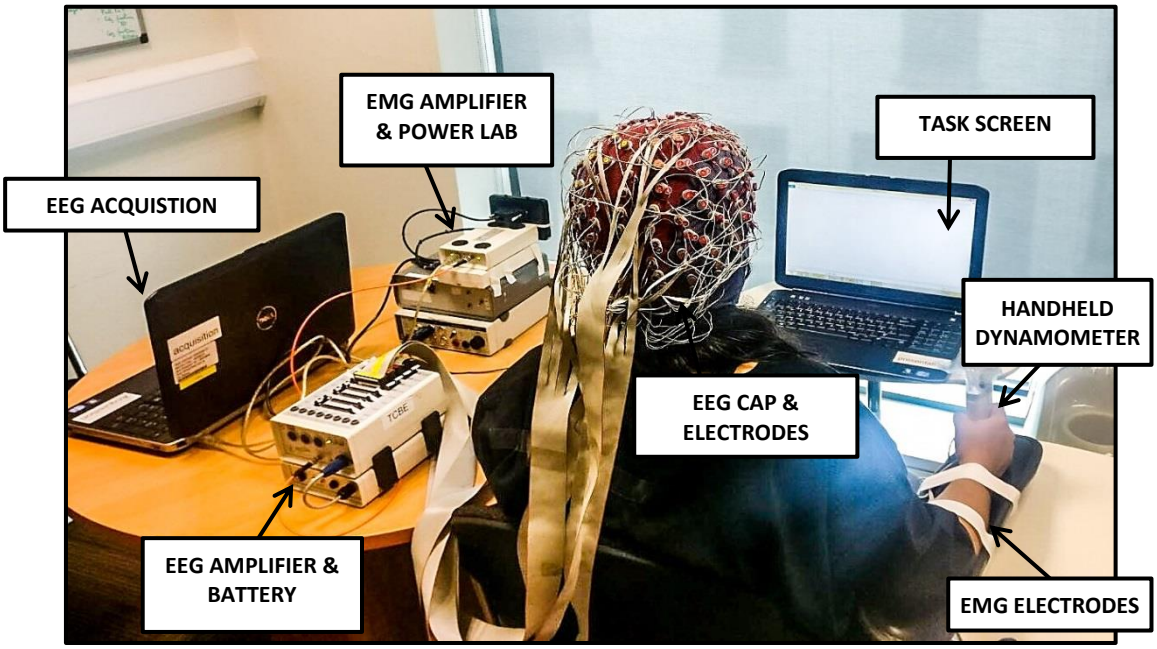


Figure 5-9: Experimental Set Up

Healthy participant is facing the task screen with their forearm restrained. The participant grips the handheld dynamometer and maintains 30% of their maximal voluntary contraction. Visual feedback is provided by the task screen (Figure). EEG and EMG are simultaneously recorded during the task.

5.4.3 Fatigue-Inducing Motor Task

Once the participant was ready to commence the motor fatigue task, a demonstration of the task and a short trial was performed to familiarise the participant with the task. Any uncertainties were addressed until full comprehension was confirmed by the participant.

In commencing the test, each participant was asked to perform three MVCs using the dynamometer, with a 10 second rest period in-between to allow for recovery. The highest of these three forces was entered into the LabChart programme and used to calculate 30% of the participants own MVC. This 30% target value was presented as a yellow horizontal line on the task screen located in front of the participant.

The participant was then instructed to perform a sustained voluntary contraction at the 30% target value for as long as possible using the hand held dynamometer, until self-perceived exhaustion.

Occasionally, the participants were verbally encouraged to continue, to prevent an early termination of the task due to motivational reasons.

The experiment stopped once the target force fell below 27% (10% of 30% MVC) of the participant's MVC for more than three seconds. This was communicated to the participant by a loud beep. After this beep, there was a three minute resting period where the participant was asked to remain in the same position without squeezing the dynamometer. After the three minute rest period, another beep signalled the end of the experiment. A questionnaire (Appendix B) was provided to CRF participants to request feedback regarding the acceptability and feasibility of the task and the study set up.

5.4.3.1 Data recording and storage

All data recorded (patient information, questionnaire scores, EMG, EEG and grip force values) followed the Data Protection Acts and were stored pseudo-anonymously. The data could be identified only by the research study entry code, and the participant name and identification details were stored in a locked cabinet in one location. This could only be accessed by the principal investigator (Professor Declan Walsh). This information will be disposed of in compliance with the Data Protection legislation.

5.4.3.2 Measures to enhance repeatability of the test

As mentioned previously, one of the unique features of this research is that it was conducted in a clinical setting, rather than a controlled laboratory environment. In order to enhance the repeatability of the measurements obtained and to keep consistency of the acquired data, a number of actions were taken:

- Wire connections were made with thin multi-stranded cables where possible, in order to avoid breakage or disconnection during movement of the equipment.
- The electronic circuits were shielded where possible.

- Uniformity was maintained in assembling and disassembling the equipment setup and verification for each recording by following a detailed step by step protocol.

5.5 Offline Analysis of Data

All data analysis was conducted offline. Self-customised scripts were written in Matlab® (Matlab and Statistics Toolbox 2014-2017a, The Mathworks). The algorithms were tested with simulated EEG and EMG signals. Statistical analysis was carried out using SPSS Version 24 (IBM Corporation, New York).

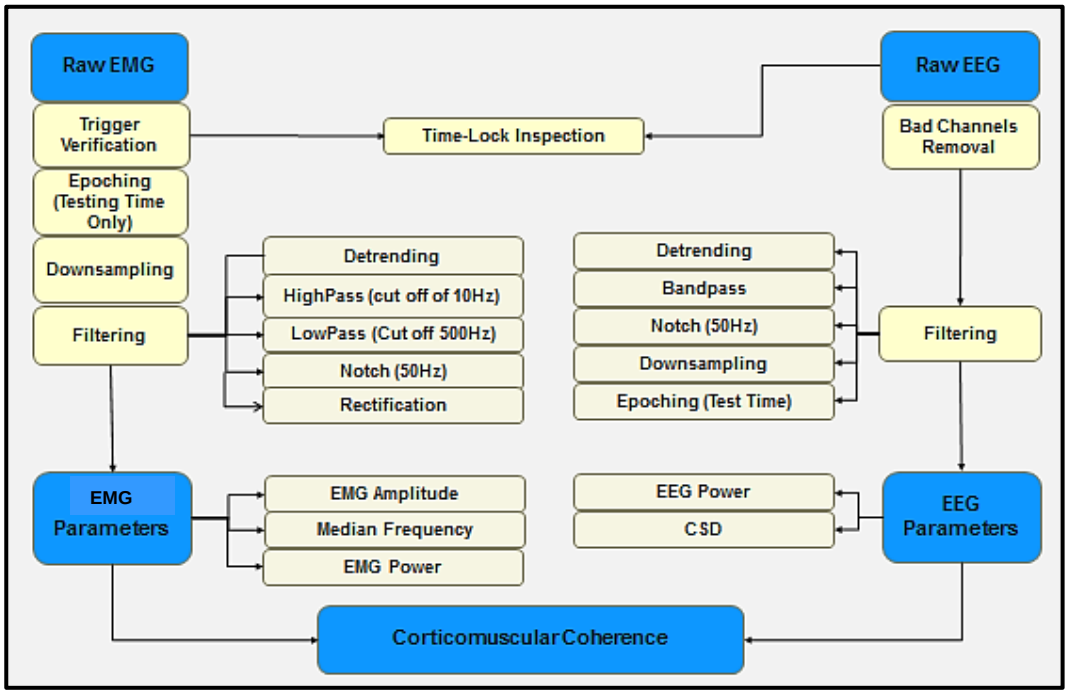


Figure 5-10: Flow diagram of the pre-processing and processing steps.

Data pre-processing and processing steps are shown in Figure 5-10**,** each step is described in more detail below. For EMG and EEG analysis the Alpha (10-14Hz) and Beta (15-35Hz) frequency bands be examined.

Prior to the start of pre-processing of the raw EMG and EEG signals, the data synchronisation pulses were verified. This was to ensure that the signals were correctly time-locked and there were no significant delays between the two signals.
As described in Section 5.3, pulses were sent constantly throughout the motor fatigue task. The difference between the pulses was the frequency with which each pulse is generated for the three distinct experimental stages. These pulses were visually presented and inspected (Figure 5-11, Figure 5-12).

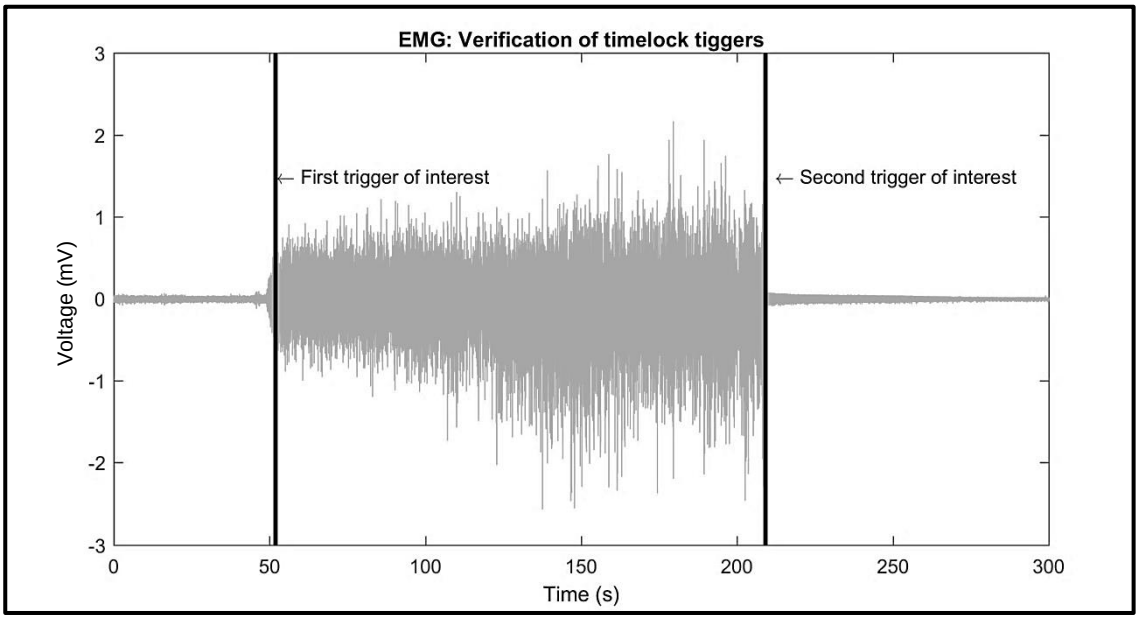


Figure 5-11: Verification of EMG time-locking pulses

First and second pulses of interest represent pulses sent at the start and end of the motor fatigue task, respectively as shown from collected data of a single participant.

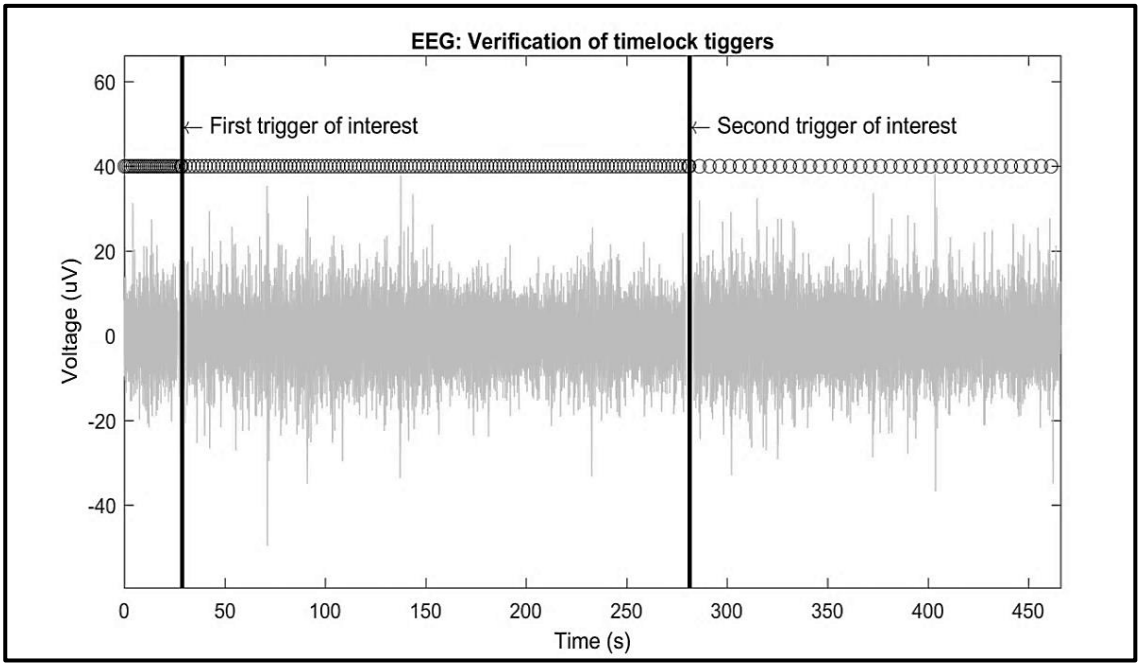


Figure 5-12: Verification of EEG time-locking pulses

First and second pulses correspond to the first and last pulses of the motor task, respectively as shown from collected data of a single participant.

5.5.1 EMG Pre-processing

EMG data were processed in the following order of steps:

1. Detrending:

   Signal was detrended to remove any baseline drift of the signal.

2. Filtering:

   Signal was filtered to remove noise artefacts and unwanted frequencies. Literature states that muscle activity of significance for surface EMG occurs between 5-450 Hz (Komi and Tesch, 1979; Viitasalo and Komi, 1977)

   Firstly, a notch filter of 50 Hz was applied to remove the powerline noise, then followed by a high pass Butterworth filter of 5^{th} order with a cut off frequency of 10 Hz was applied to remove any low frequency artefacts. Furthermore, a lowpass FIR filter with an order of 120 and a cut off frequency of 500 Hz was applied to capture significant EMG activity. The sEMG signals from the FCU and FCR forearm muscles were analysed separately.

3. Rectification:

   Rectification is a process to convert any negative values into positive values. Rectification of EMG data is intended to maximize the information about action potential timing, while supressing information related to motor unit action potential size (McClelland et al., 2011).

   Full-wave rectification was performed on EMG signals for RMS, RMS change, and normalized power. Normalized spectral power (in a certain frequency band) is with respect to the total spectral power (0-97 Hz, checked the upper frequency limit of the filter). Rectification was also performed on EMG signals used for the coherence analysis in the FieldTrip toolbox in MATLAB. Median frequency and median frequency shift was calculated using non-rectified EMG signals.

4. Epoching

   Each filtered signal was epoched into two 20 second durations; “mild fatigue” and “severe fatigue”. Mild fatigue represents the beginning of the task and severe fatigue represents the end of the task (Figure 5-13). This choice of epoching was guided by the shortest endurance time of a CRF patient (that is, 40 seconds), in order to keep all data analysis and comparisons consistent.

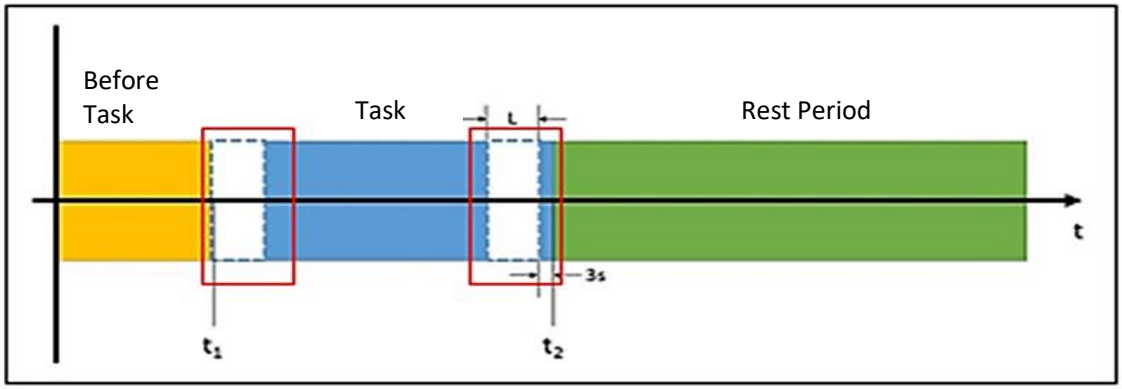


Figure 5-13: Test stages and event times of interest for EMG.

Before (yellow), task (blue), rest period (green), t1 (start of task) and t2 (end of task). Length of segment (L) was 20s.

5.5.2 EEG Pre-processing

1. Detrending

   This was performed to remove any baseline drift of the signal

2. Downsampling

   The EEG data was resampled from 2048 Hz to 128 Hz

3. Filtering

   Zero-phase band-pass filtered (Chebyshev Type I; passband of 1-47Hz) and a Notch filter of 50 Hz was applied to remove the powerline noise. Visual inspection of the raw EEG data was performed using an open source software toolbox, EEGLAB, a plugin to MATLAB (Delorme and Makeig, 2004). This was to ensure that the data was recorded correctly and to point out any bad channels.

   EEG signals were visually inspected to ensure they were artefact free (i.e. those associated with eye blinks or other activity induced noises). Bad channels were identified using automatic channel rejection and were spherically spline interpolated from the unaffected channels.

4. Epoching

   EEG data was re-referenced to an average of all electrodes and epoched into 1 second long segments. After manually rejecting components with artefacts, two 20

second data segments were selected representing “mild and severe” fatigue (Figure 5-13).

5. Independent Component Analysis (ICA)

   ICA was carried out on 28 symmetrically distributed electrodes (Figure 5-14). Then ICA data was re-referenced to the common average. EEG Beta band power was calculated for each fatigue stage, and normalized to total power (1-47Hz).

6. ADJUST

   Automatic EEG Artifact Detector based on the Joint Use of Spatial and Temporal features (ADJUST) was employed to reject the components containing artefacts.

   The independent components were then computed using the whole trial data epoched into 1s long chunks of data.

5.5.3 EMG Features

1: Amplitude

The RMS (a standard method of EMG amplitude quantification (Kisiel-Sajewicz et al., 2014)) of the epoched EMG signal was calculated to quantify the EMG amplitude. The EMG amplitude change was calculated for mild and severe stages of the motor fatigue task.

2: Power Spectral Density and Median Frequency

Median frequency is considered as an index of muscle fatigue (Konrad, 2005). With increasing fatigue, median frequency is expected to shift to lower frequencies.

It is defined as the frequency that splits the area under the curve into two equal parts (Equation 5-1).

$$\int_0^{Fmed} \boldsymbol{P(f)df} = \int_{Fmed}^{\infty} \boldsymbol{P(f)df} = \frac{1}{2}\int_0^{\infty} \boldsymbol{P(f)df} \quad \textbf{Equation 5-1}$$

Welch’s method was employed to obtain the EMG power and the median frequency. This method estimated power of the signal at different frequencies. It is based on employing periodogram spectrum estimates that result from converting a signal from the time domain into frequency domain with the application of the discrete-time Fourier transform (Welch, 1967).

The normalised mean EMG power was calculated for Alpha and Beta frequency bands. As reported in the literature, the Beta frequency band is of a particular interest for analysis when motor tasks are involved (Hashimoto et al., 2010; Yang et al., 2009). An open source toolbox, EEGLAB, was utilised to obtain topographic maps within the Beta frequency range for mild and severe fatigue stages for both participant groups.

5.5.4 EEG processing

The EEG power was calculated for each electrode separately for one of the participants. The obtained results were examined and consisted of CMC below the 95% confidence level (for more details on coherence confidence level refer to Section 5.5.6. Groups of five areas of interest (left, right, central, frontal and parietal) were identified based on the findings from the literature (Liu et al., 2007; Yang et al., 2009). The area of interest for this study was the left area over the somatosensory cortex, since the right forearm muscles are being engaged. ICA was employed for 28 symmetrically distributed electrodes (Figure 5-14). The independent components were re-referenced to an average of all electrodes.

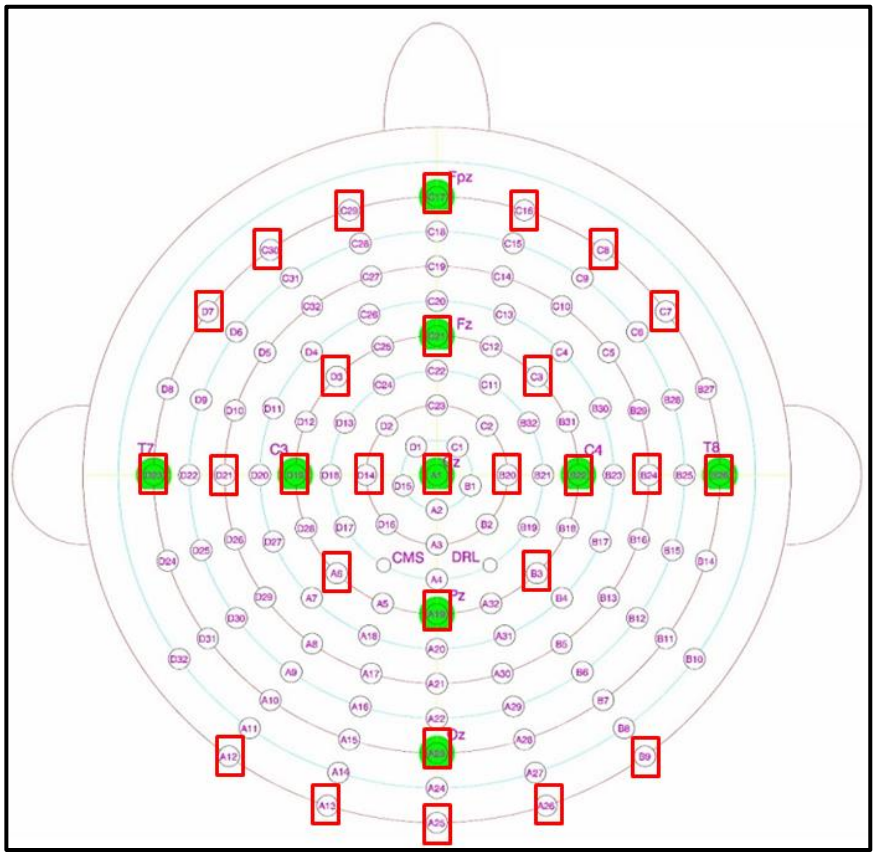


Figure 5-14: Representation of the 28 symmetrically distributed electrodes

28 electrodes (A1, A6, A12, A13, A19, A23, A25, A26, B3, B20, D21 B22, B24, B26, C3, C7, C8, C16, C29, C30, D3, D7, D23, D19, D14) marked with red boxes used in the analysis based on a BioSemi 128-electrode cap.
(Modified from:(Biosemi, 2018))

5.5.5 EEG Power

EEG power was calculated with the same approach as EMG power, by applying Welch's PSD method (Welch, 1967). The normalised mean power was calculated within the frequency band for each area of interest for both mild and severe fatigue stages within Alpha (10-14 Hz) and Beta (15-35 Hz) frequency ranges. Beta frequency range at the left hemisphere was of interest as local populations of neurons have the tendency to engage in synchronized oscillations while the somatosensory cortex is active (Lalo et al., 2007). These oscillations can be observed by changes in EEG power.

The region of interest for this study (Yang et al., 2009), focused on 5 electrodes (A6, D3, D14, D19 and D21) over the left motor cortex. By applying the large Laplacian Operator

the current source density of the electrode area above the left motor cortex, contralateral to the FCR and FCU muscles used in the task, was estimated.

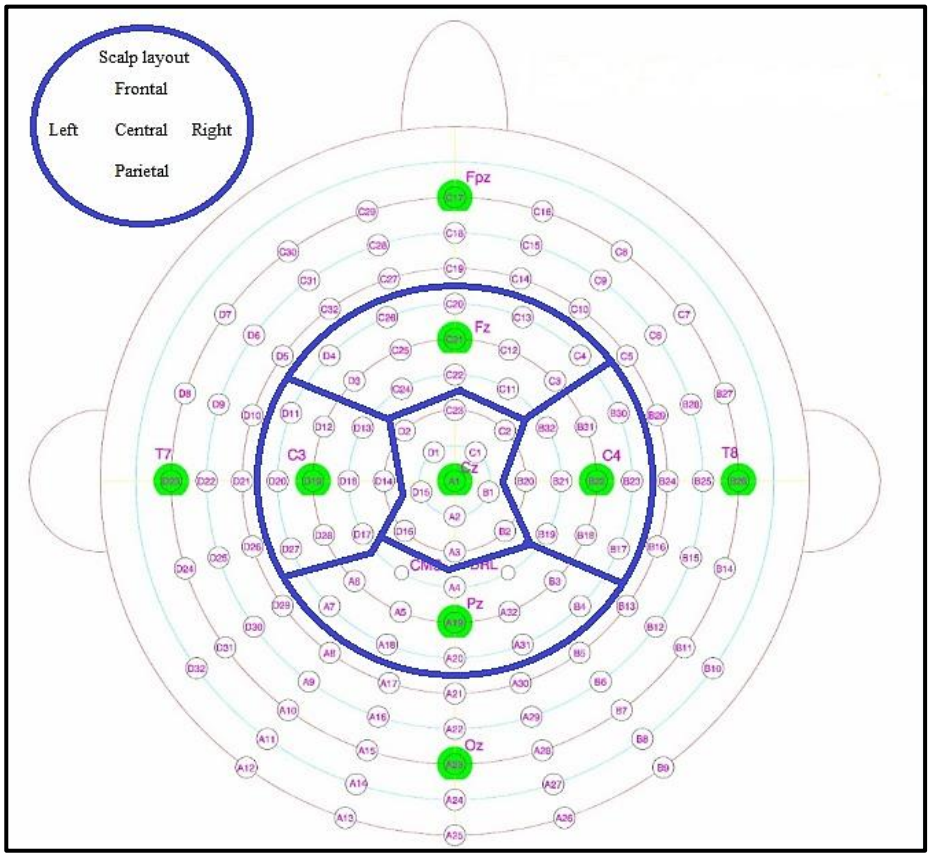


Figure 5-15: Representation of five scalp areas of interest employed in the EEG analysis

[BioSemi 128-electrode cap: Modified from (Biosemi, 2018)]

5.5.6 Corticomuscular Coherence

CMC examines a linear relationship of two signals in the frequency domain. It ranges between 0 and 1; where the higher the coherence value, the higher the coupling (synchrony) between the signals at a given frequency (Conway et al., 1995; Mima and Hallett, 1999a). A value of 1 indicates that the two signals are perfectly synchronised at the given frequency and 0 indicates that any synchrony is non-existent. The muscular force and the movement type (tonic versus phasic) are two major factors reported known to affect coherence (Mima and Hallett, 1999a). Peak frequency of the coherence is different between strong and weak contraction (Brown et al., 1999). For strong

contraction, those above 60 % of the maximal strength, CMC can be observed within the Gamma range (>35 Hz). However, during a weak to moderate contraction, CMC is generally entirely within the Beta range (15-35 Hz) (Mima and Hallett, 1999a; Conway et al., 1995; Halliday et al., 1998). The most widely employed method to obtain coherence is Welch's method. The mathematical representation of the coherence function is as follows:

$$C_{xy}(w) = \frac{P_{xy}(w)}{\sqrt{P_{xx}(w)P_{yy}(w)}}, \quad \textbf{Equation 5-2}$$

where P_{xx} and P_{yy} are power spectra of signals x and y, P_{xy} is cross-power spectrum for these signals, ω is angular frequency. The power spectrum and cross-spectrum are defined as:

$$P_{xx}(w) = [\hat{x}(w)]^2 = \hat{x}(w)\overline{\hat{x}(w)}, \quad \textbf{Equation 5-3}$$

In order to test if the observed CMC was statistically significant, a 95 % confidence level was calculated applying Equation 5-4:

$$CL(\alpha) = 1 - (1 - \frac{\alpha}{100})^{\frac{1}{(n-1)}}, \quad \textbf{Equation 5-4}$$

where α is the desired confidence level, while *n* is the number of the disjoint sections in the signal averaged to obtain the coherence (Rosenberg et al., 1989). If the coherence at the certain frequency was greater than the confidence interval, it is considered statistically significant.

EMG and EEG data were both downsampled to 128 Hz for analysis. Coherence between the EMG and EEG signals was determined using the multitaper method as originally proposed by Thomson (Thomson, 1982). It is a method used for spectral power density estimation, similar to the Fourier Transform, but provides an improved estimate because instead of rectangular bandpass filters, it uses a bank of optimal bandpass filters (Thomson, 1982). The resolution of the corticomuscular coherence estimates was 4Hz

as a taper smoothing frequency of 2 Hz was used in this case, to estimate the auto- and cross- spectra of signals in the frequency range of 8 to 45 Hz.

Coherence was computed for epochs of five seconds of the electrophysiological datasets. This allowed observing the change in coherence during fatigue progression. Pilot analysis was conducted in a CRF patient and a healthy participant. Results are presented and discussed in Section 5.5.8.

5.5.7 Current Source Density (CSD)

During neural activity, currents flow through cell membranes. Viewed from the extracellular space on a macroscopic scale, these membrane currents are sinks (inward currents) and sources (outward currents). These sinks and sources are the physical cause of the field potentials. The sink and sources can be localized and calculated from local field potentials employing a current source density method (CSD) (Mitzdorf, 1985). CSD is defined as the second spatial derivative of the local field potential. CSD analysis can extensively localise the pattern of transmembrane current flow in neural ensembles. Employing CSD analysis leads to a higher spatial resolution of the events occurring in the brain (Mitzdorf, 1985; Chen et al., 2010) (Figure 5-16).

$$CSD_j = -\frac{(u_{j-1}-u_j)-(u_j-u_{j+1})}{rh^2}, \quad \textbf{Equation 5-5}$$

Equation 5-5 provides a formula for calculation of the CSD, where u_j is field potential at electrode *j*, *h* is interelectrode distance and *rh* is tissue resistance.

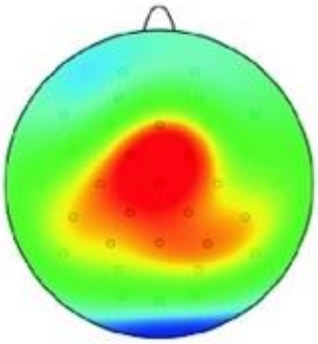


Figure 5-16: An example of a CSD topoplot.

Topographic maps are generated in order to examine the temporal changes in the spectral intensities; and compare the spectral power distribution across the scalp; in this research it will demonstrate power distribution at the start of the fatiguing task, and at severe fatigue.

CSD was implemented using the CSD Toolbox in MATLAB (http://psychophysiology.cpmc.columbia.edu/Software/CSDtoolbox/). It was calculated by averaging data points within each 5 seconds to obtain a single CSD plot. This was carried out for every 5 seconds of the first 20 seconds of the mild fatigue stage and for the last 20 seconds of severe fatigue stage, for 10 CRF participants and 10 HC participants. A pattern of activity was hypothesised to shift with the progression of fatigue.

5.5.8 Statistical Analysis

Statistical analysis was performed using SPSS software (Version 24; IBM Corporation New York). A Shapiro-Wilk test of normality was conducted to determine whether parametric or non-parametric analysis was appropriate for the observed data.

Normality of the data was confirmed; and thus parametric tests were utilised. T-tests were used for comparison of the effects of fatigue on EMG amplitude, EMG median

frequency and EMG power at the beginning and end of the motor fatigue task. T-tests were also utilised to calculate significance of mean BFI questionnaire scores, mean endurance time and mean of the maximal voluntary contraction between CRF and HC participants, requiring three paired t-tests. T-tests were selected as they explicitly account for systematic variance between participants. Calculation of significance of each EMG parameter (Amplitude, Median Frequency, Power) for differences between before and after the task for each participant group (CRF and HC) and muscle type (flexor carpi ulnaris and flexor carpi radialis) separately resulted in a total of twelve paired t-tests. Because each of these paired t-tests were testing similar hypotheses, we employed a Holm-Bonferroni correction to control the overall family-wise error rate at 0.05. Uncorrected p-values are presented in the results, however we indicate when statistical significance was lost due to multiple comparison adjustment.

EEG fatigue parameters were assessed with repeated measures 5x2 (areas of interest x fatigue stage) analysis of variance (ANOVA), in order to check the statistical significance among all five areas of interest and their interactions within the two fatigue stages. The repeated measure ANOVA was selected because it is utilised when all members of a random sample (HC participants) are measured under a number of different conditions (e.g. the five neural areas of interest for the two fatigue stages). EEG power was calculated within Alpha and Beta bands for both participant groups separately, which resulted in 4 repeated measures ANOVA tests.

A statistical test for significance of coherence was obtained by applying the equations described in Section 5.5.6. This was carried out separately for CRF and HC participants.

To test the significance of the data obtained between two participant groups and different fatigue parameters one-way multivariate analysis of variance (MANOVA) was used. ANOVA was selected as it is used to determine whether there are any differences between independent groups (healthy participants and CRF patients) on more than one continuous dependent variable (different areas of interest + different fatigue stages + different muscle types). MANOVA was utilised to obtain comparisons between healthy participants and CRF patients for all the fatigue parameters calculated in this study. This resulted in a total of ten multivariate analyses of variance tests. Whenever significance was observed, post-hoc contrast analyses were done for within group and between

group comparisons. Pearson's correlation analysis and linear regression analysis were also performed.

In order to minimise the concern of inflated type 1 error, the statistical approaches undertaken relied upon omnibus tests for global differences prior to examining pairwise comparisons. Additionally, in some cases, multivariate approaches were taken to partially pool the information provided from multiple related constructs as an additional protection against false detection. In some instances where neither approach was possible (e.g. twelve paired t-tests) a Holm-Bonferroni correction was applied to control the family-wise error rate.

5.6 Results

Given that this is a preliminary study for the neurophysiological analysis of CRF, work commenced with design development and verification of experimental methods and setup. After successful experimental data acquisition of CRF and HC participants, all data were analysed offline. MATLAB R2016a, EEGLAB and SPSS version 24, were utilised for this purpose.

The results of this study include the formation of the experimental protocol, device design (execution and optimization) for time-locked EEG-EMG acquisition, the verification of the setup, and the acceptability of testing by patients, in addition to a brief presentation of the subjective and objective outcomes of the collected data.

5.6.1 Age

As this was a preliminary study in order to test the set up and protocol, HC were not recruited to be age- and gender- matched to CRF participants. As intergroup comparisons of both subjective and objective correlates for both participant groups were performed, statistical analysis (t-test) was calculated for age between the groups. The mean age was 64.1 ± 11.7 and 28.1 ± 7.96 for CRF and HC participants respectively. There was a statistically significant difference; $p = 0.0001$.

5.6.2 Edmonton Symptom Assessment Scale

CRF participants assessed their symptoms through the Edmonton Symptom Assessment Scale (ESAS) and reported a moderate symptom burden. Where 0 represents absence of the symptom and 10 represents the worst possible severity. Two reported 1-3 symptoms, and five reported 4-6 symptoms (Figure 5-17). The most common moderate-severe symptoms reported were fatigue, anxiety and loss of appetite.

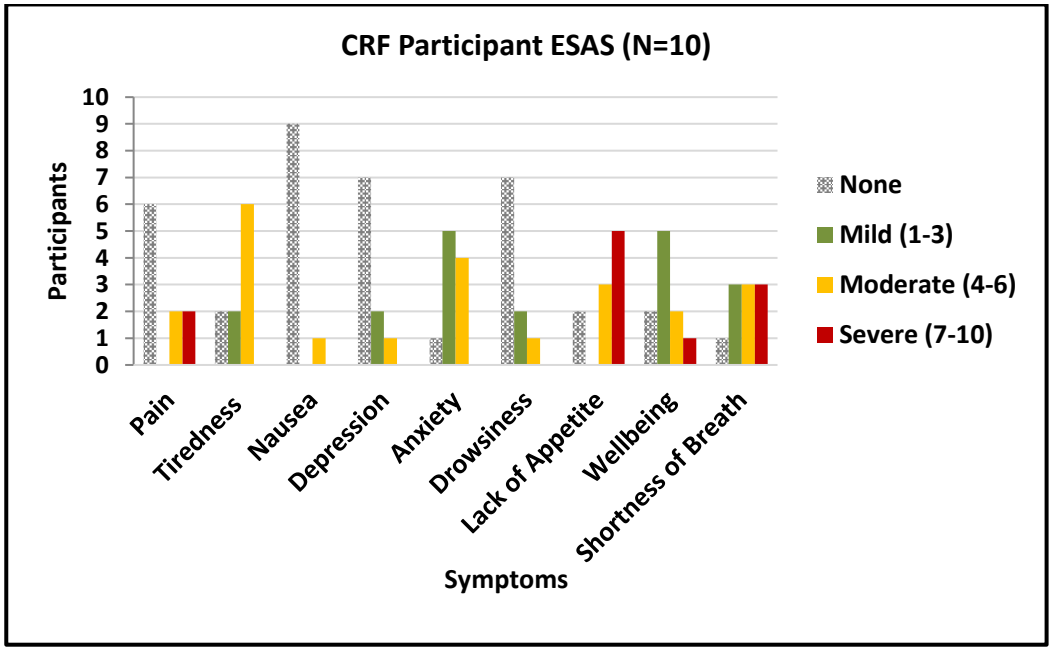


Figure 5-17: CRF Participant ESAS symptom severity scores.

CRF participant ESAS severity profile: where 0 represents no feelings of symptom and 10 represents the worst possible severity. None represents no symptoms; Mild represents a score of 1-3; Moderate represents a score of 4-6 and severe represents a score of 7-10. This graph demonstrates that 2 out of 10 CRF participants reported no "tiredness", but 6 out 10 participants reported moderate feelings of "tiredness".

5.6.3 Brief Fatigue Inventory

Both groups were first subjectively assessed on their level of fatigue through the administration of the BFI. With the mean scores of CRF participants as 3.6 ± 2 and HC participants being 1.6 ± 2, statistical significance was p=0.043.

5.6.4 Endurance Time

Endurance time was defined as the time duration from the time the grip force reached the target (30% MVC) to the time when the sustained contraction dropped below 27% and the task was terminated. Endurance time between both groups was found to be extensively varied. The mean time was significantly higher in HC than CRF participants which was expected (HC: 208.3 ± 51.2s; and CRF: 137.4 ± 76.2s (p=0.007))

5.6.5 Maximal Voluntary Contraction

The MVC (Newtons) with the greatest amplitude was used to calculate mean MVC for both participant groups. The mean MVC was higher in HC participants which was expected (HC: 379 ± 123; CRF: 222 ± 93, p=0.002)

5.6.6 EMG Measures

5.6.6.1 EMG Amplitude

EMG amplitude was assessed in flexor carpi ulnaris (FCU) and flexor carpi radialis (FCR) muscles for mild fatigue (first 20 seconds of the task) and severe fatigue (last 20 seconds of the task). There was an overall rise in amplitude in the majority of CRF and healthy participants during the experiment for both muscle types. Statistical analysis showed fatigue had a significant effect on both muscles for both groups (CRF: FCU: p=0.003 and FCR: p=0.003; HC: FCU: p=0.013, FCR: p=0.026) (Figure 5-18), though the change in radialis amplitude for the HC group was no longer significant after adjustment for multiple comparisons (HC: FCU: p=0.052, FCR p=0.052).

MANOVA was used to compare both CRF and HC participant groups. The results indicated no significant difference between either group at the start of the fatigue task for either muscles (FCU: p=0.114; FCR: p=0.361). It was noted that fatigue had a significant effect on the FCU muscle in severe fatigue (p=0.003) but not on the FCR muscle (p=0.134). This may be influenced by electrode placement or the position of the muscle, or the used of the FCU and FCR muscles, which are not the principal agonist muscles for a hand grip.

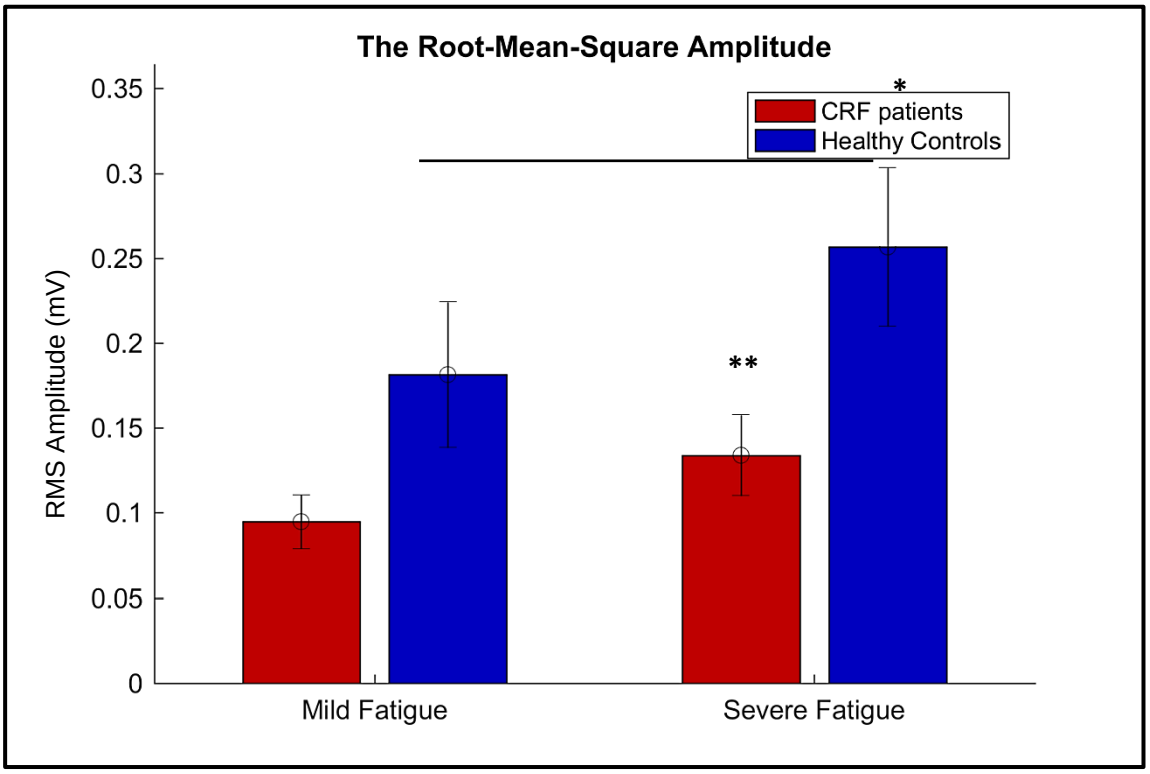


Figure 5-18: Comparison of EMG amplitude change between CRF and Healthy participants

EMG amplitude change with progression of fatigue between the CRF and Healthy Control Group for the FCU muscle only. Intergroup statistical analysis shows significance between groups for severe fatigue; p=0.003** for CRF and p=0.02* for Healthy Control group.

Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

5.6.6.2 EMG Median Frequency

With fatigue progression, a shift from higher frequencies to lower frequencies is expected in the median frequency (e.g. in Figure 5-19)

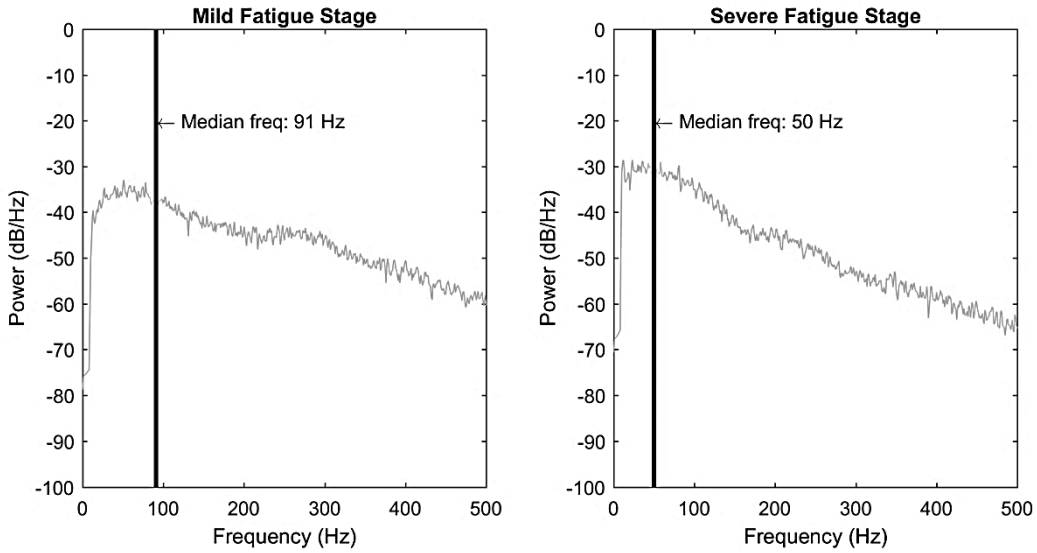


Figure 5-19: An example of median frequency shift to lower frequencies in a single CRF participant

Table 5-4: Range of Median Frequencies obtained from both Healthy Controls & Cancer Related fatigue groups for both time points of observation

Range of Median Frequencies Obtained	FCU				FCR			
	Mild		Severe		Mild		Severe	
	HC	CRF	HC	CRF	HC	CRF	HC	CRF
	54-90Hz	61-114Hz	43-70Hz	37-94Hz	57-110Hz	53-92Hz	43-88Hz	44-80Hz

A significant shift in median frequency to lower frequencies was observed in the majority of CRF and HC participants for both muscles during the task (CRF: FCU: p=0.001, FCR: p=0.001; HC: FCU: p=0.002; FCR: p=0.026).

Median frequency for both groups was calculated employing Equation 5-6 for both muscles (where *mf* refers to median frequency):

$$\boldsymbol{mfshift_{\%}} = \frac{(\boldsymbol{mf_{mild} - mf_{severe}})}{\boldsymbol{mf_{mild}}} * \mathbf{100}, \quad \textbf{Equation 5-6}$$

MANOVA was performed to test the significance between the two participant groups for both muscles in mild and severe fatigue stages. This showed no statistically

significant difference between the fatigue stages in the two participant groups for both muscles.

5.6.6.3 EMG Power

An increase in EMG power is typical with an increase in fatigue. As the Beta frequency band (15-35Hz) is of interest in this study, EMG power was assessed in the Beta band for both participant groups. Both groups displayed a significant increase in EMG power with increasing fatigue for each muscle (CRF: FCU: p=0.010, FCR: p=0.0001; HC: FCU: p=0.012, FCR: p=0.001).

A comparison between of EMG power at both fatigue stages and both muscles was carried out (Figure 5-20). A MANOVA was utilised to calculate the effects of fatigue at each stage for both groups. No statistically significant difference was noted between the CRF and HC participants during mild fatigue (FCU: p=0.28, FCR: p=0.15). However, there was a significant difference in severe fatigue (FCU: p=0.014, FCR: p=0.018).

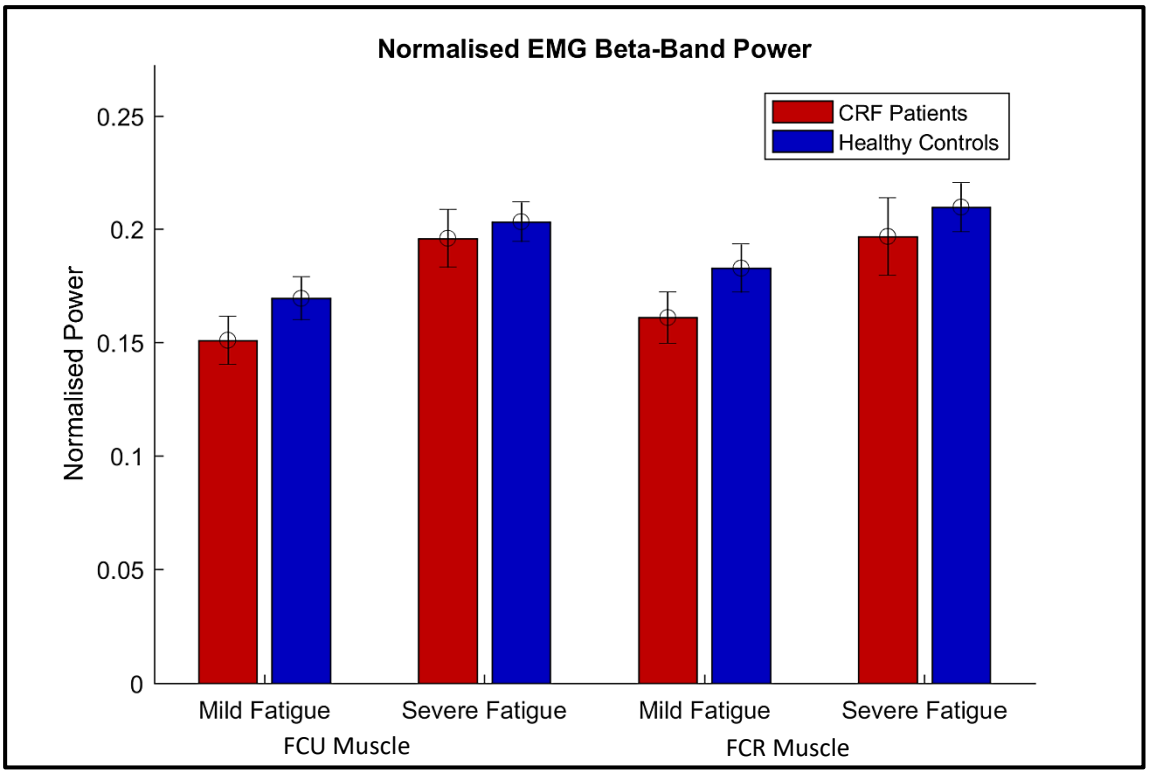


Figure 5-20: **Comparison of normalized EMG Beta band power**

Comparison of EMG Beta band power between CRF and Healthy participants for both muscles and fatigue stages.

Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

5.6.7 EEG Measures

5.6.7.1 EEG Power

An increase in EEG power is expected with increasing fatigue (Figure 5-21) (Yang et al., 2009; Moore et al., 2014a). EEG Beta (15-35Hz) frequency bands were assessed for five scalp areas of interest; left, right, central, frontal and parietal. The rationale for inclusion of these is explained in section 5.5.4 (EEG processing).

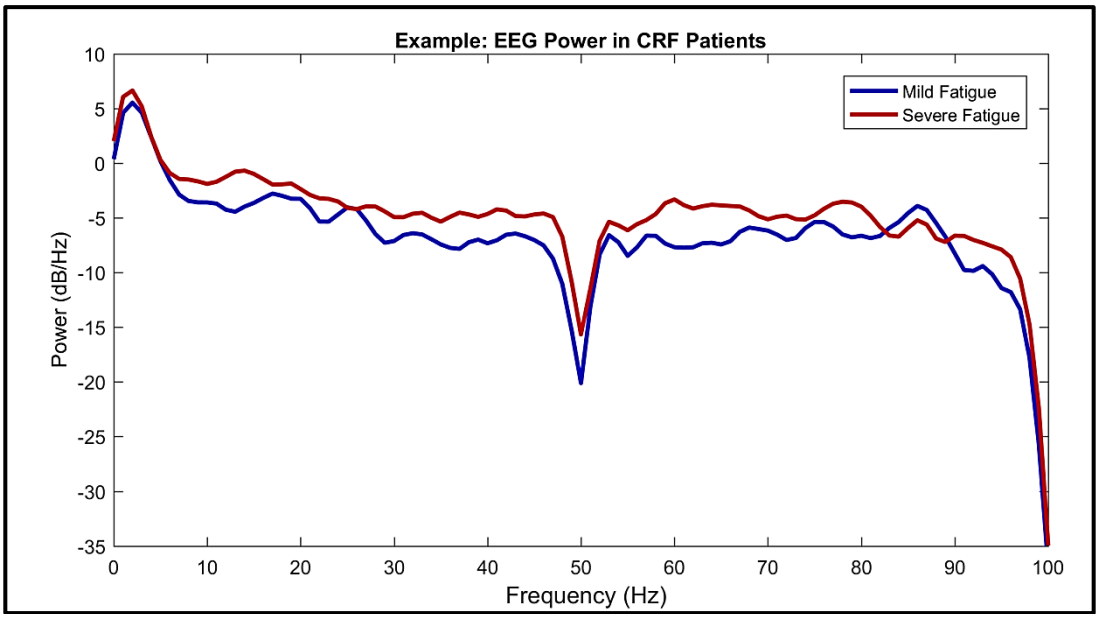


Figure 5-21: An example of an individual CRF patient's overall EEG power increase from mild to severe fatigue.

With mild fatigue representing the first 20 seconds of the task and severe fatigue representing the last 20 seconds of the task.

The majority of CRF participants experienced a power decrease within the Beta frequency band which was not in line with the hypothesis or previous studies. While HC participants experienced a slight increase. The extent of the EEG power varied between participants. A repeated measures analysis of variance for power analysis , within the Beta band for the left area for mild and severe stages, was calculated for CRF and HC

participants and this showed that despite the increase in EEG power, there was no statistical significance for either group for either fatigue stage (CRF: p=0.590, HC: p=0.919) (Figure 5-22).

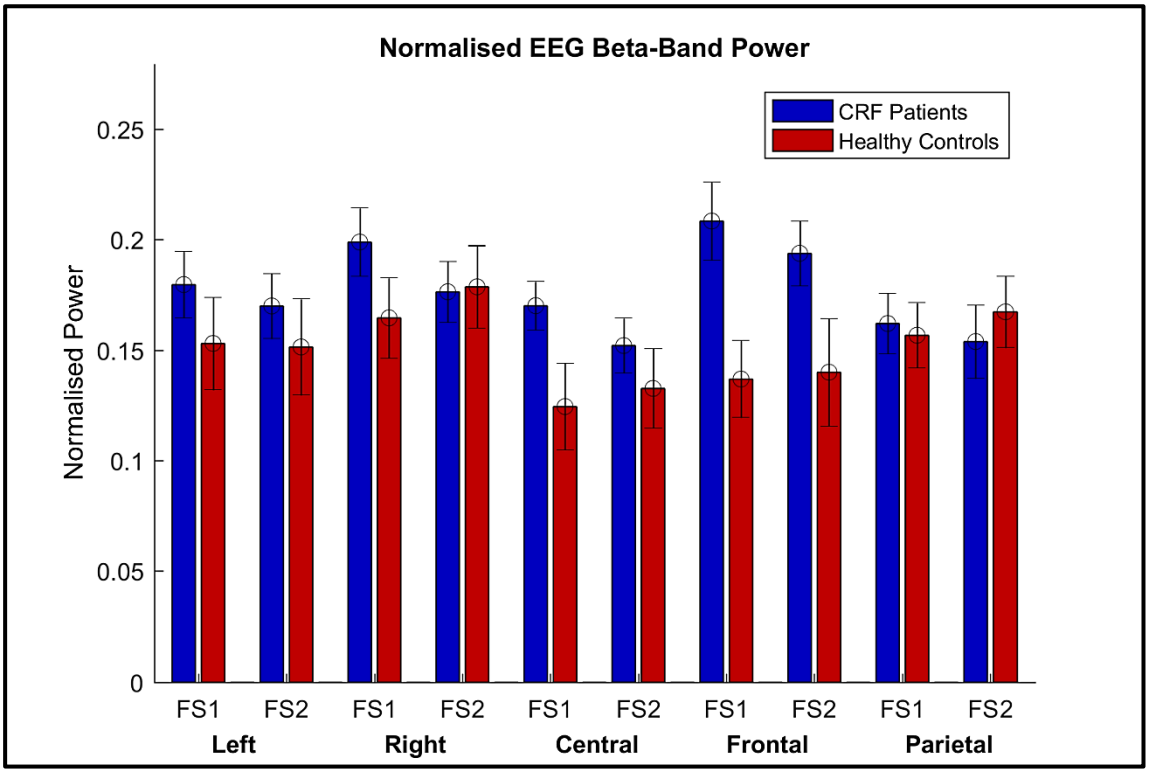


Figure 5-22: EEG power for Beta frequency band

Mean normalized EEG power within Beta band, comparison between CRF patients and healthy controls within five areas (left, right, central, frontal and parietal) . FS1= fatigue stage 1 (mild fatigue), FS2=fatigue stage 2 (severe fatigue).
Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

To obtain topographic maps for both participant groups within the Beta frequency band for mild and severe stages, an open source toolbox EEGLAB (Delorme and Makeig, 2004) was employed. This was performed to compare topographic power maps obtained by employing the Welch's method. It can be observed that as fatigue progresses the power increases within the Beta frequency band and this increase is most noticeable during severe stage for CRF participants in the frontal and left areas and healthy participants

within right and left areas. However, the extent and areas of power increase varied among participants (Figure 5-23).

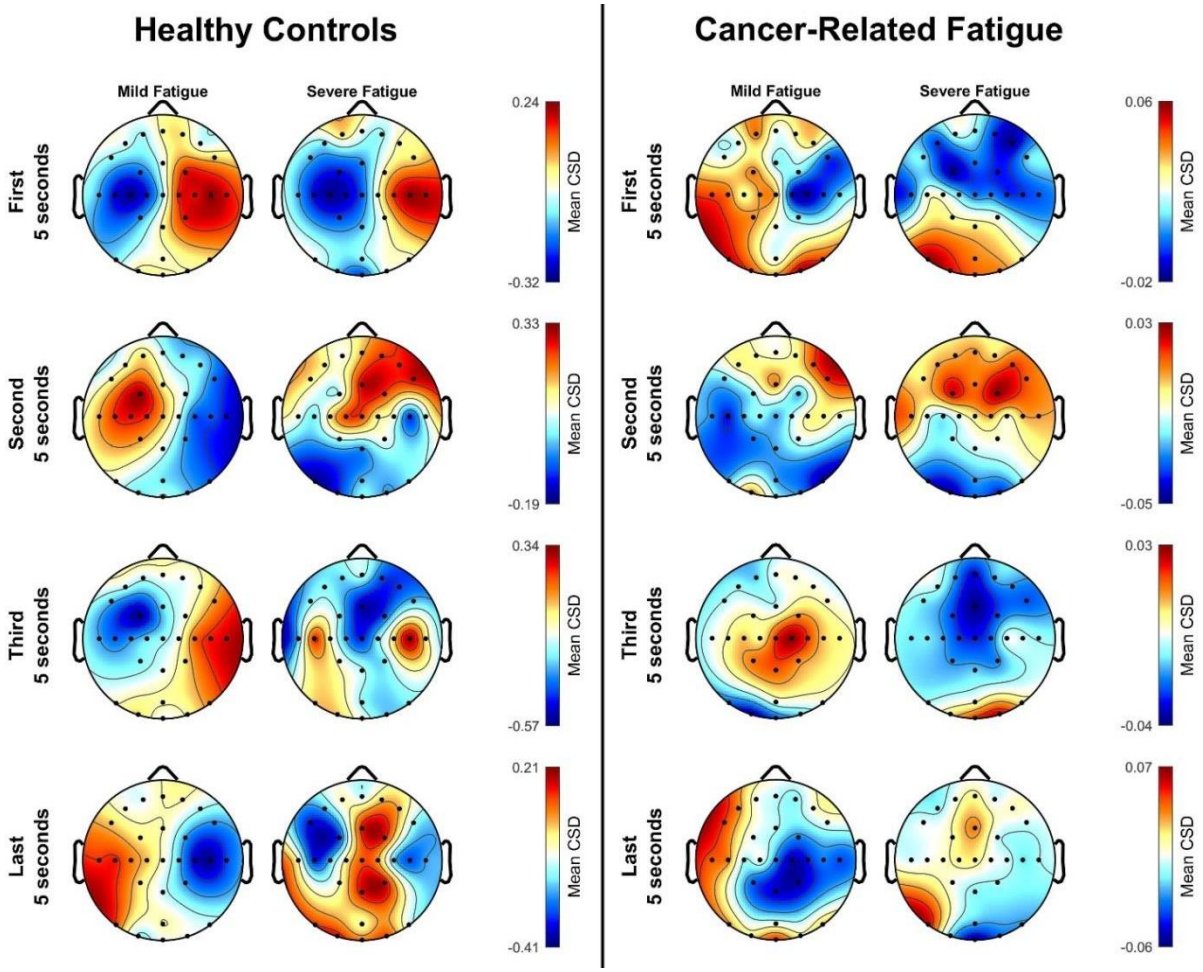


Figure 5-23: Current Source Density topographic maps for (a) CRF participants and (b) Healthy Control participants for mild and severe fatigue stages.

Each plot represents 5 seconds within the fatigue stage, with each fatigue stage representing 20 seconds of the task (beginning and end). The colour scale indicates CSD activity with blue indicating less neural activity and red indicating a "hot spot" of neural activity.

5.6.8 Corticomuscular Coherence

Based on the literature review carried out in Chapter 3, the hypothesised pattern of CMC is there is more synchrony between EEG and EMG signals within the Beta band at the onset of fatigue, which decreases as fatigue progresses; this is expected to be more pronounced in those with CRF. An example of this pattern is shown in Figure 5-23, for a single CRF participant's CMC at the left area of interest for the FCU muscle.

Particular attention was given to the area of interest overlying the left motor cortex, contralateral to the muscles employed in this test. The hypothesised pattern was not displayed among majority of CRF and HC participants within this study. Repeated measures analysis of variance was performed for the FCU muscle within the Beta frequency band for both groups individually and between group comparison for each fatigue stage, there was no statistical significance (CRF: p=0.92; HC: p=0.48, between group comparison: mild: p=0.50; severe: p=0.86)

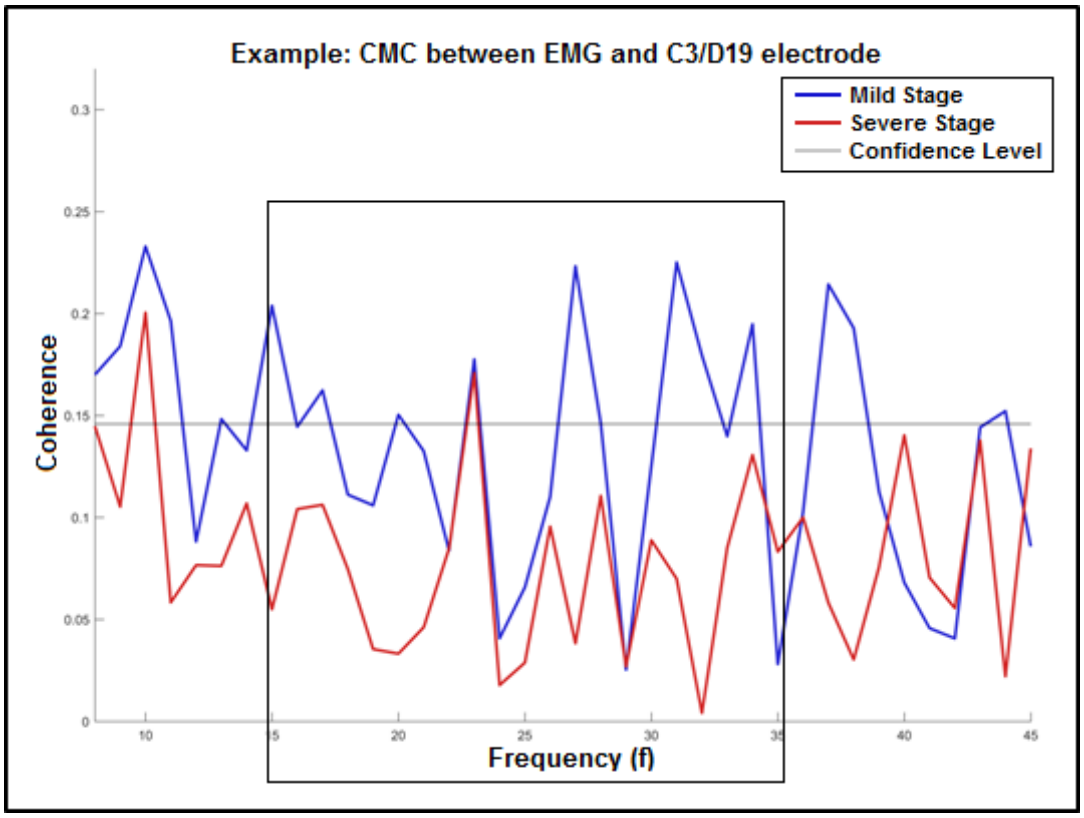


Figure 5-24: Corticomuscular coherence between EMG and C3/D19 EEG electrode for a single CRF patient over the left motor cortex for FCU muscle.

This plot shows coherence at around 20 Hz during mild fatigue, which decreases during severe fatigue. The black box represents the Beta frequency (15-35 Hz). Mild and severe stages correspond to first and last 20 seconds of motor fatigue task. The horizontal line represents a 95% confidence level.

5.7 Discussion

As mentioned, currently the primary evaluation of CRF is qualitative questionnaires undertaken exclusively by clinicians. This study was conducted with the aim of designing an experimental paradigm and protocol to test the technology employed for an assessment of objective correlates of fatigue in a clinical setting. In accordance with the literature review that has previously assessed those with CRF and Healthy controls (Chapter 3) the experimental paradigm for this research was designed to be utilized in an outpatient setting and an attempt to non-invasively analyse the possible central and peripheral contributions to CRF. As mentioned in Chapter 2, fatigue leads to loss of force during a task (Finsterer and Mahjoub, 2014; Davis and Walsh, 2010; O'Connor, 2016). Task failure can originate anywhere from the cerebral cortex to muscle fiber (Davis and Walsh, 2010) and can be either central or peripheral (Davis and Walsh, 2010; Prinsen et al., 2015). As mentioned in Chapter 2, sections 2.7 and 2.8, central fatigue is CNS-driven (Davis and Walsh, 2010); loss of voluntary muscle activation occurs proximal to the neuromuscular junction. Peripheral fatigue results from failure of the muscle excitation-contraction mechanism (Finsterer and Mahjoub, 2014; Davis and Walsh, 2010; O'Connor, 2016; Yavuzsen et al., 2009; Cai et al., 2014; Yang et al., 2009; Kisiel-Sajewicz et al., 2012). Lower MVC, decreased EMG amplitude, altered EMG spectral frequency, and increased EEG power with increasing fatigue are non-invasive ways of assessing possible peripheral and central contributions.

The equipment for neurophysiological signal acquisition for the experimental paradigm, the graphical user interface for the fatigue task and pulse generation hardware and software were generated and assembled for this study (Markicevic, 2015; O'Connor, 2016). The data acquisition was first performed in a clinical setting to ensure that the experimental methodology and protocol may be directly applied to CRF. Prior to each individual CRF and HC participant assessment, the set up and data acquisition were tested to ensure it was functioning correctly.

Validation of the signal acquisition equipment was performed and a protocol of methods was adapted and implemented from previous studies employing a subjective and objective assessment like BFI and EEG and/or EMG to assess fatigue during a prolonged

motor task in healthy and chronic illnesses with various muscles (see Chapter 3, Section 3.2.4) (Yavuzsen et al., 2009; Cai et al., 2014; Yang et al., 2009; Kisiel-Sajewicz et al., 2012; Siemionow et al., 2004). To ensure optimal performance, suitability of methods for this CRF population in this research was also assessed by an acceptance questionnaire; this was to determine if there were any concerns by patients for its use in this population, and there was 100% acceptability by both CRF and healthy participants (O'Connor, 2016). This study confirmed efficacy of the system and analysis methods.

To determine possible central and peripheral contributions to fatigue, and to maximise non-invasive objectivity of testing, several neuromuscular parameters was considered. Endurance time, MVC, EMG amplitude, EMG median frequency shift, EMG power and EEG power, with a sustained motor fatiguing task were all examined. The isometric grip (30% MVC) task was chosen because: 1) it is a widely used test due to reproducibility, 2) it has reduced artefact signal motion compared to eccentric or concentric contraction, 3) it represents daily activities and 4) is a more appropriate model to study central fatigue than maximal force (Cai et al., 2014; Lou, 2012; Taylor and Gandevia, 2008).

5.7.1 Experimental Paradigm and Equipment Set up

This study involved a motor fatiguing task with a sustained isometric handgrip on a dynamometer, set at 30% of the participants MVC. Synchronized EMG and EEG recordings were acquired from 10 CRF and 10 HC participants. Previous CMC studies involved a fatiguing exercise, typically an isometric contraction (Yavuzsen et al., 2009; Cai et al., 2014; Yang et al., 2009; Siemionow et al., 2004; Kisiel-Sajewicz et al., 2012). However, motor fatiguing tasks involving eccentric and concentric muscle contraction have also been reported in another study assessing CMC in stroke patients (Mima et al., 2001). Importantly, unlike in eccentric or concentric contraction (muscular contractions that lengthen and shorten the muscles respectively), muscles remain static in isometric contraction. An isometric contraction exercise, when compared to eccentric or concentric contraction, has a greater advantage for EMG recordings due to reduced motion artefact in the EMG signal and is easier to standardise and administer on a weak patient group (e.g. CRF participants). In addition to the use of isometric contraction,

particular care was taken to reduce motion artefact and interference due to electrical noise (which is unavoidable within a hospital environment) by adjusting the equipment arrangement and electrically shielding all the conducting portions of the data collection and time-locking trigger generation circuits.

5.7.2 Age

As part of this analysis the age differentials between the CRF and HC participants were considered. However, as this was a preliminary study and the focus was on testing the suitability of experimental design and protocol, age-matched controls were not incorporated. Age and gender may influence the outcome of fatigue tests similar to those employed in this study; particularly when analysing EEG data as it is known that neural characteristics alter with age (Hashemi and Pino, 2016).

5.7.3 The Edmonton Symptom Assessment Scale and Brief Fatigue Inventory Questionnaires

The ESAS is a reliable, valid instrument; with good test-retest validity in a cancer and palliative care population (Chang et al., 2000; Richardson and Jones, 2009). However, its use requires a sound clinical process to help interpret scores and to give them an appropriate level of attention (Richardson and Jones, 2009). The most common moderate-severe symptoms reported in this study, were fatigue, anxiety and loss of appetite, which follows previous literature (Chang et al., 2000; Richardson and Jones, 2009; Johnstone et al., 2017).

The BFI is also a validated and reliable questionnaire for cancer populations and was employed in this study as a subjective fatigue assessment (Seyidova-Khoshknabi et al., 2010; Minton and Stone, 2008; Mendoza et al., 1999; Jean-Pierre et al., 2007). The BFI was previously employed in the assessment of CRF (Yavuzsen et al., 2009; Cai et al., 2014; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014). In this study both participant groups completed the BFI prior to testing and the results confirmed CRF participants had a greater subjective feeling of fatigue. The CRF participant scores were lower than in previous studies which may be due to this CRF participant group being

newly diagnosed, prior to treatment and with a good overall performance status (ECOG (Section 5.3.1.1)). This demonstrates the subjectivity of questionnaires like BFI, and how the results are reflective of an individual's current mood and level of understanding. This further highlights how essential it is to develop an objective fatigue measurement to ensure successful CRF assessment which is unbiased by mood, unaffected by concentration and easy to comprehend by the individual at the time of assessment.

5.7.4 Endurance Time and Maximal Voluntary Contraction

Endurance time is not a direct assessment of fatigue. However, in combination with MVC it can provide information on different processes induced by exercise (Vollestad, 1997). Reliable muscle fatigue assessment can be obtained by the measurement of the participant's force generating capacity. MVC is a widely used neuromuscular test and on its own is considered a direct assessment of fatigue (Lou, 2012; Vollestad, 1997; Davis and Walsh, 2010; Finsterer and Mahjoub, 2014). Previous studies with MVC to assess muscle fatigue are said to be scientifically valid and reliable (Vollestad, 1997; Machado Rodrigues et al., 2017; Davis and Walsh, 2010; Visser et al., 2003; Yavuzsen et al., 2009; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Cai et al., 2014). In this study endurance time and MVC were significantly higher for HC than in CRF participants as was expected. This had been hypothesised, as the CRF participant group were a seriously ill group whose MVC force is affected by their fatigue. Vollestad states MVC is highly dependent on self-motivation and inhibitory effects at various levels in the central nervous system as well as at the muscle level (Vollestad, 1997; Lou, 2012; Finsterer and Mahjoub, 2014; Davis and Walsh, 2010; Gandevia et al., 1995).

5.7.5 EMG Measures

The use of EMG is a standard method and is widely used in fatigue analysis (Davis and Walsh, 2010; Cifrek et al., 2009; Gandevia, 2001; Finsterer and Mahjoub, 2014; Enoka and Stuart, 1992; Kisiel-Sajewicz et al., 2012; Cai et al., 2014; Winter, 2009b). Examining the amplitude, median frequency and power are established metrics for EMG analysis in fatigue assessment (Konrad, 2005) and previous studies have tested and validated these parameters (Davis and Walsh, 2010; Cifrek et al., 2009; Gandevia, 2001; Finsterer

and Mahjoub, 2014; Enoka and Stuart, 1992; Winter, 2009a; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Sinclair et al., 2015; Mathur et al., 2005). In a submaximal muscle contraction, where a target force is sustained for a prolonged period of time, the EMG amplitude increases. The hypothesis in this study was that EMG amplitude of the muscle would increase as fatigue progresses. As the task progressed and fatigue increased, there was a significant statistical difference observed in the amplitude change between the two groups with HC participants having a significantly higher rise in EMG amplitude at the end of the task compared to CRF participants (CRF: FCU: p=0.003, FCR: p=0.003; HC: FCU: p=0.02, FCR: p=0.01). This is supported by previous studies (Gandevia, 2001; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Finsterer and Mahjoub, 2014; Davis and Walsh, 2010; Cai et al., 2014; Yavuzsen et al., 2009).

The median frequency is expected to shift to lower frequencies as the fatigue progresses and is considered an index of fatigue as first described by Cobb and Forbes 1923 (Cobb, 1923), and also in other studies (Mathur et al., 2005; Allen et al., 2008; Vollestad, 1997; Bigland-Ritchie, 1981; Bigland-Ritchie et al., 1981; Hagg, 1992). While examining the individual median frequency shifts in HC and CRF participants, a statistically significant decrease occurred for both muscles (FCU and FCR) (CRF: FCU: p=0.0001, FCR: p=0.0001; HC: FCU: 0.002, FCR: 0.02). This significance indicates that all the participants were indeed fatiguing as the motor task progressed. However, it has been suggested that the shift does not always occur; therefore EMG median frequency should not be solely used to assess muscle fatigue (Vollestad, 1997; Bigland-Ritchie et al., 1981).

EMG power increases as more force is required to sustain the target force, as a result of extra motor units being recruited (Allen et al., 2008). This change in the EMG power spectral density can cause a shift in the EMG median frequency, as discussed in the previous section. In this study, as expected, with increasing fatigue, the EMG power of the healthy participants increased to a statistically greater extent than in CRF participants (CRF: FCU: p=0.01, FCR: p=0.0001; HC: FCU: p=0.01, FCR: p=0.001). There are numerous processes along the motor neuron pathway where fatigue may occur (Allen et al., 2008) and lead to this outcome. This may be due to the CRF participants

failing to recruit sufficient motor units to sustain the task, which resulted in a significantly lower increase in power and an earlier task failure.

The EMG measurements in this study were conducted without electrical muscle stimulation. This was done to avoid discomfort and pain for the CRF participants and to reduce the complexity of the experimental paradigm for evaluation and application in a clinical context. Results from this study demonstrate that this experimental methodology does induce fatigue in CRF participants and in healthy participants and may be used to objectively assess correlates of fatigue.

5.7.6 EEG Measures

EEG is one of the most widely used methodologies in neurophysiological assessment. The use of EEG for fatigue assessment has been tested and validated in previous studies of fatigue (Hsu and Wang, 2013; Gharagozlou et al., 2015; Nielsen et al., 2001; Trejo et al., 2005; Moore et al., 2014a; Davis et al., 2011). During a sustained muscle contraction, brain activation levels increase as the fatigue progresses (Liu et al., 2003; Siemionow et al., 2004). EEG power within the Beta frequency band was the main interest of this study as this is the frequency associated with voluntary motor activity (Yang et al., 2009; Moore et al., 2014a; Liu et al., 2003; Liu et al., 2007; Mima and Hallett, 1999b; van Duinen et al., 2007). While not significant (CRF: $p=0.59$, HC: $p=0.91$) the CRF participant group had greater neural activity at the beginning of the task to perform a lower level of muscle exertion.

5.7.7 Corticomuscular Coherence

Weakening of brain-muscle coupling has been reported in both healthy and pathological fatigue (Yang et al., 2010; Davis et al., 2011; Mima et al., 2001; Brown et al., 1999; Salenius et al., 1997; Tecchio et al., 2006; Proudfoot et al., 2018). Significant neural oscillations with rhythmic activity in the human sensorimotor cortex have been reported in the Beta frequency range (15-35 Hz), which correlates with motor output (Conway et al., 1995; Halliday et al., 1998; Kristeva et al., 2007; Yang et al., 2009). Numerous studies have shown significant correlation between EEG-EMG coherence during isometric contractions within Beta frequency range (Hashimoto et al., 2010; Chakarov et al., 2009;

Yang et al., 2009; Kristeva et al., 2007; Mima et al., 2001; Brown et al., 1999; Salenius et al., 2002; Salenius et al., 1997; Tecchio et al., 2006; Tomasevic et al., 2012; Proudfoot et al., 2018). In this study evidence was found of variation in the Beta band in both participant groups and was in agreement with other published studies (Yang et al., 2009; Yang et al., 2010; Davis et al., 2011; Tecchio et al., 2006; Proudfoot et al., 2018). However, the results from this study show that the decrease in coherence in the severe fatigue stage was minimal. Despite this, the results suggest that the mechanism of fatigue may involve the reduction or weakening of CMC, signifying a central element.

5.7.8 Experimental Protocol

The protocol and experimental procedures for this study were designed to be as non-invasive as possible for the participants and at every stage their wellbeing was prioritised. Examples of arrangements put in place are: comfortable height-adjustable seating procured, the dynamometer was chosen based on its ergonomic design and minimal discomfort during the grip task and the Graphic User Interface in LabCHART was adapted to be clearly visible to all participants. In addition, CRF patients expressed no concern about the use of neurophysiological testing for this population.

5.8 Conclusions

In this study we developed a metric to objectively evaluate correlates of fatigue in CRF and HC participants by examining neurophysiological changes during a fatiguing task. Acceptability questionnaires were given and a high level of device acceptability was reported by CRF and healthy participants (O'Connor, 2016). No participant had concerns about the use of EEG-EMG for similar patient groups.

The results from this study were treated with caution as the study number of CRF participants is low and cannot be generalized. However, the focus of this study was to validate and confirm measurements characterising neuromuscular alterations during a fatiguing task. All aspects of the experimental protocol, set up, fatigue task, recording and synchronisation of equipment, configuration and feedback of software have been assessed for suitability and validated for further fatigue analysis of CRF.

Chapter 6 will introduce Study 2 and discuss further analysis of a new patient group.

Chapter 5: Summary Points

- This study was conducted with the aim of designing an experimental paradigm and protocol to test the technology employed for objective assessment of fatigue with a fatiguing isometric motor task in a clinical setting and a pre-treatment cancer cohort.
- The cancer-related fatigue participant brief fatigue inventory scores were lower than in previous studies which may be due to this CRF participant group being newly diagnosed, prior to treatment, with a good overall performance status (ECOG).
- During the motor fatigue task, using the dynamometer the endurance time and the maximal voluntary contraction was recorded as significantly higher for healthy controls than the cancer-related fatigue group. This outcome was in line with previous studies as the cancer-related fatigue group indicated higher subjective fatigue as shown by the brief fatigue inventory.
- Cancer-related fatigue patients gave 100% acceptability for use of EEG and EMG assessment.
- The EEG, EMG and handgrip dynamometer hardware components and the software configurations were validated and are therefore ready for the next phase of patient testing in a large cohort.

Chapter 6: IDENTIFICATION & COMPARISON OF NEUROMUSCULAR IMPAIRMENT IN CANCER-RELATED & CHRONIC FATIGUE SYNDROME

STUDY 2

This study has been published as an abstract in the Journal of Supportive Care in Cancer (Volume 26, Issue 2 Supplement, June 2018).

Presented at the following international conference *(Appendix C)*:

Multinational Association of Supportive Care Cancer *(MASCC) June 2018.*

This chapter presents Study 2, a comparison of chronic fatigue syndrome, cancer-related fatigue and healthy control participants using the same experimental design and protocol as used in Chapter 5 for Study 1. This study sets out to answer research questions 2 and 7 in Chapter 4. Chronic fatigue syndrome and cancer-related fatigue are two fatigue disorders that share similar symptoms and clinical expression. Background information on chronic fatigue syndrome, its pathophysiology, treatment and prognosis are also discussed. However, a fundamental question is whether these illnesses share clinical characteristics and potentially, underlying pathophysiology.

6.1 Overview

Chronic Fatigue Syndrome (CFS) (which is also known as Myalgic Encephalomyelitis); is a common and debilitating state of fatigability unresolved with rest lasting at least 6 months or longer (Afari and Buchwald, 2003). The fatigue worsens with physical activity, impairing daily activity by 50% of the premorbid level (Servaes et al., 2001a; Bennett et al., 2007; Bennett et al., 2014; Chaudhuri and Behan, 2004; Fukuda et al., 1994; Okada et al., 2004). It is a symptom-based, clinical diagnosis, without any distinguishing gold-standard assessment i.e. physical examination or routine laboratory findings specifically for CFS. Multiple factors may cause CFS (Afari and Buchwald, 2003; Griffith and Zarrouf, 2008) and several mechanisms have been investigated which include immunological, neuroendocrine, sleep, and psychiatric disorders. A single, pathophysiological cause is unknown and an objective measure for CFS is absent. Studies have demonstrated that the central nervous system (CNS) is affected in CFS in CRF (Griffith and Zarrouf, 2008; Chaudhuri and Behan, 2004; Afari and Buchwald, 2003; Fukuda et al., 1994; Okada et al., 2004).

Chronic fatigue syndrome (CFS) similar to Cancer-related fatigue (CRF) patients often use descriptors like ‘overwhelmingly exhausted’, ‘totally empty of energy’ and frequently describe the fatigue as qualitatively different from earlier experiences (Soderlund et al., 2000; Bennett et al., 2007). Limited exertions, whether mental or physical, disproportionately worsen the sensation of fatigue. Likewise, rest or sleep does not relieve it. Despite the pathogenesis, those with CFS, like those with CRF and other chronic diseases, have a substantially impaired functional status that results in significant personal and economic morbidity (Afari and Buchwald, 2003).

6.2 Definition and Diagnosis

Despite the World Health Organization classification of CFS as a neurological disease, similar to CRF, there is no universal agreement on a definition. There are many groups

of clinical criteria that are recorded to define CFS; for example Brurberg 2014 (Brurberg et al., 2014) identified 20 or more criteria in 2014.

The array of different clinical criteria and preferences in terms of specific definitions for CFS, such as ME or systemic exertion intolerance disease (SEID), is partly due to the fact that the cause or causes of CFS are unknown and there are no objective tests to identify the condition. SEID was proposed by the US Institute of Medicine (IOM), partly because the CFS title might appear to diminish the severity and promote misunderstanding of the condition. The IOM also deemed the term myalgic encephalomyelitis as inappropriate due to 'lack of evidence' for encephalomyelitis (brain inflammation) in patients with the disease and because myalgia (muscle pain) is 'not a core symptom of the disease' (Rutherford et al., 2016a).

The most widely used case definition is that documented by the Centre for Disease Control and Prevention (CDC), 1994 (Fukuda et al., 1994; Afari and Buchwald, 2003). This CDC case definition (Fukuda et al., 1994) requires at least 6 months of persistent fatigue that substantially reduces the person's level of activity to more than 50% of pre-illness level. In addition, within the 6 month period, four or more of the following symptoms must occur with fatigue: aching or stiff muscles, impaired memory or concentration, sore throat, tender glands, multi-joint pain, headaches, unrefreshing sleep, and post-exertional fatigue (Afari and Buchwald, 2003) (Table 6-1). Any other co-morbid conditions (i.e. thyroid or sleep disorders) that may explain the prolonged fatigue as well as a number of psychiatric diagnoses (i.e. depression, psychotic disorders, bipolar disorder) must be excluded before a patient is given the diagnosis of CFS.

The diagnosis of the syndrome is clinical, due to there being no pathognomonic sign or specific test for CFS. However, as mentioned above other causes of fatigue must be ruled out first, through completion of a detailed medical history. This history must focus on the characteristics of fatigue, outlining its form and time of onset, duration, triggering factors, relationship with rest and physical activity, and the degree of limitation of the patient's regular activities (Table 6-1).

Table 6-1: CDC-definition and criteria for diagnosis of chronic fatigue syndrome

[Adapted from (Fukuda et al., 1994; Wyller, 2007)].

Main criteria (patients must adhere to all)	Additional criteria (patients must adhere to at least 4)
Persistent or relapsing fatigue of 6 months duration or more Fatigue severely affects daily activities Fatigue is not explained by any concurrent somatic or psychiatric condition Fatigue is new or definite in onset Fatigue is not the result of ongoing exertion Fatigue is not alleviated by rest	Impaired memory and/or concentration Sore throat Tender cervical and/or axillary lymph nodes Muscle pain Multi-joint pain New headaches Unrefreshing sleep Post-exertional malaise

6.3 Prevalence

It is difficult to establish the prevalence of CFS, as it depends on the diagnostic criteria used and the study population included. The peak age of onset of CFS is typically between 20 and 40 years and women are more commonly affected than men (Capelli et al., 2010). Prevalence and incidence data on CFS can be confusing and inconsistent, and the numbers of studies are limited. While most reports have come from the United States and Europe, increasing estimates are emerging from Asia and developing countries (Johnston et al., 2013). Estimates for the prevalence of current CFS using the CDC definition range from 0.007% to 2.8% in the US general adult population (Jason et al., 1999; Afari and Buchwald, 2003; Steele et al., 1998), 0.2-0.4% in the general adult population for Ireland (Trust, 2018) and a UK study using the same definition found a prevalence of 2.6% (Wessely et al., 1997). A study of CFS incidence in the United States reported a rate of 180 per 100,000 persons (Reyes et al., 2003). The varying definitions of CFS have an important bearing on prevalence estimates (Johnston et al., 2013). The issue is further complicated by the fact that subjective patient self-reporting of the

condition commonly results in significantly higher prevalence rates than those obtained in medical settings (Johnston et al., 2014).

6.4 Economic Burden

Severe CFS sufferers are largely housebound, with the most severe being bedbound and reliant on carers (ME Association 2007). In the UK, approximately 58% of individuals with CFS who access healthcare services are temporarily or indefinitely unemployed (Collin et al., 2011). The total annual cost (healthcare, disability benefits, productivity losses, informal care) of CFS to the UK economy was £3.3 billion in 2014-2015 (Collin et al., 2011; McCrone et al., 2003; Richardson et al., 2013; Sabes-Figuera et al., 2010). The annual cost of CFS in the United States on productivity loss alone was reported to be $9.1 billon (Reynolds et al., 2004).

6.5 Pathophysiology

Similar to CRF, the aetiology and pathophysiology of CFS remains unknown. In both CRF and CFS, historical diagnosis is made on the basis of subjective criteria including patient self-report and clinical assessment rather than objectively derived datasets (Bennett et al., 2007). Studies (Bennett et al., 2007; Schillings et al., 2004; Davis and Walsh, 2010; Siemionow et al., 2004; Kent-Braun et al., 1993a) of neuromuscular performance in patients with CFS indicate that the phenomenon of fatigue is attributable to a central, rather than a peripheral abnormality. There are many hypotheses for the pathophysiology of CFS but the aetiology has not been identified. Some of these overlap with the CRF hypotheses discussed in Chapter 2, Section 2.8. Earlier theories focused on the importance of symptoms that suggested an acute viral illness or psychiatric disorder. Abnormalities in a number of areas were documented in subsequent research, including brain structure and function, immune function, exercise ability, neuroendocrine responses, sleep disorders, virological studies and psychological profiles (Afari and Buchwald, 2003; Griffith and Zarrouf, 2008; Rovigatti, 2012).

6.5.1 Neuroendocrine Hypotheses

A review of CFS and neuroendocrine studies (Parker et al., 2001; Afari and Buchwald, 2003) showed that abnormalities have been identified in the hypothalamic-pituitary-adrenal (HPA) axis and serotonin pathways in CFS patients, suggesting an altered physiological response to stress (Scott et al., 2011). Those with CFS have demonstrated hypocortisolism (Parker et al., 2001) which appears to originate from a CNS source rather than a primary adrenal site (Demitrack et al., 1991; Demitrack and Crofford, 1998; Afari and Buchwald, 2003). The normal circadian rhythm of HPA axis activity is also disrupted, particularly diminishing cortisol secretion during morning hours (Cho et al., 2006; Afari and Buchwald, 2003; Demitrack and Crofford, 1998; Cleare, 2003). As for challenge tests, most studies indicate blunted HPA axis responses to exercise, hypoglycemia and the administration of stimulating pharmaceuticals (Cho et al., 2006; Cleare, 2003). The question of whether these alterations are a cause or consequence of chronic fatigue syndrome still remains unanswered (Cho et al., 2006).

6.5.2 Central Nervous System Abnormalities

Several symptoms reported by those with CFS in addition to fatigue were impaired attention concentration, memory loss, and headaches; this suggests that the CNS may be involved in the pathophysiology of the syndrome similar to CRF. Cognitive function tests have revealed attentional, information processing and memory problems, including those without psychological comorbidity. A meta-analysis (Cockshell and Mathias, 2010) revealed that there was evidence of cognitive deficits in CFS patients found primarily in the areas of attention, memory and reaction time. Neuroimaging studies of CFS have produced conflicting results. Some MRI studies have demonstrated alterations in subcortical white matter (Cook et al., 2001; Afari and Buchwald, 2003) and reduced grey matter volume (de Lange et al., 2004; Lange et al., 2005; Afari and Buchwald, 2003; Cleare, 2003), whereas another demonstrated no difference between CFS and HC (Cope and David, 1996). Studies with a motor fatiguing handgrip task with EEG and EMG have shown that CFS patients had lower ability to perform a motor task and had altered (a reduced capacity) central nervous system signals in controlling voluntary muscle activities compared to HC (Siemionow et al., 2004; Kent-Braun et al.,

1993a). Post-exercise motor cortical excitability was also reduced in CFS patients as compared with healthy volunteers (Samii et al., 1996). Observations from these studies suggest that there is a central mechanism underlying CFS (Central and peripheral components of fatigue were discussed in detail in Chapter 2, Section 2.8) and these abnormalities may be easier to classify with neurophysiological methods during motor activities that exaggerate self-perceived fatigue.

6.5.3 Sleep Disorders

Those with CFS often complain of disrupted sleep patterns, such as difficulty falling asleep, insomnia and increased daytime napping (Afari and Buchwald, 2003; Cleare, 2003). Previous studies have provided evidence of abnormal sleep patterns in CFS but no consistent pattern appears to exist (Manu et al., 1994; Fischler et al., 1997; Afari and Buchwald, 2003).

6.6 Treatment and Prognosis

6.6.1 Treatment

There is no gold standard treatment of CFS due to the unknown aetiology and pathophysiology. Many treatments and therapies have been examined and suggested and recent reviews conclude that cognitive behavioural therapy and exercise therapy have a proven benefit (Whiting et al., 2001; Edmonds et al., 2004; Avellaneda Fernández et al., 2009a; Bagnall et al., 2002; Chambers et al., 2006; Mulrow et al., 2001; Price and Couper, 1998).

6.6.2 Prognosis

The prognosis of CFS is unclear however; some studies suggest there is an average time of 5 years from the beginning of the symptoms to the diagnosis of the syndrome. Between 6% and 63% show improvement of their overall fatigue levels with total recovery rates between 0% and 37% (Cairns and Hotopf, 2005; Avellaneda Fernández et al., 2009b). Younger patients and those without concomitant psychiatric diseases show

the best prognosis, although other studies have estimated that the rates for both groups are similar (van der Werf et al., 2002).

6.7 Aim

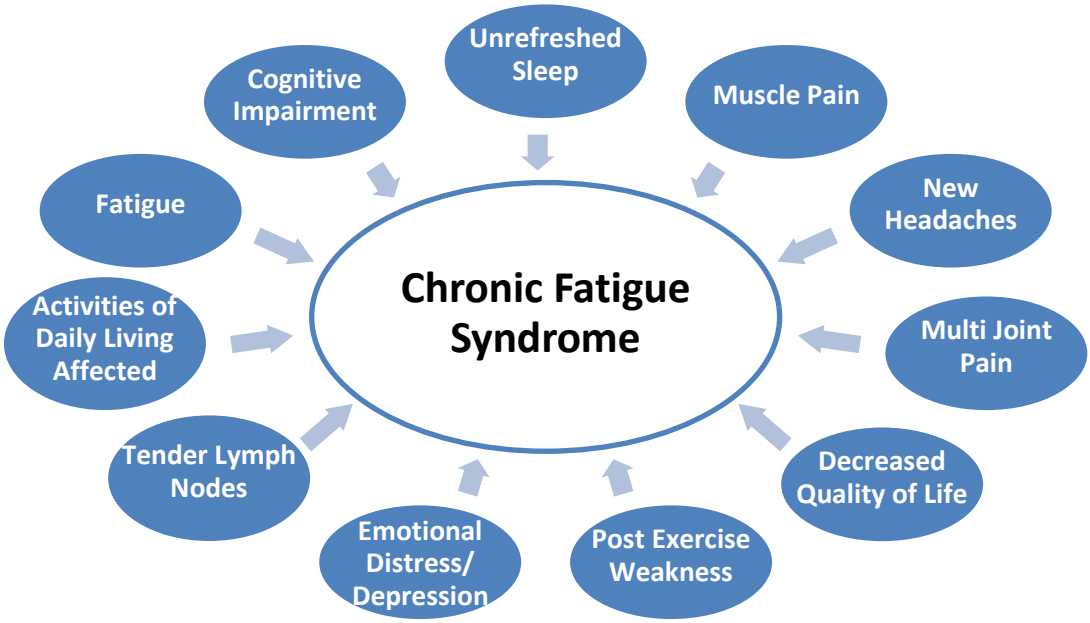
The aim of this second study was to provide an important and relevant comparison between CFS and CRF in order to better understand the fatigue aetiology. Neurophysiological signals of CFS were examined to identify differences in comparison to healthy controls.

The hypothesis for this study is that both CRF and CFS are of a more central origin due to altered central nervous system signals. In addition, CMC reflects the communication between the cerebral cortex and the muscle, and may be the cause for the feelings of fatigue (Yang et al., 2009). A secondary hypothesis for this research is that CMC will be weakened at the onset of fatigue in comparison to healthy controls (HC).

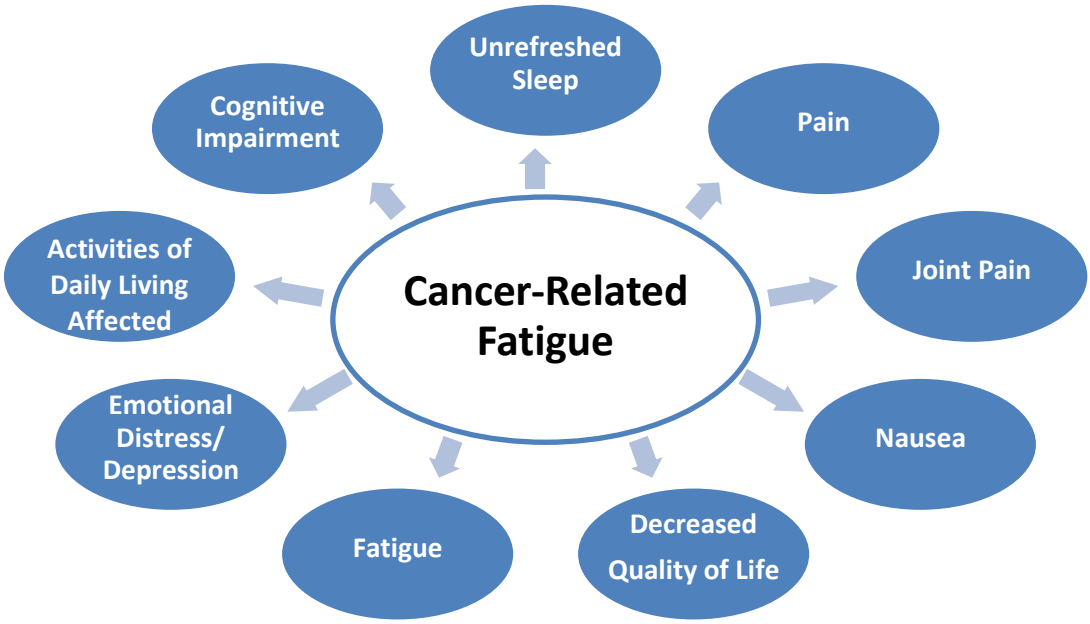
The hypothesis of this study is that both CRF and CFS are more centrally mediated disorders and display similar characteristics.

6.8 Rationale for Chronic Fatigue Syndrome as a Comparison Group

As mentioned in Chapter 2, Table 2-2; CRF and CFS are two fatigue disorders, with overlapping characteristics in terms of symptoms, potential mechanisms of onset/exacerbation, involvement of both the central and peripheral nervous systems, and a highly negative impact on the quality of life of those affected.



6-1a: Chronic Fatigue Syndrome – symptoms to diagnosis



6-1b: Cancer-Related Fatigue – diagnosis to symptoms

Figure 6-1: a & b: Context of CFS / CRF Discussion

As can be seen from Figure 6-1a and 6-1b, there is a strong correlation between CRF and CFS with regard to the symptoms reported. When looking at CRF, the genesis appears to be the cancer diagnosis i.e. type, stage, severity. The symptoms of fatigue may subsequently be observed at various stages for example, (a) pre-surgery, pre-treatment

(the stage of CRF reported in this research) (b) during treatment (c) post-treatment (d) remission / survivorship.

Paradoxically it may be suggested that there is no such genesis with CFS. It appears as a constellation of symptoms which when using the IOM/CDC guidelines can form a whole, these can then be categorised as CFS (Rutherford et al., 2016a; Fukuda et al., 1994). However, despite the divergent foundations, similarities can be observed for CRF and CFS in the type of reported symptoms. For example, unrelenting fatigue, unrefreshed sleep, and impaired memory. While there are possible multi-symptom combinations and a range of potential variables there may be scope to develop a standardised description of the aetiology and/or pathophysiology of shared symptoms. It may be hypothesised that if the individual symptoms or group of symptoms for CRF and/or CFS had an accepted classification then standard assessment and therefore standard symptom treatment may be developed.

In the study now presented neurophysiological changes in three groups i.e. pre-treatment CRF, CFS and healthy control participants, are examined. The hypothesis of this study is that both CRF and CFS are more centrally mediated disorders and display similar characteristics.

It should be acknowledged that in the comparison of these cohorts there is a limitation of the cohorts not being age or gender matched. However, the comparisons made are valid. Further in-depth discussion of this limitation can be found in Chapter 9, Section 9.4, limitations of research.

6.9 Methods

In this Chapter, the same methods utilised in Study 1 (motor fatigue task, EMG, EEG and CMC analysis) were employed across the three cohort groups.

As discussed in chapter 5, to determine central and peripheral contributions to fatigue, we examined endurance time, MVC, EMG amplitude, EMG amplitude change, EMG median frequency shift and EEG power.

6.9.1 Participant Recruitment

6.9.1.1 Power Analysis

The power analysis calculations, employing Fisher's exact test for this study, were that 20 participants in each cohort would give significant results (GraphPad software).

For this study, 12 newly-diagnosed, pre-treatment, non-small cell lung cancer participants (CRF), 12 chronic fatigue syndrome (CFS) and 12 new healthy control (HC) participants were recruited. To increase the participant population, in line with the inclusion and exclusion criteria previously mentioned in Chapter 5, Section 5.2.1; additional eligible non-small cell lung cancer patients who had no treatment and no surgical intervention were sought. As before, St. Vincent's University Hospital Lung Cancer Clinics and the Irish ME Trust were approached and over an 18 month period potential participants were contacted. However, the success of this endeavor was limited primarily caused by the challenge of recruiting from a seriously ill population. Therefore, 10 of the 12 CRF participant's datasets were from study 1. In addition, the participants are not age matched. This will be discussed in detail in Chapter 9.

6.9.1.2 Chronic Fatigue Syndrome Participants

Twelve CFS patients were recruited (Table 6-3). Recruitment took place in cooperation with the Irish CFS/ME Association and the Irish ME trust between October 2016 and August 2017. CFS participants had a medical diagnosis for the condition which was confirmed by clinicians involved with each individual. Exclusion criteria for all groups included, no previous diagnosis of malignancy or other neurological disorders, could not have significantly impaired pulmonary function, any paraneoplastic condition affecting muscle function or left-hand dominance.

Informed consent was obtained from all participants prior to testing. The study conformed to the 1964 Declaration of Helsinki and ethical approvals were obtained from the Ethics and Medical Research Committees (Appendix B). Of the 48 CFS participants

screened for recruitment, 12 participated in the study (Figure 6-2; Table 6-2) and experimental BFI, EMG and EEG data was obtained.

Table 6-2: CFS participant recruitment process

Stages of CFS Recruitment	Outcomes
Stage 1 Source of potential participants	➢ Contact was made with the Irish ME Trust and the Irish CFS/ME Association ➢ The study was advertised within their membership group seeking volunteers to participate ➢ The names of 48 potential participants were provided ➢ All 48 were contacted and exclusion / inclusion assessments were completed with them by phone ➢ **44** potential participants moved to next stage
Stage 2 Communication	➢ Participant information leaflets and detailed explanations were provided (Appendix B) ➢ **19** of the original potential participants either dropped out after this communication or were deemed ineligible as a result of further discussions with researcher
Stage 3 Scheduling of testing	➢ **24** potential participants were scheduled for testing ➢ **7** of those invited either did not attend or were unable to reschedule to another time/date
Stage 4 Testing	Of the **17** people who attended for testing: ➢ 2 reported a cancer diagnosis so data could not be utilised for this study ➢ 3 participant's results were not usable as he/she could not sustain the handgrip and due to fatigue did not want to repeat it. ➢ **12 people successfully completed the test**

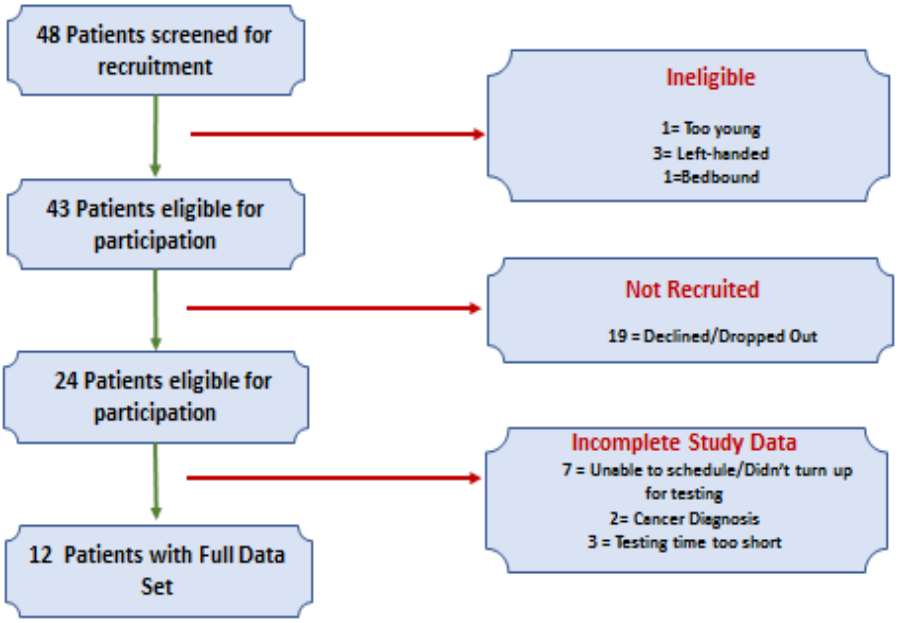


Figure 6-2: Flowchart Summary of CFS recruitment for study.

Table 6-3: Demographic details of CFS patients

Recording took place between December 2016 and February 2017 Trinity College Dublin.

Patient Study Number	Age	Gender
CFS1	43	M
CFS2	47	F
CFS3	59	F
CFS4	58	F
CFS5	39	F
CFS6	30	F
CFS7	61	F
CFS8	51	F
CFS9	46	M
CFS10	32	F
CFS11	60	M
CFS12	61	M

6.9.1.3 Healthy Control Participants

Healthy control (HC) participants (Table 6-4) were recruited through professional contacts associated with the Neural Engineering Laboratory at the Trinity Centre for Bioengineering, Trinity College Dublin (TCD). A new healthy participant group to that of Study 1 was enlisted in order to ensure age-matching. Experimental BFI, EMG and EEG data were obtained from 12 HC. All data analysis was conducted offline. The same process for recruiting CFS participants was used for HC participants using an amended inclusion/exclusion criterion.

Table 6-4: Demographic details of Healthy Control Participants

Recording took place between December 2016 and April 2017 Trinity College Dublin.

Patient Study Number	Age	Gender
HC1	60	F
HC2	61	M
HC3	56	F
HC4	56	M
HC5	35	F
HC6	60	M
HC7	66	M
HC8	30	M
HC9	50	F
HC10	33	M
HC11	33	F
HC12	59	M

6.9.1.4 Cancer-Related Fatigue Participants

Table 6-5: Details of recruited cancer-related fatigue (CRF) Participants (as in Chapter 5) with an additional 2 new participants.

Patient Study Number	Age	Gender	ECOG Score
CFP1	48	F	1
CFP2	78	M	1
CFP3	58	F	1
CFP4	65	M	1
CFP5	77	F	0
CFP6	77	F	1
CFP7	50	F	1
CFP8	60	F	2
CFP9	54	M	1
CFP10	73	M	0
CFP11	65	M	0
CFP12	69	M	0

6.9.2 Experimental Design

The same experimental protocol, set up and data collection of motor fatigue task and neurophysiological signals were employed as previously reported in the study presented in Chapter 5.

6.9.3 Statistical Analysis

Tests for normality were confirmed. T-tests (paired and independent t-tests) and general linear model repeated measures approach was employed to statistically compare the EMG, EEG parameters, and coherence between CFS and HC among different stages, muscles and areas with a covariate of age. Statistical analysis was implemented using SPSS 24 (IBM New York, USA) (Chapter 5, Section 5.5.8 for in-depth detail).

6.10 Results

After successful data acquisition from 12 CFS, CRF and HC participants, all data were analysed offline using MATLAB R2016a. The results of subjective and objective measurements obtained from this study will now be presented.

6.10.1 Age and Gender

There was a difference in age (mean CRF age: 64.5y; mean CFS age: 49y; mean HC age: 50y) for CRF vs HC group (p=0.007), and the CRF vs CFS (p=0.002). It was planned that recruitment of age-matched participants would occur, but with the challenging recruitment of cancer patients, and NSCLC occurring more commonly in older individuals and CFS being more prevalent in younger females, this was not feasible. Some aspects of fatigue are age dependent. Fatigue perception and fatigability increase with age, as well as age related muscle mass. Age does not reduce the ability to recruit motor units or central drive during motor activities however, there is greater variability in motor neuron firing with age (Davis and Walsh, 2010; Christie and Kamen, 2009, Finisterer and Mouhjab 2014). Yet it should also be recognised in this study that in the extreme case, a thirty-three-year-old healthy control is being used to compare with a seventy-eight-old cancer patient. While this is not a suggestion to discredit any findings, it worth noting that the weakening of corticomuscular coherence as well as variations in EEG characteristics with aging has been reported in the literature [Bayram et al, 2015; Davis and Walsh, 2010] and so the variation in ages between cohorts may have affected the neurophysiological results obtained in this study.

With age, there are many changes to the neuromuscular system, such as a decline in the amount of cortico-motor connections, the number of motor units, as well as a decrease in motor axon conduction velocities (Christie and Kamen 2009). However, despite these neuromuscular changes, it is reported that older individuals have greater fatigue resistance than younger individuals in several different muscle groups and under a variety of fatiguing tasks (Christie and Kamen 2009).

There was also a slight difference in gender ratio in the groups. This was not found to be statistically significant with 6:6, 8:4 and 5:7 females to males in the CRF, CFS and HC groups respectively. Ideally the gender ratios should be the same for each group.

6.10.2 Edmonton Symptom Assessment Scale

As in Chapter 5, Section 5.6.2, the CRF participants completed an Edmonton Symptom Assessment Scale (ESAS), and reported a moderate-severe symptom burden, with the most common symptoms being fatigue, anxiety and lack of appetite (Figure 6-3).

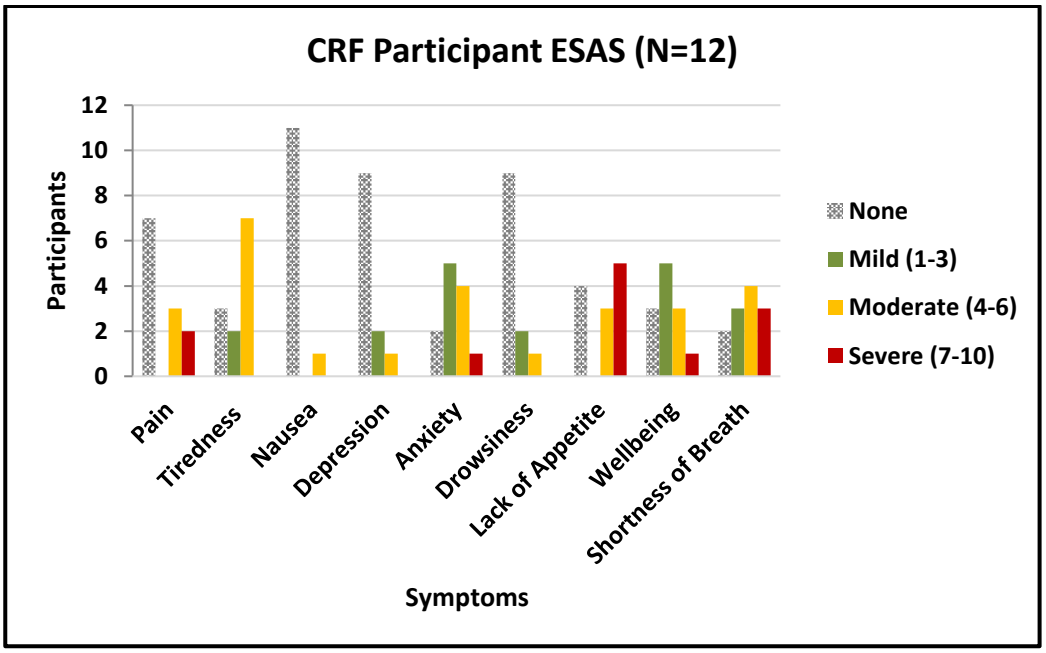


Figure 6-3: CRF Participants ESAS profile

CRF participant ESAS severity profile: where 0 represents absence of the symptom and 10 represents the worst possible severity. None represents no feelings of that symptom; Mild represents a score of 1-3; Moderate represents a score of 4-6 and severe represents a score of 7-10. This graph demonstrates that 3 out of 12 CRF participants reported no "tiredness", but 7 out 12 participants reported moderate feelings of "tiredness".

6.10.3 Brief Fatigue Inventory

All participants were assessed on their level of fatigue by the BFI questionnaire (mean BFI score in CRF = 3.2 ± 1.9; CFS = 6.6 ± 1.5; and HC = 2.3 ± 2.3). The CRF group and CFS group reported statistically significantly higher feelings of fatigue. Intergroup comparison showed significance for CRF vs CFS (p=0.0001) and CFS vs HC (p=0.0001) but not for CRF vs HC (p=0.32) (Figure 6-4).

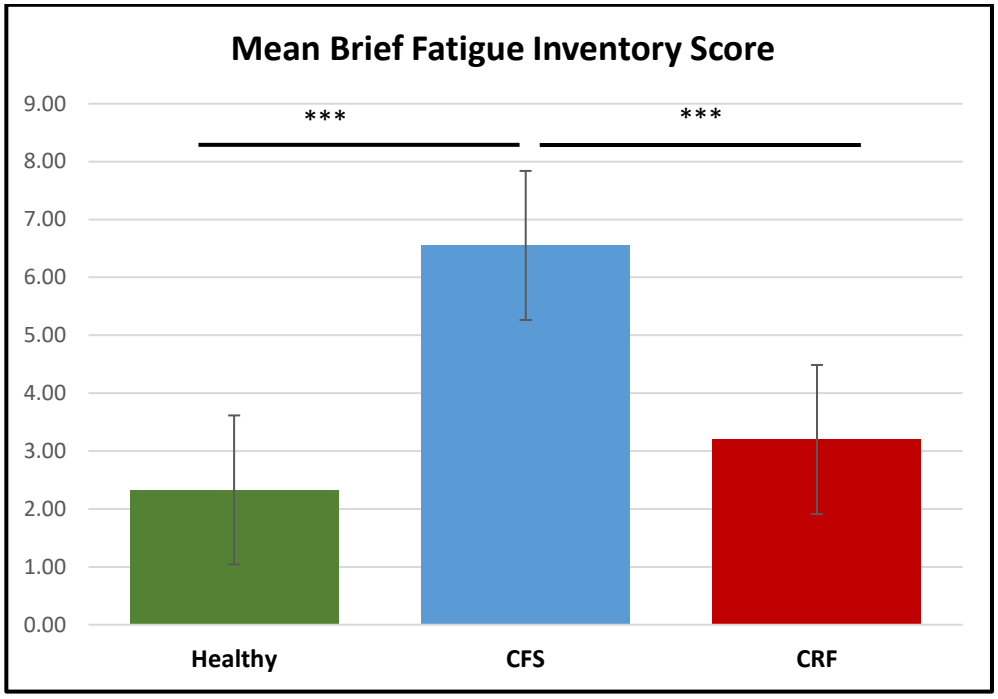


Figure 6-4: Total Mean BFI scores

Total mean BFI score of healthy controls (HC), chronic fatigue syndrome (CFS) and cancer-related fatigue (CRF) (*** indicates p<0.001).

Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

6.10.4 Endurance Time

Endurance time was defined as the duration from the moment the force reached the target (30%) to task failure. Both the CRF group and CFS group were consistently shorter in completing the task than the HC group (CRF =201s ± 165s; CFS = 291s ± 165s; HC= 512s ± 417s) but it was not statistically significant. Intergroup comparison showed

statistical significance only for CRF vs HC (p=0.02) but not for CFS vs HC (p=0.10) and CRF vs CFS (p=0.19) (Figure 6-5).

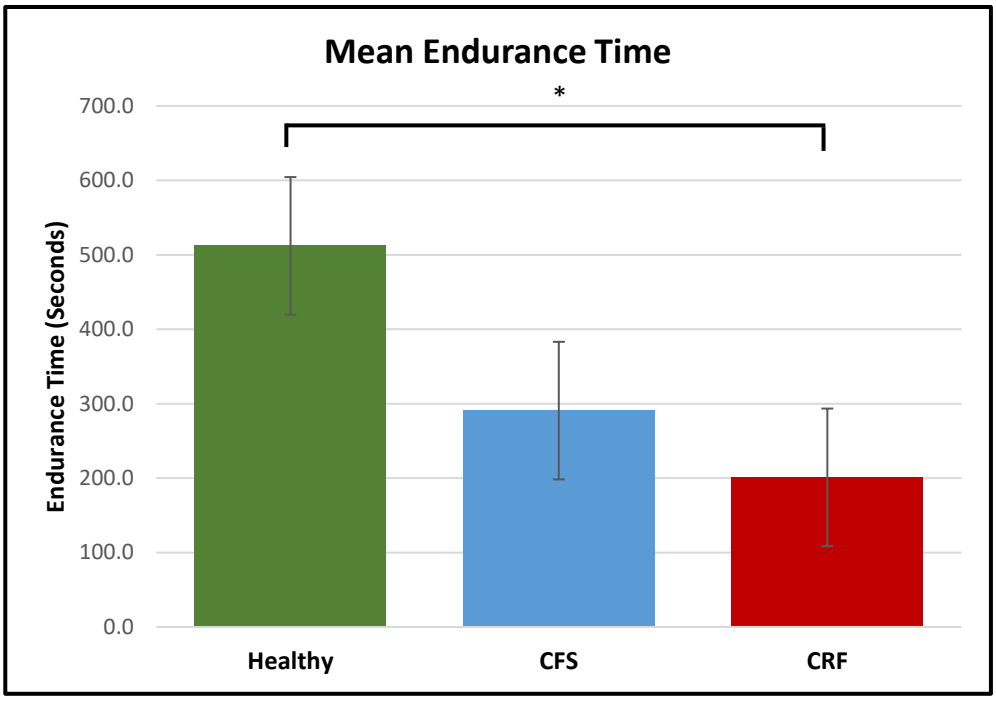


Figure 6-5: Mean Endurance Times

Mean endurance times for healthy controls (HC), chronic fatigue syndrome (CFS) and cancer-related fatigue (CRF) (* indicates p<0.05).

Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

6.10.5 Maximal Voluntary Contraction

MVC force (Newtons) was lowest for the CFS group (mean MVC: CRF = 305 ± 127N; CFS = 237 ± 65N; HC = 351 ± 152N) but only statistically significant for the CFS group vs HC group (p=0.02) (Figure 6-6).

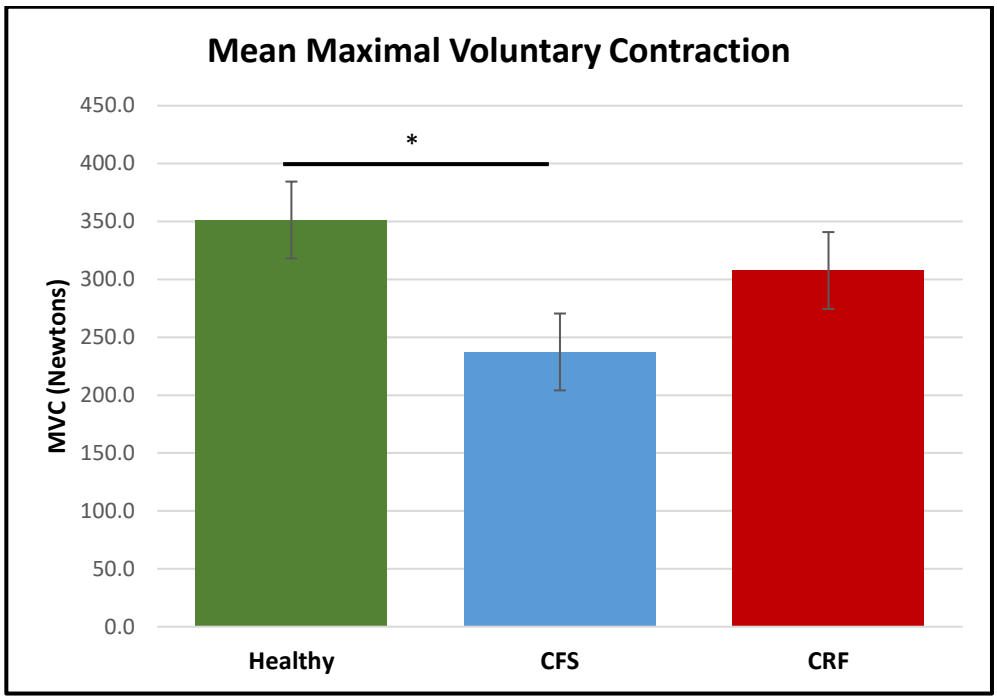


Figure 6-6: **Mean Maximal Voluntary Contraction (MVC)**

MVC for healthy controls (HC), chronic fatigue syndrome (CFS) and cancer-related fatigue (CRF) (* indicates $p<0.05$).

Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

6.10.6 EMG Measures

6.10.6.1 EMG Amplitude

As hypothesised there was an increase in each group and each muscle for EMG amplitude (RMS). This effect was less apparent in the CFS group who have been found to generally present with a lower RMS voltage level with motor task engagement (Siemionow et al., 2004; Schillings et al., 2004; Kent-Braun et al., 1993a).

The increase in RMS voltage between mild and severe was statistically significant for the CFS and HC group for FCR muscle (and CRF for FCU muscle (Figure 6-7, Table 6-6)). The intergroup comparison only showed statistical significance for CRF vs CFS groups between each muscle and fatigue stage (FCU mild: p= 0.01; FCU severe: p=0.02; FCR

mild: p=0.004; FCR severe: p= 0.01) and significance for CFS vs HC for FCR muscle at mild fatigue (p=0.05).

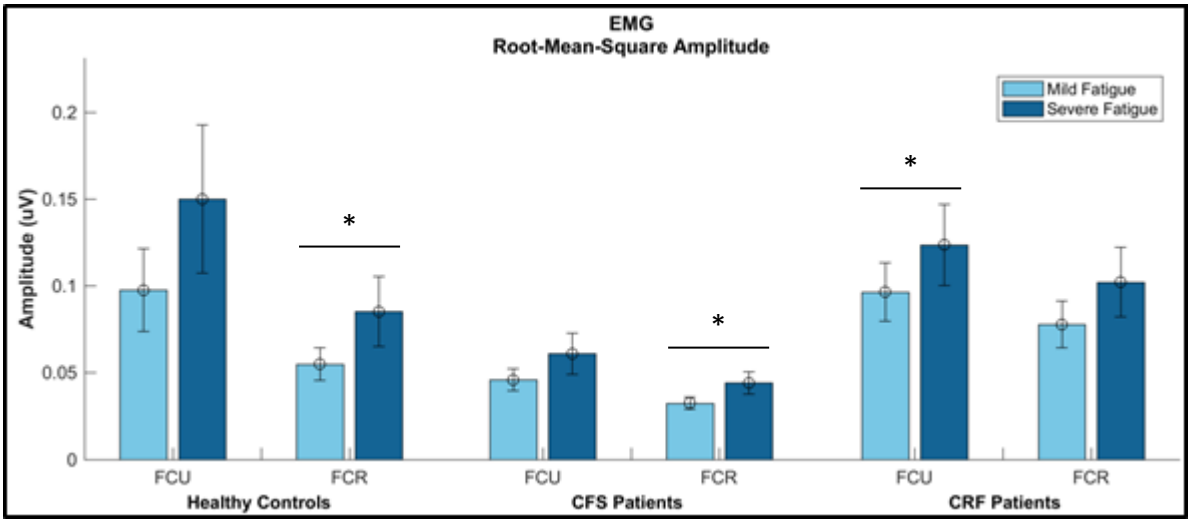


Figure 6-7: **RMS amplitude values for all three groups from mild to severe fatigue stages**

(* indicates p<0.05).

Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

Table 6-6: Statistical comparison of EMG (RMS) amplitude values for both muscles

Statistical comparison of EMG flexor carpi ulnaris (FCU) and flexor carpi radials (FCR) at mild vs severe fatigue stages for each group separately.

Groups	Muscle & Fatigue Stage	Significance P-Value
CRF	FCU Mild Fatigue vs FCU Severe Fatigue	0.04
	FCR Mild Fatigue vs FCR Severe Fatigue	0.07
CFS	FCU Mild Fatigue vs FCU Severe Fatigue	0.10
	FCR Mild Fatigue vs FCR Severe Fatigue	0.04
HC	FCU Mild Fatigue vs FCU Severe Fatigue	0.06
	FCR Mild Fatigue vs FCR Severe Fatigue	0.02

6.10.6.2 Percentage Change in EMG RMS Value

The most perceptible difference in percentage RMS voltage between fatigue stages was in the HC group (as seen in Figure 6-8). For all three groups, none of the results were statistically significant. Between group comparisons of percentage change in RMS voltage between mild and severe fatigue stage for each muscle were not significant, however the CRF vs HC group showed a slight trend towards significance (p=0.2).

Finally, RMS voltage percentage change determined if the FCU and FCR muscles behaved similarly during both fatigue stages for each group. For each muscle, from mild to severe fatigue stage (FCU mild vs FCR mild, FCU severe vs FCR severe), results were statistically significant for each group, except severe stage of FCR muscle for the CFS group which continued to show a strong trend toward significance (Table 6-7).

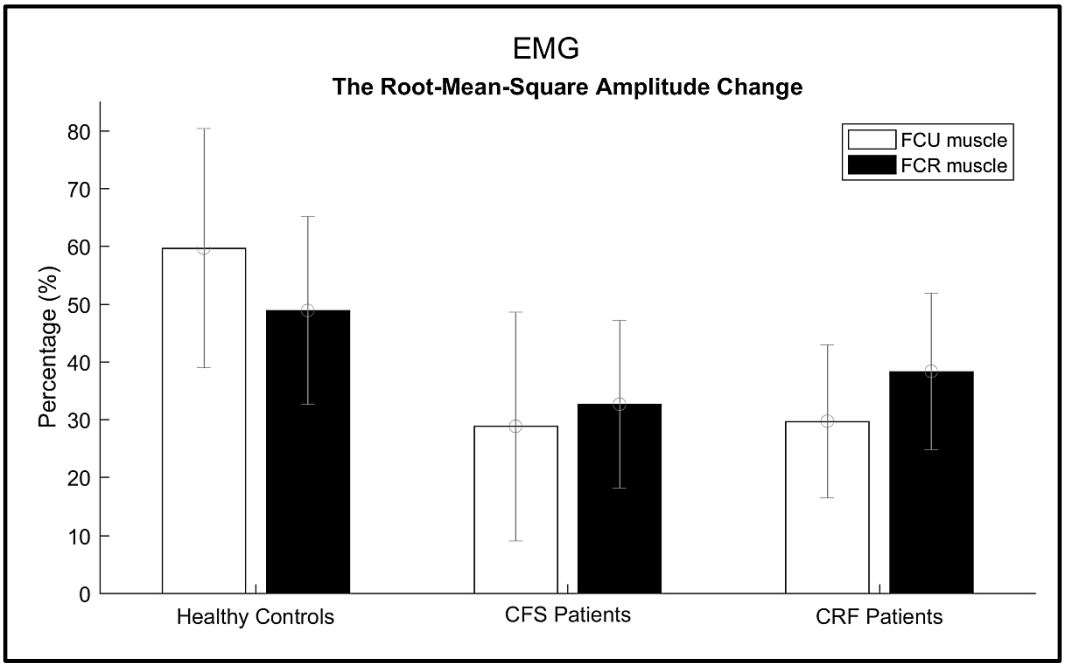


Figure 6-8: EMG RMS amplitude percentage change for each muscle and group alone.

Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

Table 6-7: Statistical comparison of EMG (RMS) amplitude percentage change

Statistical comparison for flexor carpi ulnaris (FCU) and flexor carpi radialis (FCR) muscles at mild vs severe fatigue stages for all groups.

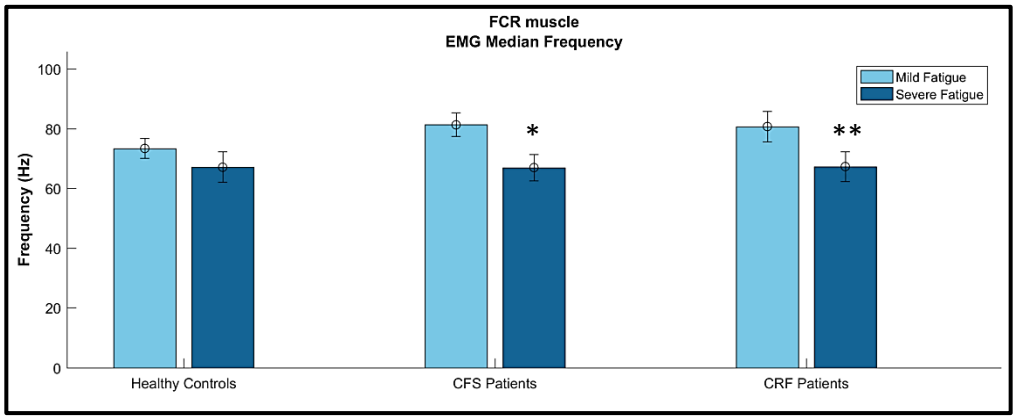
Groups	Muscle & Fatigue Stage	Significance P-Value
CRF	FCU Mild Fatigue vs FCR Mild Fatigue	0.02
	FCU Severe Fatigue vs FCR Severe Fatigue	0.03
CFS	FCU Mild Fatigue vs FCR Mild Fatigue	0.01
	FCU Severe Fatigue vs FCR Severe Fatigue	0.08
HC	FCU Mild Fatigue vs FCR Mild Fatigue	0.05
	FCU Severe Fatigue vs FCR Severe Fatigue	0.04

6.10.6.3 EMG Median Frequency

With an increase in fatigue, a shift from higher frequencies to lower frequencies should occur. As hypothesised, there was a general decrease in median frequency as fatigue progressed in each group and each muscle. Median frequency shift (Figure 6-8) was compared between fatigue stages for each muscle for each group alone. This was statistically significant for all groups for both muscles, except the HC group for FCR muscle (CRF: FCU: p=0.00001, FCR: p=0.002; CFS: FCU: p=0.00001, FCR: p=0.01; HC: FCU: p=0.006, FCR: p=0.1). Intergroup comparison of median frequency shift showed no statistical significance for either muscle or fatigue stage.

Percentage change in median frequency for both muscles and fatigue stages in all three groups was also calculated. Percentage change individually and for intergroup comparison showed no statistical significance differences.

(a)



(b)

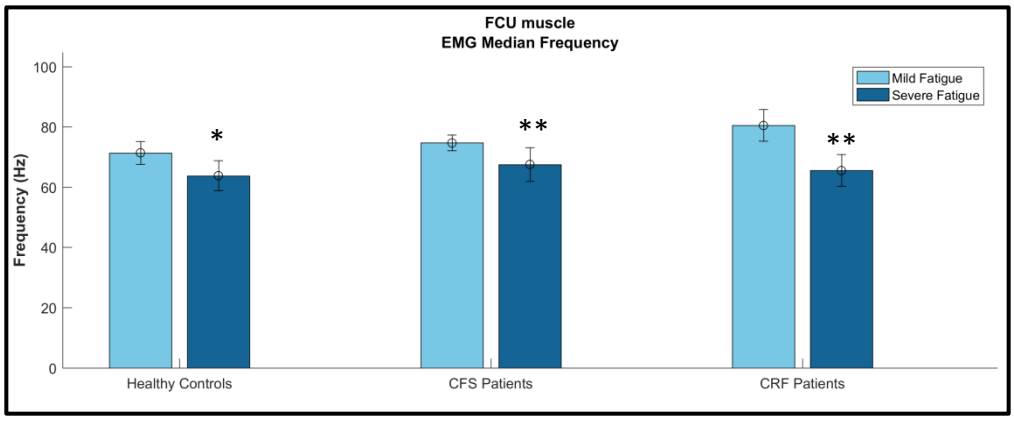


Figure 6-8: EMG Median frequency results for the FCR muscle and FCU muscle.

EMG median frequency for (a) FCR and (b) FCU muscles for all three cohorts.
* indicates p<0.05 and ** indicates p<0.01.
Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

6.10.6.4 Rate of Fatigue

As median frequency is a widely accepted parameter of fatigue, the rate of fatigue was then calculated from the rate of change of median frequency, from mild to severe fatigue for both FCR and FCU muscles:

$$R_f = \frac{MF_{mild} - MF_{severe}}{ET}$$

Where *Rf* is the rate of fatigue (Hz/s), *MFmild* is the median frequency at mild fatigue (Hz), *MFsevere* is the median frequency at severe fatigue (Hz) and *ET* is the endurance time (s).

This was to provide further information about the fatiguing behaviours between the groups, and taking the endurance times into account provides a standardised result for each subject. It was hypothesised that the CRF group would fatigue at the highest rate, followed by CFS group while the HC group were expected to fatigue the slowest. The analysis compared the groups fatigue rates for each muscle, finding statistically significant differences only for CRF vs HC groups for the FCR muscle (p=0.05).

6.10.6.5 EMG Power

The final EMG parameter that was evaluated was relative EMG power in the Beta band (15-35Hz) (Figure 6-9). As mentioned previously, an increase in EMG power is typical with an increase in fatigue. For each group and muscle individually from mild to severe fatigue stage an increase in power was statistically significant (Table 6-8). Intergroup comparison of EMG Beta band power showed significance for the CRF vs HC group for the FCU muscle only (FCU mild: p=0.03; FCU severe: p=0.04).

Table 6-8: Statistical analysis for normalized EMG power in the Beta frequency band (15-35Hz) between mild and severe fatigue for each group and muscles.

Groups	Muscle & Fatigue Stage	Significance (p-value)
CRF	FCU Mild Fatigue vs FCU Severe Fatigue	0.004
	FCR Mild Fatigue vs FCR Severe Fatigue	0.0001
CFS	FCU Mild Fatigue vs FCU Severe Fatigue	0.003
	FCR Mild Fatigue vs FCR Severe Fatigue	0.002
HC	FCU Mild Fatigue vs FCU Severe Fatigue	0.03
	FCR Mild Fatigue vs FCR Severe Fatigue	0.02

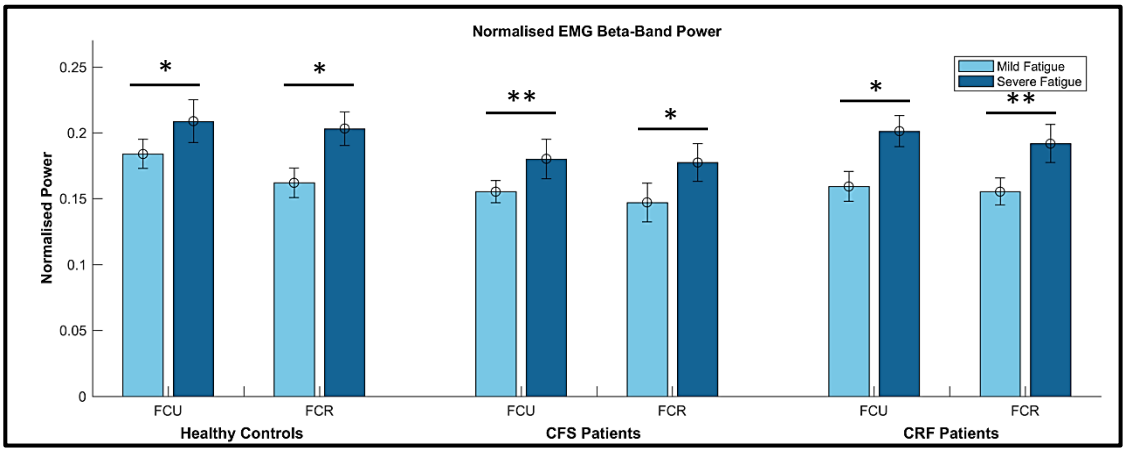


Figure 6-9: Normalised EMG power in the Beta band (15-35Hz)

Normalized EMG power in the Beta band for each group at both fatigue stages for FCU and FCR muscles. (* indicates p<0.05, ** indicates p<0.01).

Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

6.10.7 EEG Measures

6.10.7.1 EEG Power

The region of interest chosen for EEG in this study was the left motor cortex, due to the contralateral control of right arm that performs the motor task (Yang, 2008; Yang et al., 2009; Liu et al., 2007). Cortical activation sites have been found to vary with fatigue. This suggests that the brain modulates the location of cortical activation to maintain the motor output, while resting neural cells, which function in parallel (Liu et al., 2007).

An increase in EEG power is expected with fatigue progression for each participant group, particularly over the left motor cortex, with this increase more distinct in the CRF and CFS groups. EEG power within the Beta frequency band (15-35Hz) was calculated for each combination of fatigue stage in each group. The CRF and HC group did not follow the hypothesis and demonstrated decreased Beta band power from mild to severe task stages, which was not statistically significant (p=0.28, p=0.85 for the CRF group and HC group respectively). The CFS group had greater Beta band power than the CRF and HC group. The CFS group showed a slight change between mild and severe

fatigue which was also not statistically significant (p=0.96) (Figure 6-10; Table 6-9). For intergroup comparison from mild to severe fatigue, there were no significant differences for either fatigue stage in Beta band power. Individually within each group, a power increase was observed in six out twelve CRF participants, two out of twelve CFS participants and five out of twelve HC participants when progressing from the mild to severe fatigue stages.

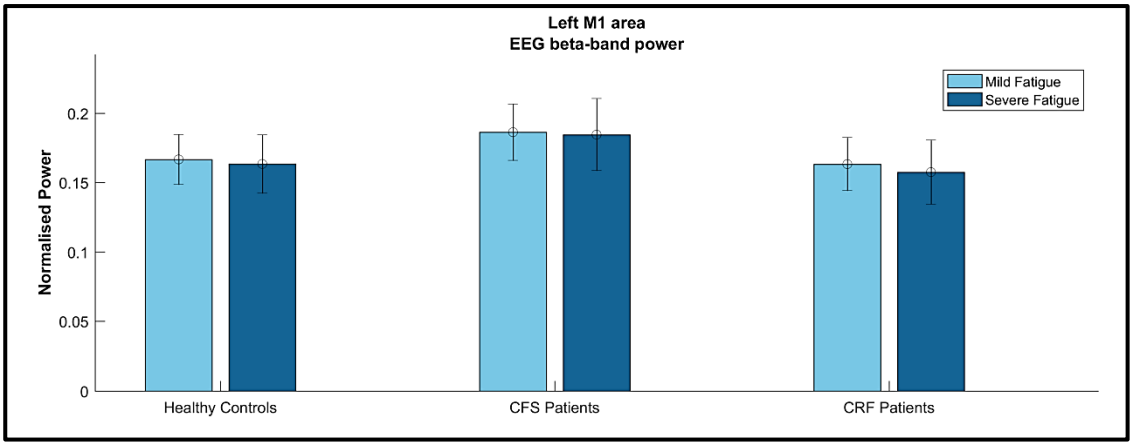


Figure 6-10: **Normalized EEG power in Beta frequency band (15-35 Hz)**

Normalized EEG power in Beta frequency band (15-35 Hz) for all groups (Cancer-Related Fatigue, Chronic Fatigue Syndrome and Healthy controls). EEG showed no significant differences in beta power for HC group; while not significant, the CRF and CFS groups show more neural activity in the Beta frequency band to begin the motor task and during mild fatigue.

Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

Table 6-9: Intergroup comparison of change in EEG Beta power (15-35Hz)

Intergroup comparison of change in EEG Beta power between task stages (mild and severe fatigue); there were no significant differences between stages for group comparison.

Groups	Fatigue Stage (Mild or Severe) EEG	Significance (p-value)
CRF vs HC	Mild	0.92
	Severe	0.68
CRF vs CFS	Mild	0.42
	Severe	0.30
HC vs CFS	Mild	0.48
	Severe	0.47

6.10.7.2 Topographic Maps

Topographic maps were generated for the three cohort groups in order to examine the temporal changes in the spectral intensities and compare the spectral power distribution across the scalp before the fatiguing task, and after the onset of fatigue. Beta frequency band power was calculated topographically for the mild and severe fatigue stages for all cohort groups. It can be observed that as fatigue progresses the power increases within the Beta frequency band and this increase is most noticeable over the left hemisphere. This pattern was observed in all participant groups. However, the extent of power increase varied among participants (Figure 6-11) with the HC group showing a “rotation” of cortical areas from mild to severe fatigue in order to modulate their fatigue and maintain the task longer.

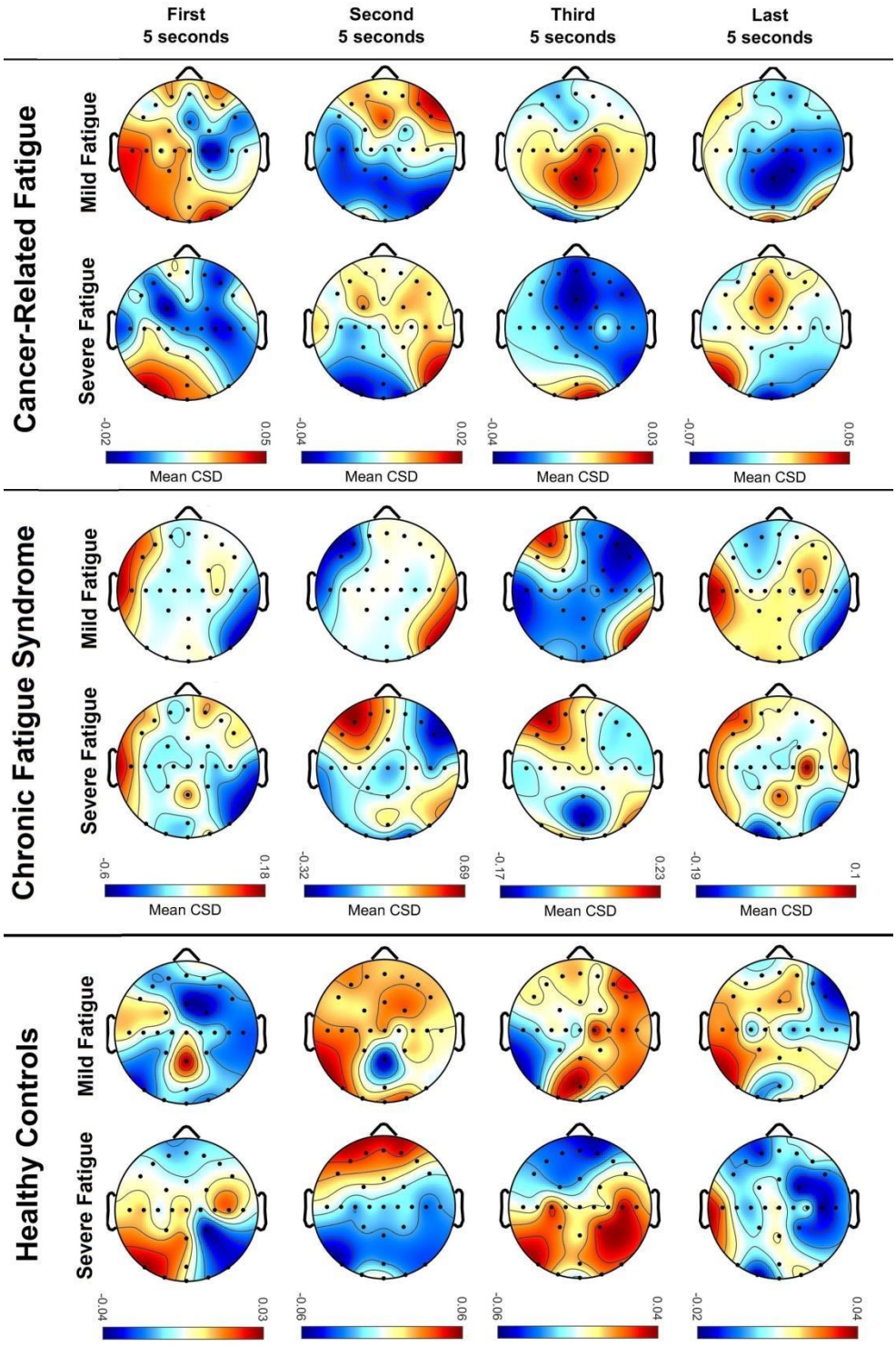


Figure 6-11: Topographic plots within the Beta frequency range for all three cohort groups

Topographic plots within the Beta frequency range for all three cohort groups for mild and severe fatigue stages. The maps demonstrate an overall increase in power with fatigue progression. With red representing a “hotspot” of neural activity, and blue representing less neural activity. The extent of power increase varied among participants, which can be observed from the plots.

6.10.8 Corticomuscular Coherence

As discussed in Chapter 5 Section 5.6.7, the hypothesised pattern of CMC in healthy individuals is that of greater synchrony between neural and muscle signals at the onset of fatigue and a reduction in synchrony as fatigue progresses. The CMC results in this study differed from previously published studies (Yang et al., 2009; Yang et al., 2010; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Davis et al., 2011), with no consistent pattern demonstrated and a less statistical significant difference in coherence between fatigue stages for each cohort group.

In this study, EEG-EMG coherence over the contralateral motor cortex decreased in the severe fatigue stage compared to mild fatigue, though not significant for any participant group. The CFS group showed a decrease in CMC in the Beta band (15-35 Hz) in both FCU and FCR muscles, while CRF showed a decrease only in the FCR ($p=0.05$). The HC demonstrated a CMC decrease only for the FCU muscle on comparing stages of mild fatigue to severe fatigue states. These results except for the FCR muscle within the CRF group were not statistically significant (Figure 6-12)

Individually, from the mild to severe fatigue stage showed for the CRF cohort:

- Seven out of twelve participants demonstrated decreased CMC for the FCU muscle.
- Nine out of twelve participants demonstrated decreased CMC for the FCR muscle.

For the CFS cohort group:

- Nine out of twelve participants demonstrated decreased CMC for FCU muscle.
- Ten out of twelve participants in the FCR muscle.

For the HC cohort group:

- Six out of twelve participants demonstrated decreased CMC for the FCU muscle.
- Seven out of twelve participants demonstrated decreased CMC for the FCR muscle.

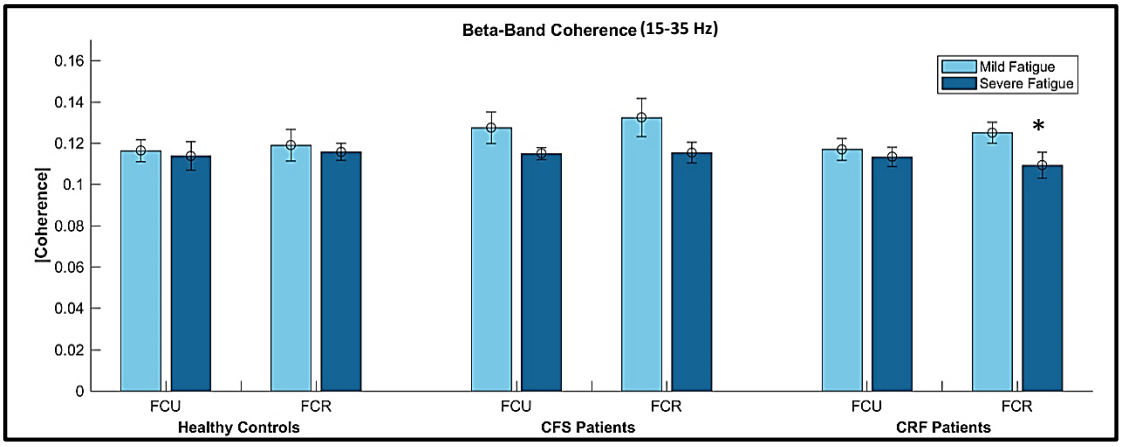


Figure 6-12: **CMC within the Beta band (15-35Hz) frequency**

CMC over contralateral motor cortex for all groups for each muscle from mild to severe fatigue stage. The CRF group displayed a significant decrease for the FCR muscle from mild to severe. (* indicates p<0.05).

Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

For the lower Beta frequency band (15-25Hz) (Figure 6-13), for the HC group individually, there was a significant decrease in CMC for the FCU muscle from the mild to severe fatigue stages (p=0.015). The CRF group demonstrated a significant decrease in CMC for the FCR muscle (p=0.0001). While the CFS group demonstrated decreased CMC, it was not statistically significant for either muscle in either fatigue stage.

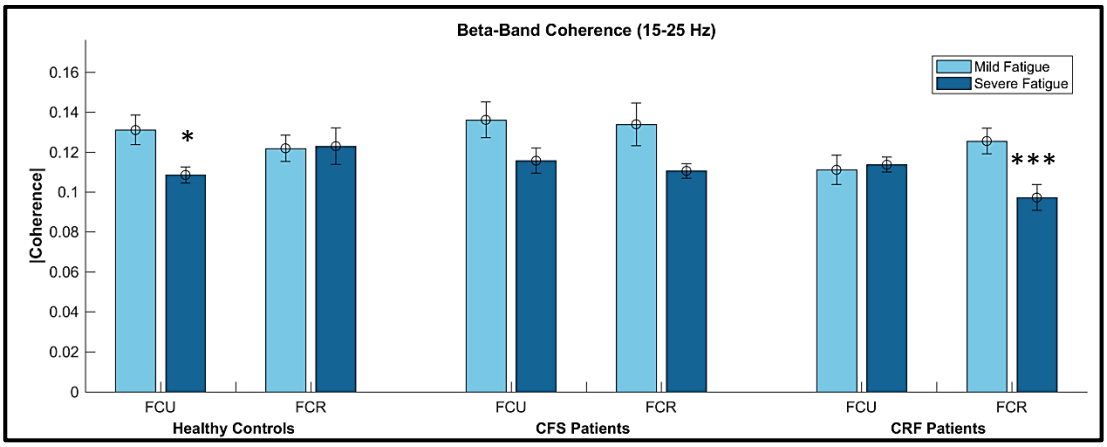


Figure 6-13: CMC within lower Beta frequency band (15-25Hz)

CMC changes over contralateral motor cortex for both muscles at each fatigue stage in all three groups for lower Beta frequency band. (*P<0.05, ***P<0.0001).

Each error bar represents a standard error: standard deviation divided by square root of the number of patients in the cohort

In overall analysis, each group showed a similar trend of decreased coherence when comparing severe fatigue during the task, particularly in the lower Beta frequency band (Figure 6-12 and Figure 6-13). For intergroup comparison within the lower Beta frequency band, there was a statistically significant change in the severe fatigue stage for FCR muscle for CFS vs HC, and mild fatigue stage for FCU for CRF vs CFS ($p=0.03$ and $p=0.04$ respectively).

6.11 Discussion

The main findings from this study demonstrated: 1) the CRF and CFS groups reported greater feelings of fatigue by BFI, 2) both the CRF and CFS groups exhibited a reduced ability to perform the motor task and perceived physical exhaustion sooner, 3) the HC group showed predominately peripheral fatigue, and 4) the CFS group showed a slightly altered EEG response compared to HC and CRF. These results were consistent with both central and peripheral abnormalities for the CRF and CFS groups, even at this stage of the cancer trajectory for the CRF group i.e. newly diagnosed, pre-treatment.

CRF participants had a moderate symptom burden which was expected, with fatigue being one of the most common symptoms reported on the ESAS questionnaire. As expected, and consistent with previously published studies, fatigue was scored higher on the BFI for CRF and CFS participants compared to the HC group. Although the CRF participants mean score (3.2) was higher than HC (2.3), the score was lower in comparison to previous studies which reported mean scores of 4.7 – 5.5 (Yavuzsen et al., 2009; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Cai et al., 2014). This lower BFI score may be a reflection of the CRF participant's ECOG score and pre-treatment status when compared to previous studies (Yavuzsen et al., 2009; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Cai et al., 2014) which assessed advanced cancer patients during treatment. This self-report of lower feelings of fatigue

may have affected the EEG and EMG data by exhibiting less prominent changes throughout the task than those of previous studies.

While endurance time alone is not a direct fatigue assessment, combined with MVC force it provides useful information on motor fatiguing processes (Lou, 2012; Vollestad, 1997; Winter, 2009b). Although the CFS group had statistically significantly higher subjective fatigue, they had a greater endurance time than the CRF group. Perhaps this was due to the CFS group having a lower MVC, and therefore less effort was required for the task, enabling them to hold the handgrip for longer. A shorter endurance time would typically imply greater fatigue (Vollestad, 1997). The shorter endurance times in this study are consistent with previous CRF studies (Cai et al., 2014; Davis et al., 2011; Davis and Walsh, 2010; Finsterer and Mahjoub, 2014; Yavuzsen et al., 2009). The CFS group reported delayed fatigue onset (i.e. capable of activities at time of test but fatigued the following day). This may be why the CFS group were able to endure the task longer than the CRF group, who have more a constant fatigue according to patient self-reports and previous published studies (Bennett et al., 2007; Cai et al., 2014; Davis and Walsh, 2010; Finsterer and Mahjoub, 2014; Siemionow et al., 2004; Yavuzsen et al., 2009).

The CFS group had a lower MVC force than the CRF and HC comparison groups. The handgrip strength (MVC force) of the CFS group was lower than the HC group, consistent with submaximal efforts being produced, perhaps due to all muscle fibres not being recruited (Gibson et al., 1993). This was an expected finding within the CFS participants as they are perhaps less active during daily living and the muscles themselves and the nervous system atrophy leading to strength loss (Siemionow et al., 2004; Lawrie et al., 2000; Gibson et al., 1993; Schillings et al., 2004). Inconsistency between the results of this study and previous publications may be due to different muscle groups and measures used (non-invasive methodology, handgrip vs elbow flexion), and/or the extent of disease in the recruited CFS participants. The higher MVC force in the CRF group (compared to CFS), may relate to their recent diagnosis and pre-treatment status which reflects a good performance status as seen from ECOG scores. Previous studies (with EMG and twitch force) have described similar results (with advanced cancer stages) and that the lower MVC and endurance in these studies were interpreted as

reduced central drive (Cai et al., 2014; Davis et al., 2011; Davis and Walsh, 2010; Kisiel-Sajewicz et al., 2014; Yavuzsen et al., 2009). The lower MVC force hints at central fatigue, as it is influenced by psychological factors like motivation and effort (Finsterer and Mahjoub, 2014) and inhibitory effects at various CNS levels and at the muscle level (Gandevia, 2001; Vollestad, 1997). Supraspinal fatigue explains 15-25% of force loss and physical fatigue during sustained contraction (Davis and Walsh, 2010). Supraspinal fatigue (rather than spinal) accounts for a significant portion of central fatigue after any exercise (Taylor et al., 2006). This suggests that fatigue reduces force generating capabilities. In this study MVC force, even before physical exertion, was less than that of healthy controls, which may imply that fatigue was present in the both the CRF group and CFS group when compared to the HC group. Further analysis (such as twitch force/muscle stimulation) is needed to assess whether that this lower MVC and endurance time is fully attributed to feelings of fatigue and/or muscle wasting due to lack of use. CFS patients often report that their fatigue causes difficulty in maintaining muscle activity due to perceived lack of energy or through muscle pain which can be so severe that it leads to the avoidance of exercise in order to “preserve” energy (Rutherford et al., 2016a).

As discussed in Chapter 2:, when fatigue occurs, the muscles’ ability to generate force declines, which leads to a decrease in strength (Enoka and Stuart, 1992). This increased fatigability may be due to the reduced use of muscles. When the use of muscles is decreased (deconditioning), the slow twitch and fatigue resistance muscle fibers are most affected. This may suggest that these muscle fibers in CFS are affected from reduced daily use.

Examining the combined endurance time with MVC force, the CRF and CFS group had a lower absolute force for a shorter time than the HC group. This may be related to neuromuscular abnormalities in the CRF and CFS group (Cai et al., 2014; Kent-Braun et al., 1993a; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Samii et al., 1996; Yavuzsen et al., 2009). These include elevated levels of proinflammatory cytokines, impaired muscle protein synthesis, low adenotriphosphate generation and intracellular calcium flux (Ryan et al., 2007). These may suggest that the abnormal muscle tissue could be the underlying cause of neuromuscular inefficiency during motor fatigue.

EMG amplitude (an index of muscle fatigue), corresponds to the size and number of motor units involved in motor fatigue, and should increase with fatigue progression. As MVC force declines, the CNS recruits more motor units which increase EMG amplitude (Bigland-Ritchie, 1981; Gandevia, 2001; Finsterer and Mahjoub, 2014; Davis and Walsh, 2010; Cai et al., 2014; Liu et al., 2007; Liu et al., 2003; Winter, 2009b; Yavuzsen et al., 2009; Bigland-Ritchie, 1984; Taylor and Gandevia, 2008; Vollestad, 1997). In central fatigue (due to impaired descending drive, reduced motor unit firing, alpha motor cord neuron firing or reduced motivation (Finsterer and Mahjoub, 2014; Davis and Walsh, 2010; Kisiel-Sajewicz et al., 2014)), EMG shows a lower or decreased amplitude and lower frequencies in median frequency. Reduced amplitude at task failure indicates either loss of recruitment or synergistic activation of multiple muscles (Finsterer and Mahjoub, 2014; Davis and Walsh, 2010; Kisiel-Sajewicz et al., 2014).

In previous cancer studies of EMG and muscle twitch force (Yavuzsen et al., 2009; Kisiel-Sajewicz et al., 2014; Cai et al., 2014; Kisiel-Sajewicz et al., 2012) lower muscle function in CRF was interpreted as reduced central drive. In this study, the EMG amplitude for CRF group did not increase like the HC group, but the CRF group did indicate muscle fatigue, which suggests the ability to recruit motor units to sustain output. Perhaps, earlier in the disease, muscle fatigue is more evident and the CNS is not yet fully affected. Furthermore, it may be possible the issue arises along the motor-control pathway, with action potential propagation along muscle fibers, or impaired neuromuscular junction transduction, this can also shorten endurance time (Gandevia, 2001; Vollestad, 1997; Yavuzsen et al., 2009), and may be consistent with central fatigue. The CFS group were hypothesised to display similar characteristics to the CRF group. As mentioned, both the CRF and CFS groups were weaker and performed the motor fatigue task at a lower absolute target force than the HC group. Thus, the CRF and CFS groups performed a smaller motor activity for a shorter total duration for the task against a lower MVC force than HC (Cai et al., 2014; Siemionow et al., 2004). It has been proposed that perhaps central rather than peripheral fatigue plays a more significant role in endurance tasks in those with CRF and CFS (Cai et al., 2014; Davis and Walsh, 2010; Kisiel-Sajewicz et al., 2012; Schillings et al., 2004; Siemionow et al., 2004; Yavuzsen et al., 2009). Therefore, EMG amplitude changes with fatigue would be more prominent in HC than either CRF or CFS participants (Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al.,

2014; Schillings et al., 2004; Siemionow et al., 2004). The findings for the CRF and CFS groups might indicate a reduced CNS ability to recruit motor units to maintain the contraction leading to earlier task failure and less muscle fatigue.

Median EMG frequency shifts to lower frequencies as fatigue progresses. This can be due to several factors, including action potential conduction velocity, muscle activation level, motor unit synchronisation and temperature (Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Lindstrom et al., 1970; Vollestad, 1997). Previous studies reported that action potential conduction velocity may have the strongest influence on frequency power spectrum (Broman et al., 1985; De Luca et al., 1982; DeLuca, 1982; Kisiel-Sajewicz et al., 2014). The cause of the frequency shift and the extent to which each of the above factors contributes is unclear (Bigland-Ritchie, 1981; Bigland-Ritchie et al., 1981; Vollestad, 1997).

The median frequency decreased as fatigue progressed in each group and in both muscles. The CRF and CFS groups presented with a higher mean median frequency at mild fatigue and both decreased similarly in both muscles from mild to severe fatigue compared to HC.

Both the CRF and CFS groups were expected to have less muscular fatigue than the HC group. However, by assessing the percentage change within the median frequency, this change was slightly greater in the CRF and CFS groups. Behavioral differences lie in the higher median frequencies at baseline for both the CRF and CFS groups. This contradicts previous literature (Kisiel-Sajewicz et al., 2014). This is the first parameter where both the CRF and CFS groups had similar characteristics. Though not statistically significant, it may be possible that both patient groups could have recruited more type II (fast-twitch) muscle fibers (which are known to fatigue at a faster rate) than the HC group. This fast-twitch fiber engagement could suggest more central mechanisms. The muscles function correctly and fatigue normally with the motor task, but perhaps the communication within the CNS is to engage these muscle fibres, and as a result causing both CRF and CFS participants fatigue faster.

EEG Power during the task was examined. During a sustained muscle contraction, it is expected that neural activation levels increase as fatigue sets in. This increased neural activity may be a reflection of increased descending command that results in recruitment of additional motor units and/or increased activity level of the active motor units to compensate for the force loss and to process additional sensory information (de Lange et al., 2004; Decker et al., 2009; Liu et al., 2003; Liu et al., 2005b). The Beta frequency band has been analysed in the literature in terms of both EEG power and EEG-EMG coherence in sustained motor task studies (Conway et al., 1995; Halliday et al., 1998; Yang et al., 2009; Yavuzsen et al., 2009; Liu et al., 2005a; Moore et al., 2014b). It is well established that Beta band activity is related to voluntary motor output (Conway et al., 1995; Halliday et al., 1998; Yang et al., 2009; Yavuzsen et al., 2009; Liu et al., 2005a; Moore et al., 2014b). There are several neurophysiology and neuroimaging studies of fatigue that have been conducted in other clinical populations, but few using a physical fatiguing task with both EEG and EMG with a pre-treatment cohort making it difficult to compare this study results in-depth. Previous research found increased cortical activity in the contralateral sensorimotor cortex (with fatigue progression) in a sustained contraction task in healthy cohorts and patients (van Duinen et al., 2007; Moore et al., 2014a; Siemionow et al., 2004; Liu et al., 2003). This reflected increased cortical descending commands to recruit more motor-units (or further stimulate already active units) to maintain force (Davis et al., 2011; Yang et al., 2009; Siemionow et al., 2004; Moore et al., 2014b). Additionally, cortical activation sites varied with fatigue (Liu et al., 2007; Liu et al., 2003; Moore et al., 2014b) and in healthy cohorts, activation sites shifted to minimise central fatigue and maintain motor output (Enoka and Duchateau, 2007; Enoka and Stuart, 1992; Liu et al., 2003; Liu et al., 2007). In this study, the HC group changes were seen over the left motor cortex. From the mild to severe fatigue stage, the HC group did not differ in EEG power within the Beta frequency band, being consistent with the theory that HC may have modulated cortical activation sites to minimise central fatigue and maintain motor output. Prior research found that advanced CRF participants are unable to maintain a sustained muscle contraction as long as healthy controls due to central fatigue at the cortical and/or spinal level (Yavuzsen et al., 2009; Cai et al., 2014; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014). For this study, it was thought that Beta band power would increase over the left motor cortex

as fatigue progressed. Comparison between the CRF and HC group showed that there was no statistically significant change in activity between mild and severe fatigue stage, however there was a greater increase in Beta band power at the start of the motor fatigue task and during mild fatigue stage for the CFS group compared to the HC. While the CFS group employed greater neural activity to begin the task, and the CRF group showed similar results to HC, unlike previous findings for CRF, which observed a statistically significant increase in severe fatigue stage (Liu et al., 2003; Yang et al., 2009; van Duinen et al., 2007). It may be possible that in early disease, CRF participants, like HC, may be able to modulate cortical activation sites as their CNS is not yet affected.

While not as statistically significant as previous research (Siemionow et al., 2004; Decker et al., 2009), or in comparison to both the CRF and HC groups, the CFS group exhibited slightly greater EEG Beta band power for the left motor cortex in both fatigue stages when compared to the CRF and HC groups. Clinically, CFS generally present with higher Alpha, Delta and Theta band power in both non-fatiguing and fatiguing motor tasks and in a resting state. This suggests altered CNS signaling for voluntary muscle activities particularly with fatigue (Cope and David, 1996; Davis and Walsh, 2010; Kent-Braun et al., 1993a; Neu et al., 2014; Siemionow et al., 2004; Wu et al., 2016; Zinn et al., 2014; Decker et al., 2009). While the difference in this study is not statistically significant this may suggest that CFS participants exert more cortical effort for a lower motor output, which is consistent with their reported higher perception of task effort and fatigue (Gibson et al., 1993). It cannot be concluded in this study whether this greater Beta band power is proportional to an increase in other frequencies such as an increase in Alpha or Delta and further analysis is needed in this area.

When the EMG results are also taken into account, EEG power changes during a sustained contraction differ between the CRF and CFS groups when compared to HC. It may be postulated that more neural activation is required to maintain lower muscle performance particularly in the CFS group and during mild fatigue for CRF group. As mentioned, the results should be treated with caution as a limitation of these studies are the cohorts not age or gender matched, and the numbers are small. However, as mentioned, the comparisons made are valid and further discussion can be found in Chapter 9, Section 9.4, limitations of research.

Muscle fatigue from voluntary motor tasks is associated with adaptations in both central and peripheral nervous systems (Liu et al., 2007; Liu et al., 2003; Yang et al., 2009). As mentioned in chapter 5; Section 5.7.7, the exact role of CMC is not completely defined or understood (Bayram et al., 2015; Kilner et al., 2000; Tecchio et al., 2006; Yang et al., 2009; Yang et al., 2010). It is accepted that the Beta frequency band coherence between the cortex and muscle is related to that of motor activity (Conway et al., 1995; Feige et al., 2000; Halliday et al., 1998; Mima and Hallett, 1999a; Yang et al., 2009; Kristeva et al., 2007). Peak coherence has been reported to occur around the 20 Hz frequency range (Mima and Hallett, 1999a). This was observed in this study, which showed peak coherence occurred in the Beta frequency band at 15-25Hz for each tested group. Weakening of brain-muscle signal coherence has been reported in other studies for healthy and disease related fatigue (Mima and Hallett, 1999a; Hashimoto et al., 2010; Proudfoot et al., 2018; Yang, 2008). Thus, the Beta frequency band over the contralateral motor cortex was the focus for CMC analysis. While results from this study showed peak CMC at the Beta frequency band at the severe fatigue stage, it did not follow the hypothesis that the two patient groups would have weakened CMC at onset in comparison to HC.

This decrease in the Beta band coherence may suggest a weakening of communication between the cortical output centres and the receiving muscles to carry out the voluntary motor task with increasing fatigue. The mechanisms involved in voluntary motor activity include cognitive processing, generation of motor command from the cortex, motor output from the spinal cord, neuromuscular junction transmission, muscle contraction and sensory feedback. Impairment at any level of these processes may cause a decrease in corticomuscular coherence.

One reason such a decrease in CMC may possibly occur is reduced central drive from the cortex to the muscle. It is posited that CRF and CFS are of a more central origin (Cai et al., 2014; Samii et al., 1996; Siemionow et al., 2004; Yang et al., 2009). The results of this study could suggest that the both groups have both central and peripheral contributions to fatigue. Both CRF and CFS groups reported greater subjective fatigue (higher BFI scores) and experiencing exhaustion sooner (with lower MVC forces and shorter ET) compared to the HC group. Physiologically, previous studies have indicated that while

CRF (Yavuzsen et al., 2009; Cai et al., 2014; Yang et al., 2009) and CFS (Siemionow et al., 2004; Samii et al., 1996; Kent-Braun et al., 1993b) participants are physically weaker they exhibit less muscle fatigue at the end of the motor task, indicating a central cause of fatigue.

Another possible reason for a decrease in CMC may be a defect in the neuromuscular junction transmission, which has been reported in previous studies (Cai et al., 2014; Yang et al., 2009; Yavuzsen et al., 2009). These studies demonstrate that the M-wave amplitude distal to the neuromuscular junction is lower in CRF participants than healthy controls, both before and after the motor fatigue task. The M-wave is a measure of muscle response by electrical stimulation of the motor nerve proximal to the neuromuscular junction. Neuromuscular junction impairment is most significant in lower level sustained submaximal contractions such as 30% MVC as used in this study. If central signals cannot be transmitted efficiently across the neuromuscular junction, the muscle will not be fully activated which would weaken the signal coherence between the CNS and muscle (Yang, 2008; Yang et al., 2008). Due to its invasive and painful nature, the cohort recruited, electrical muscle stimulation was not used as part of this study to assess neuromuscular junction activity.

Pathophysiological changes found in those with CRF may also explain the weakened CMC, such as increased pro-inflammatory cytokines, neuromuscular abnormalities (ATP and muscle contractile dysregulation), neuroendocrine changes (hypothalamic-pituitary-adrenal axis and circadian rhythm dysregulation) (Ryan et al., 2007; Saligan et al., 2015; Sood and Moynihan, 2005) (as discussed in Chapter 2, section 2.8). It was expected that both the CRF and CFS groups would have weaker CMC at mild fatigue and their decrease would not be as significant in severe fatigue in comparison to HC participants. However, one of the anomalies of this study is the significant decrease in coherence within the lower Beta band for CRF (FCR muscle). Another explanation for this may be chronological in origin. The time of day at which the task was undertaken for the CRF and CFS participants may have affected performance and any future research should include longitudinal testing over different times.

The reduction of coherence from the mild to the severe stage for all groups may likely be related to physiological changes in muscle due to fatigue. Previous literature states

that diminished CMC does not necessarily occur with decreased brain or muscle activity levels (Yang et al., 2009; Tecchio et al., 2006; Kilner et al., 2000). This could indicate that cortical recruitment and CMC are two distinct mechanisms (Tecchio et al., 2006; Yang et al., 2009; Reyes et al., 2017). During sustained submaximal contraction both brain and muscle activation levels increase with increasing fatigue (Liu et al., 2003; van Duinen et al., 2007), this increase is thought to reflect the increase in descending command from the cortex. The CFS group were observed to have slightly greater EEG power at the start of the task, and CRF had similar EEG power but both CFS and CRF had lower MVC force and EMG amplitude in comparison to HC, which demonstrates that the EEG power for both CRF and CFS group, did not transfer to greater muscle power in order to endure the task to the same extent as the HC group.

Neuromuscular correlates of CRF differ with cancer type and stage, type of exercise, physiological tests, and muscles tested (Yavuzsen et al., 2009). In addition, central drive is different for each muscle (e.g. voluntary activity for the diaphragm takes less effort than for the biceps) (Finsterer and Mahjoub, 2014; Davis and Walsh, 2010; McManus et al., 2016). Previous studies have suggested a weakening of Beta-band coherence in the flexor digitorum superficialis (Kristeva-Feige et al., 2002), biceps brachii, brachioradialis (Yang et al., 2009; Yavuzsen et al., 2009) and flexor digitorum profundus (Yang et al., 2010), while others have reported an increase in Beta-band coherence for extensor digitorum communis (Tecchio et al., 2006), the tibialis anterior (Ushiyama et al., 2011) and first dorsal interosseous muscle (McManus et al., 2016). These studies show that correlation of brain-muscle signals in the Beta-band frequency are more likely to be muscle and task specific which may relate to the weaker contribution of the corticospinal pathway (Davis and Walsh, 2010; Finsterer and Mahjoub, 2014; McManus et al., 2016).

6.12 Conclusion

The purpose of this study was to compare two clinical groups, CRF and CFS to establish whether these disorders shared similar clinical characteristics and underlying pathophysiology. This was achieved employing non-invasive methods and data derived from EEG, EMG and CMC metrics. While some results from this study were not

consistent with previous studies, an important consideration in reviewing the outcomes are the novel aspects of the CRF group being newly diagnosed, and pre-treatment, and in an outpatient setting. The CRF and CFS groups were expected to exhibit similar fatigue characteristics due to the overlap in symptoms. While central fatigue mechanisms appear to be involved in both groups, the manifestation of fatigue differs i.e. the CFS fatigue manifests the following day, whereas the CRF have consistent fatigue at rest and during activities.

This research supports the use of EEG and EMG as objective correlates of fatigue in two separate clinical populations. However, while feasibility was demonstrated, and supports further research into the use of this methodology as an objective assessment of CRF, it is important that study results be considered in the light of the small sample size (possibility of a Type II error), age matching, the limited time period of the fatiguing test and the difficulties inherent in recruiting CRF and CFS participants. Research limitations are discussed in detail in Chapter 9.

Chapter 6: Summary Points

- This chapter compared three cohort groups in this research, cancer-related fatigue, chronic fatigue syndrome and healthy controls.
- Subjective assessment through ESAS and BFI questionnaires were utilised.
- Objective assessment was utilised through endurance time, MVC, EMG amplitude, EMG amplitude change, EMG median frequency shift and EEG power with a sustained motor fatiguing task.
- Consistent with previously published studies, fatigue was scored higher on the BFI for cancer-related fatigue and chronic fatigue syndrome participants compared to healthy controls.
- The cancer-related fatigue and chronic fatigue syndrome groups reported significantly greater feelings of fatigue.
- Both the cancer-related fatigue and chronic fatigue syndrome groups exhibited a reduced ability to perform the motor task and perceived physical exhaustion sooner (Lower MVC and endurance time) than healthy controls.
- The healthy control group showed predominately peripheral fatigue.
- The cancer-related fatigue and chronic fatigue syndrome groups showed altered EEG (greater activity in mild fatigue stage in cancer-related fatigue and higher for chronic fatigue syndrome in both mild and severe compared to both groups.) compared to healthy controls.
- These results show some central and peripheral abnormalities for both cancer-related fatigue and chronic fatigue syndrome groups, even at this stage of the cancer trajectory for the cancer-related fatigue group (i.e. newly diagnosed, pre-treatment).

Chapter 7: HANDGRIP DYNAMOMETRY PERFORMANCE IN RELATION TO SELF-PERCIEVED FATIGUE

STUDY 3

This study has been published as an abstract in the Journal of Supportive Care in Cancer (Volume 25, supplement 2, June 2017) and the European Association of Palliative Care Research Network.

Presented at the following international conferences *(Appendix D)*:

Multinational Association of Supportive Care Cancer *(MASCC) June 2017*
(Journal of Supportive Care in Cancer (Volume 25, supplement 2, June 2017)
European Association of Palliative Care Research Network *(EAPC RN) October 2017*

7.1 Introduction

This Chapter focuses on the analysis of handgrip strength as a predictor of fatigue by comparing the subjective assessment of BFI to the objective assessment of handgrip strength (MVC) and endurance time.

Appropriate management of fatigue requires routine documentation from diagnosis throughout treatment using subjective/self-reported outcomes which are currently employed for assessing fatigue. The ability to properly assess fatigue and it's trajectory throughout the disease using handgrip dynamometry in clinical and hospital settings may assist health professionals in objectively assessing correlates of fatigue and determining the possibility of increased morbidity and mortality (Kilgour et al., 2013).

While there are numerous ways to measure and to assess muscle strength, the use of handgrip dynamometry has become accepted has become accepted as a means to signify overall body strength (Kilgour et al., 2011; Kilgour et al., 2013; Rantanen et al., 2003). A benefit of handgrip strength is that it is a quick and simple test to perform and can be performed in either the home, specialised laboratory or hospital setting thus reducing the burden on patients of any illness where fatigue is a common symptom, it may also provide a complementary approach to the subjective assessment currently used. (Kilgour et al., 2011; Kilgour et al., 2013; Neu et al., 2014; Schvartsman et al., 2017; Siemionow et al., 2004; Trutschnigg et al., 2008; Yavuzsen et al., 2009).

The use of a handgrip strength method has facilitated the collection of large groups of data and predictions concerning key health indictors, such as functional capacity especially with ageing populations (Bohannon, 2001; Kilgour et al., 2013; Metter et al., 2002; Norman et al., 2011) and other clinical populations where fatigue, malnutrition and cachexia are common (Bohannon, 2001; Burden et al., 2010; Cheung et al., 2013; Kilgour et al., 2013; Metter et al., 2002; Neu et al., 2014; Norman et al., 2011; Siemionow et al., 2004). Handgrip strength was also reported to have predictive capacity regarding morbidity and mortality in clinical populations (Burden et al., 2010; Cheung et al., 2013; Kilgour et al., 2013; Norman et al., 2011). For example, there is evidence that handgrip strength is an independent prognostic indicator of survival in follow-up studies of patients with chronic kidney disease who are undergoing peritoneal dialysis (Wang et al., 2005) and in those with advanced cancer (Kilgour et al., 2013; Norman et al., 2015).

The similarity in results between these clinical studies, which include ageing patients (Bohannon, 2001; Cheung et al., 2013), CRF (Brown and Kroenke, 2009; Cantarero-Villanueva et al., 2012b; Kilgour et al., 2013; Norman et al., 2015; Schvartsman et al., 2017), CFS (Neu et al., 2014; Siemionow et al., 2004), chronic renal failure (Wang et al., 2005) and other chronic illnesses (Cheung et al., 2013) demonstrate the links between fatigue, malnutrition and muscle weakness.

Where CRF and CFS are concerned, there are few studies in the literature reporting the use of handgrip strength for fatigue assessment (Cantarero-Villanueva et al., 2012a; Kilgour et al., 2011; Kilgour et al., 2013; Norman et al., 2015; Schvartsman et al., 2017; Brown et al., 2005; Siemionow et al., 2004; Neu et al., 2014). Previous studies that have employed a fatiguing motor task in an effort to overcome the limitation of subjective assessments of CRF, healthy controls and CFS, have demonstrated the effect of fatigue on grip strength (Veni 2018; O'Connor et al., 2018; Kilgour et al., 2013; Santilli et al., 2014; Schvartsman et al., 2017; Siemionow et al., 2004).

As discussed in Chapter 2, Section 2.8, peripheral muscle fatigue can directly interfere with task and result in early task failure. Fernandes et al showed that a significant reduction in strength levels occurred over the course of handgrip assessment (Fernandes A. et al., 2014; Davis and Walsh, 2010; Edwards, 1981; Gandevia, 2001). Fatigue is unavoidable in any motor activity and is likely to affect the individual's performance. The best result of strength is frequently obtained at the first trial, which indicates that the highest value obtained should be considered as the one true result if multiple tests are completed.

It is currently unknown if the loss of overall muscle strength occurs early in the disease and significantly contributes to fatigue in cancer and a decrease in quality of life.

Another question which arose from Study 1, Study 2 and Study 3 is in relation to the correlation between the subjective BFI results and handgrip strength found through the analyses of the data; do the BFI results provide a good reflection of the objective assessment? While the BFI can quantify fatigue levels, the BFI does not reflect any causality of the fatigue.

Determining the association between subjective and objective correlates of fatigue may allow assessment and monitoring of fatigue in a quick, simple way and decreased muscle function may also be useful as a physiological marker of CRF.

In this study, overall subjective fatigue scores (by BFI), and the objective correlates of muscular fatigue from a handgrip dynamometer (Figure 7-1), MVC and endurance time were assessed. The differences between CRF, CFS and healthy control participants were then examined.

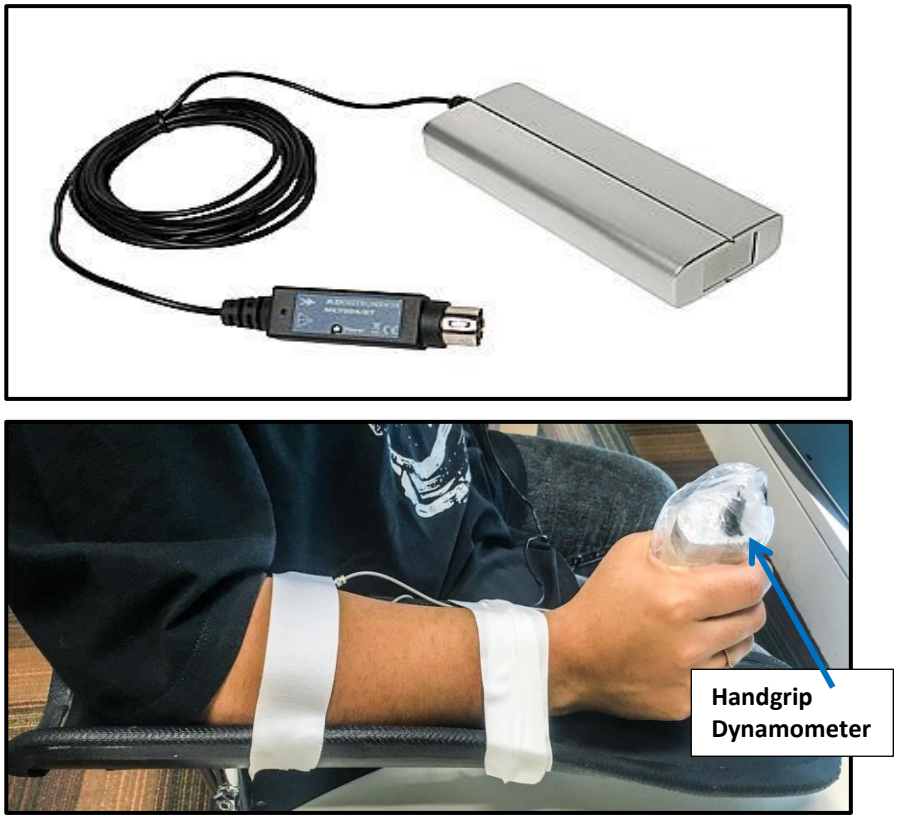


Figure 7-1: Handgrip Dynamometer

Dynamometer (MLT004/ST grip force transducer by AD Instruments (ADI)) used in the study throughout this research to assess maximum voluntary contraction.

7.2 Aims

The hypotheses of this study was that the objective assessment of MVC and endurance time by a hand-held dynamometer can predict subjective assessment of BFI and the subjective measures will correlate with the objective measures.

1) Can handgrip MVC and endurance alone be used as objective correlates of fatigue in CRF and CFS?
2) To determine the correlation of handgrip MVC and ET to the subjective measure of the BFI.

7.3 Methods

The participant dataset obtained from the experimental protocol as described Chapters 5 and 6 were used.

7.4 Results

7.4.1 Brief Fatigue Inventory, Endurance Time and Maximal Voluntary Contraction

The CFS group reported greater mean fatigue on the BFI compared to the CRF and the HC group, this difference was statistically significant when adjusting for age (Table 7-1). Maximal force (MVC) was lowest for the CFS group and statistically significant in comparison to the CRF and HC groups (Table 7-1 and Figure 7-2). For endurance time, both the CRF and CFS group were consistently shorter than the HC group (Table7-1).

Table 7-1: Details and Mean of Age, BFI, Endurance and MVC scores.
(*P<0.05, **P<0.0001 - determined with ANCOVA, Kruskal-Wallis to adjust for age)

Group	Gender	Age (years)	Brief Fatigue Inventory	Endurance Time (Seconds)	Maximal Voluntary Contraction (Newtons)
Cancer-Related Fatigue	Female: 6 Male: 6	65 ± 11	3.2 ± 2	201 ± 165	305 ± 127
Chronic Fatigue Syndrome	Female: 8 Male: 4	49 ± 11	6.5 ± 1**	291 ± 165	237 ± 65*
Healthy Controls	Female: 5 Male: 7	50 ± 13	2.3 ± 2	512 ± 417	351 ± 152

Table 7-2: Pearson's Correlation of objective and subjective measures, controlling for age

Pearson's correlation of Maximal Voluntary Contraction, Endurance Time and Brief Fatigue Inventory results between the three groups.
Pearson's correlation was used as Carifio and Perla (2008) argue that Likert-type data can be used in parametric statistical tests without affecting validity. Based on this, the BFI data was treated as interval-level data in the determination of correlations.

Group	Control Variables			Maximal Voluntary Contraction	Endurance Time	Brief Fatigue Inventory
Healthy Controls	AGE	Maximum Voluntary Contraction	Correlation	1.000	.314	.584
			Significance	-	.348	.059
		Endurance Time	Correlation	.314	1.000	-.222
			Significance	.348	-	.513
		Brief Fatigue Inventory	Correlation	.584	-.222	1.000
			Significance	.059	.513	-
Chronic Fatigue Syndrome	AGE	Maximum Voluntary Contraction	Correlation	1.000	.641	-.324
			Significance	-	.033	.331
		Endurance Time	Correlation	.641	1.000	-.147
			Significance	.033	-	.667
		Brief Fatigue Inventory	Correlation	-.324	-.147	1.000
			Significance	.331	.667	-
Cancer-Related Fatigue	AGE	Maximum Voluntary Contraction	Correlation	1.000	.528	-.722
			Significance	-	.095	.012
		Endurance Time	Correlation	.528	1.000	-.247
			Significance	.095	-	.463
		Brief Fatigue Inventory	Correlation	**-.722**	-.247	1.000
			Significance	.012	.463	-

The BFI for the cancer group but not the CFS group was strongly and significantly correlated to the MVC strength, following the hypothesis of this study (Figure 7-2).

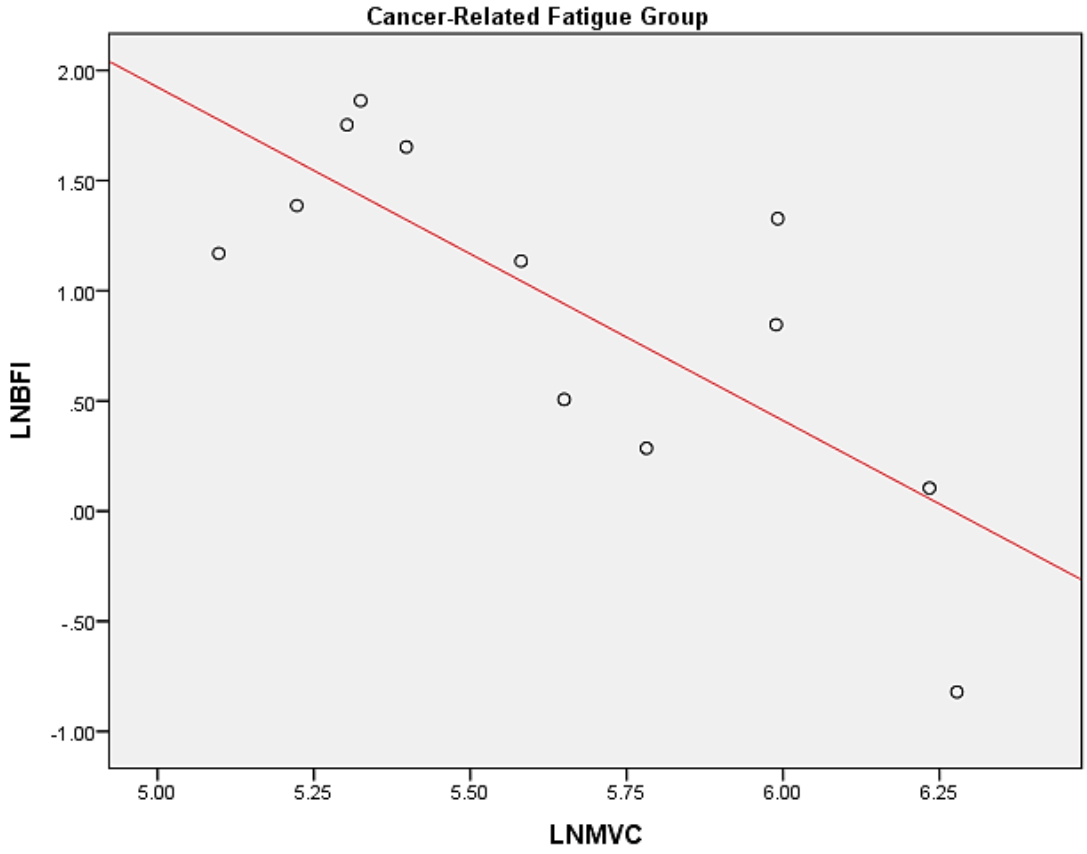


Figure 7-2: Log Linear Regression Analysis of MVC as predictor of BFI CRF Participants.

The linear regression was conducted to test the hypothesis. Both linear and log-linear values were determined. Linear regression analysis best fit model. Log values of MVC & endurance time as predictors of the BFI resulted in an R^2 value of .787 and .281 for the CRF (Figure 7-3) and CFS group respectively.

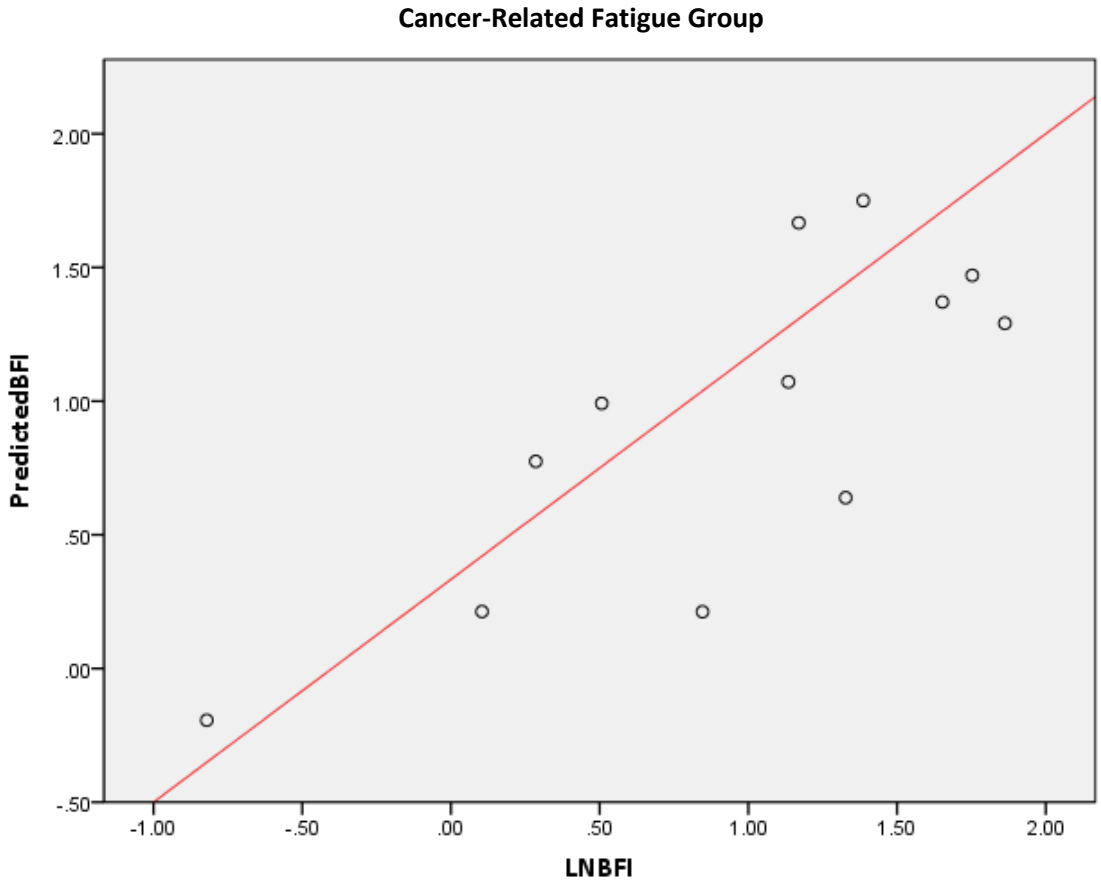


Figure 7-3: **Log Linear Regression Analysis of MVC and ET as a predictor of BFI for CRF Participants.**

7.5 Discussion

The two aims of this study were to evaluate the correlation between subjective and possible objective assessments; as well as to determine if MVC and endurance time were predictors of the BFI. Handgrip strength (MVC) and endurance time are objective measures of muscle function. Decreased muscle strength is one of the many manifestations associated with chronic diseases particularly in individuals with cancer.

The results of the BFI and the MVC from this study show a strong correlation for the CRF group but not the CFS group which may suggest a difference in mechanisms. In addition, the high R2 value (.787) for CRF patients indicates that maximum voluntary contraction and endurance time are highly predictive of BFI for this group.

CRF is a multifactorial disorder and there are other possible external factors due to the disease, other than decreases in muscle mass that may also explain the decrease in strength, however while the use of handgrip dynamometry has become an accepted means to signify overall body strength, and is a good reflection of muscle function, it cannot assess muscle mass. For example, in Kilgour 2013, participants with advanced cancer who were undergoing chemotherapy were examined and the potential for peripheral neuropathy with related loss of grip strength cannot be excluded. In this study, the confounder of treatment-related fatigue affecting muscle strength was removed by recruiting pre-treatment CRF participants.

Another possible reason for reduced handgrip strength in both CRF and CFS participant groups is that both central (e.g. brain, spinal cord, Alpha-motorneurons) and peripheral (e.g. skeletal muscle contractile properties) factors merge to control neural drive and activation of the skeletal muscles that may possibly contribute to handgrip performance. Therefore, for those with CRF and CFS, the voluntary motor drive and/or activation of skeletal muscles, particularly those that are responsible for motor control of handgrip, may be inhibited in comparison to healthy individuals.

As mentioned CRF is frequently reported by cancer patients and this may have a negative effect on handgrip performance. In a study by Kilgour and colleagues (Kilgour et al., 2011) it was reported that fatigue is negatively correlated to muscle mass and performance. Whether the fatigue is of central or peripheral origin, it is possible that it could have a negative effect on producing a maximal voluntary handgrip contraction.

As discussed in Chapter 3, there are a limited number of studies that examine the central and peripheral contributions that control maximal voluntary contractions such as handgrip strength. There is evidence to suggest that exhaustion from submaximal efforts (i.e. 30 % maximal voluntary contraction) occurs earlier in patients with advanced cancer when compared to healthy controls and that this fatigue in CRF participants is related to a more central than peripheral mechanism or those mechanisms more distal

to the neuromuscular junction (as determined by twitch force) (Cai et al., 2014; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Yavuzsen et al., 2009). In this study, it is important to note that the CRF and CFS participants had the weakest handgrip strength and also reported a significantly greater level of fatigue as measured by the BFI. This is in line with previous published studies of CRF and CFS (Cai et al., 2014; Kilgour et al., 2013; Kisiel-Sajewicz et al., 2012; Kisiel-Sajewicz et al., 2014; Santilli et al., 2014; Schvartsman et al., 2017; Siemionow et al., 2004; Yavuzsen et al., 2009).

Although a possible decrease in muscle mass may peripherally contribute to fatigue due to lack of use resulting in decreasing functionality and physical fitness, CRF and CFS are perceived as multifactorial central syndromes (Afari and Buchwald, 2003; Bower et al., 2014; Saligan et al., 2015; Siemionow et al., 2004; Stone and Minton, 2008; Yavuzsen et al., 2009). Considering the combination of contributing factors, these may directly or indirectly affect the central nervous system which appears to play a key role in the development of fatigue rather than in the increase of muscle wasting.

Early detection and classification of handgrip strength in CRF and CFS may provide clinicians with useful prognostic indicators that may assist them in planning timely and appropriate therapeutic measures. It is reasonable to assume that other chronic illnesses where fatigue is a main symptom can also benefit from analysis of handgrip as an objective correlate of fatigue.

However, a standard method is needed to enable more consistent measurement of grip strength and better assessment of CRF. A standard protocol of handgrip strength may improve the measurements within any given study, but also enable the repeatability and generalisability of results across clinical populations.

7.6 Conclusion

CFS fatigue by BFI was more severe than CRF. There was a strong correlation between MVC & BFI for cancer participants suggesting this may be used as an objective correlates of fatigue for those with CRF. This was not the case with CFS group, which suggests that while it is assumed that they are both of central origin, there may be a difference in the

underlying mechanisms. However, these underlying mechanisms still need to be defined.

Despite the complex pathophysiology of both CRF and CFS, this study established a relationship between subjective and objective fatigue assessment of BFI and handgrip strength respectively. MVC and endurance time as predictors for the BFI for the CRF group was determined.

Chapter 7: Summary Points

- Determining the association between subjective and objective assessment of fatigue may allow assessment and monitoring of fatigue in a quick, simple way.
- Decreased muscle function may be useful as a physiological marker of cancer-related fatigue.
- Handgrip dynamometry has become accepted as a valid and reliable tool that is known to signify overall body strength (Kilgour et al., 2011; Kilgour et al., 2013; Rantanen et al., 2003).
- The benefits of handgrip strength is that it is a quick and simple test to perform and can be performed in either the home, specialised laboratory or hospital setting, in turn reducing the burden on patients and it can facilitate the collection of large groups of data.
- Controlling for age, the brief fatigue inventory (BFI) for the cancer-related fatigue group (but not the chronic fatigue syndrome group) was strongly and significantly correlated to maximal voluntary contraction strength (Table 7-2) following the hypothesis of this study.
- Linear regression analysis with log values of MVC & endurance time as predictors of BFI resulted in an R^2 value of .787 and .281 for the cancer-related fatigue and chronic fatigue group respectively (Figure 7-2).
- Despite the complex pathophysiology of both cancer-related fatigue and chronic fatigue syndrome, this study established a strong relationship between subjective and objective fatigue assessment of BFI and handgrip strength respectively.
- Maximal voluntary contraction and endurance time as predictors for the BFI for the cancer-related fatigue group was determined.

Chapter 8: DETECTING AND QUANTIFYING MIND WANDERING DURING A MOTOR TASK

STUDY 4

A 4-page conference paper based on this study has been presented at and published for the international conference (Appendix E):

International IEEE EMBS Conference on Neural Engineering (IEEE) March 2019

Neural based assessment of mind wandering during a fatigue inducing motor task: Is task failure due to fatigue or distraction?

S. Hablani, C.M. O'Higgins, D. Walsh and R. B. Reilly *(Senior Member, IEEE)*

8.1 Introduction

Studies 1-3 (Chapters 5, 6 and 7) in this research employed the use of EEG, EMG and a hand-held dynamometer and the success of recording was dependent on strict adherence to the research protocol, which in turn depended on the participant's commitment to the process. The participant's motivation and sustained attention were a vital component to the standardisation of the objective outcomes. In this Chapter, the EEG data collected in the preceding studies (Chapter 5 & 6) will be analysed retrospectively to assess if the participants ability to maintain attention was affected during the task. As discussed in Chapter 2, cancer and/or its treatment causes simultaneous dysregulation of several systems in an individual and is likely to affect the CRF participant's concentration and ability to complete the task to the same standard as a healthy individual (Berger et al., 2015b; Hofman et al., 2007; Cella et al., 1999; Saligan et al., 2015; Minton and Stone, 2013).

Sustained attention is defined as the ability to maintain attention and respond consistently during a repetitive continuous activity such as the motor task employed in this research. The capacity to sustain attention is an important cognitive function crucial for the execution of day-to-day tasks and can have a significant impact on executive function processing speed, working and verbal memory (Kam et al., 2016; Clayton et al., 2015). This may explain why these are associated with the subjective sensation of mental fatigue in those with CRF (Kam et al., 2016). The ability to sustain attention over time on a task-relevant input, while simultaneously ignoring irrelevant distractions, is an integral part of many aspects of life (Robertson et al., 1997; Clayton et al., 2015; Oken et al., 2006; Robertson and Garavan, 2004).

Previous studies investigating cognitive and sustained attention changes in those with cancer and cancer survivors have concluded that there is evidence of objective decline in cognitive function (particularly verbal memory and executive function) (Ganz et al., 2013), unstable vigilance (Olbrich et al., 2011; Kam et al., 2016) and altered resting states (regional interactions that occur when an explicit task is not being performed) (Hampson et al., 2015) following cancer treatment (Minton and Stone, 2013; Ganz et al., 2013; Kam et al., 2016; Servaes et al., 2002; Olbrich et al., 2011; Hampson et al., 2015;

Pendergrass et al., 2018; Correa and Ahles, 2008). These cognitive complaints are associated with reduced quality of life and well-being which highlights the importance of establishing objective assessment for CRF and its underlying neural mechanisms.

Therefore, the examination of the area of sustained attention is important when considering the results of Studies 1, 2 and 3 and the limitations of this research. In the study presented in this chapter, mind wandering in the context of sustained attention during the motor task employed in this research will be examined, with the question, are the participants failing the task sooner due to fatigue or due to lack of concentration?

8.2 Mind Wandering

Mind wandering (MW) occurs when sustained attention is low and corresponds to distraction caused by emergence of thoughts unrelated to task at hand and therefore shifting attention away from the task (Smallwood and Schooler, 2006; Smallwood and Schooler, 2015b; Smallwood and O'Connor, 2011; Smallwood, 2011). MW can be either self-generated which causes a deliberate shift in the attention from a task or can be spontaneous (Smallwood, 2011). It can affect the cognitive and motor performance in task completion.

Research investigating mind wandering (MW) began with the examination of "day-dreaming" (Antrobus et al., 1964) which established that cognition unfolds independently of external environment (Antrobus et al., 1964; Martel, 2018; Callard et al., 2013). One of the challenges with MW is its complexity and the excessive number of different terms used to describe it (Callard et al., 2013; Smallwood and Schooler, 2015b). Several terms "day-dreaming" "task-unrelated thought", "spontaneous thought", "spontaneous cognition" and "zone outs" are used interchangeably in the literature. However, the specific term "mind wandering", is now dominant (Callard et al., 2013; Christoff et al., 2009; Braboszcz and Delorme, 2011; Smallwood et al., 2003).

MW has been examined in the context of physical tasks (Epel et al., 2013), mental health (Killingsworth and Gilbert, 2010), psychiatric conditions (Smallwood and Schooler, 2006; Smallwood et al., 2009; Smallwood and Andrews-Hanna, 2013) and its implication in

attentional control (Smallwood et al., 2007; Smallwood et al., 2008; McVay and Kane, 2010; Smallwood, 2011).

According to estimates, MW is responsible for the bulk of the brain's metabolic energy consumption (Raichle et al., 2001; Martel, 2018) and accounts for anywhere from 10 to 50% of all conscious thoughts (Kane et al., 2007; Killingsworth and Gilbert, 2010; Klinger and Cox, 1987; Smilek et al., 2010; Smallwood, 2011). Widespread scientific attention is now being given to the topic of mind wandering (McVay and Kane, 2010; Smallwood et al., 2011; Smallwood and Schooler, 2015b; Smallwood and Schooler, 2006; Martel, 2018).

8.3 Measures of Sustained Attention/ Mind Wandering

Experimental methods researching MW predominately relate to the conscious experience of an individual at a particular moment in time. Therefore, a challenge for researchers is that MW is unpredictable and is influenced by subject awareness. Data obtained from this type of testing has limited opportunities for additional data analysis.

MW is studied by finding lapses of external attention in participants and current assessment of MW research consists of employing Experience Sampling (ES) and Sustained Attention to Response Task (SART) (Smallwood et al., 2003; Christoff et al., 2009; Braboszcz and Delorme, 2011; Kam et al., 2011). ES is well known and validated; however, it is subjective and, requires the participant to report their thoughts over time. There are number of different methods of ES (Smallwood and Schooler, 2015a; Kahneman et al., 2004):

1. Probe Caught Method: this assesses the experience of individuals at varying time intervals as they perform a cognitive task (Smallwood and Schooler, 2015a).
2. Self-Caught Method: individuals are asked to respond with a button push whenever they catch themselves mind-wandering during a task.
3. Retrospective Method: data is gathered at the end of a task using a questionnaire (Barron et al., 2011).
4. Open-ended Method: where individuals are asked to describe what they experienced during a task using their own words.

The introspective requirement of these methods changes the nature of the test in terms of the participants alertness to the MW measurement and their anticipation of what is to happen, for example, in the Self-Caught method which relies on the participant's self-reporting. The strategy of triangulation employs behavioural and neurocognitive measures of self-reported data together to make inferences about mental states (Smallwood and Schooler, 2015a; Schooler and Schreiber, 2004; Varela and Thompson, 2003).

Previous research using objective measures has demonstrated that neurophysiological fronto-medial (or frontal midline) theta (FMT) signals have been associated with attentional fatigue (Lal and Craig, 2002; Clayton et al., 2015; Martel, 2018) and cognitive control (Cavanagh and Frank, 2014). FMT activity is said to increase with enhanced task performance (Wascher et al., 2014) and is also related to cognitive effort in maintaining attention over sustained periods of time, thus increasing while performing tasks with high demands on externally directed attention (Kubota et al., 2001; Sauseng et al., 2007). FMT has been suggested to reflect goal-monitoring processes (Cavanagh and Frank, 2014). This suggests that FMT is crucial for sustained attention.

EEG derived FMT power can be used as a measure of discrepancy between expected and actual outcome of cognitive testing (Cavanagh and Frank, 2014; Cohen and Donner, 2013). Reduced FMT is an indicator of decreased attention to the task at hand. Assessing the possibility of MW in CRF and CFS may provide a metric to assess their performance in this motor task, which may also be used as objective assessment of correlates of fatigue (Cavanagh and Frank, 2014; Astrand, 2018; Martel, 2018).

Due to its temporal sensitivity (as discussed in Chapter 3, Section 3.1.2), EEG is increasingly recognised as an indicator of combined cortical functions. Changes in oscillatory activity of both FMT and parietal Alpha frequencies have been extensively linked to sustained attention (Clayton et al., 2015; Braboszcz and Delorme, 2011; Martel, 2018). Increased FMT has been observed during the exercising of cognitive control e.g. maintaining attention, irrespective of whether it is directed externally (task, distraction) or internally (attention, motivation, fatigue) (Astrand, 2018; Clayton et al., 2015). Parietal Alpha power, on the other hand, indexes the inhibition of task-irrelevant

processes; inefficient inhibition interferes with memory retrieval, resisting distractions such as internal thoughts (Howard et al., 2014).

As periods of high Alpha power are associated with lapses in attention (Baldwin et al., 2017), Alpha power is expected to be greater during mind wandering relative to periods of attention to the sustained task. Modulation of Theta band activity may provide means of distinguishing mind wandering during a task from other types of distractions (O'Connell et al., 2009). However, due to the retrospective nature of the study and the initial experimental design which was not designed to include a mind wandering application, the interpretation of these results cannot be viewed as a definitive statement of evidence of minding wandering, and could be caused by other factors such as reflecting increased attentional demands and is higher for tasks with internal attention focus, and in waking eyes-closed compared with eyes-open. However, with changes to the original experimental design and participant profile there is a possibility that these results could be investigated to a deeper extent.

8.4 Why Mind Wandering?

A qualitative comparison study of CRF and CFS by Bennett and colleagues (2007) shows that many CRF and CFS participants used similar descriptors of their fatigue such as: ‘‘*I lose concentration*’’ ‘‘*I seem more absent-minded*,’’ and ‘‘*I can’t fully concentrate on anything*.’’ “*…it is such an effort to do that simple task”.*

The ‘‘perceived need to struggle to overcome inactivity’’ is listed as one of the 11 symptoms in the diagnostic criteria for CRF (Bennett et al., 2007). This experience is indicative of motivational loss; however, the participants reported “they struggled to overcome the limitations on physical and cognitive activity imposed by the fatigue state”. Also previous research suggests that individuals think about their current concerns when mind wandering e.g. their cancer diagnosis (Klinger and Cox, 1987; Kam et al., 2016).

The task employed in studies 1-3 of this research requires the CRF, CFS and HC participants to maintain concentration and not be distracted by personal current concerns, or other internal or external events.

Smallwood & Schooler (2015a) define MW as a "shift in contents of thought away from an ongoing task and/or from events in the external environment”. This content-based

perspective classifies thoughts into self-generated related or unrelated to the task, the proposal being that MW belongs to the category of self-generated thoughts that are unrelated to the task. In Figure 1 below, the various shifts in content have been classified into task-related thoughts and self-generated thoughts which lead to MW:

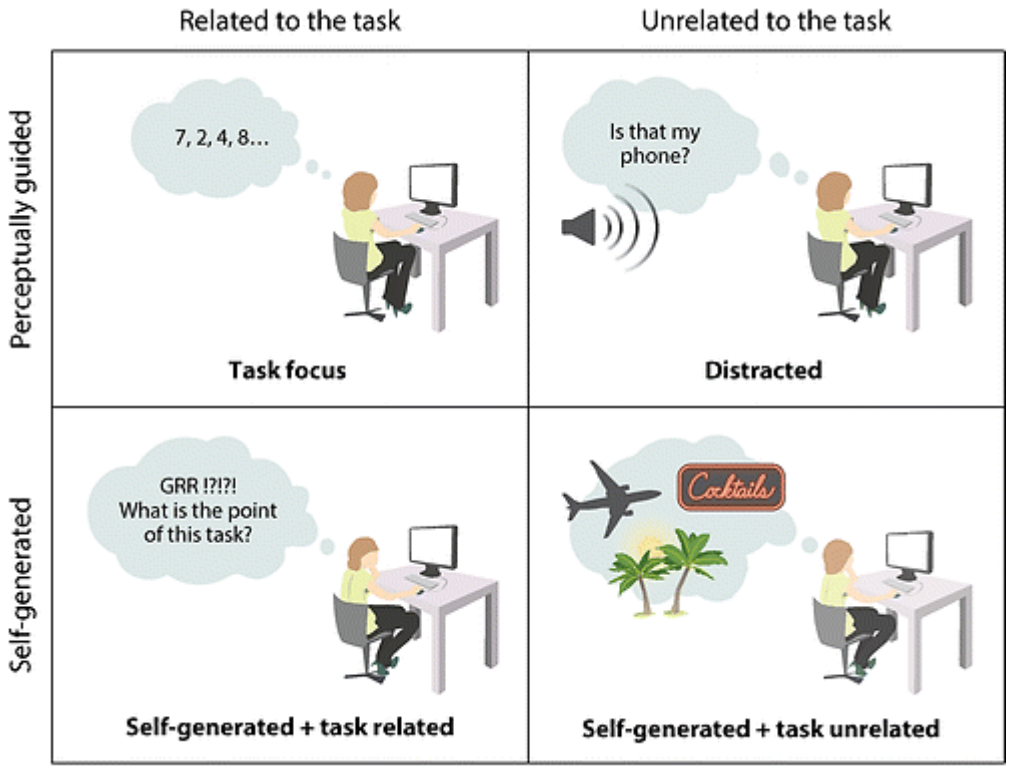


Figure 8-1: Explanation of perceptually guided and self-generated thoughts

Top left panel the participant is fully focused on the task such that the contents of thought are only those that arise from sensory input. Bottom left panel the thoughts of the participant are related to the task but are also self-generated because the task stimulus in itself does not necessitate significant thought. Top right panel the participant is distracted by a noise in the environment and so becomes temporarily disengaged from the task. Bottom right panel the participant has disengaged attention from the task and has begun to self-generate thoughts. (Reproduced, (Smallwood and Schooler, 2015a))

The task undertaken as part of the study used in this research included a period of recovery and rest at the end. It is suggested that participants experienced an episode of MW during this recovery period. This may align with the schematic presented in Figure 8-1 in the context of self-generated, task- related or unrelated MW and the EEG data obtained from Study 2 (Figure 8-2).

During the handgrip task employed in studies 1-3, it is reasonable to expect that MW may occur as the task continues (middle of task) due to monotony and the participant may become distracted (i.e. perceptually guided and distracted). When the participant starts to fatigue and force begins to drop, they refocus on the task (i.e. perceptually guided and task focused). Once the participant fails the handgrip task, a three-minute recovery period begins, where it is possible that the participants' thought process becomes self-generated and task-related or unrelated (Figure 8-2).

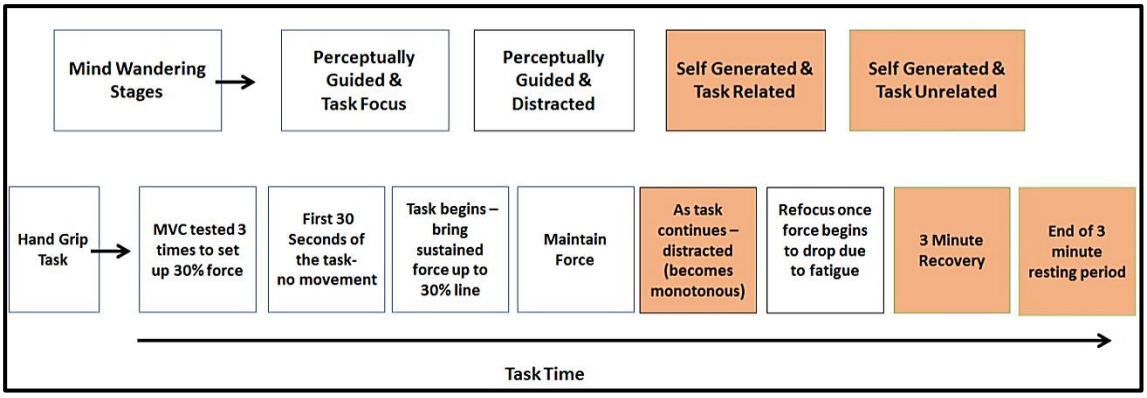


Figure 8-2: Schematic of handgrip task and possible mind wandering stages

In the layout of the motor task employed throughout this research, there are several stages in which mind wandering may occur as laid out in this diagram. It is assumed that mind wandering will occur when the task becomes monotonous and during the rest period as marked by colour.

8.5 Hypotheses

Based on the literature, it was hypothesised that neurophysiological signals should change with task progression as:

1) Theta activity in the frontal region of the brain should increase during tasks involving higher demand of concentration and, decrease in MW state.
2) Alpha activity should decrease in the parietal regions of the brain during tasks with a higher demand of concentration and increase in MW state.

8.6 Methods

8.6.1 Data Collection and Recording

The experimental set up and fatiguing-inducing motor task employed for testing and a summary of patient demographics is discussed in-depth in Chapter 5 and 6.

8.6.2 EEG Analysis

8.6.2.1 EEG Pre-processing

Refer to Chapter 5, Section 5.5.2 for in-depth detail on EEG pre-processing steps. As we were specifically interested in frontal Theta and parietal Alpha for this study (as these are the frequency bands associated with mind wandering), there was a change in the filtering step. Thus, the data was filtered with a bandpass filter with a bandwidth of 1-20 Hz.

The EEG data was segmented into various stages which marked the progress of the task and the rest period. Within these segments the beginning of the task was marked as the first ten seconds, the middle of the task was a ten second epoch around the middle of task, and the end of the task was marked as the last ten seconds of the task time. The three-minute resting period was divided into two 30 second epochs, and 60 second epochs. For this study, we investigated the first 30 seconds of the resting period (Rest 1), which followed immediately after task completion and the last 30 seconds of the resting period (Rest 4).

8.6.2.2 Spectral Power Analysis

To compare changes in neural activity that may have been caused by mind-wandering, spectral power of relevant frequency bands (frontal medial Theta (4-8Hz) and parietal Upper Alpha (11-14 Hz)) was calculated. These were compared across the various stages of task throughout the participant groups. We examined left and right frontal medial temporal Theta, this approach was chosen due to the task being performed with the right hand, and a bigger increase is expected within the left FMT Theta frequency in comparison to the right.

8.6.2.3 Peak Frequency Analysis

Peak Theta and Alpha frequencies were calculated for each of the stages of the task. The peak frequency was the frequency of maximum power within the frequency bands and regions of interest (frontal medial Theta (4-8Hz) and Parietal Upper Alpha (11-14 Hz)). The changes in the peak frequencies as the task progressed were compared and whether mind wandering affected the parameter.

8.6.2.4 Statistical Analysis

Normality was examined using histograms. Occasionally, exceptionally large values were detected (e.g. > 100 fold higher than next largest value). In order to still include this information in the analyses without further skewing the results, these values were recoded to take the value of the 99th percentile in a process analogous to Winsorization. This process occurred for 1 value both the left and right hemisphere FMT theta and for 2 values in both the upper and lower parietal alpha. For our statistical analyses, data were additionally transformed using a 1/square-root transformation for normality. Comparison of each group (CRF, CFS and HC) and stages (Beginning, Middle, End, Rest 1 and Rest 4) were compared using a mixed effects linear regression on the transformed values with person random intercept and fixed effect for stage. Between group differences in changes over stage were assessed using a group-by-stage fixed effects interaction term. Within-group comparisons between stages were conducted with a fixed effect for stage. Omnibus tests for global differences across stage were used as a protection against type 1 error inflation. In the presence of a statistically significant omnibus test ($p < 0.05$), pair-wise comparisons were conducted.

8.7 Results

A classification into the different test stages was performed for Beginning of task: first ten seconds; Middle of task: ten second epoch around the midpoint; End of task: last ten seconds of the task performance; Rest 1: First 30 seconds rest immediately after the task; Rest 2: Another block of 60 seconds rest; Rest 3: One more block of 60 second rest; Rest 4: Last 30 seconds of rest segments. An averaged time period could not be employed as each participant had a different time period for the duration of the task;

however, all participants had a three-minute resting period. Rest 1 and Rest 4 were chosen for the resting period as the participant would have just finished the task and there should be a decrease in FMT theta and increase in parietal Alpha power when reaching Rest 4.

8.7.1 Power Spectral Density

For analysis of power, five stages were examined, the beginning, middle, and end of task, in addition to the two Rest periods: Rest 1 and Rest 4. Left frontal-medial temporal, right frontal-medial temporal and parietal regions were selected for power analysis within Theta (4-8Hz) (Figure 8-3 a, b, c), Upper Alpha (11-14Hz) (Figure 8-4 a, b, c) frequency bands. Statistically significant differences between stages for each group are presented in Table 8-1 and Table 8-2.

Within the stages, an increase in the power of the frontal medial temporal Theta frequency band is expected from beginning to the end of task, and a decrease within the resting period. Alpha frequency band power is also expected to increase in the Rest period, indicating mind wandering. As the task is being performed with the right forearm, more significant differences are expected to be seen on the left hemisphere. In Table 8-1, there is a statistically significant change from Rest 1 to Rest 4 in FMT Theta power for the CFS group which implies that in Rest 1, they were still focused on the task, and mind wandered as the rest period continued. For the healthy group, there is a significant change in power from beginning of task to Rest 4 in the FMT Theta band for both left and right hemispheres indicating mind wandering during the rest stage.

Table 8-1 Frontal Medial Temporal (FMT) Theta Frequency

Significant differences between stages for each group within the frontal medial temporal regions for the Theta frequency band. These results suggest that towards the end of the task there was a period of increased attentional demand in comparison to the rest period, indicative of a relaxed state in the rest 4 stage. *p≤0.05

Group	Left hemisphere FMT Theta Power		Right hemisphere FMT Theta Power	
	Stage of Task	Significance P-Value	Stage of Task	Significance P-Value
Cancer-Related Fatigue	*Omnibus Global Test for Differences*	**0.024***	*Omnibus Global Test for Differences*	**0.023***
	Beginning vs Middle of task	0.925	Beginning vs Middle of task	0.500
	Beginning vs End of task	**0.032***	Beginning vs End of task	0.112
	Middle vs End of task	**0.025***	Middle vs End of task	**0.023***
	Beginning of task vs Rest 1	0.079	Beginning of task vs Rest 1	0.177
	Beginning of task vs Rest 4	**0.019***	Beginning of task vs Rest 4	**0.027***
	End of task vs Rest 1	0.699	End of task vs Rest 1	0.812
	End of task vs Rest 4	0.842	End of task vs Rest 4	0.535
	Rest 1 vs Rest 4	0.558	Rest 1 vs Rest 4	0.391
Chronic Fatigue Syndrome	*Omnibus Global Test for Differences*	**0.030***	*Omnibus Global Test for Differences*	0.053
	Beginning vs Middle of task	0.433	Beginning vs Middle of task	0.189
	Beginning vs End of task	0.354	Beginning vs End of task	0.094
	Middle vs End of task	0.886	Middle vs End of task	0.719
	Beginning of task vs Rest 1	0.305	Beginning of task vs Rest 1	0.215
	Beginning of task vs Rest 4	**0.001***	Beginning of task- Rest 4	**0.002***
	End of task vs Rest 1	0.920	End of task vs Rest 1	0.664
	End of task vs Rest 4	**0.029***	End of task vs Rest 4	0.178
	Rest 1 v Rest 4	**0.037***	Rest 1- Rest 4	0.075
Healthy Controls	*Omnibus Global Test for Differences*	**0.001***	*Omnibus Global Test for Differences*	**0.013***
	Beginning vs Middle of task	0.404	Beginning vs Middle of task	0.624
	Beginning vs End of task	0.054	Beginning vs End of task	0.202
	Middle vs End of task	0.276	Middle vs End of task	0.432
	Beginning of task vs Rest 1	0.056	Beginning of task vs Rest 1	0.302
	Beginning of task vs Rest 4	**<.001***	Beginning of task vs Rest 4	**0.001***

	End of task vs Rest 1	0.986	End of task vs Rest 1	0.808
	End of task vs Rest 4	**0.049***	End of task vs Rest 4	**0.044***
	Rest 1 vs Rest 4	**0.047***	Rest 1 vs Rest 4	**0.024***

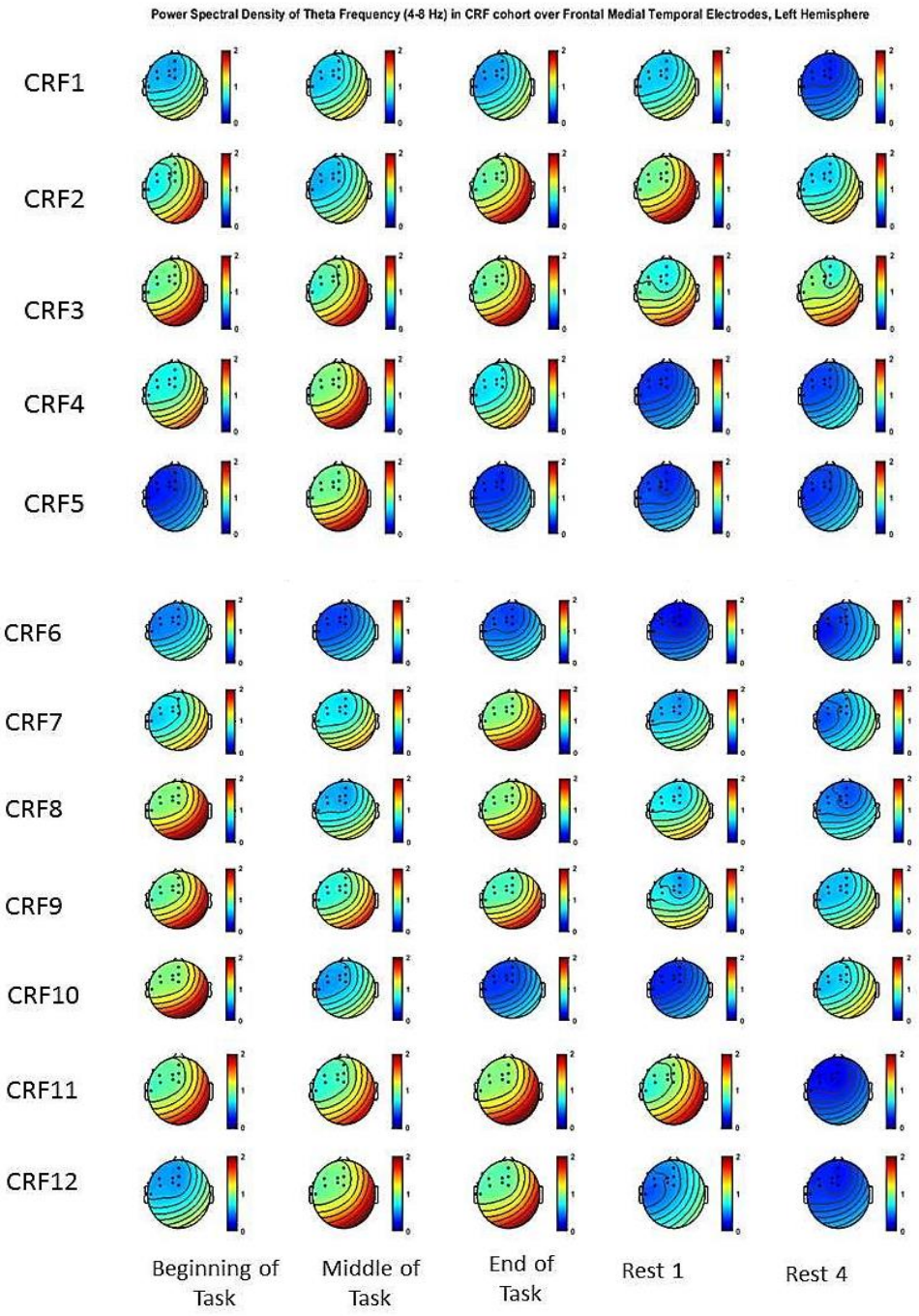


Figure 8-3 (a) Power Spectral Density of Theta Frequency band in each of the 12 cancer-related fatigue participants over the left hemisphere Frontal-Medial-Temporal electrodes throughout the sustained grip task.

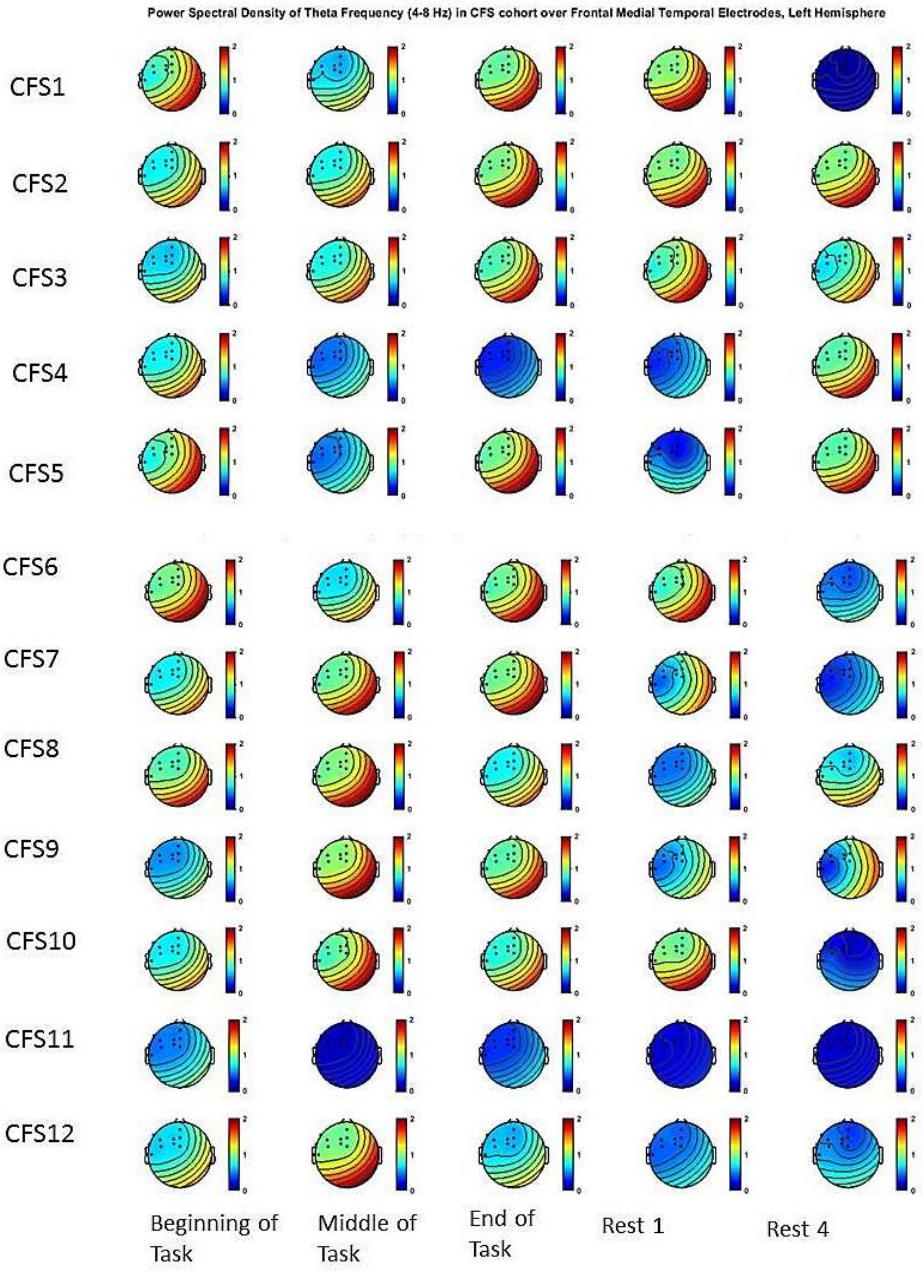


Figure 8-3 (b): Power Spectral Density of Theta Frequency band in each of the 12 chronic fatigue syndrome participants over left hemisphere Frontal-Medial-Temporal electrodes throughout the sustained grip task.

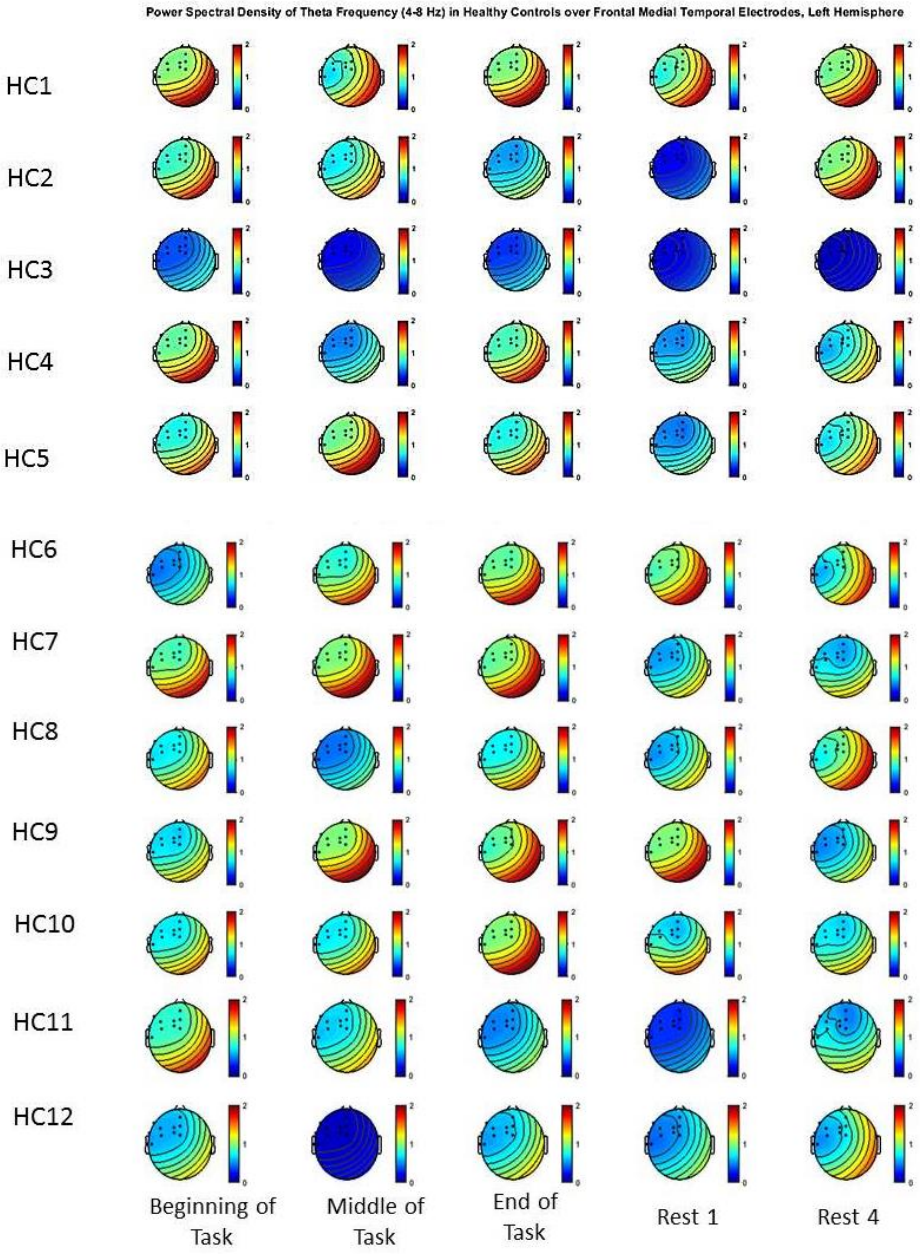


Figure 8-3 (c): Power Spectral Density of Theta Frequency band in each of the 12 healthy controls over left hemisphere Frontal-Medial-Temporal electrodes throughout the sustained grip task.

Figure 8-3 (a, b, c): We expected to see more neural activity (increased Theta band power) on the left hemisphere (contralateral to the forearm used during the task) in the beginning and end stages of the task, with a decrease in the middle and in the two rest periods indicating a decrease in attention. Of particular interest, Rest 4, appears to demonstrate that the majority of CRF participants are in line with the hypothesis (i.e. decreased Theta band power). Within the CFS group, even though it is not to the same extent as CRF, it still shows the propensity to mind wander in Rest 4. The extent of power varied among all participants, which can be observed from the above plots, however; it must be noted that the task stages are 10 seconds and rest stages are 30 second segments.

The most pronounced state-associated change on the EEG spectral activity for all groups occurred within the upper (11-14Hz) Alpha band for the left and right fronto-medial temporal and parietal regions (Figure 8-4 a, b, c) where absolute power is significantly higher in the rest stages compared to task stage (hypothesised to be mind wandering states). As can be seen in Table 8-2, significant changes in Parietal Alpha power can be seen from the beginning to the end of task and within the rest periods in all participant groups. This could be consistent with all participant groups transitioning to mind wandering towards the end and during the rest periods. However, as mentioned, this was a retrospective study and the initial experimental design did not include a mind wandering application, therefore the interpretation of these results cannot be viewed as a definitive statement of evidence of minding wandering. These results might be the result of other causative factors such as reflecting increased attentional demands, or eyes open and eyes closed which would cause a spike in Alpha frequency. However, with changes to design and participant profile there may be a possibility that these results could be confirmed.

Table 8-2: Parietal Upper Alpha and Lower Alpha Power frequency band power

Statistically significant differences between the stages for each group within the frontal medial temporal regions for the upper and lower Alpha frequency band power. These results suggest that towards the end of the task there was a period of increased attentional demand in comparison to the rest period, indicative of a relaxed state in the Rest 4 stage.

Group	Parietal Upper Alpha band Power		Parietal Lower Alpha band Power	
	Stage	Significance P-Value	Stage	Significance P-Value
Cancer-Related Fatigue	Beginning - Ending	0.03	Beginning - Ending	0.03
	Middle - Ending	0.02	Beginning - Rest 1	0.04
			Beginning - Rest 4	0.02
Chronic Fatigue Syndrome			Beginning - Rest 1	0.03
Healthy Controls	Beginning - Ending	0.03	Beginning - Ending	0.03
	Beginning - Rest 4	0.03	Beginning - Rest 4	0.03

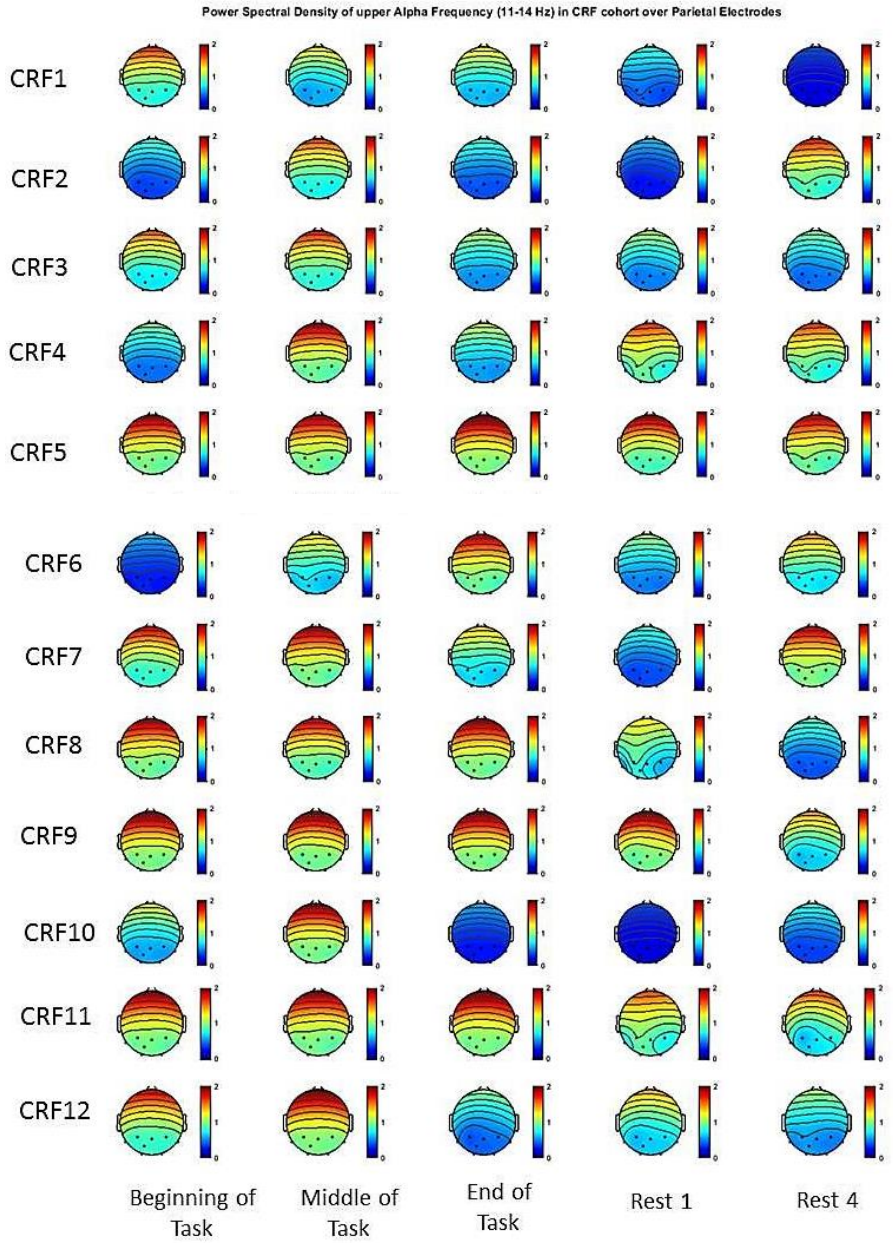


Figure 8-4 (a) Power Spectral Density of Upper Alpha frequency band for each of the 12 cancer-related fatigue participants over Parietal electrodes throughout the sustained grip task.

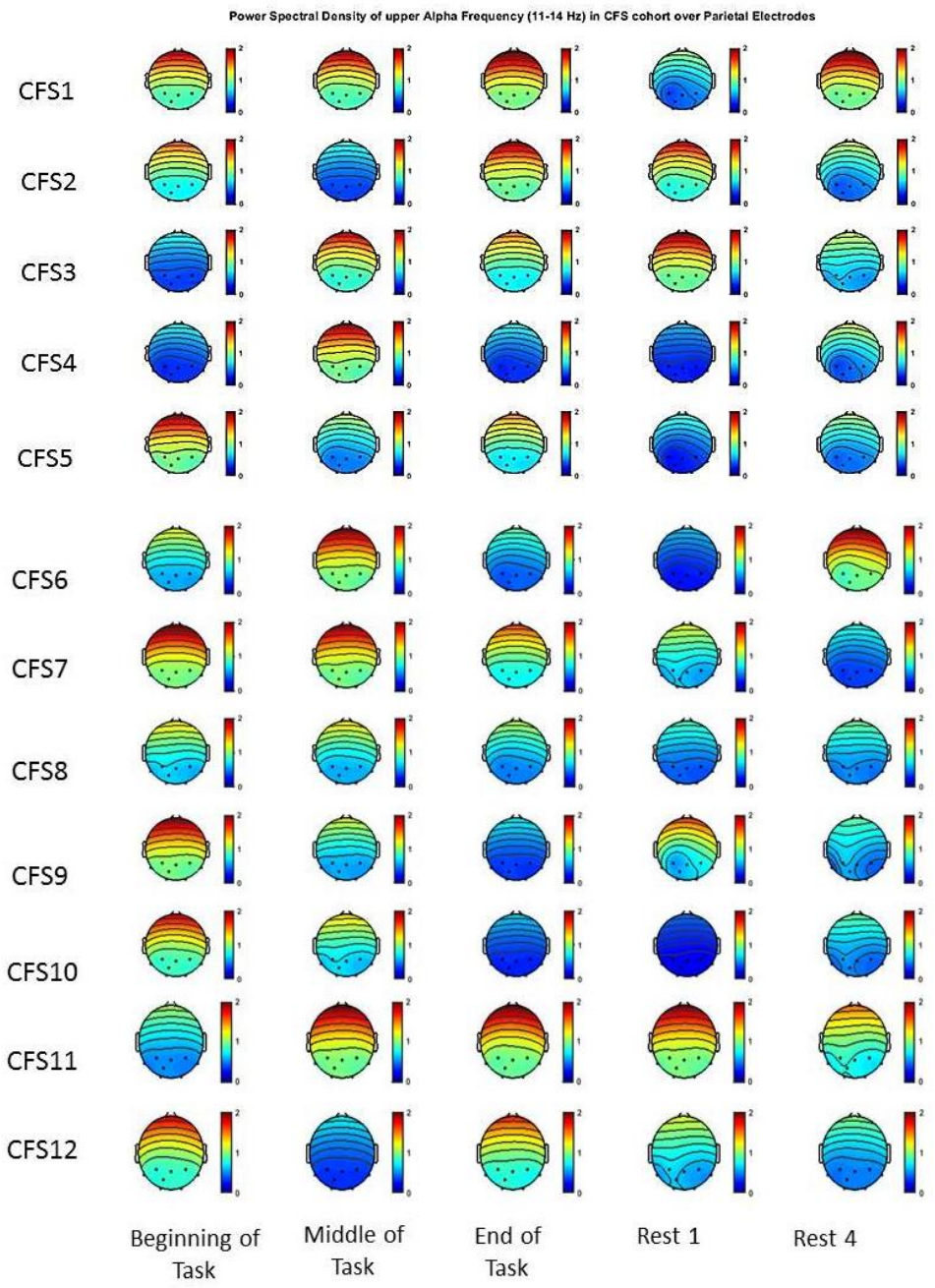


Figure 8-4 (b) Power Spectral Density of Upper Alpha frequency band for each of the 12 chronic fatigue syndrome participants over Parietal electrodes throughout the sustained grip task.

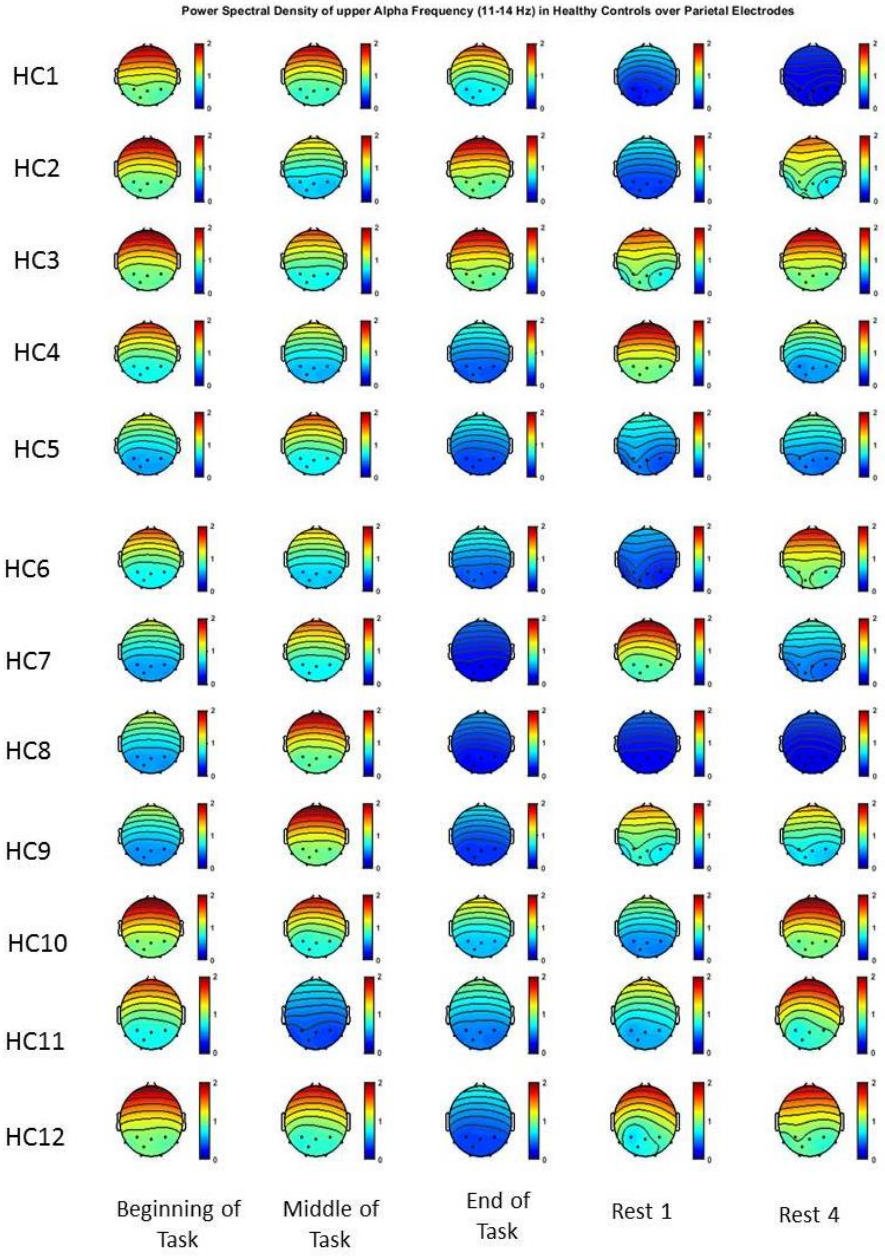


Figure 8-4 (c) Power Spectral Density of Upper Alpha frequency band for each of the 12 healthy control participants over Parietal electrodes throughout the sustained grip task.

Figure 8-4 (a, b, c) We expected to see decreased Alpha frequency band power in the parietal region in the beginning and end stages of the task, with an increase in power within the two rest periods indicating a decrease in attention. Rest 4 appears to demonstrate that majority of CRF and HC participants are in line with the hypothesis (i.e. increased Alpha band power). As with FMT Theta frequency band, the extent of Alpha band power varied among participants, which can be observed from the above plots. Within the CFS group, it shows less power increase in Rest 4. CFS are known to have higher Alpha band power at rest however within this task perhaps there was a degree of concern among CFS participants about making their fatigue worse (as discussed in Chapter 6) and they were unable to reach a fully relaxed state. However; it must be noted that the task stages are 10 seconds and rest stages are 30 seconds segments.

8.7.2 Peak Frequency

As with power analysis, five stages of the task were examined, the beginning, middle, and end of the task, in addition to two rest periods: Rest 1 and Rest 4 for the frontal medial within the Theta (4-8Hz) frequency band (Figure 8-5 a, b, c).

From the EEG data recorded during the sustained motor task, as specific interest in the frontal medial Theta frequency band, results demonstrate that the frontal-medial regions display the changes in peak Theta (4–8 Hz) frequency throughout the task and rest stages (Figure 8-5 a, b, c). It was hypothesised that an increase would be observed in Theta frequency peak from middle to end of task for all participants, which indicates increased attention once the task becomes increasingly difficult; however, this trend was not always observed. Between group comparisons showed that there was only a statistically significant difference at the beginning of task for CRF vs CFS ($p=0.008$) and within group comparisons for each stage showed a statistically significant difference for only CRF vs CFS ($p=0.04$). For individual group comparison between each stage there was only a significant difference in peak frequency for the CRF group from the beginning to the middle of the task ($p=0.03$).

Figure 8-5(a): Peak frequencies for various stages of experiment: Theta frequency band (4-8) Hz for CRF cohort: Measured over Frontal Medial electrodes.

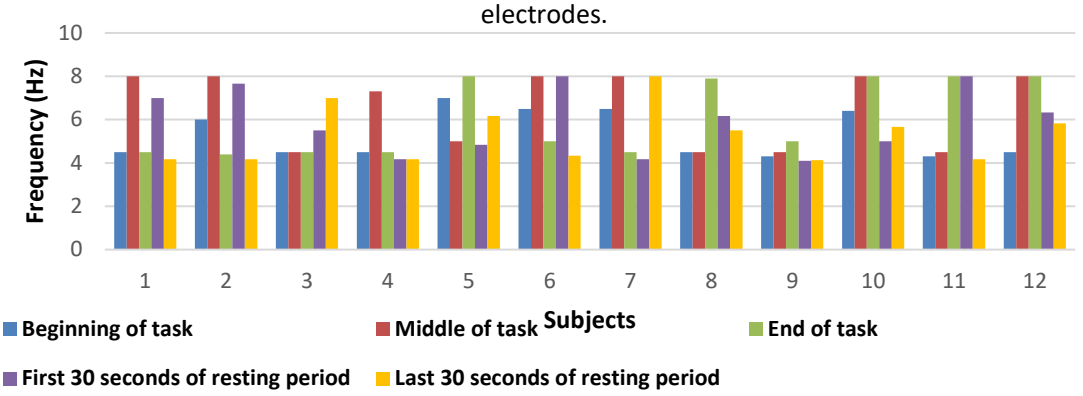


Figure 8-5(b): Peak frequencies for various stages of experiment: Theta frequency band (4-8) Hz for CFS cohort: Measured over Frontal Medial electrodes.

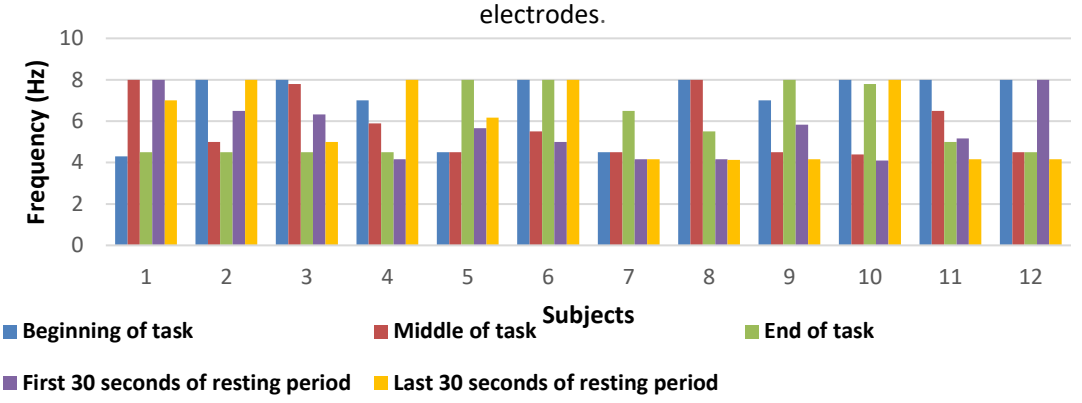


Figure 8-5(c): Peak frequencies for various stages of experiment: Theta frequency band (4-8) Hz for Healthy Controls: Measured over Frontal Medial electrodes.

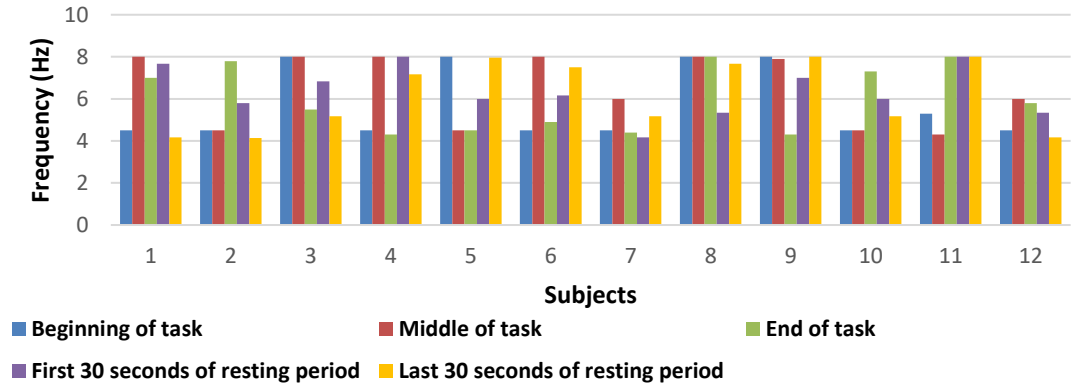


Figure 8-5 (a, b, c): Analysis of Theta Frequency Band over the Frontal Medial electrodes

This demonstrated that there were significant individual differences in peak frequencies throughout the task stages in all three groups. It was expected that there would be an increase in peak frequency from the middle to the end of task which indicates increased attention to the task, however this varied for participants in all three groups.

8.8 Discussion

Mind wandering (MW) appears to be an important part of our cognitive lives (Metzinger, 2013; Mooneyham and Schooler, 2013; Smallwood and Schooler, 2015a; Konishi and Smallwood, 2016). As mentioned, estimates suggest that the tendency for the mind to stray from the here and now in favour of thoughts unrelated to current external events constitutes as much as 50% of our waking hours (Killingsworth & Gilbert, 2010; Klinger, 1999) and MW is characterised by disassociating attention from an immediate task context toward unrelated concerns (Smallwood & Schooler, 2006; Schooler et al., 2011). The experimental paradigms of Study 1, 2 and 3 were designed to assess objective correlates of fatigue in CRF and were not intended as a mind wandering task. While these studies have confirmed that neurophysiological based methods can objectively assess correlates of fatigue within CRF, they cannot measure how much physical effort patients put into their MVC or how much they are focused on the task. Thus, for this final study, it was decided to retrospectively investigate if participants were failing the handgrip task due to fatigue or lack of concentration. The study of MW could be employed in future in addition to a sustained motor task and might provide a more comprehensive assessment of maximum effort into the fatigue task.

Of the three participant groups tested in this study, it was expected that that the possible MW experience of the HC group would manifest differently to that of the CRF and CFS groups, with HC experiencing more MW episodes throughout the task. While this study was retrospective and the results cannot be viewed as a definitive statement of evidence of MW. In addition they may not distinguish MW from other possible causes of increased Alpha and decreased Theta. The results demonstrated that both the CRF and HC groups were similar and followed the hypotheses presented. Suggesting that the results of both groups is consistent with mind wandering during the task and particularly in the rest period.

It was expected that the CRF group to be more aligned with the results of the CFS group due to the fact that they are two fatigue disorders with overlapping symptoms as discussed in Chapter 6 (Section 6.8). However, while the results were not identical, the CRF followed the trends of the HC group when examining power changes. This might be due to the fact that the CRF were newly diagnosed and pre-treatment, and cognitive

impairments might not be as significant as those with more advanced disease or impairment caused by treatment which would also lead to increased fatigue.

Previous studies have shown that those with cancer having undergone treatment demonstrated higher propensity to MW in comparison to HC, indicating higher distractibility (Kam et al., 2016; Hampson et al., 2015; Olbrich et al., 2011). Cancer and its treatment can result in cognitive impairments. Attention, memory, and executive functioning are the most frequently identified cognitive domains impacted by cancer (Pendergrass et al., 2018). These changes can affect many aspects of life such as the ability to work or even to do everyday tasks. In this research, the aim was to assess CRF participants at baseline before any treatment or interventions occurred. Perhaps this is why the CRF group were similar to the HC in relation to significant differences between stages throughout the task.

The CFS group did not have any significance differences throughout the stages of the task to the extent of the CRF and HC groups and intergroup comparisons demonstrated that the CFS group were significantly different suggesting that the task required more cognitive effort by this group. A possible explanation for such a difference between the HC and CRF group compared to the CFS group is that the individuals in the CFS group were suffering from their disease for longer. In addition, they may find it harder to relax due to more concern about performing the actual test e.g. recruited CFS participants mentioned not wanting to do the test for fear of making their fatigue worse which may cause less MW and more task related thoughts, this might explain the less significant differences between the stages in the results presented.

The HC group may not have found the task as difficult (physically or cognitively) and hence, their endurance was longer, they may have been bored during the task, which might give more opportunity to generate MW episodes in comparison to the CRF and CFS groups. An additional reason to consider is that the HC's ability to transition from task orientation to resting state could be faster than the CRF and CFS groups which may possibly be why the patient groups feel more subjectively fatigued.

Understanding MW is important and there are diverse views on whether it is positive or negative. Several studies (Klinger, 2009; Klinger and Cox, 1987; McVay and Kane, 2010; Smallwood et al., 2004) suggest that MW could positively facilitate the anticipation and planning of personal future goals, known as autobiographical planning.

Conversely, MW may be considered as a negative characteristic in many aspects of cognitive function and daily life (Mooneyham and Schooler, 2013) and may occur during tasks that impose less attention and working memory demands (Teasdale et al., 1993; McVay and Kane, 2010) There is also a view that MW may best be described as a failure of cognitive control (McVay and Kane, 2010). .

In the context of this study, MW might impact the results if, for instance the task is viewed as boring and tedious by all or some of the participants. This could possibly be the cause of early failure, however, data to confirm or dispute that MW is the cause of such occurrences was not produced during this analysis due to the retrospective and non-MW design of this research. For instance, HC participants require less effort and focus during the task compared to CRF and CFS or may become bored earlier and fail earlier for reasons other than fatigue.

For future research, a specific MW test may be designed with the sustained motor task employed and the expected result may be validated in terms of objective vs subjective outcomes. This may be achieved by additional administration of a MW ES method (e.g. self-caught method with button push) during the sustained task itself. The impact on the patient would be the addition of another element to complete during the task.

To achieve this, the motor task would have to be altered to lengthen the task time in order to perform more detailed analysis. It is important to attain the same time length for each participant in order to analyse group averages which was not possible in this study. Examining abnormal fluctuations in neural activity provides a promising objective measure of effort.

8.9 Conclusion

Widespread scientific attention is now being given to the topic of mind wandering which can affect cognitive and motor performance in task completion. The retrospective analysis of data used in this study suggested similar patterns of EEG signal changes in HC and CRF compared to CFS. The CRF and HC groups followed the hypotheses with frontal and parietal Theta frequency bands increasing in power during the task with higher demand on concentration; showing decreased Theta in the rest periods. In addition, Alpha power decreased during the task involving higher concentration and increased in

the rest periods. This study suggests that it may be possible to develop and design an experiment to objectively assess mind wandering in those with CRF.

Given the impact of fatigue and cognitive problems on quality of life and daily functioning in those with cancer, future research may benefit from examining the neural mechanisms underlying fatigue from a sustained attention perspective and this may be used an important marker of fatigue.

Chapter 8: Summary Points

- Mind wandering occurs when sustained attention is low and corresponds to distraction caused by emergence of thoughts unrelated to task at hand and therefore shifting attention away from the task.
- Many cancer-related fatigue and chronic fatigue participants used similar descriptors of their fatigue: ‘‘*I lose concentration*’’ ‘‘*I seem more absent-minded*,’’ and ‘‘*I can't fully concentrate on anything*.’’ “*…it is such an effort to do that simple task".*
- While neurophysiological data could objectively assess correlates of cancer-related fatigue, it cannot measure how much physical effort participants put into the handgrip.
- Are participants really failing the task due to fatigue, or is it due to lack of attention?
- The data obtained from the task was broken down to analyse different stages: Beginning of task, Middle of task, End of task, Rest 1, and Rest 4 and to assess power changes in neural activity within these stages.
- Hypotheses: Frontal and parietal Theta band frequencies should increase in power during tasks involving higher demand on concentration, and decrease in mind wandering states. Alpha power should decrease during tasks involving higher demand on concentration and increase in MW states.
- Results demonstrated that both the cancer-related fatigue and healthy control groups had similar trends and followed the hypotheses presented, unlike the chronic fatigue group. Suggesting that both the cancer and healthy groups mind wandered during the task and particularly in the rest period.
- These results indicate that at this stage of the cancer trajectory the cognitive impairment due to fatigue may not have fully manifested yet.
- Designing a mind wandering method in addition to a sustained motor or cognitive task such as described in this study may help assess the cognitive impairments of those with CRF.

Chapter 9: GENERAL DISCUSSION

9.1 Thesis Summary

The research described in the preceding chapters has both subjectively and objectively examined metrics for cancer-related fatigue (CRF) which is one of the most distressing and undertreated symptoms in those with cancer. An important question within this research was whether CRF is of central or peripheral origin, and if it could be assessed employing non-invasive objective correlates of fatigue. A key priority of this research was the design and testing of an objective assessment method employing neurophysiology (electroencephalography and electromyography) and acceptability by a patient population (O'Connor 2016).

Two in-depth literature reviews provided the theoretical, hypothetical and practical research and intelligence to effectively analyse and contextualise the data, analysis and conclusions reached. Together with subjective measures, including patient self-reporting, the use of objective correlates of fatigue such as the use of neurophysiological data, showed a promising opportunity to objectively establish possible central and peripheral contributions to cancer-related fatigue. This could help clinicians to evaluate fatigue and monitor the fatigue trajectory from diagnosis through treatment and survivorship. The novelty of this research lies in the development and analysis of non-invasive neurophysiological assessment of fatigue in pre-treatment, non-small cell lung cancer patients within a clinical outpatient setting. In an addition, a comparison of chronic fatigue syndrome sufferers was included to probe the question of whether cancer-related fatigue (CRF) and chronic fatigue syndrome (CFS) share clinical characteristics and potentially, underlying pathophysiology.

The ability to assess CRF employing a reproducible and standard test may provide clinicians with objective data which could aid in developing a therapeutic interventions. This, in turn, could lead to more personalised therapeutic interventions and enhance the clinical outcomes of treatment. In addition, relocation of tests from specialised laboratories to routine outpatient settings would greatly reduce the burden on patients.

In order to significantly improve possible objective methods of assessing CRF, a number of studies were carried out as described in Chapters 5-8.

Most studies investigating fatigue in cancer have primarily focused on the use of self-report questionnaires to determine whether patients suffered from CRF. Although there are many instruments available to evaluate CRF, each has its limitations, are subjective and no single standard instrument exists for assessing overall CRF (Wu and McSweeney, 2007; Seyidova-Khoshknabi et al., 2010). No single instrument has been shown to correlate with a neurophysiological marker reflecting increased feelings of fatigue. While there is limited research into the use of objective measures as discussed in Chapter 3; no biological or physiological markers of CRF have been identified.

The methods presented in this thesis provided more scientific depth to the existing literature on the research for the underlying mechanisms of CRF and previous objective measures. This was achieved by developing a metric to assess CRF with a neuromuscular index. All research aims were examined and are further discussed within this chapter.

9.2 Main Findings and Overall Discussion of Studies

The results of the studies in this research demonstrated that a neurophysiological method can provide an objective correlate of CRF and that this neuromuscular index (EEG, EMG and CMC analysis) can assist in analysing the potential central and peripheral contributions of fatigue. The importance of the research findings and the lessons learnt from this research will now be critically discussed in relation to the research questions previously posed in Chapter 4. Interpretation of the main findings will also be discussed in the light of the previous literature as detailed in Chapter 2 and 3.

9.2.1 Literature Reviews

Comprehensive literature reviews were undertaken to evaluate the current understanding of and research into the underlying pathomechanisms of CRF, in addition to the current objective assessments of CRF. It was suggested that the most commonly used definition is by the NCCN (Bower et al., 2014). It defines CRF as a “persistent subjective sense of physical, emotional, and cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity, and significantly interferes with usual functioning”. Clinicians and researchers are recognising that CRF is

a significant consequence of cancer and its treatment requires more clinical attention and intervention.

In an attempt to explain CRF, several hypotheses for central and peripheral contributions have been proposed (Saligan et al., 2015) (Figure 2-7). These hypotheses suggest that simultaneous dysregulation of important biological systems contribute to CRF. These have been largely based on evidence where fatigue is an intrinsic characteristic such as in CFS or daily activity/exercise (Ryan et al., 2007; Wang, 2008; Wang and Woodruff, 2014; Saligan et al., 2015). It has been suggested that proinflammatory cytokines may play a role throughout all the CRF hypotheses proposed. Activation of the immune system may evoke feelings of fatigue, which are mediated by proinflammatory cytokines. Detailed insight in the central role of increased activities of proinflammatory cytokines in CRF could offer an effective approach in the treatment of CRF by affecting an array of proposed causative factors e.g. anaemia, disturbances of the hypothalamic pituitary adrenal axis, and altered brain serotonin (Barsevick et al., 2010; Bower et al., 2014; Bower et al., 2002; Dantzer, 2001; Dantzer et al., 2008; Kelley et al., 2003; Kurzrock, 2001; Jager et al., 2008).

A limited numbers of studies to date have investigated these hypotheses. They have not yet been conducted in all relevant patient groups, for all aspects of fatigue (e.g. disease stage, severity vs duration, pre- and post- treatment). A thorough clinical assessment of the relationship between CRF and other cancer-related symptoms as well as co-morbid conditions, is important to advance our understanding of the complex pathophysiology behind CRF.

According to the review of the literature surrounding objective measures of assessment, it is clear that there is insufficient research which non-subjectively evaluates peripheral and central contributions to CRF. Therefore neurophysiological methods such as EEG and EMG show potential in providing an opportunity to facilitate the investigation of the central and peripheral contributions and to establish a variation pattern of fatigue.

9.2.2 Study 1: Validation, Reliability and Quantification of Cancer-Related Fatigue using Objective Neurophysiological Methods in an Outpatient Setting

A novel, non-invasive, experimental paradigm and protocol were designed to test the method employed for assessing objective correlates of CRF in a clinical outpatient setting. Results of Study 1 are presented in Chapter 5, Section 5.6. A high level of device acceptability was reported by both CRF and healthy control (HC) participants and no participant had concerns about the use of EEG and EMG for similar patient groups (O'Connor, 2016).

The results from this study, while statistically significant, were treated with caution as the number of CRF participants was low and were not age-matched to HC, therefore cannot be generalised. However, the focus of Study 1 was to confirm and validate neurophysiological methods employed to characterise neuromuscular alterations during a fatiguing task in an outpatient setting. It is believed that this is the first time that this has been carried out in a specific cohort in this setting. The experimental protocol, set up, fatigue task, recording and synchronisation of equipment, configuration and feedback of software were assessed for suitability. Additionally, these were validated by testing in the lab with the researchers and then with HC before CRF patients. Thus, confidence was obtained before the methods could be employed for further fatigue data collection and analysis of CRF. Therefore, it is evident from this study that this experimental paradigm can be used for future patient testing.

9.2.3 Study 2: Identification and Comparison of Neuromuscular Impairment in Cancer-Related Fatigue and Chronic Fatigue Syndrome

In chapter 6, a new comparator population was introduced which shares similar symptoms and clinical expression to CRF. Like CRF, chronic fatigue syndrome (CFS) is a common and debilitating state of fatigability, unresolved with rest and an unknown aetiology and pathophysiology. Previous studies of CFS show there are alterations of cognitive function (memory, attention and information processing) and decreased muscular function similar to those with cancer. This study demonstrated that the CRF and CFS groups reported statistically significantly greater feelings of fatigue, presented a reduced ability to perform the motor task and perceived physical exhaustion sooner;

and had altered EEG activity compared to the HC, while the HC group showed predominately peripheral fatigue. These results indicated both central and peripheral abnormalities for the CRF and CFS groups but contradicted the hypothesis that the two patient groups would have similar results. This additionally highlights that CRF exists at baseline before any treatment has been undertaken. Clinically, CFS present abnormal electrophysiology in Delta, Theta and Alpha band frequencies, which was also demonstrated in this study.

EEG-EMG coherence was detected during muscle fatigue in all groups, CRF, CFS and HC. It was hypothesised that CRF and CFS would have weakened coherence at the onset of fatigue, this was not observed like previous studies. Further information to examine if weakening of the corticomuscular coherence is a specific consequence of central or peripheral fatigue could not be revealed by coherence analysis employed in this study. This is due to requiring twitch force analysis (Section 9.6.3) to determine if reduced central drive or neuromuscular junction impairment was the cause of weakened coherence. Therefore, building on the findings of this study, future research may include determining directional coherence changes to further elucidate whether the weakened communication is brain to muscle or muscle to brain during fatigue and detecting CMC changes before and after treatment in those with cancer.

9.2.4 Study 3: Handgrip Dynamometry Performance in Relation to Self-Perceived Fatigue

The aim of study 3 (Chapter 7) was to evaluate handgrip dynamometry performance in relation to self-perceived fatigue by brief fatigue inventory (BFI) (objective vs subjective measures). A limited number of published studies have reported inconsistent results with some showing a strong correlation between BFI and fatigue (Kilgour et al., 2011; Kilgour et al., 2013; Stone et al., 2000; Veni et al., 2018) and others reporting a weak correlation between handgrip and subjective assessment of fatigue (Brown et al., 2005; Schvartsman et al., 2017; Stone et al., 1999). Interestingly, the findings from this study demonstrated that the BFI and the maximal voluntary contraction are strongly correlated for the CRF group but not the CFS group which may suggest a difference in underlying mechanisms.

This study provides interesting information about the possible links between CRF and neuromuscular fatigability, however limitations do exist (Section 9.4). Early detection and classification of handgrip strength in CRF may provide clinicians with useful prognostic indicators that may assist them in enhancing the screening of CRF and planning timely and appropriate therapeutic measures. It is reasonable to assume that other chronic illnesses where fatigue is a main symptom (e.g. chronic fatigue syndrome) may employ a similar static force task as an objective assessment of fatigue.

9.2.5 Study 4: Mind Wandering During a Motor Fatigue Task

Within the studies mentioned, the CRF, CFS and HC participants' motivation and sustained attention were vital requirements of the objective outcomes. For this study, mind wandering was examined retrospectively analysing the data from the previous studies, to assess if the participants were failing the task due to fatigue or lack of attention, as neurophysiological methods cannot measure how much physical effort participants put into the motor task. Mind wandering may occur when sustained attention is low and corresponds to distraction caused by emergence of thoughts unrelated to the task, therefore shifting attention away from the task at hand. Cancer and its treatment causes a disruption to many biological and physiological systems in an individual and is likely to cause CRF. This affects the individual's ability to concentrate and perform daily tasks.

It was expected that mind wandering would occur differently in HC in comparison to the patient groups in this analysis. The HC group may not have found the task as difficult (physically or cognitively) thus it was thought they may get bored during the task, giving more opportunity to generate mind wandering episodes in comparison to the CRF and CFS groups. While this analysis was retrospective and no direct inferences can be made to mind wandering, the results from this study demonstrated a similar trend for CRF and HC. This may be due to the CRF group in this research being pre-treatment and their cognitive abilities may not have been fully affected yet, unlike those with CFS who showed more instances of mind wandering. This may be due to CFS and the fact that they have suffered from their disease for longer. For future research, a specific mind wandering test may be designed in addition to the sustained motor task employed and the result might be validated in terms of objective vs subjective outcomes.

9.3 Clinical Implications of Research

Fatigue is a distressing symptom that negatively affects cancer patients' physical and psychological wellbeing and contributes to decreased quality of life long after successful completion of treatment. Due to the lack of a universal definition (Chapter 1, Section 1.3.2), there is little knowledge of the origin of fatigue and where it might occur along the pathway (Chapter 2, Section 2.7 and 2.8). As discussed in Chapter 1 and Chapter 3, CRF is currently evaluated by subjective questionnaires and patient self-reports, and while they provide useful information on the individual's levels of self-perceived fatigue, it cannot give insight to the underlying aetiology and pathophysiology of CRF.

In this research, non-invasive neurophysiological methods (EEG and EMG) were employed to identify objective correlates of fatigue in an outpatient clinical setting. We have objectively demonstrated that there are abnormal central and peripheral components to CRF (and CFS) when compared to HC, while the results are not as statistically significant as previous studies, this may be due to the specific NSCLC, pre-treatment group. Chapter 5 demonstrated that the method was valid and reliable, and that there was a high level of acceptability (100%) by patients of its use; however, there are still some limitations and challenges which will be further discussed in Section 9.4.

The objective correlates of fatigue provided by the methods used in these studies offer unbiased, clinical assessment of fatigue in comparison to the patient self-reports and checklists that are currently being used in clinical practice. The identification of neurophysiological markers would help further understanding of the underlying aetiology and pathophysiology in terms of possible central and peripheral contribution to CRF and may promote the effective use of existing interventions to reduce the impact of this symptom on the individual's quality of life. In addition, following the fatigue trajectory would allow for longitudinal monitoring and tailoring individual treatment regimes.

A major challenge for clinicians is the ability to distinguish CRF from other psychosomatic and psychological disorders, such as depression. Clinicians should consider and exclude

the possibility of an underlying affective disorder before making a diagnosis of CRF. Being able to objectively quantify and discriminate CRF from fatigue related to other medical and psychological conditions would require longitudinal study, the results of which would allow monitoring of the impact of disease modifying treatments such as chemotherapy, immunotherapy and radiation therapy. It would also facilitate in the development of randomised clinical trials and assessment of individualised therapeutic interventions to identify and control the CRF symptom more precisely. Objective assessment of CRF would also improve the efficacy of commonly employed interventions for fatigue, e.g. psychostimulants such as methylphenidate.

The methods employed within this research have so far been evaluated in a cancer and chronic fatigue syndrome population. There is potential for this method and protocol to be employed for other chronic illnesses with fatigue as a major symptom.

9.4 Limitations of Research

Although this research was carefully executed, these studies faced several limitations which should be acknowledged. These limitations will now be discussed, and then followed with recommendations for future work.

9.4.1 Preparation time

The study preparation time for the studies is substantial for both participant and researcher and often longer than the test itself. The testing time required for each participant was 60 minutes, with the majority of this time being for questionnaires and preparation for the task (i.e. gelling and attaching the EEG electrodes, correct placement of EMG electrodes and handgrip dynamometer set up). For the researcher, preparation of equipment, assembly, and verification of task set up prior to participant arrival also took 60 minutes time, as well as disassembling and cleaning of equipment following the test. The time taken to prepare for the particiapants arrival may hinder its use in a routine clinical setting. This phase of set up could be refined and simplified by employing a condensed number of electrodes which would reduce preparation time and subsequently the volume of data for analysis, however reduced electrodes may result in

noisy EEG data. In addition, ways to reduce volume of hardware and software should also be explored.

9.4.2 Recruitment of Participants

In many clinical studies, particularly studies which include greviously ill patients, the recruitment process is described as challenging and time consuming (Sygna et al., 2015; LeBlanc et al., 2013). In the knowledge of this, the aim was to design an experimental setup that would be non-invasive, have a low patient burden and ease of technology use for clinicians. For the studies conducted for this research, there was great difficulty in recruitment of CRF participants as these individuals are dealing with life altering situations. As these studies were carried out before any treatment or medication; it is understandable that such individuals would be reluctant to participate in research studies. These challenges in recruitment led to seeking participants from two additional Lung Cancer Clinics. There are also referral bias and gate keeping difficulties from clinicians and family which cannot be excluded. Their concern may underestimate the ability of the patients to participate in this or any clinical research. While we tried to reduce the patient burden by developing a non-invasive, outpatient clinic set up, we still had issues with gate-keeping. If we had used a more invasive task (e.g. needle EMG or electrical stimulation) there would have be even more difficulty in recruiting participants.

Recruitment was also a challenge when seeking participants with CFS as many were unable to undertake the test due to the severity of their fatigue. In addition, some participants cancelled due to a fear that the test would worsen their condition.

9.4.3 Age

The differences in age of participant groups was emphasised throughout as a covariate. The limitation highlighted in the preceding chapters was age matching in the recruitment of participants, with the difficulty arising due to the pre-treatment cancer cohort being on average 15 years older than the healthy controls. However, the inclusion of chronic fatigue syndrome participants provided fatigue related information

which suggested that the cancer-related fatigue group reported similar levels of fatigue to the healthy controls. The levels of fatigue of the CFS group were higher than the HC (same average ages) and the levels of fatigue were higher for CFS than the CRF group. Therefore, it could be said that these results occurred in both the absence of age differences (CFS vs HC) and in-spite of the age differences (CFS vs CRF).

While the age limitation is acknowledged and having age compatible participants would have provided more reliable data, the focus of this research was on testing the suitability of experimental design and protocol, as well as the novel approach of pre-treatment cancer patients.

9.4.4 Assessment

The studies mentioned involved a single assessment. The repeatability of the results within individuals has not yet been tested. Longitudinal assessment over the course of disease and cancer treatments would contribute to further understanding of the pathophysiology of CRF and how it manifests over time.

Another limitation of assessment through these studies was the use of the flexor carpi ulnaris and the flexor carpi radialis muscles. However, as discussed in Chapter 5, section 5.3.4, to answer the question on how best to place electrodes in order to acquire surface sEMG signals during grip hand work (Baranski and Kozupa 2014); these muscles were chosen as flexor carpi radialis muscle flexes the hand and fingers and flexor carpi ulnaris muscle flexes and adducts the hand. Needle EMG would be better for the assessment of the flexor digitorum superficialis muscle. However, as the use of needle EMG is invasive and can be painful and an important aim of this study was for the methods to be non-invasive. Therefore, the most helpful points on forearm that could be used to place EMG electrodes were both the FCU and FCR for this study. Section 9.6.4 and 9.6.5 will discuss future research to improve this.

In addition to longitudinal testing, electrical muscle stimulation/twitch force would provide additional information of the possible central and peripheral contributions.

Within this research, electrical muscle stimulation/twitch force was omitted due to its invasive nature. However, it is considered a superior metric for muscle function analysis, and can determine if the maximum fatigue state has been achieved independent of central input, mood or motivation (Finsterer and Mahjoub, 2014; Davis and Walsh, 2010; Cai et al., 2014). Electrical muscle stimulation/twitch force will be discussed in future recommendations in Section 9.6.3.

9.4.5 Data Analysis

Differences in strength between the clincial cohorts resulted in differences in duration times which necessitated laboursome data analysis to ensure each group could be compared accurately. If the task was changed to adapt to those with chronic illnesses, investigation into the fatigue progression during the task could be additionally analysed. Perhaps intermittent sustained contractions or a pre-programed specific length of time for the task could be considered for future research.

Another limitation of data analysis is within the statistical analysis. A potential concern in research is the inflation of type 1 error through the conducting of multiple statistical tests of related hypotheses. In order to minimise this concern, the statistical approaches undertaken relied upon omnibus tests for global differences prior to examining pairwise comparisons. Additionally, in some cases, multivariate approaches were taken to partially pool the information provided from multiple related constructs as an additional protection against false detection. In some instances where neither approach was possible (e.g. twelve paired t-tests) a Holm-Bonferroni correction was applied to control the family-wise error rate. Most of the findings are reported uncorrected for multiple comparisons. This predominantly serves to allow the reader to make their own judgements with regard to the evidence rather than relying on arbitrary p-value corrections which may give a false sense of certainty of the reported results. Due to the novelty of this study, it is also important to consider the balance between type 1 and type 2 error. Most importantly, the results presented here should be viewed in their

totality with regard to the consistency of the magnitude, direction, and statistical significance of reported effects across the various related hypotheses.

9.5 Strengths

As there is little literature surrounding CRF, the literature reviews conducted for this research contributed to the existing knowledge and provided a basis for future research information. These studies are novel in examining a specific pre-treatment cancer cohort in an outpatient clinical setting. In addition, the use of well-validated and highly sensitive neurophysiology instruments to collect data objectively and subjectively strengthens the validity of this study. As the equipment needed to conduct the fatigue assessments is both portable and is easy to replicate, the data can easily be recorded in numerous locations using the same methodology and protocol. This may subsequently allow access to a larger cohort of participants.

9.6 Recommendations for Future Research

9.6.1 Examining CRF in Various Cancer Stages and Tumour Types

The majority of previous research has focused on CRF in mixed, advanced cancers during or after treatment, the studies in this research focused on pre-treatment, NSCLC patients. By identifying CRF stages in cancer patients e.g. pre-treatment, treatment progression (i.e. chemotherapy, immunotherapy, radiotherapy, and surgery), post-treatment and in remission; the identification of decreases or increases in CRF severity and its trajectory may be beneficial in treatment development. Investigation into various stages of cancer with neurophysiological assessment employing the EEG, EMG, and static force methods as employed here would provide enhanced results and highlight mechanisms of CRF progress.

Structuring and extending the testing to various cancer stages may lead to the ability to build a multi-site electronic database of results. In time, this would provide information on anomalies and treatment utilisation in CRF.

9.6.2 Alternative Participant Cohort – Post-Cancer Treatment

A suggestion for future research might be the use of an alternative participant cohort e.g. post cancer treatment using an update of the research protocol used in this research. If a post treatment cohort was used it is suggested that the potential population from which to recruit could be much larger, with that population being further extended if the cancer type itself was not regarded as a significant element of the research. A classification of what denotes the post treatment would be important e.g. cessation of all treatment, partial remission or complete remission. For CFS the diagnosis of the syndrome is clinical where other symptoms for the causes of fatigue have to be ruled out first. This is achieved through completion of a detailed medical history and experience of at least 6 months persistent fatigue that substantially reduces the person's level of activity to more than 50%. Perhaps it may be possible to devise a process for post treatment cancer patient's suitability for inclusion in the research using a similar framework and to compare these two cohorts to assess the fatigue and control for the "chronicity of fatigue" between the two cohorts.

Another consideration if using a post treatment cohort could be the use of data already available from the patients themselves about their cancer fatigue journey or indeed obtaining information from their consultants / doctors with the patient's permission.

In addition, as mentioned, it is suggested that age matching, which was a limitation in this research, would more likely be achieved in a post cancer cohort due to a potentially larger, a healthier CRF population and the stage of the cancer trajectory.

9.6.3 Electrical Muscle Stimulation: Measurement of Muscle Fatigue

Surface EMG was employed in these studies, with needle EMG and electrical muscle stimulation omitted to avoid potential discomfort for the patients. However, it would be of value to add electrical muscle stimulation or nerve stimulation to future CRF studies in order to gain further insight to the extent of peripheral and central fatigue (Vollestad, 1997; Cai et al., 2014; Kisiel-Sajewicz et al., 2014; Mock et al., 2004; Davis and Walsh, 2010). In addition, it may facilitate the evaluation of neuropathology present in the brain or locate where along the pathway the issue of fatigue is occurring (e.g. before or after the neuromuscular junction).

By using maximal voluntary force to examine electrical muscle stimulation of the motorneurons or the muscle itself, any impairment located in the central nervous system can be eliminated. If the muscle can still contract significantly after the point of exhaustion with electrical stimulation, then the fatigue is of central origin. This would demonstrate that the central nervous system has failed to recruit all muscle fibres during the task. Electrical muscle stimulation/twitch interpolation methods have demonstrated small to moderate deficits in voluntary activation during brief maximal efforts and progressively increasing activation deficits (central fatigue) during exhausting exercise (Shield and Zhou, 2004). Therefore, this approach may be used as an objective correlate of fatigue, but it does have some disadvantages. For example, it is invasive and painful for the patient. In addition, excessive stimulation may lead to a block of the neuromuscular transmission (Vollestad, 1997; Jones, 1996). Nonetheless if an assessment protocol can be designed to minimise the impact on the patient with strict implementation of the stimulation this may be an effective way of assessing CRF.

9.6.4 Pupillometry: New Objective Methods to Assess Cancer Related Fatigue

It was discussed throughout these studies that many patients may not be able to generate sufficient force to sustain the motor fatigue task. Although neurophysiology-based methods can be employed to assess objective correlates of CRF, they cannot measure how much physical effort patients generate and if their maximum voluntary contraction is indeed their maximum. It is well known that pupil size increases with increasing difficulty during cognitive tests (Privitera et al., 2010; Just et al., 2003). A study by Zénon and colleagues (Zénon et al., 2014) reported that increases in physical effort (as measured using a handgrip dynamometer) elicits an increase in pupil dilation (Zénon et al., 2014). It may be of interest to investigate changes in pupil size during a fatiguing task. One hypothesis is that a significant change in pupillometry-based features (e.g. pupil size and rate of change of pupil size) occurs when the participant squeezes the dynamometer with maximum effort as opposed to moderate effort. A headset may be designed that combines EEG electrodes while tracking eye movement and pupil features. This may help to assess these features from patients during the task. Combining such physiological data with a neurophysiology-based assessment of CRF may provide a more comprehensive assessment of individual patient fatigue.

9.6.5 Multiple Muscle Assessment for Future Research

Literature on the assessment of fatigue has employed a mixture of muscles (e.g. biceps brachii, brachioradialis, tibialis anterior muscles, first dorsal interosseous, flexor digitorum superficialis, flexor digitorium profundus and contralateral extensor digitorium) to conduct voluntary motor tasks. Future investigations should develop a universal method and employ a motor task (e.g. pinch grip test) that permits EMG recordings to be obtained from the principal agonists that are engaged in generating torque/force. If a handgrip force task is employed EMG recordings and data obtained from the principal agonist muscles e.g. flexor digitorum superficialis (FDS) and flexor digitorum profundus (FDP) along with the flexor carpi unlnaris (FCU) and flexor carpi radialis (FCR) (as employed in these studies) should be recorded in order to fully assess the power of the dominant muscles.

A small study within this research was conducted to examine if FDS and FDP muscles could be recorded in addition to the FCU and FCR muscles with sEMG, and to assess the results from FDS and FDP muscles individually in a fatiguing task. No statistically significant differences were observed when the data of FDS and FDP muscles were compared to the FCU and FCR muscles. This suggests that there were no differences in the use of these muscles for a handgrip task but this may relate to small sample size and the fact that it is difficult to assess the FDS and FDP with surface EMG.

9.6.6 Combining Neuroimaging: A Multimodal Tool

The possibility of combining EEG recording with functional MRI (fMRI) neuroimaging would present an opportunity to undertake high spatial resolution analysis to uncover the regions of the brain showing changes in the fMRI signal in comparison to the high temporal resolution signal changes from EEG observed with fatigue response. During MRI scanning, participants perform a series of isometric hand grips using an MRI-compatible dynamometer and EMG electrodes. This would be a starting point from which to examine effort, other EEG rhythms, and particular types of task-related activation/deactivation.

fMRI may be important to employ in assessing CRF due fatigue being an extremely common and problematic symptom in cancer patients, and it is difficult to diagnose and treat. While EEG also looks at brain activity, it cannot look at deep brain structures. The inclusion of fMRI would increase costs and duration of testing; however, recruitment of participants may be easier due to perceived public familiarity with fMRI.

Future research should examine neural correlates of CRF by studying brain activity and connectivity within the motor network regions, in particular the sensory and frontal cortical regions due to their potential roles in supraspinal fatigue; a component of central fatigue.

In addition, other future work should attempt to pin-point the cortical areas involved in the fatigue process by using transcranial magnetic stimulation (TMS). TMS is a non-invasive, neurophysiological technique that temporarily stimulates small brain areas. Specific regions of the cortex can be activated or deactivated using TMS and the analysis of resulting changes may shed light on the neural physiology associated with general fatigue and CRF. When employed along with EMG, TMS can activate motor cortex

neurons to produce a muscle electrical excitatory response. Delays or alterations in the onset and latency of motor evoked potentials (MEP) can determine if someone deviates from age-matched normal values (Davis and Walsh 2010). TMS has several advantages compared to other methods. First, single and paired pulse TMS allows for direct examination of the cortico-spinal tract. The EMG signal can vary in magnitude relative to the amount of current applied through the magnetic coil. Secondly, it has good localisation. The main limitations are that it is confined to cortical areas, to a depth of two centimetres from the stimulated area, in addition repetitive pulses can have side-effects. Redesigning the handgrip task employed in these studies to include fMRI or TMS is recommended.

9.6.7 Use of Mobile Technology

Emerging technology may be an important area of research for example, as previously discussed, EEG is a widely used neuroimaging method with applications in assessment and neurorehabilitation. High density EEG systems require expertise, expensive equipment, and extensive setup time. Therefore, they are often limited to controlled laboratory settings. Further research into the evaluation of a low density, portable integrated EEG and EMG in a clinical environment is necessary.

A low density, portable, dry-electrode EEG system may prove to be the future in CRF assessment. However, the advantages and disadvantages of the system should be carefully weighed. While several types of portable, dry electrode EEG systems are already commercially available, currently such a system retails in the area of €20,000. EEG users and clinicians are reluctant to adopt this technology into their regular practices as the lack of conductive gel implies a higher skin-electrode contact impedance making recordings more susceptible to noise and interference (Tautan et al., 2014). There is a need to research and develop a method of testing the quality of the dry-electrode EEG signal in comparison to the gel EEG systems signals in the specific motor task employed in these studies.

The use of mobile technology is increasing and is being used extensively in the measurement of biomarkers in the health, exercise and nutrition areas. Therefore, the examination of this mobile technology in the measurement of CRF and its use by patients

before, during and after cancer treatment would be invaluable and may form part of future treatment plans.

9.7 Final Conclusions

The main findings of this research demonstrate that the developed experimental paradigm and methods can be employed to objectively assess cancer-related fatigue in an outpatient setting and confirmed that CRF is present at baseline before any treatment has commenced which had not been examined before. The research questions posed in Chapter 4 have been addressed throughout several studies. The neurophysiological methods developed in this research can provide objective information regarding the possible central and peripheral contributions to fatigue during a fatiguing motor task. This allows healthcare professionals to make more informed decisions regarding patient treatment for fatigue and its efficacy by enabling them to follow the fatigue trajectory. Moreover, this creates an opportunity to give objective feedback to patients, using the presented neurophysiological methods which may help them understand their own fatigue levels. The conclusions drawn from the experimental results shed new light on areas of recent focus in the medical literature particularly with regard to the underlying aetiology and pathophysiology of CRF. The directions proposed for future research may extend knowledge of the pathomechanisms of CRF and the neurophysiological methods described in this research.

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APPENDICES

Appendix A: Chapter 2

- Pathophysiology of Cancer-Related Fatigue: Current Controversies Paper
- Southwestern Oncology Group (SWOG) paper of the week

Appendix B: Chapter 5 (6 & 7)

- Brief Fatigue Inventory Questionnaire
- The Eastern Cooperative Oncology Group Score
- Edmonton Symptom Assessment Scale Questionnaire
- Acceptance Questionnaire
- Ethical Approval Letters
- European Association of Palliative Care Research Network 2016, Trinity College Dublin Health Research Day 2016,The Annual Irish Association for Palliative Care 2017, and Multinational Association of Supportive Care Cancer 2017 Posters

Appendix C: Chapter 7

- Multinational Association of Supportive Care Cancer 2018 Poster

Appendix D: Chapter 8

- Multinational Association of Supportive Care Cancer 2017 Poster
  European Association of Palliative Care Research Network RN 2017 Poster

Appendix E: Chapter 9

- Neural based assessment of mind wandering during a fatigue inducing motor task: Is task failure due to fatigue or distraction? IEEE paper

Appendix A: Chapter 2 Supplementary Material

Paper of the week for the Southwest Oncology Group (National Cancer Institute)

SWOG

TM Link OF THE Week

August 10, 2018

This week, we share a review of the literature on cancer-related fatigue, and a dissection of the controversies that surround its pathophysiology.

The pathophysiology of cancer-related fatigue: current controversies

C. M. O'Higgins, B. Brady, B. O'Connor, Declan Walsh & R. B. Reilly

Supportive Care in Care, Published online first June 30, 2018

Check out the articlehere.

ABSTRACT

Fatigue is one of the most common and debilitating cancer symptoms, and is associated with impaired quality of life. The exact pathophysiology of cancer-related fatigue (CRF) is poorly understood, but in any individual, it is likely multifactorial and involves inter-related cytokine, muscular, neurotransmitter, and neuroendocrine changes. Underlying CRF mechanisms proposed include central and peripheral hypotheses. Central mechanisms include hypotheses about cytokine dysregulation, hypothalamicpituitary-adrenal-axis disruption, circadian rhythm disruption, serotonin, and vagal afferent nerve function while peripheral mechanisms include hypotheses about adenosine triphosphate and muscle contractile properties. Currently, these hypotheses are largely based on evidence from other conditions in which fatigue is characteristic. The purpose of this article is to provide a narrative review of the literature and present the current controversies in the pathophysiology of CRF, particularly in relation to central and peripheral hypotheses for CRF. An understanding of pathophysiology may facilitate direct and simple therapeutic interventions for those with cancer.

Appendix B: Chapter 5 Supplementary Material

BRIEF FATIGUE INVENTORY (BFI) QUESTIONNAIRE

Study Number: _____ Date: _____ Time: _____

	Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue **RIGHT NOW** **0 1 2 3 4 5 6 7 8 9 10** No fatigue As bad as you can imagine
	Please rate your fatigue(weariness, tiredness) by circling the one number that best describes your **USUAL** level of fatigue during the **PAST 24 HOURS** **0 1 2 3 4 5 6 7 8 9 10** No fatigue As bad as you can imagine
	Please rate your fatigue(weariness, tiredness) by circling the one number that best describes your **WORST** level of fatigue during the **PAST 24 HOURS** **0 1 2 3 4 5 6 7 8 9 10** No fatigue As bad as you can imagine
	Circle the one number that describes how, during the **PAST 24 HOURS**, fatigue has interfered with your:
	a. General activity **0 1 2 3 4 5 6 7 8 9 10** Does not interfere Completely interferes
	b. Mood **0 1 2 3 4 5 6 7 8 9 10** Does not interfere Completely interferes
	c. Walking ability **0 1 2 3 4 5 6 7 8 9 10** Does not interfere Completely interferes
	d. Normal work (includes both work outside the home and daily chores) **0 1 2 3 4 5 6 7 8 9 10** Does not interfere Completely interferes
	e. Relations with other people **0 1 2 3 4 5 6 7 8 9 10** Does not interfere Completely interferes
	f. Enjoyment of life **0 1 2 3 4 5 6 7 8 9 10** Does not interfere Completely interferes

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

0. Fully active, able to carry on all pre-disease performance without restriction.

1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light sedentary nature e.g. light house work, office work.

2. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4. Completely disabled cannot carry out any self-care. Totally confined to bed or chair.

5. Dead

REVISED EDMONTON SYMPTOM ASSESSMENT SYSTEM (ESAS-r)

Study Number: _____ Date: _____ Time:

Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem_____	0	1	2	3	4	5	6	7	8	9	10	

DEVICE USER ACCEPTANCE QUESTIONNAIRE

Study Number: _____

Thank you for participating in this study. Please complete this questionnaire.

1. Please indicate if the arm electrodes posed any of the following difficulties for you:

	YES	NO	DON'T KNOW	Comment if desired
Noise				
Size				
Weight				
Discomfort				

2. Please indicate if the wireless cap posed any of the following difficulties for you:

	YES	NO	DON'T KNOW	Comment if desired
Noise				
Size				
Weight				
Discomfort				

3. Do you feel either device in this study interfered with your privacy?
   Yes No Don't know

   If yes, please explain:

_____
_____

4. Did using these devices bother you in any other way?
   Yes No Don't know
   If yes, please explain:

_____
_____

5. Having used these devices, would you have any concerns for other people using them?
   Yes No Don't know
   If yes, please elaborate:

_____
_____

Ethical Approvals

Trinity College Dublin

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Ciara O'Higgins
Trinity Biomedical Sciences Institute,
Trinity College Dublin,
152-160 Pearse Street,
Dublin 2,
Ireland.

Ref: 161211

Title of Study: Investigation of Neuromuscular Characteristics of Cancer Related Fatigue via Electrophysiology.

Dear Ciara,

Further to a meeting of the Faculty of Health Sciences Ethics Committee held in February 2017, we are pleased to inform you that the above project has been approved without further audit.

Yours sincerely,

pp Brian Brown
Prof. Brian O'Connell
Chairperson
Faculty Research Ethics Committee

Dámh na nEolaíochtaí Sláinte
Foirgneamh na Ceimice,
Coláiste na Tríonóide,
Ollscoil Átha Cliath,
Baile Átha Cliath 2, Éire.

Faculty of Health Sciences
Chemistry Building,
Trinity College Dublin,
The University of Dublin,
Dublin 2, Ireland.

www.healthsciences.tcd.ie

St James's Hospital, Dublin

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Ms. Ciara O'Higgins
Department of Palliative Medicine
Education and Research Centre
Our Lady's Hospice and Care Service
Harold's Cross
Dublin 6 W

6th July 2016

Re: Cancer Related Fatigue: Evaluation by Wireless Electrophysiology (Electroencephalography & Electromyography)

REC Ref: 2016-07 List 25 (11)
(Please quote reference on all correspondence)

Dear Ms. O'Higgins,

Thank you for your recent correspondence to SJH/AMNCH Research Ethics Committee in which you requested an amendment in relation to the above referenced study

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed this request and grants permission for this amendment.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

NSV Code: WPA 00486

Our Lady's Hospice & Care Services, Dublin

Our Lady's Hospice & Care Services
CEO's Office
tel: 01 4068725 Harold's Cross
fax: 01 4068807 & Blackrock

Ms. Ciara O'Higgins,
Education & Research Centre,
Our Lady's Hospice & Care Services.

November 23rd 2016.

Re: Research proposal: "Investigation Of Cancer-Related Fatigue via Electrophysiology"

Dear Ciara,

On behalf of the Education and Research Committee, I would like to thank you for submitting the above research proposal. I can confirm that the Committee is satisfied and has given approval for your proposal.

You will be asked to submit an update on research at six-monthly intervals and a copy of the completed project should be submitted to the E&R Committee and the Library at Our Lady's Hospice & Care Services on completion.

We wish you the very best of luck in your research.

Yours sincerely,

Audrey Houlihan, CEO,
Our Lady's Hospice & Care Services.

Our Lady's Hospice
& Care Services
Harold's Cross
Dublin 6W
www.olh.ie

St Vincent's University Hospital, Dublin

St. Vincent's Healthcare GROUP LIMITED

St. Vincent's Healthcare GROUP LIMITED

Ethics and Medical Research Committee
ELM PARK, DUBLIN 4
Tel. (01) 2214117 Fax (01) 2214428
email: joan.mcdonnell@ucd.ie or jacinta.mcmanus@ucd.ie

2nd June, 2016.

Professor Declan Walsh,
Professor of Palliative Medicine,
Department of Palliative Medicine,
Education and Research Centre,
Our Lady's Hospice & Care Services,
Harold's Cross,
Dublin 6w.

Re:- Cancer Related Fatigue: Evaluation by Wireless Electrophysiology (Electroencephalography & Electromyography) Amendment Notification Form No. 2 (Protocol Version 4) signed and dated 27/4/2016. Research Protocol Version 4 April 2016 clean and track change version. PIL/Consent version 3 April 2016. Standard Application Form.

Dear Professor Walsh,

The above amendment was reviewed at the Ethics & Medical Research Committee meeting on Wednesday 1st June, 2016.

This amendment was approved.

Yours sincerely,

Dr. E. Molloy,
Chairman,
Ethics and Medical Research Committee

Cc Ms Michelle Barrett, Research Nurse, Our Lady's Hospice & Care Services.

EAPC RN 2015 (Leeds, UK), EAPC 2016 (Dublin, Ireland), IAPC 2017 (Madrid, Spain), MASCC 2017 (Washington D.C, USA)

CANCER-RELATED FATIGUE: THE ROLE OF MOBILE TECHNOLOGY IN ASSESSMENT

B O'Connor, M Markicevic, C O'Higgins, L Newman, R Kallidil, P Ui Dhuibhir, S Sukor, E Hanrahan, JA Armstrong, S Cuffe, RB Reilly, TD Walsh

BACKGROUND

- Cancer-Related Fatigue (CRF) is common[1]
- Pathophysiology remains poorly understood[2]
- Aetiology central or peripheral: originates anywhere from brain to muscle[3,4]
- Specialized laboratory required to evaluate
- Mobile electromyography (EMG) and wireless electroencephalography (EEG) may allow evaluation in routine clinical setting

OBJECTIVES

1. Determine feasibility & acceptability of mobile EEG-EMG to evaluate CRF in outpatients
2. Correlate subjective and objective fatigue

METHODS

Study Design

- Prospective observational feasibility study
- Preceded by healthy volunteer pilot (n=10)

Population

- 10 inoperable, treatment-naive, non-small cell lung cancer patients
- Right hand dominant

Data Collection

- Subjective: Brief Fatigue Inventory (BFI)
- Objective: EEG & EMG during right-sided hand-held dynamometer fatigue task
- 2 evaluation stages: First & last 20 secs of task
- Acceptability questionnaire

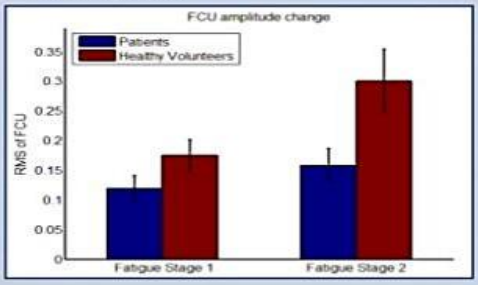
RESULTS

Fatigue Task

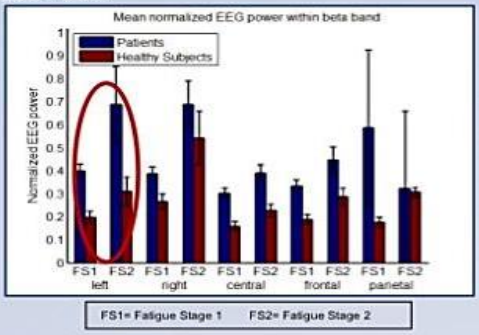
MEASURE	PATIENT	VOLUNTEER
Mean Age*	64	28
Mean BFI*	3.4	1.6
Mean Endurance Time (secs)*	137	208
Mean Maximum Voluntary Contraction (N)*	222	379

*p<0.05

EMG Amplitude



EEG Power



Subjective v Objective

- BFI >3 correlated poorly with objective EEG-EMG measurements

Acceptability

- All patients report acceptable form of evaluation
- Mild EEG discomfort: 2 patients

DISCUSSION

- Mobile EEG-EMG feasible in the outpatient setting
- Cancer patients
  - Perceive physical exhaustion sooner
  - Less voluntary muscle recruitment
  - Higher EEG Power → Lower EMG Response
- Relatively good performance status

CONCLUSIONS

1. Mobile EEG-EMG effectively evaluates CRF
2. High acceptability
3. More central fatigue in cancer patients v volunteers
4. Peripheral muscle abnormalities also evident
5. Further research: a. Longitudinal evaluation
   b. Motor cortex localization

MAXIMUM VOLUNTARY CONTRACTION & ENDURANCE TIME AS OBJECTIVE MEASURES OF CANCER-RELATED FATIGUE

Ciara M. O'Higgins[1,2,3], David Joyce[3,4], Brenda O'Connor[3,4], Marija Markicevic[1], Richard B. Reilly[1,2], Declan Walsh [2,3,4]

1.Trinity Centre for Bioengineering, Trinity College Dublin, 2.School of Medicine, Trinity College Dublin, 3. Department of Palliative Medicine, Our Lady's Hospice, 4. School of Medicine & Medical Sciences, University College Dublin.

BACKGROUND

- Cancer-related fatigue (CRF) is prevalent, highly debilitating & underdiagnosed.
- The aetiology of CRF is not well understood. There may be central & peripheral components.
- No gold standard objective measure for diagnosis of CRF.
- Hand grip strength & endurance may be useful measures of CRF.

OBJECTIVES

- To compare a subjective measure of CRF to objective measures in cancer patients (CP) & healthy controls (HC).
- To determine the contribution of objective measures, Endurance Time (ET) & Maximum Voluntary Contraction (MVC), to the subjective measure of the Brief Fatigue Inventory questionnaire (BFI).

METHODS

10 newly diagnosed, pre-chemotherapy, inoperable, non-small cell lung cancer patients.

10 Healthy Controls.

Data Collection Measures

- BFI administered.
- ET & MVC measured during a motor fatigue task using a hand-held dynamometer.

ETHICS

Approved by Ethics & Medical Research Committee of St. Vincent's Healthcare Group & Tallaght Hospital / St. James's Hospital Joint Research Ethics Committee.

RESULTS

Mean age:

Group	Mean Age
CP	64 years ± 12
HC	28 years ± 8

Mean BFI:

Group	Mean BFI Score	Significance
CP	30.2	**P=0.02**
HC	12.9	

(Higher Brief Fatigue Inventory scores indicate greater fatigue).

Mean MVC:

Group	Mean MVC (N)	Significance
CP	278 ± 115	**P=0.03**
HC	409 ± 160	

(Lower Maximum Voluntary Contraction = less strength).

Mean ET:

Group	Mean ET (Secs)	Significance
CP	134 ± 55	**P=0.02**
HC	218 ± 64	

(Shorter Endurance Time = lower endurance).

Associations of ET & MVC to BFI

BFI for all participants, was moderately & significantly correlated with ET (Spearman's Correlation r= -0.57, **p=0.01**) & MVC (Spearman's Correlation r= -0.61, **p=.004**).

BFI for cancer patients alone, was strongly & significantly correlated with MVC (Fig. 1). (Spearman's Correlation r= -0.743, **P=0.01**).

Linear regression analysis with MVC & ET as predictors of BFI resulted in an R2 of .577, .308 & .653 respectively, for participants overall, healthy controls & cancer patients.

This high R2 value for cancer patients indicates that maximum voluntary contraction & endurance time are highly predictive of BFI for this group. (Fig. 2).

RESULTS

Fig.1. BFI vs MVC for CP group alone

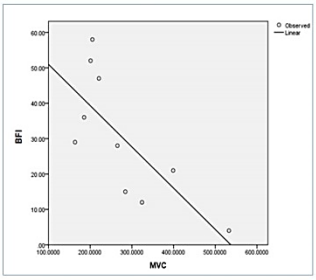
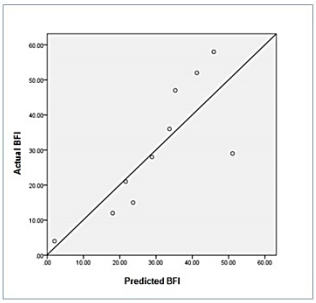


Fig.2. Actual BFI vs Predicted BFI for CP alone



CONCLUSIONS

1. There was a strong correlation between MVC & BFI for cancer patients suggesting this could be used as an objective measure of fatigue.
2. BFI was higher for the cancer patient group & MVC & ET were lower than healthy controls.
3. The notably high R2 value for MVC & ET suggests that neuromuscular fatigue accounts for over 50% of CRF in this cohort.
4. Differences in MVC & ET scores suggest that cancer patients with CRF may have neuromuscular abnormalities compared to healthy controls.

LIMITATIONS

- One time assessment
- Small Sample
- Controls were not age & gender matched

Appendix C: Chapter 7 Supplementary Material

CORTICOMUSCULAR COHERENCE IN PRE-TREATMENT CANCER-RELATED FATIGUE vs CHRONIC FATIGUE SYNDROME

Ciara M. O'Higgins*[1,2,3], Stefan Dukic[1], Brenda O'Connor[3,4], Anna Rice[2], Marija Markicevic[1], Declan Walsh [2,3,4,5] Richard B. Reilly[1,2],

1.School of Medicine, Trinity College Dublin, 2.Trinity Centre for Bioengineering, Trinity College Dublin, 3. Department of Palliative Medicine, Our Lady's Hospice, Dublin 4. School of Medicine & Medical Sciences, University College Dublin. 5. Levine Cancer Institute, Charlotte, North Carolina.

BACKGROUND

1. Fatigue is prevalent, highly debilitating & underdiagnosed in Cancer and Chronic Fatigue Syndrome (CFS)
2. The aetiology is poorly understood
3. No gold standard objective measure
4. Studies have shown a dissociation between brain and muscle signals during voluntary muscle fatigue

OBJECTIVES:

- To evaluate the effect of muscle fatigue on corticomuscular coherence by determining EEG-EMG coherence during a motor task
- We hypothesized that corticomuscular coherence in βeta-band frequency would be weakened and decrease with fatigue in CRF & CFS compared to healthy controls (HC)

METHODS

Participants:

12 newly diagnosed, pre-treatment, Non-Small Cell Lung Cancer (CRF)
12 Chronic Fatigue Syndrome (CFS)
12 Healthy Controls (HC)

Data Collection Measures

- Brief Fatigue Inventory
- EEG & EMG were simultaneously recorded during a motor fatigue task by a hand-held dynamometer (Figure 1)

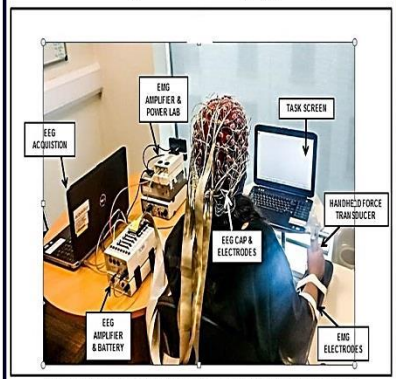


Figure 1: The participant is facing the task screen with their forearm restrained. The participant grips the handheld dynamometer and maintains 30% of their maximum voluntary contraction. Visual feedback is provided by the task screen. EEG and EMG are simultaneously recorded during the task.

RESULTS

Group	Gender	Age (years)	Brief Fatigue Inventory	Endurance Time (s)	Maximum Voluntary Contraction(N)
CRF	Female: 6 Male: 6	65 ± 11	3.2 ± 2	201 ± 165	305 ± 127
CFS	Female: 8 Male: 4	49 ± 11	6.5 ± 1**	291 ± 165	237 ± 65*
HC	Female: 5 Male: 7	50 ± 13	2.3 ± 2	512 ± 417	351 ± 152

[Table 1: Demographic details and Mean of AGE, BFI, ET and MVC scores. (*P<0.05, **P<0.001)]

- CFS significantly higher BFI mean fatigue (6.5 v 3.2, **p=0.005**) compared to CRF (Table 1)
- CRF and CFS weaker MVC and earlier exhaustion than HC (Table 1)
- EMG power (but not EEG) increased in both muscle groups in severe fatigue for HC and CRF but not CFS
- Coherence at lower βeta-band (15-25 Hz) significantly decreased in severe compared to mild fatigue (Figure 2) in FCU for HC & FCR for CRF
- Coherence at the broad βeta-band (15-35 Hz) no significant change

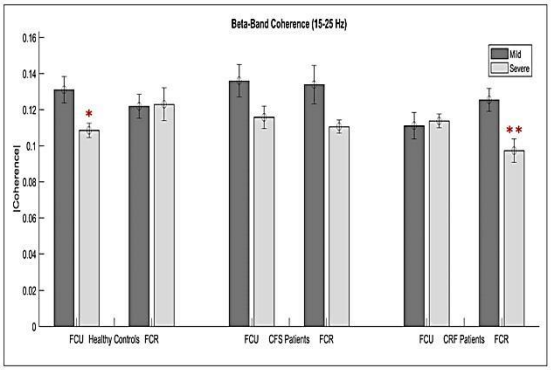


Figure 2: Lower βeta-band coherence changes over contralateral motor cortex for both muscles at each fatigue stage in all three cohorts. (*P<0.05, **P<0.001)

CONCLUSIONS

1. CRF was associated with weakened corticomuscular coherence.
2. This suggests central mechanisms may contribute to CRF and CFS with associated performance impairment.
3. Interventions to improve coherence may reduce fatigue in CRF and CFS.
4. CRF is related to physiological alterations and is present at diagnosis before treatment

Acknowledgements

The authors would like to thank Trinity Centre for Bioengineering, and Our Lady's Hospice, Harrold's Cross, St. Vincent's University hospital and St. James's hospital in Dublin, for assistance with the resources for this study. A very special gratitude towards all the volunteers who participated.

*CONTACT:

ohiggici@tcd.ie

Appendix D: Chapter 8 Supplementary Material

OBJECTIVE & SUBJECTIVE MEASURES IN CANCER-RELATED FATIGUE vs CHRONIC FATIGUE SYNDROME

Ciara M. O'Higgins*[1,2,3], David Joyce[3,4], Brenda O'Connor[3,4], Anna Rice[2], Marija Markicevic[2], Declan Walsh[2,3,4,5], Richard B. Reilly[1,2]

[1.]School of Medicine, Trinity College Dublin, [2.]Trinity Centre for Bioengineering, Trinity College Dublin, [3.] Department of Palliative Medicine, Our Lady's Hospice, Dublin [4.] School of Medicine & Medical Sciences, University College Dublin. [5.] Levine Cancer Institute, Charlotte, North Carolina.

BACKGROUND

- Fatigue is prevalent, highly debilitating & underdiagnosed, in Cancer and Chronic Fatigue Syndrome (Myalgic Encephalomyelitis)
- The aetiology is not well understood.
- There may be central & peripheral components
- No gold standard for objective measure of fatigue exists
- Maximum Voluntary Contraction (MVC) (handgrip strength) & Endurance (time grip sustained) for motor task may be useful

AIMS

- Can Maximum Voluntary Contraction & Endurance Time be used as objective measures of fatigue in CRF and CFS?
- To determine the correlation of MVC & ET to the subjective Brief Fatigue Inventory (BFI)

METHODS

Ethical Approval was obtained

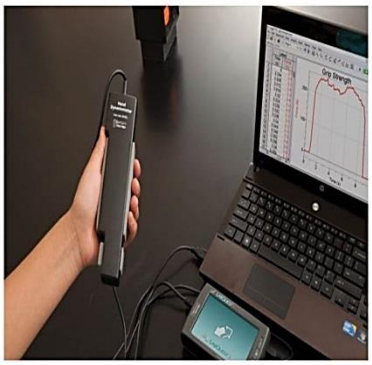
Participants:

10 newly diagnosed, pre-chemotherapy, Non-Small Cell Lung Cancer Patients (CRF)

11 Chronic Fatigue Syndrome Patients (CFS)

Data Collection Measures

- Brief Fatigue Inventory administered
- MVC & ET measured during a motor fatigue task by hand-held dynamometer



RESULTS

	Cancer-Related Fatigue	Chronic Fatigue Syndrome	Significance
Mean Age	64 ± 12	50 ± 10	
Mean BFI	3.35 ± 1.99	6.90 ± 1.34	P=0.005
Mean MVC (N)	278 ± 115	224 ± 60	P=0.43
Mean ET (Secs)	134 ± 55	144 ± 83	P=0.80

Higher mean BFI scores = greater fatigue
Lower MVC= less strength
Shorter ET = lower endurance

- Controlled for age, CFS significantly higher BFI mean (6.9 vs 3.4; **p=0.005**) compared to CRF
- Linear regression analysis of MVC & ET as predictors of log BFI; R^2 = 0.8 for CRF (Figure 1) & R^2 = 0.06 for CFS

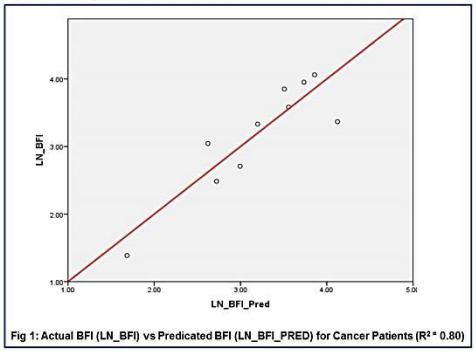


Fig 1: Actual BFI (LN_BFI) vs Predicated BFI (LN_BFI_PRED) for Cancer Patients (R^2 * 0.80)

- BFI for CRF alone, was strongly & significantly correlated with MVC (Pearson's Correlation r= -0.743, **P=0.01**) compared to CFS (r=-0.06, P=0.84)

CONCLUSIONS

1. Maximum Voluntary Contraction & Endurance Time can be used as an objective measures for Cancer-Related Fatigue but not Chronic Fatigue Syndrome
2. Strong correlation between Maximum Voluntary Contraction & Brief Fatigue Inventory for Cancer-Related Fatigue but not for Chronic Fatigue Syndrome suggests different fatigue mechanisms
3. Chronic Fatigue Syndrome fatigue as measured by Brief Fatigue Inventory is more severe than Cancer-Related Fatigue
4. Suggests that Cancer-Related Fatigue is more central & Chronic Fatigue Syndrome

Acknowledgements

The authors would like to thank Trinity Centre for Bioengineering, and Our Lady's Hospice, Harrold's Cross, St. Vincent's University hospital and St. James's hospital in Dublin, for assistance with the resources for this study.
A very special gratitude towards all the volunteers who participated.

*CONTACT:

ohiggici@tcd.ie

Appendix E: Chapter 9 Supplementary Material