A Comparison of Subjective Self-Perceptions of Fatigue with Objective Measures

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A Comparison of Subjective Self-Perceptions of Fatigue with Objective Measures

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ABSTRACT

Background. Neuromuscular fatigue is defined as an exercise-induced reduction in producing force or power from a muscle or muscle group. The origins of exercise-induced fatigue can occur anywhere in the motor system – from the brain all the way through to the muscle. Therefore, to assess central and peripheral mechanisms of fatigue, investigators must be acutely aware of what their chosen fatigue measures actually reveal about the motor system. Although stimulation techniques such as transcranial magnetic stimulation (TMS) provide excellent insight into neuromuscular fatigue, they are mostly inappropriate to use in field settings and clinical environments. Instead, a practical way of assessing fatigue in these environments is to obtain self-reported assessments of fatigue, which may be in the form of fatigue and exertion scales. To date, there have been surprisingly few investigations that assess the relationship between quantifiable measures of motor fatigue and self-reported fatigue scales.

Methods. The purpose of this project was to determine the extent to which subjective measures can be used as predictors of objective measures in the analysis of neuromuscular fatigue. Twenty healthy volunteers participated in this study (age 23 ± 3 yr, 10 female). TMS-derived measurements provided objective measures of fatigue and characteristics of the neuromuscular response to the fatiguing task. The contraction protocol consisted of ten contraction blocks. Each contraction block was a low-intensity isometric 20% maximal voluntary contraction (MVC) elbow flexion that was held for 2 min. Following each 2 min, participants immediately performed an MVC, a 75% MVC, and a 50% MVC. During each of these graded contractions, a cortical stimulation and a brachial plexus stimulation was delivered to the participant. Five subjective measures of fatigue were collected during each contraction block. These measures were a visual analogue scale, a Likert scale, an omnibus scale, a rating of perceived exertion

scale (RPE), and a rating of fatigue scale. Linear mixed-effects models were used as the basis of predictive models, so the subjective scale which best predicted TMS-derived variables could be identified.

Results. MVC torque and voluntary activation (VA) were lower from the second contraction block onwards, and resting twitch torque was lower from the fourth block onwards. Therefore, the contraction protocol was able to induce a significant level of fatigue (MVC), which had significant contributions from central (VA) and peripheral (resting twitch) mechanisms. This provided a good foundation to determine what mechanism of fatigue each subjective scale aligned to. Overall, there were marked similarities for all scales to predict quantitative measures of fatigue, where no scale clearly outperformed or provided greater prediction capability over others. However, there were scales that were marginally better than others. In particular, RPE appeared to be a good predictor of MVC torque, and the number of contractions performed in the protocol appeared to be a good predictor of VA, resting twitch torque and MEP amplitude.

Conclusions. Given the prevalence of exercise investigations that use TMS measures, of self-reported measures of neuromuscular fatigue, it is not surprising that each assessment tool in this project was able to characterise fatigue during the contraction protocol. However, it was unexpected that an individual's perception of fatigue did not have a clear alignment with quantitative measures of the motor pathway. It is clear that the additional supraspinal factor, other than activation of the motor pathway, influences the ability to perform exercise over time.

STATEMENT OF ORIGINALITY

"This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself."

Signed

15/10/2021

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1.0 INTRODUCTION

1.1 Background

Neuromuscular fatigue is defined as an exercise-induced reduction in the ability to produce force or power from a muscle or muscle group (Taylor, 2016). Neuromuscular fatigue can originate from different regions across the motor pathway, from the brain to the muscle (Bigland-Ritchie et al.,1978). Peripheral fatigue originates from the peripheral nervous system, beyond the neuromuscular junction, and relates to the contractility of the muscle itself. In contrast, central fatigue, also known as supraspinal fatigue, originates from the central nervous system and alpha motor neurons of the spinal cord (Kirkendall, 1990). Central fatigue is characterised by the inability of the brain and spinal cord to voluntary activate muscles in order to produce force. Therefore, central fatigue impacts the ability of the central nervous system to activate muscle fibres through voluntary contractions. (Post et al., 2009). Increased central nervous system inhibition is evident with the progression of fatigue which can be modelled by changes in the length of the silent period. This change is bought about by increases in intracortical inhibition of the descending drive, which leads to net increases in inhibition to corticospinal neurons and inhibition at a spinal level (Paci et al., 2021).

Magnetic and electrical stimulation provide non-invasive assessment of neuromuscular fatigue origins and insight into the characteristics of the nervous system (Millet et al., 2012). Motor evoked potentials (MEPs) via transcranial magnetic stimulation (TMS) can be used as an indicator of corticospinal excitability, where the amplitude of the MEP reflects excitation of both upper and lower motor neurons. In addition, the silent period is used to study cortical inhibitory response, where an elongation in the silent period is often attributed to inhibitory GABAergic activity (Epstein et al., 2012; Suyama, Shindo, & Iizuka, 1996). If TMS-evoked twitch responses are measured with respect to the additional amount of force that can be generated in a muscle following stimulation, TMS offers a useful tool to assess the ability of

the nervous system to activate muscle. Voluntary activation (VA) is an indicator of the ability of the central nervous system to voluntarily drive muscle activation in order to produce maximal force. VA can be assessed by motor nerve stimulation, where increments in twitch force during maximal voluntary contractions (MVC) suggests that some motor units may not be recruited and/or some motor units are not firing fast enough for muscle fibres to develop force. In contrast, increments in twitch force evoked with TMS during MVC indicates that supraspinal mechanisms contributed to reduced activation of the muscle. Hence, if motor cortical stimulation evokes a superimposed twitch during MVC, there is insufficient output from the cortex to drive spinal motor neurons.

Although stimulation techniques provide excellent insight into neuromuscular fatigue, they are mostly inappropriate to use in-field settings and clinical environments. Instead, a practical way of assessing fatigue in these environments is to obtain self-reported assessments of fatigue (Dittner et al., 2004). A review of literature has revealed that there are five scales that are commonly used in exercise studies to gauge self-reported fatigue: the Likert scale, rating of perceived fatigue, visual analogue scale of fatigue, ratings of perceived effort, and the omnibus fatigue scale. The results of each scale are dependent on the participants understanding and interpretation of the scale as well as their own conscious perception of fatigue and exertion (Rees et al., 2002; Searle, 1998). Unlike TMS-based measurements, subjective reports of effort and fatigue are not simply restricted to the direct corticospinal pathway. Instead, there is considerable influence from other factors which often fall under the umbrella term of ‘perception’ such as cognitive-emotional interactions, corollary discharge, homeostasis and psychological state (De Morree et al., 2012; Greenhouse-Tucknott et al., 2020; Kluger et al., 2013). Perceived fatigability is distinguished from performance fatigability by the possibility of its existence in resting states; where elevations on perceived fatigability can be attributed to homeostasis modulating factors such as blood glucose, core temperature, hydration,

metabolites, and oxygenation, and psychological modulating factors such as executive function, expectation, mood, and motivation (Enoka & Duchateau, 2016; Kluger et al., 2013).

1.2 Statement of the problem

Few studies investigate the direct relationship between quantifiable measures of fatigue and subjective measures of fatigue. Most review investigations explore the validation of individual scales (Chen et al., 2002; Haddad et al., 2017;). However, some studies compare individual scale results to the outcome of fatiguing tasks (Leung et al., 2004; Micklewright et al., 2017; Naclerio et al., 2011; Zamunér et al., 2011). There have been no investigations that directly compare objective, quantifiable measures to multiple subjective measures in the context of studying neuromuscular fatigue. A method of further understanding the relationship between fatigue and self-reported measures of fatigue is to perform predictive modelling analysis. Predictive models are a type of mathematical model that assess the ability of one variable (predictor) to predict or account for variability in another variable (Ding et al., 2000). If the primary interest of an investigation is to investigate which subjective scale, from a set of five common scales, best predicts TMS-derived variables obtained during single limb fatiguing exercise, there are a set of procedures that can be adhered to. Firstly, changes in neuromuscular variables and ratings on the subjective scales can be quantified during the performance of an exercise task. Secondly, five models can be fitted to variables including MVC torque, VA, and resting twitch torque data (torque-derived variables) and root mean square electromyography (RMS EMG), MEP/Mmax area, and silent period duration (EMG-derived variables) where Mmax is the maximum compound action potential (Berger et al., 2010). Each model would include a different subjective scale as a predictor variable. The five models can then be ranked according to their predictive performance to identify the best fitting model of the TMS-related data.

1.3 Purpose of the study

The purpose of this study is to determine the extent to which subjective measures can be used as predictors of objective measures in the analysis of neuromuscular fatigue. TMS-derived measurements will provide objective measures of fatigue and characteristics of the neuromuscular response to the fatiguing task. The self-reported scales will present each subject's subjective perception of fatigue throughout the fatiguing task. Together both measures will be compared to assess the usefulness of a predictive model in the assessment of neuromuscular fatigue. To address this purpose, five psychomotor measures of fatigue will be correlated to TMS-derived objective measures of fatigue throughout a submaximal elbow flexion fatiguing task.

1.4 Aims and hypotheses

There are three aims in this study. During a repeated low-intensity isometric elbow flexion task completed by healthy young adults, this study aims to:

1. To examine how the fatiguing task influenced objective measurements of neuromuscular fatigue derived from force output and TMS.
2. To assess how the fatigue task influenced subjective measures of fatigue and effort derived from the 5 self-reported scales.
3. To determine which self-reported fatigue scale best predicts force and TMS-derived variables using linear mixed-effects models.

There are three hypotheses in this study that align with the aims. It was hypothesised that:

1. Objective measures of neuromuscular fatigue will indicate the progression of fatigue throughout the exercise task, where a decline in level of VA and an increase in MEPs will be observed.
2. Self-reports of neuromuscular fatigue, including the Likert scale, rating of perceived fatigue, visual analogue scale of fatigue, ratings of perceived effort, and the omnibus fatigue scale, will all be able to detect the occurrence of fatigue during the exercise task.
3. Ratings of perceived exertion, the most common self-report of exercise-induced fatigue, will be the best predictor of declines in MVC torque, VA, and MEP amplitude.

1.5 Significance of the study

This study will identify the scales which are the greatest predictors of neuromuscular fatigue. If certain scales do not align with quantitative measures of fatigue, their use in future studies may not be appropriate. This will provide guidance for the future selection of psychomotor scales for the assessment of neuromuscular fatigue. Furthermore, if certain scales strongly align with either central or peripheral mechanisms of fatigue, this study will be foundational for future research into the alignment of psychomotor scales with central and peripheral fatigue. These results will be foundational to exercise physiologists, neuroscientists and researchers who frequently employ fatiguing protocols, scales of fatigue, and quantifiable measures of fatigue. These findings will also assist in practical contexts where measurements of neuromuscular fatigue would bebeneficial and a laboratory setting in not accessible. These contexts may include rehabilitation, field-based exercise and physiotherapy. Also, the findings of this study will indicate the accuaracy and necessity for neuroscience laboratories in measuring neuromuscular fatige. If subjective measures are able to produce a strong predictive

model, this study has the potential to make the measurement of neuromuscular fatigue more accessible and practical, particularly within sporting settings.

2.0 LITERATURE REVIEW

This literature review aims to present the current literature on the topics that this investigation uses to explore the measurement and perception of neuromuscular fatigue. Figure 2.1 presents a visual overview of the literature review. The literature review explores the following topics, muscle activation, organisation of skeletal muscle, motor unit activation during exercise, muscle afferent activity during exercise, different contraction modalities causing different fatigue responses, quantitative assessments of central and peripheral fatigue during exercise, perception of fatigue, fatigue scales commonly used to assess exercise-induced fatigue and predictive modelling.

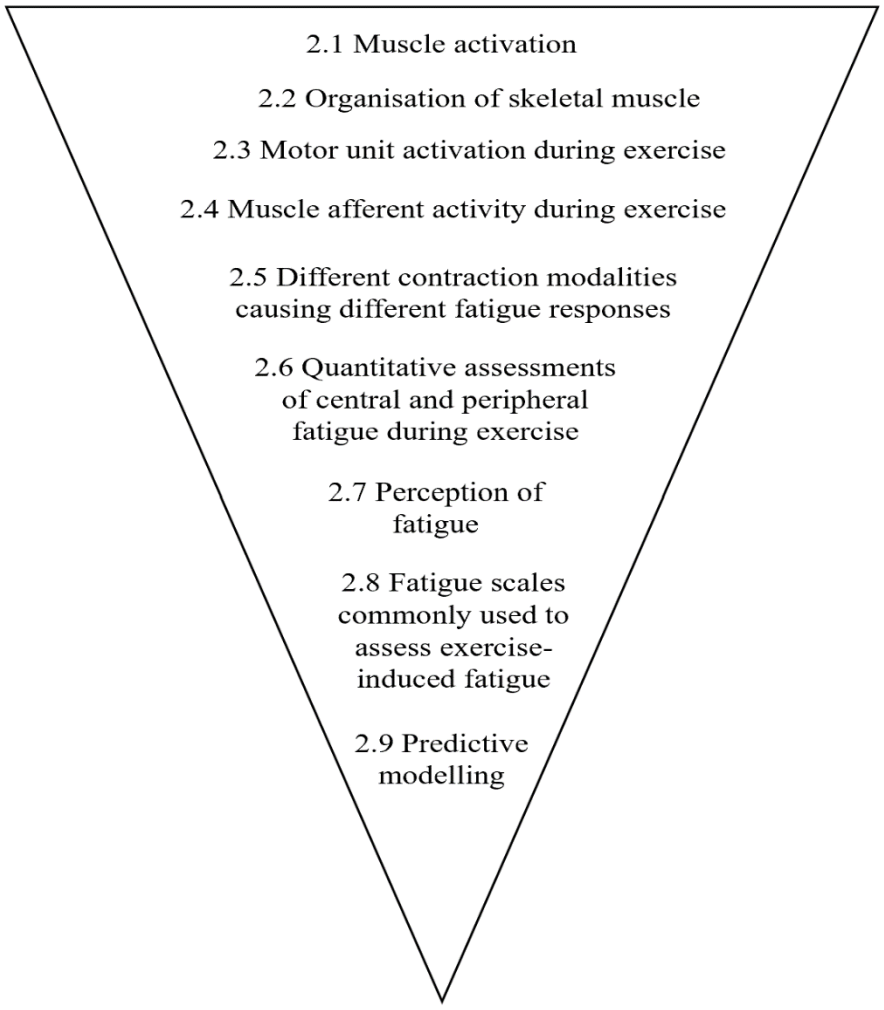

Figure 2.1. Overview of literature review. This Diagram illustrates the topics explored in the literature review.

2.1 Activation of muscle

The direct motor pathway originates in the motor cortex, where an electrical signal travels through the central nervous system to the peripheral nervous system and finally concludes at a muscle. This pathway is used to produce voluntary movement. The motor cortex is located in the frontal lobe of the brain, anterior to the central sulcus. Within the motor cortex, the premotor cortex and the primary motor cortex organise and control movement. The outer layer of the motor cortex is comprised of grey matter and the inner layer is comprised of white matter. Grey matter contains neural cell bodies, dendrites, axon terminals and unmyelinated axons whereas, white matter contains myelinated axons. The initiation of motor signals and the occurrence of synapses take place within grey matter. Myelin sheath, which is primarily found in white matter, is an electrical insulator found around axons. It facilitates the conduction of electrical signals; thus, the transfer of information primarily occurs within white matter (Stadelmann, 2019). Output of the motor pathway can be altered by afferent/reflexive facilitation and inhibition of interneuron populations. For VA of skeletal muscle, the motor cortex initiates action potentials through neural networks in the outer layers of the cortex comprised of grey matter. These travel through deeper layers of the cortex composed of white matter, the corticospinal tract, brainstem and lateral descending pathway where motor neurons and interneurons innervate skeletal muscle (Cuevas, 2007).

The descending neuromodulator system plays a key role in the excitation and inhibition of motor neurons (Johnson et al., 2014). This effect is determined by the release and reception of neurotransmitters, which are synthesised within the cell body. Serotonin, dopamine, and noradrenalin are monoamines that signal transduction between neurons and exercise-induced changes in the concentration of neurotransmitters (Taylor, 2017). The effect of serotonin and dopamine on neurons has been linked to central fatigue (Bigland-Ritchie et al., 1978). The central fatigue hypothesis indicates that increases in brain serotonin concentration induce

negative effects on arousal, sleepiness, mood, and lethargy (Newsholme et al., 1987). Cotel et al (2013) identified that central fatigue is caused by serotonin, indirectly, by the spilling over of serotonin from receptors on dendrites to receptors located on the axon initial segment. Thereby indirectly causing activation in 5-HT1A receptors leading to inhibition of firing and muscle contraction. The cellular mechanism of this process is unknown (Cotel et al., 2013). Davis and Bailey (1997) developed Newsholme's central fatigue hypothesis to suggest that the effect of neurotransmitters is not based on individual concentrations but rather on ratios of different neurotransmitters. Where a high serotonin to dopamine ratio is associated with a sense of tiredness, lethargy, and acceleration of the onset of fatigue. On the other hand, lower ratios favour improvements in performance by maintaining motivation and arousal (Davis & Bailey, 1997). The release of neurotransmitter acetylcholine is caused by the relay of action potentials that reach axon terminals and cause depolarisation, and thereby voltage gated calcium channels to open, causing an influx of calcium. The release of calcium causes the release of acetylcholine into the synaptic cleft. The release of acetylcholine results in binding to receptors on the surface of muscles, thereby causing the depolarisation and the entry of sodium/calcium ions through associated channels. The presence of sodium/calcium ions shift the resting membrane potential to become more positive, resulting in an action potential and the activation of the muscle contractile apparatus (Kuo & Ehrlich 2015; Sam, 2021). Some studies suggest that noradrenalin contributes to the development of supraspinal fatigue after prolonged exercise in temperate conditions (Klass et al., 2012; Roelands et al., 2008). Exhaustive exercise has been shown to increase the concentration of ammonia and glutamine in the brain, which are gamma-aminobutyric acid (GABA) precursors. GABA is a neurotransmitter of the central nervous system which has an inhibitory effect by decreasing the release of acetylcholine at nerve endings. Studies have shown a relationship between neurotransmitters and excitatory amino acids such as glutamate and GABA exists with central fatigue (Guezennec et al., 1998;

Malomouzh et al., 2015). Thus, the development of neuromuscular fatigue is impacted by the excitatory and inhibitory interactions of both neurotransmitters and neuromodulators (Johnson et al., 2014).

2.2 Organisation of skeletal muscle

Skeletal muscles fibres are organised into parallel bundles termed fasciculi. Fasciculi contain fascicles. Each fascicle contains muscle fibres which house contractile filaments arranged in a parallel or series configuration. Muscle fibres contain myofibrils that are comprised of actin and myosin fibres. Actin and myosin fibres make up contractile units known as sarcomeres. Bundles of myofibrils are arranged in a striated pattern, forming sarcomeres, the fundamental contractile units of skeletal muscle. With the release of calcium ions, as a result of action potential propagation, myosin heads attach to actin fibres in order to form cross-bridges. These cross bridges exert a force causing an overlap and shortening of muscle fibre length, summating to muscle contraction. Troponin C, I, T are the main regulatory proteins for the sliding mechanism of myofilaments which lead to contraction. Titin and nebulin protein contribute to the mechanical properties of muscle. T-tubules function to conduct neuronal action potentials to the muscle cell interior through invaginations of the sarcolemma. The widespread structure functions to enhance the uniformity and coordination of muscle contraction. Muscles fibres are innervated by motor neurons. The cell bodies of motor neurons are clustered within the motor nucleus, located in the spinal cord. A motor unit is comprised of a single motor nerve and all the muscle fibres it innervates (Kirk, Gilmore, Stashuk, Doherty, & Rice, 2019). Motor neurons and muscle fibres are connected to chemical synapses known as end plates; these extend across the entire muscle fibres forming a neuromuscular synapse. Neurotransmitters such as

acetylcholine are released at this synapse for depolarisation and propagation of action potentials across the sarcolemma, causing contraction of muscle fibres (Mukund, 2020).

There are two primary types of skeletal muscle fibres, slow and fast twitch. This distinction is made by the density of myosin heavy chain (MYH) isoforms present. Slow twitch fibres are known as Type 1, whereas fast twitch fibres are known as Type 2. The expression of MYH gene leads to further classification of fast twitch fibres into Type 2A, 2X and 2B. Hybrid expression of MYH allows for further subdivision into 1/2A, 2A/2X, 2X/2B. These subdivisions have a wide variety of adenosine triphosphate (ATP) usage and muscle contraction speed. Type 2B is the fastest, whereas Type 1 fibres are the slowest. Oxidative metabolism is primarily used for Type 1 and 2A fibres, whilst glycolytic metabolism is the primary energy source for Type 2X and 2B. Variation between fibre types and energy usage exist; for this reason, energy use is not an objective predictor of fibre type (Liu et al., 2012). MYH expression, cellular metabolism, sarcomere contractile machinery (fast and slow tropomyosin isoforms) are all contributing factors to the identity of fibre types. Human skeletal muscles group usually contain a mixture of different fibre types. However, certain muscles usually have dominant muscle fibre types (i.e., the triceps brachii muscle is predominantly made up of Type 2 fibres). Skeletal muscles have the power to remodel their phenotypes in order to adapt to different uses. For example, endurance training can cause increases in the presence of Type 1 fibres (Talbot et al., 2016).

2.3 Motor unit activity during exercise

A motor unit is the single motor nerve and all the muscle fibres it innervates (Kirk et al., 2019). The cross-sectional area, specific tension of the muscle fibres and the innervation ratio all

dictate the tension and force produced by a single motor unit. The innervation ratio of a motor unit is the average number of muscle fibres in contact with the motor unit, therefore indicating the density of innervation (Bodine et al., 1987). The recruitment of motor units occurs in an orderly fashion where the sequence of recruitment occurs from smallest to largest (Dideriksen & Farina, 2013; Senn et al., 1997). The firing rate of active motor neurons also dictates the force of contraction. Changing firing rates of motor units is termed 'rate coding'. The recruitment of motor units and their rate coding are largely dependent on the contraction type and size of active muscle tissue. Larger muscles such as the biceps brachii, have been shown to continuously use motor recruitment for force ranges up to 80% MVC (De Luca et al., 1982; Linnamo et al., 2003), whilst rate coding usually comes into effect with higher force outputs. Whereas smaller muscles are expected to reach maximal motor unit recruitment at lower force outputs, and therefore, rate coding becomes more prominent at a much lower point in the force spectrum (Conwit et al.,1999).

Gradual declines in discharge rate during exercise reduce the occurrence of muscle activation failure; this is a functional advantage (Enoka & Duchateau 2008; Torres-Peralta et al., 2016). As a result of the decrease in relaxation rate of twitches and the increase in twitch duration with the occurrence of fatigue, the same level of fusion inducing a tetanus contraction can be achieved at a lower rate of activation (Enoka et al., 2007). The slowing of motor unit discharge rate is often a useful adaptation to fatigue when contractions are of a continuous nature. In such a case high motor neuron discharge rates may lead to a block at the neuromuscular junction (Taylor et al., 2000). During submaximal contraction, the firing of a motor unit does not always decline, but rather, the recruited units usually show an increase in discharge rate (Carpentier et al., 2001; Garland et al., 1994; Kuchinad et al., 2004; Nordstrom & Miles, 1991). Overall, it can be concluded that the changes in motor unit recruitment and firing rate vary across different populations and different contraction types (Barry & Enoka, 2007). In addition, observations

of different types of loads and their influence on the time to failure of a task across different postures and limbs suggest that changes in motor unit activity are used by the nervous system as a control strategy to accommodate different loads. (Barry & Enoka, 2007).

2.4 Muscle afferent activity during exercise

Muscle afferents are classified in accordance with their function and conduction velocity of fibres. Group Ia and group II afferents innervate muscle spindles and signal for changes in muscle length (Kröger & Watkins 2021; Smilde et al., 2016). Group Ib afferents innervate Golgi tendon organs, which are arranged in series to muscle fibres. Muscle spindles detect the change in length and velocity of change of muscle fibres. In contrast, GTO detect tension development in the tendons of muscles. Non-spindle Group II fibres as well as a sub-population of Group III fibres (thinly myelinated) are mechanically sensitive. Therefore, they respond to mechanical properties of a shortening or lengthening muscle. Group IV and a sub-population of Group III fibres function to respond to noxious levels of mechanical strain and metabolites produced with exercise. The effect of fatigue on the discharge of afferents depends on the type of fatiguing task (Enoka & Duchateau 2017; Hunter, 2018). Investigations of humans have shown sustained submaximal contractions result in a decrease in the firing fate of Ia fibres (Macefield et al., 1991). Dynamic contractions result in a decrease in the firing of spindles, with faster contractions resulting in reductions in muscle spindle activity (Al Falahe et al., 1990; Burke et al., 1978). It is unclear whether the Ia afferents show increased sensitivity to muscle stretch as a result of fatiguing contractions or thixotropy of intrafusal muscle fibres. Throughout sustained submaximal contractions the firing of mechanically sensitive non-spindle group II and II afferents tends to decrease after the initial response to contraction. Although, if a submaximal contraction is sustained for several minutes, the firing rate will

increase again (Hayward et al., 1991). The firing of Golgi tendon organs is thought to be altered during fatiguing tasks as a result of changes in motor unit recruitment. Previous studies have indicated that following strong contractions, stretch sensitivity of Golgi tendon organs decreases for 15-30s whilst the discharge rate is decreased by 50% for the same level of force production (Hutton & Nelson 1986; Thompson et al., 1990).

2.5 Different contraction modalities cause different fatigue responses

The concept of task dependency and its influence on fatigue indicated that muscle fatigue is caused by a combination of mechanisms and that the main cause of fatigue differs between different contraction tasks. Subject motivations, contraction intensity and duration of contraction, as well as continuous or intermittent nature of tasks, have been found to influence levels of fatigue (Barry et al., 2007). Intermittent contractions demonstrate a slower development of central fatigue than sustained contractions (Bilodeau, 2006). Similarly, submaximal contractions model a slow development of both central and peripheral fatigue as muscle failure is compensated by increases in neural drive (Taylor & Gandevia, 2008). With the use of TMS, previous research has indicated that motor neurons become less responsive to synaptic input and descending drive becomes suboptimal with sustained maximal contractions (Todd et al., 2003; Tran, 2021). The occurrence of central fatigue development can be identified during brief maximal efforts throughout a submaximal contraction task. For this reason, maximal contractions are often combined with submaximal fatiguing protocols for the demonstration of changes in supraspinal fatigue (Taylor & Gandevia, 2008; Taylor et al., 2008). Sustained isometric submaximal contractions cause a progressive increase in motor neuron pool excitation as descending drive increases. This can be indicated by increases in surface EMG and MEPs by TMS stimulations. In contrast, maximal contractions model the fastest time to fatigue since neural drive cannot be compensated, thus resulting in rapid muscle

failure. Maximal contractions can be used to illustrate the progression of supraspinal fatigue by monitoring voluntary drive (Todd et al., 2003).

2.6 Quantitative assessment of central and peripheral fatigue during exercise

Central fatigue is defined as a progressive reduction in VA of muscle during exercise. It is characterised by the inability of the brain and spinal cord to voluntary activate muscle or produce neural drive therefore causing the inability to produce or maintain force (Gandevia, 2001). Peripheral fatigue originates at or beyond the neuromuscular junction and is characterised by a decline in force production as a result of muscle failure (Nordlund et al., 2004). Peripheral fatigue occurs within muscle, it has components related to the neuromuscular junction and terminal branches of the motor axons (Taylor et al., 2000). Peripheral fatigue can be defined as a decline in skeletal muscle capacity to produce force as a result of action potential failure, excitation-contraction coupling failure, or the impairment of cross-bridge cycling, which takes place in the presence of unchanged or increasing neural drive (Häkkinen, & Komi, 1983). The delineation between central and peripheral factors is often unclear since each region of the nervous system impacts the other. Perhaps the best example of this is the role of afferents during exercise. The feedback of peripheral group III and IV muscle afferents during fatiguing exercise leads to the impairment of the output from spinal motor neurons, thereby compromising voluntary muscle activation and exercise performance (Taylor et al., 2016). Investigations where a blood pressure cuff was applied to the arm after exercise to trap metabolites in the elbow flexors and thereby maintaining afferent feedback of group III and IV fibres during post exercise rest, modelled delayed recovery in both motor neuronal output and VA. In effect, indicating the role of afferent feedback with ischemia on central fatigue (Gandevia et al., 1996).

The use of paired stimulation techniques at cortical and peripheral levels during maximal and submaximal contractions can be used to decipher between types of fatigue (Wan et al., 2017). The progression of fatigue can be quantified using magnetic and electrical stimulations at the motor cortex and brachial plexus. TMS provides a measure of fatigue throughout the entire motor pathway by stimulating both central and peripheral components. Contrary to this, brachial plexus stimulations apply a stimulus to the peripheral components of the motor pathway. For this reason, when TMS and brachial plexus stimulations are paired, the resulting data distinguishes central and peripheral fatigue progression. Electrical stimulation of the brachial plexus follows the concept where supramaximal stimulation of a motor nerve is used to distinguish fatigue into the following. The first component is peripheral fatigue which is distinguished with exercise-related changes distal to the site of stimulation; these are observed as decreases in twitches or tetanic force caused by the stimulus take place (Taylor et al., 2000). The second exercise related change distinguished by brachial plexus stimulation is central fatigue. It occurs proximal to the motor axon and leads to failure in VA and a decline in MVC force (Gandevia et al., 1995). The final component is the use of brachial plexus stimulation to assess the maximal compound action potential, which is used to normalise MEP responses (Collins et al., 2017).

Measurements of superimposed twitches are utilised to determine the extent of submaximal activation during maximal voluntary contraction (MVC) where the output of the motor cortex is suboptimal to drive the muscle maximally. Superimposed twitch or the increment in force observed in the force trace with magnetic stimulation is used as an indicator of supraspinal fatigue to model the maximal evocable force of the muscle with the use of stimulation (Gandevia, 2001). Increases in superimposed twitch with exercise indicate declines in voluntary activation (Gandevia et al., 2013). This occurs as a result of the absence of some motor unit recruitment either as a result of decreases in voluntary effort to because of a decrease

in suboptimal firing rate of motor neurons in order to achieve maximal force output (Bowden et al., 2014; Gandevia et al., 2013). Superimposed twitches can be analysed by measuring the peak to peak amplitude generated by TMS stimulus during MVC. This measure is often used to indicate central fatigue since it illustrates the suboptimal voluntary recruitment of axons or their discharging at sub tetanic rates (Gandevia, McNeil, Carroll, & Taylor, 2013). Increasing amplitude of a superimposed twitch indicates the development of central fatigue.

Level of VA is often used to quantify the development of central fatigue. VA is quantified as a fraction of superimposed twitch over the estimated resting twitch torque (Thomas, Woods, & Bigland-Ritchie, 1989). VA is expected to decline with neuromuscular fatigue as a combined effect of increasing superimposed twitch and decreasing resting twitch. The measure is calculated with the following formula LoVA%= (1- ST/RT) X 100. Where, the product of superimposed twitch divided by resting twitch (ST/RT) is subtracted from 1, then multiplied by 100 to give a percentage of activation. Level of VA is expected to be greatest in unfatigued states.

With progression of fatigue, level of VA is expected to decline as excitability of the motor system and the ability to maintain force is lost (Gandevia et al., 1998). Progressive declines in VA as a result of exercise are indicators on central fatigue. Previous investigations have shown a fall in VA from 100% to 90% and an approximate 50% decline in MVC over a 3-minute MVC of biceps brachii (Gandevia et al., 1996). On the other hand, resting twitches are generated by an electrical stimulus in the potentiated muscle at rest (Toien et al., 2018). Resting twitches indicate peripheral fatigue. A reduction in resting twitch amplitude indicates the development of peripheral fatigue. Estimation of resting twitch from two or three contractions has been found to be reliable over time and characterised by low variability (Todd et al., 2004). The twitch interpolation method was first proposed by Merton (1954). It is inappropriate to use cortical stimulations at rest to produce a resting twitch since motor cortical and spinal

excitability increase with activity, also since different motor neuronal outputs are evoked in resting states (Todd et al., 2003; Todd et al., 2004). For this reason, the twitch interpolation method is used to estimate resting twitch. Estimated resting twitch torque can be extrapolated during a contraction task above 50% MVC (Todd, Taylor, & Gandevia, 2004).

Exercise-induced fatigue can also be characterised by changes in the EMG signal following TMS administration. Motor evoked potentials (MEPs) are short latency responses to stimulation where their amplitude is influenced by excitability of the cortical and corticospinal neurons, the state of the motorneuron and by the muscle fibre action potential. Both submaximal sustained and intermittent exercise cause enlargement of MEP (Ljubisavljevic et al., 1996; McKay et al., 1996; Sacco et al., 1997; Taylor et al., 1996). The area of motor evoked potentials is normalised to the area of maximum compound action potentials (Mmax) evoked via brachial plexus stimulation. A comparison of cortical and motor point stimulation together allow for the distinction between central and peripheral fatigue since motor nerve stimulation reveals impaired VA (Taylor, 2016). The interruption of EMG activity that follows MEPs is known as the silent period. The silent period represents intracortical inhibition. Increases in silent period duration are characteristic or neuromuscular fatigue. Silent periods are brought about by the inhibition of cortical drive with the activation of inhibitory neurons within the cortex. The duration of silent periods is expected to increase progressively with the development of neuromuscular fatigue (Pereira et al., 2012).

2.7 Perception of fatigue

Kluger et al. (2013) proposed a new taxonomy for fatigue dichotomised into independent attributes, perceived fatigability and performance fatigability. Perceived fatigability is broken down into homeostasis and psychological state. Homeostasis relates to blood glucose, core

temperature, hydration, neurotransmitters, metabolites, oxygenation and wakefulness. Psychological state refers to arousal, executive function, expectations, mood, motivation, pain, performance, feedback. Performance fatigability is broken down into the contractile function and muscle activation. Contractile function refers to calcium kinetics, force capacity, blood flow, metabolism, and products. Muscle activation refers to voluntary activation, activation patterns, motor neurons, afferent feedback as well as neuromuscular propagation. Unlike performance fatigability, perceived fatigability can also be assessed in resting states, where elevations in perceived fatigability are attributed to modulating factors such as those for homeostasis and psychological state (Enoka & Duchateau, 2016). Exercise-induced hypoglycaemia has been shown to attenuate activation of the central nervous system for prolonged exercise (Mata et al., 2019; Nybo, 2003). Some studies attribute this effect to reduced substrate delivery to the brain; particularly the motor cortex and regions involved in cardiorespiratory regulation (Delp et al., 2001). Where endothelial glucose becomes rate limiting for the cerebral metabolic rate of glucose when the arterial glucose concentration is below the critical point of 3.6mM (Boyle, P. J et al.,1994). Koslowski et al. (1981) indicate the importance of cerebral carbohydrate availability in the prevention of central fatigue with a study that used glucose infusion directly into the carotid artery to model a delay in fatigue. The effect of psychological state on fatigue and improvements in performance has been indicated by previous studies (McCormick et al., 2015). Methodological concerns associated with scales for the measurement of fatigue highlight the importance of clarity in definitions and understanding differences within levels of each scale (Halperin & Emanuel, 2020). The emphasis on clarity of definitions is to allow for a valid basis of comparison for results. Understanding differences between levels in scales is a methodological concern since some scales do not provide clear differences between levels, in effect leaving subjects more prone to providing inaccurate results.

2.8 Fatigue scales commonly used to assess exercise-induced fatigue

Likert Scale. The advent of the Likert scale occurred in 1932 with a 5-point scale presented by American social scientist Rensis Likert. The Likert scale was designed to group definable attitudes into clustered responses in order to measure agreeableness to a statement. The 7-point Likert scale is a modified version that uses symmetric positioning where the neural response is positioned between two extremes in an interval fashion. The 7-point scale is a variation of the 5-point scale. It provides more gradual responses compared to the 5-point scale, therefore providing responders with greater independence to select corresponding responses. The modified 7-point scale is considered superior to the 5-point scale since the increased number of response options provide an increased probability to reflect the objective reality. Rescaling studies have found that scales with more response options yield slightly lower scores relative to the upper limit of the scale. However, there is no major statistical difference between results of 5-, 7- or 10-point scales (Dawes, 2007). Numerical values from one to seven are assigned to corresponding responses. Zero is not used since it can be used to indicate neutrality as opposed to agreement, in addition attitudes have traditionally been measured in positive degrees (Joshi et al., 2015). Likert scales are ordinal and therefore are more suited to non-parametric statical tests. Non-parametric statistical tests are considered to be less statistically powerful than parametric test. Therefore, the statistical power that is drawn from Likert scales is considered limited to some extent (Bishop & Herron, 2015).

Rate of perceived exertion scale. The rate of perceived exertion scale first proposed by Gunner Borg in 1986 was designed to measure effort and exertion, dyspnoea and fatigue during physical work (Borg,1986). The scale is distinct in its simplicity as a numerical list presented

in a table. The original 20 point scale was modified to reflect heart rate to a 6-20 point scale where 6 represented 60bpm and 200 represents 200bpm (Borg, 1982). A Borg category ratio scale was then developed, which included ten points ranging from no exertion at all to extreme intensity. This modified scale is termed the Borg CR10 scale; it was designed to measure exertion and pain (Williams, 2017). Crewe et al. (2008) study the use of the RPE scale as a predictor for the duration of exercise to exhaustion in cool conditions at 65% and 70% intensities, and in hot conditions at 60 and 65% intensities. The study found that the rate of increase in RPE was significantly faster in the hot 65% and cold 70% groups in comparison to the hot 55% group. An inverse relationship between trial duration and rate of increase in RPE ($r=0.83$) was observed. The fundamental conclusion of the study is that the RPE scale can be used to predict the duration of exercise to the point of exhaustion in different environmental conditions when power output is constant. Halperin & Emanuel (2019) highlight several points on the use of the RPE scale for measurement of neuromuscular fatigue. Firstly, the scale is convenient and practical means to measure RPE beyond the laboratory. Secondly, a lack of clarity around definitions for perceived effort is a major limitation of the RPE scale since it impedes validity of results. The scale is best used with clarity on definitions and instructions and in combination with other scales.

The omnibus resistance scale. The omnibus scale (OMNI) is an adapted version of Gunner Borg's original RPE scale. The original scale was adapted by Robertson et al. and proposed in 2004. A series of OMNI scales for males, females, adults and children for walking/ running, resistance exercise, step and elliptical training were presented in the "Perceived exertion laboratory manual" (Haile et al., 2015). The omnibus resistance exercise scale incorporates a line ranging from zero to ten, a visual illustration of increasing exertion during resistance exercise and a verbal component that ranges from extremely easy to extremely hard. The series

of OMNI scales are distinguished by their strength in the ability to assess exertion in various populations and for various activities. The cross-modal application of OMNI ratings is indicated by as a strength of the scales by several studies (Pfeiffer et al., 2002; Robertson et al., 2005). Broad base applications of the study include activities include walking, running, stepping, cycling and resistance exercise. Mays et al. (2010) highlight the validity and reliability of the OMNI scale despite its limitation for lower response scores from 0-3. Robertson et al. (2003) conclude that the OMNI resistance scale provided concurrent validity for the measurement of the rate of perceived exertion for active muscles over the entire body for young recreationally active males and females.

The visual analogue scale. The visual analogue scale was first presented by Hayes and Patterson in 1921 as a graphical rating method to assess pain (Hayes, 1921). The scale is comprised of a single continuous horizontal line that use two verbal anchors, ranging from no fatigue to very severe fatigue. The left side of the scale indicates lower extremes and the right side indicated higher extremes (Yeung & Wong, 2019). Aitken (1969), on the topic of measuring feelings with the visual analogue scale, highlights that since feelings are states of self, incorporated with moods and sensations, a person may appreciate their state; however, words may fail to describe their subjective experience. The limitation of verbal anchors to capture subjective experiences is highlighted as a limitation of the visual analogue scale. However, the incorporation of an analogue element with the continuous line is a strength of the scale, since it permits liberal comparisons between different points (Aitken, 1969). Previous investigations have suggested that the visual analogue scale of fatigue is a reliable and valid measure of fatigue (Tseng et al., 2010). The discussed scales have all been validated for use; this involves checking if the scales provide valid measures (Colado et al., 2020; Halperin & Emanuel, 2020).

Rate of fatigue scale. The rate of fatigue scale was developed and validated by Micklewright et al. in 2017 (Micklewright et al., 2017). The scale is designed to track fatigue across a wide range of contexts, including daily activity, exercise, and recovery. It uses numerical, verbal, and illustrative means to demonstrate fatigue from zero, not fatigued at all to ten, total fatigue and exhaustion. Previous investigations concluded that the rate of fatigue scale is characterised by good face validity and high levels of convergent validity during ramped exercise to exhaustion. The ROF scale is distinguished by its coherence, ease of use and broad applicability. It is found to have high convergent validity as well as validity as a measure of fatigue rather than exertion (Micklewright et al., 2017). The scale has been found to demonstrate high levels of face and construct validity, particularly within the context of ramped exercise as well as resting recovery (Brownstein et al., 2021).

Table 2.1. Summary table of subjective measures of fatigue

	Origin	**Elements of description**	**Type**
Rate of perceived exertion	Gunner Borg 1986	Numerical: 1-10 Verbal: nothing-maximal/exhaustion Colour gradient: green to red	Categorical
Likert	Rensis Likert 1932	Numerical: 1-7 Verbal: strongly agree-strongly disagree	Categorical
Omnibus resistance	Robert J. Robertson et al., 2004	Linear Numerical: 0-10 Verbal: extremely easy-extremely hard Illustrative	Categorical
Visual analogue	Hayes & Patterson 1921	Linear Numerical: 0-100 Verbal: No fatigue- severe fatigue	Continuous
Rate of fatigue	Micklewright et al., 2017	Numerical: 0-10 Verbal: not fatigued at all-total fatigue & exhaustion-Nothing left Illustrative	Categorical

2.9 Predictive modelling

Predictive models are a type of mathematical model that assess the ability of one variable (predictor) to predict or account for variability in another variable (Ding et al., 2000). Unlike traditional explanatory research, which uses statics to test a hypothesis, predictive research uses statistics without a preconceived hypothesis (Chen, 2020). The first step for developing a predictive model is to select relevant predicator variables for inclusion. A full model approach includes all candidate variables, whereas a backward elimination approach uses sequential hypothesis testing to eliminate some variables. The backwards elimination approach is susceptible to selection bias. The inappropriate selection of variables causes poor model performance. The number of variables included is limited by the sample size and data set (Sanchez-Pinto et al., 2018). To validate a predictive model, the model must be tested within the derivation cohort and in a validation cohort. There is no guarantee that valid predictive models in a derived cohort will also be valid within validation cohorts. This is a result of overfitting models, missing data and interobserver variability causing measurement errors. Models can be validated internally by splitting data into training and validation sets or by cross-validation or bootstrapping (Vergouwe et al., 2005). Machine algorithms can also be used to apply approaches such as the random forest approach, where data is split into in and out of bag groups (Waljee et al., 2014). Random sampling is used for the in group to replace the initial cohort data. The out of bag group is composed of the unsampled data from the initial cohort. The out of bag group serves for internal validation. Internal validation tends to produce optimistic results since both the derivation and validation sets are similar (Steyerberg et al., 2001). Despite the inconvenience posed by collecting a new data set from new patient's external validation is a superior validation technique to internal validation. There are three

measures of overall performance for predictive models. R^2 is used for continuous data to depict the average squared difference or the variation between predicted and observed outcomes (Lee et al., 2016). Adjusted R^2 is also used for continuous data sets. Unlike R^2, it accounts for the number of predicators in order to prevent overfitting. Finally, the Brier score is used for categorical data to average the square distances from the predicted and the observed outcomes. Discrimination measures the ability of a model to distinguish between subjects who experience and have no experience of the outcome variable. It is measured in receiver operating characteristic (ROC) curves. This measure alone is considered insensitive; thus, it is usually combined with relative novel performance measures. Predicative research aims to accurately predict occurrences based on the patterns of outcome in a set variable. If a predictive model is accurate, it can be used to predict future outcomes (Waljee et al., 2014).

3.0 METHODS

3.1 Participants and ethical approval

Twenty healthy recreationally active volunteers participated in this study (age 23 ± 3 yr, 10 female). Participants were screened using a medical history questionnaire, which contained exclusion criteria specific to neurological and musculoskeletal injury, transcranial magnetic stimulation (TMS), and electrical nerve stimulation. Participants were instructed to refrain from any stimulants or depressants such as caffeine, alcohol, or exercise for at least six hours before testing commenced. Immediately prior to testing participants were asked if they had complied with the request to refrain from stimulants and depressants. If a participant had not complied with the request testing was rescheduled or cancelled. Approval for testing procedures were obtained via the Human Research Ethics committee at Griffith University. Written informed consent was obtained for all participants prior to testing. All procedures were performed in accordance with the *Declaration of Helsinki* except for registration in a database.

3.2 Setup and instrumentation

Torque and electromyography. Participants sat upright in a chair with their right arm fixed in a custom-built transducer to measure isometric elbow flexions (Figure 3.1A). The shoulder and elbow were placed in 90 degrees of flexion and the participant's arm was fixed to the device at the wrist using a non-compliant strap. A precision S-beam load cell (PT4000, PT Ltd) with a 1.1 kN range and full-scale output of 3 mV/V was used to measure elbow flexion force which was converted to elbow flexion torque. A computer monitor was positioned ~1 m in front of participants at eye level to provide real-time feedback on torque generation, and also present horizontal target lines to track when required. Surface electromyography (EMG) was recorded from the biceps brachii and triceps. Bipolar Ag/AgCl electrodes (24 mm diameter, Kendall

Arbo) were attached to the skin over each muscle with a 24 mm inter-electrode distance. A ground electrode was placed on the acromion of the test limb. Force and EMG signals were sampled at 2000 Hz using a 16-bit analog-to-digital converter (CED 1401; Cambridge Electronic Design, Cambridge, UK) and Spike2 software (version 7.02; Cambridge Electronic Design). EMG signals were amplified (×300) and bandpass filtered (10-1000 Hz) using a CED 1902 amplifier (Cambridge Electronic Design), whereas force signals remained unfiltered.

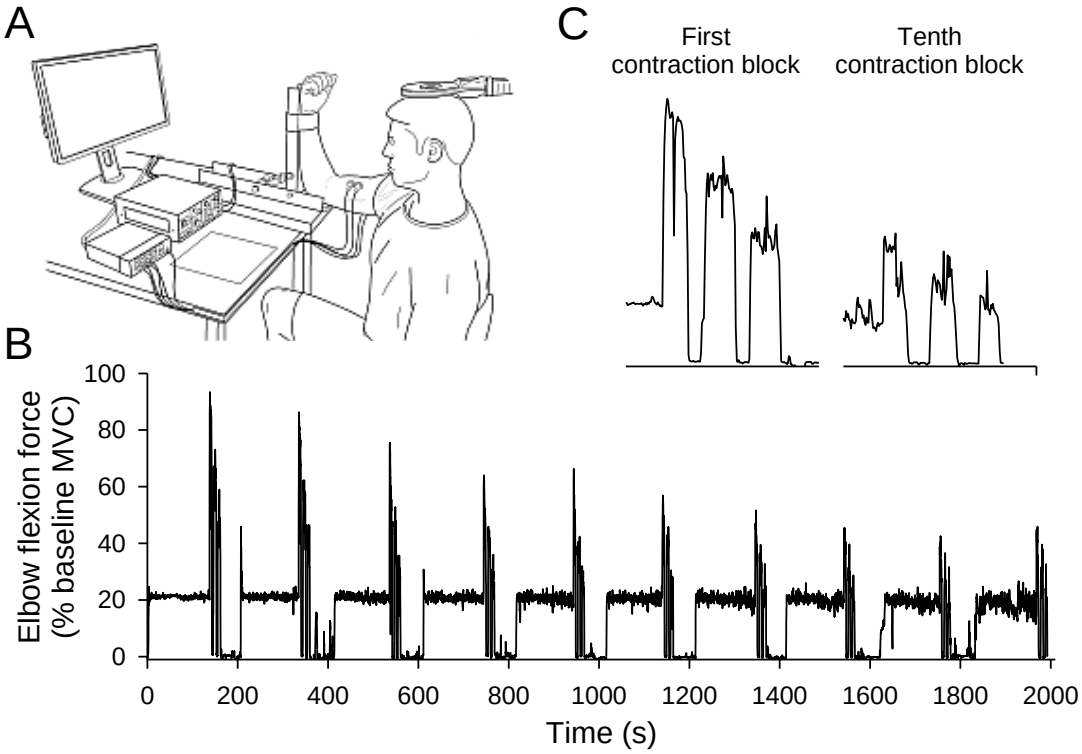

Figure 3.1. Experimental setup. Elbow flexion force was generated by participants attached to a custom-designed transducer (A). The experimental protocol consisted of ten contraction blocks, where an isometric 20% MVC elbow flexion was maintained for 2 min (B). At the end of the 2 min contraction, a brief MVC, a brief 75% MVC, and a brief 50% MVC were performed while single pulse single-pulse TMS was delivered to the motor cortex to elicit a

MEP in the biceps brachii (C). Superimposed twitches were assessed throughout the contraction protocol, and resting twitches were estimated from linear regression of TMS-evoked twitch responses during the graded contractions

Cortical stimulation. A Magstim 200^2 transcranial magnetic stimulator (TMS, Magstim Co., UK) was used with a 90 mm circular stimulating coil to elicit motor evoked potentials (MEPs) in the test limb biceps brachii. The coil was positioned over the vertex and oriented to preferentially activate the left motor cortex projecting to the participants' right arm. The stimulator intensity which elicited the highest elbow flexor twitch torque with a MEP that was greater than 80% of the biceps brachii Mmax and less than 20% of the triceps brachii Mmax during a brief isometric contraction at 50% MVC was selected as the optimal stimulus intensity for each testing sessions (70% - 75% stimulus output). This criterion ensured that the TMS pulse activated a large proportion of the biceps brachii motoneuron pool whilst minimising activation of the antagonist triceps brachii.

Brachial plexus stimulation. A constant current stimulator (DS7AH, Digitimer, Ltd., UK) was used to deliver single electrical pulses of 100 μs duration to the brachial plexus to measure the maximum compound action potential (Mmax) of the biceps and triceps brachii. A surface anode was positioned over the ipsilateral acromion and a surface cathode was positioned over the supraclavicular fossa. The optimal position of the cathode was determined by using a motor point stimulating pen before affixing the surface electrode. Optimal stimulus intensity was determined by progressively increasing the stimulator current until the Mmax of both the biceps and triceps brachii was reached. The stimulus intensity for experimental testing was then set at 130% of Mmax (52 mA – 234 mA).

3.3 Experiment protocol

Prior to performing fatigue-inducing contractions, each participant performed 4-5 brief (~2 s) maximal effort elbow flexions to establish a control MVC. Once MVC was determined, the participant performed 75% MVCs and 50% MVCs. During all baseline contractions, a cortical stimulation and a brachial plexus stimulation was delivered to the participant to establish baseline responses to stimulations. Strong verbal encouragement was present during all maximal efforts. The trial with the highest peak force was used as that participant's MVC. The neuromuscular performance of participants in the current study is reliable since the protocol is repeatable and outcomes are expected to be consistent.

The contraction protocol consisted of ten contraction blocks. Each contraction block was a low-intensity isometric 20% MVC elbow flexion that was held for 2 min. Following each 2 min, participants immediately performed an MVC, a 75% MVC, and a 50% MVC (Figure 3.1B). During each of these graded contractions, a cortical stimulation and a brachial plexus stimulation was delivered to the participant. The performance of each contraction block generated substantial fatigue, as the MVC progressively declined from the first block to the tenth block (Figure 3.1B and 3.1C).

3.4 Quantification of fatigue

Force and TMS-derived measures. Maximal voluntary torque was calculated from MVCs using a 50 ms window preceding the stimulation artefact. A decline in MVC throughout the contraction protocol was indicative of fatigue, where the maximal force generating capacity of the elbow flexors was compromised by the low-intensity sustained contractions. Superimposed twitch amplitude was calculated from the evoked changes in torque due to motor cortical stimulation. Resting twitch torques were estimated from the superimposed twitch amplitudes

during the brief MVC, 75% MVC and 50% MVC performed at baseline and at the end of each 2 min low-intensity sustained contraction. A linear regression calculated the y-intercept between the amplitude of the superimposed twitch and voluntary torque. The linear regression was performed for each maximal effort, 75% MVC, and 50% MVC associated with the same contraction block. The level of voluntary activation was calculated via the equation: voluntary activation (%) = (1-superimposed twitch/resting twitch) x 100 (Todd *et al.*, 2003).

Self-reported fatigue scales. Five subjective measures of fatigue were collected during each contraction block. These measures were a visual analogue scale, a Likert scale, an omnibus scale, a rating of perceived exertion scale, and a rating of fatigue scale. All participants were sent an via email 48 hours prior to with a copy of all scales, and how to respond to them the email also included definitions of fatigue, exertion and MVC. On test day each scale was explained and definitions were revised. During baseline contractions, participants were asked to provide a response to each scale as a practice for the assessment of fatigue and exertion. Scales were completed within the final 15seconds of the 20% MVC contraction, before the onset of MVCs. The scales were presented in the same order for each participant where the order alternated between fatigue and exertion scales. The visual analogue scale was recorded on paper; all other scales were recorded electronically. The measurement environment was standardised for all participants. The same researcher and research assistant were used for all data collection. The laboratory was limited to the participant, the researcher and the research assistant only. The same wording and explanation was provided to each participant. The specifics of the self-reported scales were:

1) The visual analogue scale (Hayes & Patterson 1921) was a 13 cm line without ticks or units. The only writing presented on the scale was at the origin of the line was labelled ‘no fatigue’

and at the end of the line was labelled ‘severe fatigue’. Participants were asked to mark a point along the line that they believed represented their level of fatigue.

2) The Likert scale (Likert, 1932) measured participant agreeableness to the written statement “I am experiencing fatigue”. The scale presented ‘(1) Strongly agree’, ‘(2) Agree’, ‘(3) More or less agree’, ‘(4) Undecided’, ‘(5) More or less disagree’, ‘(6) Disagree’, ‘(7) Strongly disagree’. The direction of this scale was the reverse of other scales in the study, whereby a higher value corresponded to less fatigue.

3) The omnibus scale (Robertson et al.,2004) was a 20 cm line with equally spaced ticks. The ticks corresponded to the labels ‘0 extremely easy’, ‘1’, ‘2 easy’, 3’, ‘4 somewhat easy’, ‘5’, ‘6 somewhat hard’, ‘7’, ‘8 hard’, ‘9’, ’10 extremely hard’. At four locations throughout the Likert scale, a visual of an exercising human was presented, where a barbell was lifted above the head with increasing number of weights on the ends of the bar.

4) The rating of perceived exertion scale (Borg, 1986) was presented as a table where numerical values were matched to descriptive text. These were ‘1 Nothing’, ‘2 Very easy’, ‘3 Easy’, ‘4 Comfortable’, ‘5 Somewhat difficult’, ‘6 Difficult’, ‘7 Hard’, ‘8 Very hard’, ‘9 Extremely hard’, ’10 Maximal/exhaustion’.

5) The rating of fatigue scale (Micklewright et al., 2017) was presented across 20 cm as a series of equally spaced numbers ranging from 0 to 10. A value of 0 was accompanied by the text ‘Not fatigued at all’ and the value of 10 was accompanied by ‘Total fatigue and exhaustion’.

3.5 Data analysis

The primary interest was to investigate which subjective scale, from a set of five, best-predicted torque-derived and EMG-derived variables obtained during single limb fatiguing exercise. First, changes in neuromuscular variables and ratings on the subjective scales across the exercise task were quantified. Second, normality of data was confirmed with Shapiro Wilks tests, and Mauchly's tests of sphericity were used to confirm that variance was equal between pairs of comparisons that were used in the statistical models. Third, five models were fit to MVC torque, VA, and resting twitch torque data (torque-derived variables) and RMS EMG, MEP/Mmax area, and silent period duration (EMG-derived variables). Each model included a different subjective scale as a predictor variable. The five models were ranked according to their predictive performance to identify the best fitting model.

Linear mixed-effects models were used to determine changes in neuromuscular variables across the exercise task. Models included a contraction block as a fixed effect—as a B-spline (five evenly spaced knots), second order polynomial, or linear term—and a random intercept for each participant in the study. Post-hoc tests compared each block to the pre-exercise value, with *p*-values family-wise corrected for 10 comparisons. Ordinal regression was used to determine if OMNI, RPE, fatigue and Likert scale responses changed across the exercise task. The OMNI, RPE and fatigue model included time as a fixed effect and a random intercept for each participant. The Likert model included time as a fixed effect. Linear regression was used to model VAS responses, with a non-linear term for block (second order polynomial) included as a fixed effect, and a random intercept for each participant.

Linear mixed-effects models were used to determine which subjective scale best predicted MVC torque, VA, resting twitch torque, EMG RMS amplitude, MEP/Mmax area, and silent period duration. Five models were fit to each outcome, with the OMNI, RPE, fatigue, Likert

or VAS included as a predictor variable in each model (fixed effect). Because the OMNI, RPE, fatigue and Likert scales are ordinal variables, they were coded as factors, with 10, 9, 10 and 7 levels, respectively. The VAS was included as a continuous predictor and fit as a B-spline (five evenly spaced knots), second order polynomial, or linear term. All models included a random intercept for each participant. To identify the best fitting model, the five models, and a base model, including block, were ranked on the root-mean-square error (RMSE) statistic. The RMSE is the SD of the residuals (i.e., prediction errors); with lower values indicating a better performing model (James et al., 2013). Cross validation (10-fold, with 5 repeats) was used to estimate the average RMSE for each model, with folds balanced for participants (Bates et al., 2021). We also obtained the marginal and conditional coefficient of determination (R^2) across model fits, from the cross-validation procedure (Nakagawa et al., 2017). Information criteria (e.g., Akaike's or Bayesian) indices were not used for model selection in order to avoid penalise models for the number of parameters, which reflect the number of levels on a given subjective scale (James et al., 2013). Finally, the predicted values from the best fitting model(s) were visually inspected to determine whether there was a monotonic change in the outcome variable, across the levels of the subjective scale.

Data are reported as the estimated marginal mean and 95% confidence interval (CI), unless otherwise stated. The alpha level for all tests was set at 5%. All analyses were undertaken in R (R Core Team, 2020). Linear mixed-effects models were fit using the *lmerTest* package (Kuznetsova et al., 2017), and ordinal models using the *ordinal* package (Christensen, 2019). There was 0.45% missing data for MEP/Mmax area—no values were imputed.

4.0 RESULTS

4.1 Participant characteristics

All participants were able to successfully complete the contraction protocol and TMS procedures in this study. TMS-based measures of fatigue obtained during unfatigued MVCs (baseline measurement) are presented in Table 4.1.

Table 4.1. Measurements obtained during unfatigued MVC

Variable	
Elbow flexion torque amplitude (N.m)	55.1 ± 22.6
Superimposed twitch amplitude (N.m)	0.55 ± 0.51
Estimated resting twitch (N.m)	15.4 ± 6.5
Voluntary activation (%)	96.2 ± 2.3
Biceps brachii EMG RMS amplitude (mV)	0.60 ± 0.32
MEP/Mmax area	0.77 ± 0.29
Silent period duration (ms)	156.2 ± 61.7

4.2 Contraction protocol effects on torque- and EMG-derived variables

There was an effect of contraction block on MVC torque, voluntary activation, resting twitch torque, RMS EMG amplitude, and silent period duration. MVC torque ($p < .001$ to $p = .01$; $d = –1.11$ to $–0.59$) and voluntary activation ($p < .001$ to $p = .029$; $d = –2.89$ to $–1.04$) were lower from contraction block two onwards (Figure 4.2A and 4.2B). Resting twitch torque was lower from block four onwards ($p = .001$ to $.017$; $d = –0.78$ to $–0.54$, Figure 4.2C). After correcting for multiple testing, RMS EMG amplitude was not statistically different at any point between

contraction block one and 10 compared to baseline (p = .14 to 1.00; d = 0.14 to 0.57, Figure 4.2D). MEP/Mmax area was not statistically different at any point between contraction block one and 10 compared to baseline (p = .95 to 1.00; d = 0.01 to 0.54, Figure 4.2E). Silent period duration was longer from contraction block one onwards (p = .005 to .007; d = 0.06 to 0.59, Figure 4.2F).

4.3 Contraction protocol effects on self-reported fatigue scales

There was an effect of contraction block on all subjective scales. RPE (OR = 1.36, 95% CI = 1.14 to 1.57, p < .001; Figure 4.3A), OMNI (OR = 1.64, 95% CI = 1.38 to 1.90, p < .001; Figure 4.3B), fatigue scale (OR = 1.86, 95% CI = 1.57 to 2.15, p < .001; Figure 4.3D) and VAS (all p <.001, d = 0.28 to 3.56; Figure 4.3E) responses increased with each contraction block. Ratings on the Likert scale decreased with each contraction block (OR = 0.48, 95% CI = 0.42 to 0.55; p < .001; Figure 4.3C).

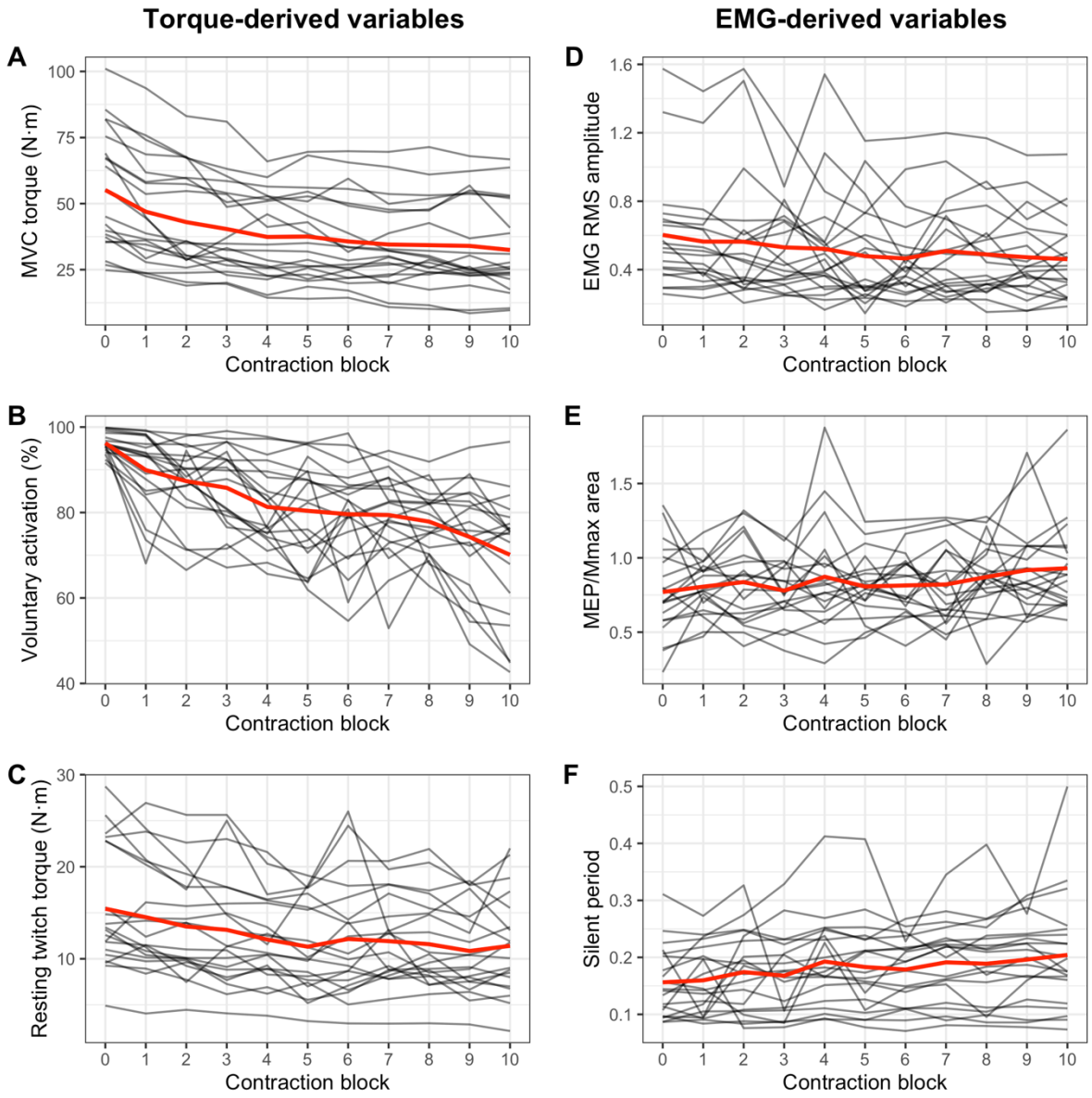

Figure 4.1 Exploratory data analysis of fatigue outcomes for the contraction protocol. Data in the left column represent the torque-derived variables of MVC torque (A), voluntary activation (B), and resting twitch amplitude (C), presented across the 10 contraction blocks performed by participants. Data in right column represent EMG-derived variables of RMS amplitude (D), MEP/Mmax area (E), and silent period duration (F). All measurements were obtained at the completion of each 2 min submaximal contraction. Grey lines indicate individual participant data, with the mean response indicated by the red line.

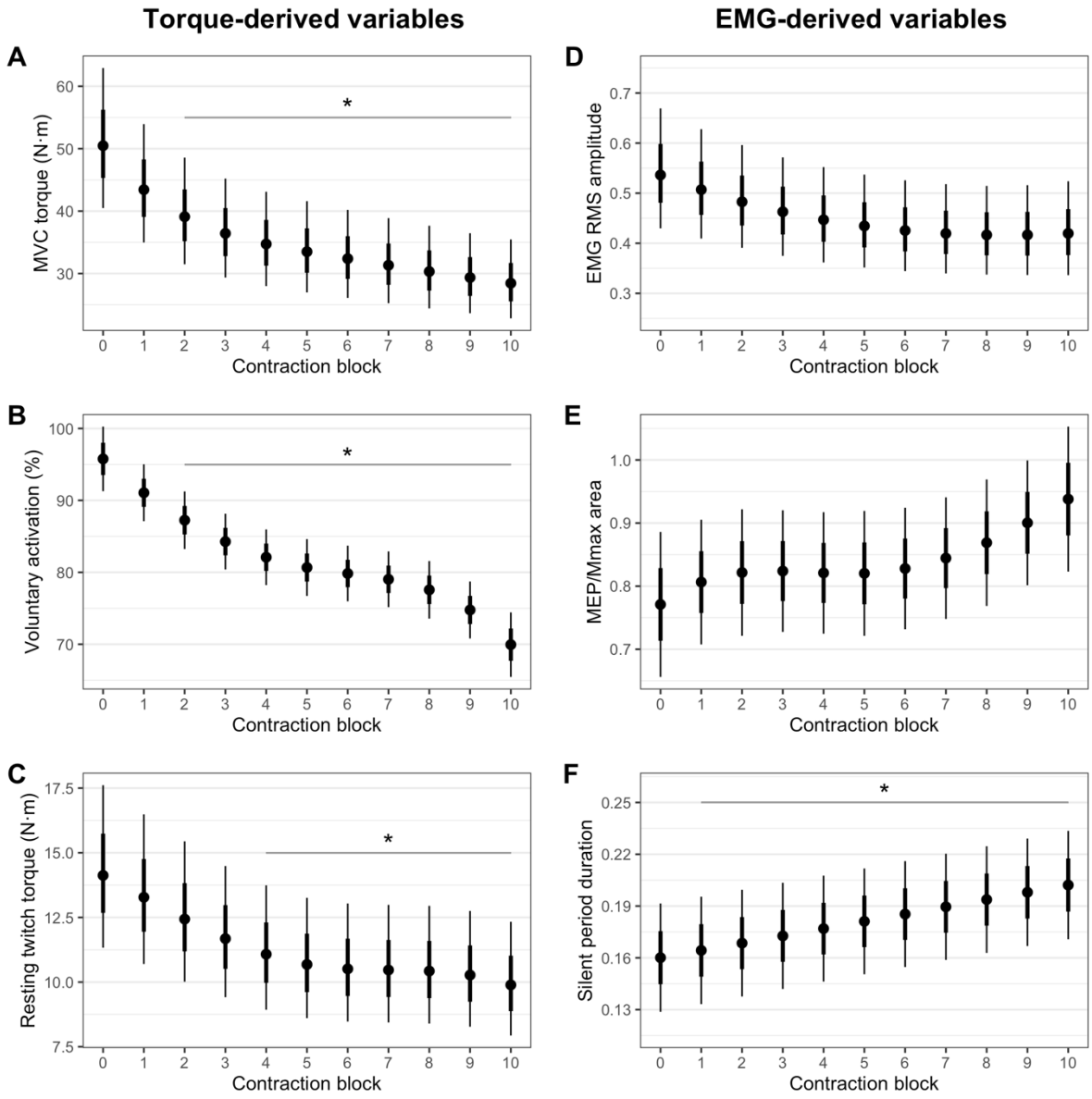

Figure 4.2. Fatigue outcomes for the contraction protocol. Data in the left column represent the torque-derived variables of MVC torque (A), voluntary activation (B), and resting twitch amplitude (C), presented across the 10 contraction blocks performed by participants. Data in right column represent EMG-derived variables of RMS amplitude (D), MEP/Mmax area (E), and silent period duration (F). All measurements were obtained at the completion of each 2 min submaximal contraction. The contraction block labelled 0 is the baseline unfatigued measurement for the variable. Data are presented as the marginal mean and error bars indicate

the 68% (thick inner line) and 95% (thin line) confidence intervals. Asterisk indicates statistically different to contraction zero.

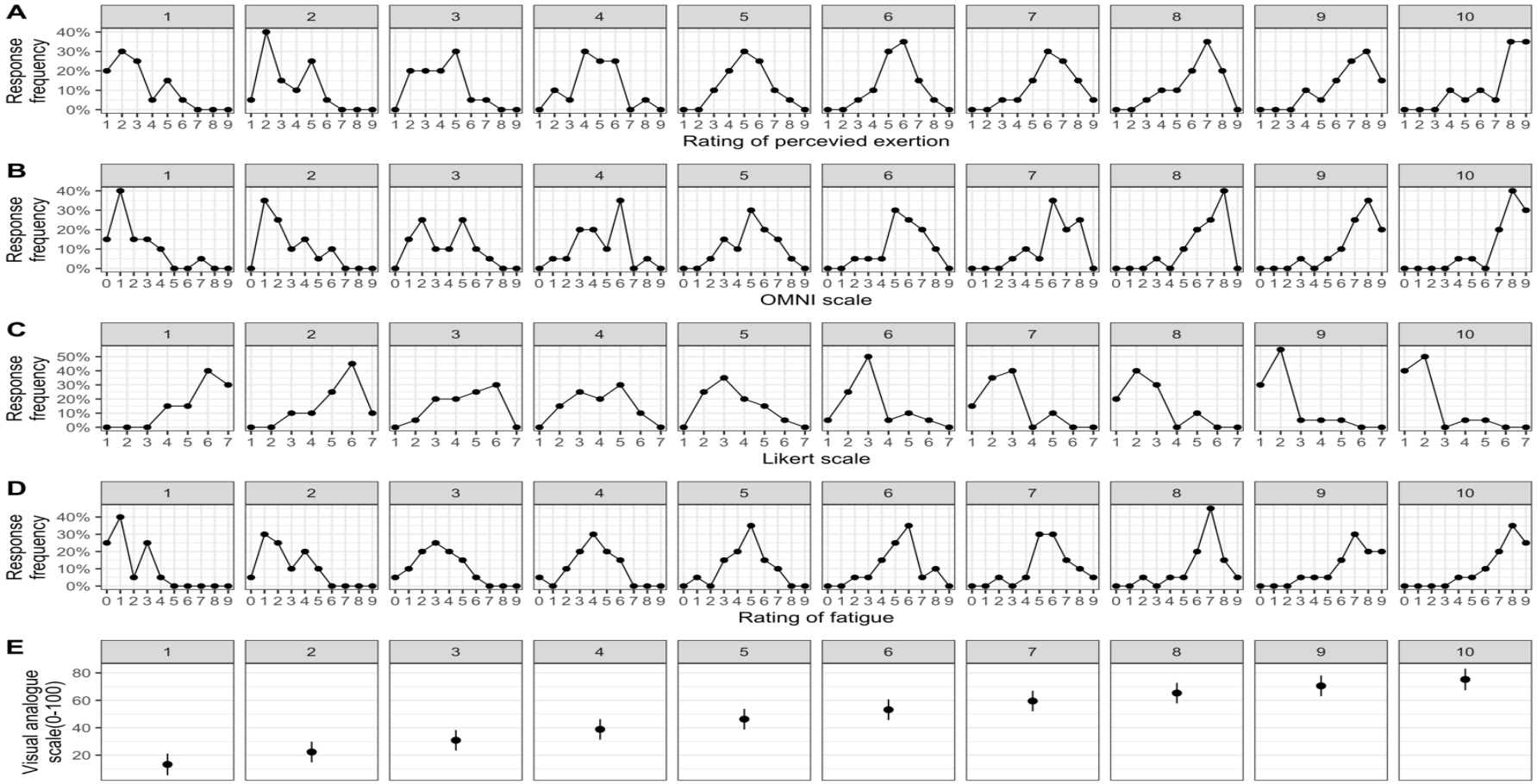

Figure 4.3. Rating of perceived exertion (A), OMNI rating of perceived exertion (B), Likert scale (C), rating of fatigue (D) and visual analogue scale (E) responses across the exercise task. Responses on panels A–D are reported as the frequency, with values in panel E reported as the mean and 95% confidence interval.

4.4 Predictive model performance

RPE was the best predictor of MVC torque, followed closely by the fatigue scale (Figure 4.4A). Ratings across the RPE and fatigue scales were generally able to differentiate between MVC torque values (Figure 4.5Ai and Figure 4.5Aii). After the base model, the Likert scale and fatigue scale were the best predictors of voluntary activation (Figure 4.4B). Ratings on the Likert scale were generally able to differentiate between voluntary activation values (Figure 4.5Bi), more so than ratings on the fatigue scale (Figure 4.5Bii). After the base model, the OMNI scale was the best predictor of resting twitch torque (Figure 4.4C). Ratings of OMNI were generally poor at distinguishing between different resting twitch torque values (Figure 4.5C).

The Likert scale was the best predictor of EMG RMS amplitude, followed closely by the RPE scale (Figure 4.4D)—ratings in the lower and upper levels of both scales were generally poor at distinguishing between different EMG RMS amplitude values. After the base model, the VAS and Likert scale were the best predictors of MEP/Mmax area (Figure 4.4E). Ratings 3–7 on the Likert were not able to distinguish between different MEP/Mmax area values, while higher VAS ratings associated with higher MEP/Mmax area values (β = 0.00108, 95% CI = 0.00001, 0.00215). The VAS was the best predictor of the silent period duration (Figure 4.4F), with higher ratings associated with a longer silent period duration (β = 0.0006 s, 95% CI = 0.004, 0.008).

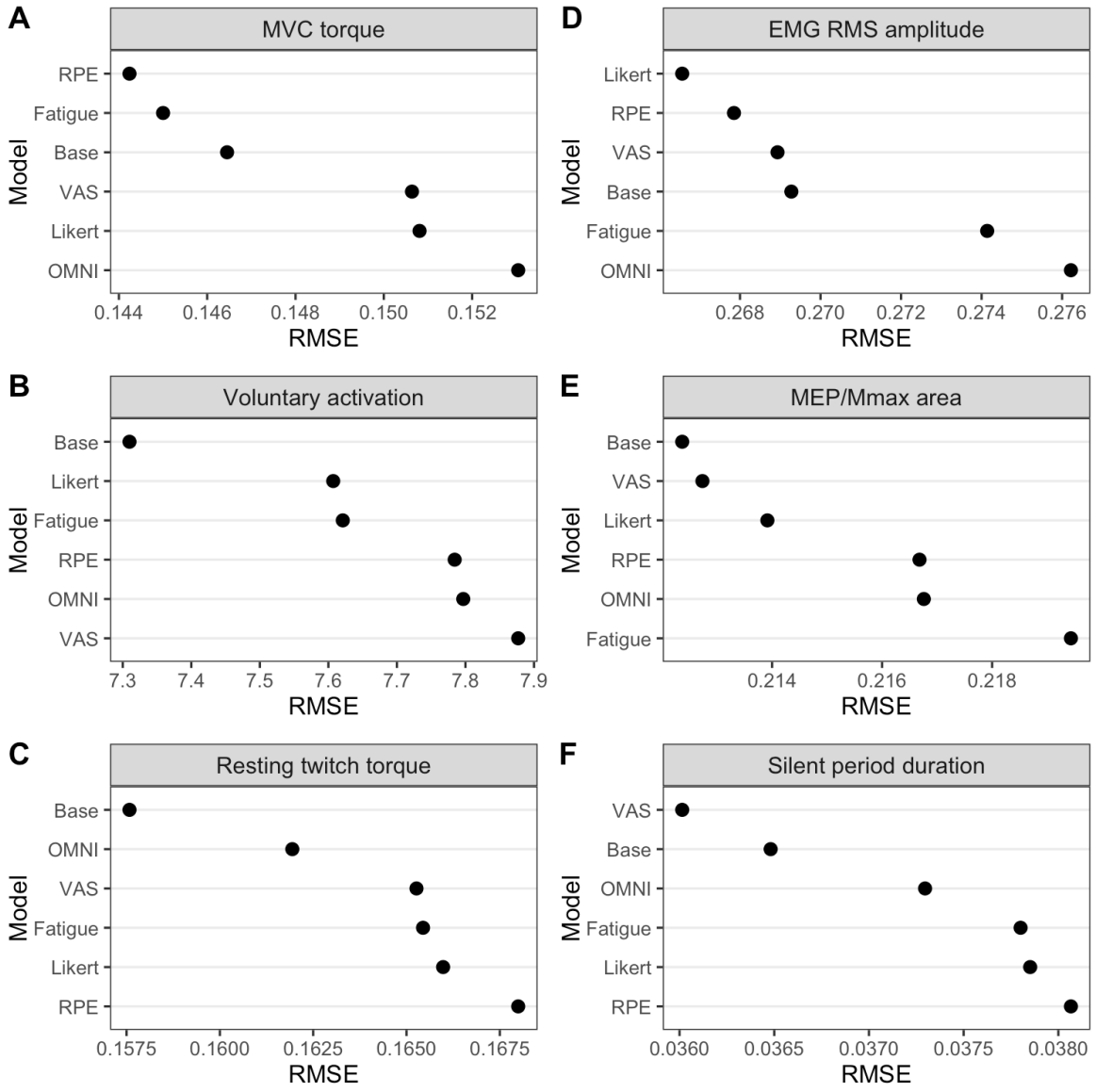

Figure 4.4. Root-mean-square error (RMSE) of models predicting maximal voluntary contraction (MVC) torque (A), voluntary activation (B), resting twitch torque (C), EMG RME amplitude (D), MEP/Mmax area (E), and silent period duration (F). MVC torque, resting twitch torque, and EMG RMS amplitude were logged before analysis. Models are ranked according to their RMSE value, in descending order, with smaller RMSE values indicating a better performing model. Base = a base model with contraction block included as a predictor variable, RPE = Rating of percevied exertion,VAS = Visual analogue scale.

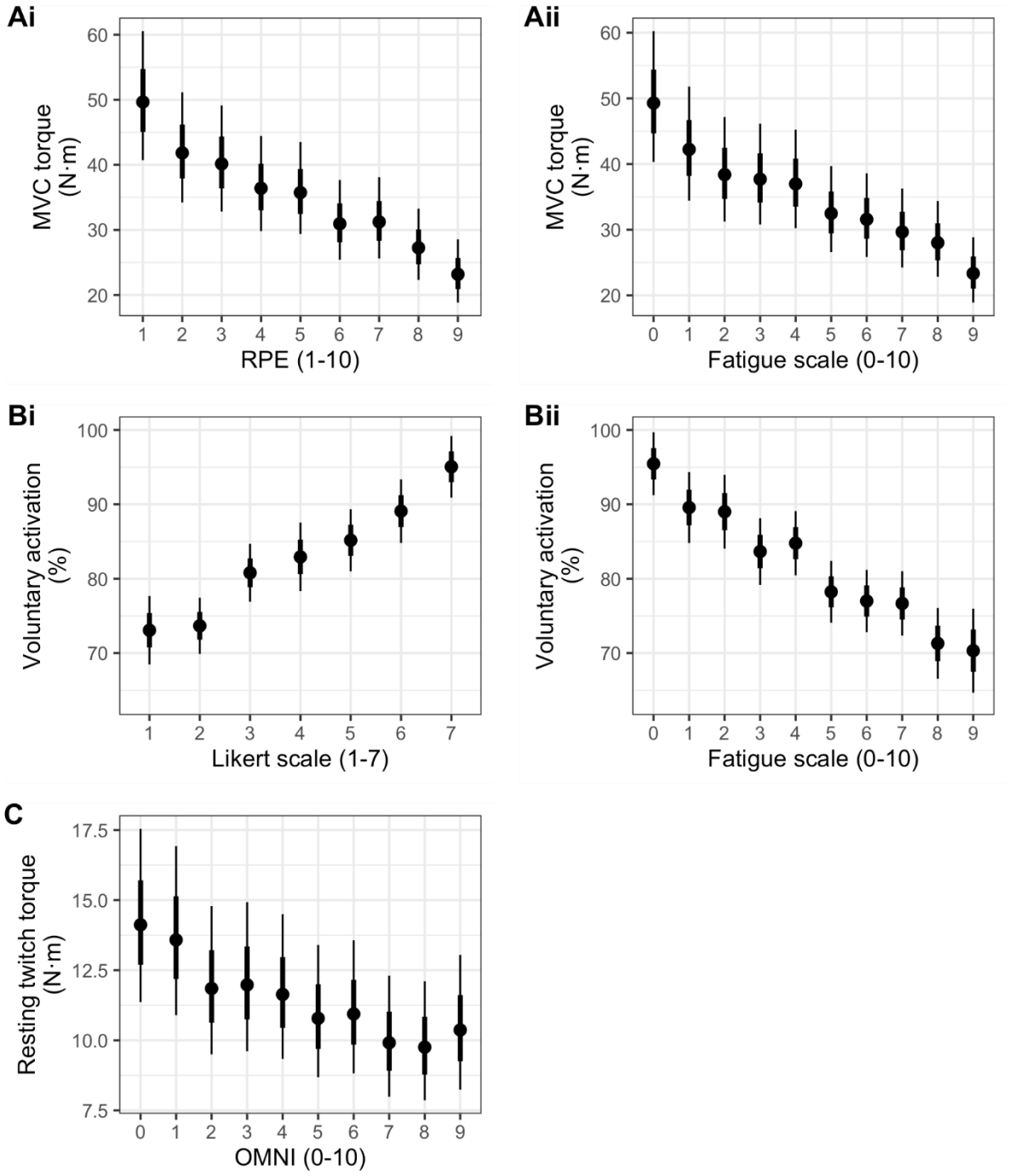

Figure 4.5. Fitted values from the models that best predicted maximal voluntary contraction (MVC) torque (A), voluntary activation (B) and resting twitch torque (C). When two models predicted similarly well, based on their root-mean-square error statistic, both models were shown (i.e., MVC torque and voluntary activation). Data are presented as the marginal mean and error bars indicate the 68% (thick inner line) and 95% (thin line) confidence intervals.

The marginal and conditional R^2 for each model is reported in Table 4.2 for torque-derived variables, and Table 4.3 for EMG-derived variables. In general, all fitted models explained ~90% of the variation in MVC torque and resting twitch torque, ~75% of the variation in EMG RMS amplitude and silent period duration, ~65% of the variation in voluntary activation, and ~50% of the variation in MEP/Mmax area.

Table 4.2. Marginal and conditional coefficient of determination (R^2) for models predicting maximal voluntary contraction torque, voluntary activation and resting twitch torque.

Model	Marginal R^2	Conditional R^2
Maximal voluntary contraction torque		
Base model	0.110	0.924
Fatigue	0.162	0.920
Likert	0.140	0.911
OMNI	0.152	0.910
Rating of perceived exertion	0.169	0.919
Visual analogue scale	0.153	0.908
Voluntary activation		
Base model	0.320	0.688
Fatigue	0.361	0.671
Likert	0.351	0.658
OMNI	0.330	0.669
Rating of perceived exertion	0.350	0.670
Visual analogue scale	0.321	0.638
Resting twitch torque		
Base model	0.051	0.906
Fatigue	0.057	0.900
Likert	0.050	0.898
OMNI	0.062	0.902
Rating of perceived exertion	0.055	0.897
Visual analogue scale	0.050	0.894

Note. The base model included *contraction block* as a fixed effect. Maximal voluntary contraction torque and resting twitch torque were logged before analysis. The marginal R^2 reflects the variance in the outcome variable explained by the fixed effects in the model only, and the conditional R^2 reflects the variance explained by both the fixed and random effects. All models included a random intercept for each participant in the study.

Table 4.3. Marginal and conditional coefficient of determination (R^2) for models predicting EMG RMS amplitude, MEP/Mmax area, and silent period duration.

Model	Marginal R^2	Conditional R^2
EMG RMS amplitude		
Base model	0.026	0.749
Fatigue	0.046	0.748
Likert	0.047	0.757
OMNI	0.041	0.749
Rating of perceived exertion	0.050	0.757
Visual analogue scale	0.033	0.745
MEP/Mmax area		
Base model	0.024	0.492
Fatigue	0.025	0.486
Likert	0.037	0.479
OMNI	0.033	0.492
Rating of perceived exertion	0.031	0.502
Visual analogue scale	0.013	0.478
Silent period duration		
Base model	0.032	0.776
Fatigue	0.048	0.769
Likert	0.037	0.766
OMNI	0.052	0.780
Rating of perceived exertion	0.046	0.770
Visual analogue scale	0.048	0.785

Note. The base model included *contraction block* as a fixed effect. EMG RMS amplitude was logged before analysis. The marginal R^2 reflects the variance in the outcome variable explained by the fixed effects in the model only, and the conditional R^2 reflects the variance explained by both the fixed and random effects. All models included a random intercept for each participant in the study.

5.0 DISCUSSION

The purpose of this study was to determine the extent to which subjective measures can be used as predictors of objective measures in the analysis of neuromuscular fatigue. An elbow flexion fatiguing protocol was conducted whilst five psychomotor measures of fatigue were used to provide self-reported measures, and single-pulse TMS measures and electrical stimulations were used to provide commonly quantified measures of fatigue. There were four main findings in this study. When performing a repeated low-intensity isometric elbow flexions, 1) participants had progressive declines in MVC torque, VA and resting twitch torque throughout the protocol, 2) participants had progressive increases in self-reported fatigue measures, and 3) although there were marked similarities for all scales to predict quantitative measures of fatigue, RPE appeared to be a good predictor of MVC torque, and 4) the number of contractions appeared to be a good predictor of VA, resting twitch torque and MEP amplitude.

MVC torque, VA, and resting twitch torque progressively declined throughout the protocol

The submaximal contraction protocol caused a progressive decline in MVCs that were collected after every 2 mins of contraction. Therefore, this result indicates that the contraction protocol was able to induce significant levels of fatigue in the cohort of healthy young adults. When used appropriately, the TMS-derived measures provide insight into whether the fatigue was caused by failure in the central nervous system to generate motor output, or by peripheral factors that reduce the ability of the muscle to contract (Smith et al., 2007; Tergau et al., 2000; Todd, 2003). VA progressively declined throughout the contraction task, which suggests that the central nervous system was unable to adequately drive the muscle to produce force. This is likely due to supraspinal fatigue, as the superimposed twitch

progressively increased across the contraction protocol. An increase in the superimposed twitch generated from single-pulse TMS reflects suboptimal output from the motor cortex (Neyroud et al., 2016; Smith et al., 2007; Søgaard et al., 2006). Declines in VA with submaximal isometric fatiguing tasks as central fatigue progresses is consistent with previous literature findings (Löscher et al., 1996. ; Søgaard et al., 2006). Declines in VA when performing submaximal isometric fatiguing contractions of the triceps surae have been found during similar protocols (Löscher et al., 1996). Likewise, the progressive decline in resting twitch with the submaximal elbow flexion fatiguing task has been associated with peripheral fatigue in previous investigations (Gandevia et al., 1998; Gandevia et al., 2013; Neyroud et al., 2016). Therefore, the current intermittent submaximal isometric elbow flexion fatiguing protocol indicates the occurrence of neuromuscular fatigue by the progression of both central and peripheral fatigue. Previous investigation into submaximal elbow flexion tasks between 15-20% MVC indicate the primary influence of central fatigue on the neuromuscular system (Bigland-Ritchie et al., 1986; Dorfman et al., 1990; Maluf & Enoka 2005; Taylor & Gandevia 2008).

Self-reported measures of fatigue progressively increased throughout the contraction protocol

Self-reported measures of fatigue are expected to reflect progressive increases in fatigue with the development of neuromuscular fatigue throughout submaximal fatiguing tasks (Enoka & Duchateau 2008) since clear interactions have been established between perceived and physiological fatiguability (Kluger et al., 2013). Although the majority of studies use the traditional RPE scale to model changes in the perceived experience of fatigue (Berchicci et al., 2013; Cruz-Montecinos et al., 2019; De Morree et al., 2012; Demura & Nagasawa 2003;

Eston, 2012; Guo et al., 2017; Morishita et al., 2018), several studies have incorporated the use of scales such as the OMNI- resistance and ROF scales (Leung et al., 2004; Micklewright et al., 2017; Naclerio et al., 2011; Zamunér et al., 2011). The rate of perceived exertion scale results declined throughout the current fatiguing protocol. In effect, indicating that the RPE scale results follow increasing trends in fatigue with submaximal tasks. The Likert scale results declined throughout the fatiguing task. This result indicates that subjects experienced increases in agreeableness to the statement "I am experiencing fatigue" (Likert 1932). The OMNI-resistance scale results increased throughout the progression of the fatiguing protocol. The rate of fatigue scale results increased throughout the fatiguing task. Likewise, the visual analogue results also increased with the progression of the experiment. The results of all self-reported measured correspond to the progression of fatigue throughout the current submaximal fatiguing protocol. This finding indicates that for each contraction block of the submaximal fatiguing task, the following conclusions can be drawn from each scale. The Likert scale indicates that subjects recorded an increase in agreement with the statement "I am experiencing fatigue", this finding is supported by previous investigations (Hauser & Holley, 2013; Leung et al., 2004). The RPE scale indicates that subjects experienced an increase in their sense of physical and mental capacity to produce force throughout the fatiguing task (Berchicci et al., 2013; Cruz-Montecinos et al., 2019). The OMNI-resistance scale indicated that subjected experienced an increase in perception of mental and physical capacity to perform the resistance exercise task (Colado et al., 2020). The visual analogue scale indicated that subjects experience increased difficulty in physical capacity to produce force (Leung et al., 2004). The rate of fatigue scale indicates that subjects experienced declines in physical capacity to produce force throughout the fatiguing task (Micklewright et al., 2017). These findings are consistent with studies in the literature, which suggest that perception of fatigue will increase with the progression of fatigue (Cruz-Montecinos et al.,

2019; Enoka & Duchateau 2008). This finding indicates that self-reported measures of fatigue can predict the progression of neuromuscular fatigue within the context of submaximal continuous isometric contractions. This finding is supported by previous investigations and also by the connection between the somatosensory and motor cortex (Enoka & Duchateau 2008; Kluger et al., 2013).

RPE is a good predictor of MVC torque

Linear mixed-effects models were used to determine which self-reported fatigue scale best predicts force and TMS-derived variables. The connection between perceived and physiological fatigability can explain the connection between RPE as a predictor of MVC torque to some extent. In addition, this connection is furthered by the proximity of the somatosensory cortex to the motor cortex, where a lot of neural connections occur, therefore connecting perception of pain, effort, fatigue and impact voluntary drive (Mauger, 2013; Taylor et al., 2016; Umeda et al., 2019). Although it was hypothesised that RPE, the most common self-report of exercise-induced fatigue, would be the best predictor of declines in MVC ,, VA, and MEP amplitude, this was not the case. In fact, RPE was the best predictor of MVC torque – but only by a very marginal amount from the rating of fatigue scale. These scales are both similar in that they assess fatigue within 10-11 levels, unlike the Likert scale, which only uses 7 levels (Borg 1982; Likert, 1932; Micklewright et al., 2017). This difference could be caused by the difference in clarity around levels within each scale or anchoring. The RPE scale provides clear differences between each level of exertion, whereas the ROF scale lacks some verbal indicators for levels 1, 2, 4, 6, 7 and 9 (Borg, 1982; Micklewright et al., 2017). In effect this difference in detail may influence the accuracy of results. This highlights 1) that the RPE scale is indeed a useful tool to describe declines in

force, and 2) there may be flexibility in designing new surveys to capture force decline. Since no previous study has compared RPE, OMNI resistance, visual analogue, Likert, and rate of fatigue using a predictive model, there are no exisiting investigations for results to be compared against.

Previous studies have indicated that RPE is a good measure of neuromuscular fatigue (Cruz-Montecinos et al., 2019; Morishita et al., 2018). De Morree et al. (2012) investigate the perception of effort with RPE during a fatiguing task with TMS to conclude that a significant correlation between RPE and MEP amplitude exists. Likewise, Guo et al. (2017) used a 30%MVC handgrip exercise to investigate the connection between RPE results and quantifiable measures of neuromuscular fatigue. The study concludes that a significant correlation exists between RPE and central motor command during fatiguing tasks. The study clearly indicates the connection to central fatigue and that a possible connection to peripheral fatigue could also exist. Thus, the connection of RPE to MVC torque and thus neuromuscular fatigue is consistent with previous investigations. Other investigations also indicate that RPE increases with fatigue since greater cognitive effort is required to plan movements under fatiguing conditions (Berchicci et al., 2013). Thus, the findings of the current study, which indicate that the RPE scale is a good indicator of overall fatigue with MVC torque, are consistent with previous investigations, which suggest that RPE models significant correlations with objective measures of fatigue (Berchicci et al., 2013; Cruz-Montecinos et al., 2019; De Morree et al., 2012; Guo et al., 2017; Morishita et al., 2018).

The number of contractions being performed is a good predictor of VA, resting twitch torque and MEP amplitude

An unexpected finding in this study was the usefulness of contraction block number for the prediction of VA, resting twitch torque and MEP amplitude. No previous investigation has explored the contraction block number as a predictor of these variables with the current protocol. The number of contraction blocks performed was used as a base condition in the predictive models, and it turned out to be a very good predictor of some variables. In particular, the TMS derived variables of VA, resting twitch, and MEP amplitude were all better predicted by the number of contractions that had been performed compared to the subjective scales that were used to assess fatigue. This may be due to the consistency in obtaining TMS-derived variables (given that our lab specialises in this technique) in comparison to the subjectivity of the scales. TMS derived measures can be considered more consistent since delivery and techniques are held constant. Whereas subjective scales are more prone to errors as a result of cognitive bias (Khalid et al., 2015; Van Damme et al., 2008). There are many reports of declines in voluntary activation being characteristic of submaximal fatiguing tasks; where neuromuscular fatigue causes declines in neural drive and the progression of central fatigue (Martinez-Valdes et al., 2020; Taylor & Gandevia 2008). The fact that contraction block number was a good predictor of VA means that for the current submaximal contraction protocol, contraction block number is an accurate predictor of voluntary neural drive and, therefore, central fatigue. Additionally, reductions in resting twitch are characteristic of fatiguing tasks; thus, the finding of this study is consistent with those in previous studies (Gandevia et al., 2013; Herbert & Gandevia 1999; Neyroud et al., 2016). This finding indicates that for the current fatiguing protocol, contraction block number can be used as a good predictor of neuromuscular fatigue at a peripheral level. Further, Previous studies indicate that MEP amplitude is expected to increase with submaximal fatiguing tasks (Aboodarda et al., 2019; Cadigan et al., 2017; Hoffman et al., 2009). Effectively this finding indicates that contraction block number can be used as a good predictor of excitability of the corticospinal tract.

Therefore, with 2 minutes of sustained 20% isometric MVC elbow flexors, followed by 45 seconds of rest, repeated ten times to produce ten stages of contraction; number of contraction blocks can be used as good indicators of central fatigue with voluntary activation, peripheral fatigue with resting twitch and declining corticomotor excitability with MEP amplitude. These results are better predictors than subjective scale results. This finding has not been indicated by previous investigations.

5.1 LIMITATIONS AND FUTURE DIRECTIONS

A limitation of this study is that it uses an exploration of fatigue perception, which is limited to one mode of fatiguing contraction. Therefore, the investigation is limited to the context of submaximal isometric continuous fatiguing tasks only. Since central fatigue occurs at a slower rate for submaximal tasks in comparison to maximal tasks (Taylor & Gandevia 2008); it is therefore not possible to apply the same predictive model to maximal tasks since the basis of comparison is different. For this reason, the results of this study can only be a reference for studies that use submaximal fatiguing tasks and cannot be generalised to other contraction types. This limitation can be addressed in future studies by incorporating additional study arms which explore maximal and intermittent fatiguing tasks into the study design.

In addition, the timing of TMS was consistent for every contraction block. However, the nature of the scale response time is not consistent. Participants may take various lengths of time for deciding on scores for each scale. Similarly, subjects may preconceive values in their mind before they have to actually report the value. For example, if participants were counting the contractions, they may have been more motivated to finish the task knowing they only had a couple of contractions left, which may result in lower perception scores. This preconception may come from previous responses, an exasperated focus on either mental or

physical energy given to the task (Marshall et al., 2013; Cosmides & Tooby, 2013). Although the timing of TMS stimulations is constant and not affected by human error, the nature of the scales is not. It is difficult to improve this limitation as it is challenging to instruct participants on 'how to think'. In addition, the subjective nature of each scale acts as a limitation since results are affected by the interpretation and understanding of the participant. Participants have pre-existing cognitive bias and understanding of terms, illustrations and levels, which affect their interpretation of different levels of self-perceived measures of fatigue. Although the scales were explained during familiarisation, it is impossible to eliminate the effect of participant's cognitive bias on the interpretation of the scales.

Prolonged contractions with attachment to the load cell via a wrist strap often cause pain. This occurs particularly since the wrist strap is tightened to decrease compliance in the apparatus. Previous investigations have indicated that pain decreases exercise tolerance, neuromuscular performance as well as exertion (Aboodarda et al., 2020; Taylor et al., 2017). For this reason, pain caused by the wrist strap would have impacted TMS derived measures, torque derived measures as well as perceived measures of fatigue and exertion. It is difficult to improve on this limitation without sacrificing the accuracy of results by allowing compliance. An additional error between subjects is introduced with the loosening of the wrist strap during rest periods.

6.0 CONCLUSION

Given the prevalence of exercise investigations that use TMS and of self-reported measures of neuromuscular fatigue, it is not surprising that each assessment tool in this project was able to characterise fatigue during the contraction protocol. However, it was unexpected that an individual's perception of fatigue did not have a clear alignment with quantitative measures of

the motor pathway. It is clear that the additional supraspinal factor, other than activation of the motor pathway, influences the ability to perform exercise over an extended period.

APPENDIX A: MEDICAL HISTORY QUESTIONNAIRE

School of Allied Health Sciences

Neural Control of Movement Laboratory

Name: _____

Address:_____

_____

_____

Phone: ( ) _____ (W)

Phone: ( ) _____ (H)

DOB: _____

Age: _____

Height:_____

Weight:_____

Ethnicity: _____

Preferred hand:_____

Please read the following questions very carefully. If you have any difficulty or questions, please refer to the investigators of this project.

1. **Family History**. Indicate if any of your immediate family (parents, brothers, sisters, grandparents) have experienced any of the following, the age at which diagnosis occurred, and the person's relationship to you.

Relationship & Age

High Blood Pressure _____

High Cholesterol _____

Heart Disease _____

Stroke _____

Diabetes _____

Cancer _____

Other _____

2. **Personal Medical History**. Indicate symptoms that apply to you.

- ☐ Pain or discomfort in chest following exercise, eating or exposure to cold
- ☐ Frequent heart palpitations or flutter
- ☐ Pain in lower lungs when walking or climbing stairs
- ☐ Unusual shortness of breath
- ☐ Very poor exercise tolerance
- ☐ Frequent dizziness
- ☐ Chronic cough
- ☐ Frequent colds or flu

- ☐ Frequent headaches
- ☐ Frequent aches or pains in joints
- ☐ Frequent backache
- ☐ Other current symptoms that exercise may affect

3. Are you currently pregnant or have you recently given birth?

- ☐ Yes
- ☐ No
- ☐ Unsure

Details _____

4. Do you have any form of epilepsy?

- ☐ Yes
- ☐ No

Details _____

5. Have you ever been diagnosed with Bipolar Affective Disorder or Schizophrenia?

- ☐ Yes
- ☐ No

Details _____

6. Do you have any metallic objects in your body such as an implanted pacemaker or surgical clips?

☐ Yes

☐ No

Details _____

7. Are you presently experiencing, or have you ever been treated by a doctor for any of the following?

Allergies: Hayfever, Eczema, Other rashes.

☐ Yes

☐ No

Details _____

8. Do you have any known allergies?

☐ Yes

☐ No

Details _____

12. Lung Problems (Asthma/Emphysema/Bronchitis/Shortness of Breath/Other)

☐ Yes

☐ No

Details _____

13. Heart Problems (Rheumatic Fever/Chest Pains/Palpitations/Arrhythmia/Ankle Swelling/Prolonged QT interval/Other)

☐ Yes

☐ No

Details _____

14. Blood Pressure Problems

☐ Yes

☐ No

Details _____

15. Cholesterol Problems

☐ Yes

☐ No

Details _____

16. Easy Bruising

 Yes

 No

Details _____

17. Liver problems

 Yes

 No

Details _____

18. Kidney problems

 Yes

 No

Details _____

19. Diabetes/ Thyroid problem/ other endocrine

 Yes

 No

Details _____

20. Fitting, Fainting, Blackouts, Loss of consciousness, Muscle Weakness, Loss of Sensation.

☐ Yes

☐ No

Details _____

21. Headaches

☐ Yes

☐ No

Details _____

22. Nervous System Conditions

☐ Yes

☐ No

Details _____

23. Bone or Joint Injury (Back/Knee/Ankle/Hip/Shoulders)

☐ Yes

☐ No

Details _____

24. Do you muscles ever feel extremely stiff? Have you been diagnosed with any form of muscle spasticity?

☐ Yes

☐ No

Details _____

25. Are you currently, or have previously been treated for depression?

☐ Yes

☐ No

Details _____

26. Have you had any surgical procedures in the last 10 years?

☐ Yes

☐ No

Details _____

27. Work Related Injuries

☐ Yes

☐ No

Details _____

28. Are you exposed to a noisy/or dusty environment?

☐ Yes

☐ No

Details _____

29. How often do you take over the counter medications such as paracetamol, aspirin, etc?

- Daily
- Weekly
- Occasionally
- Never

Details _____

_____

30. How often do you take herbal medications or supplements, e.g. calcium or fish oil?

- Daily
- Weekly
- Occasionally
- Never

Details _____

_____

31. Medication. Are you taking any medication prescribed by your Doctor or other Health Care provider? If so, list details, i.e. medication name and dose

_____

_____

_____

_____

_____

_____

_____

32. Have you stopped or started any medications in the last 14 days?

☐ Yes

☐ No

Details _____

33. Sleeping Patterns. How many hours do you sleep on average per night? _____ hours

34. Do you ever have trouble falling asleep?

- Yes
- No
- Occasionally

35. Smoking Status

- Never smoked
- Quit smoking more than 10 years
- Quit smoking less than 10 years
- Currently smoke (number of years __

36. Physical Activity. How many times per week do you exercise for at least 20 - 30 minutes continuously?

- Do not have a regular program
- Once per week
- 2 - 3 times per week
- 4 - 5 times per week
- more than 5 times per week

37. Resistance Training. How many times per week do you undertake resistance training with the upper body for at least 20 - 30 minutes continuously?

- Do not have a regular training program
- Once per week

- 2 - 3 times per week
- 4 - 5 times per week
- more than 5 times per week

38. In the past two weeks list how many drinks on **average** you had **per day.**

- Did not drink in the past two weeks
- Less than 1 drink per day
- 1 drink per day
- 2 - 3 drinks per day
- 4 or more drinks per day

39. Have you consumed any alcoholic beverages or related substances in the last 24 hours?

- Yes
- No

Details _____

APPENDIX B: INFORMATION AND CONSENT FORM

Do perceived measures of fatigue align with quantitative measure of fatigue?

Participant Information sheet

Who is conducting the research	**Chief Investigator** Associate Professor Justin Kavanagh School of Allied Health Sciences (07) 5552 8057 j.kavanagh@griffith.edu.au	**Student Researcher** Miss Monica Marzouk School of Allied Health Sciences monica.marzouk@griffithuni.edu.au

Why is the research being conducted?

Perceived scales of fatigue are used widely across several disciplines such as sport science, psychology, neuroscience and physiotherapy. However, previous research has highlighted the need for further investigations into the validity and accuracy of such scales. This investigation will determine the association of perceived scales of fatigue with objective quantifiable fatigue, thereby indicating the accuracy of perceptual scales of fatigue. The current study will employ a combination of Transcranial Magnetic Stimulation (TMS) and peripheral nerve stimulation (PNS) to quantify neural activity within the central and

peripheral nervous systems. Participants will also report their perception of fatigue via 5 commonly used scales in fatigue studies.

What you will be asked to do

If you agree to participate in this study, you will need to visit the School of Allied Health Sciences Neural Control of Movement laboratory (G02 room 2.12) for approximately 90 minutes. The experiment itself runs for approximately 60 minutes, which consists of approximately 30 minutes of preparation followed by 60 minutes of muscle contractions. Preparation involves introduction to scales, skin cleaning and abrading, electrode placement for our muscle measurement devices, and obtaining baseline measurements of muscle function. Our 10 minute contraction protocol involves 10 repetitions of a 2 minutes low-intensity contraction of the biceps.

At the end of each 2 min biceps contraction, a single-pulse of transcranial magnetic stimulation will be applied to the top of your head so that we can assess how easily the brain was able to activate the biceps in the presence of fatigue. Immediately following this magnetic stimulation, a single-pulse of electrical stimulation will be delivered to biceps with a peripheral nerve stimulator. Each stimulation will make your biceps contract involuntarily. The stimulations we use simply replace normal human processes for activating muscles. While you are at a very low risk of experiencing any harm, a stimulation from either device can feel a bit uncomfortable the first time you experience it. Although these stimulations may initially feel uncomfortable, they should not elicit pain. In fact, we often describe to ‘first

time participants' that a stimulation feels like a tennis ball being tapped against your bicep. If at any point during testing you feel that you cannot tolerate the stimulations we will stop testing. We will communicate with you throughout the testing session to ensure your comfort is well maintained.

During the contraction protocol you will be asked to report how fatigued you are feeling. This will be achieved by completing a visual analogue scale of fatigue, a Likert scale of fatigue, the OMNI scale of fatigue, a rating of perceived exertion (RPE), and a modified Borg dyspnoea and rate of fatigue (ROF) scales. These have all been commonly used in fatigue experiments. You will be familiarised with these scales using briefing session and preparation.

The basis by which participants will be selected or screened

We are recruiting healthy individuals between the ages of 20 and 30 years. You will not be eligible for the study if you have a known neurological, cardiac or respiratory disorder, are pregnant, have an implanted medical device such as a pacemaker, are currently taking neurological, pulmonary or cardiovascular medications, or are currently undertaking resistance training more than three times a week. You will be asked to complete a medical history questionnaire so we can screen your suitability to undertake our study.

The expected outcomes of the research

Once the results of the study have been analysed, the findings will be used in Miss Monica Marzouk's thesis required for her Masters (MMR) candidature, and a manuscript containing

the results of the study will be submitted to an international peer-reviewed journal. No publications or presentations of the findings of the study will include your name or identity. Data will be presented in the form of group results.

Risks to you

The stimulation procedures used in this study trigger electrical events in nerves and muscles that occur naturally in the human body up to a billion times every day. Therefore, the risks associated with brain and nerve stimulation are low in healthy individuals. The sensation of magnetic and electrical stimulation can be described as a short sharp twitch in the target muscle that can initially be uncomfortable, but most people quickly become used to it. In very occasional circumstances, some participants may experience a headache or some light headedness during testing.

In the unlikely event that you require medical treatment due to our testing procedures, you will be immediately attended by the supervising researcher who manage your care. For serious events, an ambulance will be called and you will be taken to the emergency department of the hospital as directed by the paramedical staff and all the associated expenses will be covered as per university policy. Specifically, if an adverse reaction occurs, insurance cover for this study is via the Griffith University public liability policy under the ‘legal liability for personal injuries to a third party caused by an event in connection with our business.’ In the case of any event one of the chief investigators of the study or a doctor associated with the university will write a letter for you to present to your general practitioner advising them of the findings.

Your confidentiality

Associate Professor Kavanagh and Miss Marzouk will be the only people with access to your records, which will be stored in a secure place (G02 room 2.16) without reference to your name. The records (aside your medical history questionnaire) will be coded and these codes will be used throughout the analysis of the results to ensure that the investigators are the only people who can match your records and results with your name. Personal information (including your medical history questionnaire) will be stored for a period of 5 years following the completion of the study to meet with requirements of State and Commonwealth governments. Following this period all data will be destroyed via approved and safe mechanisms at Griffith University.

Your participation is voluntary

It is important that you freely volunteer to take part in this study. You are free to withdraw from the study at any time, and of course, there will be no penalty if you choose to do so. Any decision to withdraw from the study will not impact on your relationship with the university.

Feedback to you

If you would like a summary of your results, you are welcome to contact Associate Professor Justin Kavanagh via email (j.kavanagh@griffith.edu.au). He will then provide a short document

in plain language which describes how your results fit into the context of the study.

Questions or further information?

If any aspect of the study concerns you, or you have other questions regarding the investigation, please do not hesitate to contact one of the chief investigators whose contact details appear on the front page.

The ethical conduct of this research

This project has been approved by the Griffith University Human Research Ethics Committee (GU ref no: 2020/785). Griffith University conducts research in accordance with the *National Statement on Ethical Conduct in Human Research*. If you have any concerns or complaints about the ethical conduct of the research project you should contact the Manager, Research Ethics on 3735 4375 or research-ethics@griffith.edu.au.

Privacy Statement

The conduct of this research involves the collection, access and use of your identified personal information. As outlined elsewhere in this information sheet, your de-identified personal information may appear in publications arising from this research. This is occurring with your consent. Any additional personal information collected is confidential and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. A de-identified copy of this data may be used for other research purposes. However, your anonymity will at all times be safeguarded, except where you have consented

otherwise. For further information consult the University's Privacy Plan at http://www.griffith.edu.au/about-griffith/plans-publications/griffith-university-privacy-plan or telephone (07) 3735 4375.

Thank you for your assistance in this research project

Do perceived measures of fatigue align with quantitative measure of fatigue?

Consent form

Research team	**Chief Investigator**	**Student Researcher**
	Associate Professor Justin Kavanagh	Miss Monica Marzouk
	School of Allied Health Sciences	School of Allied Health Sciences
	(07) 5552 8057	monica.marzouk@griffithuni.edu.au
	j.kavanagh@griffith.edu.au	

This project has been approved by the Griffith University Human Research Ethics Committee (GU ref no: 2020/785). By signing below, I confirm that I have read and understood the information package and in particular have noted that:

- I understand that my involvement in this research will include one visit to the Neural Control of Movement laboratory (G02 room 2.12), where I will undergo the experimental protocol outlined in the participant information sheet;
- I have had any questions answered to my satisfaction;
- I understand the risks involved;
- I confirm that I do not have any of the exclusion criteria listed on the participant information sheet;

- I understand that there will be no direct benefit to me from my participation in this research;
- I understand that my participation in this research is voluntary, and I understand that my decision to participate in no way impacts upon the service I receive from Griffith University or the Investigators of this project;
- I understand that if I have additional questions I can contact the research team;
- I understand that I am free to withdraw at any time, without explanation or penalty;
- I understand that I can contact the Manager, Research Ethics, at Griffith University Human Research Ethics Committee on 3735 4375 (or research-ethics@griffith.edu.au) if I have any concerns about the ethical conduct of the project; and
- I agree to participate in the project.

Signature: _____

Name: _____

Date: _____

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