Can resistance training improve hand and finger dexterity and quality of life in essential tremor patients?

Graeme Marc Sequeira

BSc (Sport and Exercise Science), PgDipSci (Exercise Rehabilitation)

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Faculty of Health and Environmental Science

School of Sport and Recreation

Primary Supervisor: Associate Professor Justin Keogh

Abstract

Essential tremor (ET) is a common neurological movement disorder occurring in 1 - 5% of the general New Zealand population. ET is typically characterised by a kinetic tremor with the upper limb most often affected. A number of pathologies have been proposed to underlie ET however no definitive consensus has yet been reached.

The enhanced tremor symptomatic in ET can have a serious negative effect on a number of areas including an individual's quality of life (QoL) and daily functioning. Therefore, finding an effective rehabilitation therapy would be of significant value. Currently a number of medical and clinical treatments such as non-specific medication, surgery and bio-behavioural treatment have been proposed for ET. Each option however, carries limitations, risks and varying levels of effectiveness.

A novel therapy option may be that of resistance training (RT). RT has been shown to induce neuromuscular adaptations such as reduced motor unit firing rate variability and upper limb co-activation. These RT induced changes have been shown to reduce postural tremor and improve manual dexterity in neurologically normal older adults. Therefore this pilot study examined the effect of a general, short-term dumbbell-based upper limb RT programme on upper limb strength, hand and finger dexterity and quality of life in individuals with ET. Six subjects (5 female, 1 male, age: 74 $\pm$ 7 years, years diagnosed: 19 $\pm$ 7 years) were recruited with one being excluded from the results analysis due to an unrelated hospitalisation. Each participant performed familiarisation and baseline testing prior to undergoing a six week period of RT. This was immediately followed by a post-intervention test and a six week training withdrawal period. A final assessment was then performed after the withdrawal period. Assessment sessions included an upper limb strength examination using a five repetition maximum (5RM) strength test, hand and finger manual dexterity test using the Purdue Pegboard Test (PPT), and two quality of life measures: the Short Form 36 (SF-36) and Quality of Life in Essential Tremor (QUEST) questionnaires.

Following the general RT programme, ET participants experienced significant improvements in some strength and hand and finger dexterity measures. There were however, no significant changes in quality of life. The findings of this pilot study provide evidence that further investigation into RT as a potential therapy for ET is warranted.

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Ethical approval for this research was granted by the Northern Regional Y Ethics committee; reference NTY/10/03/025.

Statement of Originality

I hereby declare that this submission is my own work and that to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the qualification of any degree or diploma of a university or other institution of higher learning, except where due acknowledgement is made in the acknowledgements.

Graeme Sequeira
Faculty of Health and Environmental Science
School of Sport and Recreation
AUT University

Thesis Organisation

The thesis is organised into seven chapters. Chapter 1 is an introduction. Chapter 2 is a review of the literature initially providing a brief background into tremor in general followed by a comprehensive examination of ET. Areas such as characteristics, pathology and rehabilitative options available to ET are described based on key empirical evidence. Chapter 3 describes the study method including design, participants, assessment measures, and training intervention. The results are presented in Chapter 4 followed by a discussion of the results in Chapter 5. Chapter 6 identifies possible limitations of the study and future directions for further research followed by a conclusion in Chapter 7.

List of Publications

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Chapter 1 - Introduction

Essential tremor (ET) is a common, neurological movement disorder. ET is suggested to occur between 0.5% and 4% in the general population (Troster & Woods, 2010) with prevalence increasing with aging (Louis, Ottman, & Allen Hauser, 1998). While most people think of Parkinson's disease (PD) when the word tremor is mentioned, it is estimated that occurrence of ET may be 20 times greater than that of PD (Louis, 2005; Louis, et al., 1998). The prevalence of ET in New Zealand is unknown however it is believed to occur in 1-5% of the general population (New Zealand Essential Tremor Support Group, 2010). As such it is difficult to assess the exact social and financial cost of ET in New Zealand however it is potentially significant when considering the associated disability and relation to loss of employment or early retirement from work (Louis, 2005). An insight into potential cost/benefit can be seen in a report by the National Service and Technology Review Advisory Committee to the District Health Boards, regarding a business case for Deep Brain Stimulation (DBS) in movement disorders (Ministry of Health, 2008). The report highlighted potential immediate direct savings across New Zealand of $153 065 per year if the suggested programme was implemented with further on-going savings across five years (Ministry of Health, 2008). These potential savings were calculated using Australian figures, based on the reduced need of pharmacotherapy only and did not take into account potential savings from other areas such as valued quality of life (QoL) improvements and ability to return to work.

ET is typically characterised by a kinetic tremor that has a frequency of 4-12Hz, however postural and intention tremor may also be present (R. Elble, 2009; Louis, 2005, 2010b). This disorder commonly affects the upper limb but may also occur in lower limbs, head and voice (Lorenz & Deuschl, 2007; Louis, 2005). Though the pathology of ET is not fully understood, it may reflect dysfunction in the olivocerebellar and thalamocortical pathways (R. J. Elble, 2009). Sensorimotor characteristics of ET can include abnormal entrainment of motor unit activity at the frequency of the tremor, and inappropriate patterns of agonist-antagonist muscle activation and reduced force steadiness of the digits (M. E. Héroux, Pari, & Norman, 2010; Lundervold & Poppen, 2004b). These sensorimotor changes may contribute to the kinetic tremor in combination with postural tremor commonly seen in ET. This can have a considerable negative impact on function such as manipulating and reaching. Such movements are part of a number of daily living activities including eating, drinking, and writing (W. C. Koller, Busenbark, & Miner, 1994; Louis, et al., 2001; A. Rajput, Robinson, & Rajput, 2004). ET patients often experience a loss of hand and finger dexterity, and as a result disability due to a loss of independence and even incapacitation (Louis, 2005). This disability and loss of independence with ET can dramatically effect psychosocial status, with significant declines in QoL evident (Deuschl & Elble, 2009). Furthermore, alterations to eye-hand coordination (Trillenberg, et al., 2006), eye-blink reflex (Deuschl & Elble, 2009) and disturbances in cognitive function have also been observed in ET (Louis, 2010a).

ET is typically managed via pharmacological therapies, with Propranolol and Primidone the most commonly used (R. Elble, 2009). Initial effectiveness has been reported as low as 50%, with the magnitude of effectiveness diminishing over time (R. Elble, 2009; Lyons, Wilkinson, & Pahwa, 2006). Potentially, the most potent drug available to ET is alcohol however due to its addictiveness and social ramifications if abused, it is not a widely recommended option (Klebe, et al., 2005; Nahab & Hallett, 2006). If pharmacological interventions prove ineffective, the option of surgical interventions such as DBS may be considered for those severely affected. Surgical options, such as DBS, provide positive results however are invasive, carry associated risks and are costly (Lyons & Pahwa, 2008).

A potential movement-based rehabilitative method, bio-behavioural therapy has also been investigated for use in ET. This has shown some potential with reductions seen in tremor ratings, EMG activity and improvements in some reported activities of daily living (Chung, Poppen, & Lundervold, 1995; Lundervold & Poppen, 2004a). This method too has some limitations, including a short-term window of improvement and questionable long-term cost effectiveness (Lundervold, Belwood, Craney, & Poppen, 1999).

A novel rehabilitation therapy may be that of resistance training (RT), potentially due to the neuromuscular adaptations and improvement in QoL that occur (Enoka, 1997). Mechanisms behind such neuromuscular changes may include increased neural drive, motor unit changes and muscle activation (Bruton, 2002; Engardt, Knutsson, Jonsson, & Sternhag, 1995; Hakkinen, et al., 1998). These adaptations are seen in a number of different populations including older adults and those with other movement conditions (Cochrane, Munro, Davey, & Nicholl, 1998; de Goede, Keus S.H.J, Kwakkel, & Wagenaar, 2001; de Paula, Teixeira-Salmela, Coelho de Morais Faria, Rocha de Brito, & Cardoso, 2006).

Only one study has examined the effect of RT on ET, finding an increase in maximum force production and an improved force steadiness in participants that had undergone the higher intensity RT programme (Bilodeau, Keen, Sweeny, Shields, & Enoka, 2000). Though the mode of training was a limited, lab specific programme, a more general RT method has been shown to reduce postural tremor amplitude (J W. L. Keogh, Morrison, & Barrett, 2010) and force steadiness in older adults (J.W.L Keogh, Morrison, & Barrett, 2007). This study incorporated dumbbell-based elbow flexion, wrist flexion and wrist extension exercises.

Purpose & Hypotheses

The purpose of this thesis was to assess the impact of a general, dumbbell-based RT programme in an ET population. This original pilot work will provide insights into potential improvements relating to strength, hand and finger dexterity, and QoL. This will power larger randomised controlled trials in the future, if the preliminary results of this study are positive. The specific hypotheses of the pilot study were that following a six week, general RT programme significant improvements would occur in upper limb strength, hand and finger dexterity, and QoL.

Originality

Investigations into other rehabilitative therapies for ET are warranted, due to limitations associated with current available options. RT may potentially be such an option, however only one study has examined the effect of a task specific RT programme on ET (Bilodeau et al., 2000). Following a four week period of RT, the authors reported significant improvements in muscle force steadiness. This improvement however, did not translate to improved functionality. A six week, general RT study created by Keogh, et al. (2007) showed significant reductions in postural tremor amplitude and tri-digit force variability in neurologically normal older adults (J.W.L Keogh, et al., 2007; J W. L. Keogh, et al., 2010). Utilising the RT programme described by Keogh, et al. (2007), this pilot study was the first to assess what potential a general RT programme may have on ET.

Chapter 2 - Literature Review

In certain populations the ability to control motor functions is impaired which may result in reductions in physical function and QoL. This literature review examines such a movement disorder, specifically that of ET and its impact, pathology and available rehabilitative options.

Tremor

Tremor has been defined in the Movement Disorder Society's consensus statement as the "rhythmical involuntary oscillation of a body part" (Deuschl, Bain, & Brin, 1998, p. 1). In the healthy adult population, involuntary tremor may be evident when performing fine motor tasks. Incidence of this tremor, often described as physiological tremor, becomes more prevalent in later life (R. Elble, 2009). Tremor may also be symptomatic of pathology, such as the tremor seen in ET. As is the case with ET, the pathophysiology of the condition and the resulting tremor are not well understood and are under investigation (Lorenz & Deuschl, 2007). Pathological tremor may be categorised according to its occurrence, with common descriptions being postural, resting, kinetic, and intention tremor (Deuschl, et al., 1998). Further to this, tremor may be triggered or enhanced by environmental factors such as a stressful environment or social phobia (Louis, 2010a; Lundervold, Pahwa, & Lyons, 2009; Lundervold & Poppen, 2004b).

Essential Tremor

Epidemiology

ET is recognised as a neurological movement disorder and is cited as one of the most common tremor disorders (Louis, 2005). Though further research is required, incidence of ET is suggested to be between 0.5% and 4% in the general population (Troster & Woods, 2010). Occurrence of ET is estimated to be 20 times greater than PD (Louis, et al., 1998).

A recent survey conducted in Turkey by Sur et al. (2009) of 2227 people reported an ET prevalence of 3.09% in the adult population (over 18 years of age) spread evenly across both genders. Similarly Rajput et al. (1984), found no difference between genders with an adjusted prevalence rate of 2.37% for ET in the population of Minnesota, USA. Interestingly Tan et al. (2005) found prevalence differences between three ethnicities living in Singapore. The authors found that incidence in the sampled Indian community were 4.94%, with 2.77% in the Chinese community and no evidence of ET in the Malay community sample. The variation of findings reported in these epidemiology studies may be due to differing criteria used to diagnose ET (Lorenz & Deuschl, 2007). As it stands the prevalence of ET in New Zealand is unknown however it has been suggested to occur in 1-5% of the population (New Zealand Essential Tremor Support Group, 2010).

Characteristics/Symptoms of ET

Historically ET was known as 'Benign Essential Tremor' however due to the negative impact it can have on different aspects of a person's life, 'benign' has been removed (W. C. Koller, et al., 1994; Troster & Woods, 2010). ET currently has no widely agreed upon classification with a range of anatomical and clinical definitions cited in the literature. Examples of these proposed definitions for ET include definite ET and probable ET (Deuschl, et al., 1998), hereditary, senile and sporadic ET (Deuschl & Elble, 2009), cerebellar ET and non-Lewy body variant ET (Louis, 2010b). This lack of agreement has lead to some difficulty in literature comparison.

ET can impede a person's ability to perform daily and occupational activities such as eating, dressing and writing (W. C. Koller, et al., 1994; Louis, et al., 2001; A. Rajput, et al., 2004). ET can also have a significant adverse affect on an individual's QoL and morale (Lorenz, Schwieger, Moises, & Deuschl, 2006; Louis, Benito-Leon, & Bermejo-Pareja, 2008). Functional ability may also be reduced in people with ET (M E. Héroux, Parisi, Larocerie-Salgado, & Norman, 2006). For example, Parisi, Heroux, Culham and Norman (2006) assessed balance and gait performance in 30 people with ET and 28 healthy controls. The authors found that the ET group displayed significantly less functional ability than the control group in measures of Timed Up and Go, Dynamic Gait Index, Berg Balance Scale, and two activities based questionnaires. However it was noted that ET scores were still above thresholds of the balance tests that would indicate a greater risk for falls. In post-hoc analysis Parisi et al. (2006) found that participants classed in the sub-group of ET with head tremor (16 participants) scored significantly worse on these outcomes when compared to the 14 ET participants without head tremor.

ET is typically characterised by a kinetic tremor that has a frequency of 4-12Hz which commonly effects the upper limb (Lorenz & Deuschl, 2007; Louis, 2005). It is thought that the 8-12Hz tremor is more prevalent in younger ET persons, with it decreasing to 4-6Hz in later life (Hallett, 1998). This concept was recently supported by Hellwig, et al. (2009) who performed a longitudinal study following 60 ET patients over a period of up to 51 months. The authors found that across this period the frequency of tremor dropped at a rate of 0.12Hz per year.

Initially ET was only thought of as a form of kinetic tremor however the heterogeneity of the disease is now gaining recognition (Lorenz & Deuschl, 2007; Louis, 2010b). Other symptoms such as postural and intention tremor are also evident (R. Elble, 2009; Louis, 2005). Gait ataxia (Klebe, et al., 2005), reduced eye-hand coordination (Trillenberg, et al., 2006) and altered eye-blink reflex (Deuschl & Elble, 2009) have also been associated with ET. Furthermore disturbances in cognitive function and association of dementia onset with ET are evident (Louis, 2010a). ET tremor does not only affect the upper limbs but can also affect areas such as the head, voice and lower limbs, with a wide range of severity between and within individuals (R. Elble, 2009; Louis, 2005).

Pathophysiology of ET

There is debate in the literature as to whether ET is due to neurodegeneration or neural dysfunction (Deuschl & Elble, 2009; Louis, 2010b). Certainly a link between the typical kinetic tremor and the cerebellum, responsible for error correction during force production, is evident in the dysfunctions seen in ET (Louis, et al., 2001). A number of difficulties surround the ability to identify the pathology of ET including varying classifications, misdiagnosis and inadequate controls (R. J. Elble, 2009; Lorenz & Deuschl, 2007). Furthermore, it is often difficult to separate effects of co-morbidities and general aging from ET on the neural system (Deuschl & Elble, 2009).

Pathophysiology - Neural dysfunction

Neural dysfunction can be thought of as comprising two subgroups, that of a central and peripheral pathology. Central pathology in this review examines alterations occurring in ET that relate to central areas such as that of the cerebellum or inferior olive while peripheral pathology identifies the influence of stretch reflex and motor unit entrainment in ET.

Central pathology

ET typically exhibits a kinetic tremor of 4-12Hz (E. Louis, 2005). Various possible sources for this oscillation have been suggested including the cerebellarthalamocortical pathway and olivocerebellar pathway (R. J. Elble, 2009; Pinto, Lang, & Chen, 2003).

The possible involvement of the cerebellum in the pathology of ET has been identified through the use of imaging tools such as Positron Emission Tomography (PET), dysfunction in tasks related to cerebellar function (Trillenberg, et al., 2006), the disappearance of tremor after cerebellar stroke (Pagan, Butman, Dambrosia, & Hallett, 2003) and the use of DBS to successfully treat tremor (Jenkins, et al., 1993; Yu & Neimat, 2008). Jenkins, et al. (1993) assessed 11 ET patients and 8 controls using PET during postural and rest conditions. The authors found that at rest the ET group had increased levels of cerebellar blood flow and showed a bilateral over-activity of the cerebellum during postural conditions. Increased thalamic activity was also seen in the ET group during postural conditions. Cerebellar dysfunction was also pointed to in a multi-voxel magnetic resonance spectroscopy study using N-acetylaspartate to Choline (NAA/Cho) and N-acetylaspartate to Creatine (NAA/Cr) ratios (Pagan, et al., 2003). Changes from healthy NAA/Cho and NAA/Cr ratio levels may indicate presence of neuronal and/or axonal damage (Bozgeyik, Burakgazi, Sen, & Ogur, 2008). Pagan, et al. (2003) found reduced NAA/Cr and NAA/Cho ratios of the cerebellum in 10 ET patients when compared to 10 healthy controls. Though the authors found this dysfunction they also noted that there was no neural degeneration in this group of ET patients.

Manifestations of this cerebellar dysfunction include abnormalities in gait, balance and intention tremor which have been identified in ET patients (Klebe, et al., 2005; Louis, 2010a). Kronenbuerger et al., (2008) used conditioned eyeblink response, a model of non-declerative learning, to evaluate the role of the cerebellum and inferior olive in ET. The authors compared 33 age-matched participants made up of 11 ET patients who had undergone DBS, 11 ET with no history of DBS and 11 healthy controls. The results showed that the ET participants with DBS had improved conditioned responses when compared to non-DBS ET participants, and theorised that DBS may act on the olivocerebellar pathway. Kronenbuerger, et al. (2008) also noted that these findings may support a functional rather than degenerative pathology behind ET.

Gait ataxia has also been identified in ET and is associated with cerebellar dysfunction (Lundy-Ekman, 2007). Klebe, et al., (2005) investigated gait ataxia in ET patients and how ingesting ethanol may reduce this effect. After ingestion of alcohol ET participants showed a significant improvement in gait measures, with no comparable change in the control group. Klebe, et al. (2005) also noted that there was no relation between levels of ataxia and self-rated severity of tremor. The authors hypothesised that alcohol may have a mediatory effect on cerebellar receptors or complex spike activity generated by the inferior olive. It was also suggested that due to the ability of alcohol to alter the ataxia it seemed more likely that ET reflects central dysfunction as opposed to neural degeneration.

The inferior olive has been implicated as a possible oscillatory source of ET, propagating though the olivocerebellar pathway and resulting in the associated cerebellar dysfunctions noted in ET (Deuschl, Raethjen, Lindemann, & Krack, 2001; R. J. Elble, 2009; Lorenz & Deuschl, 2007). The olivocerebellar network may act to control motor timing and have a role in motor correction (Llinás, 2009). Structurally, inhibitory afferent impulses from the inferior olive travel via climbing fibres to Purkinje cells found in the cerebellum (Velarde, Nekorkin, Makarov, Makarenko, & Llinás, 2004). Inferior olive oscillatory activity is evoked by the action of normal sodium and potassium conductors and three membranous ion channels (Rothwell, 1998). These channels include a low threshold calcium somatic membrane ion channel, a high threshold calcium dendritic ion channel and a calcium-dependant potassium conductance channel (Llinás, 2009; Rothwell, 1998; Velarde, et al., 2004). Olive neurons have the ability to fire individually or synchronously as a group through their electric coupling via gap junctions (Rothwell, 1998). This coupling may provide another reason why alcohol is effective in ET as it is thought to have the ability to inhibit this activity (Klebe, et al., 2005; Rothwell, 1998).

Peripheral pathology

Besides potential central mechanisms of ET, there is the possibility that peripheral sources may influence and/or enhance the severity of the tremor seen in ET. Such sources are that of the stretch reflex, motor unit entrainment and antagonist co-contraction (Deuschl, et al., 2001; M. E. Héroux, et al., 2010; Lundervold & Poppen, 2004a).

The potential role of the stretch reflex in tremor can be understood if we consider a movement, such as one performed in this study's intervention, the wrist extension. As the wrist extensor muscles act as agonists to perform the movement, the wrist flexors which act as antagonists to this movement undergo stretch, resulting in an afferent volley from the muscle spindles of the flexors. The net result is the flexors will then contract, causing a stretch in the extensors. This then results in further contraction of the extensors (Shumway-Cook & Woollacott, 2007). It is conceivable that with the appropriate reflex arc conduction time and/or reflex gain a pathologic tremor may occur (Deuschl, et al., 2001; Rothwell, 1998). Raethjen, et al. (2000) investigating coherencies in tremor, theorised that such reflexes may directly act on the central system via the spinal cord. The authors suggested this could be the reason behind their findings of a number, instead of a single central oscillatory source of tremor in ET participants. The authors however acknowledged that this possibility has yet to be fully investigated. The potential influence of peripheral sources in ET was initially seen in a study by Lee and Stein (1981). The authors assessed tremor phase resetting after mechanically 'disturbing' wrist tremor in 11 ET and 13 PD participants. Tremor pattern and a Normalised Resetting Index (NRI) with 0 = complete reset, 1 = not reset at all, were measured. Lee and Stein (1981) found that in ET mechanical perturbation lead to significant tremor phase resetting (mean NRI = 0.64) however this did not occur in the PD participants (mean NRI = 0.16). The presence of this phase resetting coupled with similar tremor amplitudes in the ET and PD participants was purported by the authors to suggest that ET has a greater peripheral contribution to its tremor. Lee and Stein (1981) therefore proposed that pathological tremor is not so much limited to either central or peripheral sources but rather a contribution of both, with the differences reflecting different relative contributions of these components.

Such possible coupling between central and peripheral oscillators was shown by Elble, Higgins and Hughes (1992) who further examined phase resetting in 10 ET patients and 10 healthy controls. They found that the central oscillator responsible for ET can be coupled with the stretch reflex. Interestingly the reflex was identified to be not abnormally enhanced, as results were similar between the ET and control group. The authors suggested that this coupling may have a bearing on tremor amplitude, and suggested this may explain the inter-individual differences in tremor observed in ET.

Adding a load to a limb dampens the mechanical resonance of the limb and alters the mechanical reflex tremor frequency. With this in mind Heroux, Pari and Norman (2009) examined the effect of an unsupported, light to moderate load on wrist tremor in ET. The authors found that applying a load equal to 15% of a maximum load, to the hand, resulted in significant decreases in tremor amplitude. This loading also resulted in postural tremor spectral power frequency separation of the mechanical and central elements. From this the authors suggested that peripheral factors may contribute to the amplitude of the tremor via interaction with the central oscillations. Interestingly Heroux, et al. (2009) found an increase in wrist EMG activity without a corresponding increase in EMG tremor spectral power. As a result the authors raised the possibility that a component of ET may relate to entrainment of motor units. Further evidence of the potential role of the stretch reflex was found when the authors compared results from 21 participants that had been part of both, the unsupported loading Heroux, et al. (2009) study and the supported loading Heroux, Pari and Norman (2010) study. By using the method of supported loading, mechanical reflex influences were reduced (M. E. Héroux, et al., 2010). When the two results were compared the authors noted that tremor amplitude was lower in the supported loading method. They suggested that this difference may further highlight the contribution of the stretch reflex to tremor (M. E. Héroux, et al., 2010).

Motor unit entrainment may occur at the centrally driven 8-12Hz frequency seen in ET and can share the same oscillation frequency of the wrist (Elble, 2003). Interestingly ET severity may relate to motor unit entrainment. Heroux, et al. (2010) investigated the effect of muscle contraction under progressive loads (5%, 10%, 20% and 30% of a maximum load) measuring EMG activity and tremor variables. The authors found EMG activity and force fluctuations increased with increasing loads however tremor spectral power did not, supporting their earlier findings. In this study the authors had used two sub-groups of ET based on tremor severity. This grouping allowed them to find that greater force fluctuations occurred in the more severe ET subgroup. The authors postulated that this may be because of an association between greater motor unit entrainment and a greater tremor severity.

Altered co-contraction of the antagonist muscle has been proposed to possibly have a weak role in ET. Lundervold, et al. (2004a) found a small correlation between agonist and antagonist co-contraction in one of three participants in a bio-behavioural intervention study. Interestingly increased levels of antagonist co-contraction are seen with aging, with greater levels of co-contraction seen in healthy older adults compared to younger adults (Laursen, Jensen, & Ratkevicius, 2001; Tracy & Enoka, 2002). As physiological tremor increases with age it is conceivable that this co-contraction may have a role in the peripheral contribution to tremor (Morrison, Mills, & Barrett, 2006).

Pathophysiology - Neurodegeneration

Post-mortem research on donated ET brains is providing some insight into possible degeneration that may occur in ET patients. In a recent review, Louis (2010b) discussed recent post-mortem investigations of ET brains and the differences that were observed in the cerebellum. In examination of a total of 33 brains across a number of studies (Deuschl & Elble, 2009), three main findings were noted; firstly that of changes to and loss of Purkinje cells, secondly changes to the basket cell resulting in the presence of "hairy baskets"; and finally the presence of Lewy bodies. Controversy surrounds this neurodegenerative research, with factors such as degeneration due to natural aging, comorbidities, sample size and variation in methodology cited as possible reasons for the observed results (Deuschl & Elble, 2009; A. H. Rajput, Robinson, Rajput, & Rajput, 2010).

Purkinje cells

Purkinje cells are found at the piriform layer and Purkinje cell dendrites at the molecular layer of the cerebellum. These cells have an inhibitory effect on the central nuclei of the cerebellum (Fitzgerald, Gruener, & Mtui, 2007). In the ET brain, two changes may occur to these cells, that of "torpedo" formation and cell loss. "Torpedoes" are described by Louis, et al. (2009, p1.) as "rounded swelling of the proximal portion of the Purkinje cell axon". Upon closer investigation the authors found that the torpedoes consisted of a disorganised congregation of neurofilaments, smooth endoplasmic reticulum, mitochondria and were immunoreactive. In a study by Louis, et al. (2009) comparisons of the number of these torpedoes were made in brains from patients with ET, Alzheimer's and PD as well as age matched controls. The results showed that there were significantly greater number of torpedoes in patients with ET when compared to healthy controls (10.5 times greater), Alzheimer's (2.5 times greater) and PD (2.5 times greater).

With normal healthy aging some loss of Purkinje cells is expected however the loss of these cells may be greater in ET. Axelrad, et al. (2008) assessed 14 ET brains, which were classified into two groups (ET 'with Lewy bodies, present and ET 'without Lewy bodies') and compared to 11 age matched controls. The authors found that in the age matched control group cell density had a mean of 3.46 cells/mm compared with 2.14 cells/mm for brains classified as ET 'without Lewy bodies' and 3.33 cells/mm for brains classified as ET 'with Lewy bodies'. These results indicated a moderate loss of Purkinje cells in the ET group classified as ET 'without Lewy bodies'.

However, a recently published study by Rajput, et al. (2010) presented conflicting results to those discussed above. In the study Rajput et al. (2010) examined 7 ET brains (which were matched to the 'without Lewy body' classification), 6 PD brains and 2 controls with no medical history of any neurological condition. Three different methods for counting Purkinje cells were used, including the method used by Axelrad, et al. (2008) whereby a cell was only counted if there were visible nuclei. Rajput, et al. (2010) found that there was no significant difference between ET and the controls in all three methods of counting and the same for two out of the three counting methods compared to that of PD. The difference between ET and PD (less Purkinje cells in the ET sample) was found when using the visible nuclei counting method, the method utilised by Axelrad, et al. (2008). The authors surmised that previously reported differences in Purkinje cell loss were likely due to methodological reasons as opposed to true neurodegenerative factors.

Basket cells

Basket cells are found in the molecular layer of the cerebellum and synapse around the soma of the Purkinje cells. These are GABAergic inhibitory only cells, with one basket cell synapsed to around 250 Purkinje cells (Fitzgerald, et al., 2007). Under the categorisation of "Cerebellar ET" Erickson-Davis, et al. (2010) described the presence of abnormal basket cells. The authors termed these cells "hairy baskets", and used a visual rating scale of 0 (few/none) to 3 (dense/tangled axonal plexus) to distinguish between normal and abnormal cells. ET brains were found to be much more likely to have hairy baskets when compared to controls (Alzheimer's, PD, non-disease) with 25% of ET brains assessed having a rating of 3 compared to 5% for Alzheimer's, 6.7% for PD and 4.8% for neurologically healthy controls.

Lewy bodies

Lewy bodies are described as intraneuronal, eosinophilic inclusions (de la Fuente-Fernandez, Schulzer, Mak, Kishore, & Calne, 1998) and have an unknown role in disease (Tompkins & Hill, 1997). Lewy bodies are found in a number of neurodegenerative diseases such as PD (de la Fuente-Fernandez, et al., 1998), and Alzheimers (Perry, Irving, & Tomlinson, 1990). There is evidence that Lewy bodies appear as part of the aging process, with Perry, Irving and Tomlinson (1990) showing a 2.3% incidence in a healthy older adult population. Their presence has been noted in ET and has lead to the classification of Lewy body variant of ET (ET 'with Lewy bodies') and Cerebellar ET (ET 'without Lewy bodies'). Louis, et al. (2005) noted in the post-mortem of one ET patient, the presence of Lewy bodies in the Locus Coeruleus. A further study by

Louis, et al. (2006) examined 10 ET brains of which 6 had Lewy bodies. Of these, 4 had a high density of Lewy bodies in the Locus Coeruleus. The possible role Lewy bodies may have in ET is poorly understood.

Medical treatments

A number of medical options are utilised for the treatment of ET including the use of certain medications and surgery. Though there is no specific ET drug, two commonly prescribed medications are Propranolol and Primidone (R. Elble, 2009). Propranolol is a beta-blocking agent, designed primarily for cardiac and hypertensive conditions (Medsafe, 2010a). It has the ability to cross the blood brain barrier (Medsafe, 2010a), but may cause fatigue and depression amongst other side effects (R. Elble, 2009). Primidone is an anti-convulsant, anti-epileptic agent, reducing the central nervous system's sensitivity to seizures (Medsafe, 2010b). It too carries side effects such as nausea and weakness (R. Elble, 2009). ET patients display a variable and sometimes poor response to these two medications with initial effectiveness often reported as low as 50%. Unfortunately in those that respond to the medication, the magnitude of these benefits decreases over time (R. Elble, 2009; Lyons, et al., 2006). An assessment of 223 ET patients by Diaz and Louis (2010) reported that 70.9% of the ET patients had been on either medication, of which 56.3% stopped taking them. Other medications such as Atenolol and Gabapentin have also been used in ET patients with similar limited success (Lyons & Pahwa, 2008).

A surgical option for ET patients is that of DBS. DBS is an invasive intervention involving the placement of electrodes in the Ventral Intermediate (VIM) nucleus of the thalamus (Lyons & Pahwa, 2008). DBS potentially works via blocking abnormally oscillating cells (Yu & Neimat, 2008) or increasing excitability of central motor areas (Anderson, Burchiel, Hart, Berk, & Lou, 2009). It is believed that stimulation of this area poses less risk and is more effective in reducing tremor than thalamotomy (lesioning of the thalamus) (Tasker, 1998). DBS can improve voice tremor (Sataloff, Heuer, Munz, Yoon, & Spiegel, 2002), eye-blinking (Kronenbuerger, et al., 2008) and activities of daily living (Bryant, et al., 2003) in ET patients. DBS however, is costly to perform (Zhang, Poignet, Widjaja, & Ang, 2010) and comes with a number of risks including pain, paraesthesia, headache, cognitive disruption and even rare instances of death (Lyons & Pahwa, 2008; Woods, Fields, Lyons, Pahwa, & Tröster, 2003).

Other treatments

Other treatment options that may assist in controlling ET-related symptoms have been sought. Examples include bio-behavioural training, alcohol, and RT.

Bio-behavioural Training

ET patients tremor can be exacerbated under certain environmental/behavioural conditions such as a pressured situation or feelings of anxiety related to a task (Lorenz & Deuschl, 2007; Lundervold & Poppen, 2004b). An example of such a situation is when filling out a form or document in a public setting. Bio-behavioural training which teaches relaxation and tremor control, was proposed as a possible way of addressing this issue (Lundervold & Poppen, 2004b). Chung, et al. (1995) assessed this type of training's effect on tremor on an adult male with ET and an adult male with PD. The training involved performing two sessions per week, comprising performance of different relaxation postures in a seated and supine position for 20-25 minutes, while receiving feedback of muscle activity based off EMG recordings. A further 10 minutes of home training twice per week was also prescribed. For the ET participant significant reductions in tremor ratings, EMG activity and some improvements in activities of daily living were reported. For the PD participant there were improvements in tremor ratings however there was no change in the EMG recordings. Lundervold, et al. (1999) used this bio-behavioural training method in two ET adults and also found significant improvements in a number of self-reported and clinical scales of tremor. A comparison between bio-behavioural training and biofeedback was conducted with three ET participants (Lundervold & Poppen, 2004a). Improvements were seen with each participant however there was no difference noted between the two training modes. Though bio-behavioural training shows promise for individuals with ET, studies with larger subject numbers and randomised controlled trial designs need to be performed. There is also a large detraining effect with this mode of rehabilitation and the long-term cost effectiveness could be questioned as it has been shown to be more expensive than standard care (Lundervold, et al., 1999; Lundervold & Poppen, 2004a).

Alcohol

Though not clinically recommended as an option for tremor control due to its addictiveness and possible legal and social ramifications, alcohol is an effective non-prescribed drug (Klebe, et al., 2005; Nahab & Hallett, 2006). A study of 678 ET patients by Koller, Busenbark and Miner (1994) found of those that knew of alcohol's effect, 74% reported a noticeable reduction in tremor after its use. Alcohol is most effective when taken orally and has been shown to be more effective than the commonly prescribe beta blocker propanolol (W. Koller & Biary, 1984). Ethanol and 1-octanol are two effective forms of alcohol that have been studied. In a placebo controlled trial by Nahab and Hallett (2006), 1-octanol was found to be safe and effective however the authors did note a number of limitations and problems facing further research and development of this alcohol. Klebe, et al. (2005) administered Ethanol to 16 ET patients and 11 age matched controls. The authors found that gait ataxia scores and missteps significantly improved in the ET subject group due to the ingestion of ethanol. They suggested that ethanol consumption may aid by acting on inferior olive activity mediating complex spikes or cerebellar γ-aminobutyric acid receptors.

Resistance training

The ability to perform everyday tasks, often identified in activity of daily living questionnaires, require a measure of physical function and ability. Often a key component of this physical function is that of muscular strength and dexterity. RT is one such means to maintain and improve these components (Cormie, McGuigan, & Newton, 2011a; Folland & Williams, 2007; Seguin & Nelson, 2003).

RT comes in many forms, using a wide range of equipment, from weight lifting through to specific ranges of motion and even static holds using one's body weight. Programmes can be designed specifically to target a type of goal for instance, strength versus power training (Cormie, McGuigan, & Newton, 2011b). Variables such as speed of lift, number of sets and repetitions, the load lifted and rest periods between sets can all be altered to align with the desired training goals (Cormie, et al., 2011b; Franklin, Whaley, & Howley, 2000). It is through this flexibility that RT, once thought of as belonging only to the realms of athletes or confined to gyms, is now recognised as a core component of general health and well-being for all ages (Folland & Williams, 2007; Peterson, Rhea, Sen, & Gordon, 2010; Seguin & Nelson, 2003). RT also forms part of international rehabilitation exercise programming guidelines (Franklin, et al., 2000). RT's importance in improving physical function and QoL in special populations is well documented. With appropriate prescription and progression it can have a significant role in a comprehensive rehabilitative programme (Franklin, et al., 2000). Special populations with conditions such as cardiovascular (Levinger, Bronks, Cody, Linton, & Davie, 2005), pulmonary (Kongsgaard, Backer, Jørgensen, Kjær, & Beyer, 2004) and metabolic diseases (Gordon, Benson, Bird, & Fraser, 2009) all benefit from RT. The beneficial effects of RT have also been investigated in neuromuscular conditions such as stroke and PD (Durstine & Moore, 2003; Engardt, et al., 1995; Hirsch, Toole, Maitland, & Rider, 2003). In PD, RT has been effectively used to improve function, QoL and strength (de Paula, et al., 2006; Falvo, Schilling, & Gammon, 2008). For example Hirsch, et al. (2003) utilised high-intensity resistance training in combination with balance training in 15 participants with idiopathic PD.

The authors found that the combination of these two training regimes significantly improved balance when compared to balance only training.

Of particular interest to this study are the neuromuscular adaptations that occur with RT. After a short (<6 weeks) period of resistance training there is evidence of increased strength however there isn't the corresponding change in muscle hypertrophy (Housh, et al., 1998; Staron, et al., 1994). Early studies into RT and older adult populations recognised this size/strength discrepancy, with reasoning pointing towards an inherent muscle weakness or alterations to fibre type (Aniansson, Ljungberg, Rundgren, & Wetterqvist, 1984; Young, Stokes, & Crowe, 1985). After investigating the effect of a 12 week RT programme Jones & Rutherford (1987) found that while force increased by 35%, quadriceps cross-sectional area only increased by 5%. The authors described this as a 25% increase in force per unit area and suggest the mechanisms underlying this change potentially related to alterations in fibre size, tendon attachment and increases in connective tissue.

With the benefit of further research into effects and mechanisms there is now a greater understanding of the neuromuscular contribution to adaptations seen in RT (Cormie, et al., 2011a; Enoka, 1997). Along with the size/force changes, other neuromuscular adaptations are evident in effects such as the specificity of training effect and the cross-over phenomenon (Enoka, 1997; Kidgell & Pearce, 2010c; Reeves, Narici, & Maganaris, 2006). Specificity refers to an effect where change in strength relates directly to the type of training performed (Folland & Williams, 2007). This adaptation is often seen with RT interventions including those with ET (Adkins, Boychuk, Remple, & Kleim, 2006; Beck, et al., 2007; Bilodeau, et al., 2000). The cross-over (cross-education) effect refers to occurrences of strength gains in an untrained limb or muscle group (Folland & Williams, 2007). Lee, Gandevia and Carroll (2009) found that after a four week period of RT the maximum voluntary contraction (MVC) of the untrained limb significantly improved by 8.2%, which was lower than the trained limb but greater than the control group which showed no significant change. An improvement in cortical drive was suggested to be behind the improvements due to a smaller superimposed twitch used during the post intervention testing compared to that used at baseline. This finding was similar to the significant cross-over effect in the untrained limb reported in a pilot study by Kidgell and Pearce (2010c) who found a strength increase of 26.4% in the trained limb and a 16.3% increase in the untrained limb. From this study it was suggested that improved activation of the primary motor cortex seen, via an increase in motor evoked potential amplitude, may have been one mechanism underlying this change.

Other mechanisms behind such neuromuscular changes may include increased neural drive, motor unit changes and muscle activation (Bruton, 2002; Engardt, et al., 1995; Hakkinen, et al., 1998). Reeves, Narici and Maganaris (2006) examined the effect of a RT programme on healthy older adults and found significant increases in maximal concentric and isometric force in the RT group. The authors also suggested that in the RT group, there was evidence of increased neural drive in the agonist muscle group, with increases seen in EMG activity after training. Similar strength and neural drive increases of the agonist muscle group was seen in RT study by Hakkinen, et al. (1998). Interestingly it was revealed that in their older adult training groups, for both men and women, there was a significant reduction in antagonist activity not seen in the control group, indicating a reduction in co-activation. Novel reductions in corticospinal inhibition after RT have also been found (Kidgell & Pearce, 2010a, 2010b). This reduced inhibition, measured via EMG Silent Period, came about after a 4 week isometric RT programme (Kidgell & Pearce, 2010b). After similar short periods of RT there is also evidence of changes to the motor unit such as motor unit synchronisation and firing frequency (Folland & Williams, 2007; Moritani, 1993). Fling, Christie, and Kamen (2009) examined 10 healthy adults who regularly weight trained to a control group who did not. The authors found that the weight trained group exhibited greater motor unit synchronisation for the first dorsal interosseous and bicep brachii muscles. Such changes have wide ranging ramifications for movement control, and may be observed in small time-frames such (i.e. < 6 weeks).

Considering the above mentioned functional changes and underlying neuromuscular adaptations occurring as a result of RT, there is potential for it to be used as a rehabilitative tool for ET (Figure 1).

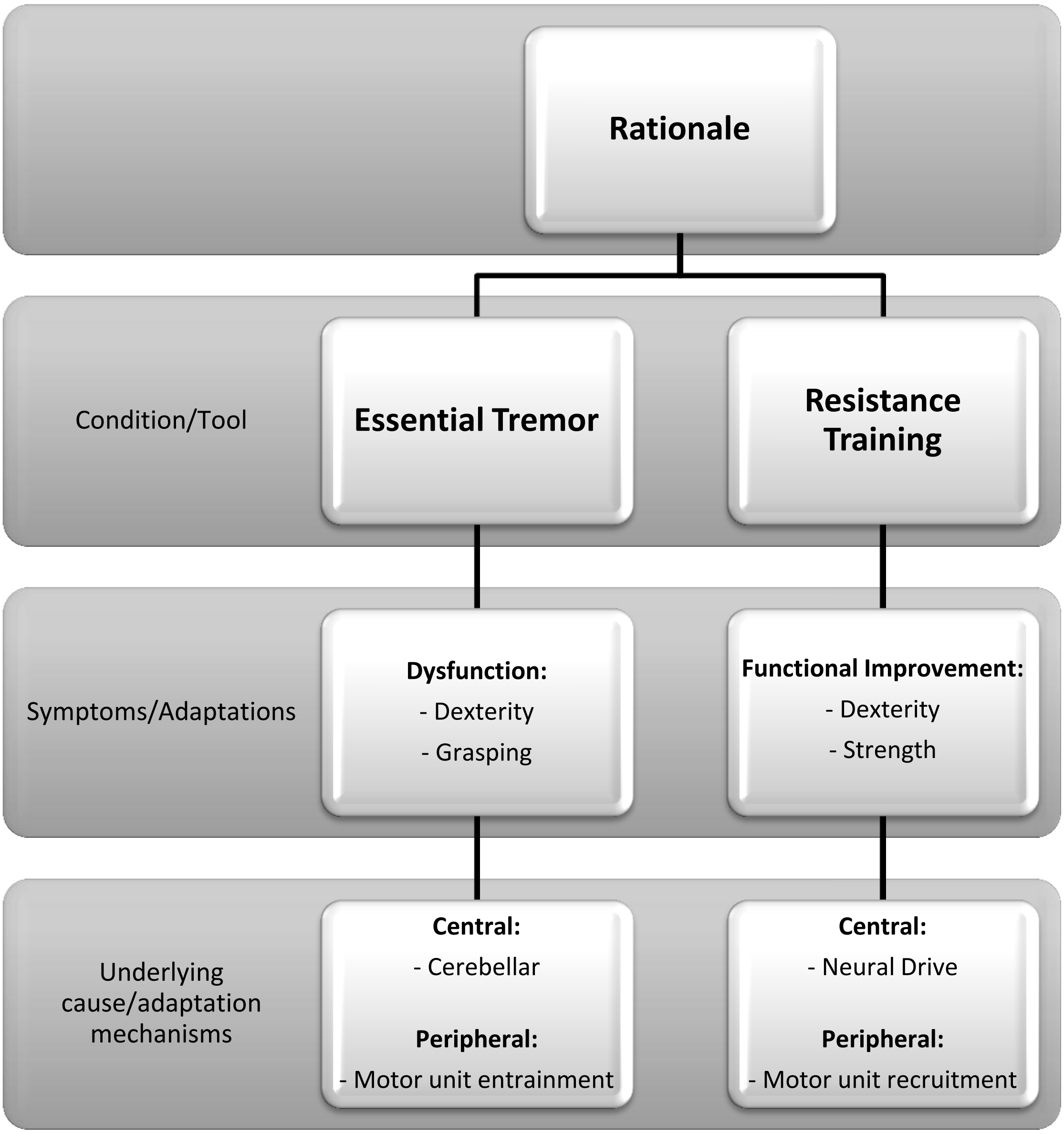

Figure 1: Rationale for RT as a rehabilitative tool for ET

Only a small number of studies have so far examined RT's possible effect on tremor (Bilodeau, et al., 2000; J W. L. Keogh, et al., 2010; Kornatz, Christou, & Enoka, 2005; Ranganathan, Siemionow, Sahgal, Liu, & Yue, 2001). Only one study so far has specifically examined ET and RT (Bilodeau, et al., 2000). Most of these studies have examined the effect of RT on tremor in older adults, and though ET may occur at any age, its prevalence is greater in the later years of life. A summary of these studies is presented in Table 1.

Table 1: Review of training studies with a focus on tremor

Study	Design	Sample	Resistance based training group	Result
Bilodeau et al. (2000)	RCT	• 13 ET (6M |7F) • 8 training • 5 control	• Index finger abduction/adduction • 3 d/w x 4 wks • 6 sets x 10 reps • Load - 80% 1RM vs 20% 1RM (C)	• ↓ Force fluctuations • ↑ Strength • ↔ Peak tremor power/amplitude • ↔ Functional tasks • ↔ Control
Ranganathan et al. (2001)	RCT	• 28 OA • 14 training • 14 control	• 'Weighted ball' hand rolling task • 6 d/w x 8 wks • 2 x 10 min/d • Load – 150g	• ↑Finger pinch force • ↓Force fluctuations • ↑ Dexterity • ↔ Hand grip strength • ↔ Control
Kornatz et al. (2005)	Crossover	• 10 OA (5M | 5F)	• Index finger abduction • 3 d/w x 6 wks • 6 sets x 10 reps • Load – 10% 1RM (2 wks) • 70% 1RM (4 wks)	• ↑ Strength • ↑ Dexterity • ↓Force fluctuations • ↓ Motor unit firing rate variability
Keogh et al. (2007)	RCT	• 11 OA (M) • 7 training • 4 control	• D/B Elbow flexion, wrist flexion & wrist extension • 2 d/w x 6wks • 3 sets x 8-10 reps	• ↑ Strength • ↓Finger pinch force variability • ↓Targeting error • ↑ Strength in untrained limb (cross-over) • ↔ Control
Keogh, et al (2010)	RCT	• 19 OA (M) • 7 Strength • 7 co-ordination • 5 control	• D/B Elbow flexion, wrist flexion & wrist extension • 2 d/w x 6 wks • 3 sets x 8-10 reps	• ↓ Tremor amplitude • ↓ Tremor peak • ↓ Tremor power • ↑ Strength • ↓Muscle co-activation • Similar effects for co-ordination • ↔Control

RCT = randomised controlled trial, ET = Essential tremor, OA = older adult, d/w = days per week, wks = weeks, reps = repetition, RM = repetition max, min/d = minutes per day, D/B = dumb bells, ↑ = increase, ↓ = decrease, ↔ = no change.

Kornatz, Christou and Enoka (2005) investigated practised, and then four weeks of loaded finger abduction in older adults and found the training resulted in reduced motor unit discharge variability and improvement in dexterity as measured by the Purdue Pegboard Test (PPT). Similarly Ranganathan, et al. (2001) found significant improvements in dexterity (using the PPT) as well as greater finger pinch force and precision with the utilisation of an eight week 'weighted ball' co-ordination training programme (150g per ball). A general, six week RT programme incorporating dumbbell based elbow flexion, wrist flexion and wrist extensions was used by Keogh, et al. (2007). A group of seven healthy older adults performed the RT programme and were compared to four age-matched controls. The authors found that finger force control, targeting error and strength improved significantly in the RT training group compared to the control group. In a further study by Keogh, et al. (2010) the effect of RT and a coordination training programme for older adults was examined. Three groups consisting of seven participants performing RT, seven performing coordination training, and five as controls trained over a six week period. The authors found that in both training groups there were significant reductions in peak 8-12Hz tremor amplitude and coactivation of upper limb muscles.

Bilodeau, et al. (2000) appears to be the only study that has examined the effects of RT on ET patients. The training group of eight participants involved performing finger abduction with a load based at 80% of the individuals 1RM for a four week period. This was then compared to the control group of five consisting of two participants involved in the true control group (no training) and three in a light load training group (20%

of maximum). The grouping of true control and light load cohorts was due to reported difficulties in recruitment and the desire for strong statistical power in the heavy RT group. The results from this study showed that there was an increase in strength and improved force control (steadiness) in participants that had undergone the 80% RT. No changes were noted in the control group. Similar to the well recognised ability for untrained individuals to achieve greater gains than trained individuals, Bilodeau, et al. (2000) noted that the changes in force control were relative to the severity of the tremor, with those with greatest tremor having larger improvements in force control.

Conclusions

ET is characterised by a disabling involuntary tremor, with the upper limb commonly being the most affected. While some level of tremor is evident in normal function, the severity of tremor experienced in ET can negatively impact on hand and finger dexterity and QoL. Possible mechanisms driving this pathological tremor may potentially be reduced or beneficially altered with the introduction of RT. RT is understood to elicit neuromuscular changes within a short period of time (<6 weeks), which have been related to improvements in dexterity and QoL in healthy older adult populations. Therefore, the introduction of a short, general RT programme may be an effective therapy to improve hand and finger dexterity and QoL in ET. Such results would further support greater investigation of RT as a therapy in ET.

Chapter 3 - Methods

Participants

Six participants (five female, one male, age: 74 $\pm$ 7 years), were recruited via the Auckland branch of the New Zealand Essential Tremor Support Group. Each participant had been clinically diagnosed as having ET by a neurologist (years diagnosed: 19 $\pm$ 7 years, Table 2). To be eligible, no participant could have had a recent history of strength training, and mobility of the upper limb had to be normal. Participants continued with their current drug therapies and were requested to maintain this throughout the study. If medication change was directed by a neurologist then they were to notify researchers. Prior to the intervention each participant received an information sheet outlining the study and their rights as participants. Following this, written informed consent was given by participants. Participants were then screened and assessed using the American College of Sports Medicine risk stratification protocol for suitability to partake in an exercise programme (Franklin, et al., 2000).

Experimental design

This pilot study sought to examine the effect of general, upper limb RT on strength, hand and finger dexterity, and QoL in ET patients. To investigate this, a single group, dual pre-post quasi-experimental study design was used (as seen in Figure 2). This design was used due to the novelty of this pilot study and the relative difficulty in recruiting sufficient participants for a randomised controlled trial due to the small size of NZETSG Auckland branch who numbered only 20 individuals from throughout the greater Auckland region. Similar designs have been used in other studies examining novel interventions for people with neurological conditions (Behrman & Harkema, 2000; Page, Levine, & Leonard, 2005)

Study Protocol

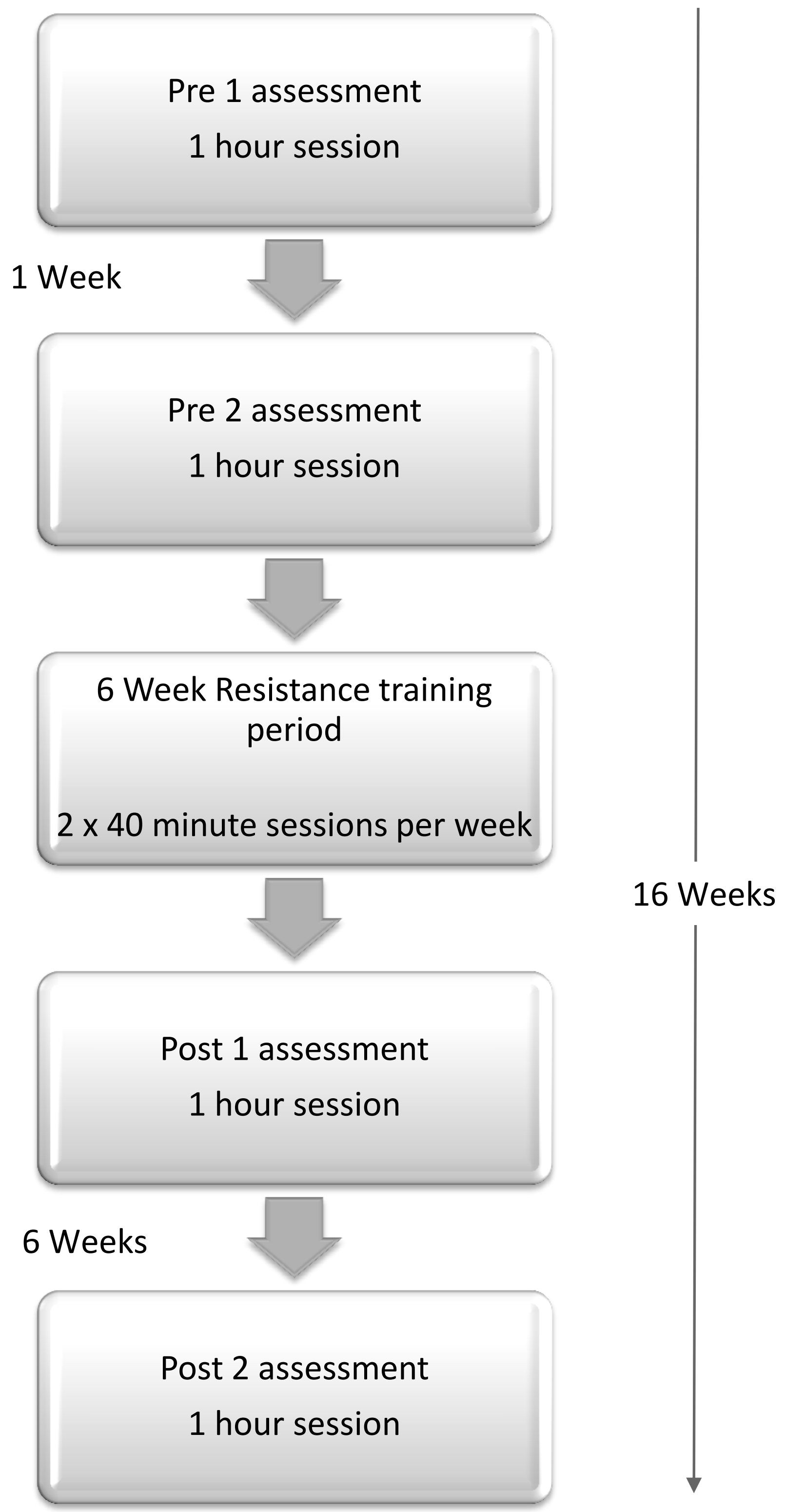

Figure 2: Study protocol schematic

Ethics

Ethics approval for the study was granted by the Northern Regional Y Ethics Committee (reference: NTY/10/03/025).

Resistance training intervention

The resistance training intervention used in the present study was identical to the RT programme used successfully by Keogh, et al. (2007) and Keogh, et al. (2010) to reduce finger force variability and postural tremor, respectively in neurologically normal older adults. The programme consisted of three unilateral dumbbell exercises; an elbow flexion, wrist flexion and wrist extension (Figures 3-5). Each exercise was performed for four sets of 8-10 repetitions. The first set was a warm-up set, with the load being 50% of the 5RM established during the strength tests. The following three sets had training loads set at an intensity that would allow for the completion of at least eight repetitions. If three full sets of 10 repetitions were able to be performed, the load was then increased by between 1kg for the next session. A two minute rest period was given between each set of an exercise.

This programme was performed over a period of six weeks, with each week involving two sessions of approximately 40 minutes each. Between each session there was a rest period of at least 48 hours. Every session was supervised by a clinical exercise physiologist.

Figure 3: Dumbbell elbow flexion

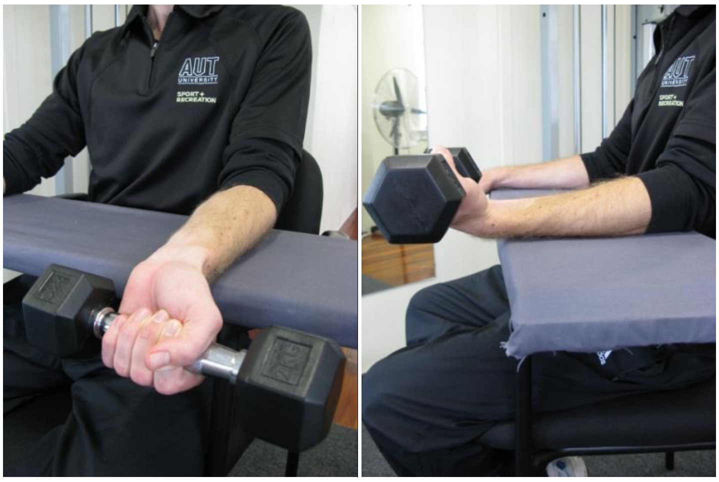

Figure 4: Dumbbell wrist flexion

Figure 5: Dumbbell wrist extension

Assessment measures

Four assessment occasions were utilised in this study, two baseline and two post intervention. The first assessment, the familiarisation assessment (Pre 1), was performed a week before the baseline assessment (Pre 2). This was followed by the six week RT intervention immediately after which the first post assessment was performed (Post 1). The second post assessment (Post 2) was done after a 6 week detraining period following the Post 1 assessment. At each of these testing occasions, the participants performed assessments for hand and finger dexterity and strength as well as general and ET specific measures of QoL. The order of each task during the assessment was standardised, with the two QoL measures being assessed first followed by the hand and finger dexterity test (PPT) and then finally the strength tests. The dexterity test was performed prior to the strength test so as not to be affected by any potential fatigue induced by the strength test (Viitasalo & Gajewski, 1994).

Strength

5RM

Strength assessments commonly involve assessing a person's ability to lift a maximum load for a certain number of repetitions. For example performing a 1RM strength test will find the maximum weight an individual can perform for one full repetition. In the case of this study a 5RM strength test was used. This method of testing is shown to be a valid and reliable method of strength testing (Roth, Martel, & Ivey, 2001; Storer, Casaburi, Sawelson, & Kopple, 2005), with 5RM intra-class correlation coefficients (ICC) reported at 0.82-0.91 in a group of healthy older adults (Wood, et al., 2001). Strength tests can be used to assess upper and lower body strength through varying planes of movement. The 5RM has also been shown to be an appropriate mode of testing for the older adult population (J.W.L Keogh, et al., 2007; Martel, Roth, & Ivey, 2006).

Participants performed a 5RM test using the methods of Keogh, et al. (2007, 2010) for three movement planes using dumbbells to provide load. The movements assessed were the elbow flexion, wrist flexion and wrist extension (as seen in Figures 3-5). All three movements were performed using strict technique in a seated position, with no movement of the trunk or segments proximal to the involved upper limb joint allowed. Two warm-up sets were performed that increased in load prior to starting the 5RM lift attempt. Based on their warm-up and description of physical activity an initial 5RM load was selected. If the participant was able to successfully lift the load for five repetitions, they received a three minute rest period followed by another 5RM attempt with a heavier load. A 5RM lift was only deemed successful if the participant maintained good technique for each repetition; that is moving through a full range of motion and in the absence of other bodily movement. The elbow flexion was the first movement performed, followed by the wrist flexion and then the wrist extension exercises.

Hand and finger dexterity

Purdue Pegboard

The PPT (Purdue Pegboard Model 32020, Lafayette Instrument Company, Indiana, USA) was used to measure hand and finger dexterity. The PPT has been shown to be valid and has high test-retest reliability (ICC – 0.82-0.91) (Desrosiers, Hebert, Bravo, & Dutil, 1995; Tiffin & Asher, 1948). There is a large pool of normative data, with age and gender specific values available (Desrosiers, et al., 1995). The test has been implemented in a number of health outcome trials assessing fine dexterity (Adler, Hentz, Joyce, Beach, & Caviness, 2002; Müller & Benz, 2002). The PPT has been used in a number of tremor affected populations, such as ET (A. Rajput, et al., 2004) and PD (Müller & Benz, 2002; Proud & Morris, 2010), and has shown to be able to distinguish ET patients from non-ET older adults (M. E. Héroux, et al., 2009). It is sensitive to difference and change, being able to distinguish between the preferred and non-preferred hands (Triggs, Calvanio, Levine, Heaton, & Heilman, 2000), injured and non-injured limbs (Skinner & Curwin, 2007) and to improve as a result of interventions such as resistance training in an older adult population (Kornatz, et al., 2005).

As described by Tiffin and Asher (1948), the PPT requires the participant to take pegs, one at a time, from the peg-holder at the top of the board and place them into evenly spaced holes on the board (Lafayette Instrument Company, 2002). The PPT is a time-based measure and encompasses four tasks; left hand only, right hand only, both hands and an assembly task (Figure 6).

Figure 6: PPT in an unilateral handed task, bilateral handed task and assembly task configuration

For the dominant and non-dominant hand tasks the participant uses only the stipulated hand. These tasks have a time limit of 30 seconds in which to place as many pegs as possible into the holes on the board. The both handed test is similar with a 30 second time limit, however both hands are used. During the both handed task participants were instructed to maintain synchronisation between hands; so that both the left and right hand retrieved and placed pegs at the same time. For the assembly task there is an additional component with the assembly made up of the pegs, washers and collars (Lafayette Instrument Company, 2002). The assembly formation is created by first placing a peg, then a washer, a collar and another washer. This task allows for 60 seconds in which to form as many assemblies as possible (Lafayette Instrument Company, 2002). For the both handed task and the assembly task, participants are instructed to begin the test with the dominant hand.

The order of the PPT tests performed in this study was right hand only task, left hand only task, both handed task, and assembly task. The pegboard was placed on a table, and participants were seated on a backed-chair. This allowed for participants to have their forearms parallel to the table, with their elbows at 90^{O}. Each task was performed three times to reduce possible learning effect and improve the reliability of the test (Tiffin & Asher, 1948). The median score of the three trials was used for the results.

Quality of life

SF-36

The SF-36 questionnaire is a widely used method of assessing an individual's perception of their health related QoL (Failde & Ramos, 2000; Izquierdo-Porrera, et al., 2005). It encompasses eight domains covering both physical and mental function. The physical domains include physical function, role physical, pain and general health. The mental domains assess vitality, social function, mental health and role emotional. Each domain was scored, via the standard algorithm, to range from 100 representing the best state, to 0 representing the worst state. The SF-36 has been shown to be a suitable measure for use in older adult populations (Chia, Chia, Rochtchina, Wang, & Mitchell, 2006;

Takata, et al., 2010) and as a pre/post measure of change in QoL due to a physical activity intervention (Cochrane, et al., 1998). The SF-36 has been used in a number of studies assessing the ET population (Lorenz, et al., 2006; Nguyen, Ngian, Cordato, Shen, & Chan, 2007).

Participants were given the SF-36 to fill out themselves, though were allowed to ask questions of the tester in order to clarify a question if needed.

QUEST

The QUEST is a relatively new QoL measure designed specifically for ET patients (Troster, Pahwa, Fields, Tanner, & Lyons, 2005). It involves 30 questions that examine functional, psychological and social areas involved in daily living. The QUEST can be broken down into 5 subscales; physical, psychosocial, communication, hobbies/leisure and work/finance. Patients rate each statement on a 0-4 scale, with 0 being “never” through to 4 being “always”. The higher the score the greater the negative impact their tremor has on QoL. It has been shown to be a reliable and valid measure (Troster, et al., 2005) and acceptable for use in ET patients (Martınez-Martın, et al., 2010).

Participants were given the QUEST to fill-out themselves, though were allowed to ask questions of the tester in-order to clarify a question if needed.

Adherence and Injury

Adherence rates and any injury/illness (adverse effect) were recorded throughout the study. For the purposes of this study, an adverse effect was defined as "any occurrence that caused a participant to miss a scheduled training or assessment session". If any adverse effects were reported, details surrounding the event, e.g. its cause and effect and if it was believed to be associated with training or assessment, were reported.

Statistics

Performance in all of the assessments at each of the four time-points (Pre 1, Pre 2, Post 1 and Post 2) was described by the group means and standard deviations. As demonstrated by the results of paired T-tests, there were no significant differences in any dependent variable between Pre 1 and Pre 2 sessions. Therefore pre-exercise data was averaged to give a better representation of performance. In order to maximise the statistical power of the analyses, paired t-tests were then used to determine if strength, manual dexterity and quality of life were significantly improved at Post 1 and Post 2 in comparison to the mean baseline scores (McDonald, 2009). Significance in the current study was set at $p < 0.05$. Magnitude of effect was determined by calculating an adaptation of Cohen's effect size (ES). Percent change scores were also calculated between the pre-exercise data and the Post 1 and Post 2 data, with such data presented in Figures within the Results section.

Additionally, the group data for each of the four time-points is presented in Appendix C.

As this was a preliminary study for which there were no previous data to conduct a power analysis, the statistical power of the study was determined post-hoc using G*Power-3 software. The power analyses were conducted for all muscular strength and PPT performance variables with a two-tailed test using the *Means: differences between two dependent means (matched paired)* function and a p value of 0.05. These power analyses indicated that the strength measures which exhibited significant improvements from baseline had between 91-99% power. These analyses also indicated that the unilateral PPT tests which attained statistical significance had 81-82% power.

Chapter 4 - Results

All six participants (Table 2) successfully completed and adhered (100%) to all 12 sessions of the training programme. One participant was omitted from statistical analysis due to an unrelated injury which may have impacted assessment scores. No training related musculoskeletal injuries or adverse reactions were reported during the training period.

Inspection of the two baseline tests (Pre 1 and Pre 2) indicated no significant differences for any outcome measures. Therefore, all statistical analyses and figures presented in this section involve a comparison between the mean of the two baseline tests compared to the Post 1 and Post 2 results, respectively. Figures depicting the data for each of the four testing occasions (Pre 1, Pre 2, Post 1 and Post 2) can be found in Appendix C.

Table 2: Participant demographics

Part[τ].	Age	Gender	Years diag.	Medication	Surgery	Family history	Tremor site[†] (severity)[‡]	Dominant hand
P1	68	Male	12	None	No	Unknown	R UL (marked) L UL (marked)	Right
P2	72	Female	27	None	Thalamotomy (performed 17 years ago)	Yes	Head (severe) Voice (severe) R UL (severe) L UL (mild) L LL (mild) R LL (mild)	Right
P3	83	Female	15	Betaloc*	No	Unknown	Voice (marked) L UL (marked) R UL (moderate)	Right

P4	68	Female	30	Propanolol	No	No	L UL (marked) Head (mild) R UL (mild)	Left
P5	83	Female	20	Nadolol*	No	No	L UL (severe) Voice (moderate) R UL (mild)	Right
P6	70	Female	11	Primidone, Propanolol	No	Yes	R UL (marked) L UL (marked) Head (mild) R LL (mild) L LL (mild)	Right

$^{\tau}$ Participant

* Medication primarily prescribed for control of blood pressure

† R = right, L = left, UL = upper limb, LL = lower limb

‡ Self rated level of tremor severity based on a 0-4 likert scale (0 = none, 1 = mild, 2 = moderate, 3 = marked, 4 = severe)

Strength - 5RM Assessment

No significant changes were observed for any of the strength measures between the two baseline testing (Pre 1 and Pre 2) occasions ($p = 0.10$ – 0.99). Significant increases in a number of the strength tests were evident in both the most and least affected limbs at Post 1. Following the six week withdrawal period (Post 2) all strength measures had returned to non-significant levels ($p = 0.07$ – 0.38).

Elbow flexion

Following the six week RT intervention unilateral elbow flexion strength significantly increased by 19% for the most affected limb (p = 0.04, ES = 0.31 ± 0.22), with no significant change for the least affected limb (p = 0.06, ES = 0.53 ± 0.42) (Figure 7).

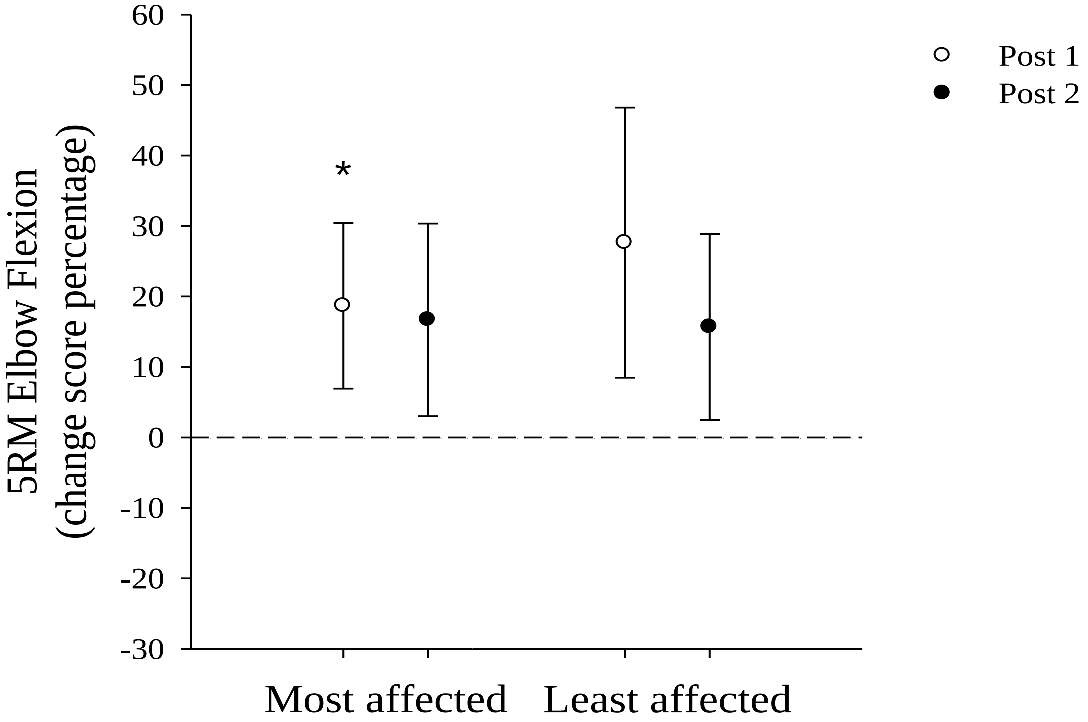

Figure 7: Performance in the 5 Repetition Maximum (5RM) Elbow Flexion Strength Assessment when using only the arm of most affected limb, and only the arm of the least affected limb. Post 1 and Post 2 data were calculated as change scores from pooled pre-exercise data and expressed as a percentage change of the pre-exercise data. Positive values indicate an increase of strength following the exercise intervention. Data are reported as means and 95% confidence intervals. * = Significant change (p<0.05).

Wrist flexion

Following the six week RT intervention unilateral wrist flexion strength increased significantly by 44% for the most affected limb ($p = 0.02$, ES = 0.75 ± 0.47) and 32% for the least affected limb ($p = 0.02$, ES = 0.49 ± 0.25) (Figure 8).

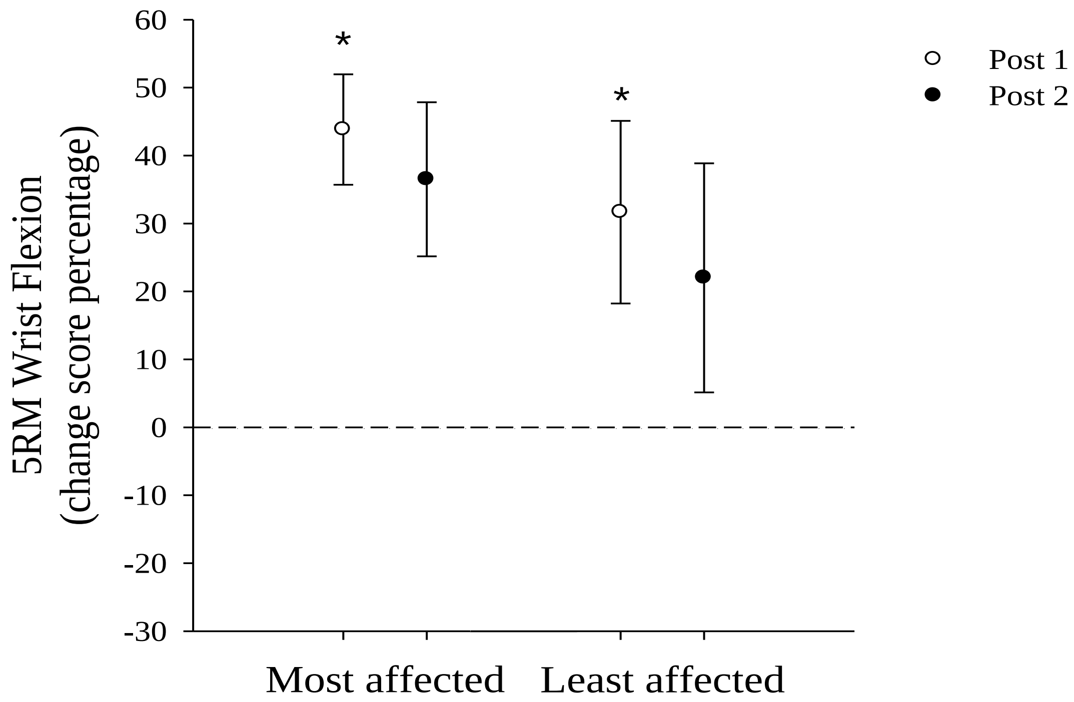

Figure 8: Performance in the 5 Repetition Maximum (5RM) Wrist Flexion Strength Assessment when using only the arm of most affected limb, and only the arm of the least affected limb. Post 1 and Post 2 data were calculated as change scores from pooled pre-exercise data and expressed as a percentage change of the pre-exercise data. Positive values indicate an increase of strength following the exercise intervention. Data are reported as means and 95% confidence intervals. * = Significant change ($p<0.05$).

Wrist extension

Following the six week RT intervention unilateral wrist extension strength did not significantly change in the most affected limb (p = 0.1175, ES = 0.33 ± 0.35), but significantly increased by 24% in the least affected limb (p = 0.04, ES = 0.42 ± 0.31) (Figure 9).

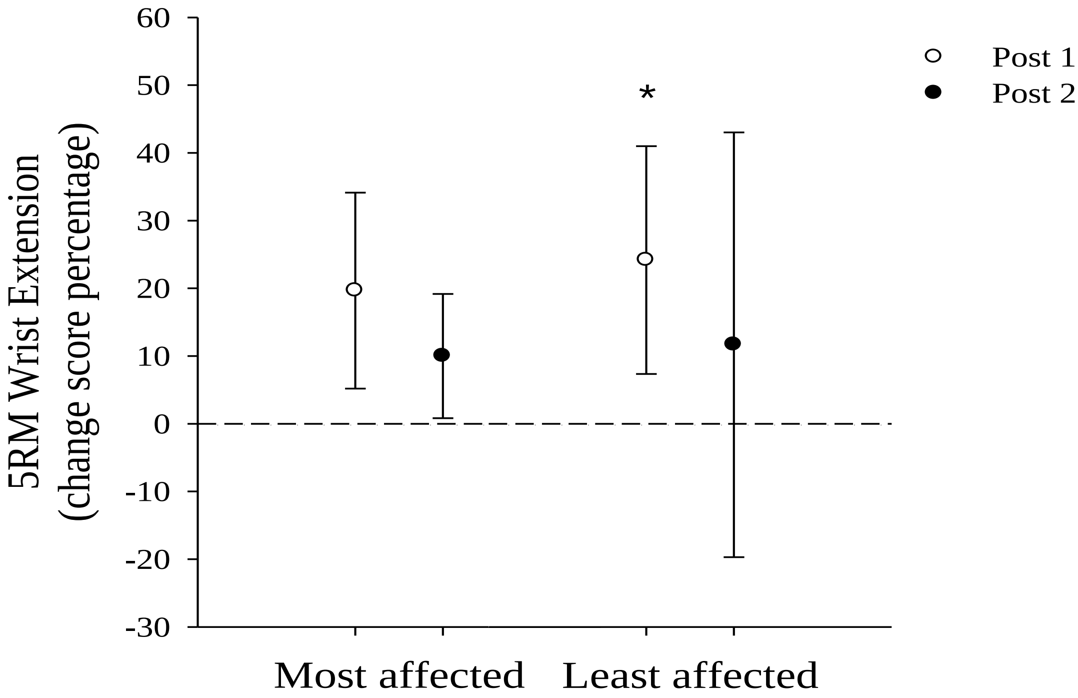

Figure 9: Performance in the 5 Repetition Maximum (5RM) Wrist Extension Strength Assessment when using only the arm of most affected limb, and only the arm of the least affected limb. Post 1 and Post 2 data were calculated as change scores from pooled pre-exercise data and expressed as a percentage change of the pre-exercise data. Positive values indicate an increase of strength following the exercise intervention. Data are reported as means and 95% confidence intervals. * = Significant change (p<0.05).

Hand and finger dexterity - Purdue Pegboard Assessment

No significant changes were observed for any of the PPT measures between the two baseline testing (Pre 1 and Pre 2) occasions ($p = 0.16$ – 0.97). A number of significant increases in unilateral, but not bilateral PPT performance were observed in the most affected hand at Post 1 or Post 2.

Single handed tasks

Following the six week RT intervention the unilateral handed PPT task significantly improved for the most affected hand by 15% ($p = 0.02$, ES = 0.23 ± 0.14), with no significant change for the least affected hand ($p = 0.37$, ES = 0.28 ± 0.35) (Figure 10). Following the 6 week withdrawal period, Post 2 scores indicated significant improvements of 16% for the most affected hand ($p = 0.02$, ES = 0.27 ± 0.23) and 13% for the least affected hand ($p = 0.02$, ES = 0.67 ± 0.17) compared to baseline.

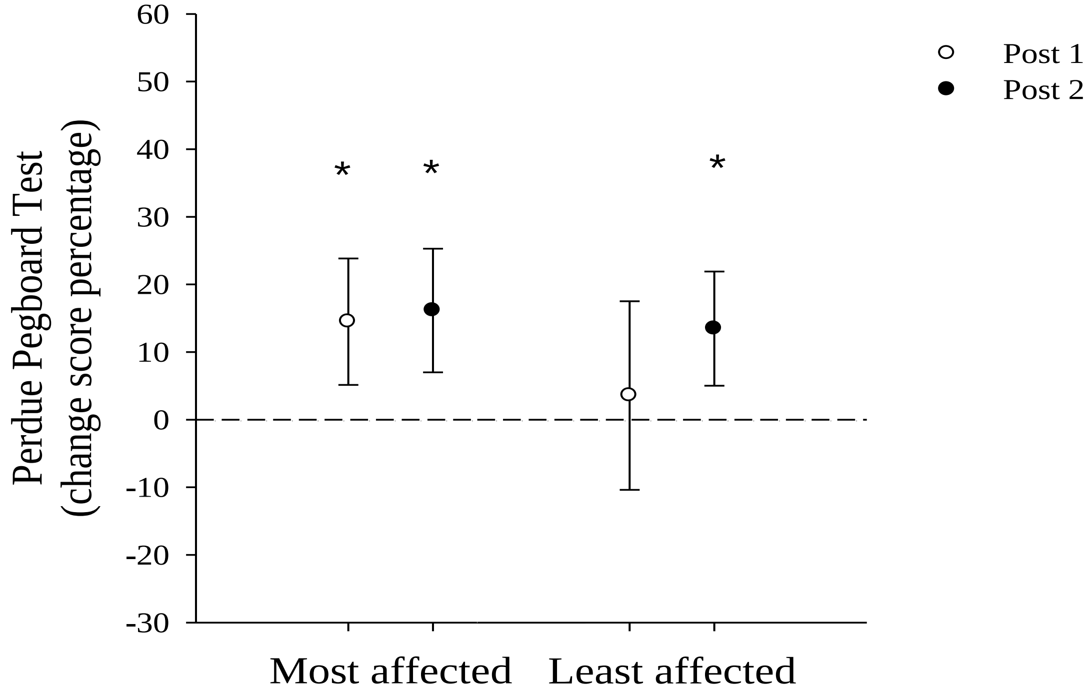

Figure 10: Performance in the Purdue Pegboard Test (PPT) when using only the hand of the most affected limb and only the hand of the least affected limb. Post 1 and Post 2 data were calculated as change scores from pooled pre-exercise data and expressed as a percentage change of the pre-exercise data. Positive values indicate an increase of strength following the exercise intervention. Data are reported as means and 95% confidence intervals. * = Significant change (p<0.05).

Following the six week RT intervention no significant changes were observed in the bilateral Both (p = 0.77, ES = -0.06 ± 0.38) and Assembly (p = 0.73, ES = 0.16 ± 0.96) PPT tasks (Figure 11).

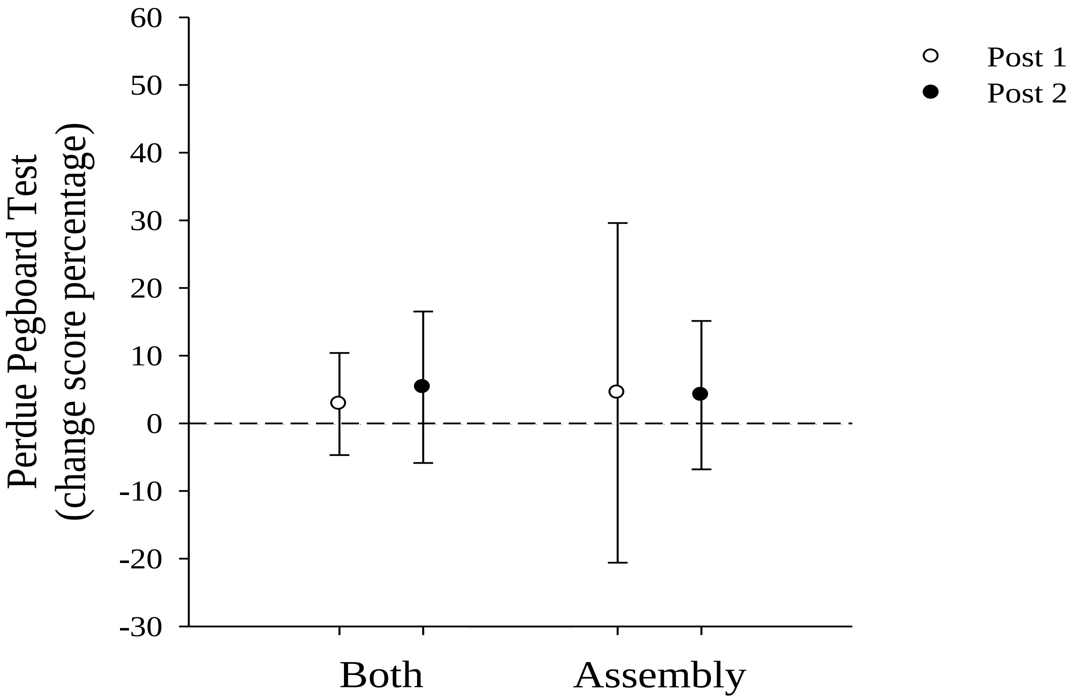

Figure 11: Performance in the Purdue Pegboard Test (PPT) when performing bilateral tasks. Post 1 and Post 2 data were calculated as change scores from pooled pre-exercise data and expressed as a percentage change of the pre-exercise data. Positive values indicate an increase of strength following the exercise intervention. Data are reported as means and 95% confidence intervals.

Quality of Life (general) - SF-36

No significant changes were observed for any of the domains of SF-36 QoL measure between the two baseline testing (Pre 1 and Pre 2) occasions ($p = 0.06 – 0.91$). Following the six week RT period there were no significant changes in any SF-36 score at Post 1 or Post 2 compared to baseline.

Physical Health and Mental Health

Following the six week RT intervention there was no significant change for either the Physical Health or the Mental Health scores (Figure 12). Unsurprisingly, there were also no significant changes in the four sub-domain scores Physical Function, Role Physical, Bodily Pain and General Health that comprised the Physical Health; and the four sub-domains Vitality, Social Functioning, Role Emotional and Mental Health that comprise the Mental Health score. No data for these eight sub-domains are presented here, although it can be found in Appendix C.

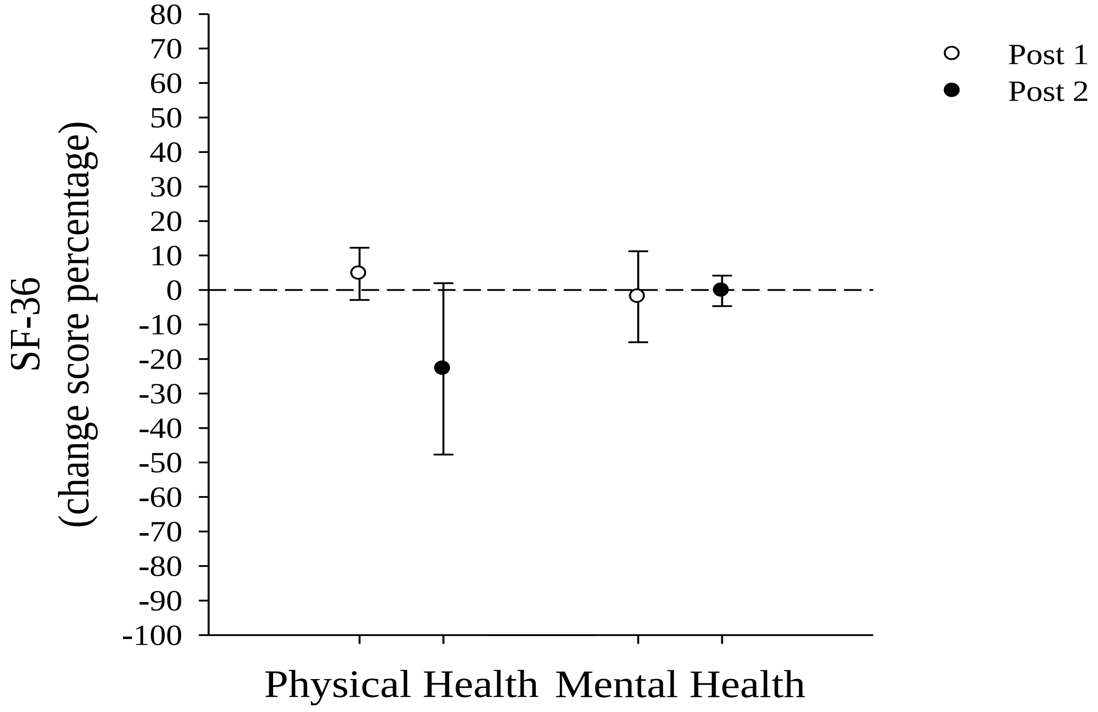

Figure 12: Performance in the Short Form 36 (SF-36) quality of life (QoL) questionnaire for Physical Health and Mental Health domains. Post 1 and Post 2 data were calculated as change scores from pooled pre-exercise data and expressed as a percentage change of the pre-exercise data. Positive values indicate an increase of strength following the exercise intervention. Data are reported as means and 95% confidence intervals.

Quality of Life (ET Specific) - QUEST

No significant changes were observed for any of the domains of ET-specific QUEST QoL measure between the two baseline testing (Pre 1 and Pre 2) occasions ($p = 0.37 – 0.86$). Following the six week RT period there were no significant changes at Post 1 or Post 2 compared to baseline.

Physical and Psychosocial

Following the six week RT intervention there was no significant change for Physical (p = 0.48, ES = 0.27 ± 0.74) and Psychosocial scores (p = 0.94, ES 0.03 ± 0.90) QUEST scores (Figure 13).

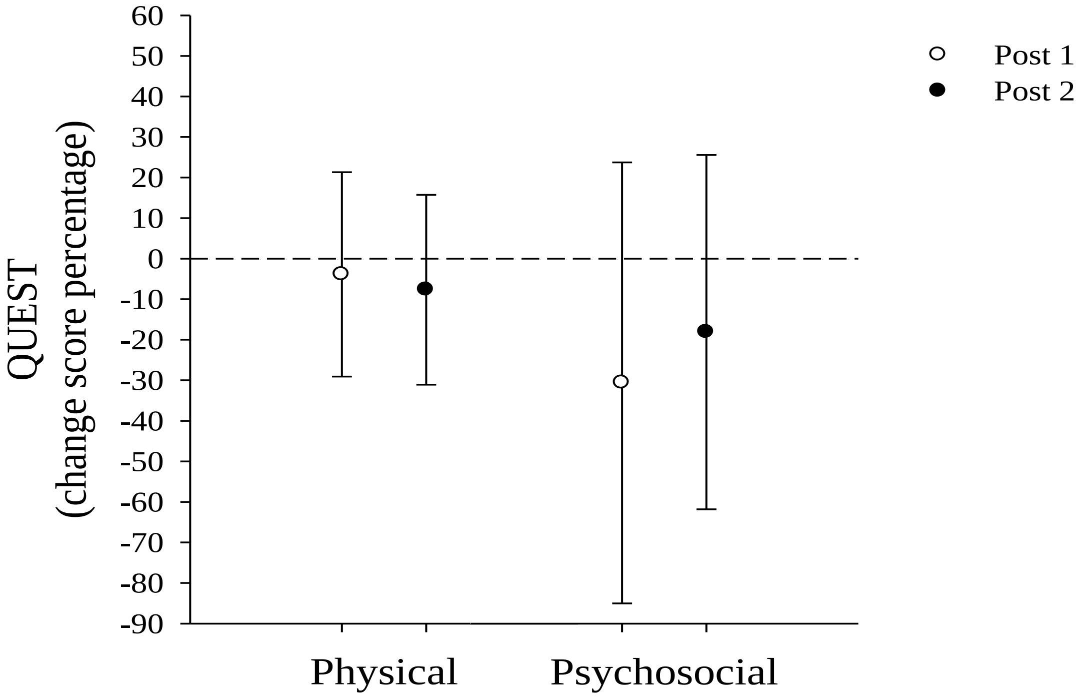

Figure 13: Performance in the Quality of Life in Essential Tremor (QUEST) questionnaire for Physical and Psychosocial domains. Post 1 and Post 2 data were calculated as change scores from pooled pre-exercise data and expressed as a percentage change of the pre-exercise data. Positive values indicate an increase of strength following the exercise intervention. Data are reported as means and 95% confidence intervals.

Communication and Hobbies and Leisure

Following the six week RT intervention there was no significant change for Communication (p = 0.99, ES = 0.00 ± 0.54) and Hobbies and Leisure (p = 0.61, ES = 0.34 ± 1.64) QUEST scores (Figure 14).

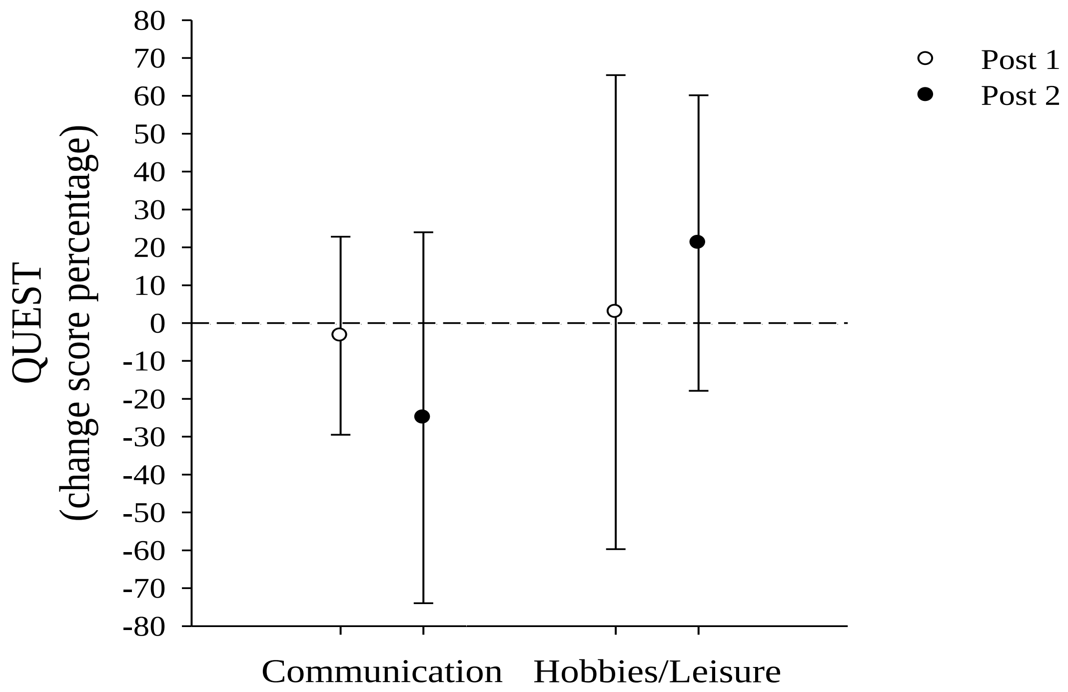

Figure 14: Performance in the Quality of Life in Essential Tremor (QUEST) questionnaire for Communication and Hobbies and Leisure domains. Post 1 and Post 2 data were calculated as change scores from pooled pre-exercise data and expressed as a percentage change of the pre-exercise data. Positive values indicate an increase of strength following the exercise intervention. Data are reported as means and 95% confidence intervals.

Work and Finance

Following the six week RT intervention there was no significant change for Work and Finance (p = 0.61, ES = 0.29 ± 1.53) QUEST scores (Figure 15).

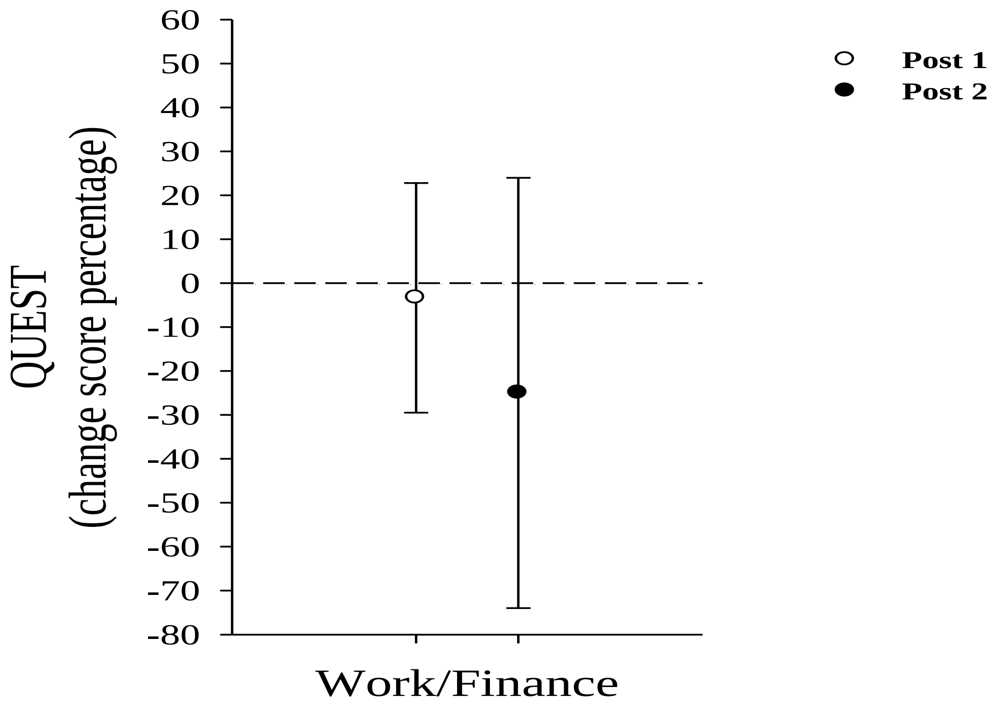

Figure 15: Performance in the Quality of Life in Essential Tremor (QUEST) questionnaire for Work and Finance domain. Post 1 and Post 2 data were calculated as change scores from pooled pre-exercise data and expressed as a percentage change of the pre-exercise data. Positive values indicate an increase of strength following the exercise intervention. Data are reported as means and 95% confidence intervals.

Chapter 5 - Discussion

This pilot study set out to investigate the effect of a general dumbbell-based upper limb RT programme on strength, hand and finger manual dexterity and QoL in older adults with ET. In accordance with the first two hypotheses, there was a significant increase in strength in some muscle groups and unilateral dexterity measures after the six week RT programme. Conversely, there was no significant change seen in either of the QoL measures, which did not allow for the confirmation of the third hypothesis of this study.

Strength

Following the six week RT intervention there were significant gains in strength, however these gains tended to vary across muscle groups (~44%). Significant improvements were seen in elbow and wrist flexion for the most affected limb, while wrist flexion and extension improved for the least affected limb. Furthermore these changes were only evident immediately post the RT intervention, with gains dissipating following the six week cessation of RT. The magnitude of these gains are relatively consistent with the findings of previous RT interventional studies (Folland & Williams, 2007; Peterson, et al., 2010; Seguin & Nelson, 2003) and that of the only other RT study in an ET population (Bilodeau, et al., 2000). Bilodeau et al. (2000), described a 13.4% increase in MVC finger pinch force after two weeks of heavy, finger abduction/adduction resistance training in eight people with ET.

Often decreases in function and motor control are seen as a consequence of ageing and disease. While multi-factorial in nature, these declines may reflect changes in morphology, e.g. sarcopenic-related reductions in muscle cross-sectional area, relative loss of fast-twitch motor units as well as changes in neuromuscular function related to changes in motor unit size and firing properties in the agonist and antagonist muscles (Hess & Woollacott, 2005; Peterson, et al., 2010; Seguin & Nelson, 2003). Such changes have been correlated with age, though interestingly some have also been correlated to the decline in strength (Sosnoff & Newell, 2006). Sosnoff and Newell (2006) compared force variability and strength in young and older adults and found that there was significantly greater finger force variability in the older age group. However when accounting for age in the analysis, a significant relationship between higher force variability and lower levels of strength were seen. Though there is a link between strength and function, it can be complex with a number of factors playing a role in functional improvement (Shumway-Cook & Woollacott, 2007). A good example of this is seen in issues of balance in older adults. Factors such as altered vestibular or proprioceptive system function can have a negative effect on balance performance as does reduced leg strength (Hess & Woollacott, 2005). Where there is reduced leg strength, balance performance can be greatly improved with resistance training (Hess & Woollacott, 2005). Likewise, with a period of RT increases in dexterity have been observed (Kornatz, et al., 2005). As such the improvement of strength observed in this study could be of functional significance to older adults with ET-related upper limb losses of hand and finger manual dexterity.

Mechanisms behind the significant improvements in strength seen in the present six week RT study may primarily be the result of neuromuscular adaptations such as reduced co-activation and motor unit variability as well as increased neural drive (Beck, et al., 2007; Folland & Williams, 2007; Reeves, et al., 2006). Although the present study did not directly assess any of these neural adaptations, it was hypothesised that such adaptations would result in improved hand and finger dexterity (Olafsdottir, Zatsiorsky, & Latash, 2008).

Hand and finger manual dexterity

The mean PPT scores achieved in this study, ~9 pegs for the single handed tasks and 6.8 pegs for the Both hand task, were substantially lower than scores reported in studies of healthy older adults. Murata, et al. (2010) assessed dexterity, via the PPT, in four different healthy female age groups and reported mean scores of 12.8 pegs for the 75-79 year old group and 12.6 pegs for the 80-85 year old group. Similarly, Pennathur et al. (2003) observed mean scores of 12.9 and 11.3 for the single handed (dominant and non-dominant respectively) tasks and 9.5 pegs for the Both hand task in healthy older adults. This observed difference in PPT performance between the current study and the literature for neurologically normal older adults supports the use of the PPT as a valid measure of hand and finger dexterity disability for individuals with ET (R. J. Elble, 2009; Louis, 2010a).

The current pilot study utilised the same, dumbbell-based general RT programme created by Keogh, et al. (2007; 2010). This RT programme has been shown to significantly improve finger pinch force control and reduce postural tremor in neurologically normal older adults (J.W.L Keogh, et al., 2007; J W. L. Keogh, et al., 2010). Utilising this general RT programme, there was a significant increase in hand and finger dexterity as assessed in the unilateral tasks of the PPT. The most affected hand task displayed improvement at both the Post 1 and Post 2 assessments, while the least affected hand showed significant improvement at the Post 2 assessment only. These findings complement those of Bilodeau, et al. (2000); where, after a period of RT, ET patients with a greater severity of tremor had the greatest improvements in force steadiness. Similar improvements in PPT performance after a period of RT have been seen in previous studies (Kornatz, et al., 2005). Kornatz, et al. (2005), prescribed RT for the non-dominant hand only in older adults. After the six week RT intervention, PPT dexterity results for the non-dominant hand had significantly improved to scores on par with those achieved in the dominant hand task. The resulting gains of strength and dexterity after training were also found to have a mild but significant correlation ($r = 0.41$, $p=0.03$).

It is conceivable that for long-term ET patients, as used in this study, the most affected hand would be used relatively infrequently in tasks requiring hand and finger dexterity. This could mean that the most affected limb may have a functional role similar to the non-dominant hand in those without pathological tremor. The earlier changes seen in PPT performance seen in the current study for the most affected hand may be in part due to the different functional and physiological characteristics of the two upper limb limbs. The non-dominant hand is known to have greater motor unit force variability and reduced force steadiness and strength than the dominant hand (Adam, de Luca, & Erim, 1998). The less favoured hand has also been shown to exhibit greater tremor amplitudes when compared to the dominant hand (Bilodeau, Bisson, DeGrace, Despres, & Johnson, 2009). This may suggest that the most affected hand has a greater scope for improvement with RT.

Neither bimanual PPT tasks showed any significant improvement in the present study. While such a result was initially a little surprising when compared to that of the unilateral PPT tasks, it would appear somewhat consistent with the principle of specificity. This principle the greatest change in performance occurs in tasks similar to that done in training. As training only involved unilateral dumbbell RT exercises, the significant improvements in unilateral PPT performance and lack of change in the two bilateral PPT tasks appears plausible. The non-significant change for bimanual dexterity tasks may reflect the complex CNS relationship between changes in function brought on by RT and performance in visuomotor tasks such as the PPT. Adding further complexity to the issue, some aspects of cortical and sub-cortical processing also differ depending on whether unilateral or bilateral coordination tasks are being performed (van den Berg, Swinnen, & Wenderoth, 2011). Our findings reinforce the concept of specific task-related changes to RT, and supports the task-related alterations in the control of movement evident in a previous ET RT training study (Bilodeau, et al., 2000). Therefore, training programs which include task-specific activities, such as unilateral and bilateral strength and coordination movements, may further improve functionality in ET patients.

Significant improvements in PPT performance such as that seen in the study of Kornatz, et al. (2005) may also result in some reductions in tremor. Héroux, et al. (2006) found a significant correlation (r = -0.61) between changes in dexterity and tremor severity in a study of 31 ET patients and 28 controls. Comparing PPT scores to a measure of tremor severity, the authors found that for the non-dominant hand there was an exponential relationship between tremor and PPT function, such that an increase in tremor amplitude correlated to a lower PPT score. This training- related reduction may be due to improvements in a number of aspects of neuromuscular function. While no such measures were obtained in the present study, previous exercise studies involving RT protocols in neurologically normal and ET populations have demonstrated significant reductions in motor unit firing rate variability (Bilodeau, et al., 2000; Kornatz, et al., 2005) and co-activation (J W. L. Keogh, et al., 2010). Furthermore these changes may also reflect potential central adaptations, perhaps occurring at the cerebellum, or inferior olive, due to their relation to ET and role in error correction of force production (Llinás, 2009).

Quality of life

The SF-36 and QUEST questionnaires were used to measure possible changes in QoL. The SF-36 is a general health-related QoL scale used in many studies involving older adults and the QUEST is a recently developed ET specific QoL scale. Disease specific QoL questionnaires, such as the QUEST are important as they address concerns specific to a group with a given disease (Louis & Rios, 2009), with a few being developed for ET that include individual and clinical tremor ratings and embarrassment domains (Elble, et al., 2006; Lundervold, Pahwa, Ament, & Corbin, 2003; Traub, Gerbin, Mullaney, & Louis, 2010).

The mean baseline SF-36 scores of this study were observed to be, on average, lower than those of the general older adult population of New Zealand and Australia (Australian Bureau of Statistics, 1997; New Zealand Ministry of Health, 1999). This observation was comparable to the results found by Lorenz et al. (2006) who compared 102 ET patients to the general German population. The authors found SF-36 scores of the ET group to be lower than the scores attained by the general German population.

Improvements in muscular strength may potentially translate to improved QoL (Kell, Bell, & Quinney, 2001). In this study however, there were no significant effects noted after the training period for either QoL scale. This also contrasts previous findings in special populations such as PD and stroke, where a RT intervention has resulted in QoL improvements (Dibble, Hale, Marcus, Gerber, & LaStayo, 2009; H. Lee, Kim, & Noh, 2008). It is possible that the short duration of this project did not allow for sufficient time to achieve meaningful gains in physical function that may have resulted in improved QoL. There also appeared to be some within-subject variation in their scores on some of these outcomes between assessment occasions. While the QoL measures have been shown to be valid and reliable measures (Chia, et al., 2006; Troster, et al., 2005) such variability may reflect a difficulty in "translation" to a different population (New Zealand older ET patients) than that used in the reliability / validation studies or inherent variability in individual perceptions of QoL over a 14 week period.

Practical Significance

The findings of this pilot study indicate that RT may warrant further investigation as a therapy for improving hand and finger dexterity in ET patients, but that six weeks of RT may prove ineffective in improving QOL.

Chapter 6 - Study limitations & future studies

Due to the exploratory nature of this pilot study, only a small sample size was obtained. With the help and support from the NZETSG we were able to recruit six of the ~20 active members attending the Auckland branch of the NZETSG meeting. The small sample size limits the inferences that can be made from this study and limits the external validity of the findings. There is also potential for variation in physiological and neuromotor status with older adult ET participants. A greater period between pre testing sessions (i.e. six weeks which was the duration of the training programme) may have better captured this variability. Future studies would also benefit from using randomised controlled trial designs, comprised of a larger sample size from the wider community. This would allow for a greater understanding of the potential effect and magnitude of the changes with RT and reduce any potential sampling bias.

There is some debate regarding the diagnostic criteria of ET (Lorenz & Deuschl, 2007). This may impact on how, and if, ET participants should be stratified into subgroups for research projects. This is a significant issue to address as potential findings may be affected by the subgrouping or lack-of in such studies.

Though this study was primarily concerned with investigating the effect of RT on hand and finger dexterity, a more direct measure of tremor would be of value in future studies. Though there is no widely accepted gold-standard measure of tremor, with varying methods of differing quality being employed by different studies, it is important to take into account the possible correlation between QoL, activities of daily living and tremor measures/mechanisms. This could be applied to the application of appropriate rehabilitation programmes in clinical practice (Lundervold, et al., 2003). Such a step was recently presented by Deuschl, Raethjen et al. (2011) who described an algorithm, based on clinical ratings and tremor amplitude, to assess the effect of rehabilitative treatments such as medications and DBS which are available to ET patients. Future research could aim to correlate changes in tremor measured, for example via accelerometery, and its relation to meaningful changes in activities of daily living such as holding a full glass and self-perceived QoL. This may offer a greater insight into potential mechanisms underlying the changes in tremor and its effect on ET individuals' QoL.

Though neural adaptations occur predominantly in the first six weeks of RT, altering the duration and/or intensity variables of the training may have yielded greater results. Published RT training studies typically last between six and twelve weeks. It may be that training-related changes in hand and finger dexterity takes longer to manifest in those with ET than neurologically normal populations. Therefore a study, comprising of a longer training period, may bring to light results that were not seen in this study.

Chapter 7 - Conclusion

ET has a significant impact on an individual's life with potential reductions in function including hand and finger dexterity and QoL. A six week general RT programme involving simple dumbbell exercises resulted in many significant improvements in strength and hand and finger dexterity.

Though a number of limitations exist within this pilot study, the improvements seen in this ET population to RT is encouraging. This is especially so when considering the number of functional benefits evident from previous studies involving RT for older adults and those with other neurological conditions. With larger, more highly powered randomised controlled trials the true effect of RT on ET may be better elucidated.

With consideration to the changes observed in this pilot study and the positive findings of previous studies, RT as a therapy for ET patients warrants further investigation.

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Appendices

Appendix A - Abbreviations

ET	Essential Tremor
QoL	Quality of life
RT	Resistance training
5RM	5 Repetition maximum
PPT	Purdue Pegboard Test
SF-36	Short Form-36
QUEST	Quality of Life in Essential Tremor Questionnaire
DBS	Deep brain stimulation
PD	Parkinson's disease
EMG	Electromyography
EEG	Electroencephalographic
PET	Positron Emission Tomography
NAA/Cho	N-acetylaspartate to Choline
NAA/Cr	N-acetylaspartate to Creatine
NRI	Normalised Resting Index
MVC	Maximum Voluntary Contraction
Pre 1	Familiarisation assessment prior to training intervention
Pre 2	Baseline assessment prior to training intervention
Post 1	First assessment immediately post training intervention
Post 2	Second assessment 6 weeks post training intervention

Appendix B - Ethics Approval

- Northern Regional Y Ethics Committee approval, reference NTY/10/03/025.

Health and Disability Ethics Committees

Northern Y Regional Ethics Committee
Ministry of Health
3rd Floor, BNZ Building
354 Victoria Street
PO Box 1031
Hamilton 3204
Phone (07) 858 7021
Fax (07) 858 7070
Email: northerny_ethicscommittee@moh.govt.nz

2 July 2010

Dr Justin Keogh
School of Sport & Recreation
Auckland University of Technology
Private Bag 92 006
Auckland

Dear Justin

Ethics ref:	**NTY/10/03/025 (please quote this reference in all correspondence)**
Study title:	**Can resistance training improve upper limb function and quality of life in essential tremor patients?**
Investigators:	**Dr Justin Keogh, Mr Graeme Sequeira**
Localities:	**New Zealand Essential Tremor Support Group, Excercise Solutions, Auckland University of Technology**

This study was given ethical approval by the Northern Y Regional Ethics Committee on 2 July 2010.

Approved Documents
-Study Protocol.
-Participant Information Sheet version 1 dated 4/06/2010.
-Questionnaires – QUEST ADL, SF-36.

This approval is valid until 30 December 2011, provided that Annual Progress Reports are submitted (see below).

Access to ACC
For the purposes of section 32 of the Accident Compensation Act 2001, the Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out. Participants injured as a result of treatment received in this trial will therefore be eligible to be considered for compensation in respect of those injuries under the ACC scheme.

Amendments and Protocol Deviations
All significant amendments to this proposal must receive prior approval from the Committee. Significant amendments include (but are not limited to) changes to:

- the researcher responsible for the conduct of the study at a study site
- the addition of an extra study site
- the design or duration of the study
- the method of recruitment
- information sheets and informed consent procedures.

Significant deviations from the approved protocol must be reported to the Committee as soon as possible.

Appendix C - Mean and Standard deviation data

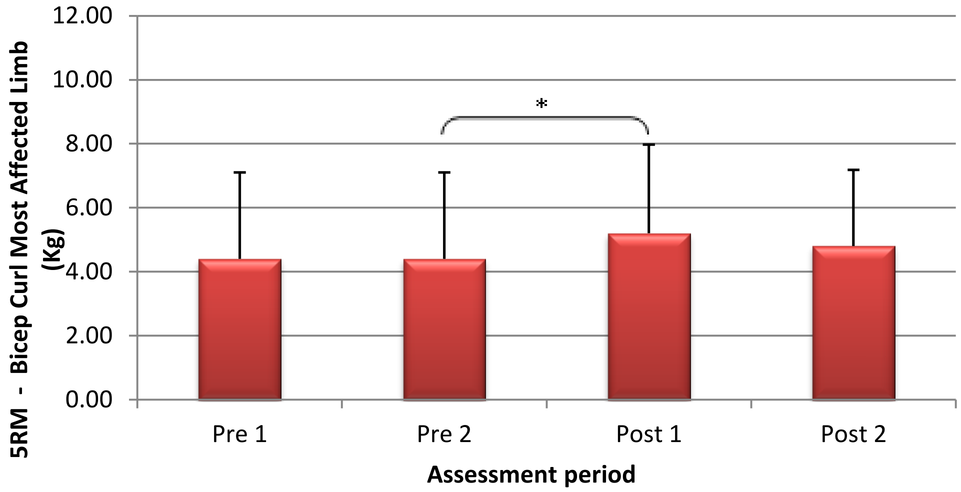

Figure 16: 5RM Strength Test –Mean (Kg) & SD for elbow flexion of the most affected limb. * = Significant change (p<0.05).

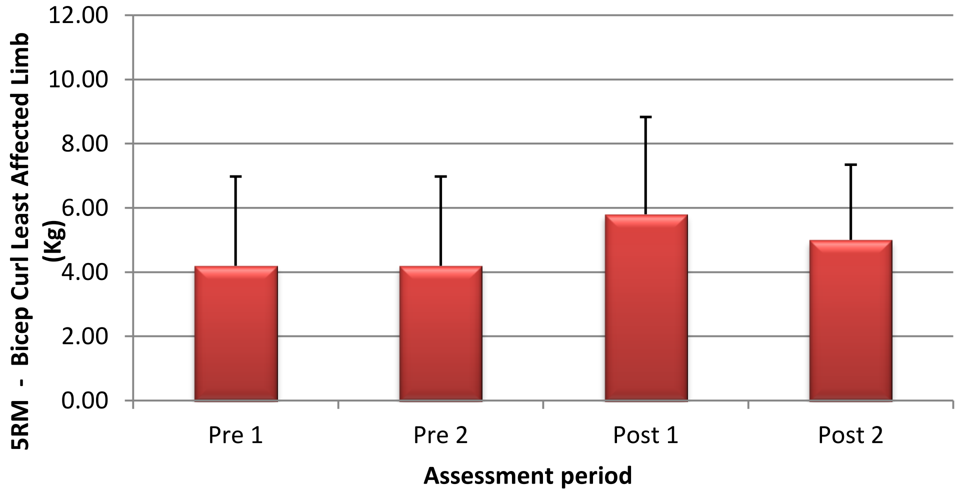

Figure 17: 5RM Strength Test –Mean (Kg) & SD for elbow flexion of the least affected limb

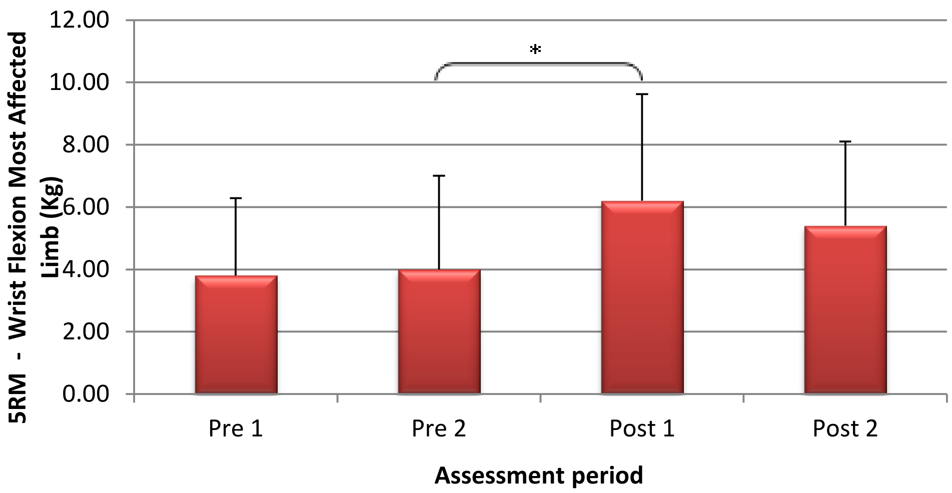

Figure 18: 5RM Strength Test –Mean (Kg) & SD for wrist flexion of the most affected limb. * = Significant change ($p<0.05$).

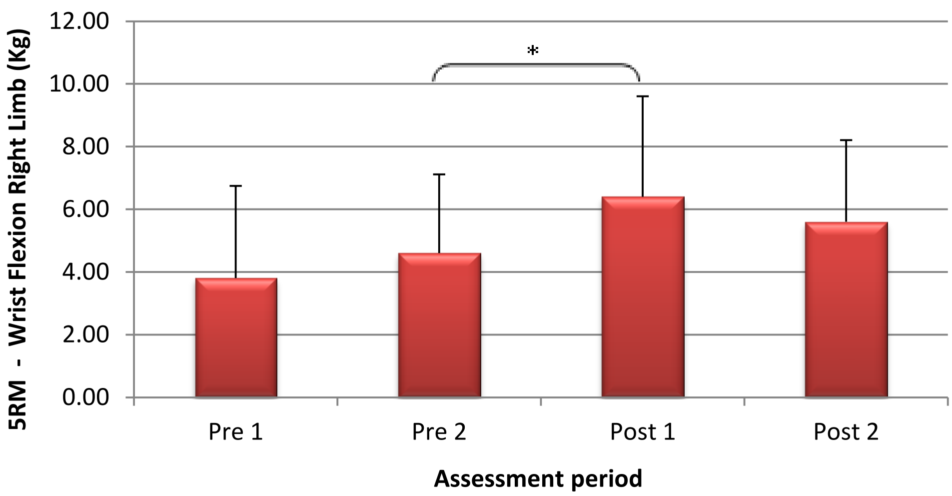

Figure 19: 5RM Strength Test –Mean (Kg) & SD for wrist flexion of the least affected limb. * = Significant change ($p<0.05$).

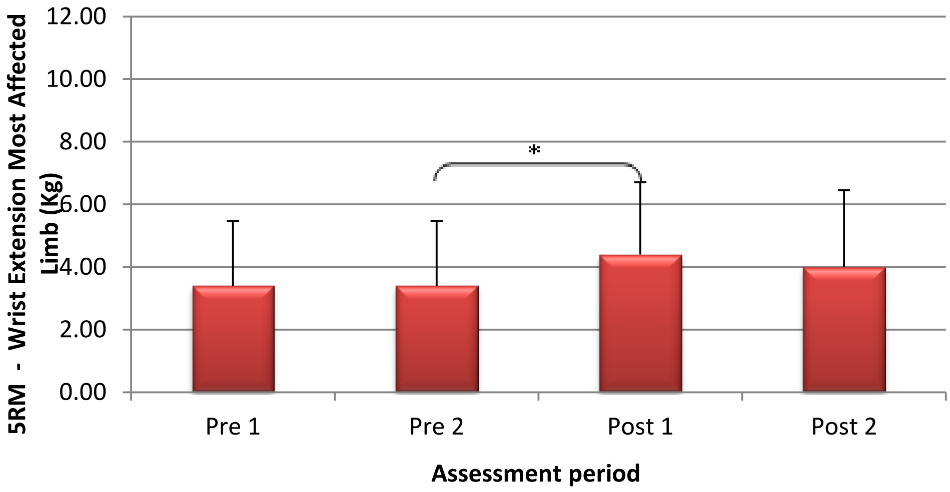

Figure 20: Strength Test –Mean (Kg) & SD for wrist extension of the most affected limb. * = significantly different ($p < 0.05$).

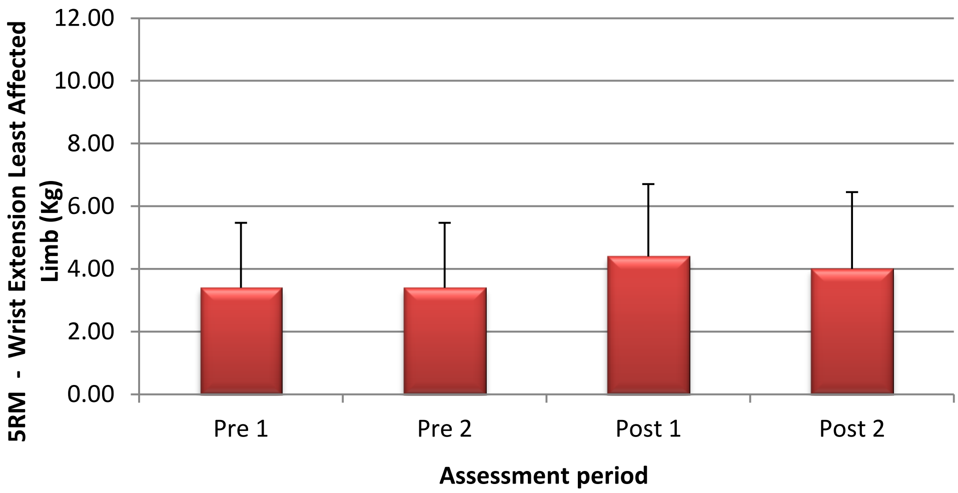

Figure 21: Strength Test –Mean (Kg) & SD for wrist extension of the least affected limb

Hand and Finger dexterity

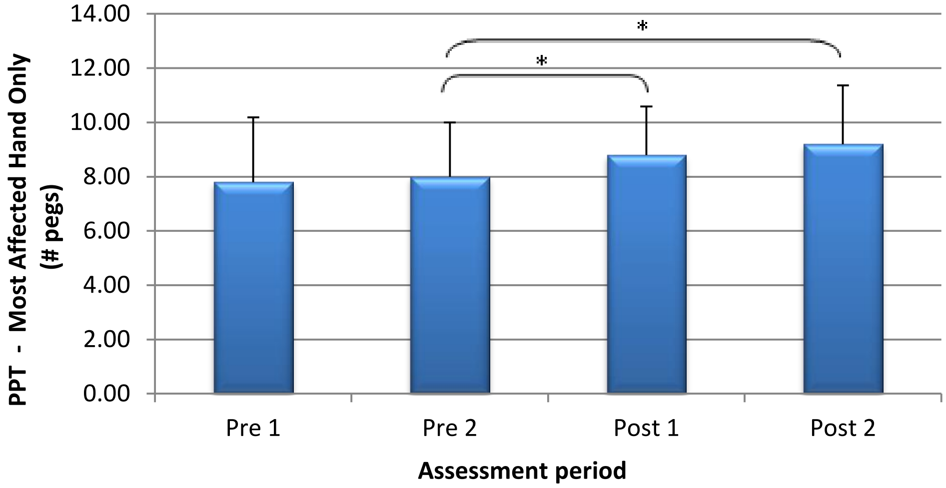

Figure 22: Purdue Pegboard scores of most affected hand only task. * = significantly different ($p < 0.05$).

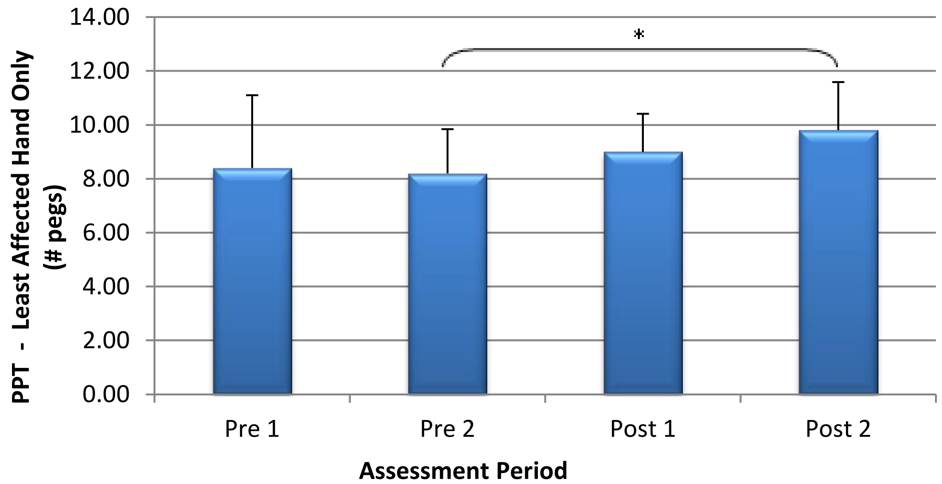

Figure 23: Purdue Pegboard scores of least affected hand only task. *= significantly different ($p < 0.05$).

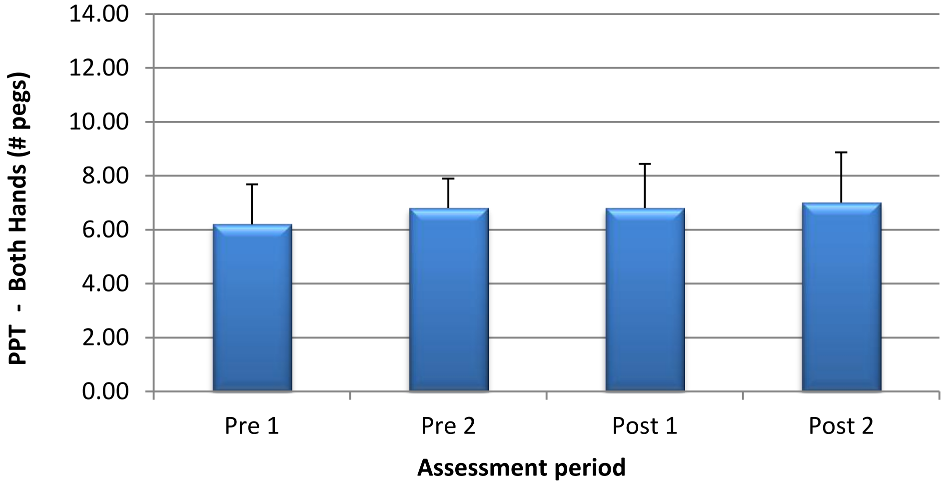

Figure 24: Purdue Pegboard scores of Both hand task.

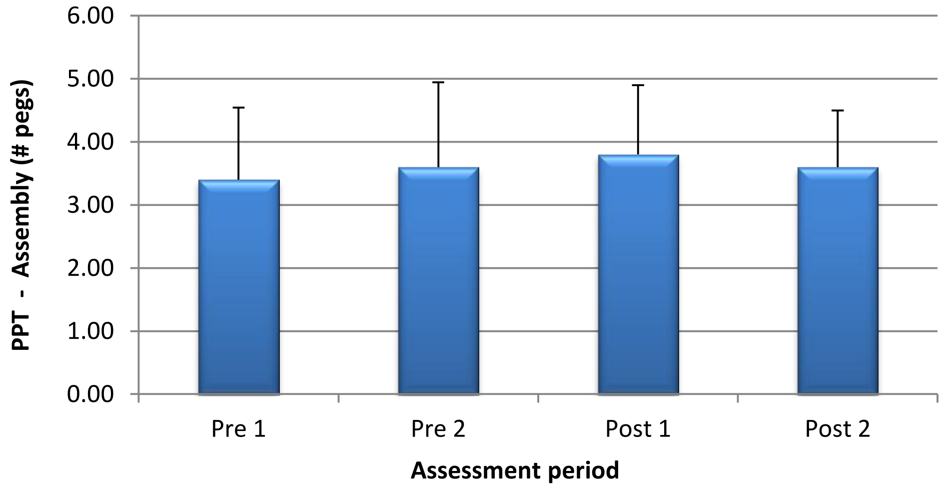

Figure 25: Purdue Pegboard scores of Assembly task

Quality of life – SF-36

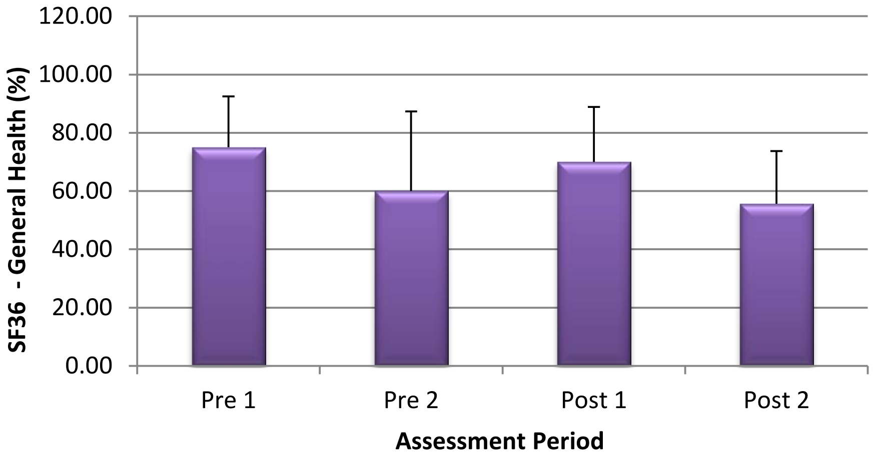

Figure 26: SF-36 scores for the General Health domain

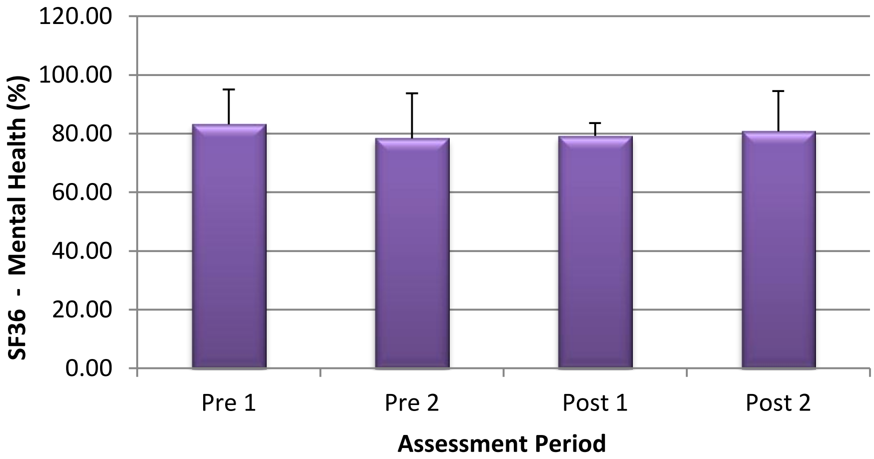

Figure 27: SF-36 scores for the Mental Health domain

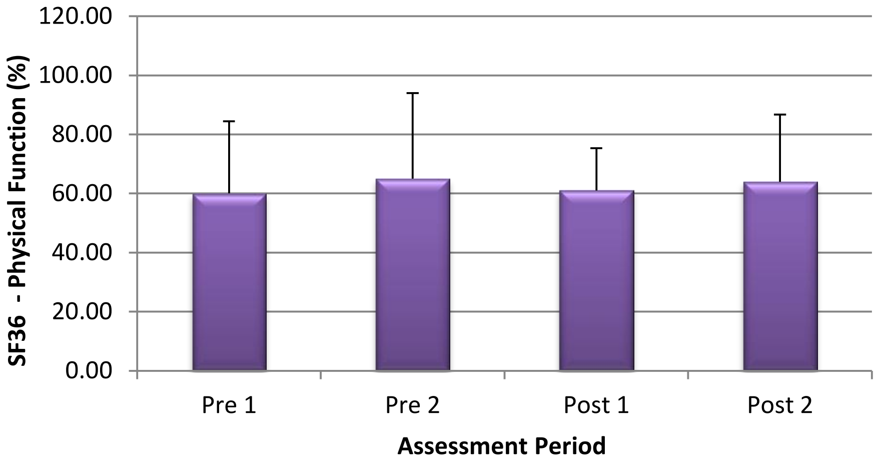

Figure 28: SF-36 scores for the Physical Function domain

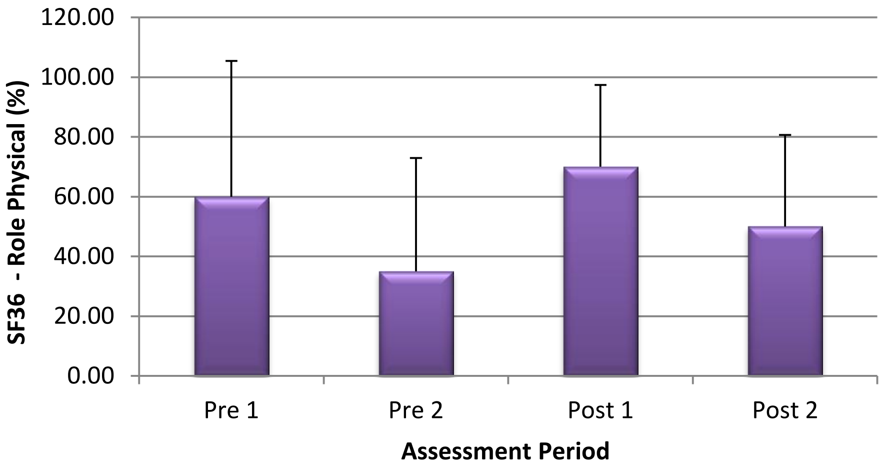

Figure 29: SF-36 scores for the Role Physical domain

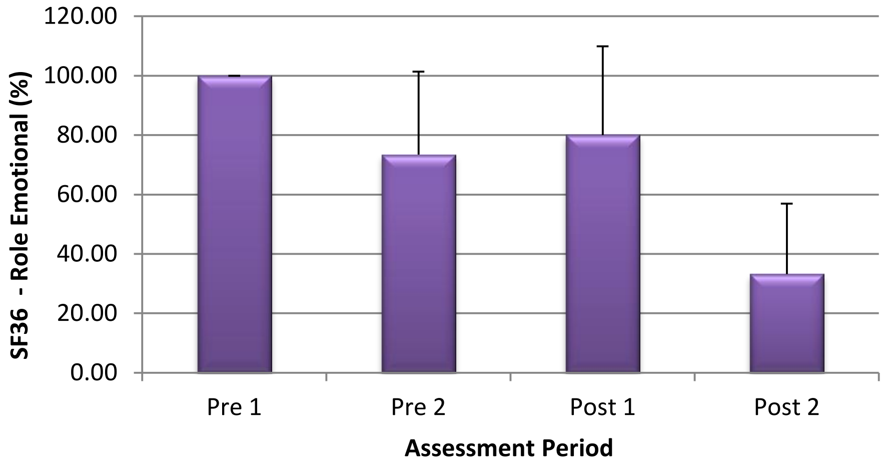

Figure 30: SF-36 scores for the Role Emotional domain

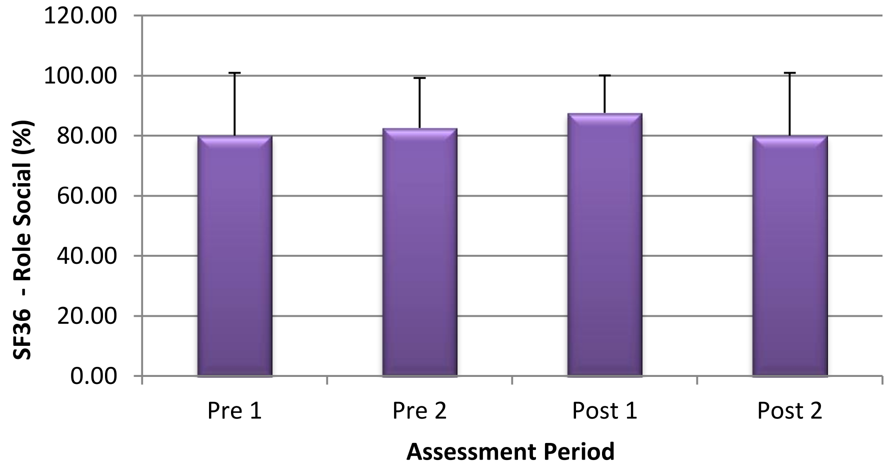

Figure 31: SF-36 scores for the Role Social domain

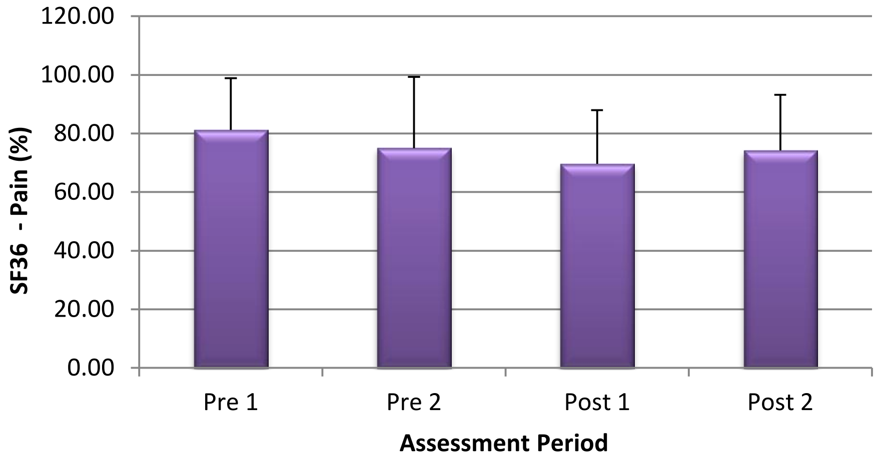

Figure 32: SF-36 scores for the Pain domain

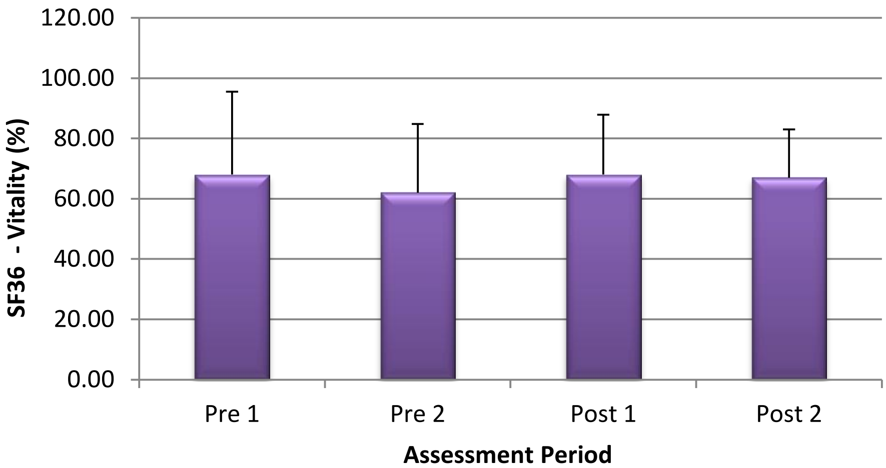

Figure 33: SF-36 scores for the Vitality domain

Quality of Life - QUEST

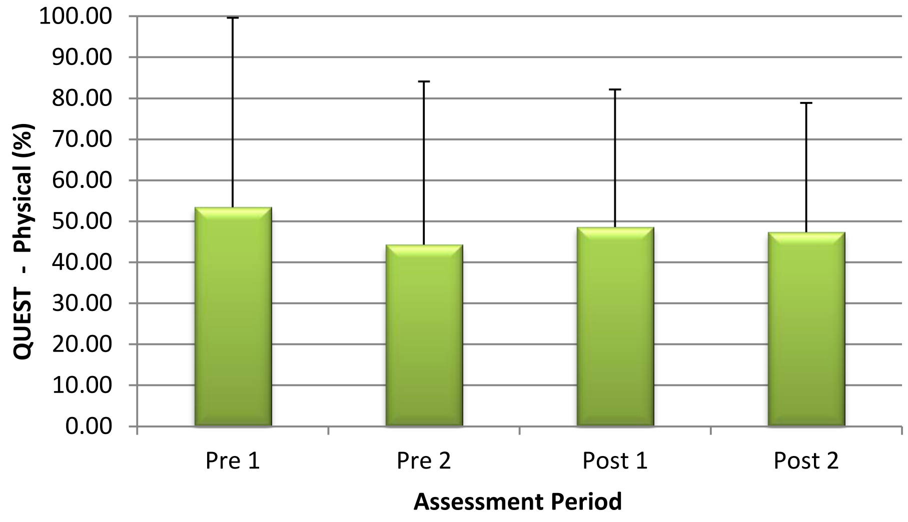

Figure 34: QUEST scores for the Physical domain

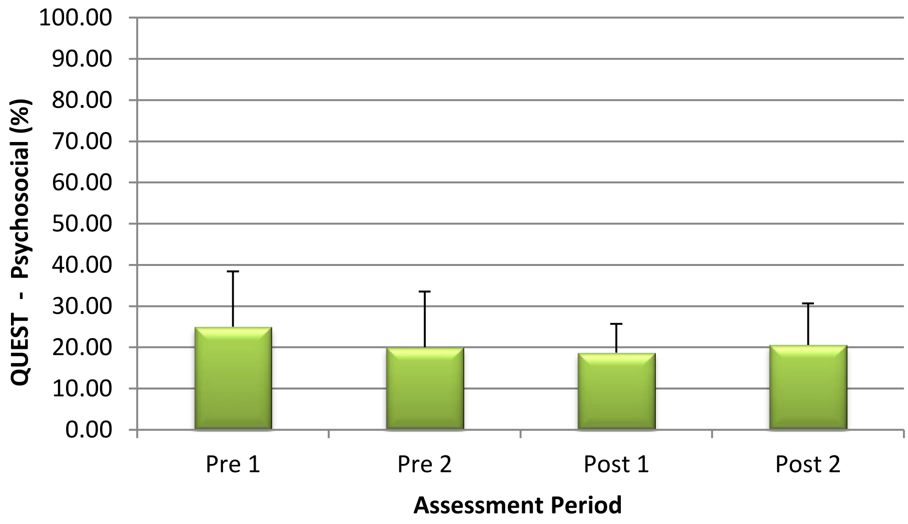

Figure 35: QUEST scores for the Psychosocial domain

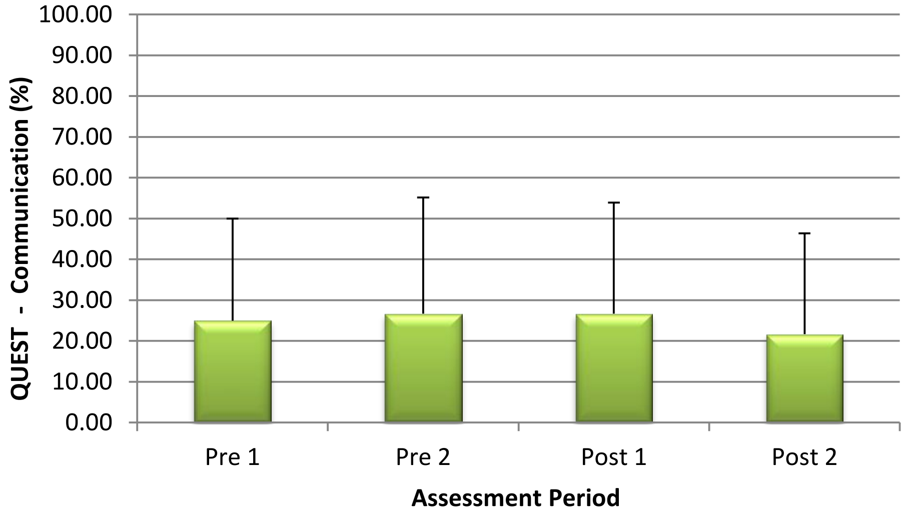

Figure 36: QUEST scores for the Communication domain

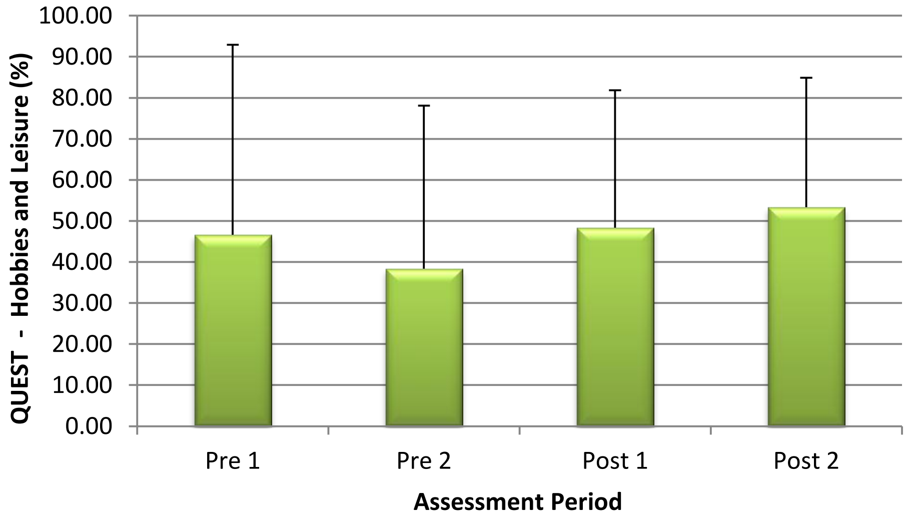

Figure 37: QUEST scores for the Hobbies and Leisure domain

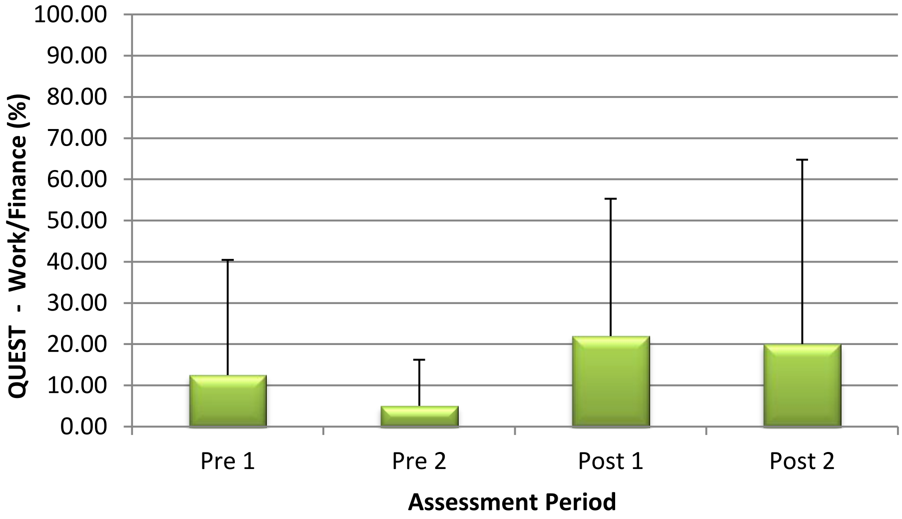

Figure 38: QUEST scores for the Work and Finance domain