1996

Central Fatigue in Chronic Fatigue Syndrome

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CENTRAL FATIGUE IN CHRONIC FATIGUE SYNDROME

by

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Bachelor of Science (Sports Science)

A thesis submitted in partial fulfilment of the requirements for the award of

Bachelor of Science Honours (Sports Science)

Date of Submission :

15 November 1996

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ACKNOWLEDGMENTS

My Gratitude must be extended to many people both directly and indirectly involved in the completion this work. Without the help and encouragement of many I would not have had the drive or fortitude to complete this task, nor indeed to return to tertiary studies. To all the staff in the Department of Human Movement, thanks for your perseverance and assistance in times of need and for the grounding in academic fundamentals. Thanks to Gary and Michelle at the ANRI for their insights into solving problems with a smile, sorry I was such a nuisance. Thank you Dr. Paul Sacco who when disaster seemed imminent kept saying "It will all work out in the end" and he was right. Thanks for putting up with me when I was slow to understand. To those who participated in the study my profound gratitude. To my parents, Jean and John Hope, from whom I inherited my inquisitiveness and the stubbornness that kept me going when self doubt set in, thank you for a life time of support. To my friends who encouraged me to return to study and who kept me going for four years, thank you for the moral support, the free dinners, and the shoulders to cry on. Special mention to Karen, without whose love and constant support I would surely have given in a long time ago. Thanks to our unborn child for giving me a unique focus on why I did it. My apologies to Jaimee for my bad tempers and foul moods. The confidence of these people in my abilities often outweighed my own and carried me in times of despair. A final word to prospective students who read this, leap in with both feet and commit to it. If you believe in your self and set your goals high, people will turn up to help you reach them.

ABSTRACT

Fatigue associated with activity is a normal response, seeking to prevent damage or conserve energy. Some individuals show heightened fatigue responses with no distinct aetiology. In chronic fatigue syndrome (CFS), peripheral fatigue mechanisms display no apparent abnormalities, indicating some central mechanism. Transcranial magnetic stimulation (TMS) was used to compare force, perceived exertion, electromyogram response, motor evoked potentials (MEP) and silent periods (SP) following stimulation in normal and chronic fatigue groups. Participants (n=12) were physically matched and performed a sustained sub-maximal (20% of MVC) isometric contraction of the elbow flexors. There were no significant differences ($p < 0.05$) in elbow flexor strength or time to reach fatigue. CFS participants showed a significant difference in perception of effort at outset. Differences were also noted in MEP amplitude and SP duration ($p<0.05$). Controls showed an increase in MEP amplitude and SP duration during the fatigue protocol, while CFS group showed no change. The central nervous system responses to fatigue in CFS group appears abnormal. This confirmed previous studies indicating a change in the normal inhibitory response. While specific sites for such disruptions are not indicated, findings support literature in suggesting that a disruption to responses of inhibitory interneurones may be responsible. This confirms that a clear and distinct pathology is associated with the CFS. Recommendations for further research into the process of central fatigue are given.

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GLOSSARY OF ABBREVIATIONS

UNITS

Système International units were used throughout this thesis.

ABBREVIATIONS

CFS	Chronic Fatigue Syndrome
CMAP	Compound Muscle Action Potential
CNS	Central Nervous System
EMG	Electromyogram
MEP	Motor Evoked Potential
MVC	Maximum Voluntary Contraction
OTS	Overtraining Syndrome
RPE	Rate of Perceived Exertion
SEM	Standard Error of Mean
SP	Silent Period, of evoked potential
TMS	Transcranial Magnetic Stimulation

CHAPTER ONE

INTRODUCTION

1.1 Background to the Study

With high intensity exercise, or a new activity, fatigue will occur. Fatigue is a normal response of muscular activity but the causes and sites of fatigue are not clearly understood (Ganong, 1987, p. 569; Fox, Bowers, & Foss, 1993, p. 124). The fatigue response seeks to limit damage or minimise depletion of energy reserves. In the field of exercise science an understanding of the process of fatigue can lead to not only improved performance and training methods, but also to reduced injury risks associated with excessive muscle activity (Fox et al. 1993; Powers & Howley, 1994).

In some individuals, extreme responses of fatigue occur and result in a state of chronic fatigue. This heightened response is debilitating and its cause undetermined. Extreme and chronic states of fatigue are also associated with general illness, specific disorders such as multiple sclerosis, rheumatoid arthritis, or Lyme disease, and some non-specific illnesses such as chronic fatigue syndrome (CFS) (Waddy, Wessely, & Murray, 1990; Gordon, 1993, p. 3). In CFS, fatigue is persistent and the ability to recuperate impaired. No single physiological or biochemical indicator has been identified to explain the onset of chronic fatigue in CFS. Further, several researchers suggest a link between fatigue experienced during regular activity, such as sports or exercise, and conditions of chronic fatigue states such as CFS (Parry-Billings, Blomstrand,

McAndrew, & Newsholme, 1990; Fry, Morton, & Keast, 1991a). As CFS frequently follows viral infection, an immunological disruption has been suggested as causative.

The fatigue process due to exercise and training is considered to exist on a continuum, where increasing levels of activity lead to an exacerbation of the fatigue response, leading to over-fatigue and eventually overtraining (Fry et al. 1991a; Rowbottom, Keast, & Morton, 1996). An identifiable state known as overtraining syndrome (OTS) is fairly well documented and shares much symptomology with CFS (MacKinnon & Hooper, 1992; Parker & Brukner, 1994). Speculation as to the existence of a fatigue continuum extending to CFS has yet to be confirmed (Keast & Morton, 1992; Rowbottom et al. 1996). A diagnostic measure may serve to confirm that fatigue linked to overtraining and fatigue linked to CFS are manifestations of the same or a similar process.

No objective diagnostic tool is currently available for assessing the symptomology of CFS. With exclusion being the guiding criteria, a wide range of assumptions and eliminatory tests are currently required (Holmes, 1991). A relatively inexpensive tool for determining the status of patients with chronic fatigue syndrome could aid both diagnosis and treatment.

Possible sites for fatigue mechanisms are classified as either peripheral or central. Peripheral fatigue refers to those fatigue sites in the muscle, while sites for central fatigue are considered to be located in the motor cortex, spinal cord, or

peripheral nerves, refer to figure 2.1. No distinct pathology, linked to peripheral sites for fatigue, have been detected in CFS which leads to speculation about fatigue in the central chain of command sites.

Voluntary activity of muscles, leading to fatigue, is driven by the motor cortex. The possibility of a fatiguing mechanism contained there warrants investigation. Further, the role that central fatigue plays in the overall fatigue process gives rise to the need to investigate such processes in chronic states of fatigue as well as in healthy groups. Previously, electrical stimulation has been used to elicit post fatigue responses in muscles. It is now possible to non-invasively stimulate the motor cortex itself. This may be done through transcranial magnetic stimulation (TMS) at site specific locations (Barker, Jalinous, & Freeston, 1985; Day, Dressler, Maertens, Marsden, Nakashima, Rothwell, & Thompson, 1989).

While widely used in mapping the human motor cortex TMS has also proven useful in understanding, exploring and diagnosis of functionality of the human body (Mortifee, Stewart, Schulzer, & Eisen, 1994; Stoloy, 1995; Sacco, Thickbroom, & Mastaglia, 1996). Muscle responses to TMS, observed by electromyogram (EMG), can provide useful information regarding the motor pathway involved. This leads to a need for inquiry into the muscular responses to cortical stimulation.

Neural feedback mechanisms may also be affected through increased inhibitory nerve excitation. Such secondary fatigue impediment also needs to be observed.

Thus central fatigue must be observed in CFS sufferers and compared to normal responses to ascertain if any intrinsic abnormalities or differences, which may reflect the pathology of the disorder, can be detected

1.2 Purpose of the Study

The purpose of this study is to quantify central fatigue in chronic fatigue syndrome (CFS) following a sustained submaximal isometric contraction of the biceps brachii. The time course of fatigue development will be observed and compared to a control group. Muscle strength, force-EMG characteristics, cortical stimulation responses, time to fatigue, and perceptions of exertion will be observed in participants during the fatiguing contractions.

The aim is to compare the responses to fatiguing voluntary muscle activity between individuals with chronic fatigue syndrome (CFS), and normal healthy participants. A further aim of the study is for it to act as a pilot study into the feasibility of central fatigue measures, or stimulation responses, as an objective diagnostic tool.

1.3 Hypothesis

A voluntary, sub-maximal, isometric contraction to fatigue will display altered characteristics for participants with CFS than those in control group. Such changes will be manifest by:

1. Reduced time to onset of fatigue,
2. Altered perceptions of exertion, and
3. Altered motor responses to magnetic stimulation of the muscle : such as motor evoked potentials (MEP's) and duration of EMG silent period (SP) following stimulation.

1.4 Organisation of the Thesis

Chapter One provides an overview of the purpose of the study and a brief discussion on the background and significance, as well as outlining the hypothesis to be tested. This is followed in Chapter Two by a review of literature pertaining to fatigue in activity, central fatigue, chronic fatigue syndrome, and transcranial magnetic stimulation (TMS). Chapter Three describes the theoretical framework underlying the study, while Chapter Four details the methodology and procedures of both study and analysis. Results and findings of significance are presented in Chapter Five. A summary of the findings, and their link to broader literature and knowledge, is discussed in Chapter Six. Chapter Seven, then, presents the conclusions and implications of the findings, and suggests direction for future research

CHAPTER TWO

REVIEW OF THE LITERATURE

2.1 Introduction

Muscle fatigue can be described as "a state of physiological inability to contract" (Marieb, 1995, p. 270). Such a definition considers the muscle in isolation. This allows for an understanding of peripheral fatigue processes however it fails to account for neurally based fatigue or cortical involvement in voluntary movement. Peripheral fatigue mechanisms have been explored for many years and physiological mechanisms are relatively well understood (Jones & Round, 1990), yet the role of neural feedback and central control mechanisms has not been fully explored (Maton, 1991). This has largely been due to the invasive nature of observing central nervous system (CNS) responses to fatigue. With the development of transcranial magnetic stimulation (TMS) a non-invasive tool is now available to enable the CNS and motor pathways to be observed in a safer manner (Sacco et al. 1996).

Recent studies have searched for a biochemical marker to indicate CFS (Parry-Billings, Budgett, Koutedakis, Blomstrand, Brooks, Williams, Calder, Pilling, Baigrie, & Newsholme, 1992; Keast, Arstein, Harper, Fry, & Morton, 1995; Rowbottom et al. 1996). While some success has been achieved, no single marker, useful in diagnosis, has yet been identified (Lloyd & Pender, 1994). The extension of the existing continuum of fatigue, from normal activity to overtraining syndrome (OTS), to include CFS has yet to be confirmed.

Similarities of symptoms between CFS and OTS has lead to speculation about extending the continuum of fatigue. No research has yet to confirm this (Keast & Morton, 1992; Rowbottom et al. 1996). Should such a diagnostically useful measure be found this may serve to confirm that CFS is indeed a manifestation of a similar process to that accompanying normal activity. Investigation of normal fatigue responses may then be extrapolated to having relevance to the chronic fatigue sufferer. If, however, a different process is involved much of the present thinking on CFS may need serious reviewing.

In addition to the contractile mechanisms, a second site for fatigue lies within the motor cortex and associated peripheral nervous system. An exploration of the corticomotor responses of fatigue would prove useful in identifying any central fatigue mechanism. A further problem lies in quantifying fatigue for the purpose of diagnosis and treatment. Activation of muscle is driven by the motor cortex, thus any possibility of a fatiguing mechanism contained there warrants investigation. Skeletal muscle response to TMS can be measured and therefore it may be possible to obtain some measurable outcome that reflects central fatigue (Edwards & Gibson, 1991).

2.2 Central Fatigue

In addition to peripheral based definitions, fatigue has also been defined as a "failure to sustain muscle force or power output" (Edwards & Gibson, 1991, p. 4) and as such can be measured. Other definitions refer to the decrease in capacity of skeletal muscle to perform work during activity and to increased

perceptions of effort associated with such activity (Nethery, 1991). This 'effort sense' is more difficult to measure as its origin and processes lie in the cerebral cortex. The inclusion of perception in such definitions indicates the close association of fatigue and the operations in the cortex. Further, the proprioceptive mechanisms returning information to the cortex may have a more profound effect on the determination of fatigue as a concept than is currently thought. Thus a chain of command for muscle activation is considered to also reflect a pathway for fatigue mechanisms.

The origin of fatigue is thought to reside in one or more links in the chain of command (see figure 2.1). The two categories involved are central: involving "the central nervous system and nervous pathways", and peripheral: "events occurring within the muscle" (Edwards & Gibson, 1991, p. 4).

Command Chain	Sites for potential fatigue
Motor Cortex	**Central**
Spinal Cord	
Peripheral nerves	
Neuromuscular Junction	**Peripheral**
Muscle Cell Membrane	
Transverse Tubular System	
Sarcoplasmic Reticulum	
Myofiliments	

Figure 2.1. Chain of Command for muscle activation and potential sites for fatigue. (Adapted from Lewis & Haller, 1991, p.126.)

Peripheral fatigue involves the physiological and metabolic measures of fatigue present in the muscle. Central fatigue, on the other hand, is indicative of fatigue manifested by alterations to the nervous system and the motor cortex processing of stimuli for the relevant muscle groups.

Just as increases in motor drive, or neural processes, affect performance in activity and sport, so too reduced stimulation of neural pathways will have a performance affect. Reduction of motor drive, or inhibition of motor pathways may limit outputs. "Reduced motor drive (central fatigue mechanisms) may similarly have profound effects on strength" (Edwards, Clague, Gibson, & Helliwell, 1994, p. 251). Thus clinical or subjective evaluations of strength may be unreliable. Most such tests are unable to distinguish between peripheral and central fatigue and therefore may only be providing a partial picture to the diagnostician. A diagnostic procedure that incorporated both peripheral and central factors, or which isolated them, should be of benefit in the management and treatment of fatigue related illnesses.

The application of electrophysiological assessment of muscle function has proven useful in analysing muscle performance independent of volition (Edwards et al. 1994, p. 253). The application of percutaneous electrical stimulation has been used for several years with good results. Unfortunately this technique fails to account for the motor pathway prior to the neuromuscular junction at the motor end plate.

Stimulation through TMS, however, may prove beneficial as it "evokes compound muscle action potentials (CMAP's) in the healthy subject ... [with] shape and amplitude similar to those of electrical stimulation" (Glocker, Magistrus, Rosler, & Hess, 1994, p. 118). Given the similar responses between electrical and magnetic stimulation and that stimulation of the cortex, through TMS, provides information about the central mechanisms linked to fatigue, it is clearly beneficial to use TMS.

Some results would seem to indicate that there is a mismatch between the afferent and efferent activity (Edwards et al. 1994, p. 253). It is suggested that an extended silent period following TMS is indicative of the inhibitory processes activating . Some research proposes that the Ia inhibitory interneurones are largely responsible (Porter & Lemon, 1993, p. 205; Young, Triggs, & Gerstle, 1995, p. 1290). The precise role and process of such inhibitory process is uncertain.

In one study Edwards et al. (1994) found indications that CFS patients were often not exercising to their physiological capacity, making comparisons with controls extremely difficult. This implies that some voluntary drive process may also a limiting factor. By setting any exercise testing parameters in relation to the individual's baseline it should be possible to eliminate any ambiguities in the results of such testing. By normalising for time, considering time as a portion of the total task time, it is considered that observations of identifiable responses may be legitimately compared.

A further psychological benefit from exercise testing is also suggested by Edwards et al. (1994, p. 255). Patients may attain some therapeutic benefit from having their actual capabilities shown to be greater than they may perceive. Further conjecture may be made regarding the patient's ability to self-monitor improvements as identified by exercise testing. Such testing, if kept relative to the individual, may be the foundation of self-identifiable recovery. While the psychological and sociological benefits of such outcomes are far beyond the scope of this paper, such benefits are essential for the patient. Existing clinical practices do not permit an objective indicator of a measurable capability. Thus, there is a need, and a desire, for a simple and effective diagnostic tool for the determination of fatigue related illnesses (Lloyd & Pender, 1994).

It is generally considered that histopathological, metabolic and physiological changes in the muscle are not sufficient to explain the symptoms of CFS (Edwards et al. 1994, p. 257). It may be that the CFS patient has a lowered threshold for sensation during exercise, or that they have an "additional perception of fatigue at rest over and above that experienced during exercise" (Edwards et al. 1994, p. 256). Past inability to determine any such effect on effort sense may have more to do with study design. The linking of a measure of perceived exertion with physiological correlates may shed some light on this grey area.

Failure to determine any differences in motor pathways from central triggering, may indicate disturbances in the higher, 'executive' pathways. Such speculation is again beyond the scope of the present study.

Central fatigue relates to a reduced motor drive leading to a failure to maintain muscle activation, while peripheral fatigue, in contrast, involves processes of the contractile mechanisms within the muscle itself. Lewis and Haller (1991) point to the "paucity of data ... comparing voluntary and involuntary contraction" (p. 124). The majority of studies to date seem concerned with peripheral fatigue as responsible for voluntary fatigue in healthy participants yet little research seems to have been conducted on patients suffering CFS. In the case of CFS most physiological and biochemical responses of muscle appear normal. Some innovative work is currently raising hopes regarding glutamine levels as a readily identifiable blood born indicator but as yet this is still in the research phase (Rowbottom et al. 1996).

Central fatigue, therefore, is a failure to achieve full voluntary activation of motor units and either conscious or unconscious mechanisms may be responsible. Conscious mechanisms prevail when an individual decides that sensations from proprioceptive feedback mechanisms are unacceptable. The individual then consciously reduces activity (Jones & Round, 1990, p. 135). Such reductions may be linked to either a real or perceived sense of effort. Unconscious mechanisms are reflected through afferent information from muscle, joint or tendons, which modulate activity at a spinal or supra-spinal

level. In much the same way that inhibitory interneurones limit force production in unusual activity, excessive feedback may manifest in an altered perception of fatigue or have some unknown effect on the processing of fatigue responses in the cortex. An exploration of the neural responses during fatiguing activity may yield information about the interaction between central and peripheral fatigue mechanisms.

2.3 Chronic Fatigue Syndrome (CFS)

A major problem in understanding chronic fatigue in a variety of illnesses is the elusive nature of a definition. For illnesses of undetermined aetiology the problem is exacerbated. Thus, clear case definitions are required, and indeed are being developed and reviewed. These generally seek to facilitate both research and treatment (Lloyd & Pender, 1994).

> The development of a standard case definition is an important step toward understanding and studying any illness of unknown aetiology. A standard case definition facilitates research because it enhances the comparability of the experiences or study results that are obtained by clinicians and investigators in the field (Holmes, 1991, p. S53).

During the later half of this century, especially in the 1980's, an apparently new chronic illness, characterised by multiple non-specific chronic symptoms, absence of abnormal physical findings, and associated with "apparently elevated titres of Epstein-Barr virus" (Holmes, 1991, p. S54). The syndrome became known as Chronic Epstein Barr virus disease (CEBV). Early reports of elevated

titres later conflicted with apparent relationship with controls. In addition several other viral triggers where noted or suspected, such as the Coxsackie virus. These early anomalies where generated through inconsistent and occasionally conflicting definitions (Holmes 1991, p. S54; Bearn & Wessely, 1994, p. 79).

Without knowing what is being referred to it is possible for clinicians and researchers to use differing titles and definitions to refer to essentially the same illness. More recent research findings indicate a limited association with any specific virus such as Coxsackie or Epstein-Barr. Linking specific viral issues to the naming of the disorder was less specific and proved unreliable. International consensus is to use the term 'chronic fatigue syndrome' as it is brief, accurate and avoids assumption of aetiology (Bearn & Wessely, 1994, p. 79).

CFS is characterised by persisting, or relapsing, unexplained fatigue and exhaustion after even mild exertion. Symptoms include myalgia, sore throat, difficulty sleeping and lethargy, similar to post-viral responses. Psychological disturbance in mood, memory and concentration are also noted, though most psychological symptoms are regarded as reactive (Parker & Brukner, 1994).

While initially diagnosed in 1869 (Parker & Brukner, 1994) several terms have been used to describe CFS, including Chronic Epstein Barr Virus, Royal Free Disease, and post-Viral Syndrome. CFS is a debilitating illness that has had much attention since the early 1980's. Various aetiologies have been postulated

with some contention as to the mechanism of CFS. Generally it is perceived to be an immunological cause yet this is not reflected in its varied symptomology (Parker & Brukner, 1994).

General feelings of lethargy and fatigue often follow acute viral infection associated with onset of both CFS and OTS. However, some cases have no discernible immunologic link. Generally, diagnosis is through exclusion of any other pathological responses, or traceable viral responses (Parker & Brukner, 1994; Fukuda, Straus, Hickie, Sharpe, Dobbins, & Komaroff, 1994). One major difficulty for diagnosing CFS is the elimination of other medical problems, or psychiatric disturbances.

A range of conditions and illnesses have been described as CFS. Fry, Morton, & Keast (1991b) produced a list of such that have been referred to as CFS in the past, to indicate the broad range of illnesses and diseases that share common traits and the vast range of potential causes that are linked to CFS. (This list is reproduced in table 2.1).

A primary problem in researching CFS is the need for a clear case definition (Bearn & Wessely, 1994). To remedy this situation the Centers for Disease Control (Atlanta, USA) convened a meeting in 1987 to develop a working case definition (Holmes, Kaplan, Gantz, Komaroff, Schonberger, Straus, Jones, Dubois, Cunningham-Rundles, Pahwa, Tosato, Zegans, Purtilo, Brown, Schooley, & Brus, 1988; Holmes, 1991, S54). A summary of the arising definition is located in table 2.2.

Table 2.1

Conditions which have been described as chronic fatigue syndrome

Addington disease	Neuritis vegetiva
Akureyi disease	Neurasthenia
Allergic fatigue syndrome	Neuromyasthenia
Allergic tension fatigue syndrome	Neurocirculatory asthenia
Anxiety neurosis	Post viral fatigue syndrome
Anxiety reaction	Post infection fatigue syndrome
Autonomic imbalance	Psychoneurosis
Benign myalgic encephalomyelitis	Royal Free disease
Cardiac neurosis	Shell shock
Chronic Epstein-Barr virus infection	Soldiers heart
Chronic hyperfatiguability syndrome	Somatization reaction general
Chronic mononeucleosis	Somatization psychogenic asthenic
Chronic mononucleosis-like syndrome	reaction
Combat fatigue	Somatization psychogenic
Da Costa's syndrome	cardiovascular reaction
Disordered action of the heart	Somatization reaction psychogenic
Effort syndrome	cardiovascular reaction
Epidemic myalgic encephalomyelitis	Syndrome X
Epidemic vegetative neuritis	Tapanui flu
Icelandic disease	Vaso regulatory asthenia
Irritable heart	Vasomotor instability
Lake Tahoe mystery disease	Vasomotor neurosis
Myalgic encephalomyelitis	Yuppie flu
Nervous exhaustion	20th Century disease
Nervous tachycardia	

(From Fry, Morton, & Keast, 1991b)

Table 2.2

Summary of the working case definition of Chronic Fatigue Syndrome (CFS)

Both major criteria and either ≥ 6 symptomatic criteria plus ≥ 2 physical criteria or ≥ 8 symptomatic criteria must be present to fulfil the case definition.

Major criteria

Persistent or relapsing fatigue or easy fatiguability that:
- does not resolve with bed rest
- is severe enough to reduce average daily activity by ≥ 50%

Other chronic clinical conditions have been satisfactorily excluded, including pre-existing psychiatric disease.

Minor criteria

Symptomatic or historical criteria : persistent or recurring symptoms lasting ≥ 6 months:

Mild fever (37.5° C-38.6° C oral if documented by the patient) or chills

Sore throat

Lymph node pain in anterior or posterior cervical or axillary chains

Unexplained generalised muscle weakness

Muscle discomfort, myalgia

Prolonged (≥24 h) generalised fatigue following previously tolerable levels of exercise

New, generalised headaches

Migratory noninflammatory arthralgia

Neuropsychological symptoms

- photophobia
- transient visual scotomata
- forgetfulness
- excessive irritability
- confusion
- difficulty thinking
- inability to concentrate
- depression

Sleep disturbance

Patient's description of initial onset of symptoms as acute or subacute

Physical criteria: documented by a physician on at least two occasions, at least 1 month apart:

1. Low grade fever (37.6° C-38.6° C oral or 37.8° C-38.8° C rectal)
2. Nonexudative pharyngitis
3. Palpable or tender anterior or posterior cervical or axillary lymph nodes (<2 cm in diameter).

Holmes, 1991, p. S54 (adapted from Holmes et al,. 1988)

The case definition of CFS developed, permits an inclusive approach for several fields of inquiry. Fields such as anthropology, epidemiology, immunology, history, medicine, neurology, physiology, psychiatry, psychology, sociology, and virology all have a legitimate interest in CFS research (Bearn & Wessely, 1994). A clear case definition is useful in permitting communication between and across fields of inquiry.

The removal of previous modifiers such as 'post viral' or 'immune deficiency' permits speculation on a variety of aetiological agents. This allows an integrated approach to a complex illness that may have physical, social and psychological effects on the patient. While still largely exclusion based, the integration of several major and minor criteria allow diagnosis to be made relatively accurately. In addition it will, until a more accurate aetiology is found, permit the relating of both physiological and psychological research to assist in the diagnosis and management of this debilitating illness.

While not all symptoms occur for each individual, a combination of symptoms, especially if post-viral, may indicate CFS. It is interesting to note that many of the symptoms for CFS are identical to those for overtraining syndrome (OTS) outlined in table 2.3 (MacKinnon & Hooper, 1991). OTS presents as a state of chronic fatigue in athletes who have been seen to train beyond their essential recovery limits.

Table 2.3

Sample of various symptoms common to CFS and OTS

Physical	Emotional/Behavioural
Decrements in performance	Depression
Inability to maintain training load	Decreased self-confidence
Chronic fatigue	Mood changes
Elevated resting heart rate	Apathy
Hormonal changes	Lethargy
Low serum ferritin levels	Low motivation
Persistent muscle soreness	Lack of concentration
Frequent illness (colds, flu, etc)	Anxiety

(Adapted from Fry, Morton & Keast, 1991b)

This common symptomology provides a clear link with the process of normal fatigue, due to physical activity, which presents with similar symptoms to those of CFS. Some biochemical links have recently been indicated between these two syndromes (Rowbottom et al. 1996). The prevalence of so much in common lends credence to extending the fatigue continuum (Keast & Morton, 1992) to include CFS. This connection between the two syndromes needs clarification before a clear and objective diagnostic tool can be developed.

The CFS represents a significant cause of morbidity and economic burden in Australia. The estimated cost to Australia's healthcare system is in the vicinity of $59 million (Lloyd & Pender, 1992). This includes costs directly related to treatment and indirectly associated treatment for subsequent relapses and psychological problems associated with CFS. However, it does not account for costs associated with lost productivity, nor for the distress and problems of stress placed on family and friends of the primary sufferer. A further cost

associated with CFS is the practice of 'diagnosis shopping'. This is a fairly common practice with CFS, where sufferers attend several medical practitioners until they attain a satisfactory explanation or diagnosis. A clearer picture of the process of fatigue will assist in improved diagnosis and reduced expense, both to the community and the individual.

Despite numerous studies, little evidence of neuromuscular pathology or peripheral neurophysiological abnormalities have been found which could account for the chronic fatigue and post-exercise exhaustion which are features of this condition. In conclusion then, fatiguability in CFS cannot be accounted for by muscle contractile failure or other physiologically determinable mechanisms. Nor is a lack of motivation proven to be responsible. Hence, peripheral fatigue sites are not considered as causative. Therefore, the possibility of some central, corticomotor pathway mechanism involvement in the syndrome warrants further study.

2.4 Fatigue in Exercise and Overtraining Syndrome (OTS)

Fatigue related to high intensity activity and excessive exercising has been explored for many years. Clear physical signs are frequently monitored in athletes to minimise the effect of fatigue on training and performance. However, some athletes still manage to exceed their limits and are known to fall into a state of fatigue that persists and can become a chronic state of fatigue. This has come to be known as overtraining syndrome (OTS). OTS has been defined as "Prolonged fatigue and under-performance following periods of heavy training"

(Rowbottom et al. 1996, p. 3). Fatigue is considered to lie on a continuum with OTS and normal responses at opposing ends.

While first identified in the early part of this century, a variety of terms have been used to describe essentially the same condition (MacKinnon & Hooper, 1991). These include 'overstress', 'staleness', 'burnout', 'failing adaptation', and 'overreaching'. The use of differing terminology invariably leads to confusion, not only for the suffering athlete but also the diagnostician. Regardless of the sport, overtrained athletes exhibit similar symptoms, including poor or inconsistent performance, inability to train or compete and the experiencing of prolonged bouts of fatigue (Fry et al. 1991a; MacKinnon & Hooper, 1991).

The defining of OTS, like CFS, is difficult as no physiological or biochemical measure is available. However in the case of overtrained athletes, in-situ evaluation of performances gives a field assessment of measurable decrements in performance. This is often associated with reports of extended lethargy and tiredness (Fry et al. 1991a; Fry et al. 1991b; Parker, Brukner & Rosier, 1996). This performance monitoring may act as an objective tool for early diagnosis. In the case of OTS, early identification can prevent a worsening condition and more serious problems.

The symptoms of overtraining have been wide and varied with few cases exhibiting precisely the same symptoms in precisely the same order. In a

comprehensive review of OTS symptoms, Fry, Morton, and Keast (1991c) reported 317 varying symptoms in 12 categories, refer to table 2.4.

Further, more consistent symptoms include; elevated basal and resting heart rates; elevated blood pressures; low motivation; lethargy; depression; or increased susceptibility to illness (Fry et al. 1991c, p 48). While not all symptoms appear in OTS, a combination of several is invariably seen in overtraining. A more comprehensive listing is available in Appendix D.

Table 2.4.

Factors attributed to excessive exercise stress : The symptoms of overtraining

Category	Number of
Biochemical/Haematological	15
Cardiorespiratory function	24
Drinking/Nutritional Disorders	12
Hormonal	23
Intectious disease	49
Musckuloskeletal complaints	17
Performance related	17
Physical	13
Physiological	13
Psychological	91
Sensorimotor performance	25
Sleep related	7

From Fry, Morton, & Keast (1991c, p. 48-52). Full listing available in appendix D. Full references available from authors.

These prolonged bouts of fatigue are similar in their debilitating nature to those of CFS. This has led to speculation as to extending the fatigue continuum to include CFS (Rowbottom et al. 1996). While little has been found to support such continuum theory, the similarity of symptomology is too great to ignore further exploration. As can be seen in table 2.3, previously, the common symptoms of both OTS and CFS are diverse. However, it has yet to be shown whether the same aetiological process is responsible for such similar symptomatology. Should the same process be responsible then observation of fatigue processes in healthy people may be of benefit in understanding states such as OTS and CFS.

2.5 Muscle Fatigue and Motor Cortex Responses

Altered physiology can lead to reorganisation of the motor cortex (Wilson, Lockwood, & Thickbroom, 1993). This predominantly occurs with spinal lesions and amputations. Unfortunately little research exists on fatigue responses of the motor cortex during activity. Further questions remain as to whether physiology is altered due to immunological dysfunction and how this relates to muscular and perceived exertion. Most of the measured alterations are in relation to spinal lesions and amputations (Wilson et al. 1993).

Historically this has been due to a reliance on invasive methods of measuring response. Until recently most measures of cortical response involved sub-cranial placement of electrodes. While this has served as a great tool for understanding the functioning of the motor cortex, it has precluded studies of active healthy

participants. With the development of transcranial magnetic stimulation (TMS) a non-invasive means of observing responses to motor cortex stimulation is available.

The study of corticomotor responses during exercise will address the possibility of a central mechanism for those symptoms associated with CFS. It is anticipated that this study will provide insight into the fatigue mechanisms of chronic fatigue states, and CFS in particular, and may add weight to the argument of the existence of a continuum of fatigue (Rowbottom et al. 1996).

2.6 Transcranial Magnetic Stimulation of the Cerebral Cortex.

The cerebral cortex is involved in mental activities such as conscious thinking, reasoning, learning, memory, intelligence, and sense of responsibility. It is also concerned with perception of the senses and the initiation and control of voluntary muscle contraction (Newton & Joyce, 1990, p. 259).

Motor areas are regions where electrical stimulation produces and controls muscular movement (Newton & Joyce, 1990, p. 260). Until recently, stimulation of the motor cortex has been possible by maintaining direct contact, either intraoperatively or subdurally (Wilson et al. 1993). Although these studies have provided fundamental insights into the organisation of the motor cortex, their usefulness has been limited by their invasive nature and by ethical consideration since studies have largely been confined to patients undergoing surgery (Wilson et al. 1993).

With TMS the cortex is painlessly stimulated as a consequence of the rapid discharge of current through a magnetic coil held over the scalp (Barker et al. 1985). The technique uses a large pulse of magnetic field to induce currents below the stimulus point. The current flow induced in the underlying cortex by the magnetic pulse is sufficient to activate neurones trans-synaptically (Day et al. 1989) and, under some circumstances, directly (Berdelli, Inghilleri, Cruccu, & Manfredi, 1990; Wilson et al. 1993). When the membrane excitability reaches threshold, a measurable response of the motor evoked potential (MEP) is recorded by surface electromyogram (EMG). The size of the MEP is directly related to the number of motorneurones activated, hence the excitability of the motor pathway is dependant on the stimulus intensity (Valles-Sole, Tolosa, & Pujol, 1992). Thus, TMS provides a tool which can compare a known stimulus with a measurable response. An example of the MEP induced by TMS is presented in figure 2.2. The MEP response measurable, the peak to peak summation, and the silent period (SP) measures are indicated.

TMS has been used in exploratory studies of the corticomotor representation, particularly under conditions of altered physiology (Wilson et al. 1993). It has further been used to examine duration of silent periods following stimulation and to explore central fatigue processes (Fritz, Braune, Pylatiuk, & Wagner, 1995; Miller, Braun, & Weiner, 1995; Mortiani, 1995). Given the link between CFS and OTS, and physiological fatigue adaptations it would seem reasonable to expect some alteration in cortical drive.

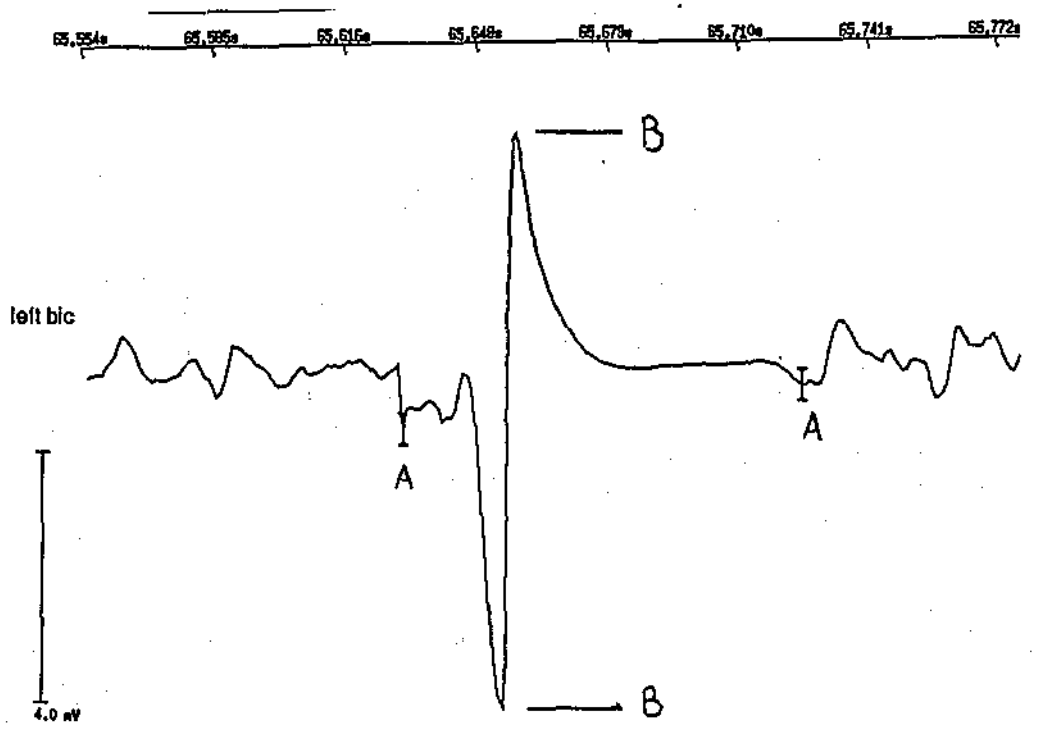

Figure 2.2. Example of an evoked potential (MEP) due to TMS, AA = SP duration ; BB = MEP (peak to peak summation).

2.7 Summary

The close associations between extreme fatigue due to exercise, such as OTS, and CFS in both onset and symptomology support the suggestion of a fatigue continuum. While no biochemical or physiological marker of either syndrome currently exists both are difficult to diagnose and treat. This leads to a need to determine the location of the fatigue mechanisms underlying the syndromes. The processing of motor control via the cerebral cortex seems to suggest that a central fatigue mechanism might be located in the motor cortex. Such evidence is lacking in the current literature and therefore warrants further examination. The recent advances in non-invasive magnetic cortical stimulation permit an observation of motor pathway responses and thereby may provide some measure of central fatigue in these debilitating conditions.

CHAPTER THREE

THEORETICAL FRAMEWORK

The origin for activation of muscles lies in the motor cortex and through motor pathways. As muscular activity is so closely linked with neuromuscular interaction so too some myalgic illnesses may be more closely linked to the motor pathways than is currently suspected. States of chronic fatigue are related to excessive activity, such as overtraining syndrome (OTS). This activity linked syndrome shares many symptoms with chronic fatigue syndrome (CFS). Given the lack of identifiable peripheral aetiology for CFS an exploration of the motor pathways is required.

Non-invasive magnetic stimulation of the motor cortex provides a tool for such research. Stimulation of motor drive sites permits observation of responses to stimulation. These responses may be assessed and regarded as reflective of the motor pathway processes. In so doing it may prove possible to identify altered fatigue responses of the central nervous system that to date have been unreported. Such a diagnostic tool may have benefits for CFS sufferers as well as for other states of severe fatigue or other neurological dysfunctions.

It is suggested that responses to fatigue, of the motor pathway, may encompass altered responses such as duration and amplitude of motor evoked potentials. Observation of any such changes will serve to improve the understanding of fatigue processes. They may also serve to indicate relative intensity of chronic fatigue states, thus providing an objective diagnostic tool.

CHAPTER FOUR

METHODOLOGY

4.1 Design of Study

A between groups comparison design was used to observe any differences in responses to exercise. The two groups were closely matched for age, gender and activity levels and a single observation was taken. Activity levels were indicated using a self report scale (Sharkey, 1991, p. 61), see appendix H. Thus, leaving the previously confirmed condition of CFS as the prime determinant responsible for any variation.

4.2 Outline

Maximal voluntary contraction (MVC) forces were measured prior to, during, and after a fatiguing exercise protocol. These, along with electromyogram (EMG) readings of evoked potentials and manually recorded ratings of perceived exertion (RPE) were compared to evaluate any differences in the process of fatigue, the integration of, or reaction to the fatigue process induced by exercise. Force and EMG measures of the twitch interpolation, peak to peak amplitude, and subsequent silent period (SP) induced by TMS were also followed. Comparisons of the two groups were made to assess and explain any differences found. For the purposes of this study, only those participants with onset post viral infection, who met diagnostic criteria (table 2.2), and had been diagnosed within the past three years were considered. Furthermore,

participants did not have any related medical conditions, psychological, or psychiatric influences.

4.3 Participants

The participants (n=12), mean age 29 years (range 18.2 years to 47.8 years), were not currently participating in upper body training, such as weight training. Participants formed a convenience sample and were selected from two categories; clinically determined CFS and healthy controls. Participants were informed as to the procedures prior to participation and written consent was obtained, refer to appendix A. Participants were briefed on the procedure at initial contact and again immediately prior to testing. They were informed that they may withdraw from the study at any stage without consequence. All procedures had prior approval from the Edith Cowan University Ethics Committee and the Sir Charles Gairdner Hospital Ethics Committee.

4.3.1 CFS Group

Participants in the CFS group (n=6), mean age 31.3 years (range 18.3 years to 47.8 years), consisted of four females and two males who had been previously diagnosed with chronic fatigue syndrome, contracted post virally, and met diagnostic criteria as detailed earlier. Histories were reviewed to ensure that other neuromuscular, medical and psychiatric conditions were excluded. A summary of the history and status of these participants is detailed in appendix G. Participants were volunteers drawn from a local CFS support group, covering the metropolitan area of Perth, and from centrally located medical practitioners.

4.3.2 Control Group

Control group participants (n=6), mean age 26.6 years (range 19.3 years to 39.4 years), consisted of four females and two males, and were selected to match, as closely as possible, the CFS group. Groups were matched for age, gender, and current activity levels as indicated on a self report scale, see appendix H. Participants were all currently non-participatory in upper body strength training. Healthy controls were drawn from volunteers drawn from the staff and student bodies of the Edith Cowan University

4.4 Instrumentation

Instruments used for this study included:

Analog to Digital Converter

Data test sheets (Appendix I)

Goniometer

IBM Microprocessor

Kin-Com Isokinetic Dynamometer (Chattex Corp., USA)

Magstim 200 Magnetic Stimulator (Magstim Co., UK)

Preacher Bench (45°) modified

Sapphire EMG machine

SUN Microprocessor

Surface EMG electrodes (1 cm diameter, Grass)

Translucent rubber cap, adhesives tape, electrode gel

4.5 Instrument Protocol

4.5.1 Magnetic Stimulation

Transcranial magnetic stimulation (TMS) of the motor cortex was carried out using a Magstim 200 magnetic stimulator (Magstim Co., U. K.) (appendix B). A 50 mm diameter figure eight coil was used to magnetically stimulate the site found best to affect the non-dominant arm. The figure eight coil configuration provides stimulation to a specific area, essential for this study. A flexible skull cap, with markings radiating from the apex and spaced 1 cm apart, permitted repeated locations at the same site. The stimulator was held tangential to the skull, handle posterior, with the centre of the coil over the site to be stimulated. This anterior posterior positioning has been found to produce the most consistent responses (Fritz, Braune, Pylatiuk, & Wagner, 1995). The threshold for responses in the biceps brachii muscle was determined and a stimulus of 20% above threshold was used for all participants. A computer (386-PC) digitised and displayed the data, with analysis conducted later through a SUN microsystems workstation using custom designed software.

4.5.2 EMG Activity

Surface electrodes were used to record motor evoked potentials (MEP's) and EMG activity of the muscle. Two gold electrodes (Grass), 1 cm in diameter, were placed, 3 cm part, over the distal portion of the biceps brachii. Signals were processed through a Sapphire EMG analyser and the amplified signal was both high and low pass filtered prior to being digitised in an independent PC (386). Measures of elbow flexion force and EMG activity were combined in a

purpose built software package and transferred to a SUN station for later analysis. Manual recordings of test duration and perceived exertion were later matched to computerised data.

4.5.3 Force Measures

A kinetic communicator (KinCom) isokinetic dynamometer measured force output at the wrist. A purpose built preacher curl bench supported the arm at 45° from horizontal, with an elbow flexion of 90°. A gravity allowance was made while the participants arm was in a state of relaxation. Force measures were displayed in a moving line format on a colour monitor to enable the participant to maintain a steady submaximal output of 20% MVC.

4.5.4 Perceived Exertion

Perceived exertion was monitored using a modified Borg scale (Borg, 1982), with participants reporting on their perceived exertion in relation to a maximal contraction. The Borg scale was presented on a large chart, a reduced version is presented in appendix J. Participants were asked to report, using the Borg scale, on how they sensed effort in relation to the previously measured MVC. Other comments on physical sensation were reported on at the same time but cast no bearing on the present study.

4.5.5 Activity Index

Participants completed an activity index questionnaire prior to commencement. This permitted cross matching of the control group and was based on a

previously used model (Sharkey, 1991). This provided a measure of the participant's self determined activity level on a scale of one to 100. A copy of the activity index used is available in appendix H.

4.5.6 Miscellaneous

MEP's were digitised and recorded for analysis on a microprocessor (386-PC). In addition to the peak to peak amplitude of stimulated MEP response, the time course of the post MEP silent period (SP) was also followed. This permitted the state of excitation to be observed and correlated with the stimulus response. Results of data were analysed in digitised form on a SUN station. Time course of SP duration was measured individually for each stimulation..

All measures were taken in a single visit to the Australian Neuromuscular Research Institute (ANRI). Sessions lasted approximately two hours.

4.6 Test Procedures

Participants were seated astride a purpose built preacher curl bench with the arm supported at 45° from horizontal, with an elbow flexion of 90°. Force, of the elbow flexors, was measured at the wrist continuously by a computerised isokinetic dynamometer (Kin-Com), with readouts displayed graphically to participants via a colour PC monitor.

The operation and purpose of the Borg scale for perceived exertion was explained to participants and the entire test protocol was explained a second

time. Participants were permitted to familiarise themselves with the Borg scale and with the movement of the target line on the computer monitor.

4.6.1 Protocol

To establish individual maximal force, each participant performed three MVC's of three seconds duration with 60 seconds rest between each contraction. Average of the best two performances was the basis for determining the submaximal activity level used, set at 20% MVC. Baseline MEP and SP measures were taken. Participants then proceeded to perform the sustained isometric contraction until fatigue.

The sub maximal fatigue test consisted of sustaining a target line, displayed on the PC monitor, at 20% of MVC until fatigue. Fatigue was determined by an inability to maintain target force for three seconds. At this point participants were encouraged to make a continuous maximal effort lasting ten seconds. Force and EMG were monitored continuously by computer. Rates of perceived exertion (RPE) were assessed each minute until exhaustion using a modified Borg scale (Borg, 1982). Magnetic stimulation occurred each minute and responses recorded via an independent computer.

4.7 Data Analysis and Statistical Analysis

Data was analysed using purpose designed software (Waves) on a Sun Station micro processor. Subsequent data was further analysed using Microsoft Excel version 5.0. Differences in participant responses to all measures during activity

were compared using non-paired Mann-Whitney U-tests, or paired Wilcoxon signed ranks tests. The significance of changes in parameters measured over the course of fatiguing exercise was determined using the Friedman two-way analysis of variance by ranks. All statistical analyses were conducted using the statistical package for social sciences (SPSS for Windows, version 6.0), with significance taken at the 95% confidence interval ($p \leq 0.05$).

4.8 Limitations and Assumptions

4.8.1 Participant Limitations

The participants may differ in strength, level of daily activity, and susceptibility to fatigue. These individual differences may contribute to a variability in responses. In order to minimise this risk, cross matching of participants was conducted and all participants were required to be non-participatory in upper body strength training. A further limitation included the participant's ability to maintain voluntary contraction for the duration of the exercise. The subjective nature of the RPE scale interpretation risked leading to some ambiguity. This was checked for consistency within groups. It was assumed that participants would participate with maximal effort until volitional fatigue.

4.8.2 Delimitations

Delimitations include the availability of suitable participants as determined by the exclusion criteria and selection processes. The time available for the use of neurology clinic equipment (ANRI) restricted the study and this limited the number of possible testing sessions.

4.8.3 Muscle Recording Limitations

While the use of surface electrodes is non-invasive it is difficult to obtain precise recordings from single muscles. Activity from surrounding muscles might also be recorded. Accurate location, based on anatomical landmarks, assisted in minimising such peripheral input to MEP recordings.

4.8.4 Data Limitations

Limitations on data analysis included the limited scope of studies involving normal and CFS participants. This study sought to augment the limited information regarding stimulated responses in a normal population. Further, results of control groups were checked with previously existing data, obtained by the ANRI on healthy participants, to confirm validity of observations.

CHAPTER FIVE

RESULTS

Individual results and data, normalised for time, are located in appendix E. All group means are expressed in text ± standard error of the mean (SEM). The range of times taken to complete fatigue protocol made comparison of data between individuals difficult. This was overcome by normalising for the time on task (TOT) and extracting values at start, 20%, 40%, 60%, 80%, and 100% of TOT. The total time was considered and the nearest stimulation, producing an MEP, was taken as the normalised data point for each participant. This permitted a comparison between groups using the same baseline, time related, scale.

One participant, CFS 2, recorded post recovery MVC force in excess of initial MVC, This was regarded as indicative of a failure to achieve true maximal force initially and as such submaximal loads would have been too low. For the purposes of strength comparisons data for CFS 2 has been discarded.

5.1 Participants

Participants age, weight, height, and activity index (AI) data was evaluated and tested using Mann Whitney U test and a test of means for age and activity index (AI). Physiological parameters appear in table 5.1 (CON) and table 5.2 (CFS) below. No significant differences were found between groups, for age or AI, at a probability value of $p \leq 0.05$. Initial MVC force also showed no significant difference between groups at $p \leq 0.05$.

Table 5.1

Physiological parameters for control group (CON)

Subject	Sex	Age	Mass (kg)	Height (cm)	AI	Initial MVC
CON1	m	19.3	70.0	168	64	226.8
CON2	f	37.8	60.0	173	12	139.0
CON3	f	39.4	54.0	157	64	184.0
CON4	m	21.3	82.0	190	36	200.0
CON5	f	22.5	62.0	166	64	100.7
CON6	f	19.6	55.0	163	48	131.0
range		19.3 - 39.4	54 - 82	157 - 190	12 - 64	100.7 - 226.8
mean		26.6	63.8	169.5	48.0	163.6
SEM	±	3.8	4.3	4.6	8.6	19.5

SEM = standard error of means

Table 5.2

Physiological parameters for chronic fatigue group (CFS)

Subject	Sex	Age	Mass (kg)	Height (cm)	AI	Initial MVC
CFS1	f	28.8	64	175	6	118.0
CFS2	m	47.8	92	183	64	80.0
CFS3	f	46.9	76	180	6	96.8
CFS4	m	27.0	63	155	27	221.0
CFS5	f	18.9	52	163	64	107.0
CFS6	f	18.3	57	165	6	118.0
range		18.3 - 47.8	52 - 92	155 - 183	6. - 64	80 - 221
mean		31.3	67.3	170.2	28.8	123.5
SEM	±	5.4	5.9	4.4	11.6	20.4

SEM = standard error of means

5.2 Time on Task

Mann Whitney U test of the time on task (TOT) for each group also showed no significant differences ($p \geq 0.05$), with controls exhibiting a mean TOT of 17.7 (± 3.5) minutes, and CFS having mean TOT of 14.5 (± 4.5) minutes.

While the time on task was not statistically significant it is important to note the ranges covered (CON - 10 to 29 minutes; CFS - 6 to 32 minutes). Figure 5.1, below, shows clearly that while no participants in the control groups were less than 10 minutes TOT, the CFS group had three (50% of group) subjects less than 10 minutes TOT.

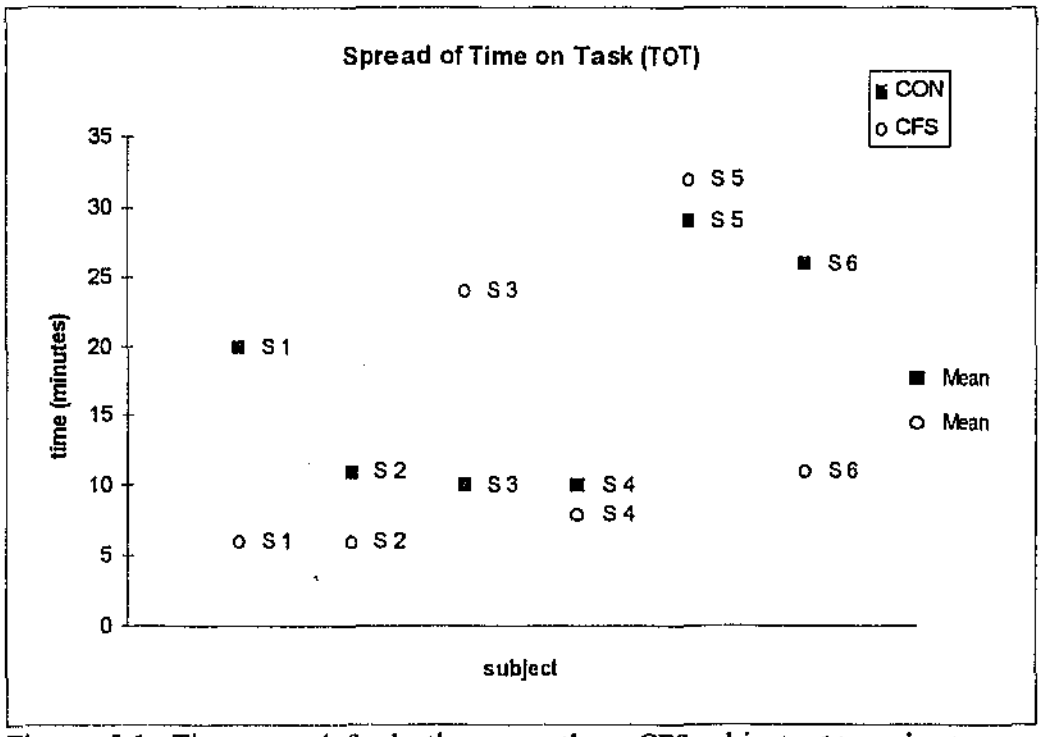

Figure 5.1. Time on task for both groups, three CFS subjects < ten minutes.

5.3 Force Production

Isometric force was monitored throughout and following a recovery period. Force measurements were normalised and expressed as a percentage of initial MVC force. This was done to reduce variability for comparison between individuals.

Maximum force production at the end of fatigue in the CFS groups fell to 54.5 % (± 6.2 %) of initial MVC force, while control group dropped to 53.0 %, (± 4.4 %) of initial MVC. Mann Whitney U Tests showed no significant differences, between groups ($p \leq 0.05$), between starting forces and forces at the end of fatigue protocol. However, by the end of a 20 minute recovery period isometric force had recovered to 72.4 % (± 9.0 %) initial MVC for CFS, and 85.1 % (± 14.8 %) initial MVC for CON.

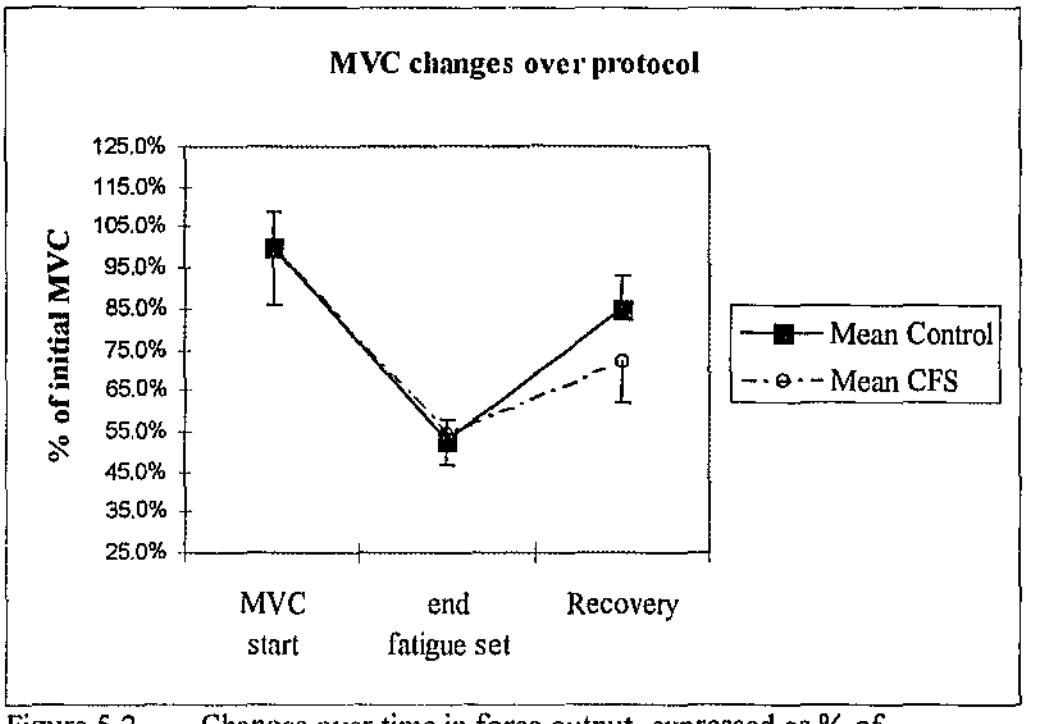

Figure 5.2 Changes over time in force output, expressed as % of initial MVC (error bars = SEM)

Between groups Mann Whitney U tests showed no significant difference ($p \leq 0.05$). However, an exact p value of 0.08 suggests a trend that may require greater numbers to show as significant. Recovery rates may indicate a more rapid recovery in controls than CFS. Larger group numbers would be needed to establish significance in future studies.

Peripheral muscular fatigue is indicated by the consistent decrement in MVC capacity. This is similar for both groups with no significant differences, as shown in figure 5.2. Notice should be made of the apparent differences after recovery.

5.4 Perception of Exertion

Figure 5.3, below, shows the development of perception of effort for both CFS and CON. Perceptions of effort are significantly different ($p \leq 0.05$) between groups at start, mean 11.2 ± 0.6 (CFS) and 9.2 ± 0.5 (CON), and after 20% TOT, mean 14.2 ± 0.5 (CFS) and 12.0 ± 0.7 (CON). Subsequently no significant difference is found between groups.

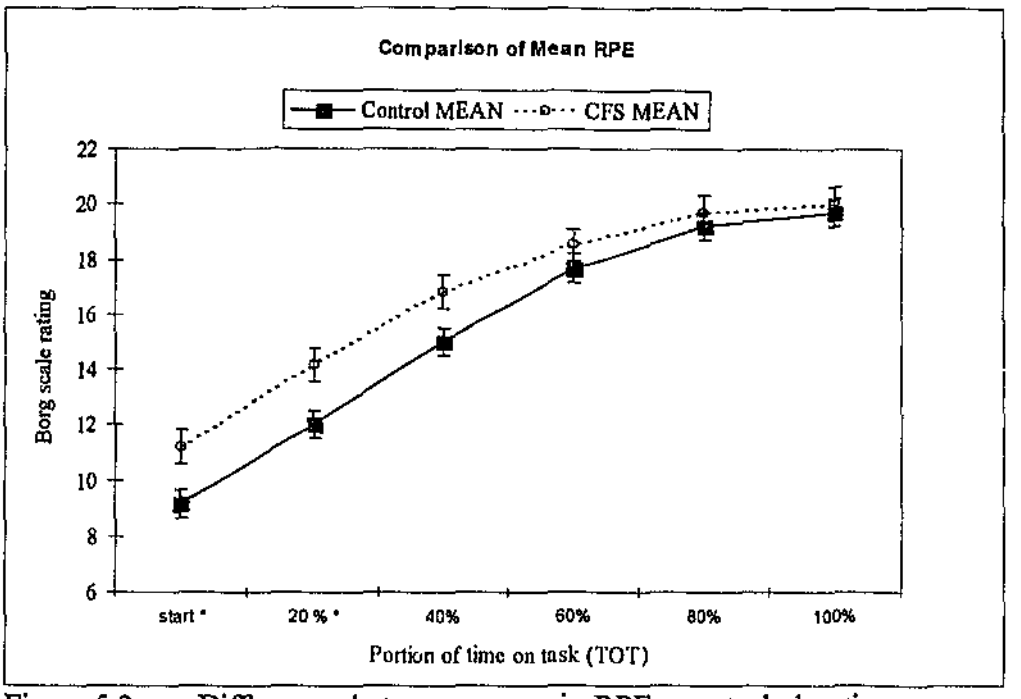

Figure 5.3 Differences between groups in RPE over task duration (error bars = SEM), * denotes significant.

Wilcoxon signed ranks tests indicate that both groups showed a significant difference, within groups, from starting RPE during task (at $p \leq 0.05$).

5.5 Evoked Potentials

The size of the peak to peak amplitude of the MEP due to stimulation was followed and data normalised. MEP peak to peak amplitude (mV) and respective p values, for differences between groups, appear in table 5.3 below. The difference between CON and CFS groups towards the end of the protocol is not significant (at p value of 0.05), with the exception of results at 80% TOT.

However, the trends at 60% and 100% TOT show a clear divergence of responses. This is illustrated in Figure 5.4, where a divergence of the means is seen. If figure

5.4 is considered in conjunction with fatigue, as related to RPE (figure 5.3), different responses are observed for the same output in muscle force.

Table 5.3

Mean MEP (millivolts) for groups showing respective significance. Statistical significance determined using Mann Whitney U test.

	CON	CFS	exact p value
start	8.3	5.5	0.52
20%	9	3.8	0.11
40%	10.8	6.8	0.11
60%	10.9	5.8	0.08
80%	10.7	4.8	0.03
100%	10.1	6.4	0.08

Wilcoxon matched-pairs signed-ranks test for start and finish values indicate no significant difference, within groups, from start and finish values ($p > 0.05$), for either CFS or controls. The one exception was between groups at 80% TOT, where CFS group shows a slight drop (exact $p = 0.03$).

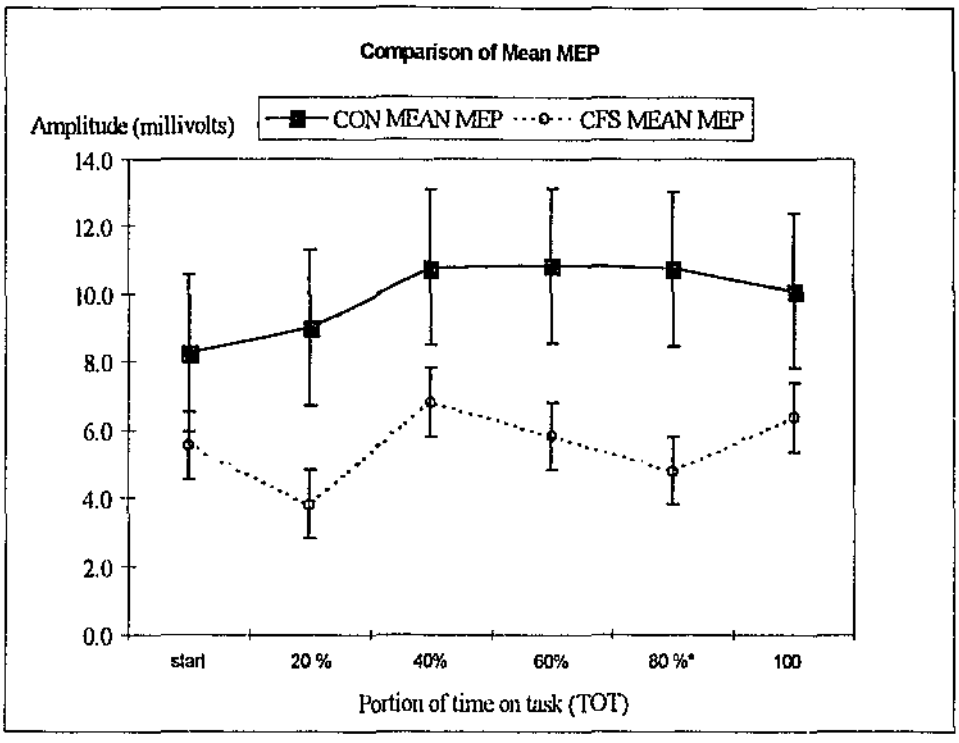

Figure 5.4 Graph of mean MEP amplitude changes over time, error bars indicate SEM, * denotes significant difference.

While not statistically significant the trend is to an apparently differing response, and as such warrants further exploration.

5.6 Duration of Silent Period (SP)

Duration of the EMG silent period (SP) following TMS was measured, in milliseconds (ms), from immediately after the stimulation trigger to when normal, asynchronous, EMG activity was detected. The changes in SP duration for controls, from start to 100% TOT, was found to be significant, Wilcoxon signed rank (exact $p = 0.03$), as was the SP at 60% TOT ($p = 0.05$). The SP at 80% TOT does not present as statistically significant however, an exact p value of 0.07 suggests a trend at the latter end of fatigue that requires further exploration.

A within groups assessment for SP duration in CFS was found to be not significant (at $p \leq 0.05$), for any of the fatigue protocol. These are displayed graphically in figure 5.5 .

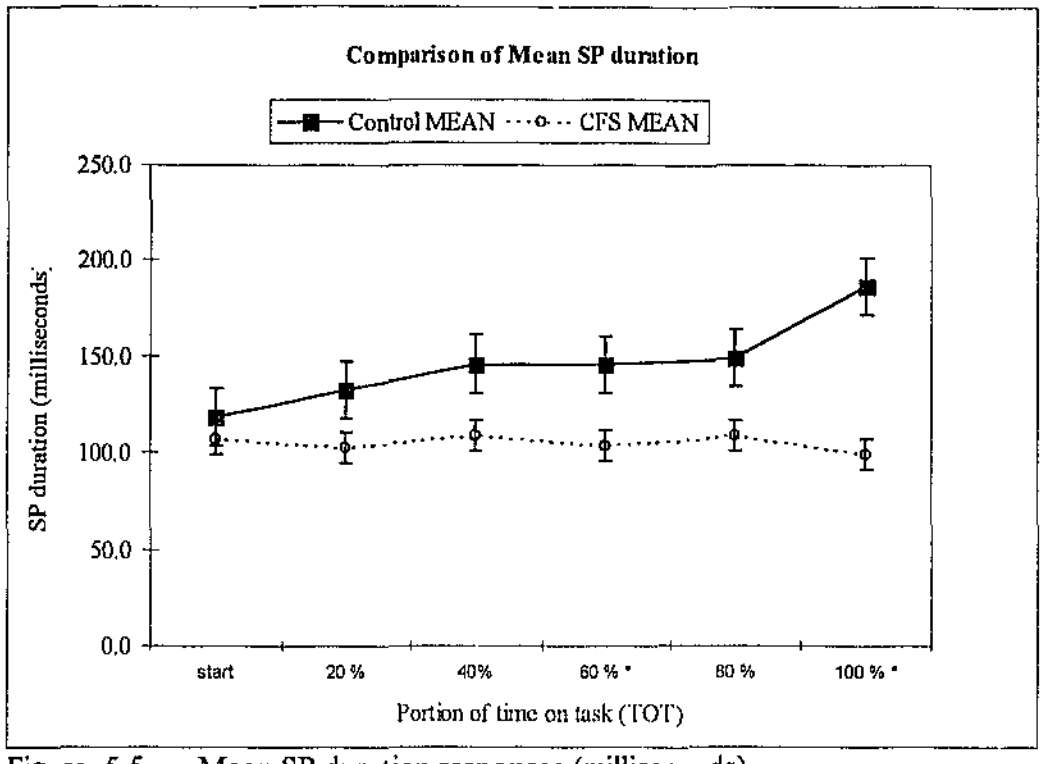

Figure 5.5 Mean SP duration responses (milliseconds)
error bars = SEM, * denotes significant difference

A between groups, Mann-Whitney U-Test, shows a significant difference during later part of protocol. Only starting values, as expected, and values at 20% TOT are found to be non-significant ($p \geq 0.05$). Thus, it is clear that responses of CFS group are different to those of CON group over the course of the activity.

5.7 Force changes during protocol.

In order to compare force responses, a twitch/force ratio was calculated. This was done by measuring the force increase in response to TMS, and dividing by the base force being produced at 20% of initial MVC. At the final stage, 100% TOT, participants were required to produce a maximal effort, thus changing the force baseline. Figure 5.6 below, shows force and MEP responses to TMS at start and 100% TOT for one participant (CFS 3). This participant showed some increase in MEP and some slight difference in SP duration. The force line appears to present as greater but it should be recalled that the baseline force has been altered as the final response is evoked under maximal contraction.

Twitch force production in controls increased while the base remained constant. A change in the base, as at the end of fatigue where a maximal effort was called for, produced a very different result. A within group evaluation shows significant differences (at $p \leq 0.05$) from starting levels throughout protocol except for 100% TOT when the base force was altered.

No significant changes to twitch ratio occurred within CFS group, at $p \leq 0.05$. This leads to a significant difference in response between the groups, Mann-Whitney U-test ($p \leq 0.05$), for twitch ratios at 60% and 80% TOT. Responses at 100% TOT are at maximal effort and therefore appear to respond differently.

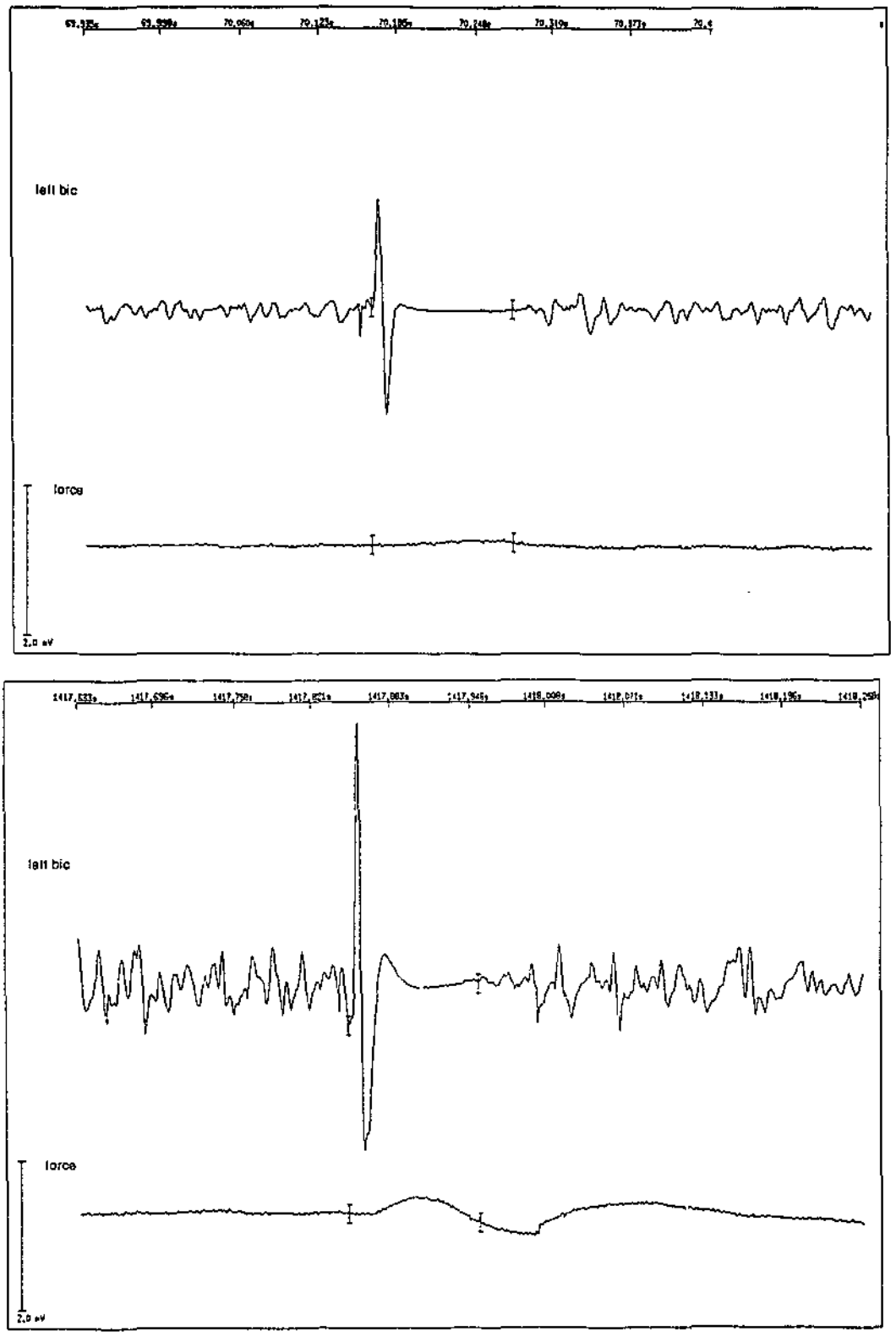

Figure 5.6 MEP and force output for CFS 3, showing responses to TMS at start and end (100% TOT) of fatigue protocol.

Thus ratios may be useful in indicating altered responses to sustained levels of workload. The increasing force output due to TMS for controls seems to indicate a steady rise in response to greater stimulation. Of interest is the decrease shown by both groups at 100% TOT. This highlights the differences between responses to maximal efforts and sustained low level efforts. Both groups appear, therefore, to have similar responses to maximal output, while a differing response is apparent for sub-maximal workloads.

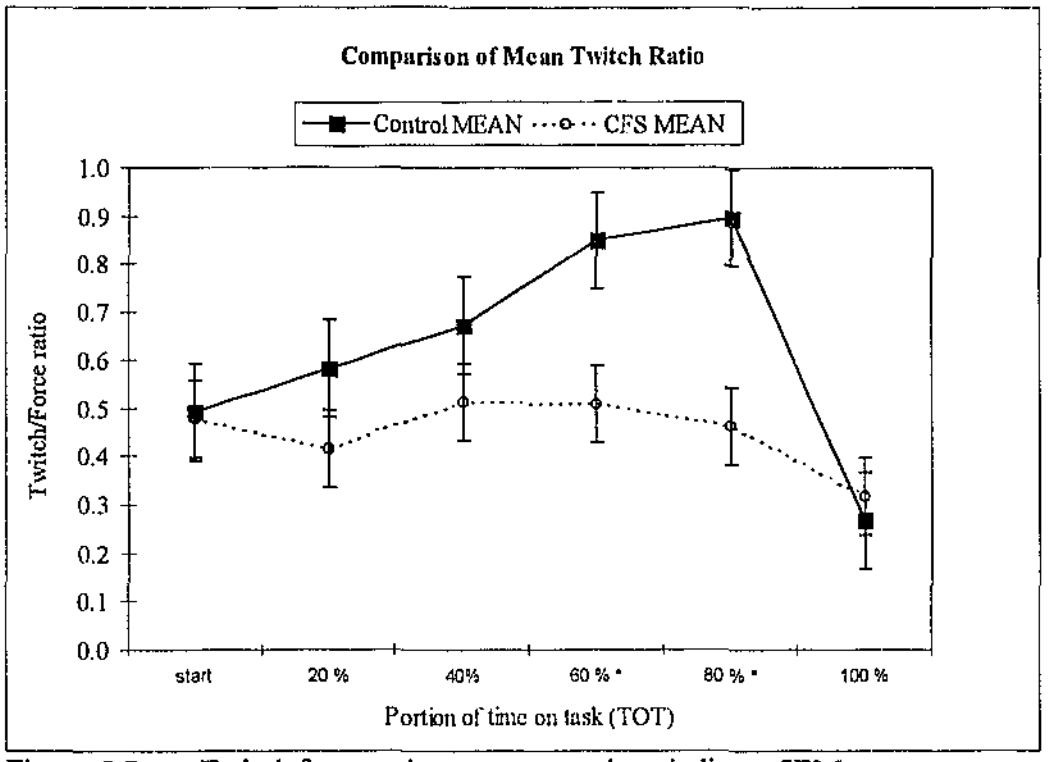

Figure 5.7 Twitch force ratio means, error bars indicate SEM

The within group force twitch ratios from start to finish were, CON mean start 0.49 (± 0.09), finish mean 0.27 (± 0.04), no significant difference (exact p value 0.17); CFS mean start 0.48 (± 0.08), finish mean 0.32 (± 0.05), no significant difference (exact p value of 0.09).

A between groups comparison show a significant difference in twitch force ratios at 60% and 80 % TOT, ($p = 0.05$), this is shown in figure 5.7. Thus, sustained submaximal contractions appear to be producing a variation in response, yet subsequent maximal efforts appear to produce similar twitch force responses. Figure 5.7 also shows the apparent lack of change in twitch force for CFS group, while the CON group shows steady rise in twitch ratio with a subsequent drop at 100% TOT. It should be noted that the final fifteen seconds was under conditions of a maximal contraction.

CHAPTER SIX

DISCUSSION

The main purpose of the study was to investigate differences in responses to fatigue between normal participants and those suffering from chronic fatigue syndrome (CFS). A problem in research into CFS is that prolonged inactivity, or reduced activity levels, leads to atrophy and impaired ability to perform exercise (Friman, 1977, p. 307; Friman, 1978, p. 107). In order to minimise such an effect the control group (CON) was matched for age, height, weight, and for a self reported activity index (AI), refer to appendix H. This allowed the comparison of what were relatively similar groups. If activity levels were similar, a similar response to the protocol could be expected and therefore any subsequent differences in response should be attributable to the independent variable, which was the pathology associated with CFS.

6.1 Participant Comparisons

Results for age, height, and weight, of groups showed no statistically significant differences, as shown in tables 5.1 and 5.2. This study observed a mean age of 29.0 years (range 18.3 to 47.8 years). Other Australian studies, of individuals suffering from CFS, found mean ages of 34 years (Lloyd, Gandevia, & Hales, 1991, p. 90), 33.7 years (Lloyd & Pender, 1992, p. 600), with a female to male ratio of 1.3:1.0, and 31 years (Parker, Brukner & Rosier, 1996, p.271) with a female male ratio of 1.4:1.0. Others, from the USA, have reported an 80% prevalence of females with a mean age of 37.6 years (Gunn, Connell, & Randall,

1993, p.83). The high ratio of females in some studies may have more to do with selection procedures and self presentation into studies. The small numbers in this study are considered responsible for providing an apparent imbalance with a female to male ratio of 2.0:1.0.

While the activity index (AI) showed no statistical significance, several CFS subjects had extremely low activity indices (AI < 10), refer to table 5.1. Problems associated with diagnosis of CFS and the ranges in AI may represent some outlier effect. Outlier effect may also be apparent due either to mis-diagnosis, or early diagnosis, or to a good response to treatment.

6.2 Strength Comparisons

The initial maximum voluntary contractions (MVC) for both groups (tables 5.1 and 5.2) were not significantly different. This is as would be expected for groups matched for physical characteristics. The higher figures for CON (mean 163.6 ± 19.5 N) over CFS (mean 123.5 ± 20.4 N) would seem to suggest some additional strength at the start. These differences may be more closely linked to disuse and normal atrophic responses to inactivity than to any pathological responses. General atrophic effects are known to be associated with disuse from inactivity linked to CFS and illnesses (Friman, 1978, p. 107; Preedy, Smith, Salisbury, & Peters, 1993, p.725). Preedy et al. (1993) suggest that strength decrements may be linked to poor management of the disease rather than any pathological effect. For the purposes of this study the similarity between the groups was deemed to be acceptable.

Previous findings have also shown no significant difference to exist between controls and CFS patients in terms of MVC or strength outputs (Lloyd, Hales, & Gandevia, 1988, p.1318; Lloyd, Gandevia, & Hales, 1991, p. 91; Preedy et al. 1993, p. 725; Wessely & Edwards, 1993, 9. 312). The present study, therefore, confirms such findings, that minor aberrations in strength are related to atrophy through non-use and inactivity rather than any intrinsic pathology.

6.3 Duration of Test; Time on Task (TOT)

The first hypothesis was that the symptoms of fatigue experienced in CFS would lead to a reduced time to onset of fatigue identified by a reduced time on task (TOT). The results from the study found no significant difference between groups for TOT (mean CON 17.7 ± 3.5 minutes, mean CFS 14.5 ± 4.5 minutes). However, in viewing figure 5.1 it is noted that a large portion of the CFS group where incapable of sustaining sub-maximal effort in excess of ten minutes. Thus, CFS participants showed a trend for shorter task times in spite of non- statistical significance being presented. Future research, incorporating greater numbers of participants, may show a tighter range of TOT for both groups.

A problem to be considered in suggesting such a trend is the validity of measuring the 20% MVC used as the target baseline. If one, or more, CFS participants did not achieve full MVC in the preliminary measures then the 20% target will have been below their actual level thus leading to an extended time to duration. One participant (CFS 2) attained a higher MVC after recovery than initial MVC. This was taken as an indication that initial MVC was not in fact

maximal and that, as a result, their sub-maximal target was suspect. This data was excluded from subsequent analysis of force production. However, based on force and RPE measures, it is assumed that others attained a maximal or near maximal effort.

Muscle ischaemia is known to affect task duration (Fox et al. 1993, p. 172). Use of sub-maximal levels should alleviate any problems associated with occlusion and metabolite build up thus mimicking activities of daily living (ADL) and also minimising disruption due to physical impediments. Thus any differences infer a central fatigue effect.

Those subjects exhibiting higher TOT were generally younger and more recently diagnosed. If early diagnosis and treatment is a factor in restricting the pathology of CFS this augments the need to develop a diagnostic procedure that will aid early detection. The small sample size may have distorted the data. This leads to the need to perform similar tests on larger populations in order to establish a clearer picture of fatigue time. Given similar fatigue times for the sub-maximal test it would be suspected that ADL for CFS and controls would also be similar. These were not assessed in this study but may need to be correlated with activity indicators in subsequent studies.

6.4 Responses to Stimulation

The final hypothesis suggested that there would be an alteration in the motor responses to TMS during the fatigue protocol. MEP's, SP duration, and twitch force evoked by TMS as influenced by fatiguing exercise. Several studies have observed such responses to fatiguing protocols (Lloyd, Gandevia, & Hales, 1991; Preedy et al. 1993) and to TMS (Brouwer & Packer, 1994, p. 1210). These provide data about normal responses enabling comparative assessments of both the control and CFS group. Evoked potentials, associated with cortical activity, appear to be a useful measure about the processing of information (Wessely, 1993, p. 220).

6.4.1 MEP changes

The peak to peak summation of EMG response was measured as the MEP due to TMS. This is in effect an indicator of the level of cortical excitability and of activation of motor units. As the protocol continues it can be seen that CON show an increasing response to stimulation, see figure 5.7. This supports previous reports where the fatigue resulted in an increase in cortical excitability in normal subjects (Maton, 1991; Brouwer & Packer, 1994, p. 1211).

In the CFS groups no significant changes for MEP are found. The between groups test, Mann-Whitney U-test at p= 0.05, shows a significant difference between CFS and CON at 80% TOT. However, the differences between groups at 60% and 100% TOT present with an exact p value of 0.08 suggesting a trend of difference is occurring. Thus it may be concluded that the CFS group is

presenting with an altered response of MEP due to stimulation. This implies that the enhanced corticomotor excitability observed in controls is not present in CFS. Brouwer and Packer (1994, p. 1211) found unstable responses in CFS. Such increased excitability in controls tends to result in an increased force production, as displayed by twitch force ratios, above baseline target.

Such a change in MEP may indicate an increased response of the neural pathways, and subsequent enhanced responses from the muscle. As fatigue sets in and the peripheral mechanisms become strained, the control group's response increases. The CFS groups, on the other hand, seem to stabilise, or diminish somewhat. Thus it may be speculated that control and CFS participants are experiencing different responses under a condition of sub-maximal loading. These data seem to suggest an altered neurological response to the fatigue process, with CFS not apparently having the ability to modulate activity output through feedback into the CNS. Future research may confirm these findings that CFS has some pathological factor associated with the nerve pathways, or disrupted inhibitory mechanisms.

6.4.2 Silent Period (SP) Duration

The SP duration in response to TMS shows a distinct change over time for the CON. With a steady increase in SP duration over the task, statistical significance is seen at, and beyond, 60% TOT. Starting SP duration presented as a mean of 119 ± 15.7 milliseconds (ms), while at the end the mean was 186 ± 20.9 ms. Figure 5.5 shows the clear and steady rise in SP duration over task.

Duration of the SP following evoked potential remained constant in the CFS group with no significant difference from starting SP. Mean SP at start was 107 ± 7.5 ms, and SP at end had a mean of 100 ± 7.7 ms ($p > 0.05$). This indicates that normal EMG activity of muscular contraction is resumed within the same time scale regardless of effort, fatigue or decreased capacity to maintain contraction. This suggests that inhibitory feedback from proprioceptors or Ia type interneurones, which is believed to modulate SP duration, is impaired. Increases in SP are associated with isometric contraction (Porter & Lemon, 1993, p. 204), and usually signal inhibitory interneurones in action. Normal SP increase is a reflection of an effect on interneurones. This may be triggered by proprioceptive mechanisms sending inhibitory signals to the CNS (Young, Triggs, & Gerstle, 1995, p. 1290), or direct effect on the inhibitory interneurones. Thus, presynaptic and postsynaptic, or a combination of both inhibitory mechanisms may be in operation (Leis, Stetkarova, Beric, & Stokic, 1995, p. 1468).

The duration of SP following evoked potentials is regarded as indicative of the level of cortical inhibition. This may serve to prevent the muscle from over working or reaching a state of excessive fatigue. Altered cortical inhibition, during activity, is not observed in CFS. This, in turn, may cause an excessive response to activity leading to a state of excessive fatigue.

A role of inhibition may be to prevent excessive activation through any one nerve pathway. Should such a mechanism be incapacitated in CFS it may

explain an increased response to fatigue, which would be expressly noticeable in recovery. Response to fatigue, in CFS, therefore may be showing a decreased neural feedback, from receptors or from a failure of inhibitory interneurones.

6.4.3 Twitch Force Ratio Changes

Even in maximal voluntary activity there is an amount of potential force that is not used (Wilson, G., 1995, p. 3). TMS is seen to elicit additional force over the baseline of facilitation. Thus twitch force is an indicator that additional force is available and that nerves are being activated to produce extra force.

Twitch force production in controls increased significantly while the base force remained constant. Non-significant changes occurred in CFS. The increasing force output due to TMS for controls seems to indicate a steady rise in response to stimulation, as seen in MEP responses. The relative lack of change in CFS may indicate an altered response to neural input to the muscle. This may be due to reduced cortical excitability. Twitch force and maximal force are limited by neural feedback, such as muscle spindles and the golgi tendon organ (GTO) (Wilson, 1995, p. 3). Therefore, increases in twitch force ratios imply that inhibitory mechanisms have been overridden. It can be seen that controls present a rise in twitch force, implying that inhibitory mechanisms are functioning in a normal manner. Such increases are not seen in CFS which may serve to indicate that inhibition is not working properly. The precise reason is still unclear.

Of interest is the decrease shown by both groups at 100% TOT. This highlights the differences between responses to maximal efforts and sustained low level efforts. Both groups appear, therefore, to have similar responses to maximal efforts, as has been noted in other studies (Lloyd et al. 1988; Lloyd et al. 1991; Wessely & Edwards, 1993). Little work appears to have been conducted on sustained sub-maximal contractions which was found to produce differing responses. Thus ratios may be useful in indicating altered responses to sustained levels of workload.

6.4.4 Summary of Physiological Responses

Abnormal or altered electrophysiological responses in CFS have been reported (Jamal & Hanson, 1985, p. 693; Brouwer & Packer, 1994, p. 1212). The silent period (SP) following evoked potentials shows a clear difference between groups. Considering the same fatigue levels, strength and RPE measures, differences should be due to neurological responses to muscular activity linked to the condition prevalent. Differences in the SP duration lead to speculation that some failure of the normal inhibitory response, seeking to prevent overload of the muscle, is occurring. This may reflect a disruption of integration of proprioceptive mechanisms within the muscle or an inability of the CNS to process the responses optimally. Some findings suggest that Ia inhibitory interneurones could be responsible for such inhibition (Porter & Lemon, 1993, p. 205).

It would appear from the findings of this study that some neurological or neurophysiological differences are present as a result of the pathology associated with the CFS. While no differences are noted in initial MVC, the decrement, following recovery, points toward some impairment in physiological capacity of the muscle. Thus, some interplay between the neurological and physiological processes is clearly occurring.

6.5 Perception of Effort

The second hypothesis was that there would be an altered perception of exertion in CFS sufferers. The initial rates of perceived exertion, measured on the modified Borg scale, (Borg, 1982), were significantly different with CFS participants finding a 20% MVC to be more demanding than controls. Previous research suggestions, of elevated or exaggerated effort sense, are therefore confirmed (Lloyd et al. 1988; Brouwer & Packer, 1994, p. 1212) and support this hypothesis. However, difference between groups was only noted in the early stages, being identified at the start and at 20% TOT. Subsequently both groups followed the same rate of increase in line with increasing effort and showed no significant difference either within or between groups, refer to figure 5.5. Therefore, during activity similar perceptions occur while at rest the CFS present with a perception that effort is harder. This trend may well imply that some homeostatic mechanism for the regulation of effort has been disrupted in CFS. If so, this would concur with findings from this study that some disruption has occurred at a cortical level. Investigation whether this is at a supraspinal or at an executive (cognitive) level is beyond the scope of this study.

Thus the same relative increase may be indicative of a similar sense of effort with a different starting point being the only major factor in perception. The finding of a different RPE base would seem to be logical given the lack of activity in CFS. Yet, it would also seem logical to expect low activity to be responsible for RPE levels in matched controls. It has yet to be determined if such perception is more closely associated with peripheral feedback mechanisms, or from alteration in the central (executive) processing of fatigue. Some changes in performance are known to be attributed to altered sensory input (Friman, 1977, p. 307). During this task little difference was detected between CON and CFS. Starting RPE was different, but it should be borne in mind that this may be linked to disuse in management of the pathology rather than in response to the pathology itself (Preedy et al. 1993). A symptom of CFS is heightened fatigue awareness while at rest (Lloyd et al. 1988, p. 1316), leading to suspicion of sensory input involvement. The results of this study suggest that differences seen during fatiguing exercise are not merely a perception but a real and valid result of the pathology associated with CFS. While RPE is a subjective measure (Preedy et al. 1993) , it still may have value for assessing CFS until some clear objective diagnostic measure is presented.

6.6 Force Recovery

The capacity to produce force, as indicated by changes in MVC as a result of the protocol, and subsequent recovery (figure 5.2), serve to indicate a consistent level of peripheral fatigue for both groups, both in force and time responses.

The results show that both groups suffered a similar decrement in muscle force capacity. Drop from initial MVC being, CON 53.0% (± 4.4%) and CFS 54.5% (± 6.2%). Subsequent differences should reflect a response of the central fatigue mechanisms involved. Differences between the groups should also reflect altered properties, or responses, of the central fatigue mechanisms.

It has been shown that maximal isometric strength (MVC) is not affected by CFS (Lloyd et al. 1988, p. 1321; Preedy et al. 1993). These findings were confirmed in this study by the similarity of responses in MVC pre-test, at the end of fatigue protocol, and post recovery, between CON and CFS. Initial MVC outputs and the MVC at end of task were similar. A discrepancy appears following recovery, see figure 5.3. After twenty minutes recovery CFS produced 72.4 (± 9.0)% of initial MVC while CON produced 85.1 (± 14.8)%. This was not significant. However, an exact p value of 0.07 between groups shows some trend to recovery differences, which is also suggested by Lloyd et al. (1988). While responses during activity were similar, responses following recovery may suggest that some recovery mechanism is associated with the pathology of CFS. Should a different recovery time be required, for the same effort, this may limit ADL by restricting the time between doing different tasks. This possibility was beyond the scope of this study but warrants future investigation.

CHAPTER SEVEN

CONCLUSION AND RECOMMENDATIONS

One of the great difficulties in examining CFS as a disease is the widespread adaptation of various definitions for clinical evaluation. The CDC definition, applied in this study, is primarily a definition to help research in establishing a common ground (Holmes et al. 1988; Holmes, 1991; Lloyd & Pender, 1994). As such it may be of little benefit to the clinician treating the patient. Therefore, there is still a need for a "concise and universally accepted medical definition" (Preedy et al. 1993, p. 725). Objective indicators, as explored in this study, may prove beneficial, especially if correlated with results from other research.

The first hypothesis was not confirmed by the results. It was seen that no alteration in the time to fatigue occurs. It would appear that time to fatigue is indicative of normal musculature response associated with peripheral fatigue. This would concur with previous studies suggesting that CFS has no apparent distinct peripheral pathology (Lloyd et al. 1991; Preedy et al. 1993; Wessely & Edwards, 1993). While no significant difference was found, the range of times for CFS participants appears wider than for controls. Further, participants tended to present at the extremes of the range with half CFS showing endurance of less than ten minutes. The endurance capacity in CFS requires further exploration before any conclusion can be drawn linking fatigue, endurance and pathology.

The second hypothesis was that an altered perception of effort would exist. This was shown with the CFS group presenting a greater perception of effort at start of task. Considering the matching of controls it would appear that the sense of effort is altered as a result of CFS pathology. The interpreting of sensory and neural inputs may be impaired, or a cognitive process may be disrupted. Which ever the case perception of exertion requires clearer correlation with the central and peripheral components of fatigue. There has been speculation about a disturbed, centrally based, homeostatic mechanism (Maton, 1993; Ware, 1993, p. 69; Kent-Braun, Sharma, Weiner, Massie, & Miller, 1993, p. 129). Disturbed rating of perceived exertion may reflect this, but such speculation requires more research.

The final hypothesis was that altered motor response would be observed. Stimulation showed different responses between groups. Controls showed a steady increase in MEP amplitude and SP duration. These imply a functioning of inhibitory interneurones. Inhibition of activation is a normal response, and increased inhibition, identified through increased silent period, is seen to be associated with extended isometric activities (Porter & Lemon, 1993, p. 203-205). Inhibitory processes may serve to focus and direct neural activity in order to prevent overuse and thus damage. CFS participants showed a difference with no apparent increase in either MEP amplitude or SP duration. This implies that the normal inhibitory mechanisms are not operating optimally.

The results from this study, in conjunction with previous findings seem to indicate a disrupted inhibitory mechanism for CFS. Both SP duration and MEP

increased in normals while no such change occurred in CFS. Therefore it may concluded that a normal increase in motorneurone excitability (Maton, 1993) is not seen in CFS. This leads to speculation on the mechanisms that might be disrupted for failure of MEP and duration of EMG silent period (SP) following stimulation.

Disruption of inhibitory mechanisms may be responsible for the increased perception effort and associated fatigue at rest, seen in CFS. The homeostatic balance would appear to be disturbed and it may transpire that this neurophysioligical disruption has 'reset' the cortical determination of fatigue. This would be exhibited by excess fatigue and a subsequent need for increased recovery times. Therefore it may be concluded that at sub-maximal activity levels an impaired central fatigue processing occurs in CFS.

Chronic fatigue syndrome is a serious and complex illness characterised by incapacitating fatigue, neurological problems and a constellation of other debilitating symptoms. Traditional scientific medicine has tended to dichotomise the mind and body (Ware, 1993, p. 69). Perhaps in observing central fatigue, a mechanism where the mind and body interface may be identified. Extension of the present study with greater numbers would serve to confirm the findings presented. A clearer picture of the endurance capacity of muscle in CFS, in conjunction with central fatigue measures, may determine where the root cause of the pathology lies. A continuation of an integrated approach to research is recommended in attempting to understand the pathology and aetiology of this debilitating disorder.

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APPENDIX A

Informed Consent Sheets

Central Fatigue in Overtraining and Chronic Fatigue Syndrome

Informed Consent

This study seeks to investigate the responses of the nervous system to muscle fatigue. All procedures are non-invasive.

One pair of recording electrodes will be taped to the biceps. These will measure muscle activity which will be fed into a computer. In order to examine the responses of the brain to fatiguing activity we will use transcranial magnetic stimulation. A small magnetic coil will be positioned above the skull, that part of the brain will be stimulated with a magnetic pulse. Each stimulus will be very short and is not painful, but some movements of the elbow flexor muscles will be noticed. Occasionally a tingling or tap on the head may be felt.

During the session you will be asked to contract muscles in the arm as hard as possible against a padded resistance for less than 5 seconds. You will also be asked to perform a sustained, low-level, isometric contraction of the biceps until fatigue. Your non-dominant arm will be used to minimise disruption to regular activity. Some localised discomfort may be experienced but should be dissipated with a few days. The whole procedure will take between 1 and 2 hours.

If you have any doubts or questions pleased ask the staff on hand or contact Peter Hope (Principal Investigator) on 400 5054, or Dr. Paul Sacco (Research Supervisor) on 400 5642.

All data collected will be coded to ensure your personal confidentiality. No information will be reported in a manner that can allow you to be identified from the results. Your permission to perform this testing is voluntary. You are free to stop the test or withdraw at any point.

I have read the informed consent and any questions have been answered to my satisfaction. The tests and associated risks have been fully explained to me. I agree to participate in this study voluntarily realising that I may withdraw at any time. To the best of my knowledge I am not pregnant, do not have raised blood pressure or any heart problems and have no metal plates in my head

Name ..... Signature.....

Witness ..... Date .....

APPENDIX B

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation

TMS uses a large pulse magnetic field to induce currents within the body. Theses pulsed magnetic fields can stimulate both the central and peripheral nervous systems. According to the laws of electromagnetism, a time varying magnetic field will induce an electrical field in any specified loop in its vicinity. TMS causes changes in the structural integrity of projections of the corticospinal pathways in humans. These responses reflect the output of the stimulated population of cortical neurones to motorneurones. In neurological disorders there may be abnormal excitability of the motor pathways.

TMS applied over the scalp of the relaxed individual activates contralateral muscles in a distinct pattern apparent from their order of recruitment and amplitudes of the muscle responses. The upper limbs, hand and forearm muscle have the lowest thresholds for activation, hence the largest compound EPSP's are produced in the motor neurones innervating intrinsic hand muscles.

Magnetic stimulation is virtually painless, with minor discomfort due to the evoked muscle contraction. There have been no deleterious effects in investigations using TMS. There is a small amount of thermal energy deposited, equivalent to approximately on per cent of that generated by normal metabolism in the brain.

There are many advantages to the use of TMS. Theses include the ability to penetrate all human tissue without attenuation, hence advantageous when stimulating regions below layers of bone. It does not cause large electrical fields at the surface, nor does it require physical or electrical contact with the body. No skin preparation or the removal of clothing is necessary at the stimulation site. It is blind to smearing effects of extra cerebral layers thereby allowing a more precise measurement of the threshold for excitation of motor evoked potentials, and is able to influence endogenous processes of movement preparation externally without disrupting the conscious perception of volition. Disadvantages of TMS include the equipment's relative bulkiness. The stimulation rate is relatively slow, with the site of stimulation not well defined.

APPENDIX C

Borg Scale - Perceived Exertion

SCALE FOR RATING PERCEIVED EXERTION

6.	
7.	very, very light
8.	
9.	very light
10.	
11.	fairly light
12.	
13.	some what hard
14.	
15.	hard
16.	
17.	very hard
18.	
19.	very, very hard
20.	

The Borg scale of perceived exertion (Borg, 1972), is widely used in the form of a chart placed in front of participants . Its key benefits is that it allows them to indicate how they perceive their present state of 'effort sense' using a single number. This minimises distraction and also allows for standardised comparisons across time and between individuals

APPENDIX D

Symptoms Associated With OTS

Factors attributed to excessive exercise stress :

The symptoms of overtraining (OTS)

BIOCHEMICAL/HAEMATOLOGICAL

Altered cyclic adenosine monophosphate metabolism
Decreased haematocrit
Decreased haemoglobin (anaemia)
Decreased iron absorption
Decreased red blood cells
Decreased serum ferritin
Decreased serum iron
Elevated 3-methylhistidine
Elevated Ketosteroids in urine
Increased iron loss
Increased urea concentrations
Increased uric acid production
Low resting haptoglobin
Lowered TIBC
Negative nitrogen balance
(NUMBER = 15)

CARDIORESPIRATORY FUNCTION

Abnormal rate in heart rate during standard workout
Breast pain
Consciousness of heart rate
Decreased maximum heart rate
Decreased morning heart rate
Decreased vital capacity
Disturbed feeling around the heart
Elevated systolic blood pressure
Heart discomfort on slight exertion
Higher heart rate at standard workload
Impeded respiration and subcostal aching during normal activity
Increased difference between lying and standing heart rate
Increased frequency and lowered volume of pulse
Increased frequency of respiration
Increased heart rate (5-10 beats from normal)
Increased quotient of heart volume and maximum oxygen pulse
Marked palpitation during exercise
Quick return of heart rate to pre-exercise levels
Shortness of breath
Slight pain in pericardial areas
Slower recovery of heart rate following standard load
(NUMBER = 24)

DRINKING/ NUTRITIONAL DISORDERS

Anorexia nervosa
Bulemia
Constipation
Decreased evening post workout weight
Digestive disturbance
Feels thirsty/ chronic dehydration
Gastrointestinal disturbances
Inadequate diet
Increased fluid intake in the evening
Loss of appetite
Mineral depletion
Vitamin E deficiency
(NUMBER = 12)

HORMONAL

Adrenal gland sensitivity
Adrenal hypofunction
Adrenal overstimulation
Adrenocortical insufficiency
Ammenhorea/ oligomenhorea
Decreased adrenalin at maximal workloads
Decreased adrenalin at standard submaximal workloads
Decreased bone mineral content
Decreased exercise induced elevation of catecholamines
Decreased noradrenalin at standard submaximal workloads
Decreased ration of testosterone to cortisol
Delayed menarche
Depressed prolactin
Depressed serum testosterone
Disharmonic hormonal control
Elevated serum cortisol
Elevated sex hormone binding globin
Hypothalmic dysfunction
Impaired GH, ACTH, Cortisol and PRL response to insulin induced hypoglycaemia
Parasympathetic dominance
Pituitary gland insufficiency
Thyroid hyperfunction
(NUMBER = 23)

INFECTIOUS DISEASE

Adrenal gland swelling
Altered glutamine metabolism
Altered interferon metabolism
Aseptic meningitis
Bacterial infection
Bacterial meningitis
Decreased functional activity of neutrophil adherence
Decreased immunoglobulin (serum)
Decreased neutrophil bacteriocidal activity
Decreased neutrophil mediated oxygen radical response
Decreased nonspecific immunity
Decreased salivary IgA
Depressed immune function

Flu-like illnesses
Frequent or persistent colds
Glandular fever
Heart failure
Increased antistreptolysin-0 titre
Increased blood eosinophil count
Increased immunoglobulin
Increased noxiousness of coxackie B3 virus
Increased susceptibility to and severity of polio
Increased susceptibility to hepatitis
Increased susceptibility to illness/ colds/ allergies
Lymph glands atrophy
Minor scratches heal slowly
More days off through illness
More frequent and severe upper respiratory tract infection
Myocarditis
One day colds
Pericarditis
Re-activation of Herpes viral infection
Reduced response to mytogens
Severely debilitating states
Sinusitis
Skin rashes
Skin sepsis
Sore throats
Suffer head colds/ allergic reactions
Swelling of lymph glands
Thymus gland wittles
Tracheitis
Tracheobronchitis
Unconfirmed glandular fever
Worsen disease
Worsening of hepatitis
(NUMBER = 49)

MUSCULOSKELETAL COMPLAINT

Decreased circumferential measures in exercised limbs
Elevated C-reactive protein
Elevated, CPK, LDH, SGOT
Increased incident of injury/ overexercise injury
Joint pain
Muscle damage
Muscle soreness/ tenderness
Muscle stiffness
Myoglobinaemia
Myoglobinuria
Necrotic fibres
Periosteal complaints
Rhabdomyolysis
Stress fractures
Tendency towards pulled muscles
Tendinosotic complaints
Unaligned Z-lines
(NUMBER = 17)

PERFORMANCE RELATED

Career terminated
Chronic fatigue
Decreased ability to sprint
Decreased maximum work capacity
Decreased muscular strength
Decreased performance in training/ competition
Decreased time trail performance
Decreases in the level of speed and endurance
Desire to quit during competition
Failure to improve muscular strength
Fatigue lasts longer than usual
Feelings of heaviness
Inability to meet performance standard criteria
Increased fatigue during exercise/rest
Loss of joy of competition
Recovery prolonged
Reduced toleration of loading
(NUMBER = 17)

PHYSICAL

Backaches
Change in pallor of the skin
Cold feet and hands
Death
Decreased body fat
Eyestrain
Haemolysis
Headaches
Nausea
Peptic ulcers
Physical distress
Profuse perspiration
Spastic colon
(NUMBER = 13)

PHYSIOLOGICAL

Acute oligururic renal failure
Decreased maximal lactate production
Decreased maximal oxygen consumption
Depressed insulin glycogen concentration
Depressed lactate levels at maximal workloads
Elevated basal metabolic rate
Elevated blood sugar levels
Flat glucose tolerance curves
Free radical damage to enzymes, membranes, etc.
Free radical mediated red cell lysis
Lean tissue loss
Low fasting blood glucose
Mild hypoglycaemia
(NUMBER = 13)

PSYCHOLOGICAL

Alienation form others

Antipathy for training sites

Appears nervous/feels nervous/ increased anxiety

Athlete endeavours to spare energy/ avoid physical effort

Athlete feels alienated

Athlete looks drawn, sallow and depressed

Become unduly upset at trivial incidents

Becomes aggressive

Becomes cynical

Changes in behaviour

Changes in personality

Decreased ability to narrow concentration

Decreased capacity to deal with large amounts of information

Decreased concentration

Decreased energy

Decreased positive affect expression

Decreased self esteem/worsening feelings of self

Decreased tolerance to stress

Decreased vigour

Depression, of clinical significance

Depressive ill humour

Difficulty in concentrating at training

Difficulty in concentrating at work

Discomfort when training

Doesn't feel any better after a few days rest

Dramatic changes in values and beliefs eg: poor weather, bad officials, etc.

Emotional instability

Exaggerated negative influence of external factors

Expressions of or feelings of increased anger

Fear of competition

Feeling of being locked into routines

Feelings of anticlimax and boredom

Feelings of depression

Feelings of frustration

Feelings of heaviness

Feelings of heaviness

Feelings of helplessness

Feelings of inadequacy

Feelings of listlessness

Feelings of resentment towards the whole training process

Feelings of tension

Feelings of tiredness/drowsiness

Feels phlegmatic

General apathy

Gives up when the going gets tough

Growing feelings of incompetence

Hesitant to train/ loss of joy in competition/loss of thirst for competition

Impaired academic performance

Increased confusion

Increased consumption of coffee, tobacco, alcohol

Increased excitability

Increased in emotional and behavioural impulsivity

Increased internal and external distractability
Increased irritability
Increased perceived effort
Increased restlessness
Irascible
Isolate self from team mates/coach
Isolates self emotionally
Lack of fighting power
Lack of initiative
Lethargy
Letting minor stresses bother
Loses confidence
Loss of interest in training
Loss of interest in work
Loss of libido
Loss of purpose and energy for living
Miserable
Motivational imbalance/loss of enthusiasm
Negative changes in frame of mind
No desire to practice or improve
Not eating well
Not enjoying life generally
Peevish
Perceived low achievement
perceived sense of loss of control
Progressive loss of idealism
Psychic unrest
Quarrelsome/provocative behaviour
Rundown feeling
Sense of insecurity
Sensitive to criticism
Sensitivity to environmental and emotional stress
Sluggishness
Sluggishness that persists longer than 24 hours
Slump in morale
Suppressed moods
Unable to get ready for practice
Unable to relax
Unreasonable complaints
(NUMBER = 91)

SENSORIMOTOR PERFORMANCE

Actions slower and less precise
Decreased aerobic efficiency
Decreased mechanical efficiency/
Decreased amplitude of movement
Decreased nervous conduction
Decreased reaction time
Exaggerated postural hypotension
Exaggerated reflexes
General clumsiness
Hypersensitivity to sensory stimulation of pain or noise with exaggerated responses to these stimuli
Inconsistency in performing rhythmical movements
Increased distractability
Increased hear rate at a given workload
Increased muscle tension
Increased ventilation at a given workload

Lack of stability

Lengthening of decision time

Loss of co-ordination

Loss of muscle tone

Poor muscular control and balance

Psychomotor retardation

Reappearance of mistakes already corrected

Reduced capacity of differentiation and correcting technical faults

Reduced or lowered critical flicker-fusion frequency

Slowing of sensory motor performance

Tremors hands and eyelids

(NUMBER = 25)

SLEEP RELATED

Awake frequently at night

Decreased hours of sleep

Insomnia

Night sweats

Sleep disturbance

Sleep not refreshing

Trouble falling asleep

(NUMBER = 7)

From Fry, Morton, & Keast (1991c, p. 48). Full listing available from authors.

APPENDIX E

Normalised Data

	normalised portion of time	start	20 %	40%	60%	80%	100 %
CON 1	SP Duration (ms)	97	104	130	119	98	139
CON1	MEP Amplitude (mV)	17.48	18.43	19.03	18.93	19.90	15.64
CON1	Twitch Force (newtons)	14.2	15.2	18.4	24.2	25.2	24.2
CON1	base force	43.8	43.8	43.8	43.8	43.8	148.3
CON1	twitch ratio	0.3	0.3	0.4	0.6	0.6	0.2
CON1	RPE (0.5 min)	11	15	18	20	20	20
CON2	SP Duration (ms)	89	99	135	120	123	169
CON2	MEP Amplitude (mV)	11.55	13.27	13.42	13.98	13.90	11.98
CON2	Twitch Force (newtons)	22.6	25.8	26.8	26.3	24.7	11.6
CON2	base force	27.4	27.4	27.4	27.4	27.4	56.9
CON2	twitch ratio	0.8	0.9	1.0	1.0	0.9	0.2
CON2	RPE (0.5 min)	9	11	13	15	16	18
CON3	SP Duration (ms)	122	171	150	137	148	126
CON3	MEP Amplitude (mV)	4.56	7.75	8.38	7.66	7.09	9.76
CON3	Twitch Force (newtons)	10.0	12.6	11.0	22.6	13.8	34.2
CON3	base force	37.7	37.7	37.7	37.7	37.7	95.8
CON3	twitch ratio	0.3	0.3	0.3	0.6	0.4	0.4
CON3	RPE (0.5 min)	10	11	12	17	20	20
CON4	SP Duration (ms)	189	148	149	179	165	208
CON4	MEP Amplitude (mV)	10.26	8.12	13.28	11.93	11.81	11.34
CON4	Twitch Force (newtons)	17.3	16.8	25.2	43.1	51.5	31.0
CON4	base force	50.7	50.7	50.7	50.7	50.7	86.9
CON4	twitch ratio	0.3	0.3	0.5	0.9	1.0	0.4
CON4	RPE (0.5 min)	8	10	13	16	19	20
CON5	SP Duration (ms)	128	164	184	193	190	214
CON5	MEP Amplitude (mV)	1.59	2.79	2.99	2.90	3.40	4.45
CON5	Twitch Force (newtons)	15.2	16.3	20.5	22.6	23.7	8.4
CON5	base force	21.6	21.6	21.6	21.6	21.6	48.2
CON5	twitch ratio	0.7	0.8	0.9	1.0	1.1	0.2
CON5	RPE (0.5 min)	8	13	17	19	20	20
CON6	SP Duration (ms)	87	109	127	126	170	262
CON6	MEP Amplitude (mV)	4.12	3.71	7.56	9.72	8.38	7.46
CON6	Twitch Force (newtons)	12.1	19.4	22.1	26.8	35.2	16.8
CON6	base force	24.7	24.7	24.7	24.7	24.7	48.2
CON6	twitch ratio	0.5	0.8	0.9	1.1	1.4	0.3
CON6	RPE (0.5 min)	9	12	17	19	20	20

	normalised portion of time	start	20%	40%	60%	80%	100%
CFS1	SP Duration (ms)	95	65	97	77	89	86
CFS1	MEP Amplitude (mV)	5.32	1.86	6.40	0.41	2.57	9.53
CFS1	Twitch Force (newtons)	13.1	3.7	8.4	6.8	3.7	12.6
CFS1	base force	22.2	22.2	22.2	22.2	22.2	41.9
CFS1	twitch ratio	0.6	0.2	0.4	0.3	0.2	0.3
CFS1	RPE (0.5 min)	14	16	18	19	20	20
CFS2	SP Duration (ms)	106	107	90	111	133	79
CFS2	MEP Amplitude (mV)	9.87	5.31	9.94	8.69	5.51	2.70
CFS2	Twitch Force (newtons)	14.7	14.2	15.2	14.2	10.5	23.1
CFS2	base force	17.4	17.4	17.4	17.4	17.4	70.1
CFS2	twitch ratio	0.8	0.8	0.9	0.8	0.6	0.3
CFS2	RPE (0.5 min)	10	13	17	19	20	20
CFS3	SP Duration (ms)	113	103	114	125	124	125
CFS3	MEP Amplitude (mV)	2.87	3.37	5.03	4.67	6.26	5.68
CFS3	Twitch Force (newtons)	6.8	8.4	9.5	11.6	13.7	15.2
CFS3	base force	18.8	18.8	18.8	18.8	18.8	28.3
CFS3	twitch ratio	0.4	0.4	0.5	0.6	0.7	0.5
CFS3	RPE (0.5 min)	11	14	17	18	19	20
CFS4	SP Duration (ms)	101	106	105	103	113	107
CFS4	MEP Amplitude (mV)	3.73	4.19	6.85	9.26	2.82	10.12
CFS4	Twitch Force (newtons)	19.4	22.6	24.2	28.9	28.4	34.2
CFS4	base force	45.1	45.1	45.1	45.1	45.1	110
CFS4	twitch ratio	0.4	0.5	0.5	0.6	0.6	0.3
CFS4	RPE (0.5 min)	11	14	16	17	19	20
CFS5	SP Duration (ms)	140	138	125	109	108	115
CFS5	MEP Amplitude (mV)	6.22	4.62	7.46	7.00	6.78	5.79
CFS5	Twitch Force (newtons)	7.9	7.9	10.0	8.4	8.4	13.7
CFS5	base force	21.8	21.8	21.8	21.8	21.8	51.6
CFS5	twitch ratio	0.4	0.4	0.5	0.4	0.4	0.3
CFS5	RPE (0.5 min)	11	15	18	20	20	20
CFS6	SP Duration (ms)	88	99	122	97	85	85
CFS6	MEP Amplitude (mV)	5.18	3.51	5.18	4.89	4.83	4.37
CFS6	Twitch Force (newtons)	7.4	5.3	8.4	7.4	6.8	12.6
CFS6	base force	26.2	26.2	26.2	26.2	26.2	77
CFS6	twitch ratio	0.3	0.2	0.3	0.3	0.3	0.2
CFS6	RPE (0.5 min)	10	13	15	18	20	20

CON	MEAN SP	119	133	146	146	149	186
	SEM	15.7	13.2	8.6	13.1	13.7	20.9
	MEAN MEP	8.3	9.0	10.8	10.9	10.7	10.1
	SEM	2.4	2.4	2.3	2.2	2.4	1.6
	MEAN Twitch Force	15.2	17.7	20.7	27.6	29.0	21.0
	SEM	1.8	1.9	2.3	3.2	5.3	4.3
	MEAN base force	34.3	34.3	34.3	34.3	34.3	80.7
	SEM	4.7	4.7	4.7	4.7	4.7	15.8
	MEAN Twitch Ratio	0.49	0.58	0.67	0.85	0.90	0.27
	SEM	0.09	0.11	0.12	0.09	0.15	0.04
	MEAN RPE	9.2	12.0	15.0	17.7	19.2	19.7
	SEM	0.5	0.7	1.1	0.8	0.7	0.3

CFS	MEAN SP	107	103	109	104	109	100
	SEM	7.5	9.5	5.7	6.6	7.7	7.7
	MEAN MEP	5.5	3.8	6.8	5.8	4.8	6.4
	SEM	1.0	0.5	0.7	1.3	0.7	1.2
	MEAN Twitch Force	11.6	10.4	12.6	12.9	11.9	18.6
	SEM	2.1	2.9	2.5	3.4	3.6	3.5
	MEAN base force	25.3	25.3	25.3	25.3	25.3	63.2
	SEM	4.2	4.2	4.2	4.2	4.2	11.9
	MEAN Twitch Ratio	0.48	0.42	0.51	0.51	0.46	0.32
	SEM	0.08	0.10	0.08	0.09	0.09	0.05
	MEAN RPE	11.2	14.2	16.8	18.5	19.7	20.0
	SEM	0.6	0.5	0.5	0.4	0.2	0.0

APPENDIX F

Statistical Analysis

Combined

	N	Mean	Std Dev	Minimum	Maximum
AGE	12	28.95000	11.12855	18.25	47.75
AI	12	38.41667	25.85082	6.00	64.00
MVC_PRE	12	141.50000	47.19688	80.00	221.00
SEX	12	1.33333	.49237	1.00	2.00
TASKTIME	12	16.08333	9.49122	6.00	32.00
GROUP	12	1.50000	.52223	1.00	2.00

Control Group
Number of valid observations (listwise) = 6.00

Variable TOT time on task

Mean	17.667	S.E. Mean	3.490
Std Dev	8.548	Variance	73.067
Kurtosis	-2.286	S.E. Kurt	1.741
Skewness	.408	S.E. Skew	.845
Range	19.000	Minimum	10.00
Maximum	29.00		

Valid observations - 6 Missing observations - 0

- -

Variable AGE

Mean	26.642	S.E. Mean	3.809
Std Dev	9.331	Variance	87.068
Kurtosis	-1.800	S.E. Kurt	1.741
Skewness	.915	S.E. Skew	.845
Range	20.100	Minimum	19.30
Maximum	39.40		

Valid observations - 6 Missing observations - 0

- -

Variable AI activity index

Mean	48.000	S.E. Mean	8.579
Std Dev	21.014	Variance	441.600
Kurtosis	.559	S.E. Kurt	1.741
Skewness	-1.167	S.E. Skew	.845
Range	52.000	Minimum	12.00
Maximum	64.00		

Valid observations - 6 Missing observations - 0

- -

Variable MVC mvc pre-fatigue

Mean	160.167	S.E. Mean	15.982
Std Dev	39.148	Variance	1532.567
Kurtosis	-2.114	S.E. Kurt	1.741
Skewness	-.016	S.E. Skew	.845
Range	95.000	Minimum	110.00
Maximum	205.00		

Valid observations - 6 Missing observations - 0

CFS group

Number of valid observations (listwise) = 6.00

Variable TOT time on task

Mean	14.500	S.E. Mean	4.455
Std Dev	10.913	Variance	119.100
Kurtosis	-.609	S.E. Kurt	1.741
Skewness	1.078	S.E. Skew	.845
Range	26.000	Minimum	6.00
Maximum	32.00		

Valid observations - 6 Missing observations - 6

- -

Variable AI activity index

Mean	28.833	S.E. Mean	11.606
Std Dev	28.428	Variance	808.167
Kurtosis	-2.098	S.E. Kurt	1.741
Skewness	.669	S.E. Skew	.845
Range	58.000	Minimum	6.00
Maximum	64.00		

Valid observations - 6 Missing observations - 6

- -

Variable AGE

Mean	31.258	S.E. Mean	5.363
Std Dev	13.138	Variance	172.601
Kurtosis	-1.876	S.E. Kurt	1.741
Skewness	.546	S.E. Skew	.845
Range	29.500	Minimum	18.25
Maximum	47.75		

Valid observations - 6 Missing observations - 6

- -

Variable MVC mvc pre-fatigue

Mean	122.833	S.E. Mean	20.542
Std Dev	50.317	Variance	2531.767
Kurtosis	4.353	S.E. Kurt	1.741
Skewness	1.970	S.E. Skew	.845
Range	141.000	Minimum	80.00
Maximum	221.00		

Valid observations - 6 Missing observations - 6

	N	Mean	Std Dev	Minimum	Maximum
MVC_PRE	12	141.50000	47.19688	80.00	221.00
TASKTIME	12	16.08333	9.49122	6.00	32.00
GROUP	12	1.50000	.52223	1.00	2.00

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

MVC_PRE
by GROUP

Mean Rank	Cases	
4.83	6	GROUP = 1.00 CFS
8.17	6	GROUP = 2.00 control
	12	Total

	Exact	Corrected for ties

U	W	2-Tailed P	Z	2-Tailed P
8.0	29.0	.1320	-1.6041	.1087

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

TASKTIME time on task
by GROUP

Mean Rank	Cases	
5.58	6	GROUP = 1.00 CFS
7.42	6	GROUP = 2.00 control
	--	
	12	Total

		Exact		Corrected for ties
U	W	2-Tailed P	Z	2-Tailed P
12.5	33.5	.3939	-.8854	.3760

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

MVC_FAT MVC at end of fatigue protocol
by GROUP

Mean Rank	Cases	
5.67	6	GROUP = 1.00 CFS
7.33	6	GROUP = 2.00 control
	12	Total

U	W	Exact 2-Tailed P	Z	Corrected for ties 2-Tailed P
13.0	34.0	.4848	-.8006	.4233

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

MVC_PRE
by GROUP

Mean Rank	Cases	
4.83	6	GROUP = 1.00 CFS
8.17	6	GROUP = 2.00 control
	12	Total

U	W	Exact 2-Tailed P	Z	Corrected for ties 2-Tailed P
8.0	29.0	.1320	-1.6041	.1087

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

MVC_REC MVC post recovery
by GROUP

Mean Rank	Cases	
4.33	6	GROUP = 1.00 CFS
8.00	5	GROUP = 2.00 control
	11	Total

U	W	Exact 2-Tailed P	Z	Corrected for ties 2-Tailed P
5.0	40.0	.0823	-1.8257	.0679

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

MVCDROP % drop MVC due to fatigue protocol
by GROUP

Mean Rank	Cases	
5.58	6	GROUP = 1.00 CFS
7.42	6	GROUP = 2.00 control
	12	Total

U	W	Exact 2-Tailed P	Z	Corrected for ties 2-Tailed P
12.5	33.5	.3939	-.8838	.3768

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

STARTRPE RPE start fatigue
by GROUP

Mean Rank	Cases	
8.75	6	GROUP = 1.00 CFS
4.25	6	GROUP = 2.00 control
	12	Total

U	W	Exact 2-Tailed P	Z	Corrected for ties 2-Tailed P
4.5	52.5	.0260	-2.2249	.0261

	N	Mean	Std Dev	Minimum	Maximum
RATIO100	12	.30000	.09535	.20	.50
RATIO20	12	.71667	.76257	.20	3.00
RATIO40	12	.59167	.25746	.30	1.00
RATIO60	12	.68333	.27579	.30	1.10
RATIO80	12	.68333	.35633	.20	1.40
RATIO_ST	12	.48333	.19462	.30	.80
REP100	12	19.83333	.57735	18.00	20.00
RPE20	12	13.08333	1.83196	10.00	16.00
RPE40	12	15.91667	2.15146	12.00	18.00
RPE60	12	18.08333	1.56428	15.00	20.00
RPE80	12	19.41667	1.16450	16.00	20.00
RPESTART	12	10.16667	1.64225	8.00	14.00
SP100	12	142.91667	58.40370	79.00	262.00
SP20	12	117.75000	30.92844	65.00	171.00
SP40	12	127.33334	25.73407	90.00	184.00
SP60	12	124.66666	32.70900	77.00	193.00
SP80	12	128.83333	33.47953	85.00	190.00
SPSTART	12	112.91666	29.32718	87.00	189.00
GROUP	12	1.50000	.52223	1.00	2.00

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

RATIO100 twitch ratio at 100%
by GROUP

Mean Rank	Cases	
7.08	6	GROUP = 1.00 CFS
5.92	6	GROUP = 2.00 control
	12	Total

		Exact		Corrected for ties	
U	W	2-Tailed P	Z	2-Tailed P
14.5	42.5	.5887	-.5935	.5528

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

RATIO20 twitch ratio at 20%
by GROUP

Mean Rank	Cases	
5.00	6	GROUP = 1.00 CFS
8.00	6	GROUP = 2.00 control
	12	Total

		Exact		Corrected for ties	
U	W	2-Tailed P	Z	2-Tailed P
9.0	30.0	.1797	-1.4591	.1445

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

RATIO40 twitch ratio at 40%
by GROUP

Mean Rank	Cases	
5.75	6	GROUP = 1.00 CFS
7.25	6	GROUP = 2.00 control
	12	Total

		Exact		Corrected for ties	
U	W	2-Tailed P	Z	2-Tailed P
13.5	34.5	.4848	-.7416	.4583

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

RATIO60 twitch ratioa at 60%
by GROUP

Mean Rank	Cases	
4.17	6	GROUP = 1.00 CFS
8.83	6	GROUP = 2.00 control
	12	Total

U	W	Exact 2-Tailed P	Z	Corrected for ties 2-Tailed P
4.0	25.0	.0260	-2.2904	.0220

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

RATIO80 twitch ratio at 80%
by GROUP

Mean Rank	Cases	
4.42	6	GROUP = 1.00 CFS
8.58	6	GROUP = 2.00 control
	12	Total

U	W	Exact 2-Tailed P	Z	Corrected for ties 2-Tailed P
5.5	26.5	.0411	-2.0193	.0435

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

RATIO_ST twitch ratio at start
by GROUP

Mean Rank	Cases	
6.83	6	GROUP = 1.00 CFS
6.17	6	GROUP = 2.00 control
	12	Total

U	W	Exact 2-Tailed P	Z	Corrected for ties 2-Tailed P
16.0	41.0	.8182	-.3290	.7422

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

REP100 RPE at 100% TOT
by GROUP

Mean Rank	Cases	
7.00	6	GROUP = 1.00 CFS
6.00	6	GROUP = 2.00 control
	12	Total

U	W	Exact 2-Tailed P	Z	Corrected for ties 2-Tailed P
15.0	42.0	.6991	-1.0000	.3173

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

RPE20 RPE at 20% TOT
by GROUP

Mean Rank Cases

8.58 6 GROUP = 1.00 CFS
4.42 6 GROUP = 2.00 control
--
12 Total

		Exact	Corrected for ties	
U	W	2-Tailed P	Z	2-Tailed P
5.5	51.5	.0411	-2.0266	.0427

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

RPE40 RPE at 40% TOT
by GROUP

Mean Rank Cases

7.67 6 GROUP = 1.00 CFS
5.33 6 GROUP = 2.00 control
--
12 Total

		Exact	Corrected for ties	
U	W	2-Tailed P	Z	2-Tailed P
11.0	46.0	.3095	-1.1515	.2495

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

RPE60 RPe at 60% TOT
by GROUP

Mean Rank Cases

7.17 6 GROUP = 1.00 CFS
5.83 6 GROUP = 2.00 control
--
12 Total

		Exact	Corrected for ties	
U	W	2-Tailed P	Z	2-Tailed P
14.0	43.0	.5887	-.6556	.5121

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

RPE80 RPE at 80% TOT
by GROUP

Mean Rank Cases

6.67 6 GROUP = 1.00 CFS
6.33 6 GROUP = 2.00 control
--
12 Total

		Exact	Corrected for ties	
U	W	2-Tailed P	Z	2-Tailed P
17.0	40.0	.9372	-.1925	.8474

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

RPESTART RPE at start
by GROUP

Mean Rank Cases

8.75 6 GROUP = 1.00 CFS
4.25 6 GROUP = 2.00 control
--
12 Total

		Exact		Corrected for ties
U	W	2-Tailed P	Z	2-Tailed P
4.5	52.5	.0260	-2.2249	.0261

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

SP100 SP duration at 100% TOT
by GROUP

Mean Rank	Cases	
3.50	6	GROUP = 1.00 CFS
9.50	6	GROUP = 2.00 control
	12	Total

		Exact		Corrected for ties
U	W	2-Tailed P	Z	2-Tailed P
.0	21.0	.0022	-2.8823	.0039

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

SP20 SP duration at 20% TOT
by GROUP

Mean Rank	Cases	
4.92	6	GROUP = 1.00 CFS
8.08	6	GROUP = 2.00 control
	12	Total

		Exact		Corrected for ties
U	W	2-Tailed P	Z	2-Tailed P
8.5	29.5	.1320	-1.5239	.1275

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

SP40 SP duration at 40% TOT
by GROUP

Mean Rank	Cases	
3.50	6	GROUP = 1.00 CFS
9.50	6	GROUP = 2.00 control
	12	Total

		Exact		Corrected for ties
U	W	2-Tailed P	Z	2-Tailed P
.0	21.0	.0022	-2.8823	.0039

- - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

SP60 SP duration at 60% TOT
by GROUP

Mean Rank	Cases	
3.83	6	GROUP = 1.00 CFS
9.17	6	GROUP = 2.00 control
	12	Total

		Exact		Corrected for ties
U	W	2-Tailed P	Z	2-Tailed P
2.0	23.0	.0097	-2.5621	.0104

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

SP80 SP duration at 80% TOT
by GROUP

Mean Rank	Cases	
4.50	6	GROUP = 1.00 CFS
8.50	6	GROUP = 2.00 control
	12	Total

		Exact		Corrected for ties
U	W	2-Tailed P	Z	2-Tailed P
6.0	27.0	.0649	-1.9215	.0547

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

SPSTART SP duration at start
by GROUP

Mean Rank	Cases	
6.33	6	GROUP = 1.00 CFS
6.67	6	GROUP = 2.00 control
	12	Total

		Exact		Corrected for ties
U	W	2-Tailed P	Z	2-Tailed P
17.0	38.0	.9372	-.1601	.8728

	N	Mean	Std Dev	Minimum	Maximum
REP100	12	19.83333	.57735	18.00	20.00
RPE20	12	13.08333	1.83196	10.00	16.00
RPE40	12	15.91667	2.15146	12.00	18.00
RPE60	12	18.08333	1.56428	15.00	20.00
RPE80	12	19.41667	1.16450	16.00	20.00
RPESTART	12	10.16667	1.64225	8.00	14.00

- - - - - Friedman Two-Way Anova

Mean Rank	Variable	
5.58	REP100	RPE at 100% TOT
2.00	RPE20	RPE at 20% TOT
3.00	RPE40	RPE at 40% TOT
4.17	RPE60	RPe at 60% TOT
5.25	RPE80	RPE at 80% TOT
1.00	RPESTART	RPE at start

Cases	Chi-Square	D.F.	Significance
12	56.9048	5	.0000

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

SP100 SP duration at 100% TOT
by GROUP

Mean Rank	Cases	
3.50	6	GROUP = 1.00 CFS
9.50	6	GROUP = 2.00 control
	12	Total

U	W	Exact 2-Tailed P	Corrected for ties Z	Corrected for ties 2-Tailed P
.0	21.0	.0022	-2.8823	.0039

- - - - - Mann-Whitney U - Wilcoxon Rank Sum W Test

SPSTART SP duration at start
by GROUP

Mean Rank	Cases	
6.33	6	GROUP = 1.00 CFS
6.67	6	GROUP = 2.00 control
	12	Total

U	W	Exact 2-Tailed P	Corrected for ties Z	Corrected for ties 2-Tailed P
17.0	38.0	.9372	-.1601	.8728

- - Description of Subpopulations - -

Summaries of SPSTART SP duration at start
By levels of GROUP

Variable	Value	Label	Sum	Mean	Std Dev	Cases
For Entire Population			1355.00	112.9167	29.3272	12
GROUP	1.00	CFS	643.00	107.1667	18.2583	6
GROUP	2.00	control	712.00	118.6667	38.4638	6

Total Cases = 16
Missing Cases = 4 or 25.0 Pct

	N	Mean	Std Dev	Minimum	Maximum
MEP100	6	10.10500	3.86707	4.45	15.64
RATIO100	6	.28333	.09832	.20	.40
REP100	6	19.66667	.81650	18.00	20.00
SP100	6	186.33333	51.26662	126.00	262.00
MEPSTART	6	8.26000	5.91863	1.59	17.48
RATIO_0	6	.48333	.22286	.30	.80
RPE0.0	6	9.16667	1.16905	8.00	11.00
SPSTART	6	118.66666	38.46384	87.00	189.00

- - - - - Wilcoxon Matched-Pairs Signed-Ranks Test

MEP100 MEP at 100% TOT
with MEPSTART MEP at 0%

Mean Rank	Cases	
3.60	5	- Ranks (MEPSTART LT MEP100)
3.00	1	+ Ranks (MEPSTART GT MEP100)
	0	Ties (MEPSTART EQ MEP100)
	6	Total

Z = -1.5724 2-Tailed P = .1159

- - - - - Wilcoxon Matched-Pairs Signed-Ranks Test

```
     RATIO100  twitch ratio at 100%
with RATIO_0   twitch ratio at start
     Mean Rank    Cases

          2.00        2  - Ranks (RATIO_0 LT RATIO100)
          4.25        4  + Ranks (RATIO_0 GT RATIO100)
                      0    Ties  (RATIO_0 EQ RATIO100)
                     --
                      6    Total

         Z =   -1.3628           2-Tailed P =  .1730
```

- - - - - Wilcoxon Matched-Pairs Signed-Ranks Test

```
     REP100    RPE at 100% TOT
with RPE0.0    RPE at start
     Mean Rank    Cases

          3.50        6  - Ranks (RPE0.0 LT REP100)
           .00        0  + Ranks (RPE0.0 GT REP100)
                      0    Ties  (RPE0.0 EQ REP100)
                     --
                      6    Total

         Z =   -2.2014           2-Tailed P =  .0277
```

- - - - - Wilcoxon Matched-Pairs Signed-Ranks Test

```
     SP100     SP duration at 100% TOT
with SPSTART   SP duration at start
    Mean Rank    Cases

          3.50        6  - Ranks (SPSTART LT SP100)
           .00        0  + Ranks (SPSTART GT SP100)
                      0    Ties  (SPSTART EQ SP100)
                     --
                      6    Total

         Z =   -2.2014           2-Tailed P =  .0277
```



```
               N        Mean     Std Dev  Minimum  Maximum

RATIO100       6      .31667      .09832      .20      .50
REP100         6    20.00000      .00000    20.00    20.00
SP100          6    99.50000    18.75900    79.00   125.00
FINISH         6     6.36500     2.90962     2.70    10.12
RATIO_ST       6      .48333      .18348      .30      .80
RPESTART       6    11.16667     1.47196    10.00    14.00
SPSTART        6   107.16666    18.25833    88.00   140.00
MEPSTART       6     5.53167     2.44106     2.87     9.87
```

- - - - Wilcoxon Matched-Pairs Signed-Ranks Test

```
     RATIO100  twitch ratio at 100%
with RATIO_ST  twitch ratio at start
     Mean Rank    Cases

          2.50        1  - Ranks (RATIO_ST LT RATIO100)
          3.70        5  + Ranks (RATIO_ST GT RATIO100)
                      0    Ties  (RATIO_ST EQ RATIO100)
                     --
                      6    Total

         Z =   -1.6773           2-Tailed P =  .0935
```

- - - - - Wilcoxon Matched-Pairs Signed-Ranks Test

```
     REP100    RPE at 100% TOT
with RPESTART  RPE at start
     Mean Rank    Cases

          3.50        6  - Ranks (RPESTART LT REP100)
           .00        0  + Ranks (RPESTART GT REP100)
                      0    Ties  (RPESTART EQ REP100)
                     --
                      6    Total

         Z =   -2.2014           2-Tailed P =  .0277
```

- - - - - Wilcoxon Matched-Pairs Signed-Ranks Test

```
     SP100      SP duration at 100% TOT
with SPSTART    SP duration at start
     Mean Rank     Cases

          3.00         2   - Ranks (SPSTART LT SP100)
          3.75         4   + Ranks (SPSTART GT SP100)
                       0     Ties  (SPSTART EQ SP100)
                      --
                       6     Total

         Z =     -.9435            2-Tailed P =   .3454
```

- - - - - Wilcoxon Matched-Pairs Signed-Ranks Test

```
     FINISH     100% TOT
with MEPSTART   start
     Mean Rank     Cases

          4.00         3   - Ranks (MEPSTART LT FINISH)
          3.00         3   + Ranks (MEPSTART GT FINISH)
                       0     Ties  (MEPSTART EQ FINISH)
                      --
                       6     Total

         Z =     -.3145            2-Tailed P =   .7532
```

* * * * * * Analysis of Variance -- design 1 * * * * * *

Adjusted and Estimated Means
Variable .. MVC_PRE

CELL	Obs. Mean	Adj. Mean	Est. Mean	Raw Resid.	Std. Resid.
1	123.467	142.915	123.467	.000	.000
2	170.100	150.652	170.100	.000	.000

* * * * * * Analysis of Variance -- design 1 * * * * * *

Combined Adjusted Means for GROUP
Variable .. MVC_PRE

GROUP		
CFS	UNWGT.	142.91484
control	UNWGT.	150.65183

	N	Mean	Std Dev	Minimum	Maximum
MVC_PRE	11	144.66364	53.34859	80.00	226.80
MVC_FAT	11	74.09091	34.72891	28.30	148.30
MVC_REC	11	120.86364	60.53973	53.10	224.00

- - - - - Friedman Two-Way Anova

Mean Rank	Variable	
2.82	MVC_PRE	
1.00	MVC_FAT	MVC at end of fatigue protocol
2.18	MVC_REC	MVC post recovery

Cases	Chi-Square	D.F.	Significance
11	18.7273	2	.0001

	N	Mean	Std Dev	Minimum	Maximum
MVC_PRE	11	144.66364	53.34859	80.00	226.80
MVC_FAT	11	74.09091	34.72891	28.30	148.30
MVC_REC	11	120.86364	60.53973	53.10	224.00
GROUP	11	1.45455	.52223	1.00	2.00

	N	25th Percentile	(Median) 50th Percentile	75th Percentile
MVC_PRE	11	100.7000	118.0000	200.0000
MVC_FAT	11	48.2000	70.1000	95.8000
MVC_REC	11	81.6000	94.6000	166.6000
GROUP	11	1.0000	1.0000	2.0000

- - - - - Friedman Two-Way Anova

Mean Rank	Variable	
3.82	MVC_PRE	
2.00	MVC_FAT	MVC at end of fatigue protocol
3.18	MVC_REC	MVC post recovery
1.00	GROUP	

Cases	Chi-Square	D.F.	Significance
11	31.0364	3	.0000

APPENDIX G

History and Status of Participants in the CFS Group

code	CFS 1	☐ post-viral 6m - 2yr
DOB	10/12/67	☒ post-viral 2 - 5 yr
gender	F	☐ non-viral
Affected	5 years (2 badly)	☐ Psych
Diagnosed	2 years	☒ Acceptable
Physician	Dr Alistar Nuttall	
Address (Dr)	Beufort St, Inglewood, 6052	
Medication	Prothiadene (antiinflammatory)	
Symptom onset	Suspect recurring bouts of glandular fever triggered onset.	

code	CFS 2	☐ post-viral 6m - 2yr
DOB	3/12/48	☒ post-viral 2 - 5 yr
gender	M	☐ non-viral
Affected	3 yrs	☐ Psych
Diagnosed	3 yrs	☒ Acceptable
Physician	Dr Chris Denz	
Address (Dr)	Forest Chase	
Medication	Arourex (1200mg)	
Symptom onset	Lethargy, run down, concentration loss, out of sorts. Positive for Ross river, Glandular fever, Cytomega virus.	

code	CFS 3	☐ post-viral 6m - 2yr
DOB	24/10/49	☒ post-viral 2 - 5 yr
gender	F	☐ non-viral
Affected	4 yrs	☐ Psych
Diagnosed	4 yrs	☒ Acceptable
Physician	Dr Papaelias (gp)	
Address (Dr)		
Medication	Prozac	

Symptom onset

Exhaustion, sore throat, headaches, weak & shaky all day. Related to stress at work & following relation break up. Now single.

code	CFS 4	☒ post-viral 6m - 2yr
DOB	23/10/69	☐ post-viral 2 - 5 yr
gender	M	☐ non-viral
Affected	May 96	☐ Psych
Diagnosed	6/96	☒ Acceptable
Physician	Dr Chris Denz	
Address (Dr)	Forest Chase	
Medication	Tryptanol, vitamins.	

Symptom onset

Ross River virus onset May. nagging tiredness, chest pains (sternum), increasing tiredness, became bed ridden.

code	CFS 5	☒ post-viral 6m - 2yr
DOB	14/10/77	☐ post-viral 2 - 5 yr
gender	F	☐ non-viral
Affected	6 months	☐ Psych
Diagnosed	4 months	☒ Acceptable
Physician	Dr Chris Denz	
Address (Dr)	Forest Chase Medical Centre	
Medication	None	

Symptom onset

Recurring fatigue following glandular fever, headaches, fatigue, dizziness.

code	CFS 6	☒ post-viral 6m - 2yr
DOB	18/6/78	☐ post-viral 2 - 5 yr
gender	F	☐ non-viral
Affected	1 year	☐ Psych
Diagnosed	9 months	☒ Acceptable
Physician	Dr	
Address (Dr)		
Medication	Vitamin supplements	

Symptom onset

Glandular fever (3rd time), never seemed to recover.

APPENDIX H

Activity Index

Activity Index

Based on your regular daily activity, calculate your activity index by multiplying your score for each of the three categories (score = frequency x intensity x time)

Daily Activity	Score
Frequency	
Daily or almost daily	5
3 to 5 times per week	4
1 to 2 times per week	3
A few times per month	2
Less than once a month	1
Intensity	
Sustained heavy breathing and perspiration (running etc)	5
Intermittent heavy breathing and perspiration (tennis jogging)	4
Moderately heavy (recreation sports or cycling etc)	3
Moderate (softball, golf etc)	2
Light (fishing, walking etc)	1
Time	
Over 30 min	4
20 to 30 min	3
10 to 20 min	2
under 10 min	1

Total Score _____ X _____ X _____ = _____

Name _____

Height _____ Weight _____ Age _____

APPENDIX I

Data Collection Sheets

CFS BICEPS FATIGUE TEST

Patient..... dob.....

dot..... filename.....

comments

n-i..... i-a..... sapphire gain..... max rms.....

sites used..... threshold..... intensity.....

lever arm..... resting force..... MVC.....(20%.....)

min	PE	rms	comments