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The clinical utility of multidisciplinary rehabilitation in individuals with Huntington's Disease

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The Clinical Utility of Multidisciplinary Rehabilitation in Individuals with Huntington's Disease

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Doctoral Thesis

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School of Medical Science

Faculty of Health, Engineering and Science

EDITH COWAN UNIVERSITY

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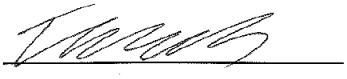
Travis Miles Cruickshank  Date: 26/02/2015

ABSTRACT

Background

Huntington's disease (HD) is a chronic neurodegenerative disorder characterised by a progressive loss of cognitive function, motor control and psychiatric features. Individuals also display a variety of systemic features. Progressive neuronal dysfunction and neuronal cell death are thought to underlie the onset and progression of many clinical features of HD.

Despite scientific progress, there is still no cure or disease modifying therapy for HD, and available pharmaceutical agents only provide partial relief of motor and psychiatric features. An emerging body of evidence indicates that lifestyle enrichment may delay the onset and progression of clinical features, and exert favourable effects on neuropathological aspects of HD. Few studies have evaluated the effects of lifestyle enrichment strategies like multidisciplinary rehabilitation on the clinical features of HD. Moreover, no study has evaluated the effects of multidisciplinary rehabilitation on neuropathological aspects of HD.

Aims

The initial aim of this thesis was to determine factors that contribute to features of the disease that negatively impact on activities of daily living such as mobility and balance (Chapter 2), and to identify, using a literature review, a rehabilitation strategy that could positively impact on these features of HD (Chapter 3). These studies informed our ultimate aim which was to investigate the clinical utility of multidisciplinary rehabilitation on clinical and neuropathological features of HD (Chapters 4, 5 and 6)

Methods

In study 1 (Chapter 2), 22 participants were assessed using a battery of balance, mobility, cognitive tests, assessments of muscle strength and body composition measures. Data was

then statistically examined using stepwise linear regression to identify factors that contribute to balance and mobility impairments in individuals with manifest HD. In study 2 (Chapter 3), a systematic search of journal databases was made from inception to July 2014 for studies reporting on resistance exercise in patients with neurodegenerative disorders. Selected studies were abstracted and critically appraised using a quality control checklist.

For the intervention studies, (3 and 4 Chapters 4 and 5), 20 participants with manifest HD were randomly assigned to either a control or training group. Individuals randomised to the intervention group were provided with a nine month multidisciplinary intervention comprising once weekly supervised clinical exercise, thrice weekly home based exercise and fortnightly occupational therapy, while those randomised to the control group were asked to continue with their standard care and daily activities. Participants were assessed using motor, cognitive, psychological, body composition and quality of life measures at baseline and at the completion of the intervention. In study 5 (Chapter 6), 15 participants with manifest HD were assessed using magnetic resonance imaging and a battery of cognitive assessments after nine months of multidisciplinary rehabilitation to see whether such a therapy is capable of inducing favourable changes in brain structure and cognitive function.

Results

The main factors that contribute to mobility and balance impairments in patients with manifest HD were found to be lower limb muscle weakness and a loss of cognitive function (Study 1). Systematic evaluation of the effects of resistance exercise for neurodegenerative disorders showed that it is beneficial for multiple sclerosis and Parkinson's disease. In particular, improvements in muscle strength, mobility, balance, clinical disease progression, fatigue, functional capacity, quality of life, disease biology, electromyography activity, mood, skeletal muscle volume and architecture were reported in individuals with multiple sclerosis

or Parkinson's disease (PD) after resistance exercise. The most robust effects of resistance exercise were found for muscle strength outcomes, and were more pronounced in individuals with PD (Study 2).

The multidisciplinary rehabilitation intervention studies conducted as part of this thesis significantly improved isometric and isokinetic muscle strength, self-perceived balance, body mass, lean tissue mass and fat mass in patients with HD (Studies 3 and 4). Moreover, multidisciplinary rehabilitation also increased grey matter (GM) volume in the caudate nucleus and dorsolateral prefrontal cortex of patients. The significant increases in GM volume were accompanied by, and correlated to, a significant improvement in performance in verbal learning and memory.

Conclusions

The work presented here shows that lower extremity muscle weakness and a loss of cognitive function significantly contribute to impairments in mobility and balance. This work also shows that strength training has favourable effects on motor function, including strength, mobility and balance, as well as other clinical features in similar neurodegenerative disorders, and thus should be integrated into multidisciplinary rehabilitation interventions for HD. In addition, this study provides evidence that multidisciplinary rehabilitation can significantly improve aspects of motor control, cognitive function and body composition. Finally we show, for the first time, that multidisciplinary rehabilitation can increase GM volume in structures known to degenerate in HD, and that such increases are functionally related to changes in verbal learning and memory. Future work is urgently required to confirm and expand on these exciting findings, particularly with respect to the neurorestorative properties of multidisciplinary rehabilitation.

ACKNOWLEDGMENTS

The work presented in my thesis is dedicated to my grandmother (Hilda) and uncle (Bob). This thesis would not have been possible without the gracious help of my supervisors, laboratory colleagues, collaborators, friends and family.

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This thesis is submitted as a series of papers.

As a result of the work performed for this thesis, two papers have been published and three papers have been submitted for publication:

An Assessment of the Factors That Contribute to Balance and Mobility Impairments in Individuals with Huntington's Disease

Travis Cruickshank, Alvaro Reyes, Luis Peñailillo, Jennifer Thompson & Mel Ziman

Published: Basal Ganglia, 2014 April 8th; 4 (2): 67-70

A Systematic Review and Meta-Analysis of Resistance Exercise Trials in Individuals with Multiple Sclerosis or Parkinson's Disease

Travis Cruickshank, Alvaro Reyes & Mel Ziman

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The Effects of Multidisciplinary Rehabilitation in Patients with Early-to-Middle Stage Huntington's Disease: a Pilot Study

Jennifer A. Thompson*****, Travis M. Cruickshank*****, Luis E. Penailillo, Joseph W. Lee, Robert U. Newton, Roger A. Barker, & Melanie R. Ziman

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***J.A.T and T.M.C contributed equally to this work**

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The Effect of Multidisciplinary Rehabilitation on Brain Structure and Cognition in Huntington's Disease: an Exploratory Study

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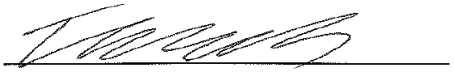
STATEMENT OF CONTRIBUTION TOWARDS PUBLICATIONS

For studies 1, 4 and 5, I contributed to the study design, intervention design and delivery, data collection, data analysis, manuscript writing and editing. For study 2, where I am joint first author, I contributed to the study design, search for research trials, analysis of the included trials, writing and editing of the manuscript entitled "A Systematic Review and Meta-Analysis of Resistance Exercise Trials in Individuals with Multiple Sclerosis or Parkinson's Disease". Finally for study 3, where I am also joint first author, I contributed to the study design, intervention design and delivery, data collection, data analysis, writing and editing of the manuscript entitled "The Effects of Multidisciplinary Rehabilitation in Patients wirth Early-to-Middle Stage Huntington's Disease: a Pilot Study.

Research Candidate Signature:  **Date** 26/02/2015

Research Supervisor Signature:  **Date** 26/02/2015

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LIST OF ABBREVIATIONS

6MWT	6 Minute Walk Test
BBS	Berg Balance Scale
BDNF	brain derived neurotrophic factor
CAG	cytosine-adenine-guanine
CREB	cAMP response element-binding protein
DBS	Disease Burden Score
DDARP-32	Dopamine-and cAMP-regulated phophoprotein, Mr 32 kDA
DNA	deoxyribonucleic acid
D1/D2	Dopamine receptors 1 & 2
ETC	electron transport chain
GLT1	glutamate uptake transporter 1
HEAT	Huntingtin, Elongation Factor 3, PR65/A subunit of protein phosphatase 2A and TOR1 the target of rapamycin
HSP	heat shock protein
HD	Huntington's disease
HTT	Huntingtin gene
Htt	huntingtin protein
3-HK	3-hyroxykynurenine

mRNA	messenger ribonucleic acid
mGlu2R	metabolic glutamate receptor 2
MS	multiple sclerosis
Mhtt	mutant huntingtin protein
NMDA	N-methyl-D-aspartate
NES	Nuclear export signal
NLS	Nuclear localisation signal
PD	Parkinson's disease
PET	positron emission tomography
PPAR-γ	peroxisome proliferator-activated receptor-γ
PGC-1α	coactivator-1α
PN	proteosome network
PolyQ	polyglutamine stretch
PolyP	polyproline domain
PSD95	postsynaptic protein density 95
QA	quinolinic acid
RSST	Repeated Sit to Stand Test
RNA	ribonucleic acid
SOT	Sensory Organisation Test

TWT	Timed Walk Test
TRiC	TCP-1 ring complex
UHDRS	Unified Huntington’s Disease Rating Scale
UPS	ubiquitin-proteasome system

CHAPTER 1 - GENERAL INTRODUCTION

1.1 HISTORY OF HD

Huntington's disease (HD), formerly known as 'Huntington's chorea', was first comprehensively described by George Sumner Huntington in his self-titled publication 'On Chorea' in 1872 (Figure 1.1) (Huntington, 1872). This landmark publication vividly described the autosomal dominant inheritance, adult-onset and central features of HD. Huntington's description laid the foundation for future genetic investigations, which over a century later mapped the Huntington gene (*HTT*) to chromosome 4 (Gusella et al., 1983). The ensuing decade led to the isolation of the *HTT* gene (4p16.3) and identification of the expanded cytosine-adenine-guanine (CAG) sequence responsible for HD (MacDonald et al., 1993). In the years that followed, many scientific advances were made, including the genetic engineering of transgenic HD mice (Carter et al., 1999; Mangiarini et al., 1996). These mouse models have, over the last two decades, enabled the investigation of pathological mechanisms involved in HD, as well as genetic manipulation and pharmacological/molecular interventions.

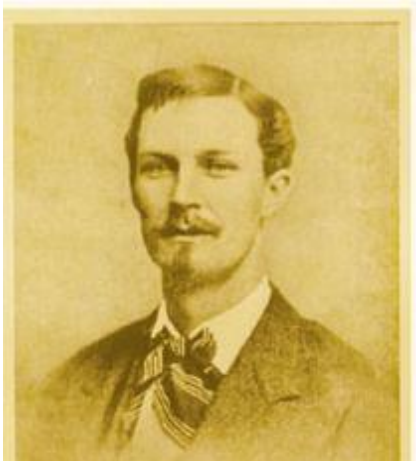

Figure 1.1 George Huntington (1850-1916)

1.2 EPIDEMIOLOGY OF HD

The exact worldwide prevalence of HD is unknown, however recent estimates suggest a prevalence of 5-8 per 100,000 (Kumar et al., 2010). Countries of European ancestry display a higher prevalence of HD (3-10 per 100,000) than countries of non-European ancestry (0.11-0.45 per 100,000) (Gatto et al., 2014). Recent figures indicate that the prevalence of HD is 12.3 per 100,000 in the United Kingdom (Evans et al., 2013) and 7 per 100,000 in Australia (Harper, 1992; Pridmore, 1990). By contrast, the prevalence of HD within Asia is a mere 0.4

per 100,000 (Pringsheim et al., 2012). “Demographic hot spots”, have also been identified, such as the Zulia region of Venezuela, where the prevalence of HD is extraordinarily high (~50%), owing to a founder effect (Wexler, 2004).

1.3 CLINICAL VARIANTS OF HD

Individuals carrying the mutant *HTT* gene typically present during midlife (4^{th} to 6^{th} decades of life) (Tabrizi et al., 2009; 2012; 2011a; 2013), however early and late age of onset variants are also well documented (Foroud et al., 1999; James et al., 1994; Lipe and Bird, 2009; Mahant et al., 2003; Robertson et al., 2012; Roos et al., 1993). Early onset HD, termed Juvenile HD (JHD) accounts for 4.92% of all HD cases worldwide (Quarrell et al., 2012). Often arising through paternal transmission (Merritt et al., 1969), JHD cases typically carry 60 or more CAG repeats and present before 21 years of age (Cloud et al., 2012; Douglas et al., 2013; Quarrell et al., 2013). Typical features of JHD include a progressive rigid-ataxic like phenotype, cerebellar signs, chorea, speech and language problems, oropharyngeal problems, epilepsy, seizures (tonic-clonic and myoclonic), depression, aggression, weight loss and cachexia (Barker and Squitieri, 2009; Cannella et al., 2004; Cloud et al., 2012; Gonzalez-Alegre and Afifi, 2006; Nance and Myers, 2001; Quarrell et al., 2013; Ribaï et al., 2007; Yoon et al., 2006). Late onset HD, in stark contrast to JHD, is characterised by mild chorea and more globalised dementia (not too dissimilar to Alzheimer’s disease) (Aziz et al., 2008; Foroud et al., 1999; James et al., 1994; Lipe and Bird, 2009; Mahant et al., 2003; Roos et al., 1993). Interestingly, in late onset HD, individuals typically succumb to age-related diseases like cancer, cardiovascular disease and Alzheimer’s disease rather than the disease-related processes of HD (Bürger et al., 2002; Lipe and Bird, 2009).

1.4 HUNTINGTON GENE

The gene responsible for HD, *IT15 ('interesting transcript'*) or *HTT,* was located on the short arm (p) of chromosome 4 by Gusella and colleagues in 1983. Over the next ten years, a dedicated group of scientists exhaustively investigated chromosome 4 using emerging gene-mapping and genomic technology, which in 1993 led to the isolation of *HTT* (4p16.3) and discovery of the mutation responsible for HD. The causative mutation is an expanded cytosine-adenine-guanine (CAG) repeat sequence in exon 1 of *HTT*. Under normal circumstances healthy individuals possess between 6 and 35 CAG repeats. While individuals with HD typically possess in excess of 39 CAG repeats. Although rare, individuals that possess between 36 and 39 CAG repeats are said to have incomplete penetrance, and may develop HD at some stage in their lifetime (MacDonald et al., 1993).

1.5 INTRICATE ROLE OF THE CAG REPEAT

Robust evidence shows that the length of the expanded CAG sequence is strongly correlated with age at onset (Andrew et al., 1993; Claes et al., 1995; Duyao et al., 1993; MacDonald et al., 1993; MacMillan et al., 1993; Nørremølle et al., 1993; Snell et al., 1993; Zühlke et al., 1993). The length of the CAG expansion is estimated to account for 47% to 72% of the variance in age at onset (Brinkman et al., 1997; Craufurd and Dodge, 1993; Ranen et al., 1995; Rosenblatt et al., 2001; Squitieri et al., 2000). The remainder of the variance in age at onset is influenced by environmental and additional genetic factors. In line with this, Wexler et al (2004) found that environmental factors accounted for 62% of the remaining variance in age at onset in four hundred and fifty eight individuals with HD. Interestingly, Kremer et al (1993) has shown that the length of the CAG expansion only accounts for 7% of variation in the age of onset of individuals beyond fifty years of age. This indicates that the effect of the CAG repeat length on age of onset may diminish with increasing age.

1.6 HUNTINGTIN PROTEIN STRUCTURE

Huntingtin (Htt) is an extremely large protein comprising 3114 amino acids (Johnson and Davidson, 2010). The high molecular mass of Htt (348-kDa) has hampered the full elucidation of its structure (Zuccato et al., 2010). Structural domains of Htt have nevertheless been identified and described in detail. The most recognisable structure within Htt is the polyglutamine stretch (PolyQ), which commences at the 18th amino acid (Perutz et al 1994; Huntington's Disease Collaborative Research Group). Immediately following the PolyQ is a polyproline domain (PolyP), which is believed to stabilise the PolyQ (Darnell et al., 2007; Kim et al., 2009; Steffan et al., 2004). Downstream of the PolyQ and PolyP regions, 16 Huntingtin, Elongation Factor 3, PR65/A subunit of protein phosphatase 2A and TOR1 the target of rapamycin (HEAT) repeat sequences have been identified (Andrade and Bork, 1995; Neuwald and Hirano, 2000; Takano and Gusella, 2002). The precise role of these HEAT repeat sequences still remains unclear, however increasing evidence indicates an involvement in protein-protein interactions (Medicine, 2013; Takano and Gusella, 2002). Htt also possesses well-characterised cleavage sites, where proteolytic enzymes such as caspases, calpains and aspartyl proteases cleave Htt into smaller fragments (Kim et al., 2001; Zuccato et al., 2010). An active nuclear export signal and a less active nuclear localisation signal have also been found on Htt, which indicates that Htt may also be involved in the transport of molecules from the nucleus to the cytoplasm (Desmond et al., 2013; Xia et al., 2003). Many post-translational modification sites are also present on the Htt protein, particularly in polypeptide sequences enriched in proline, glutamate, serine and threonine (PEST domains) (Warby et al., 2008), where ubiquitination (Bhat et al., 2014), phosphorylation (Aiken et al., 2009; Humbert et al., 2002; Khoshnan et al., 2004; Rangone et al., 2004; Schilling et al., 2006), SUMOylation (Steffan et al., 2004), palmitoylation (Yanai et al., 2006) and acetylation (Jeong et al., 2009) of Htt can take place. The exact role of these post-

translational modifications is not yet clear, however they have been postulated to modulate protein-protein interactions as well as influence the stability and localisation of Htt (Bates et al., 2014).

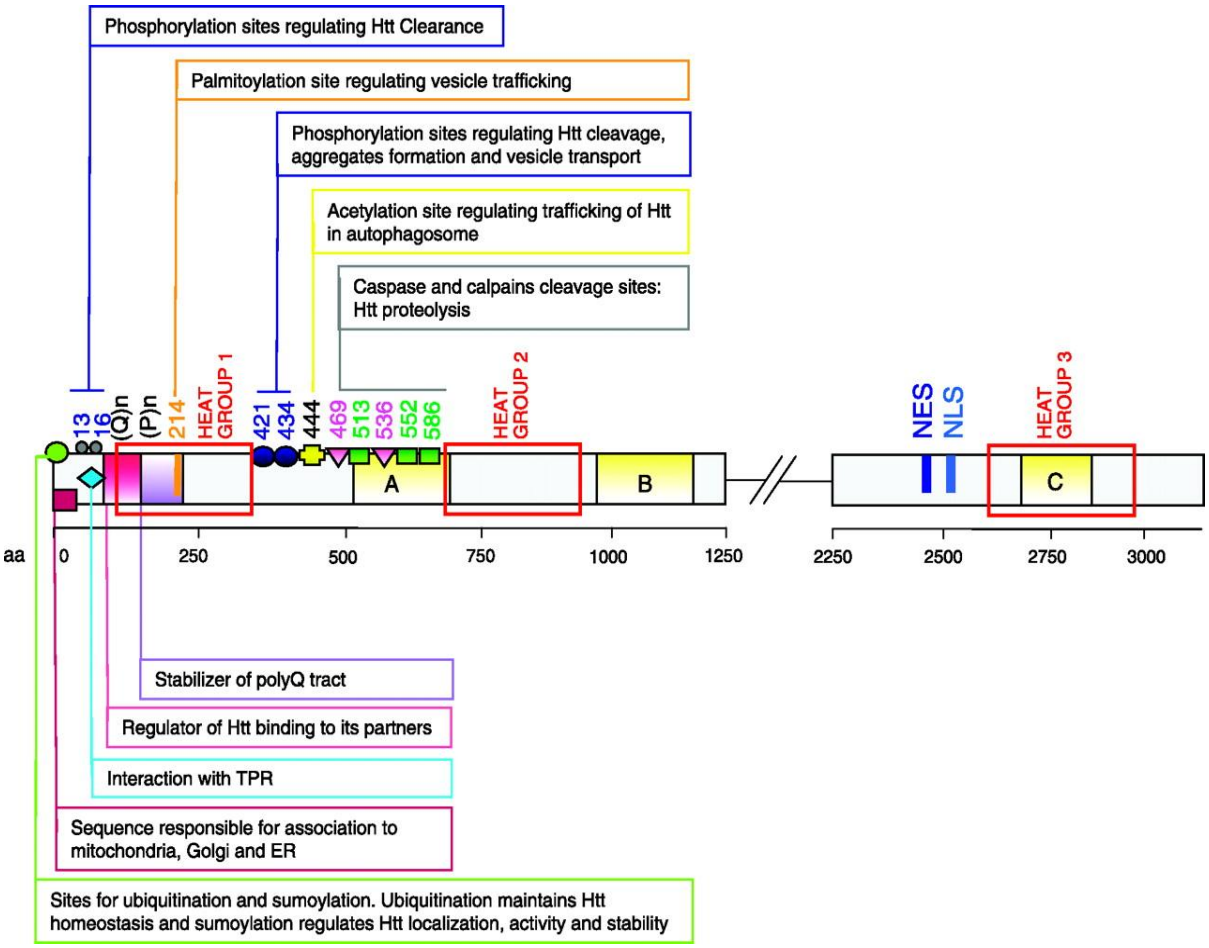

Figure 1.2 Schematic diagram of the Huntingtin (Htt) amino acid sequence

(Q)n indicates the polyglutamine tract, which is followed by the polyproline sequence (P)n; the red emptied rectangles indicate the three main HEAT repeats (HEAT group 1, 2, 3). The small green rectangles indicate the caspase cleavage sites and their amino acid positions, while the small pink triangles indicate the calpain cleavage sites and their amino acid positions. Boxes in yellow: B, regions cleaved preferentially in the cerebral cortex; C, regions of the protein cleaved mainly in the striatum; A, regions cleaved in both. Posttranslational modifications: ubiquitination (UBI) and/or sumoylation (SUMO) sites (green); palmitoylation site (orange); phosphorylation at serines 13, 16, 421 and 434 (blue); acetylation at lysine 444 (yellow). NES is the nuclear export signal while NLS is the nuclear localisation signal. The nuclear pore protein translocated promoter region (TPR, azure) is necessary for nuclear export. Htt huntingtin. ER, endoplasmic reticulum (Image from Zuccato et al 2010).

1.7 HUNTINGTIN PROTEIN EXPRESSION

Htt is ubiquitously expressed throughout neuronal and non-neuronal tissues (Landwehrmeyer et al., 1995; Vonsattel and DiFiglia, 1998), with the greatest enrichment in the central nervous system and testes (Sapp et al., 1997; Sharp et al., 1995; Wood et al., 1996). Modest expression of Htt is also evident in the lungs, heart, kidneys, liver and muscle (Sharp et al., 1995; Wood et al., 1996). In the cell, Htt co-localises with most organelles, including the nucleus, mitochondria, endoplasmic reticulum and golgi apparatus (Atwal and Truant, 2008; Choo et al., 2004; DiFiglia et al., 1995; Gutekunst et al., 1998; Milakovic and Johnson, 2005; Panov et al., 2002; Velier et al., 1998). Studies using immunolabeling and immunoprecipitation have also shown that Htt associates with vesicle membranes and microtubules (DiFiglia et al., 1995; Gutekunst et al., 1995; Sharp et al., 1995). Its ubiquitous expression and numerous interactions with cellular organelles suggest that Htt is vital for normal molecular and cellular function.

1.8 HUNTINGTIN PROTEIN FUNCTION

The biological role of Htt is not well understood. Studies in transgenic animal models and cell lines have however provided insights into the molecular and cellular roles of Htt. Early investigations in mice showed that constitutive inactivation of Htt causes embryonic lethality between embryonic day 8.5 and 10.5 (Duyao et al., 1995; Nasir et al., 1995). Experimental reduction of Htt below 50% of resting levels has been shown to cause epiblast defects as well as profound cortical and striatal architectural anomalies (Auerbach et al., 2001; White et al., 1997). These studies clearly implicate wild-type Htt involvement in the formation of the central nervous system.

In vitro and *in vivo* studies indicate that Htt is also involved in antiapoptotic activities (Ho et al., 2001; Leavitt et al., 2006; Sardo et al., 2012). Elegant work by Rigamonti et al (2001;

2001) has shown that striatal cells overexpressing wild-type Htt are resistant to lethal biological stresses, such as serum deprivation and 3-nitropropionic acid. However depleting wild-type Htt using short inhibitory RNA compounds has been found to increase the vulnerability of cells to apoptotic events (Zhang et al., 2006).

Studies in animal models and cell lines have also shown that wild-type Htt stimulates the production of brain derived neurotrophic factor (BDNF) by activating BDNF promoter II (Benn et al., 2008; Zuccato et al., 2001). BDNF has known roles in synaptogenesis and neurogenesis, and is highly expressed in corticostriatal structures, which degenerate in HD. These findings indicate that wild-type Htt may mediate the transcription of neuronal genes involved in maintaining neuronal homeostasis (Zuccato and Cattaneo, 2007).

A number of studies also implicate wild-type Htt involvement in axonal and vesicle transport (Gunawardena et al., 2003). Experimentally lowering wild-type Htt to 50% of resting levels has been documented to impair fast axonal trafficking of mitochondria as well as BDNF transport in mammalian neurons (Gauthier et al., 2004; Trushina et al., 2004).

Finally, wild-type Htt has been reported to interact with cytoskeletal and synaptic vesicle proteins involved in exocytosis and endocytosis, implicating its involvement in synaptic activity (Smith et al., 2005). Early investigations showed that wild-type Htt binds to the SH3 domains of postsynaptic density protein 95 (PSD95) (Sun et al., 2001). PSD95 is a multivalent scaffolding protein that colocalises with N-methyl-D-aspartate (NMDA) receptors at the postsynaptic density and controls synaptic transmission (Sun et al., 2001). A decreased interaction between wild-type Htt and PSD95 leads to an increased interaction between PSD95 and NMDA receptors causing an over activation and sensitisation of NMDA receptors promoting excitotoxicity (Fan et al., 2009).

These findings collectively indicate that a loss of wild-type Htt function at least in part contributes to the molecular and cellular pathology witnessed in HD.

1.9 PATHOLOGICAL MECHANISMS INVOLVED IN HD

Studies investigating wild-type Htt have shown that it interacts with many proteins involved in transcription, synaptic transmission, energy metabolism and protein degradation. Thus a loss of wild-type Htt and toxic gain in mutant Htt results in wide scale molecular and cellular dysfunction.

1.9.1 Transcriptional dysregulation in HD

Transcription anomalies maybe one of the earliest pathological events in HD (Cha, 2007). *In situ* hybridisation experiments on the post-mortem human HD brain have documented decreased expression of preproenkephalin, substance P, dopamine receptors D1 and D2, glutamate transporter 1 (GLT-1) and NMDA subunits NR1 and NR2B messenger RNA (mRNA) (Arzberger et al., 1997; Augood et al., 1997; Augood et al., 1996). Similar findings have also been reported in the R6/2 mouse model (Cha et al., 1999; Cha et al., 1998). A number of mechanisms have been proposed through which mutant Htt may disrupt transcription regulation (Cha, 2007; Luthi-Carter and Cha, 2003). For instance, mutant Htt may perturb the interaction between transcription factors (e.g. Sp1) (Schaffar et al., 2004), their transcriptional coactivators (Zhai et al., 2005) and target DNA thereby reducing the expression of many important target genes. Mutant Htt may also aberrantly interact with the core transcription machinery, such as RNA polymerase II, Transcription Factor II F, Transcription Factor II D, TATA-Associated Factor $_{II}$130 and TATA binding protein, causing transcriptional dysregulation (Dunah et al., 2002; Luthi-Carter et al., 2002b; Shimohata et al., 2000; Zhai et al., 2005).

1.9.2 Altered synaptic activity in HD

Alterations in synaptic activity are well documented and may be responsible for many of the clinical features of HD (Gil and Rego, 2008; Milnerwood and Raymond, 2010; Raymond et al., 2011; Sepers and Raymond, 2014; Smith et al., 2005). Mutant Htt interacts with a variety of cytoskeletal and synaptic vesicle proteins involved in synaptic function (Caviston and Holzbaur, 2009; Dominguez and Munoz-Sanjuan, 2014; Li et al., 2003; Qin et al., 2004). leading to synaptopathology (Li et al., 2003; Smith et al., 2005).

Studies in mouse models and postmortem HD brain tissue have reported changes in neurotransmitter release, uptake and postsynaptic signalling in corticostriatal pathways (Sepers and Raymond, 2014). In particular, elevated glutamate release is evident in early HD, followed by a decrease in glutamate release later in HD (Joshi et al., 2009; Miller and Bezprozvanny, 2010).

1.9.3 Impaired energy metabolism in HD

Impairments in energy metabolism are considered central to the pathogenesis of HD (Aziz et al., 2010b). Disruptions in cell metabolism have been reported in central and peripheral tissues in human and rodent models of HD (Aziz et al., 2010b; Underwood et al., 2006). Investigations using positron emission tomography (PET) have reported decreased glucose metabolism in striatal structures in people with manifest HD (Antonini et al., 1996; Kuwert et al., 1990; Underwood et al., 2006; Young et al., 1986). There is also evidence of increased lactate levels in the cerebral cortex and an elevated lactate-to-pyruvate ratio in the cerebrospinal fluid of both manifest and pre-manifest HD patients (Jenkins et al., 1998; Jenkins et al., 1993; Koroshetz et al., 1997). Decreased adenosine triphosphate (ATP) levels have additionally been observed in the brain and muscle (Ciarmiello et al., 2006; Cross et al., 1986; Miller and Bezprozvanny, 2010).

Accumulating evidence suggests that mitochondrial dysregulation mediates many of the outlined deficits in energy metabolism. For example, impairments in electron transport chain (ETC) complexes I, II and III have been reported in HD (Browne et al., 1997; Gu et al., 1996; Parker et al., 1990; Stahl and Swanson, 1974). Impaired ETC activity has been found to correlate with reduced ATP synthesis and an increase in reactive oxygen species (ROS) in HD (Chakraborty et al., 2014; Tabrizi et al., 1999). Impeded axonal transport of mitochondria to cellular sites with high energy demands, like neurons, synapses and muscles has also been reported (Reddy and Shirendeb, 2012; Shirendeb et al., 2011). Mutant Htt has also been found to decrease the expression of peroxisome proliferator-activated receptor-γ (PPAR- γ) coactivator-1α (PGC-1α) through cAMP response element-binding protein-dependent transcriptional inhibition (Cui et al., 2006). Down-regulation of PGC-1α decreases mitochondrial energy metabolism by impairing oxidative phosphorylation (Lin et al., 2005).

1.9.4 Impaired protein degradation pathways in HD

Strong evidence indicates that protein degradation pathways are also impaired in HD (Gu et al., 1996). Protein degradation pathways are essential for removing dysfunctional and damaged proteins, ensuring cellular homeostasis (Labbadia and Morimoto, 2013). Two pathways responsible for degrading mutant Htt include the ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (Rubinsztein, 2006). Briefly, the UPS degrades short-lived misfolded, oxidized and mutant proteins (Young et al., 1986). In contrast, the autophagy-lysosome pathways degrade dysfunctional or damaged cytosolic proteins in lysosomes (Jenkins et al., 1993).

In HD, an accumulation of ubiquitinated mutant Htt fragments is observed within cells, particularly neurons, indicating an impairment in the UPS (Ciarmiello et al., 2006; Jenkins et al., 1998). The inability of the UPS to degrade mutant Htt has been proposed to stem from its

inability to unfold the stabile β–sheet structure formed by the poly-Q stretch. These observations suggest that autophagy degradation pathways may be preferentially used to degrade mutant Htt. Like the UPS, autophagy degradation pathways appear impaired in HD (Koroshetz et al., 1997). Elegant work by Maria Cuervo's group has shown that mutant Htt impairs the recognition of cytosolic cargo not enabling the degradation of dysfunctional or damaged proteins (Martinez-Vicente et al., 2010). Deficient autophagy degradation pathways do not enable the recycling of important organelles, like mitochondria, which accumulate in cells in HD, facilitating homeostatic distress and proteasome destabilisation (Martinez-Vicente et al., 2010).

1.10 NATURAL HISTORY AND DIAGNOSIS OF HD

The clinical course of HD is incredibly complex but can be simplistically divided into three disease stages; asymptomatic, premanifest and manifest HD. Asymptomatic or 'at risk' terminology is used to describe individuals with an affected parent, who have not undergone genetic testing and do not display clinical features of HD. Genetic testing is available to individuals at risk of inheriting HD from eighteen years of age, however the uptake of genetic testing services remains low worldwide. Individuals that undertake genetic testing and are identified as gene positive, but do not possess clinical features by which to make a formal diagnosis of HD, are typically termed premanifest. The premanifest disease stage typically spans 15-20 years, during which time an individual transitions from completely asymptomatic to displaying subtle motor, cognitive and psychological signs. The Unified Huntington's Disease Rating Scale (UHDRS) is currently the preferred clinical tool for assessing the onset of HD (Hungtington, 1996). While the scale comprises cognitive, behavioural, emotional and functional components, formal diagnosis rests on the presence of unmistakable motor features. In particular, clinicians are required to provide a 'diagnostic confidence score', indicating their level of certainty that any observed motor signs are

representative of HD (0-4; where 0 indicates no motor abnormalities suggestive of HD and 4 indicates motor abnormalities likely to be due to HD with ≥ 99% certainty). Gene positive individuals with a score of 4 are said to display manifest HD. This period is marked by the presentation and gradual worsening of clinical features, which over time renders the affected individual functionally impaired and eventually results in death (Bates et al., 2014; Tabrizi et al., 2009; Tabrizi et al., 2012; Tabrizi et al., 2011a; Tabrizi et al., 2013).

1.11 NEURODEGENERATION IN HD

1.11.1 Neurodegeneration in HD

Neuronal cell loss is a pathological hallmark of HD (Georgiou-Karistianis et al., 2013c; Kim et al., 2014; Ross et al., 2014; Thu et al., 2010). Studies on the post-mortem HD brain and more recent *in vivo* neuroimaging investigations reveal a striking degeneration of cortical and subcortical structures over time in HD (Aylward et al., 2011; Georgiou-Karistianis et al., 2013a; Guo et al., 2012; Hobbs et al., 2010; Kim et al., 2014; Majid et al., 2011; Nana et al., 2014; Ross et al., 2014; Tabrizi et al., 2012; Tabrizi et al., 2011a; Tabrizi et al., 2013; Thu et al., 2010; Vonsattel et al., 1985). Morphometric investigations of the post-mortem HD human brain (n=385) have documented significant whole brain atrophy (mean HD brain weight 1067g vs mean healthy brain weight 1350g) and regional atrophy within the striatum, frontal, temporal, parietal and occipital lobes as well as an enlargement of the lateral ventricle (Suzanne et al., 1988; Vonsattel et al., 1985; Vonsattel, 2008; Vonsattel and DiFiglia, 1998). These macroscopic findings have now been robustly confirmed *in vivo* using a variety of neuroimaging approaches (Aylward et al., 2000; Ginestroni et al., 2010; Harris et al., 1992; Peinemann et al., 2005; Ruocco et al., 2006; Tabrizi et al., 2012; Tabrizi et al., 2011a; Tabrizi et al., 2013; Vandenberghe et al., 2009)

1.11.2 Striatal degeneration in HD

Strikingly selective striatal atrophy is evident in HD (Aylward et al., 1997; Ross et al., 2014; Suzanne et al., 1988; Tabrizi et al., 2009; Tabrizi et al., 2012; Tabrizi et al., 2011a; Tabrizi et al., 2013; Vonsattel, 2008; Vonsattel and DiFiglia, 1998). Striatal degeneration typically follows an ordered and topographic pattern over the natural course of the disease (Vonsattel, 2008; Vonsattel and DiFiglia, 1998). Degeneration typically begins in the tail and body of the caudate nucleus and progresses over time in caudorostral, dorsoventral and mediolateral directions encompassing the putamen and globus pallidus (Vonsattel, 2008; Vonsattel and DiFiglia, 1998). Annual volume losses of 2.9 to 4.9% and 4.5% in the caudate nucleus and putamen of individuals with manifest HD are observed *in vivo* (Aylward et al., 2011; Tabrizi et al., 2011a). The most vulnerable neuronal populations within the striatum are GABAergic medium spiny neurons, which constitute 90-95% of striatal neurons (Graveland et al., 1985). Perplexingly, less common striatal interneurons (5-10%) appear to be relatively spared in HD (Albin et al., 1992; Ferrante et al., 1985; 1991; 1987; Reiner et al., 1988; Richfield et al., 1995). Differences in the neurochemical properties of each neuronal population are thought to account for the discrepancy in neuronal vulnerability (Cicchetti et al., 2000).

The medium spiny neurons of the striatum are involved in direct and indirect striatal pathways that modulate motor control through attenuating and facilitating movement (Calabresi et al., 2014; Gerfen and Surmeier, 2011). The indirect striatal pathway comprises medium spiny neurons that predominantly express dopamine receptor 2 and project to the external segment of the globus pallidus (Gerfen and Surmeier, 2011; Gerfen and Wilson, 1996). In contrast, the direct striatal pathway comprises medium spiny neurons that express dopamine receptor 1, dynorphin and substance P and project to the globus pallidus interna and substantia nigra reticulata (Gerfen and Surmeier, 2011; Gerfen and Wilson, 1996). Disruption of these pathways contributes to the onset and progression of hyperkinetic and

dyskinetic movements in HD. Studies investigating the indirect striatal pathway have found that a loss of medium spiny neurons coincides with the onset and progression of choreoathetoid features (Bates et al., 2014). By contrast, a preferential loss of medium spiny neurons in the direct striatal pathway has been shown to be associated with the onset and progression of parkinsonism features (André et al., 2011; Galvan et al., 2012).

1.11.3 Extrastriatal degeneration in HD

It is becoming increasing clear that extra-striatal structures are also susceptible to the neurodegenerative processes involved in HD (Douaud et al., 2006; Forno and Jose, 1973; Heinsen et al., 1999; Kassubek et al., 2004; Kremer, 1992; Kremer et al., 1991; Kremer et al., 1990; Lange et al., 1976; Mühlau et al., 2007; Roizin et al., 1979; Rüb et al., 2013; Suzanne et al., 1988; Tellez-Nagel et al., 1974; van den Bogaard et al., 2011). Pathological studies have reported significant cortical volume loss in frontal, temporal, parietal and occipital lobes of the post-mortem HD human brain (Halliday et al., 1998). Widespread cortical volume loss has also been documented *in vivo* using MRI (Jernigan et al., 1991; Nopoulos et al., 2011; Rosas et al., 2005; Rosas et al., 2002; Rosas et al., 2008; Tabrizi et al., 2011a). For instance, Rosas et al (2008) reported significant cortical thinning in primary motor, sensory and visual cortical regions, with the most pronounced thinning being found in primary motor and visual cortices.

Pathological and *in vivo* neuroimaging studies have also reported significant volume loss in the globus pallidus (Lange et al., 1976), substantia nigra (Campbell et al., 1961; Hallervorden, 1957; Kiferle et al., 2013; Lewy, 1923; Richardson, 1990; Schröder, 1931; Spielmeyer, 1926), nucleus accumbens (Lange et al., 1976), subthalamic nucleus (Lange et al., 1976; Spielmeyer, 1926), thalamus (Gavazzi et al., 2007; Heinsen et al., 1999; Heinsen et al., 1996; Kassubek et al., 2005; Mühlau et al., 2007), hypothalamus (Douaud et al., 2006;

Kassubek et al., 2004; Kremer, 1992; Kremer et al., 1991; Kremer et al., 1990; Politis et al., 2008; Vogt, 1952), hippocampus (Rosas et al., 2003; Suzanne et al., 1988), cerebellum (Fennema-Notestine et al., 2004; Rosas et al., 2003; Rüb et al., 2013) and cingulate gyrus (Henley et al., 2009; Kim et al., 2014; Ruocco et al., 2008; Thu et al., 2010) in manifest HD. Within the thalamus, significant neuronal loss has been reported in the dorsomedial nucleus (23.8%) and centromedial parafascicular nucleus at post-mortem (Grade 3 & 4) (1999; Heinsen et al., 1996). Significant neuronal loss has also been reported by Kramer et al (1992; 1991; 1990) in the lateral tuberal nucleus of the hypothalamus (90%). Lastly, Rosas et al (2003) has documented significant volume loss in the hypothalamus (95%) and amygdale (24%) *in vivo*, using MRI.

1.11.4 Neurodegeneration and clinical expression

Accumulating evidence suggests that neuronal dysfunction and cell loss mediate the clinical expression of HD (Delmaire et al., 2013; Guo et al., 2012; Kim et al., 2014; Nana et al., 2014; Scahill et al., 2013; Sprengelmeyer et al., 2014; Thu et al., 2010). In particular, cortical interneuron loss in the primary motor cortex and anterior cingulate cortex has been found to correlate with the expression of motor features and mood (Kim et al., 2014; Thu et al., 2010). Moreover, neuronal cell loss in the striatum, subthalamic nuclei, primary motor, primary sensory, secondary visual cortex as well as associational cortices in frontal, temporal and parietal lobes has been found to be associated with the expression of motor symptoms (Guo et al., 2012; Nana et al., 2014). Lastly, cortical thinning has been found to be associated with cognitive and motor performance (Bechtel et al., 2010; Peinemann et al., 2005; Rosas et al., 2005).

1.12 COGNITIVE FUNCTION AND HD

Cognitive decline is an invariable trait of HD. Cognitive deficits markedly worsen throughout the disease in a non-linear pattern (Paulsen, 2011), leading to a severely impaired cognitive state, at which point facilitative support is often required (Wheelock et al., 2003). Consistent with a frontal-subcortical profile, cognitive features often include cognitive slowing, impaired verbal fluency (Eddy and Rickards, 2014), declines in working memory (Bonelli and Cummings, 2008; Ho et al., 2003), perceptual and spatial difficulties, impaired construction of higher intellectual thoughts and visuoconstructional difficulties (Beglinger et al., 2010). Memory problems initially manifest as absent-mindedness, though later develop into more debilitative problems including episodic, semantic and nondeclarative memory impairments (Knowlton et al., 1996; Rohrer et al., 1999), which greatly impede the affected individual's everyday functioning (Eddy and Rickards, 2014; Hart et al., 2013). Though not consistent with frontal-subcortical deficits, features of aphasia, agnosia and anosagnosia may also develop in latter stages of the disease, owing to a more cortical profile, as is commonly observed in AD (Bonelli and Cummings, 2008). Impairments in executive functioning also feature prominently. In particular, deficits in planning, organisation, multi-tasking, attention and concentration have been reported previously (Caine et al., 1977). Deficits in attention and concentration often manifest early in the disease and likely underpin distractibility in HD (Pillon et al., 1991).

1.13 AFFECTIVE FEATURES AND HD

Affective disorders vary considerably between affected individuals and progress in an unpredictable manner. Typical manifestations include depression (Epping and Paulsen, 2011), irritability (Craufurd et al., 2001; Kingma et al., 2008), apathy (Baudic et al., 2006; Reedeker et al., 2011) and obsessive-compulsive behaviours (Anderson et al., 2001;

Beglinger et al., 2007), though features of aggression (Rosenblatt and Leroi, 2000), impulsivity, mania (Mendez, 1994; Shiwach, 1994), psychosis-like states (Paulsen et al., 2001) and schizophrenia-like delusional states (Folstein et al., 1983a; Folstein et al., 1983b; Pflanz et al., 1991) may also present (Thompson et al., 2012). A depressive syndrome has long been recognised in HD, even dating back to Huntington's original description (Huntington, 1872). In fact, major depression is estimated to be present in 30-40% of patients during their lifetime and subsyndromal depressive mood is estimated to be present in 35-60% of HD patients (Craufurd et al., 2001; Paulsen et al., 2001). Depression is often accompanied by suicidal ideation, which coupled with life stressors can lead to impulsive urges to commit suicide. Suicide is estimated to be 5-10% higher in HD than in the general population (Walker, 2007), and is greatest in individuals presenting with soft neurological features awaiting clinical diagnosis (Paulsen and Conybeare, 2005). Apathy is a distressing psychiatric feature of HD, regularly reported by spouses, family members and friends. Typified by a reduction in purposeful behaviour, apathy was recently shown, in a longitudinal study to progressively worsen throughout disease course (Thompson et al., 2013). In addition, in the same study, irritability was shown to be very common in HD individuals, with 80% of patients exhibiting poor temper control and almost 50% reporting some level of physical aggression. Obsessive and compulsive features are also observed in 20 to 50% of HD patients (Anderson et al., 2001; Beglinger et al., 2007), while obsessive and compulsive behaviour is only present in 5.5% of the general population (Degonda and Angst, 1993).

1.14 CLINICAL HD MOTOR FEATURES

Progressive impairments in motor control are a clinical hallmark of HD. Throughout the course of the disease, two distinct movement disorders typically emerge, an involuntary (hyperkinetic) movement disorder and a loss of voluntary motor control. The temporal expression of motor features tends to follow a biphasic pattern, with involuntary movement

problems presenting early and voluntary movement problems presenting later on in the disease course.

1.14.1 Hyperkinetic motor features

Chorea is often the most visible sign of HD. By definition, chorea refers to involuntarily abrupt, asynchronistic movement of the limbs, trunk and/or face. For most adult-onset cases of HD, chorea is often witnessed early in the disease process. Early manifestations of chorea often resemble exaggerated 'fidgetiness', with low amplitude (electromyography activity), relatively infrequent, choreic manifestations evident, such as finger flicking, eyebrow raising and transient facial changes (smiling and grimacing) (Wild and Tabrizi, 2007). In some HD cases, early choreic manifestations can be effectively managed with pharmaceutical intervention (i.e. Tetrabenazine) (Pidgeon and Rickards, 2013; Venuto et al., 2012). However, as the disease progresses, chorea typically worsens (frequency and severity), becoming less manageable with pharmaceutical intervention. The magnitude and severity of chorea is often exacerbated by life stressors (workplace and family problems), anxiety, fatigue and illicit stimulant drugs (Sturrock and Leavitt, 2010). Although disruptive, chorea in most cases does not severely impair balance, mobility and upper limb function in HD patients (Sturrock and Leavitt, 2010).

1.14.2 Hypokinetic motor features

While chorea is inconvenient, impairments in voluntary motor control are often viewed as the most disabling motor aspects of HD. Notable features of the voluntary movement disorder include impairments in motor learning, motor impersistence, bradykinesia, ataxia and delayed postural reflexes. These features contribute to a diversity of clinical problems including, pulmonary dysfunction, swallowing problems, speech impairments, mobility and balance disturbances and a loss of muscle strength. The onset and progression of these clinical

problems are salient predictors of facilitated care, nursing home placement and a reduced quality of life (Helder et al., 2001; Ho et al., 2009; Jankovic and Roos, 2014).

1.14.3 Balance in HD

Balance impairments are a physically disabling trait of HD (Medina et al., 2013; Panzera et al., 2011; Quinn et al., 2013; Salomonczyk et al., 2010; Tian et al., 1992; Tian et al., 1991) Clinical and laboratory examinations reveal static and dynamic perturbations in balance in people living with manifest HD (Medina et al., 2013; Panzera et al., 2011; Quinn et al., 2013; Salomonczyk et al., 2010; Tian et al., 1992; Tian et al., 1991). Common indications of balance problems include an increased base of support (Koller and Trimble, 1985; Rao et al., 2005), excessive postural sway (Reilmann, 2012; Tian et al., 1992; Tian et al., 1991) and delayed postural reflexes (Medina et al., 2013; Panzera et al., 2011; Salomonczyk et al., 2010). Evidence indicates that impairments in static and dynamic balance surface early in the disease process and worsen over time increasing the propensity for falls and subsequent wheel chair use (Kloos et al., 2012; Rao et al., 2008; Wheelock et al., 2003).

1.14.4 Mobility in HD

Evidence indicates that mobility deficits emerge early in the disease process (Rao et al., 2008) and progressively worsen over time increasing the likelihood of falls (Quinn and Rao, 2002), assistive aid use (cane, zimmer frame, wheelchair) (Kloos et al., 2012) and nursing home placement (Wheelock et al., 2003). Mobility deficits include decreases in gait velocity (Churchyard et al., 2001; Delval et al., 2006; Koller and Trimble, 1985; Rao et al., 2005), stride length (Bilney et al., 2005; Churchyard et al., 2001; Koller and Trimble, 1985; Rao et al., 2005) and frequency (Bilney et al., 2005; Churchyard et al., 2001; Delval et al., 2006; Koller and Trimble, 1985; Rao et al., 2005) as well as increased stride-to-stride variability (Churchyard et al., 2001; Delval et al., 2006; Rao et al., 2005).

1.14.5 Muscle strength in HD

Evidence, albeit limited, shows that decreases in muscle strength are also evident in people with HD (Busse et al., 2008). Busse et al (2008), using hand-held dynamometry, showed evidence of significant lower limb muscle weakness in people with HD. The origins of muscular weakness are not known, however neuronal degeneration (Tabrizi et al., 2012; Tabrizi et al., 2011a; Tabrizi et al., 2013; Vonsattel et al., 1985; Vonsattel, 2008), mitochondrial abnormalities, and muscular pathology (Kosinski et al., 2007) as well as sedentary behaviour may all contribute to its development. Muscular weakness, particularly in the lower limbs contributes to impairments in balance and mobility as well as an increased likelihood of falls (Aziz and Roos, 2013; Cruickshank et al., 2014).

1.15 ADDITIONAL CLINICAL HD FEATURES

The presence of non-central nervous system abnormalities are increasingly being recognised in people with HD. Common peripheral aspects of the disease include weight loss, skeletal muscle atrophy, bone mineral density loss, sleep disturbances and cardiac dysfunction (Goodman et al., 2008; van der Burg et al., 2009).

Weight loss is perhaps the most common peripheral feature in HD (Aziz et al., 2008; Aziz and Roos, 2013). Clinical investigations of weight loss have shown that it surfaces in premanifest HD and worsens over time resulting in profound cachexia by late stage HD (Mochel et al., 2007; Robbinsa et al., 2006; Sanberg et al., 1981; Trejo et al., 2005; Trejo et al., 2004). Aetiological factors underpinning weight loss are not well understood, however several lines of evidence from rodent models of HD implicate changes in metabolism (Goodman et al., 2008; Mochel et al., 2007; van der Burg et al., 2008), hormonal irregularities (Andreassen et al., 2002; Björkqvist et al., 2005; Boesgaard et al., 2009) and malabsorption along the digestive tract (van der Burg et al., 2011). Weight loss has been

shown to be associated with a faster rate of disease progression in people with HD (Myers et al., 1991), and may therefore represent a useful clinical endpoint for evaluating disease modifying strategies.

Skeletal muscle wasting is also evident in people with HD (Kosinski et al., 2007; Trejo et al., 2004). Histological examinations of skeletal muscle have shown muscle fibre degeneration (Kosinski et al., 2007), abnormal muscle fibre morphology (Arenas et al., 1998) and enlarged mitochondria (Kosinski et al., 2007). Histochemical and *in vivo* imaging studies have additionally shown evidence of respiratory chain dysfunction, cytochrome c release, increased caspase activity, increased lactate production, decreased adenosine triphosphate synthesis and a reduced phosphocreatine to phosphate ratio, implicating mitochondrial dysfunction as a potential mediator of skeletal muscle wasting (Arenas et al., 1998; Ciammola et al., 2011; Koroshetz et al., 1997; Lodi et al., 2000; Turner et al., 2007). The molecular events mediating mitochondrial dysfunction are not currently known. However, direct interaction between mitochondria and mutant huntingtin (Bossy-Wetzel et al., 2008; Orr et al., 2008) as well as a decrease in the expression of peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1α (PGC-1α) may at least in part underlie mitochondrial dysfunction (Chaturvedi et al., 2009).

Recent evidence also suggests that bone mineral density loss may also be a feature in HD (Goodman and Barker, 2011). Using dual-energy x-ray absorptiometry, Goodman and Barker (2011) showed that bone mineral density is decreased in people with premanifest HD relative to healthy controls. The mechanisms underpinning bone mineral density loss are yet to be elucidated. However, it may arise as a side effect of medication, a lack of physical activity or hormonal irregularities.

1.16 CLINICAL MANAGEMENT OF HD

Discovery of the CAG mutation in 1993 was met with great excitement and a belief that HD could soon be medically solved. Unfortunately, twenty one years on, a cure or disease modifying therapy has yet to be unveiled. In the absence of a cure or disease modifying therapy, pharmaceutical interventions have been used, and remain the main treatment for people suffering with HD.

1.16.1 Pharmaceutical management of clinical features in HD

Drug agents are commonly used to treat HD (Ross and Tabrizi, 2011). However there are no effective drug agents for treating cognitive symptoms in HD (Mason and Barker, 2009; Nance, 2012; Novak and Tabrizi, 2010; Ross and Tabrizi, 2011; Venuto et al., 2012). There is also a dearth of peer reviewed evidence indicating that drug agents are effective for treating psychiatric symptoms in people with HD (Pidgeon and Rickards, 2013). Evidence does however indicate that drug agents are effective in alleviating chorea in HD. In a recent guideline document, the American Academy of Neurology found level B evidence for the efficacy of tetrabenazine, amantadine and riluzole to treat chorea in people with manifest HD (Armstrong and Miyasaki, 2012).

In summary, there is limited evidence to support the use of drug agents for treating the clinical features in HD. In addition, there is no validated evidence showing that drug agents are effective for treating pathological mechanisms underpinning HD. Furthermore, many drug agents are associated with unwanted side effects such as malaise, sedation and a depressive mood state, which may predispose individuals to falls and suicidal ideation. Drug agents nevertheless remain the mainstay approach for managing symptoms of HD.

1.16.2 Promising neuroprotective therapies for HD

A number of pharmaceutical compounds with disease-modifying properties have been identified over the past twelve years. Unfortunately, none have to date, demonstrated true disease-modifying effects in people with HD. There are, however, many promising compounds on the horizon (Burgunder, 2013; Dominguez and Munoz-Sanjuan, 2014; Schapira et al., 2014).

The most advanced compounds with potential disease-modifying properties include creatine monohydrate, PBT2 (a metal protein-attenuating compound) and cysteamine bitartrate. In a recent phase II trial, creatine monohydrate was found to be safe, well tolerated and associated with a significant reduction in cortical and striatal atrophy in forty-seven HD gene carriers (Rosas et al., 2014). While peer review evidence is not yet available, a recent press release by Prana Biotechnology LTD reported benefits in executive function in individuals with manifest HD taking PBT2 (Huntington Study Group, 2015). Raptor Pharmaceuticals has also recently released intermediate findings from their 36 month phase II trial of cysteamine bitartrate (Raptor Pharmaceuticals, 2014). The intermediate findings indicate that cysteamine bitartrate has a positive effect on motor function. While positive, subsequent phase III investigations are required to recapitulate these findings in larger cohorts of individuals with HD.

A number of alternative pharmaceutical strategies are also being investigated. The most promising strategy involves lowering the expression of the mutant Htt protein with antibody compounds or by inhibiting gene expression with RNA interference and antisense RNA oligonucleotides (Sah and Aronin, 2011). RNA interference has been shown to decrease mutant Htt expression and ameliorate the phenotype in mouse models and non-human primates (Grondin et al., 2012; Kordasiewicz et al., 2012; McBride et al., 2011). Direct infusion of antisense RNA oligonucleotides into the lateral ventricle of mouse models has

similarly been shown to repress the expression of mutant Htt (Carroll et al 2011). While positive, many challenges still need to be overcome to ensure success in the clinic, such as the delivery of these compounds to appropriate sites, assessing the distribution of these compounds centrally and determining safe, long term doses of these compounds (Dominguez and Munoz-Sanjuan, 2014).

Another therapeutic approach involves increasing PGC-1α activity via PPARs activators thereby restoring metabolic homeostasis (Chandra et al., 2014). PPAR agonist, bezafibrate has been shown to reduce striatal atrophy and the loss of medium spiny neurons in the striatum, as well as improve survivability and rotarod performance in the R6/2 mouse model (Johri et al., 2012). Activation of sirtuin 1 and 3 with nicotinamide riboside has also been shown to increase the expression of BDNF and PGC-1α and improve the motor phenotype of the R6/1 mouse model of HD (Hathorn et al., 2011).

Other promising therapeutic approaches include histone deacetylase and kynurenine 3-monoxygenase inhibitors (Dominguez and Munoz-Sanjuan, 2014). Histone deacetylase inhibitors encourage acetyl tagging of histones facilitating normalised gene expression and mutant Htt clearance (Bürli et al., 2013). Kynurenine 3-monoxygenase inhibitors increase the expression of kynurenic acid, a neuroprotective metabolite, and decrease the expression of 3-hydroxykynurenine (3-HK) and quinolinic acid (QA) metabolites in the brain. The use of such compounds has been shown to improve survivability in R6/2 mice (Zwilling et al., 2011).

In summary, there are many promising pharmaceutical compounds with disease modifying properties being trialled now. Unfortunately, history has shown that many of these compounds will not be successful (futility and/or safety) (Bates et al., 2014). Furthermore, if successful, many of these compounds could take up to a decade to become publicly available.

Therefore identifying and developing treatments that can be implemented in the short term is of paramount importance.

1.17 LIFESTYLE FACTORS AND HD

Accumulating evidence indicates that lifestyle factors can have a profound impact on the onset and progression of HD. Recent evidence by Bonner-Jackson et al (2013b) showed that greater cognitive reserve (composite of premorbid intellectual level, occupational status, and years of education) was associated with a slower rate of volume loss in the caudate nucleus and putamen in HD gene carriers. Lopez et al (2011) in another study reported a significant association between better clinical UHDRS scores and a higher level of education in individuals with manifest HD. In an earlier investigation by Trembath and colleagues (2010), greater sedentary behaviour was also found to be associated with an earlier motor onset in HD gene carriers.

A wealth of evidence also indicates that environmental factors influence the age of onset, clinical presentation and progression in HD (Anca et al., 2004; Friedman et al., 2005; Georgiou et al., 1999; Wexler, 2004). In a landmark investigation conducted in Venezuela, Wexler et al (2004) found that after controlling for the CAG repeat expansion (accounts for 40-70% of variability in the age of onset), environmental modifiers accounted for 60% of the remaining variability in the age of onset. Clinical case reports and general observations of monozygotic twins have reported similar findings. In particular, Friedman et al (2005) observed a seven year difference in the age of onset between monozygotic twins, despite identical genotypes (39 CAG repeats). Authors found evidence that smoking and exposure to pollutants contributed to discrepancies in the age of onset between these twins. Georgiou et al (1999) in another investigation reported marked phenotypic differences between monozygotic twins. In particular, one twin (A) displayed more pronounced motor

impairments, while the other twin (B) had more pronounced impairments in attention. Interestingly, this investigation further reported that twin B had a more rapid rate of deterioration that twin A. Similar to Friedman et al (2005), authors concluded that epigenetic pre and postnatal environmental factors may have influenced the different clinical profiles in the twins.

These findings indicate that lifestyle factors influence the onset, progression and expression of HD. Lifestyle interventions may therefore have a positive impact on disease progression as well as clinical expression in people with HD.

1.18 ENVIRONMENTAL ENRICHMENT AND MOUSE MODELS OF HD

Numerous studies over the last decade have investigated the effectiveness of environmental enrichment as a treatment approach in HD R6/1, R6/2 and N171-82Q mouse models (for a comprehensive overview of the genetic and phenotypic characteristics of the mouse models see Appendix 1). The first such study was conducted by van Dellen and colleagues (2000) who demonstrated the effectiveness of environmental enrichment in delaying the onset of HD in male R6/1 mice. Statistically significant reductions in cerebral volume degeneration were noted, along with significant improvements in static horizontal rod deficits. Additionally, significant reductions in rear paw clasping rates were noted. Hockly et al (2002) also investigated three levels of environmental enrichment in R6/2 mice and similarly utilised rotarod assessments and post mortem brain volume to measure benefits. R6/2 mice at 4 weeks of age were randomly placed in non-enriched, minimally-enriched or highly-enriched living conditions until 12 weeks of age. Quantitative testing at 4, 8 and 12 week intervals revealed delayed rotarod deficits ($p<10^{-5}$) and statistically significant improvements in grip strength ($p=0.03$) in R6/2 mice in enriched environments relative to non-enriched mice. Enriched R6/2 mice also had delayed peristriatal cerebral volume loss, supporting the

previous findings by van Dellen and colleagues (Hockly et al., 2002; van Dellen et al., 2000). Schilling et al (2004) found the same using the N171-82Q mouse model of HD. Mice placed in environmentally enriched cages (with exercise wheels and hiding tubes) for three weeks exhibited a 73% improvement in the rotarod assessment compared to non-enriched mice in standard cages ($p<0.0001$). Further longitudinal studies (21 weeks) revealed longer life expectancy in mice in enriched environments relative to mice in standard caging (Lazic et al., 2006).

Following on from their earlier studies, van Dellen et al (2008) investigated the effectiveness of environmental stimulation relative to that of exercise alone in R6/1 HD transgenic mouse models. Motor performance measures and quantitative brain volume assessments taken at 5 and 9 months showed that mice in standardised housing failed the static horizontal rod test while both the environmentally enriched and wheel running groups showed a delay in static horizontal rod deficits. Greatest improvements were exhibited by those mice in the environmentally enriched housing; the environmentally enriched group showed no deficits on the static horizontal rod test at 160 days, whereas the wheel running group exhibited an 80% deficit. In addition only the environmentally enriched housing group exhibited statistically significant improvements on the accelerating rotarod test ($p<0.001$). Lastly neither environmental enrichment nor wheel running housing conditions ameliorated shrinkage of the striatum and anterior cingulate cortex, or brain volume at nine months of age. These results indicate that environmental enrichment and wheel running effectively improve motor performance in the R6/1 mouse models, without changing the chronic brain atrophy that is seen in this murine model of HD (Van Dellen et al., 2008).

Several other studies have now documented the neurological benefits of environmental enrichment. Spires et al (2004) rescued deficits in, Dopamine-and cAMP-regulated phosphoprotein, Mr 32 kDA (DDARP-32) and brain derived neurotrophic factor (BDNF) in

the striatum of R6 mice housed in environmentally enriched cages, which was important given that DDARP32 is primarily involved in the regulation of dopamine signalling, whilst BDNF may play a crucial role in some aspects of adult neurogenesis, synaptic plasticity and cell survival (Lee et al., 2002; Zuccato et al., 2001). In this last respect, Lazic and colleagues (2006) documented increased hippocampal neurogenesis and neuronal maturation in R6/1 mouse models reared in an environmentally enriched cage.

Whilst these results are positive, it is important to note that animal models of HD do not recapitulate the human HD condition. It is currently not known whether environmental enrichment strategies will be beneficial for people living with HD. To date only a handful of uncontrolled studies have evaluated the effects of environmental and/or lifestyle approaches in individuals with HD. The effects of environmental and/or lifestyle approaches have been beneficial in individuals with other neurodegenerative diseases such as multiple sclerosis (MS) and Parkinson's disease (PD) and provide a rationale for such interventions to be used in HD.

1.19 LIFESTYLE INTERVENTIONS IN NEURODEGENERATIVE DISEASES

Accumulating evidence indicates that multidisciplinary rehabilitation is beneficial for people living with other neurodegenerative disorders, such as MS and PD (Asano et al., 2014; Beer et al., 2012; Khan et al., 2007; Khan et al., 2011; Parashos, 2012; Post et al., 2011; Prizer and Browner, 2012; van der Marck and Bloem, 2014).

Many studies have now shown that multidisciplinary rehabilitation is beneficial for people living with MS. In particular, short term multidisciplinary rehabilitation has been found to have positive effects on disability (Craig et al., 2003; Freeman et al., 1997; Judica et al., 2011), physical impairment (Judica et al., 2011), fatigue (Judica et al., 2011; Sacco et al.,

2011), gait (Sacco et al., 2011; Salhofer-Polanyi et al., 2013), transfer skills (Patti et al., 2003), bladder impairment (Khan et al., 2010), sphincter control (Freeman et al., 1997), self-care (Freeman et al., 1997; Patti et al., 2003), mood (Patti et al., 2002), social function (Patti et al., 2002) and quality of life (Patti et al., 2002) in people with MS. Longer duration multidisciplinary rehabilitation interventions have similarly reported improvements in disability (Khan et al., 2008), fatigue (Di Fabio et al., 1998) and functional independence (Kidd et al., 1995) in people living with MS.

Multidisciplinary rehabilitation has also been reported to be beneficial for people suffering with PD. Short duration multidisciplinary rehabilitation interventions (ranging from 21 days to two months) have been reported to improve disability (Frazzitta et al., 2015), dyskinesia (Frazzitta et al., 2012a; Frazzitta et al., 2013), transfer skills (Ellis et al., 2008; Frazzitta et al., 2015), mobility (Ellis et al., 2008; Frazzitta et al., 2015; Trend et al., 2002), balance (Frazzitta et al., 2014), voice articulation (Trend et al., 2002), speech (Trend et al., 2002), depression (Trend et al., 2002), mood (Guo et al., 2009), activities of daily living (Guo et al., 2009), upper extremity function (Ellis et al., 2008) and quality of life (Guo et al., 2009; Tickle-Degnen et al., 2010; Trend et al., 2002) in people living with PD. Recent evidence also shows that short duration multidisciplinary rehabilitation can improve clinical measures of disease progression (Unified Parkinson's Disease Rating Scale Version II & III) as well as increase serum BDNF levels ((Frazzitta et al., 2012b; Frazzitta et al., 2013; Frazzitta et al., 2015; Frazzitta et al., 2014). Longer duration multidisciplinary rehabilitation interventions have similarly reported benefits in people with PD, including improvements in motor function (Carne et al., 2005a; Carne et al., 2005b), depression (Marck et al., 2013), psychosocial functioning (Marck et al., 2013) and quality of life (Marck et al., 2013).

Collectively, these findings indicate that multidisciplinary rehabilitation is useful for treating a diversity of problems in people with neurodegenerative disorders such as MS and PD.

1.20 MULTIDISCIPLINARY REHABILITATION AND HD

Multidisciplinary rehabilitation is an interdisciplinary approach for treating clinical conditions. It typically comprises cognitive and motor exercises as well as social interaction in conjunction with pharmaceutical treatment. Specialised interdisciplinary teams often design, deliver and evaluate the therapeutic utility of multidisciplinary rehabilitation interventions for people with clinical conditions. The type, number and experience of specialists differ in each clinical setting considerably. Multidisciplinary rehabilitation is used to treat clinical features in other neurodegenerative disorders such as MS and PD that do not respond to pharmaceutical treatment alone (Parashos, 2012; Veenhuizen and Tibben, 2009).

Expert opinion, preclinical evidence and clinical findings in other neurodegenerative disorders suggest that multidisciplinary rehabilitation may have a positive impact on symptoms and perhaps the disease processes involved in HD (Bates et al., 2014; Nance, 2012; Spires et al., 2004; van Dellen et al., 2000; Veenhuizen and Tibben, 2009). Despite this positive sentiment, few studies have evaluated the therapeutic effectiveness of multidisciplinary rehabilitation for people living with HD. Preliminary evidence however suggests that multidisciplinary rehabilitation is safe, well tolerated and beneficial for people with HD (Piira et al., 2013; Veenhuizen et al., 2011; Zinzi et al., 2007).

Zinzi and colleagues (2007) were the first group to evaluate the effectiveness of multidisciplinary rehabilitation in people with HD. In this study, multidisciplinary rehabilitation comprised six days of high intensity training, conducted for three weeks, three times a year, for two years. Significant improvements in balance, gait and functional capacity were found as a result of the intervention.

In another study, Veenhuizen et al (2011) evaluated the effect of an outpatient multidisciplinary care program in twenty individuals with manifest HD. Individualised

multidisciplinary care models were prescribed to patients after consultation with a specialised multidisciplinary team (physician, psychologist, speech and language therapist, social worker, occupational therapist and case manager). Multidisciplinary care models were revised every six months to ensure that models were stimulating and achievable. Following eighteen months of outreaching multidisciplinary rehabilitation, patients, carers, and health care professionals were asked to complete a survey on the effectiveness of the program. Results of the survey showed that patients, carers and health care professionals were appreciative and perceived the program to be beneficial. Moreover, caregivers felt that the multidisciplinary rehabilitation program prolonged the time that patients lived at home.

More recently, Piira et al (2013) investigated the effectiveness of an inpatient multidisciplinary rehabilitation intervention in thirty seven individuals with manifest HD. The multidisciplinary rehabilitation intervention comprised five times per week therapy (physiotherapy, occupational therapy, hydrotherapy and resistance exercise) for eight hours, for three weeks, three times during a year. Significant improvements in gait balance, physical quality of life, anxiety and depression were found in patients after the multidisciplinary rehabilitation intervention.

These preliminary findings indicate that multidisciplinary rehabilitation is safe, well tolerated, and beneficial for motor and psychiatric features of HD. While informative, the previously mentioned trials lacked a control group limiting the validity of the conclusions derived. In addition, previous trials have not evaluated the impact of multidisciplinary rehabilitation on neuropathological features of the disease. It is therefore clear that additional evidence from randomised controlled investigations is required to confirm and expand on these promising findings.

1.21 THEORETICAL FRAMEWORK

There is no cure or disease modifying strategy, and available pharmaceutical agents only provide partial relief of motor and psychiatric features of the disease. Prospective observational evidence indicates that lifestyle factors influence the onset and progression of clinical features as well as the rate of striatal volume loss in individuals with HD. Evidence from preclinical studies additionally shows that environmental enrichment preserves peristriatal structures, improves the clinical phenotype and survival of HD transgenic mouse models. Lastly, emerging evidence shows that rehabilitation programs can have major effects on clinical features, neuronal function and disease progression in those suffering with MS and PD.

Despite these findings and expert recommendations, only three studies have investigated the effectiveness of multidisciplinary rehabilitation in people suffering with HD. These studies have shown that multidisciplinary rehabilitation can have favourable effects on motor function, mood, anxiety and physical quality of life. While encouraging, additional work is required to confirm and expand on these uncontrolled findings and determine its true effects on disease course. Studies investigating the factors underlying more debilitating aspects of HD are also required.

Mobility and balance impairments contribute to a loss of ambulation and nursing home placement in HD. Despite these serious health implications, no study has investigated the factors that contribute to impairments in mobility and balance. Identifying factors that contribute to these impairments should inform the design of multidisciplinary rehabilitation interventions. The first aim of this thesis was therefore to investigate the factors that contribute to impairments in mobility and balance in people with manifest HD.

Accumulating evidence suggests that resistance training is beneficial for those living with neurodegenerative disorders. However, consensus regarding its utility still remains contentious among health care professionals. To better inform the present study and provide greater clarification for health care professionals, the therapeutic utility of resistance training on clinical aspects of neurodegenerative disorders was investigated through a literature review.

The ultimate aim of this thesis was to confirm and expand on previous findings by comprehensively evaluating the effects of multidisciplinary rehabilitation on motor control, cognitive function, mood, body composition and quality of life in patients with manifest HD. This thesis also aimed to investigate, for the first time, the effects of multidisciplinary rehabilitation on neurodegeneration in cortical and sub-cortical structures and how this relates to cognitive function in individuals with manifest HD using magnetic resonance imaging.

1.22 HYPOTHESIS AND AIMS

The overarching hypothesis of this thesis is that multidisciplinary rehabilitation improves clinical and neuropathological features of HD.

Study 1 Aim:

To identify factors that contribute to impairments in balance and mobility in HD.

Study 2 Aim:

To systematically evaluate the quality of published evidence on the effects of resistance exercise for individuals with neurodegenerative disorders.

Study 3 Aim:

To determine the effects of multidisciplinary rehabilitation on body composition, postural control, depression, quality of life and disease status in individuals with manifest HD.

Study 4 Aim:

To determine the effects of multidisciplinary rehabilitation on motor function and lean tissue mass in individuals with HD.

Study 5 Aim:

To determine the effects of multidisciplinary rehabilitation on structural brain changes and cognitive function in individuals with manifest HD.

CHAPTER 2 - An Assessment of the Factors That Contribute to Balance and Mobility Impairments in Individuals with Huntington's Disease

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2.1 ABSTRACT

Mobility and balance problems are common and often debilitating features of Huntington's disease (HD). In this exploratory study we aimed to investigate the influence of disease severity, severity of motor deficits, lower limb muscle strength, cognition, executive function, lean muscle mass and reactivity on mobility and balance.

Twenty-two individuals with HD were recruited from the North Metropolitan Area Mental Health Service, Perth, Australia. Pertinent demographic, genetic and disease progression information was recorded prior to testing. Balance was assessed using dynamic and static balance tasks. Mobility was assessed using self-paced and fast-paced mobility measures. Cognitive and executive measures were used to assess verbal learning and memory, information processing speed, attention, response inhibition and cognitive flexibility. Lower limb muscle strength was evaluated by maximal isokinetic and isometric voluntary contractions. Lean tissue mass was quantified using Dual-energy X-ray absorptiometry. Reactivity was measured using Moyart equipment.

Univariate and multivariate linear regression statistical models were used to examine the influence of these measures on mobility and balance. Univariate analyses showed that disease severity as well as measures of information processing speed, attention, cognitive flexibility, response inhibition and lower limb strength, were strongly related with mobility and balance. Additionally multivariate analyses showed that disease severity, cognitive flexibility and knee flexion strength together were better able to explain mobility and balance performance than any single measure (50%-85%).

In conclusion, our preliminary results suggest that as well as disease severity, cognitive and executive impairment and reduced lower limb strength contribute significantly to mobility and balance problems.

Key Words

Balance

Mobility

Muscle Strength

Cognition

Executive Function

2.2 INTRODUCTION

Problems with balance and mobility are commonly reported by individuals suffering with HD. Problems occur early in the disease course and worsen with disease progression (Rao et al., 2008). Impairments in balance and mobility often predict nursing home placement, increase the likelihood for falls and can severely impact on health related quality of life (Rao et al., 2005; Reilmann et al., 2012).

There are no clinically proven treatment strategies for addressing balance and mobility problems in people with HD. Previous studies examining mobility and balance in people with HD have documented decreases in gait velocity and stride length, increases in stride-to-stride variability, double support time and step time, and increased postural sway (Delval et al., 2007; Delval et al., 2006; Delval et al., 2008; Hausdorff et al., 1998; Hausdorff et al., 1997; Panzera et al., 2011; Tian et al., 1991). While providing a vivid description of mobility and balance issues, previous studies have failed to investigate clinical features that contribute to mobility and balance problems in HD.

Studies in people with Parkinson's disease (PD) have reported strong associations between muscle power and strength and performance on balance and mobility tasks (Nocera et al., 2010; Paul et al., 2013b; Schilling et al., 2009). Task dependent relationships between cognition and mobility and balance have also been documented in PD (Paul et al., 2013b). Similar associations have been reported in people with multiple sclerosis (MS) (D'Orio et al., 2012; Hoang et al., 2014; Kalron et al., 2011; Sosnoff et al., 2013b). In the elderly, age related losses of lean tissue have been reported to strongly predict mobility and balance problems (Krause et al., 2012). Individuals with HD, in addition to displaying movement symptoms, exhibit progressive cognitive and executive impairment (Stout et al., 2012; Tabrizi et al., 2009; Tabrizi et al., 2012; Tabrizi et al., 2011a; Tabrizi et al., 2013) as well as

skeletal muscle atrophy throughout the disease course (Robbinsa et al., 2006; Thompson et al., 2013), which may similarly adversely impact on balance and mobility.

Emerging evidence suggests that in HD, reduced muscle strength, cognitive and executive problems as well as skeletal muscle atrophy are remediable to interdisciplinary rehabilitation approaches (Bonner-Jackson et al., 2013b; Khalil et al., 2013; Thompson et al., 2013). This exploratory study therefore aimed to investigate the influence of motor, cognitive, executive and body composition features of the disease on mobility and balance performance in people with HD as a better understanding of the contribution of these deficits to balance and mobility may lead to improved therapies in HD.

2.3 MATERIALS AND METHODS

2.3.1 Ethics approval

This study was approved by the Human Research Ethics Committee at Edith Cowan University and the North Metropolitan Area Mental Health Service (NMAMHS) Human Research Ethics Committee. All participants provided written informed consent.

2.3.2 Participants

Sixty-two potential participants were identified using the Neuroscience Unit database of the NMAMHS. Participants were only included if they had received a positive genetic test, were formally diagnosed as symptomatic (Unified Huntington's Disease Rating Scale Total Motor Score [UHDRS-TMS] $\geq$ 5), and had the ability to follow verbal or written instruction. Participants were not included if they had recent substance abuse, an unstable psychiatric state, confounding neurological condition or concomitant physical injury.

2.3.3 Study procedures

Participants were evaluated over two weekends at Edith Cowan University using a variety of mobility and balance tasks as well as cognitive, executive, lower limb muscle strength, lean tissue mass and reactivity measures. All assessments were performed by accredited independent examiners.

2.3.4 Outcome measures

Dynamic and static balance was examined using the berg balance scale (BBS), sensory organisation test (SOT) and the repeated sit to stand test (RSST). Mobility over short and long distances was quantified using the timed walk test (TWT) and the six minute walk test (6MWT) (Quinn et al., 2013). These measures have previously been demonstrated to be reliable in individuals with HD (Khalil et al., 2010; Quinn et al., 2013).

2.3.5 Predictor measures

Disease severity and severity of motor abnormalities were quantified using the disease burden score and the UHDRS-TMS. Cognition and executive function was examined using a variety of clinically validated measures. The Hopkins Verbal Learning Test-Revised (HVLT-R) was used to measure verbal learning and memory (Brandt, 1991; Thompson et al., 2013). Information processing speed and attention were examined using the Symbol Digit Modalities Test (SDMT) (Smith, 1973; Thompson et al., 2013). Response inhibition and cognitive flexibility were examined using the Delis-Kaplan Executive Function System (D-KEFS) Colour Word Interference Test (CWIT) and Trail Making Trials (TMT) (Thompson et al., 2013). Reactivity was measured using a visual response task. Dual-energy X-ray absorptiometry (DEXA; Hologic Discovery A) was used to quantify lean tissue mass (g) (Goodman and Barker, 2011; Thompson et al., 2013). Lower limb muscle strength was

quantified using a maximal voluntary isometric and isokinetic knee flexion and extension contractions with automated dynamometry (Biodex, System 3, USA). Isokinetic knee extension and flexion strength was examined using $180°\cdot s^{-1}$ (fast) and $30°\cdot s^{-1}$ (slow) maximum voluntary contraction (MVC) test protocols. Isometric knee extension and flexion strength were also measured at 60° flexion. Individuals performed three maximal voluntary contractions for each strength protocol.

2.4 STATISTICAL ANALYSIS

Data is presented as mean, range and standard deviation (SD). Associations between balance and mobility tasks (outcome variables), disease severity, severity of motor abnormalities and measures of cognition, executive function, lower limb strength, lean tissue mass and reactivity (predictor variables) were determined using univariate linear regression analysis. Associations between multiple predictor variables and balance and mobility were then determined using multivariate linear regression. The results of the univariate linear regression analysis showed that measures of disease severity, attention, information processing speed, cognitive flexibility and response inhibition associated strongly with balance and mobility tasks. These predictor variables were entered into a multivariate linear regression model and assessed for association with each of the mobility and balance tasks. Backward selection estimation was then used to obtain the most significant multivariate model. Statistical significance was set at $p \leq 0.05$. All statistical analyses were performed using STATA version 9.1.

2.5 RESULTS

Of the sixty-two potential participants, twenty-two individuals agreed to voluntarily participate in the study (Table 2.1.). Of these, 16 were taking antidepressants, 12 anti-psychotics and 5 anti-choreic medications. Demographic, disease severity, severity of motor

abnormalities, cognition, executive function, lower limb strength, lean tissue mass, reactivity, mobility and balance data are displayed in Tables 2.1 and 2.2.

2.5.1 Balance

Univariate analyses revealed significant associations between disease severity and performance on balance tasks (18%-50.0% for disease burden score). Moreover, measures of information processing speed, attention, cognitive flexibility, response inhibition and lower limb strength were significantly associated with performance on balance tasks (20.3-27% for correct oral, 18.2%-53.0% for word reading, 26.3%-49.5% for motor speed, 24.5%-42.7% for 60˚ MVC knee flexion; Supplementary Tables 2.3, 2.4 and 2.5). Task dependent associations between measures of verbal learning and memory and performance on the RSST task were also found (total recall 21.3%). Lean tissue mass, reactivity and severity of motor abnormalities were found not to be related to balance task performance (Supplementary Tables 2.3, 2.4 and 2.5).

Multivariate analyses showed that performance on the BBS was best explained by disease severity (disease burden score explained 57%; Supplementary Table 2.9). For the SOT, performance variability was best explained by disease severity and cognitive flexibility measures (disease burden score and motor speed together explained 50% of variability; Supplementary Table 2.9). Performance variability on the RSST was best explained by measures of cognitive flexibility and knee flexion muscle strength (motor speed and 60˚ MVC knee flexion strength together explained 72%; Supplementary Table 2.9).

Table 2.1 Participant characteristics

Variables	Mean (SD) (n=22)	Range
Age (Years)	50.85 ± 9.24	30.3-70
Disease Duration	3.95 ± 4.26	0.3-17.3
CAG (n)	44.22 ± 2.99	39-51
Disease Burden Score	427.22 ± 118.05	269.5-596
UHDRS-Total Motor Score	26.45 ± 12.41	5-45

CAG (n), cytosine-adenine-guanine repeat length, UHDRS, Unified Huntington's Disease Rating Scale

Table 2.2 Study participant performance on outcome measures

Study Assessments	Mean (SD)	Range
Predictor Variables		
Cognition Assessments		
SDMT		
Correct Written	26.33 ± 10.57	10.00-48.00
Incorrect Written	1.66 ± 1.95	0.00-6.00
Correct Oral	29.71 ± 13.40	8.00-60.00
Incorrect Oral	1.85 ± 2.34	0.00-7.00
HVLT-R		
Total Recall	16.52 ± 6.20	4.00-30.00
Delayed Recall	5.13 ± 2.35	1.00-9.00
Retention	77.00 ± 22.59	33.00-129.00
Recognition Discrimination Index	8.00 ± 3.08	2.00-15.00
D-KEFS TMT		
Visual Scanning	35.42 ± 15.83	16.00-70.00
Number Sequencing	59.57 ± 21.84	33.00-124.00
Letter Sequencing	79.10 ± 55.56	31.00-234.00
Number-Letter Sequencing	142.00 ± 54.24	61.00-239.00
Motor Speed	65.44 ± 35.16	18.00-147.00
D-KEFS CWIT		
Colour Naming	44.05 ± 15.72	22.00-78.00
Word Reading	35.14 ± 13.81	20.00-73.00
Inhibition	89.42 ± 33.52	40.00-186.00
Lower Limb Strength Measures		
$30°\cdot s^{-1}$MVC Knee Extension	127.23 ± 54.36	40.80-217.10
$180°\cdot s^{-1}$MVC Knee Extension	71.05 ± 29.92	20.90-128.45
$30°\cdot s^{-1}$ MVC Knee Flexion	71.88 ± 32.44	15.60-138.95
$180°\cdot s^{-1}$ MVC Knee Flexion	50.19 ± 19.33	14.30-96.00
60° MVC Knee Extension	157.30 ± 49.06	71.10-238.95
60° MVC Knee Flexion	65.46 ± 18.73	14.80-100.25
Body Composition Assessment		
Lean Tissue Mass	52224.47 ± 10332.29	34362.20-68907.30
Reactivity Assessments		
Visual Reaction Time (DOM)	0.69 ± 0.24	0.34-1.20
Visual Reaction Time (NON)	0.67 ± 0.25	0.26-1.21
Outcome Variables		
Balance Assessments		
SOT	54.04 ± 15.63	22.00-80.00
BBS	46.59 ± 7.83	26.00-56.00
RSST	28.62 ± 12.76	12.00-64.00
Mobility Assessments		
TWT (Fast-paced)	6.17 ± 2.81	3.08-16.72
TWT (Self-paced)	8.10 ± 2.63	5.90-17.18
6MWT	466.19 ± 127.37	87.00-630.00

DOM= dominant hand, NON= non-dominant hand

2.5.2 Mobility

Univariate analyses showed significant associations between disease severity and performance of mobility tasks (disease burden score 43%-50%). Measures of attention, information processing speed, cognitive flexibility, response inhibition and lower limb strength measures were also associated with mobility task performance (correct oral 20%-40.1%, word reading 34.1%-52.2%, motor speed 26.7%-52.8%, 60˚ MVC knee flexion strength 43%-60%; Supplementary Tables 2.6, 2.7 and 2.8). Task dependent associations between verbal learning and memory and mobility task performance were also evident (total recall, 19.5%; Supplementary Tables 2.6, 2.7 and 2.8). There was no evidence of associations between lean tissue mass, reactivity or severity of motor abnormalities and performance on mobility tasks (Supplementary Tables 2.6, 2.7 and 2.8).

Multivariate analyses revealed that when measures were collectively considered, disease severity, cognitive flexibility and knee flexion strength measures explained a significantly greater proportion of performance variability on mobility tasks than any single measure (TWT-SP 85%, TWT-FP 72%, 6MWT 85%; Supplementary Table 2.9).

2.6 DISCUSSION

This study found that disease severity, lower limb muscle strength, cognition and executive function significantly influenced performance on balance and mobility tasks, while reactivity and lean tissue mass did not. Furthermore, this study showed that when all measures were collectively considered, the factors most critically related to performance on balance and mobility tasks were disease severity, cognitive flexibility and knee flexion strength, and together these measures better explained balance and mobility performance than any single measure.

An important finding of this study was that cognition and executive function significantly influenced performance on balance and mobility tasks. Similar findings have been found in people suffering from PD (Herman et al., 2014; Paul et al., 2013a; Paul et al., 2013b) and mild cognitive impairment (MCI) (Persad et al., 2008). Paul et al (2013a; 2013b) in two recent studies showed that executive function and cognition significantly influenced balance and falls in people with PD. Persad et al (Persad et al., 2008), in a similar study found that cognition and executive function were strongly related to balance and mobility in people with MCI. These findings highlight that deterioration of cognitive and executive function adversely impacts upon balance and mobility in people with neurodegenerative diseases.

The relationship of lower limb strength with balance and mobility task performance was not unexpected. Interestingly though, we found that relationships were often dependent on the muscle group involved and the type of contraction performed, with the 60˚ MVC knee flexion measure demonstrating significant association with all balance and mobility tasks. Both $30°\cdot s^{-1}$ MVC knee flexion and $180°\cdot s^{-1}$ MVC knee flexion measures similarly demonstrated strong associations with performance on mobility tasks but not balance tasks. Broekmans et al (2013a) in a similar study found knee flexion strength to strongly predict walking capacity in people with MS. Knee flexor involvement during stabilization and mobility tasks in healthy individuals is well established (Chandler et al., 1998; Hughes et al., 2001; Pavol et al., 2002), and likely explains our findings. Multidisciplinary interventions have been shown to improve lower limb strength and perception of balance in people with HD (Thompson et al., 2013), therefore mobility and balance problems may be amenable to such interventions.

As expected, a strong relationship was observed between disease severity and performance on balance and mobility tasks, indicating a significant contribution of HD progression to movement disability. Of interest, is the finding that severity of motor abnormalities, as

measured by the UHDRS-TMS, was not significantly associated with performance on balance and mobility tasks. This finding has important clinical implications for the assessment of balance and mobility in HD. It illuminates the importance of identifying specific measures to supplement the UHDRS-TMS that can more sensitively quantify balance and mobility decrements.

Lean tissue mass and reactivity demonstrated negligible associations with mobility and balance. This was an unexpected finding, considering that studies in PD have reported reactivity and lean muscle mass to be important clinical determinants of balance and mobility performance (Dibble et al., 2006; Paul et al., 2013a; Paul et al., 2013b). Discrepancies between findings are likely due to pathological and clinical differences between PD and HD (Jankovic, 2008; Sturrock and Leavitt, 2010), as well as methodological and sample size differences between the studies.

Our findings result from a relatively small sample of individuals with manifest HD, most of whom were taking medication, as such our findings should be interpreted with a degree of caution.

2.7 CONCLUSION

Here we provide preliminary evidence that disease severity, lower limb weakness, cognitive impairment and executive dysfunction significantly influence mobility and balance in people with HD. Moreover, we show that key clinical features, when considered together, better explain performance on balance and mobility tasks than any single measure. Findings while preliminary, provide insight into the multiple clinical features that contribute to balance and mobility problems in HD, and provide a venue for targeted multidisciplinary rehabilitation strategies.

2.8 ACKNOWLEDGMENTS

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2.9 SUPPLEMENTARY DATA

Supplementary Table 2.3 Univariable associations between impairments (Predictor Variables) and performance on the BBS (Outcome Measure)

Predictor Variable	Adjusted R^2 (%)	P Value	Unstandardised B (95% CI)
BBS			
Demographic Variables			
Age	0.6	0.728	-0.066(-0.460:0.327)
Disease Duration	0.6	0.713	-0.152(-1.00:0.701)
CAG repeat	9.9	0.154	-0.824(-1.98:0.334)
Disease Burden Score	34	0.004*	-0.038(-0.0639:-0.0137)
UHDRS-TMS	2.7	0.467	-0.094(-0.036:0.172)
Cognitive Measures			
SDMT			
Correct written	14.5	0.088	0.285(-0.047:0.618)
Correct Oral	22.1	0.031*	0.278(0.027:0.528)
HVLT-R			
Total Recall	9.2	0.181	0.38(-0.19:0.97)
Delayed Recall	7.2	0.226	0.89(-0.60:2.38)
Retention	0.3	0.795	-0.02(-0.181:0.141)
Recognition Discrimination Index	8.2	0.194	0.73(-0.404:1.864
D-KEFS TMT			
Visual Scanning	4.2	0.371	-0.104(-0.34:0.133)
Number Sequencing	17.3	0.061	-0.152(-0.313:0.007)
Letter Sequencing	15.5	0.086	-0.057(-0.124:0.000)
Number-Letter Sequencing	0.2	0.879	-0.007(-0.11:0.103)
Motor Speed	26.3	0.030*	-0.121(-0.22:-0.13)
D-KEFS CWIT			
Colour Naming	15.2	0.099	-0.204(-0.45:0.042)
Word Reading	22.4	0.030*	-0.271(-0.51:-0.029)
Inhibition	13.5	0.122	-0.09(-0.207:0.026)
Lower Limb Strength Measures			
30°·s^{-1} MVC Knee Extension	4.5	0.343	0.03(-0.035:0.096)
180°·s^{-1} MVC Knee Extension	3	0.440	0.045(-0.07:0.16)
30°·s^{-1} MVC Knee Flexion	10.5	0.141	0.07(-0.028:0.18)
180°·s^{-1} MVC Knee Flexion	12.3	0.110	0.141(-0.035:0.318)
60˚ MVC Knee Extension	0.1	0.849	0.00(-0.06:0.08)
60˚ MVC Knee Flexion	13	0.018*	0.154(-0.042:0.351)
Body Composition Measures			
Lean Tissue Mass	0.5	0.753	0.00 (-0.00:0.00)
Reactivity Measures			
Visual Reaction Time (DOM)	2.4	0.492	0.00 (-0.00:0.00)
Visual Reaction Time (NON)	4.2	0.357	-6.42(-20.63:7.78)

DOM: dominant hand; NON: non-dominant hand; * Significant at the 0.05 level

Supplementary Table 2.4 Univariable associations between impairments (Predictor Variables) and performance on the SOT (Outcome Measure)

Predictor Variable	Adjusted R^2 (%)	P Value	Unstandardised B (95% CI)
SOT (composite score)			
Demographic Variables			
Age	0.1	0.850	-0.0721(-0.859:0.715)
Disease Duration	0.6	0.730	-0.286(-1.99:1.418)
CAG repeat	12.9	0.101	-1.87(-4.15:0.400)
Disease Burden Score	29.4	0.009*	-0.071(-0.123:-0.0198)
UHDRS-TMS	7.5	0.218	-0.316(-0.83:0.202)
Cognitive Measures			
SDMT			
Correct Written	15.4	0.079	0.56(-0.07:1.21)
Correct Oral	27	0.015*	0.596(0.127:1.06)
HVLT-R			
Total Recall	14.7	0.086	0.95(-0.147:2.047)
Delayed Recall	10.9	0.133	2.19(-0.72:5.11)
Retention	0.2	0.813	0.037(-0.28:0.359)
Recognition Discrimination Index	16.3	0.062	2.04(-0.11:4.2)
D-KEFS TMT			
Visual Scanning	6.8	0.254	-0.263(-0.73:0.204)
Number Sequencing	17.3	0.061	-0.15(-0.31:0.007)
Letter Sequencing	15.5	0.086	-0.057(-0.124:0.009)
Number-Letter Sequencing	0.2	0.879	-0.007(-0.11:0.103)
Motor Speed	26.3	0.030*	-0.121(-0.22:-0.013)
D-KEFS CWIT			
Colour Naming	3.7	0.434	-0.183(-0.66:029)
Word Reading	18.2	0.050*	-0.47(-0.95:0.007)
Inhibition	6.7	0.275	-0.11(-0.34:0.103)
Lower Limb Strength Measures			
$30°\cdot s^{-1}$ MVC Knee Extension	4.2	0.360	0.058(-0.07:0.19)
$180°\cdot s^{-1}$ MVC Knee Extension	3	0.434	0.091(-0.148:0.331)
$30°\cdot s^{-1}$ MVC Knee Flexion	9.8	0.154	0.151(-0.061:0.364)
$180°\cdot s^{-1}$ MVC Knee Flexion	10.4	0.143	0.26(-0.096:0.617)
60˚ MVC Knee Extension	4.2	0.355	0.065(-0.079:0.211)
60˚ MVC Knee Flexion	24.5	0.026*	0.427(0.055:0.798)
Body Composition Measures			
Lean Tissue Mass	0.1	0.865	0.00(-0.00:0.00)
Reactivity Measures			
Visual Reaction Time (DOM)	0.4	0.758	3.65(-20.75:28.05)
Visual Reaction Time (NON)	4.8	0.325	11.16(-11.91:34.24)

DOM: dominant hand; NON: non-dominant hand; * Significant at the 0.05 level

Supplementary Table 2.5 Univariable association between impairments (Predictor Variables) and performance on the RSST (Outcome measure)

Predictor Variable	Adjusted R^2 (%)	P Value	Unstandardised B (95% CI)
RSST			
Demographic Variables			
Age	4	0.373	0.275(-0.354:0.906)
Disease Duration	0.0	0.897	0.0876(-1.307:1.482)
CAG repeat	1.0	0.649	0.438(-1.541:2.418)
Disease Burden Score	18	0.050*	0.045(0.000:0.0914)
UHDRS-TMS	3.9	0.379	0.186(-0.245:0.618)
Cognitive Measures			
SDMT			
Correct Written	22	0.032*	-0.58(-1.10:-0.056)
Correct Oral	20.3	0.041*	-0.43(-0.85:-0.02)
HVLT-R			
Total Recall	21.3	0.032*	-0.98(-1.88:-0.094)
Delayed Recall	7.8	0.208	-1.511(-3.93:0.913)
Retention	0.7	0.697	0.049(-0.212:0.3121)
Recognition Discrimination Index	17.5	0.053	-1.73(-3.48:0.021)
D-KEFS TMT			
Visual Scanning	10.9	0.143	0.273(-0.101:0.647)
Number Sequencing	10.4	0.154	0.192(-0.079:0.464)
Letter Sequencing	22.51	0.035*	0.114(0.009:0.219)
Number-Letter Sequencing	0.0	0.967	-0.003(-0.177:0.171)
Motor Speed	49.5	0.001*	0.26(0.121:0.400)
D-KEFS CWIT			
Colour Naming	25	0.029*	0.33(0.039:0.63)
Word Reading	53	0.000*	0.68(0.377:0.99)
Inhibition	7.3	0.264	0.085(-0.070:0.241)
Lower Limb Strength Measures			
$30°\cdot s^{-1}$ MVC Knee Extension	4.1	0.363	-0-047(-0.155-0.059)
$180°\cdot s^{-1}$ MVC Knee Extension	15	0.075	-0.165(-0.34:0.01)
$30°\cdot s^{-1}$ MVC Knee Flexion	16.8	0.058	-0.161 (-0.32:0.006)
$180°\cdot s^{-1}$ MVC Knee Flexion	15.7	0.068	-0.261(-0.544:0.020)
60˚ MVC Knee Extension	2.7	0.466	-0.042(-0.162:0.077)
60˚ MVC Knee Flexion	42.7	0.002*	-0.465(-0.731:-0.198)
Body Composition Measures			
Lean Tissue Mass	0.1	0.865	0.00(-0.00:0.00)
Reactivity Measures			
Visual Reaction Time (DOM)	0.4	0.758	3.65(-20.75:28.05)
Visual Reaction Time (NON)	4.8	0.325	11.16(-11.91:34.24)

DOM: dominant hand; NON: non-dominant hand; * Significant at the 0.05 level

Supplementary Table 2.6 Univariable association between impairments (Predictor Variables) and performance on the 6MWT (Outcome measure)

Predictor Variable	Adjusted R^2 (%)	P Value	Unstandardised B (95% CI)
6MWT			
Demographic Variables			
Age	6.0	0.281	-3.315(-9.57:2.94)
Disease Duration	2.9	0.461	-5.27(-19.95:9.40)
CAG repeat	7	0.246	-11.01(-30.25:8.23)
Disease Burden Score	41.2	0.002*	-0.675(-1.06:-0.288)
UHDRS-TMS	18	0.056	-4.05(-8.2:0.108)
Cognitive Measures			
SDMT			
Correct Written	37.9	0.003*	7.41(2.86:11.97)
Correct Oral	40.1	0.002*	6.07(2.56:9.58)
HVLT-R			
Total Recall	19.5	0.045*	9.07(0.229:17.922)
Delayed Recall	15.21	0.081	21.00(-2.80:44.82)
Retention	0.2	0.828	0.282(-2.39:2.95)
Recognition Discrimination Index	13.4	0.102	16.38(-3.59:36.36)
D-KEFS TMT			
Visual Scanning	24	0.028*	-4.55(-8.56:-0.546)
Number Sequencing	21.4	0.040*	-2.83(-5.52:-0.143)
Letter Sequencing	31.6	0.012*	-1.32(-2.32:-0.32)
Number-Letter Sequencing	0.0	0.950	-0.062(-2.23:2.11)
Motor Speed	52.8	0.001*	-2.81(-4.28:-1.35)
D-KEFS CWIT			
Colour Naming	45	0.002*	-5.309(-8.311:-2.306)
Word Reading	52.2	0.000*	-6.66(-9.72:-3.60)
Inhibition	26.4	0.024*	-1.90(-3.53:-0.27)
Lower Limb Strength Measures			
$30°\cdot s^{-1}$ MVC Knee Extension	7.1	0.242	0.63(-0.462:1.722)
$180°\cdot s^{-1}$ MVC Knee Extension	14	0.094	1.59 (-0.295:3.479)
$30°\cdot s^{-1}$ MVC Knee Flexion	25.2	0.020*	1.96 (0.341:3.59)
$180°\cdot s^{-1}$ MVC Knee Flexion	21.9	0.033*	3.04(0.28:5.80)
60˚ MVC Knee Extension	1.8	0.558	0.373(-0.936:1.683)
60˚ MVC Knee Flexion	44.2	0.002*	4.74(2.01:7.47)
Body Composition Measures			
Lean Tissue Mass	0.2	0.828	0.00(-0.00:0.00)
Reactivity Measures			
Visual Reaction Time (DOM)	10	0.162	-167.21(-407.8:73.38)
Visual Reaction Time (NON)	16.7	0.066	-203.17:14.78)

DOM: dominant hand; NON: non-dominant hand; * Significant at the 0.05 level

Supplementary Table 2.7 Univariable association between impairments (Predictor Variables) and performance on the TWT (Self Paced) (Outcome Measure)

Predictor Variable	Adjusted R^2 (%)	P Value	Unstandardised B (95% CI)
TWT (Self Paced)			
Demographic Variables			
Age	2.6	0.482	0.048(-0.092:0.189)
Disease Duration	5.1	0.325	0.155(-0.166:0.4763)
CAG repeat	13.4	0.103	0.336(-0.074:0.747)
Disease Burden Score	50	0.000*	0.0164(0.008:0.0243)
UHDRS-TMS	13	0.115	0.075(-0.019:0.170)
Cognitive Measures			
SDMT			
Correct Written	0.17	0.059	-0.11(-0.22:0.004)
Correct Oral	20	0.042*	-0.094(-0.18:-0.003)
HVLT-R			
Total Recall	10.2	0.158	-0.14(-0.35:0.061)
Delayed Recall	12.5	0.116	-0.422(-0.95:0.11)
Retention	0.0	0.911	-0.003(-0.062:0.056)
Recognition Discrimination Index	8.5	0.199	-0.28(-0.74:0.165)
D-KEFS TMT			
Visual Scanning	12.8	0.121	0.073(-0.021:0.168)
Number Sequencing	11.8	0.139	0.046(-0.016:0.109)
Letter Sequencing	10.3	0.180	0.017(-0.008:0.043)
Number-Letter Sequencing	0.7	0.806	0.005(-0.047:0.058)
Motor Speed	26.7	0.034*	0.045(0.003:0.086)
D-KEFS CWIT			
Colour Naming	8.5	0.199	-0.28(-0.74:0.165)
Word Reading	34.1	0.009*	0.108(0.031:0.185)
Inhibition	29.3	0.011*	0.110(0.028:0.192)
Lower Limb Strength Measures			
$30°\cdot s^{-1}$ MVC Knee Extension	6.8	0.251	-0.013(-0.03:0.10)
$180°\cdot s^{-1}$ MVC Knee Extension	11.2	0.139	-0.031(-0.073:0.011)
$30°\cdot s^{-1}$ MVC Knee Flexion	6.8	0.251	-0.013(-0.037:0.010)
$180°\cdot s^{-1}$ MVC Knee Flexion	14.6	0.087	-0.055(-0.119-0.008)
60˚ MVC Knee Extension	5.6	0.300	-0.014(-0.042:0.013)
60˚ MVC Knee Flexion	43	0.002*	-0.104(-0.165:-0.043)
Body Composition Measures			
Lean Tissue Mass	1.5	0.588	0.00(-0.00:0.00)
Reactivity Measures			
Visual Reaction Time (DOM)	2.4	0.502	1.81(-3.73:7.36)
Visual Reaction Time (NON)	7.8	0.217	3.09(-1.98:8.16)

DOM: dominant hand; NON: non-dominant hand; * Significant at the 0.05 level

Supplementary Table 2.8 Univariable associations between impairments (Predictor Variables) and performance on the TWT (Fast Paced) (Outcome Measure)

Predictor Variable	Adjusted R^2 (%)	P Value	Unstandardised B (95% CI)
TWT (Fast Paced)			
Demographic Variables			
Age	7	0.246	0.073(-0.055:0.202)
Disease Duration	9.6	0.171	0.199(-0.094:0.492)
CAG repeat	8.5	0.200	0.25(-0.144:0.646)
Disease Burden Score	43	0.001*	0.0142(0.006:0.0221)
UHDRS-TMS	13.6	0.100	0.073(-0.015:0.161)
Cognitive Measures			
SDMT			
Correct Written	16.7	0.067	-0.10(-0.211:0.007)
Correct Oral	18.33	0.053	-0.084(-0.169:0.001)
HVLT-R			
Total Recall	16.2	0.071	-0.17(-0.35:0.015)
Delayed Recall	20.1	0.037*	-0.51(-0.98:-0.034)
Retention	1.2	0.63	-0.012(-0.067:0.042)
Recognition Discrimination Index	11.8	0.128	-0.318(-0.735:0.099)
D-KEFS TMT			
Visual Scanning	16.9	0.072	0.078(-0.00:0.164)
Number Sequencing	11.11	0.151	0.042(-0.016:0.100)
Letter Sequencing	16.0	0.089	0.02(-0.00:0.043)
Number-Letter Sequencing	0.2	0.897	0.002(-0.042:0.047)
Motor Speed	35.3	0.012*	0.047(0.012:0.083)
D-KEFS CWIT			
Colour Naming	29	0.017*	0.08(0.017:0.160)
Word Reading	43.4	0.001*	0.125(0.056:0.194)
Inhibition	15.5	0.095	0.030(-0.005:0.066)
Lower Limb Strength Measures			
$30°\cdot s^{-1}$ MVC Knee Extension	7.7	0.221	-0.013(-0.036:0.008)
$180°\cdot s^{-1}$ MVC Knee Extension	9.8	0.165	-0.027(-0.067:0.012)
$30°\cdot s^{-1}$ MVC Knee Flexion	19.3	0.046*	-0.035(-0.07:-0.00)
$180°\cdot s^{-1}$ MVC Knee Flexion	11.6	0.132	-0.045(-0.106:0.015)
60˚ MVC Knee Extension	4.8	0.338	-0.012(-0.039:0.014)
60˚ MVC Knee Flexion	60	0.000*	-0.112(-0.16:-0.06)
Body Composition Measures			
Lean Tissue Mass	1.2	0.634	0.00(-0.00:0.00)
Reactivity Measures			
Visual Reaction Time (DOM)	1.1	0.645	1.16(-4.05:6.39)
Visual Reaction Time (NON)	4.5	0.352	2.20(-2.63:7.03)

DOM: dominant hand; NON: non-dominant hand; * Significant at the 0.05 level

Supplementary Table 2.9 Associations between impairments (Predictor Variables) and task performance (Outcome Measure) from multiple Multivariable regression models

Predictor Model	Adjusted R^2 (%)	p-value	Unstandardised B (95% CI)
Performance on balance tasks			
BBS			
Disease Burden Score	57	0.001	-0.051 [-0.076: -0.026]
SOT			
Disease Burden Score	50	0.020	-0.073 [-0.133:-0.0138]
Motor Speed		0.093	-0.177 [-0.388:0.034]
RSST			
60˚ MVC Knee Flexion	72	0.011	-0.314 [-0.544: -0.085]
Motor Speed		0.002	0.577 [0.238:0.896]
Performance on mobility tasks			
TWT (Self Paced)			
Disease Burden Score	85	0.002	0.010 [0.004: 0.016]
60˚ MVC Knee Flexion		0.003	-0.067 [-0.105: -0.029]
Motor Speed		0.052	0.020 [-0.000:0.0404]
TWT (Fast Paced)			
Disease Burden Score	72	0.001	0.015 [0.007:0.024]
60˚ MVC Knee Flexion		0.028	-0.062 [-0.116:-0.007]
Motor Speed		0.041	0.021 [-0.000:0.0403]
6MWT			
Disease Burden Score	85	0.002	-0.519 [-0.802:-0.237]
60˚ MVC Knee Flexion		0.039	1.975 [0.114: 3.83]
Motor Speed		0.002	-1.76 [-2.759:-0.768]

CHAPTER 3 - A Systematic Review and Meta-Analysis of Strength Training Trials in Individuals with Multiple Sclerosis or Parkinson's disease

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3.1 ABSTRACT

Background: Strength training has, in recent years, been shown to be beneficial for people with Parkinson's disease and multiple sclerosis. Consensus regarding its utility for these disorders nevertheless remains contentious among healthcare professionals. Greater clarity is required, especially in regards to the type and magnitude of effects as well as the response differences to strength training between individuals with Parkinson's disease or multiple sclerosis.

Objective: To examine the effects, magnitude of those effects and response differences to strength training between patients with Parkinson's disease or multiple sclerosis.

Data Sources: A comprehensive search of electronic databases including PEDro, PubMED, EMBASE, Cochrane Central Register of Controlled Trials, and CINAHL was conducted from inception to July 2014.

Study Eligibility: English articles investigating the effect of strength training for individuals with neurodegenerative disorders were selected. Strength training trials that met the inclusion criteria were found for individuals with Parkinson's disease or multiple sclerosis.

Participants: Individuals with Parkinson's disease or multiple sclerosis.

Intervention: Strength training interventions included traditional (free weights/machine exercises) and non-traditional programs (eccentric cycling).

Study Appraisal: Included articles were critically appraised using the PEDro scale.

Results: Of the five hundred and seven articles retrieved, only twenty articles met the inclusion criteria. Of these, fourteen were randomised and six were non-randomised controlled articles in Parkinson's disease or multiple sclerosis. Six randomised and two non-

randomised controlled articles originated from three trials and were subsequently pooled for systematic analysis. Strength training was found to significantly improve muscle strength in people with Parkinson's disease (15%-83.2%) and multiple sclerosis (4.5%-36%). Significant improvements in mobility (11.4%) and disease progression were also reported in people with Parkinson's disease after strength training. Furthermore, significant improvements in fatigue (8.2%), functional capacity (21.5%), quality of life (8.3%), power (17.6%) and electromyography activity (24.4%) were found in individuals with multiple sclerosis after strength training.

Limitations: Heterogeneity of interventions and study outcomes in Parkinson's disease and multiple sclerosis trials.

Conclusions: Strength training is useful for increasing muscle strength in Parkinson's disease and to a lesser extent multiple sclerosis.

Implications of key findings: Strength training is a useful adjunct treatment for Parkinson's disease and multiple sclerosis.

3.2 INTRODUCTION

Neurodegenerative disorders such as Parkinson's disease and multiple sclerosis represent a major medical concern for health professionals and national healthcare bodies (Nance, 2012). Both disorders result from progressive neuronal dysfunction and neuronal cell death leading to progressive disability and eventual death (Lin and Beal, 2006). Classical signs and symptoms customary to both disorders include motor problems, cognitive impairment, behavioural disturbances and systemic abnormalities (Benedict and Zivadinov, 2011; Mitchell and Borasio, 2007; Olanow et al., 2009).

There is no cure and few cost effective drug agents for treating people with Parkinson's disease or multiple sclerosis (Evans et al., 2011; Lu et al., 2012). Recent advances in understanding the pathogenic mechanisms responsible for each disorder may aid in the identification and development of cost effective disease modifying agents in the future (Noyes et al., 2011). However, cost effective treatments, with disease modifying properties and symptomatic benefits are required in the short term.

Accumulating evidence suggests that strength training is a useful therapy for addressing many of the clinical features that present in individuals with neurodegenerative disorders (Falvo et al., 2008; Hindle et al., 2013; Kjølhede et al., 2012). By definition, strength training refers to an intervention, in which participants train a muscle or group of muscles against an external resistance (Esco, 2013). While evidence suggests that lower limb strength training (i.e. leg press, knee extension and knee flexion) is beneficial for individuals with Parkinson's disease and multiple sclerosis (Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; Dodd et al., 2011; Schilling et al., 2010; Shulman et al., 2013), consensus regarding the effects, magnitude of those effects and disease dependent responses remain contentious. By contrast, the therapeutic utility of strength training is well recognised in the

elderly (Nelson et al., 2007), individuals with mild cognitive impairment and in those that have suffered a stroke. Health benefits associated with strength training in elderly individuals include improvements in strength (Fiatarone et al., 1990; Nelson et al., 1994), cardio-respiratory capacity (Pereira et al., 2012), functional capacity (Mangione et al., 2010; Pereira et al., 2012), muscle activity (Cadore et al., 2013), body composition (Avila et al., 2010), mood (Pereira et al., 2013), cognition (Cassilhas et al., 2007; Liu-Ambrose et al., 2010), health related quality of life (Levinger et al., 2007) and enhanced hemodynamic activity on functional magnetic resonance imaging tasks (Nagamatsu et al., 2012). In individuals who have suffered a stroke, strength training has been found to improve muscular strength, upper and lower limb function and performance on functional tasks (Ada et al., 2006; Harris and Eng, 2010; Ouellette et al., 2004). Improvements in selective attention, conflict resolution, associative memory and regional patterns of functional brain activity have also been observed after strength training in seniors with mild cognitive impairment (Nagamatsu et al., 2012).

In the last two years, three systematic reviews have evaluated the effects of strength training in either Parkinson's disease or multiple sclerosis (Brienesse and Emerson, 2013; Kjølhede et al., 2012; Lima et al., 2013). Findings from these reviews suggest that strength training is useful for improving muscle strength and some measures of functional capacity in these disorders. Since the publication of these reviews, a number of randomised controlled trials have been published (Brienesse and Emerson, 2013; Kjølhede et al., 2012; Lima et al., 2013), somewhat limiting the informative capacity of previous reviews. Previous systematic reviews have also included trials with confounding supplementary interventions (i.e. creatine monohydrate and balance training) (Brienesse and Emerson, 2013; Lima et al., 2013) as well as trials without a disease control or comparison group (Brienesse and Emerson, 2013; Kjølhede et al., 2012). These methodological limitations may have led to an inaccurate appraisal of the effects of strength training as a therapy in individuals with Parkinson's

disease or multiple sclerosis. It is of vital importance that systematic reviews accurately evaluate experimental therapies like strength training as such documents inform health professionals.

In this systematic review we provide the most recent evidence to support a robust evaluation of the effect of strength training in people with Parkinson's disease or multiple sclerosis. Unlike previous reviews, our study evaluates the effect of strength training alone, in people with Parkinson's disease or multiple sclerosis. In addition, our study only selects trials that included individuals with multiple sclerosis or Parkinson's disease in the control or comparison group. Moreover, our study evaluates through a meta-analysis, the magnitude of strength improvements in individuals with multiple sclerosis or Parkinson's disease in response to strength training. Finally, unlike previous reviews, our study explores whether differences in response to strength training exist between individuals with multiple sclerosis or Parkinson's disease.

3.3 MATERIAL AND METHODS

3.3.1 Search strategy

A comprehensive search of electronic databases was conducted from inception to July 2014. Electronic searches were performed using PEDro, PubMED, EMBASE, Cochrane Central Register of Controlled Trials, and CINAHL databases. The search strategy utilised a population, intervention, comparison and outcome (PICO) approach (Moher et al., 2010). The population key words were "Parkinson's disease", "multiple sclerosis", Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and spinocerebellar ataxia; the intervention key words were "strength training", "progressive strength training", "resistance training", "weight training" and "strengthening programs"; and the outcome key words included "strength", "disease severity", "gait", "balance", "fatigue", "functional capacity",

"mood" and "quality of life". This initial search only found trials on strength training in individuals with Parkinson's disease or multiple sclerosis.

As this was a literature review and did not involve the recruitment and assessment of patients, ethical approval was not necessary.

3.3.2 Eligibility criteria

Randomised controlled trials and non-randomised controlled trials that examined the effect of strength training in individuals suffering with multiple sclerosis or Parkinson's disease were included in the review. Strength training was defined as an intervention in which participants exercised a muscle or group of muscles against an external resistance (Esco, 2013). Eligible studies included those examining the effect of strength training in individuals with multiple sclerosis and Parkinson's disease. Exclusion criteria were as follows: (1) case studies; (2) observational studies; (3) studies with healthy controls or healthy comparison groups; and (5) studies employing supplementary intervention therapies in addition to or different from strength training.

3.3.3 Data extraction

Two independent authors (T.C and A.R) extracted data from the included studies. A specialised extraction form was designed and recorded the following methodological details for each study:

- Publication details: authors and year of publication.
- Details of the study: study design and number of participants, experimental and control interventions and reported outcomes (controls and experimental).
- Participant characteristics: disease population, disease status and age.

- Specific intervention details: intervention groups, mode of strength training, targeted anatomical regions, setting in which the study was conducted, level of supervision, duration of the intervention (weeks), frequency of strength training, specific exercises employed, exercise intensity, number of sets and repetitions performed for each exercise, rest taken between sets and exercises and the progression method used for strength training interventions.

- Moderator variables: participant retention and dropouts, participant adherence and adverse effects associated with strength training.

Corresponding authors of studies were contacted as necessary for supplementary information not detailed in the publication. In cases where authors did not respond or did not provide supplementary methodological information pertaining to their publication, a not reported (NR) statement was assigned.

3.3.4 Quality assessment

All articles that satisfied the pre-defined inclusion criteria were independently rated for quality by two reviewers (T.C and A.R) using the Physiotherapy Evidence Database (PEDro) scale (Maher et al., 2003). The PEDro scale is an eleven points scale designed to examine the methodological quality of intervention studies. The scale evaluates the following methodological aspects: (1) specific eligibility criteria, (2) randomisation allocation, (3) concealed allocation, (4) baseline demographic similarities, (5) participant blinding, (6) therapist blinding, (7) outcome assessor blinding, (8) whether more than 85% of participants completed follow up for at least one primary outcome, (9) intention to treat analysis, (10) between group statistical comparisons and (11) point estimates and variability for at least one of the primary outcome measures. When rating each study, only criteria two-eleven are considered for the PEDro scale. Initial discrepancies between the independent authors were

resolved by consensus. In instances where discrepancies could not be resolved a final decision was made by another independent author (M.Z).

3.3.5 Data analysis and synthesis

For analysis, studies were categorised according to disease. The heterogeneity of populations and extensive variety of reported outcomes prevented a meta-analysis for all outcomes, with the exception of strength. While fifteen articles reported on strength as an outcome (Corcos et al., 2013; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; Dibble et al., 2006; Dibble et al., 2009; Dodd et al., 2011; Fimland et al., 2010; Hass et al., 2012; Medina-Perez et al., 2014; Sabapathy et al., 2011; Schilling et al., 2010; Shulman et al., 2013), three articles by Dalgas et al (Dalgas et al.; 2010b; 2013) and two articles by Dibble et al (2006; 2009) appeared to originate from the same trial. Strength data from three articles by Dalgas et al (2009; 2010b; 2013) were pooled together into a single effect size for a better interpretation of the effects of strength training on strength as an outcome. Standardised effect sizes were calculated for the meta-analysis using pre and post strength mean values for each group (intervention and comparison) (Hedges and Olkin, 1985). Effect sizes were corrected for the magnitude of sample size of each study as suggested by Hedges and Olkin (1985). The risk of publication bias in trials was examined statistically using the egger regression test, with a significant publication bias considered to be $p \leq 0.10$. All statistical analyses were performed using STATA 9.1 (StataCorp LC, Texas, USA).

3.4 RESULTS

3.4.1 Articles included

The database search strategy and results are presented in Figure 3.1. Five hundred and seven articles were identified by the initial search strategy. Four hundred and seventy one of the

identified articles were excluded based on their title. The abstracts of the remaining thirty-six articles were evaluated and six articles were excluded (Figure 3.1). Full texts of the remaining thirty articles were retrieved and reviewed, resulting in the exclusion of ten articles (Figure 3.1). Of the twenty articles included in the systematic review, eight appeared to originate from three separate trials. Subsequently the extracted and reviewed data is representative of fifteen independent trials.

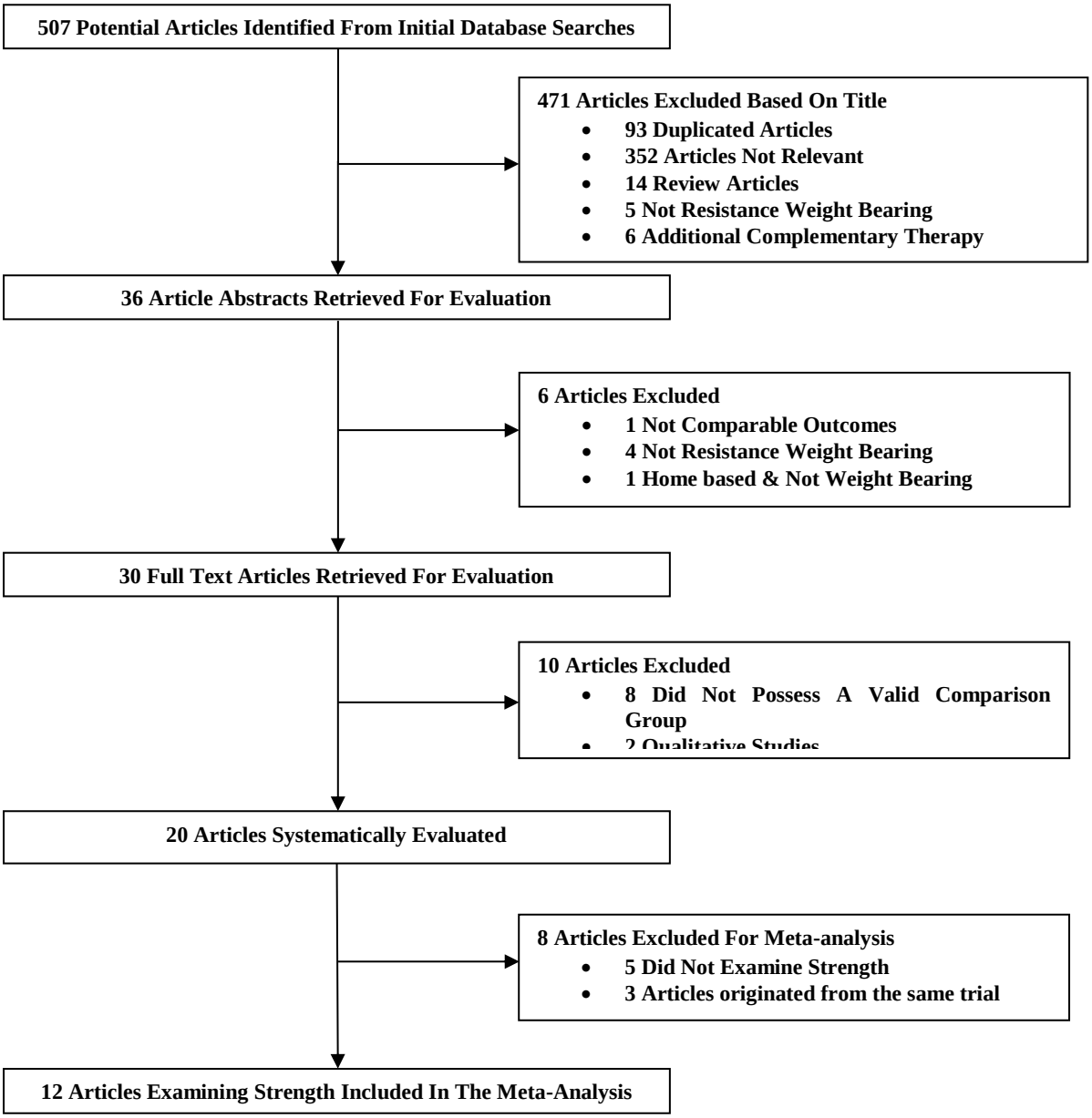

Figure 3.1 Flowchart for selection of studies and included meta-analysis

3.4.2 Methodological quality

The methodological quality of included trials varied considerably in both Parkinson's disease and multiple sclerosis populations. PEDro scores ranged from four to eight points in both Parkinson's disease (Bloomer et al., 2008; Corcos et al., 2013; Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2012; Paul et al., 2014; Prodoehl et al., 2015; Sage et al., 2011; Schilling et al., 2010; Shulman et al., 2013) and multiple sclerosis trials (Broekmans et al., 2011; Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; DeBolt and McCubbin, 2004; Dodd et al., 2011; Fimland et al., 2010; Medina-Perez et al., 2014; Sabapathy et al., 2011) (Table 3.1).

3.4.3 Participants characteristics

The number of trials included was eight in Parkinson's disease (Bloomer et al., 2008; Corcos et al., 2013; Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2012; Paul et al., 2014; Prodoehl et al., 2015; Sage et al., 2011; Schilling et al., 2010; Shulman et al., 2013) and seven in multiple sclerosis (Broekmans et al., 2011; Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; DeBolt and McCubbin, 2004; Dodd et al., 2011; Fimland et al., 2010; Medina-Perez et al., 2014; Sabapathy et al., 2011). Disease population, study design, number of participants, stage of disease, mean age and standard deviation, trial intervention and trial outcomes are shown in Tables 3.2 and 3.3.

Table 3.1 Trial inclusions rated according to the PEDro scale

Trials		PEDro criteria											Total Score
		#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	
Parkinson's disease													
RCT	Paul et al (2014)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	8/10
	PRET-PD RCT Corcos et al (2013) & Prodoehl et al (2015)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7/10
	Shulman et al (2013)	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes	6/10
	Sage et al (2011)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	7/10
	Bloomer et al (2008)	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
non-RCT	Hass et al (2012)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/10
	Schilling et al (2010)	Yes	Yes	No	Yes	No	No	No	No	Yes	No	Yes	4/10
	Dibble et al (2006; 2009)	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/10
Multiple Sclerosis													
RCT	Medina-Perez et al (2014)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/10
	Dalgas et al (2010a; 2009; 2010b; 2013)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	6/10
	Dodd et al (2011)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10
	Broekmans et al (2011)	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	6/10
	Fimland et al (2010)	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
Non-RCT	Sabapathy et al (2011)	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
	De Bolt et al (2004)	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	6/10

RCT randomised controlled trial, non-RCT non-randomised controlled trial

Table 3.2 Overview of trials of strength training interventions in individuals with Parkinson's disease or multiple sclerosis

Reference	Experimental/ control (n)	Stage of disease	Mean age (SD)	Experimental Intervention	Control/Comparison Intervention	Measures/ Results
Parkinson's disease						
RCT						
Paul et al (2014)	Exp=20 Con=20	Hoehn & Yahr	Exp=68.1 ± 5.6 Con=64.5 ± 7.4	Lower Body RE/Machine (non-continuous)	Sham low intensity exercises trunk/lower body	Power ↑ Strength ↑ Movement speed ↑ Falls → Balance → Mobility → Functional capacity →
PRET-PD RCT Corcos et al (2013) & Prodoehl et al (2015)	Exp=24 mFC=24	Hoehn & Yahr I-V	Exp= 59.0 ± 4.6 mFC=58.6 ± 5.6	Full Body RE/ Machine & Free Weights (non-continuous)	Modified fitness counts	UPDRS-III ↑ Strength ↑ Quality of life → Balance ↑* Mobility ↑* Functional capacity →
Shulman et al (2013)	Exp=28 LIT=26 HIT=26	Hoehn & Yahr I-III	Exp=65.3 ± 11.3 LIT=65.8 ± 11.5 HIT=66.1 ± 9.7	Lower Body RE/ Machine (non-continuous)	Low Intensity Treadmill High Intensity Treadmill	Mobility ↑* Strength ↑ UPDRS-III (motor) ↑* Falls → Fatigue → Quality of life → Mood →
Sage et al (2011)	Exp=18 Con=18 Aerobic=17 Aquatic=12 SAFEx=24	NR	Exp=68.7 ± 8.3 Con=68.6 ± 8.1 Aerobic=65.8 ± 9-9 Aquatic=63.1 ± 9.2 SAFE=68.0 ± 11	Whole body work out (non-continuous)	Daily living activities	UPDRS-III ↑*
Bloomer et al (2008)	Exp=8 Con=8	Hoehn & Yahr I-II	Exp= 61.0 ± 2.0 Con= 57.0 ± 3.0	Lower Body RE/ Machine (non-continuous)	Standard care	Oxidative & antioxidant markers ↑
Non-RCT						
Hass et al	Exp=9	Hoehn & Yahr	Exp= 67 ± 8.0	Lower Body & Core/	Standard care	Mobility ↑

(2012)	Con=9	I-III	Con= 64 ± 7.0	Machine & Theraband (non-continuous)		Strength ↑
Schilling et al (2010)	Exp=9 Con=9	Hoehn & Yahr I-II/III	Exp= 61.3 ± 8.6 Con= 57.0 ± 7.1	Lower Body/ Machine (non-continuous)	Standard care	Strength ↑ Functional capacity → Mobility ↑* Balance →
Dibble et al (2006; 2009)	Exp=10 Con=9	Hoehn & Yahn I-III	Exp=64.3 ± 9.6 Con= 67.0 ± 10.2	Eccentric resistance training ergometer (continuous)	Standard care	Strength ↑ Quadriceps muscle volume ↑* UPDRS-III (motor) → Quality of life ↑ Mobility ↑ Functional capacity (TUG) ↑ (stair descent) ↑ *
Multiple sclerosis						
RCT						
Medina-Perez et al (2014)	Exp=30 Con=12	EDSS: 1.0-6.0	Exp= 49.6 ± 11.0 Con= 46.2 ± 7.5	Lower Body/Machine (non-continuous)	Standard Care	Strength ↑ Power ↑ Muscle Endurance →
Dalgas et al (2010a; 2009; 2010b; 2013)	Exp=19 Con=19	EDSS: 3.0-5.5 DC: RR	Exp= 49.1 ± 8.4 Con= 47.7 ± 10.4	Lower Body/Machine (non-continuous)	Standard care	EMG activity ↑ Strength ↑ Thigh Volume ↑* Fatigue ↑* Mood ↑* Quality of life (physical) ↑* CSA II/IIa muscle fibres ↑* Functional capacity ↑*
Dodd et al (2011)	Exp= 39 Con= 37	AID: 2,3 or 4 DC: RR	Exp= 47.7 ± 10.8 Con= 50.4 ± 9.6	Lower Body/Machine (non-continuous)	Standard Care	Strength ↑ Muscle Endurance ↑ Fatigue ↑ Quality of life (physical domain) ↑ Mobility →
Broekmans et al (2011)	Exp=11 Exp+ES=11 Con=14	EDSS: 2.0-6.5	Exp=4.5 ± 1.3 Exp+ES=4.4 ± 0.9 Con=4.1 ± 1.1	Lower Body/Machine (non-continuous)	Normal living habits	Strength ↑ Mobility → Balance ↑

Fimland et al (2010)	Exp=7 Con=7	EDSS: 2.0-6.5 DC: NR	Exp= 53.0 ± 4.0 Con= 54.0 ± 2.0	Lower Body/Machine (non-continuous)	Standard care	Strength ↑ EMG activity↑ Motor output ↑
Non-RCT						
Sabapathy et al (2011)	Exp=15 END=6	DSS: 1-3 DC: RR, SP, PP	Exp= 55.0 ± 7.0	Upper & Lower Body & Core (non-continuous)	Endurance Exercise	Balance → Mobility → Strength → Mood → Quality of Life → Fatigue → MSIS physical→ MSIS psychological →
DeBolt et al (2004)	Exp= 19 Con=17	EDSS: 2.0-6.0	Exp=51.6 ± 7.2 Con=47.8 ± 10.5	Weighted vest Home based resistance training (non-continuous)	Standard care	Leg extensor power ↑ Functional capacity → Balance →

↑ indicates significant improvement, → indicates no significant change, ↓ indicates significant deterioration, ↑* time effect, RCT = randomised controlled trial, non-RCT = non-randomised controlled trial, Exp = experimental group, Con = control group, RE = resistance exercise, ES = electro-stimulation, UPDRS-III = Unified Parkinson's Disease Rating Scale Version-III, END = endurance training, SAFE = sensory attention focused-exercise, AID = ambulation index score, DC = disease course, RR = relapse remitting, EDSS = expanded disability status scale, DSS = disease steps scale, SP = secondary progressive, P = Primary progressive, EMG = electromyography, CSA= cross sectional area, MSIS = multiple sclerosis impact scale

Table 3.3 Summary details of the specific strength training interventions used in Parkinson's disease or multiple sclerosis trials

Trial	Location	Supervision	Duration	Frequency	Exercises	Multi vs Single Joint	Intensity	Sets	Repetitions	Rest	Progression
RCT (Parkinson's disease)											
Paul et al (2014)	University Lab	Supervised (ratio NR)	12 Weeks	Twice Weekly	Leg extension, knee flexion, hip flexion, hip abduction	Single-joint	1st set 40% (1RM) 2nd set 50% (1RM) 3rd set 60% (1RM)	3 Sets	8 Reps	NR	5%
PRET-PD RCT Corcos et al (2013) & Prodoehl et al (2015)	NR	1:1 1st 6 months TA 18 months	104 Weeks	Twice Weekly	Chest Press, Lat Pull Down, Reverse Flys, Leg Press, Hip Extension, Biceps Curl, Rotary Cuff, Shoulder Press, Tricep Extension, Back Extension, Knee Extension	Multi-joint & single-joint	1st 8 Weeks (30-40% 1RM upper body/50-60% 1RM lower body 2nd 8 Weeks (70-80%1RM)	1st 8 Weeks (3 sets) 2nd 8 Weeks (2 sets)	1st 8 Weeks (8 reps) 2nd 8 Weeks (12 reps)	NR	5% or as allowed by equipment
Shulman et al (2013)	Medical Centre	Supervised (ratio NR)	12 Weeks	Thrice Weekly	Leg Press, Leg Extension, Leg Curl	Multi-joint & single-joint	NR	2 Sets	10 Reps	NR	NR
Sage et al (2011)	Community based training facilities	Supervised 1:8 /1:10	12 Weeks	Thrice Weekly	Whole body workout	Multi-joint & single-joint	NR	3 Sets	10-15 Reps	NR	NR
Bloomer et al (2008)	NR	Supervised (ratio NR)	8 Weeks	Twice Weekly	Leg Press, Leg Curl, Calf press	Multi-joint & single joint	NR	3 Sets	5-8 Reps	2-3 minutes	5-10%

Non-RCT (Parkinson's disease)											
Hass et al (2012)	NR	Supervised (ratio NR)	10 Weeks	Twice Weekly	Leg Press, Knee Extension & Flexion, Abdominal Curl, Back Extension, Seated Calf Raise	Multi-joint & single joint	70% 1RM	2 Sets	12-20 Reps	5 minutes	10%
Schilling et al (2010)	NR	Supervised (ratio NR)	8 Weeks	Twice Weekly	Leg Press, Leg Curl, Calf Raises	Multi-joint & single joint	NR	3 Sets	First 2 Sets 8 Reps Third Set 5-8	NR	5-10%
Dibble et al (2006; 2009)	NR	Supervised (ratio NR)	12 weeks	Thrice Weekly	Eccentric resistance training ergometer	Multi-joint & single joint	Rate of Perceived Exertion 7-13	1 set	-	-	Week 1-2: 5 mins Week 3: 5-10 mins Week 4: 10-15 mins Week 5-12: 15-30 mins
RCT (multiple sclerosis)											
Medina-Perez et al (2014)	Rehabilitation Centre	Supervised (ratio NR)	12 Weeks	Twice Weekly	Knee extension (bilateral, concentric/eccentric)	Single-joint	35-70% (MVIC)	3 Sets	8-13 Reps	3 minutes	NR
Dalgas et al (2010a; 2009; 2010b; 2013)	NR	Supervised 1:2/1:4	12 Weeks	Twice Weekly	Leg Press, Knee Extension & Flexion, Hip Flexion & Extension	Multi-joint & single joint	NR	Weeks 1-4 3 Sets; Weeks 5-10 4 Sets; Weeks 11-12 3 Sets	Weeks 1-2 10 Reps; Weeks 3-6 12 Reps; Weeks 7-8 10 Reps; Weeks 9-12 8 Reps	2-3 minutes (sets + exercise)	NR
Dodd et al (2011)	Community Gym	Supervised 3:12	10 Weeks	Twice Weekly	Leg Press, Knee	Multi-joint & single	NR	2 Sets	10-12 Reps	2 minutes	NR

					Extension & Flexion, Calf Raises, Reverse Leg Press	joint					
Broekmans et al (2011)	NR	Supervised 1:3	20 Weeks	50 training sessions (~60) min	Leg Press Leg extension Leg Curl	Multi-joint & single joint	1-2 week: minimal reps 3-6: 50-60% 1RM 7-8: 60% 1RM 9-10: 60% 1RM 11: 60% 1RM 12-14: 15 RM 15-17: 12 RM 18-20:10 RM	1-2: 1 3-6: 1 7-8: 2 9-10: 2 11: 2 12-14: 2 15-17: 2 18-20: 2	1-2: 10 3-6: 10 7-8: 10 9-10: 12 11: 12 12-14: 15 15-17: 12 18-20: 10	NR	NR
Fimland et al (2010)	NR	Supervised (ratio NR)	3 Weeks	Five Times Weekly	Leg Press & Seated Calf Raise	Multi-joint & single joint	85-90% 1RM	4 Sets	4 Reps	1-2 minutes	NR
Non-RCT (multiple sclerosis)											
Sabapathy et al (2011)	Health Facility	Supervised (ratio NR)	8 Weeks	Twice Weekly	Chest Press, Seated Row, Shoulder Abduction, Sit to Stand, Lunges, Hip Abduction, Step Ups & Tandom Stance	Multi-joint & single joint	NR	2-3 Sets	6-10 Reps	0.5-1 minute	NR
DeBolt et al (2004)	Home Based	NR	8 Weeks	Thrice weekly	Chair raises Forward	Multi-joint & single	NR	Weeks 1 & 3 2	Weeks 1 & 3 8-12 Reps;	NR	–

					lunges Step-ups Heel toe raise Leg curls	joint		Sets; Weeks 2 & 4 3 Sets; Weeks 5-8 2 Sets	Weeks 2 & 4 8-12 Reps; Weeks 5-8 8-10 Reps		

NR = Not reported, RCT = randomised controlled trial, Non-RCT = non randomised controlled trial

3.4.4 Intervention characteristics

Of the eight trials conducted in individuals with Parkinson's disease (Bloomer et al., 2008; Corcos et al., 2013; Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2012; Paul et al., 2014; Prodoehl et al., 2015; Sage et al., 2011; Schilling et al., 2010; Shulman et al., 2013) (five randomised controlled trials (Bloomer et al., 2008; Corcos et al., 2013; Paul et al., 2014; Prodoehl et al., 2015; Sage et al., 2011; Shulman et al., 2013) and three non-randomised controlled trials (Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2012; Schilling et al., 2010)), five used lower body strength training interventions (Bloomer et al., 2008; Dibble et al., 2006; Dibble et al., 2009; Paul et al., 2014; Schilling et al., 2010; Shulman et al., 2013), two used a full body strength training intervention (Corcos et al., 2013; Prodoehl et al., 2015; Sage et al., 2011) and one used a lower body and core strength training intervention (Hass et al., 2012) (Tables 3.2 and 3.3). Training protocols ranged from two to twenty-four months of twice to thrice weekly training (Bloomer et al., 2008; Corcos et al., 2013; Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2012; Paul et al., 2014; Prodoehl et al., 2015; Sage et al., 2011; Schilling et al., 2010; Shulman et al., 2013). Only two trials conducted in individuals with Parkinson's disease reported on the level of supervision for strength training interventions (Corcos et al., 2013; Prodoehl et al., 2015; Sage et al., 2011).

Of the seven trials conducted in multiple sclerosis (Broekmans et al., 2011; Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; DeBolt and McCubbin, 2004; Dodd et al., 2011; Fimland et al., 2010; Medina-Perez et al., 2014; Sabapathy et al., 2011) (five randomised controlled trials (Broekmans et al., 2011; Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; Dodd et al., 2011; Fimland et al., 2010; Medina-Perez et al., 2014) and two non-randomised controlled trials (DeBolt and McCubbin, 2004; Sabapathy et al., 2011)), five trials trained the lower body (Broekmans et al., 2011; Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; Dodd et al.,

2011; Fimland et al., 2010; Medina-Perez et al., 2014) and two trials trained the full body (DeBolt and McCubbin, 2004; Sabapathy et al., 2011) (Tables 3.2 and 3.3). Intervention protocols utilised in multiple sclerosis trials ranged from three weeks to six months of two to five times weekly training (Broekmans et al., 2011; Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; DeBolt and McCubbin, 2004; Dodd et al., 2011; Fimland et al., 2010; Medina-Perez et al., 2014; Sabapathy et al., 2011). Of the seven trials conducted in individuals with multiple sclerosis, only three trials reported on the level of supervision for strength training interventions (Broekmans et al., 2011; Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; Dodd et al., 2011).

3.4.5 Risk of bias

Statistical examination using the egger regression test revealed no publication bias (p=0.131).

3.4.6 Intensity and progression of resistance exercise

Two randomised (Corcos et al., 2013; Paul et al., 2014; Prodoehl et al., 2015) and two non-randomised controlled trials (Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2012) conducted in Parkinson's disease reported on the intensity of strength training performed throughout the intervention, while three randomised controlled trials (Broekmans et al., 2011; Fimland et al., 2010; Medina-Perez et al., 2014) reported on the intensity of strength training in multiple sclerosis. The progression of strength training was reported by three randomised (Bloomer et al., 2008; Corcos et al., 2013; Paul et al., 2014; Prodoehl et al., 2015) and three non-randomised controlled trials (Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2012; Schilling et al., 2010) in Parkinson's disease. In contrast, there were no trials that reported on the progression of strength training in multiple sclerosis.

3.4.7 Participant retention, adherence, and adverse events

Participant retention ranged from 75% to 100% in Parkinson's disease trials (Bloomer et al., 2008; Corcos et al., 2013; Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2012; Paul et al., 2014; Prodoehl et al., 2015; Sage et al., 2011; Schilling et al., 2010; Shulman et al., 2013) and from 73.3% to 100% in multiple sclerosis trials (Broekmans et al., 2011; Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; DeBolt and McCubbin, 2004; Dodd et al., 2011; Fimland et al., 2010; Medina-Perez et al., 2014; Sabapathy et al., 2011) (Table 3.4). Four trials in multiple sclerosis ([Medina-Perez et al (2014) strength training group 95.4%; control group NR], [Dodd et al (2011) strength training group 92%; control group 62%], [Broekmans et al (2011) ~99% all groups] and [DeBolt et al (2004) strength training group 95%]) and one trial in Parkinson's disease reported on participant adherence (Paul et al (2014) strength training group 84.1%; control group 94.1%) (Table 3.4). Five trials in Parkinson's disease (Corcos et al., 2013; Hass et al., 2012; Paul et al., 2014; Prodoehl et al., 2015; Sage et al., 2011; Shulman et al., 2013) and six trials in multiple sclerosis (Broekmans et al., 2011; Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; Dodd et al., 2011; Fimland et al., 2010; Medina-Perez et al., 2014; Sabapathy et al., 2011) reported on adverse events (Corcos et al., 2013; Hass et al., 2012; Paul et al., 2014; Prodoehl et al., 2015; Sage et al., 2011; Shulman et al., 2013), with only minor or clinically unrelated medical issues reported (Table 3.4).

Table 3.4 Summary of retention, adherence and adverse events in Parkinson's disease or multiple sclerosis strength training trials

Trial Reference	Participant Retention	Dropouts	Participant Adherence	Adverse Events
Parkinson's disease				
RCT				
Paul et al (2014)	RE: 18/20 (90%) CG: 18/20 (90%)	RE: 2/20 (10%) CG: 2/20 (10%)	RE: 84.1% CG: 94.1%	RE: pelvic fracture (UTI), low back pain CG: exacerbated hernias (UTI)
PRET-PD RCT Corcos et al & Prodoehl et al (2015)	RE: 19/24 (79.2%) CG: 16/24 (66.6%)	RE: 5/24 (20.8%) CG: 8/24 (33.3%)	NR	RE: 1 (wrist pain) CG: 1 (back surgery)
Shulman et al (2013)	RE: 22/28 (78.5%) CG: 22/26 (84.6%) CG: 23/26 (88.4%)	RE: 6/28 (11.5%) CG: 4/26 (15.4%) CG: 3/26 (11.6%)	NR	No serious adverse events
Sage et al (2011)	RE 18/18 (100%) CG: 18/18 (100%)	RE: 0/10 (0%) CG: 0/10 (0%)	NR	No adverse events
Bloomer et al (2008)	RE: 6/8 (75%) CG: 7/8 (87.5%)	RE: 2/8 (25%) CG: 1/8 (12.5%)	NR	NR
non-RCT				
Hass et al (2012)	RE: 9/9 (100%) CG: 9/9 (100%)	RE: 0/9 (0%) CG: 0/9 (0%)	NR	No adverse events
Schilling et al (2010)	RE: 8/9 (88.8%) CG: 7/9 (77.7%)	RE: 1/9 (11.2%) CG: 2/9 (22.3%)	NR	NR
Dibble et al (2006; 2009)	RE: 10/10 (100%) CG: 9/10 (90%)	RE: 0/10 (0%) CG: 1/10 (10%)	NR	NR

Multiple sclerosis				
RCT				
Medina-Perez et al (2014)	RE: 30/30 (100%) CG: 12/12 (100%)	RE: 0/30 (0%) CG: 0/12 (0%)	RE: 95.4% CG: NR	No adverse events
Dalgas et al (2010a; 2009; 2010b; 2013)	RE: 15/19 (78.9%) CG: 16/19 (84.2%)	RE: 4/9 (21.1%) CG: 3/19 (15.8%)	NR	RE: 1 (lower back pain)
Dodd et al (2011)	RE: 36/39 (92.3%) CG: 31/37 (83.7%)	RE: 3/39 (7.7%) CG: 6/37 (16.3%)	RE: 92% CG: 62%	No adverse events
Broekmans et al (2011)	EXP: 11/11 (100%) EXP+ES: 10/11 (90%) CON: 12/14 (86%)	EXP: 0/11 (0%) EXP+ES: 1/11 (9%) CON: 2/14 (14%)	~99% all groups	Severe relapse Perceived lack of time to continue Mild stroke (unrelated)
Fimland et al (2010)	RE: 7/7 (100%) CG: 7/7 (100%)	RE: 0/7 (0%) CG: 0/7 (0%)	NR	No adverse events
Non-RCT				
Sabapathy et al (2011)	RE: 11/14 (73.3%) CG: 5/6 (83.3%)	RE: 3/14 (26.6%) CG: 1/6 (16.7%)	NR	No adverse events
DeBolt et al (2004)	RE: 19/20 (95%) CG: 17/17 (100%)	RE: 1/20 (5%) CG: 0/17 (0%)	95%	NR

RE resistance exercise, CG comparison group, NR not reported

3.4.8 Outcomes measures

Strength as an outcome measure in Parkinson's disease

Three randomised controlled trials evaluated the effect of strength training on strength in people with Parkinson's disease (Corcos et al., 2013; Paul et al., 2014; Shulman et al., 2013). Strength was evaluated across trials using one repetition maximum (1RM) and maximum voluntary isometric contraction (MVIC) protocols with torque transducers, pneumatic resistance machines and dynamometers. Corcos et al (2013) found a significant improvement in elbow flexor muscle strength (1RM, 15%) in the strength training group, whilst off medication, after twenty-four months of upper and lower body resistance training. No significant differences in strength were found for the control group in this trial. Shulman et al (2013) in another trial found a significant improvement in leg press and leg extension strength (1RM, 16%) in individuals within the strength training group, but not in the high or low intensity treadmill training groups, after three months of thrice weekly resistance training. Paul et al (2014) also reported a significant improvement in lower limb strength (1RM, leg extension, 14.6%; knee flexion, 18.6%; hip flexion, 39.8%; hip abduction, 33.9%) and power (leg extension, 17.3%; knee flexion, 20.6%; hip flexion, 46.3%; hip abduction, 43.1%) in the strength training group in comparison to the sham comparison group after 12 weeks of lower body resistance training.

Three non-randomised controlled trials also evaluated the effect of strength training on strength and found significant improvements (Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2012; Schilling et al., 2010). Hass et al (2012), after ten weeks of twice weekly lower body strength training, found a significant improvement in knee extension (1RM, 76%) and knee flexion (1RM, 57%) strength in the intervention group, but not in the control group. Schilling et al (2010) in another trial reported a significant improvement in leg press strength

(1RM, 22%) in the intervention group, whereas the control group showed no significant differences. Dibble et al (2006; 2009) similarly reported a significant improvement in quadriceps muscle strength (MVIC) in the more (average torque 23%; peak torque 18%) and less affected leg (average torque 16%; peak torque 83.2%) in the strength training intervention group only.

Strength as an outcome in multiple sclerosis

Five randomised controlled trials reported on strength as an outcome after strength training (Broekmans et al., 2011; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; Dodd et al., 2011; Fimland et al., 2010; Medina-Perez et al., 2014), with all five trials reporting significant improvements in strength. Strength was evaluated across trials using MVIC, maximum voluntary dynamic contraction (MVDC) and 1RM strength protocols with pneumatic resistance machines, dynamometers and the Leg Extensor Power Rig. Medina-Perez et al (2014) reported a significant improvement in knee extension strength (MVIC, 7.7%) and power (40% MVIC, 15.6%) in the intervention group, but not in the control group after twelve weeks of strength training. Significant improvements in leg press strength (1RM, 15%) in the intervention group, but not the control group were also reported by Dodd et al (2011) after strength training. Broekmans et al (2011) in line with Medina-Perez et al (2014), reported significant improvements in isometric strength in the knee flexors and extensors (MVIC, average knee extension 45° change: 10.8, average knee extension 90° change: 10, average knee flexor 45° change: 4, average knee flexion 90° change: 2.3) in the intervention group as a result of strength training. In another trial, Dalgas et al (2010a; 2009; 2010b; 2013) reported significant improvements in isokinetic, isometric and angular impulse knee extensor and flexor strength in the intervention group ([Dalgas et al (2013), MVIC at 70° knee flexion; knee extension: 13.2%, knee flexion: 13.8%], [Dalgas et al (2010b); MVDC, knee extension 90º: 4.5%; knee extension 180º:10.2%; knee flexion 90º: 21.3%; knee flexion 180º: 18.6%],

[Dalgas et al (2009), MVIC, knee extension: 15.7%, knee flexion: 21.3%]), but not in the control group as a result of resistance training. Dalgas et al (2009) additionally reported a significant improvement in leg press strength. Fimland et al (2010) in another trial reported a significant improvement in plantar flexion strength (MVIC, 36%) in the strength training intervention group, but not in the control group. In a non-randomised controlled trial, DeBolt et al (2004) reported a significant improvement in leg extensor power (24%) in the intervention group, whereas the disease control group showed no changes after strength training.

In addition to muscle strength, significant study specific improvements in gait, clinical disease progression, functional capacity, quality of life, oxidative biomarkers, mood, fatigue, falls, skeletal muscle volume and electromyography activity were observed after strength training in individuals with multiple sclerosis or Parkinson's disease (Bloomer et al., 2008; Broekmans et al., 2011; Corcos et al., 2013; Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; DeBolt and McCubbin, 2004; Dibble et al., 2006; Dibble et al., 2009; Dodd et al., 2011; Fimland et al., 2010; Hass et al., 2012; Medina-Perez et al., 2014; Paul et al., 2014; Prodoehl et al., 2015; Sabapathy et al., 2011; Sage et al., 2011; Schilling et al., 2010; Shulman et al., 2013).

Parkinson's disease measures

Unified Parkinson Disease Rating Scale Version 3

Three randomised (Corcos et al., 2013; Sage et al., 2011; Shulman et al., 2013) and one non-randomised controlled trial (Dibble et al., 2009) conducted in Parkinson's disease evaluated the effect of strength training on clinical disease progression using the Unified Parkinson's Disease Rating Scale Version 3. Corcos et al (2013) reported a significant improvement on the Unified Parkinson's Disease Rating Scale Version 3 in the intervention group (7.4 point

decrease), but not in the control group after twenty-four months of strength training. Shulman et al (2013) in another study similarly reported a significant improvement on the motor subscale of the Unified Parkinson's Disease Rating Scale Version 3 in the strength training group. Furthermore, Sage et al (2011) found a significant improvement on the Unified Parkinson's Disease Rating Scale Version 3 in the strength training group. Dibble et al (2009) by contrast found no improvement on the Unified Parkinson's Disease Rating Scale Version 3 in the intervention group after strength training.

Functional Mobility

Three randomised (Paul et al., 2014; Prodoehl et al., 2015; Shulman et al., 2013) and three non-randomised controlled trials (Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2012; Schilling et al., 2010) evaluated the effect of strength training on mobility in individuals with Parkinson's disease. Mobility was assessed across trials using the 10 Meter Timed Walk Test, 6 Minute Walk Test, 50 Feet Walk Test and Timed Up and Go. Paul et al (2014) did not report significant changes in mobility after strength training. In contrast, Prodoehl et al (2015) and Shulman et al (2013) found significant improvements in mobility as a result of strength training. The three non-randomised controlled trials (Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2012; Schilling et al., 2010) that reported on mobility as an outcome also documented improvements.

Balance

Two randomised (Paul et al., 2014; Prodoehl et al., 2015) and two non-randomised controlled trials (Sabapathy et al., 2011; Schilling et al., 2010) examined the effect of strength training on balance outcomes in Parkinson's disease. Balance was evaluated across trials using a variety of outcomes including the Single Leg Stance, Choice Stepping Task, Berg Balance Scale, Functional Reach Test, 5 Time Sit To Stand Test and the Activities-specific Balance

Confidence scale. Paul et al (2014) did not find a significant improvement in balance as a result of strength training. Prodoehl et al (2015) by contrast reported a significant improvement in balance after strength training. Both non-randomised controlled trials (Sabapathy et al., 2011; Schilling et al., 2010) were unable to find a significant improvement in balance after strength training.

Functional Capacity

One randomised trial (Corcos et al., 2013) examined the effect of strength training on functional capacity. Corcos et al (2013) assessed functional capacity using the modified Physical Performance Test and reported no significant changes after strength training in the intervention or control group.

Quality of Life

Two randomised (Corcos et al., 2013; Shulman et al., 2013) and one non-randomised controlled trial (Dibble et al., 2009) evaluated the effect of strength training on quality of life. All three trials assessed quality of life using the 39-Item Parkinson's Disease Questionnaire. Both randomised controlled trials (Corcos et al., 2013; Shulman et al., 2013) did not report a significant improvement in quality of life after strength training. Dibble et al (2009) by contrast reported a significant improvement in quality of life in the intervention group after strength training.

Oxidative and Anti-oxidant Markers

One randomised controlled trial (Bloomer et al., 2008) in Parkinson's disease measured changes in blood oxidant and anti-oxidant marker levels and reported significant increases in anti-oxidant marker levels (superoxide dismutase [9.9%] and glutathione peroxidase [1.8%])

and a significant reduction in oxidative stress marker levels (malondialdehyde [15%] and hydrogen peroxide [16%]).

Mood

One randomised controlled trial (Shulman et al., 2013) evaluated the effect of strength training on mood in Parkinson's disease. Shulman et al (2013) found no significant changes in mood after strength training using the Beck Depression Inventory.

Fatigue

One randomised controlled trial (Shulman et al., 2013) evaluated the effect of strength training on fatigue in Parkinson's disease. Shulman et al (2013) used the 16-item Parkinson Fatigue Scale and found no significant change in fatigue after strength training in the strength training intervention group or high and low intensity treadmill intervention groups.

Falls

Two randomised controlled trials (Paul et al., 2014; Shulman et al., 2013) evaluated the effect of strength training on falls in people with Parkinson's disease. Falls were assessed using the New Freezing of Gait Questionnaire (Paul et al., 2014) and Falls Efficacy Scale (Shulman et al., 2013). No trial reported a significant effect on falls outcomes after strength training.

Skeletal Muscle Volume

One non-randomised controlled trial (Dibble et al., 2006) evaluated the effect of strength training on quadriceps muscle volume in Parkinson's disease. Dibble et al (2006) found a significant increase in quadriceps muscle volume using magnetic resonance imaging after strength training in the intervention group only.

Multiple sclerosis

Functional Mobility

Two randomised (Broekmans et al., 2011; Dodd et al., 2011) and two non-randomised controlled trials (DeBolt and McCubbin, 2004; Sabapathy et al., 2011) evaluated the effect of strength training on functional mobility in multiple sclerosis. Functional mobility was assessed across trials using the 2 Minute Walk Test, 10 Meter Walk Test, Timed 25 Foot Walk and Timed Up and Go. No trial reported a significant improvement in mobility as a result of strength training.

Balance

One randomised (Broekmans et al., 2011) and two non-randomised (DeBolt and McCubbin, 2004; Sabapathy et al., 2011) controlled trials evaluated the effect of strength training on balance in multiple sclerosis. Balance was evaluated across trials using the Functional Reach Test (Broekmans et al., 2011; Sabapathy et al., 2011), Four Square Step Test (Sabapathy et al., 2011) and Accusway^{PLUS} force platform (DeBolt and McCubbin, 2004). Broekmans et al (2011) reported a significant improvement in balance in the intervention group only as a result of strength training. However, Sabapathy et al (2011) and DeBolt et al (2004) did not find significant improvements in balance after strength training.

Functional Capacity

One randomised controlled trial (Dalgas et al., 2009) evaluated the effect of strength training on functional capacity outcomes in multiple sclerosis. Dalgas et al (2009) reported a significant improvement in functional capacity (computed as ¼ [Chair Stand Test $_{post}$ / Chair Stand Test $_{pre}$] + [Stair Climb Test $_{post}$ / Stair Climb Test $_{pre}$] + [10 Meter Walk Test $_{post}$ /10

Meter Walk Test $_{pre}$] + [6 Minute Walk Test $_{post}$ / 6 Minute Walk Test $_{pre}$] × 100) as a result of strength training.

Quality of Life

Two randomised (Dalgas et al., 2010a; Dodd et al., 2011) and one non-randomised controlled trial (Sabapathy et al., 2011) reported on quality of life outcomes after strength training in multiple sclerosis. Quality of life was assessed across trials using the Short Form-36 (Dalgas et al., 2010a; Sabapathy et al., 2011) and the World Health Organisation Quality of Life-BREF (Dodd et al., 2011). Dodd et al (2011) and Dalgas et al (2010a) reported a significant improvement in quality of life in the intervention group as a result of strength training. In contrast, Sabapathy et al (2011) found no significant improvement in quality of life after strength training.

Electromyography Activity

Two randomised controlled trials (Dalgas et al., 2013; Fimland et al., 2010) assessed the effect of strength training on electromyography activity during maximum voluntary isometric contractions. Dalgas et al (2013) recorded surface electromyography signals from the Vastus Lateralis, Rectus Femoris and Semitendinosus during maximal voluntary isometric contractions of the knee flexors and extensors (assessed at 70° knee flexion), using bipolar electrodes. The upper electrode of each pair was placed at the midpoint between the Spina Iliaca anterior superior and patellar basis. After twelve weeks of strength training, Dalgas et al (2013) found significant improvements in maximal isometric (μV) knee extension and knee flexion activity (Semitendinosus: 27.6%; Vastus Lateralis: 27%; Rectus Femoris: 28%) in the intervention group, but not the control group. Fimland et al (2010) recorded surface electromyography activity during maximum voluntary isometric contractions of the plantar flexors (ankle positioned at 90°), using bipolar surface electrodes placed according to Surface

Electromyography for the Non-Invasive Assessment of Muscles (SENIAM) recommendations. Fimland et al (2010) reported significant improvements (15%) in surface electromyography activity of the plantar flexors after three weeks of strength training in the intervention group in comparison to the control group.

Skeletal Muscle Volume and Architecture

Only one randomised controlled trial (Dalgas et al., 2010b) measured changes to thigh volume, muscle fibre numbers, type and size. Muscle biopsies of the Vastus Lateralis (middle portion) were taken to assess changes in muscle fibre number, type and size. Dalgas et al (2010b) reported a significant increase in the cross sectional area of type II and IIa vastus lateralis muscle fibres after strength training in the intervention group only.

Fatigue

Two randomised (Dalgas et al., 2010a; Dodd et al., 2011) and one non-randomised controlled trial (Sabapathy et al., 2011) evaluated the effect of strength training on fatigue in multiple sclerosis. Fatigue was assessed across trials using a variety of outcomes including the Modified Fatigue Scale and Fatigue Severity Scale, Multidimensional Fatigue Inventory. Dodd et al (2011) reported a significant improvement in the level of fatigue experienced (24%) after ten weeks of twice weekly strength training. Similar findings were reported by Dalgas et al (2010a), who reported a 10% improvement in the level of fatigue experienced after strength training. Sabapathy et al (2011) also reported a significant improvement in the level of fatigue experienced as a result of strength training.

Mood

One randomised (Dalgas et al., 2010a) and one non-randomised controlled trial (Sabapathy et al., 2011) examined the effect of strength training on mood outcomes in multiple sclerosis.

Dalgas et al (2010a) reported significant improvements (-2.4 points) in mood using the Major Depression Inventory as a result of strength training. In contrast, Sabapathy et al (2011) found no significant changes in mood using the Beck Depression Inventory after strength training.

Muscle Endurance

Two randomised controlled trials (Dodd et al., 2011; Medina-Perez et al., 2014) evaluated the effect of strength training on muscle endurance in multiple sclerosis. Medina-Perez et al (2014) measured muscle endurance as the maximum number of repetitions that a participant could perform during a single set of knee extension using a load of 40% of the maximum voluntary isometric contraction, while Dodd et al (2011) measured endurance by counting the number of repetitions that a participant could complete on the seated leg press and reverse leg press using a load of 50% of 1 RM. Medina-Perez et al (2014) did not find a significant change in muscle endurance in the intervention or control group after strength training. In contrast, Dodd et al (2011) reported a significant improvement in muscle endurance in the intervention group relative to the control group after strength training.

3.5 DISCUSSION

This review found that strength training is useful for improving muscle strength in Parkinson's disease and to a lesser extent multiple sclerosis. Evidence also showed that strength training is helpful for improving clinical measures of disease progression and mobility in Parkinson's disease. However, the evidence is unclear regarding the efficacy of strength training on falls, quality of life, fatigue, functional capacity and balance in Parkinson's disease. In multiple sclerosis, strength training was also found to improve fatigue, quality of life, muscle power, electromyography activity and functional capacity. However, its effect on balance and mood remains equivocal.

An increase in strength was the most consistently reported benefit of strength training in people with Parkinson's disease and multiple sclerosis. A meta-analysis of the extracted strength data revealed that strength training had a larger effect on strength in people with Parkinson's disease (d=0.87) than multiple sclerosis (d=0.33) (Figure 3.2). Different pathological mechanisms underpinning impairments in strength in each disease are likely to account for this discrepancy. For instance, impairments in strength in multiple sclerosis are thought to be mediated by central (de Haan et al., 2000; Ng et al., 2004) (spinal and supraspinal mechanisms) and muscular deficits (Carroll et al., 2005; Garner and Widrick, 2003; Kent-Braun et al., 1997), while in Parkinson's disease impairments in strength are thought to result from central deficits only (Bridgewater and Sharpe, 1998; Corcos et al., 1996; Yanagawa et al., 1989). This finding suggests that strength training may only produce meaningful benefits in strength in people with Parkinson's disease.

Strength training trials in Parkinson's disease also reported improvements in mobility. The improvements were reported on short and longer duration mobility assessments, suggesting that strength training has a favourable effect on multiple aspects of mobility. This finding is consistent with the supposition that muscle strength strongly predicts mobility in people with Parkinson's disease (Allen et al., 2010; Paul et al., 2013b). Surprisingly, no improvements in mobility were reported in individuals with multiple sclerosis after strength training. This finding was unexpected, as the strength training interventions in Parkinson's disease and multiple sclerosis trials, for the most part, used similar training frequencies (two-three times per week), resistance exercises (leg press, knee extension, knee flexion and calf raises) and sets per exercise (two-three). This may indicate that strength training is not capable of improving mobility in individuals with multiple sclerosis. The inability to improve mobility may be explained by the smaller improvements in strength observed in individuals with multiple sclerosis. Indeed, recent findings show that muscle strength significantly predicts

performance on mobility tasks in individuals with multiple sclerosis (Broekmans et al., 2013b). Alternatively, it is possible that the strength training interventions used in the multiple sclerosis trials were unable to provide a stimulus sufficient to improve mobility in multiple sclerosis, and perhaps more intense or specific training interventions may be required.

In addition, strength training was found to have a positive effect on disease progression in people with Parkinson's disease (Unified Parkinson's Disease Rating Scale-Version 3). Interestingly, improvements in disease progression were observed in a cohort with mild to advanced disability that were not on medication, suggesting that strength training alone, may be capable of positively impacting on disease progression in individuals at all stages of Parkinson's disease. The positive effect of strength training on disease progression may have been mediated by favourable central changes. For instance, recent evidence shows that repetitive force generation increases neuronal activation in the basal ganglia, thalamus, parietal cortex, cerebellum and motor cortex (Dai et al., 2001; Dettmers et al., 1995; Ehrsson et al., 2000; Florin et al., 2013). Furthermore, emerging evidence has shown that exercise interventions can increase regional brain volume and structural connectivity in patients with Parkinson's disease and other neurodegenerative disorders (Bonzano et al., 2014; Burciu et al., 2013; Prosperini et al., 2014b; Sehm et al., 2014). Further studies are required to confirm the latter remarks.

In multiple sclerosis trials, improvements in strength were accompanied by significant improvements in fatigue, quality of life, muscle power, maximal electromyography activity and functional capacity. The reported improvements in fatigue are of clinical interest given that 33-75% of individuals with multiple sclerosis suffer from fatigue (Berger et al., 2013; Comi et al., 2001; Freal et al., 1984). Nevertheless this finding was not surprising, given that exercise has previously been reported to improve fatigue in multiple sclerosis (Andreasen et

al., 2011). The improvements in fatigue may in part explain the benefits observed in quality of life, especially considering that fatigue is an important predictor of quality of life in people with multiple sclerosis (Amato et al., 2001; Kargarfard et al., 2012). The increases in muscle power and maximal electromyography activity are consistent with the observed improvements in strength. The reported improvements in lower limb strength, fatigue and muscle power likely contributed to the improvement in functional capacity documented by Dalgas et al (2009). Indeed, recent findings have shown that strength (Broekmans et al., 2013a), fatigue (Motl et al., 2013) and muscle power (Paul et al., 2013b) significantly influences functional capacity in individuals with multiple sclerosis and other neurodegenerative disorders.

It is important to note that most trials included in this systematic review recruited individuals with mild to moderate disability. The higher level of disability in individuals at advanced stages of Parkinson's disease or multiple sclerosis may have led researchers to only include individuals at early to middle stages of both diseases. The same level of benefits after strength training may not be possible in individuals at more advanced stages of Parkinson's disease or multiple sclerosis. Future trials assessing the effect of strength training in individuals with Parkinson's disease and multiple sclerosis with a severe level of disability are therefore warranted.

In general, the trials displayed adequate methodological quality, with PEDro scores ranging from four to eight in both diseases. The major methodological shortcomings found using the PEDro scale included a failure to report concealed allocation (criteria 3), participant blinding (criteria 5), therapist blinding (criteria 6), and outcome assessor blinding (criteria 7). It is important to acknowledge that it is often not possible to blind participants or therapists to exercise or group allocation (Foley et al., 2006). Trial scores generated using the PEDro scale may therefore underestimate the quality of evidence.

In addition to evaluating trials using the PEDro scale, we also performed a critical appraisal of specific intervention characteristics important to strength training trials. This appraisal found that specific intervention characteristics were typically well detailed, with the exception of the level of supervision and strength training intensity. The lack of data reported on the level of supervision and the intensity of strength training performed is of concern in particular, as a high level of supervision as well as an appropriate intensity of strength training is required to maximise therapeutic benefits and avoid potential injury (Dalgas et al., 2007). The poor level of reporting on strength training progression in multiple sclerosis trials is also concerning, given that modulating the progression of strength training is important to avoid injury and training plateaus (Medicine, 2013). The inadequate reporting of participant adherence in both disease populations was also worrisome, as it does not enable internal and external examination of what dose of strength training is required to maximise therapeutic benefits and avoid injury in such populations.

Based on our findings and American College of Sports Medicine guidelines, we recommend that individuals with multiple sclerosis or Parkinson's disease perform progressive sub-maximal strength training(whole body single and multi-joint resistance exercises) on at least two non-consecutive days per week for an hour under direct supervision (e.g. physiotherapist, exercise physiologist, strength and conditioning specialist) to improve muscle strength and other disease specific clinical features (Parkinson's disease: mobility and disease progression; multiple sclerosis: fatigue, quality of life, muscle power, maximal electromyography activity and functional capacity).

Limitations

Lack of consistent reporting and heterogeneity of study outcomes between trials made it difficult to draw firm conclusions beyond improvements in muscle strength with respect to the benefits of strength training for individuals with multiple sclerosis or Parkinson's disease.

3.6 CONCLUSION

Trials investigating the effect of strength training in individuals with Parkinson's disease or multiple sclerosis are in their infancy. Nevertheless, benefits in strength were found after strength training in individuals with Parkinson's disease and, to a lesser extent, in multiple sclerosis. Some evidence was also found to suggest that strength training has a positive effect on clinical disease progression and mobility in individuals with Parkinson's disease. Similarly, some evidence showed that strength training is beneficial for muscle power, maximum electromyography activity, fatigue, functional capacity and quality of life in individuals with multiple sclerosis. Additional trials employing high quality methodological designs are required to confirm and expand on these findings. Such trials may provide evidence based rationale for using strength training as a therapy for other neurodegenerative disorders such as Alzheimer's disease and Huntington's disease.

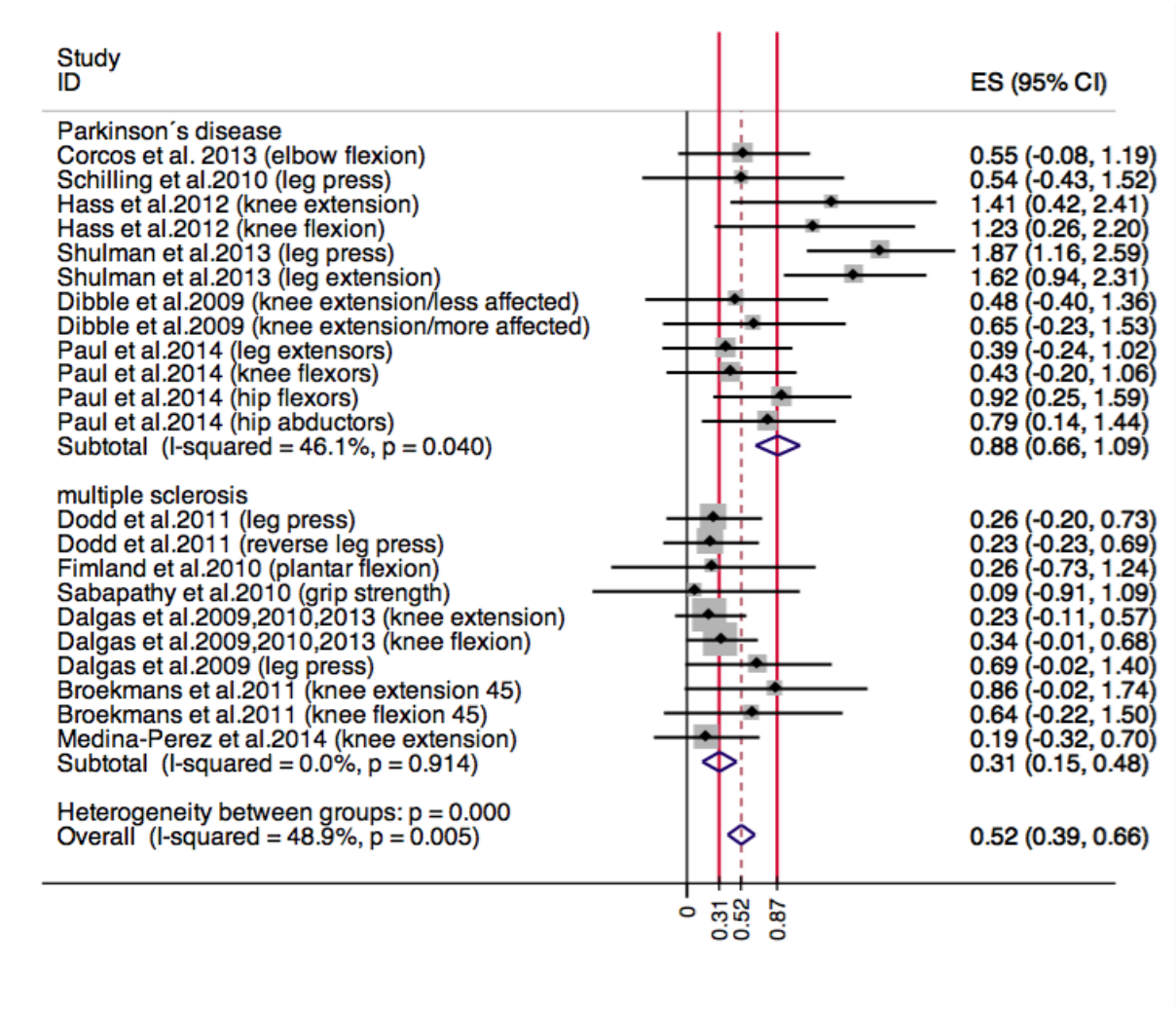

Figure 3.2 Meta-analysis of trials that measured muscle strength

3.7 CONFLICT OF INTEREST

The authors of the manuscript declare no actual or potential conflicts of interest.

3.8 ACKNOWLEDGEMENTS

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3.9 AUTHOR CONTRIBUTIONS

Mr Travis Cruickshank and Mr Alvaro Reyes contributed equally to the concept of the study, development of the search strategy analysis, analysis of the results, and writing of the manuscript. Both authors had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Professor Mel Ziman contributed to the interpretation of the results, critical revision of the article for important intellectual content, editing of the manuscript and final approval of the version to be published.

CHAPTER 4 – The Effects of Multidisciplinary Rehabilitation in Patients with Early-To-Middle-Stage Huntington's Disease: A Pilot Study

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4.1 ABSTRACT

Background

Despite advances in the understanding of Huntington's disease (HD), treatment remains symptomatic. Multidisciplinary rehabilitation, however, appears to impact disease progression. Here we show the feasibility, safety and efficacy of a nine-month multidisciplinary rehabilitation program in a small cohort of early-to-middle-stage HD patients.

Methods

Twenty HD patients were assigned to two groups, equally matched for cognitive and motor scores. One group received the intervention, whilst the other served as control. The Unified-Huntington's-Disease-Rating-Scale-Total-Motor-Score was the primary outcome measure. Neurocognitive/psychological tests, body composition, postural stability, strength and quality of life assessments were secondary outcome measures.

Results

The intervention reduced motor and postural stability deterioration, with minor improvements in depression, cognition and quality of life. Significant gains were observed for fat-free mass and strength.

Conclusion

This pilot study suggests that a prolonged multidisciplinary rehabilitation program in early-to-middle-stage HD is feasible, well-tolerated and associated with therapeutic benefit. Further explorative, larger studies are warranted.

4.2 INTRODUCTION

Huntington's disease (HD) is a neurodegenerative disorder characterised by progressive motor, behavioural and cognitive impairments. No cure or disease-modifying therapies exist (Nance, 2012), and treatment remains symptomatic. There is an urgent need, therefore, to identify therapies capable of impacting on the disease.

Multidisciplinary rehabilitation has improved gait, balance, depression, quality of life (QOL) and cognition in people with Alzheimer's and Parkinson's disease (Ellis et al., 2008; Trend et al., 2002; Wade et al., 2003), yet few studies have examined multidisciplinary rehabilitation in HD. The most extensive study to-date examined the effect of an intense, intermittent two-year program in 40 early-to-middle-stage HD patients (Zinzi et al., 2007). The program was feasible, well-tolerated and associated with positive motor benefits. Similarly, another study in HD demonstrated that 18 months of multidisciplinary care was feasible and perceived as beneficial (Veenhuizen et al., 2011).

We therefore designed and implemented a nine-month multidisciplinary rehabilitation program, and assessed the effect on motor function, cognition, depression, body composition, postural stability and QOL in a small cohort of early-to-middle-stage HD patients to evaluate its feasibility, safety and efficacy.

4.3 METHODS

4.3.1 Design

Twenty early-to-middle-stage HD patients were assigned to two equal groups based on cognitive and motor scores, with the intervention group randomly assigned. Research was conducted in accordance with the Declaration of Helsinki, with informed consent provided. Ethics approval was granted by the Human Research Ethics Committee of Edith Cowan

University and the North Metropolitan Area Mental Health Service (NMAMHS). This project was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12610000218099).

4.3.2 Participants

Participants in Perth, Australia were recruited utilising NMAMHS databases. Inclusion criteria included a positive genetic test, clinical disease diagnosis (Unified-Huntington's-Disease-Rating-Scale-Total-Motor-Score [UHDRS-TMS] ≥5), ability to follow verbal instruction and perform sub-maximal exercise. Exclusion criteria included recent substance abuse, an unstable psychiatric or medical condition, or confounding neurological conditions. Medication was adjusted by physicians where necessary. Some individuals in the intervention (I) and control (C) groups commenced new medication; anti-psychotics (I 2; C 2), anti-depressants (I 0; C 1), anxiolytics (I 1; C 2) and anti-dyskinetics (I 0; C 1).

4.3.3 Outcome Measures

The primary outcome measure was the UHDRS-TMS, performed by J.L. Secondary outcome measures, assessed over one day per timepoint, are detailed below. All assessors except occupational therapists (OTs) were blinded.

Body composition was quantified using Dual Energy X-Ray Absorptiometry (Hologic Discovery A). Postural stability/balance assessments utilised the Sensory Organisation Test (Neurocom SMART Balance Master) and the Activities-Specific Balance Confidence (ABC) Scale. Strength was assessed throughout rehabilitation. Neurocognitive/psychological tests included Symbol Digit Modalities Test (SDMT), Hopkins Verbal Learning Test-Revised (HVLT-R), D-KEFS Colour Word Interference Test and Trail Making Trials, Beck Depression Inventory-II (BDI-II). The Goal Attainment Scale (GAS) examined achievement

of patient-derived goals. QOL perceptions were evaluated using the SF-36v2 Health Questionnaire and Huntington's-Disease-Quality-of-Life-Battery-for-Carers (HDQOL-C).

4.3.4 Intervention

Following baseline data analysis, exercise physiologists and physiotherapists designed clinical and home-based exercise programs, and OTs formulated personalised patient-focused programs targeting deficits detected by psychologists.

The clinical exercise program comprised supervised group sessions (nine-months, once-weekly; 5 minute warm-up, 10 minutes aerobic exercise, 40 minutes resistance exercise, 5 minute cool-down) in an exercise clinic. A tailored, self-monitored home-based exercise program (six-months, three-times weekly) was employed after careful instruction. OT programs were provided for one hour per fortnight, for six-months.

4.4 STATISTICAL ANALYSIS

Student's independent or paired t-tests assessed continuous variables. Mann Whitney U and Fischer's Exact tests assessed ordinal variables. Results are reported as mean ± standard error of the mean (SEM), with $p<0.05$ considered significant. Effect size calculations (Cohen's *d*), performed using G*Power Software Version 3.0.10 (Faul et al., 2007), were interpreted as small (d=0.20), medium (d=0.50) or large (d=0.80).

4.5 RESULTS

Fifty-six HD patients were approached, and twenty-five volunteered to participate. Three withdrew prior to randomisation (frailty, falls, delusions) and two prior to completion (no wish to continue; I 1: C 1), with one participant transferred to the control group due to an adverse medication reaction. No statistical between-group differences existed for baseline demographics, depression, motor or cognitive assessments (Table 4.1). Participants

demonstrated high adherence to clinical exercise and OT sessions (85%), and moderate adherence to the home-based exercise program (56%). No adverse events were reported.

Rehabilitation produced a medium-large effect on UHDRS-TMS scores (Figure 4.1a), impacting on chorea (medium-large effect) and tandem walking (p=0.015) components. Significant between-group differences were observed for fat mass, fat-free mass, lower/upper body strength, written errors (SDMT) and for the walking-up-and-down-stairs component of the ABC-UK, with a large effect for the walking-around-the-house component (Table 4.1; Figure 4.1b-d). Small-to-medium effects were noted for D-KEFS, HVLT-R, BDI-II, QOL and postural stability (Table 4.1; Figure 4.1). GAS revealed partial or complete achievement of goals in 7 of 9 intervention participants.

Table 4.1 Participant Characteristics (n; I=9; C=11).

Variable	Intervention		Control		*p*
Demographics					
Age (Years)	53.8 ±2.9		52.2 ±2.6		>0.05
CAG (n)	43.1 ±1.1		43.7 ±0.7		>0.05
CAG Index	399.0 ±53.7		416.1 ±23.3		>0.05
Body composition	**Baseline**	**Final**	**Baseline**	**Final**	***p***
Fat-Free Mass (kg)	52.1 ±3.9	53.4 ±4.2	55.4 ±3.2	54.6 ±2.9	0.047
Fat Mass (kg)	21.6 ±2.5	22.5 ±2.6	21.9 ±2.6	20.4 ±2.6	0.014
Total Mass (kg)	73.7 ±4.6	75.8 ±5.0	77.3 ±3.8	75.0 ±3.3	0.017
Body Mass Index (kg/m^2)	26.2 ±1.3	26.9 ±1.4	27.1 ±1.3	26.7 ±1.3	0.070
Bone Mineral Density (g/cm^3)	1.1 ±0.0	1.1 ±0.0	1.1 ±0.0	1.1 ±0.0	>0.05
SDMT					
Written Correct Incorrect	 30.0 ±4.9 2.6 ±0.8	 27.4 ±3.9 1.2 ±0.3	 25.4 ±3.3 0.6 ±0.3	 23.3 ±2.8 1.4 ±0.6	 >0.05 0.042
Oral Correct Incorrect	 35.8 ±5.4 3.0 ±0.9	 30.8 ±5.3 2.1 ±0.8	 25.9 ±3.2 5.6 ±5.0	 28.0 ±3.4 1.0 ±0.4	 >0.05 >0.05
HVLT-R					
Total Recall	19.2 ±1.8	16.3 ±2.6	14.3 ±1.7	14.7 ±1.6	>0.05
Delayed Recall	5.9 ±0.7	5.8 ±1.3	5.4 ±0.7	4.5 ±0.7	>0.05
Retention	80.3 ±7.7	75.9 ±10.8	85.3 ±5.9	68.7 ±10.1	>0.05
RDI	8.3 ±0.9	7.3 ±1.3	7.3 ±0.9	7.9 ±1.0	>0.05
D-KEFS					
TMT					
Visual Scanning	34.3 ±5.3	43.2 ±6.7	31.4 ±3.5	36.8 ±4.2	>0.05
Number Sequencing	55.6 ±6.2	63.8 ±9.6	59.9 ±5.8	57.5 ±7.7	>0.05
Letter Sequencing	67.9 ±14.0	71.0 ±14.3	78.2 ±17.0	65.2 ±11.3	>0.05
Number/Letter Switching	150.4 ±21.7	144.3 ±27.8	192.0 ±27.1	122.2 ±17.9	>0.05
Motor Speed	54.1 ±9.4	61.4 ±11.2	69.5 ±11. 8	60.8 ±7.7	>0.05
CWIT					
Colour Naming	46.6 ±6.7	50.63 ±8.2	42.8 ±4.4	47.8 ±5.8	>0.05
Word Reading	33.8 ±3.8	33.25 ±4.1	30.2 ±3.1	29.9 ±3.7	>0.05
Inhibition	90.9 ±16.9	90.9 ±17.0	87.3 ±7.0	86.2 ±8.1	>0.05
BDI-II	10.8 ±3.2	5.6 ±1.6	12.9 ±2.6	10.0 ±2.5	>0.05
ABC-UK					
Walking around the house Walking up or down stairs	81.1 ±8.7 63.3 ±12.9	87.1 ±6.0 72.7 ±12.6	81.4 ±5.9 71.8 ±8.2	75.6 ±9.6 63.3 ±13.4	0.077 0.024

ABC-UK, Activities-specific Balance Confidence Scale; BDI-II, Beck depression Inventory-II; CAG, cytosine-adenine-guanine; CWIT, Colour Word Interference Test; D-KEFS, Delis-Kaplan Executive Function System; HVLT-R, Hopkin's Verbal Learning Test-Revised; RDI, Recognition Discrimination Index; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Trials.

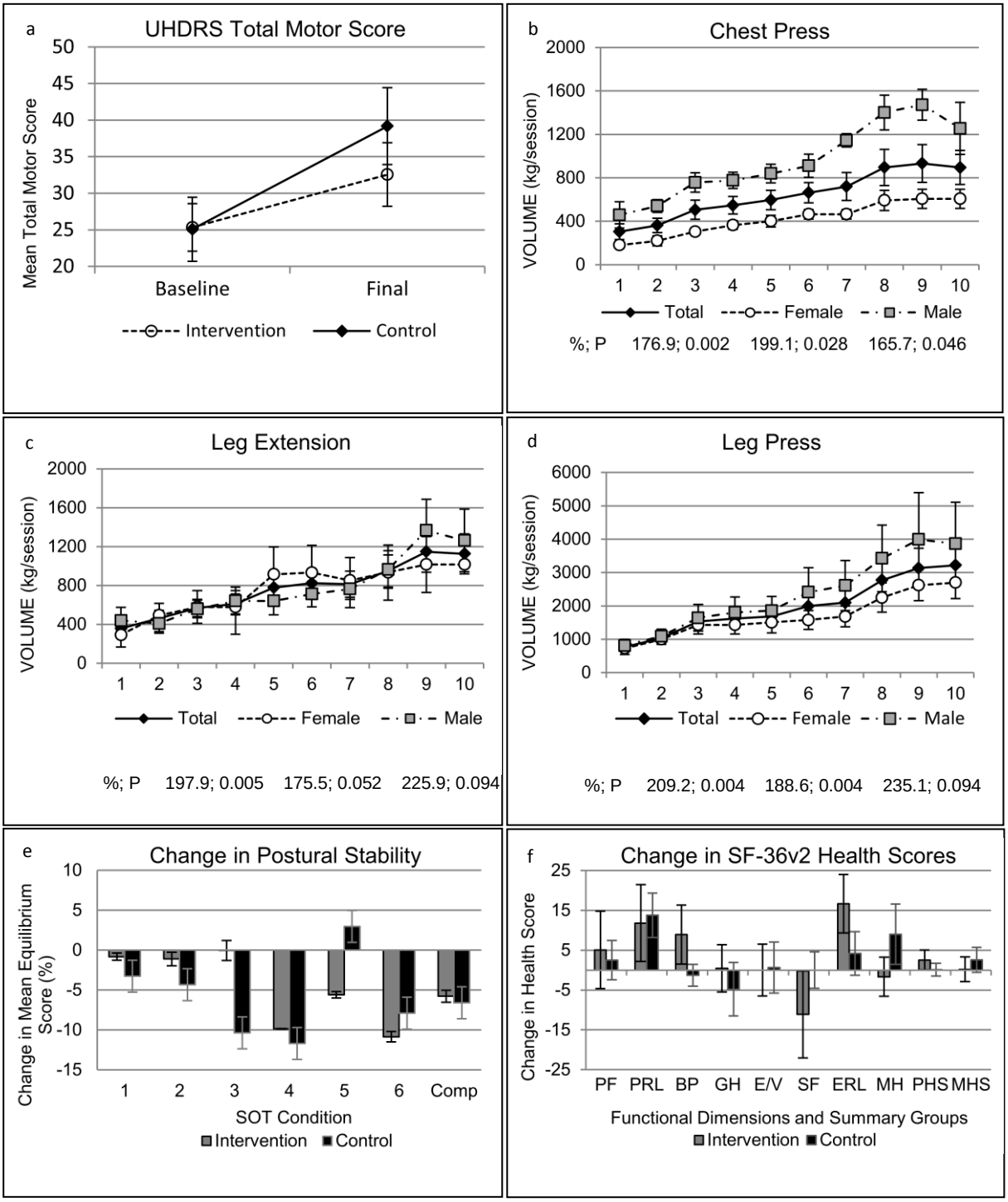

Figure 4.1 (a-f) Changes to clinical outcomes after multidisciplinary rehabilitation

a) Unified-Huntington's-Disease-Rating-Scale-Total-Motor-Score at baseline and final assessment (n; I=9; C=11); b-d) Strength outcomes for upper and lower body (n; I=9; C=11); values are shown for the intervention group as a whole, and for female and male sub-groups to indicate gender response. Percentage of overall change (%) and statistical significance (*p*) from commencement of maximal training (point 3) to final assessment are also indicated; e) Changes in postural stability at final assessment relative to baseline (n; I=9; C=11); f) Changes in SF-36v2 health scores at final assessment relative to baseline (n; I=9; C=11).

4.6 DISCUSSION

This pilot study demonstrates the feasibility and safety of a nine-month multidisciplinary rehabilitation program in twenty HD patients. Relative to control subjects, intervention recipients exhibited reduced motor and postural stability deterioration, and significant increases in fat-free mass and strength. Strength improvements have not been reported to-date, perhaps because previous programs spanned only eight weeks (Khalil, 2012). The minimal impact on cognitive outcomes observed here may be obscured by lack of sensitivity of testing procedures, normally requiring large sample sizes (Stout et al., 2012). Changes in QOL perceptions reflected functional outcomes.

Although positive**,** the pilot study has significant limitations, including lack of long-term follow-up (precluding examination of a carry-over effect on cessation), limited sample size, and low frequency of supervised rehabilitation, optimally requiring two-three sessions per week. Assessment tools may also lack sensitivity to detect subtle changes.

In conclusion, we demonstrate that early-to-middle-stage HD patients can successfully participate in prolonged multidisciplinary rehabilitation as an adjunct to medication and further explorative, larger studies are warranted. Encouragingly, despite the small sample size and low exercise frequency, small improvements were detected. Future studies would benefit from more frequent rehabilitation, including a high-intensity aerobic component (Baker et al., 2010) to maximise cognitive improvements.

4.7 ACKNOWLEDGEMENTS

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CHAPTER 5 The Impact of Multidisciplinary Rehabilitation on Muscle Mass and Motor Function in Individuals with Huntington's disease

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5.1 ABSTRACT

Background: Progressive neurological dysfunction with secondary muscle wasting and weakness is a physically disabling trait of Huntington's disease (HD) that contributes to impairments in functional capacity. Preliminary evidence suggests that multidisciplinary rehabilitation is useful for treating impairments in functional capacity and therapeutically addressing body composition abnormalities in individuals with manifest HD. Resistance exercise also appears helpful for increasing muscular strength and lean tissue mass in other neurodegenerative disorders. The purpose of this study was to evaluate the utility of a multidisciplinary rehabilitation intervention encompassing resistance exercise on muscle wasting and weakness and related functional impairments in individuals with HD.

Methods: Twenty-two participants with manifest HD were recruited and randomly assigned to an intervention or control group. Participants in the intervention group were provided with a nine month multidisciplinary rehabilitation intervention, while those in the control group maintained their usual care. Participants were assessed using muscle wasting (loss of lean tissue mass), lower extremity muscle strength, balance and mobility measures before and after the trial. Paired t-tests were used to examine changes within each group for muscle wasting, lower extremity muscle strength, balance and mobility measures. Unpaired t-tests were used to examine changes in relative values between groups for muscle wasting, lower extremity muscle strength, balance and mobility measures.

Results: Significant increases in muscle strength in the knee extensors and flexors were found in the intervention group. The intervention group also displayed significantly greater lean tissue mass than the control group after multidisciplinary rehabilitation. Furthermore, a significant deterioration in mobility was observed in the control group, whereas the

intervention group showed no such changes. There were no significant changes in balance in either group.

Conclusions: Multidisciplinary rehabilitation is useful for improving muscular strength in the lower extremities as well as preserving lean tissue mass and mobility in manifest HD.

Trial Registration: This study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12610000218099)

Keywords: balance, mobility, muscle strength, muscle mass, Huntington's disease

5.2 BACKGROUND

Huntington's disease (HD) is a chronic neurodegenerative disorder of the nervous system. Over the course of the disease individuals suffer from progressive neurological deficits leading to secondary muscle wasting (Kosinski et al., 2007; Turner et al., 2007) and weakness (Busse et al., 2008; Kosinski et al., 2007). The development of these clinical features contributes to functional impairments (Cruickshank et al., 2014), a reduced quality of life (Ho et al., 2009) and nursing home placement (Rao et al., 2005).

Muscular wasting has been described previously in patients and rodent models of HD (Aziz and Roos, 2013; Ribchester et al., 2004; Sanberg et al., 1981). The mechanisms underpinning it are not yet clear, however lifestyle passivity, mitochondrial dysfunction (Rivera-Sánchez et al., 2014), transcriptional dysregulation (Luthi-Carter et al., 2002a; Strand et al., 2005) and myocyte defects (van der Burg et al., 2009) are thought to be the primary aetiological factors. Muscular wasting and associated weakness, particularly in the lower extremities (Busse et al., 2008; Kosinski et al., 2007), contributes to impairments in functional capacity (Cruickshank et al., 2014).

Recent evidence from our group shows that muscular weakness in the lower extremities contributes to impairments in balance and mobility in individuals with manifest HD (Cruickshank et al., 2014). Similar findings have been reported in individuals with other neurodegenerative disorders (Broekmans et al., 2013a; Paul et al., 2013b). In particular, Paul et al (Paul et al., 2013a; Paul et al., 2013b) showed that muscle weakness in the lower extremities contributes to impaired balance and mobility as well as falls in individuals with Parkinson's disease (PD). Furthermore, Broekmans et al (Broekmans et al., 2013a) showed that lower extremity muscle strength is a significant predictor of walking capacity in individuals with multiple sclerosis.

Therapeutic strategies that positively impact on muscle weakness/mass and the underlying aetiological mechanisms may favourably impact on functional capacity in individuals with HD. Accumulating evidence suggests that multidisciplinary rehabilitation is a useful therapeutic approach for treating functional impairments that present in HD. For example, Zinzi et al (2007) reported improvements in balance and mobility in a small sample of individuals with HD after twelve months of intensive, intermittent, multidisciplinary rehabilitation. More recently, Piira et al (2013) found improvements in mobility, balance, mood and quality of life after twelve months of intensive tri-monthly multidisciplinary rehabilitation. Finally recent work by our group has shown that weekly multidisciplinary rehabilitation over nine months favourably impacts on weight loss and adipose tissue loss in individuals with manifest HD (Thompson et al., 2013). When assessed separately, resistance exercise has been shown to increase lean tissue mass and muscular strength in individuals with multiple sclerosis and PD (Dalgas et al., 2009; Dalgas et al., 2010b; Dibble et al., 2006; Shulman et al., 2013). Multidisciplinary rehabilitation interventions encompassing resistance exercise may therefore be useful for treating muscular wasting and weakness as well as related functional impairments in individuals with HD.

The objective of this study was to evaluate the utility of a nine month multidisciplinary rehabilitation intervention, encompassing resistance exercise, on lean tissue mass, muscle strength, balance and mobility in individuals with manifest HD.

5.3 METHODS

5.3.1 Study design

The present study was a nine month randomised controlled pilot trial. A simple randomisation procedure was used to assign participants to an intervention or a control group, using computer generated random numbers. Participants in the intervention group were

provided with a nine month multidisciplinary rehabilitation intervention, while participants in the control group were asked to maintain their usual care throughout the trial. After the trial, participants in the control group were provided with the same nine month multidisciplinary rehabilitation intervention for ethical purposes. Both groups were tested at baseline (pre-trial) and after nine months (post-trial) using lean tissue mass, lower extremity muscle strength, mobility and balance measures.

5.3.2 Study approval, registration, and patient consent

Ethical approval was granted by the Human Research Ethics Committees at Edith Cowan University and North Metropolitan Area Mental Health Service (NMAMHS). Written informed consent was provided by all study participants. This study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12610000218099).

5.3.3 Participants

Potential participants were identified using the Neuroscience Unit database of the North Metropolitan Area Mental Health Service (NMAMHS). Inclusion criteria included a family history of HD, a positive genetic test for the HD mutation (CAG >39), manifest disease (Unified Huntington's Disease Rating Scale-Total Motor Score [UHDRS-TMS] ≥5), the capacity to follow written or verbal instruction, the ability to perform sub-maximal aerobic and resistance exercise and aged 18 years or older. Participants were excluded if they had recent drug or alcohol abuse, possessed a confounding neurological condition or concomitant physical condition which was a contraindication for exercise.

5.3.4 Multidisciplinary rehabilitation intervention

The trial intervention was designed following baseline assessment by physical therapists, exercise physiologists and occupational therapists. The intervention was designed to target

muscular wasting and weakness in the lower extremities as well as balance and mobility. The intervention comprised a clinical exercise program, home based exercise program and fortnightly occupational therapy. The clinical exercise program consisted of once weekly aerobic and resistance exercise for an hour in a clinical exercise centre. The home-based exercise program (to be performed thrice weekly) consisted of muscle strengthening and fine motor exercises. The home-based exercise program was only provided to participants after careful instruction and familiarisation. Occupational therapy consisted of cognitive and functional exercises designed to enhance cognitive and functional independence (see Supplementary Tables 5.4, 5.5 and 5.6).

5.3.5 Study procedures

Participants were examined by formally trained assessors. The same assessors were used at baseline and at the nine month assessment time point to ensure the reliability of collected data. All assessors were blinded to group allocation.

5.3.6 Outcome measures

Lean tissue mass

Total lean tissue mass was quantified to evaluate muscle wasting using dual-energy X-ray Absorptiometry (Hologic, Inc, Waltham, MA)(Goodman and Barker, 2011; Thompson et al., 2013).

Lower extremity muscle strength

Maximum voluntary contraction of knee flexors and extensors was examined using isokinetic and isometric strength test protocols with automated dynamometry (Biodex Medical Systems, Shirley, NY, USA). Automated dynamometry has been previously shown to be a reliable measure of muscle strength changes in people with neurodegenerative disorders (Dalgas et

al., 2009). Prior to testing, participants were comfortably seated and safely secured using two padded chest straps and one padded waist strap. Additional straps were placed just above the knee and ankle to secure the tested limb and restrict extraneous movement. Once securely seated, participants were positioned with their lateral condyle aligned with the dynamometers axis of rotation. Participants were then instructed to perform three sub-maximal isokinetic extension and flexion contractions at 30%, 50% and 70% of their perceived maximum voluntary contraction (MVC). Isokinetic and isometric muscle strength testing was performed shortly after the individuals performed the sub-maximal contractions. Isokinetic muscle strength protocols examined knee extensor (KE) and knee flexor (KF) and muscle strength at $180°\cdot s^{-1}$ (fast) and $30°\cdot s^{-1}$ (slow) velocities. Isometric knee extensor and flexor muscle strength was also examined at 60° of knee flexion. Each individual performed three contractions per test, with one minute separating each testing protocol. The average of the two highest values recorded was used for statistical analysis.

Mobility

Changes to fast and self-paced walking were examined using the 10 m Timed Walk Test (Quinn et al., 2013). Fast-paced walking was also examined using the 4 m Timed Walk Test. Time was recorded for both tests using a standard stopwatch. Walking endurance was assessed using the 6 Minute Walk Test (Quinn et al., 2013). The total distance travelled for the 6 Minute Walk Test was recorded using a trundle wheel. These measures were specifically chosen as they have previously been documented to be reliable measures of mobility performance in people with manifest HD (Khalil et al., 2010; Quinn et al., 2013).

Balance

Changes to dynamic and static balance were assessed using the Berg Balance Scale (BBS) and the 10 repetition Chair Stand Test (CST) (Khalil et al., 2010; Quinn et al., 2013). Time

taken to complete the CST was recorded using a standard stopwatch. Participants performed two trials for each assessment. These measures were specifically chosen as they have previously been documented to be reliable measures of mobility performance in people with manifest HD (Khalil et al., 2010; Quinn et al., 2013).

5.4 STATISTICAL ANALYSIS

Changes within each group for lean tissue mass, lower extremity muscle strength, mobility and balance outcomes were examined using a paired t-test. An unpaired t-test was used to assess relative changes in lean tissue mass, muscle strength, mobility and balance between groups. Relative changes were calculated as the mean difference between pre-trial and post-trial values. Data are presented as mean and standard deviations. Statistical examination of the data was performed with STATA version 9.1 (Stata Corp, 4905 Lakeway Dr, Texas 77845 USA).

5.5 RESULTS

Between January 2010 and May 2010 sixty six individuals with manifest HD were identified and invited to participate in this research trial. Twenty five (38%) satisfied the inclusion criteria and consented to participate. Three participants (12%) withdrew prior to randomisation (due to frailty, excessive falls and delusions) and three (13.6%) before the conclusion of the trial (did not want to continue) (see Figure 5.1).

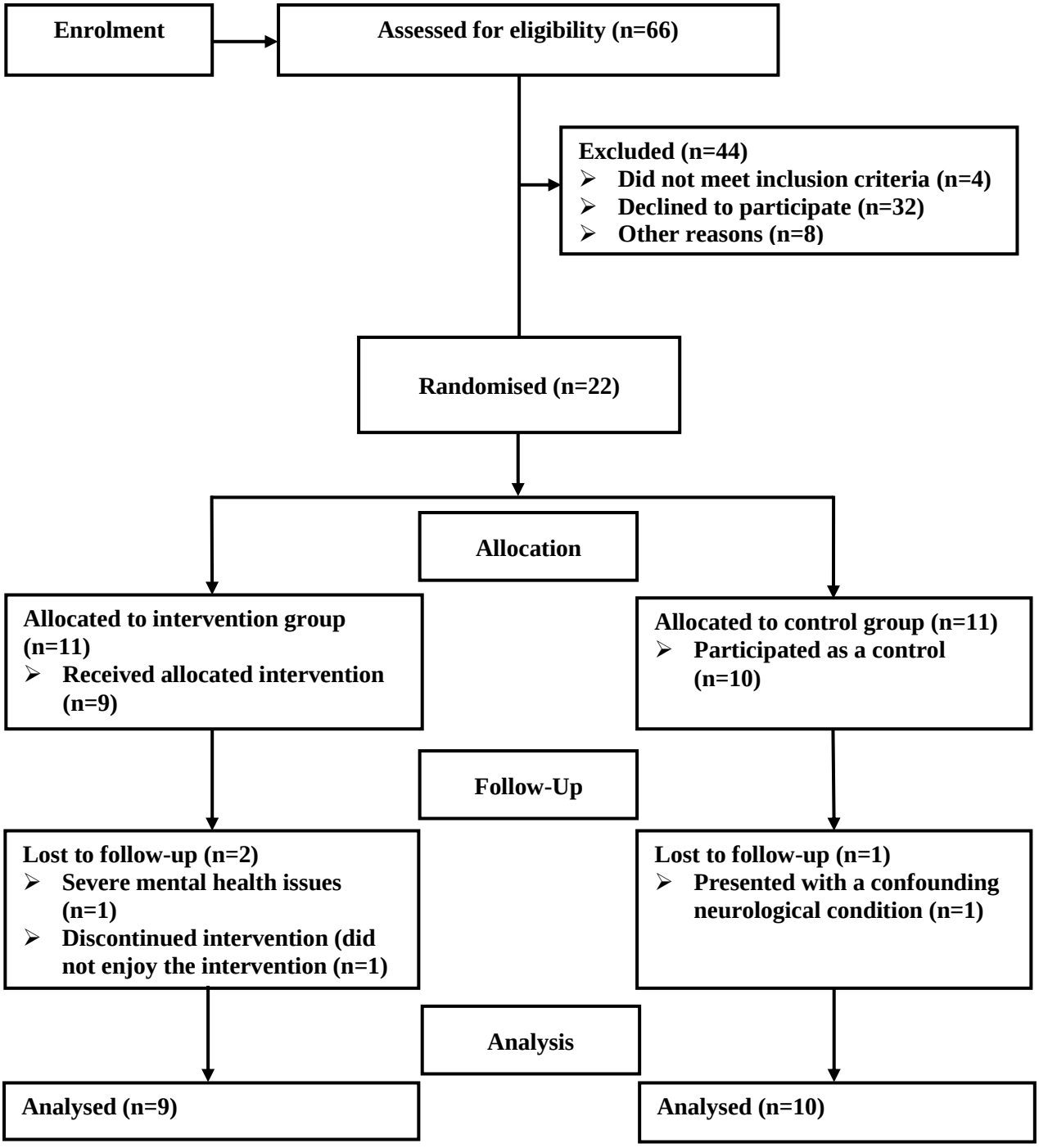

Figure 5.1 Participant recruitment and study flow

Participants in the intervention group displayed high adherence to the supervised clinical program (85%), moderate adherence to the home based program (56%), and high adherence to occupational therapy sessions (84.2%).

Table 5.1 displays demographic data and information on disease severity, disease duration, and the severity of motor abnormalities (UHDRS-TMS) in the intervention and control groups. Table 5.2 displays changes in medication and supplements throughout the study. Figure 5.2 and Table 5.3 show measures of lean tissue mass, muscular strength in the lower extremities and balance and mobility before and after the trial and relative changes in these values. There were no significant differences between groups at baseline for demographics, disease severity, disease duration, severity of motor abnormalities or for any of the recorded outcome measures.

Table 5.1 Participant demographics at baseline (Mean ± SD)

Variable	Intervention group	Control group	*p* value
No. (M/F)	9 (4/9)	10 (6/4)	
Age (years)	53.77 ± 8.56	50.80 ± 7.81	NS
CAG (n)	43.11 ± 3.25	44.1 ± 1.96	NS
Disease Burden Score	399.40 ± 161.33	428.20 ± 71.57	NS
UHDRS-TMS	24.88 ± 13.56	25.20 ± 12.29	NS

CAG (n), cytosine-adenine-guanine expansion; UHDRS-TMS, Unified Huntington's Disease Rating Scale-Total Motor Score; NS, not significant

Table 5.2 Participant medication and supplements throughout the study

Participants	Trial	Active Follow-up
Intervention Group		NA
Participant 1	Fish Oil	NA
Participant 2	-	NA
Participant 3	Aripiprazole, Amantadine, Citalopram, Olanzapine	NA
Participant 4	Folate, Activated B3, Multivitamins, CoQ10	NA
Participant 5	Haloperidol, Paroxetine, Atorvastatin	NA
Participant 6	Olanzapine, Escitalopram, Fish Oil, Vitamin D, Zimtat	NA
Participant 7	Aripiprazole, Escitalopram	NA
Participant 8	Tetrabenazine, Fluoxetine	NA
Participant 9	Atorvastatin, Aspirin, Prazosin	NA
Control Group		
Participant 10	Telmisartan, Clonazepam, Olanzapine, Amantadine, Omega 3	Telmisartan, Vesicare, Amantadine, Clonazepam, Olanzapine, Mirtazapine
Participant 11	Venlafaxine, Mirtazapine, Dimebon, Olanzapine	Venlafaxine, Mirtazapine, Olanzapine
Participant 12	Pariet, Mirtazapine, Olanzapine, Escitalopram, Benzhexol, Varenidine Tartrate	Aripiprazole, Olanzapine, Mirtazapine, Pariet, Escitalopram, Nitrazepam
Participant 13	Escitalopram, Olanzapine, Megafolate, CoQ10	Escitalopram, Olanzapine, Megafolate, CoQ10
Participant 14	Thyroxine, Escitalopram, Olanzapine, Multivitamins	Thyroxine, Escitalopram, Olanzapine, Multivitamins, Simvastin
Participant 15	Mirtazapine, Thyroxine	Mirtazapine, Escitalopram, Aripiprazole, Lorazepam, Iron tables
Participant 16	Olanzapine, Citalopram, Mirtazone	Olanzapine, Citalopram, Mirtazone
Participant 17	Escitalopram, Olanzapine, Propranolol	Aripiprazole, Neurontin
Participant 18	Setraline	Setraline
Participant 19	Cadesartan Cilexitil	-

NA, not applicable

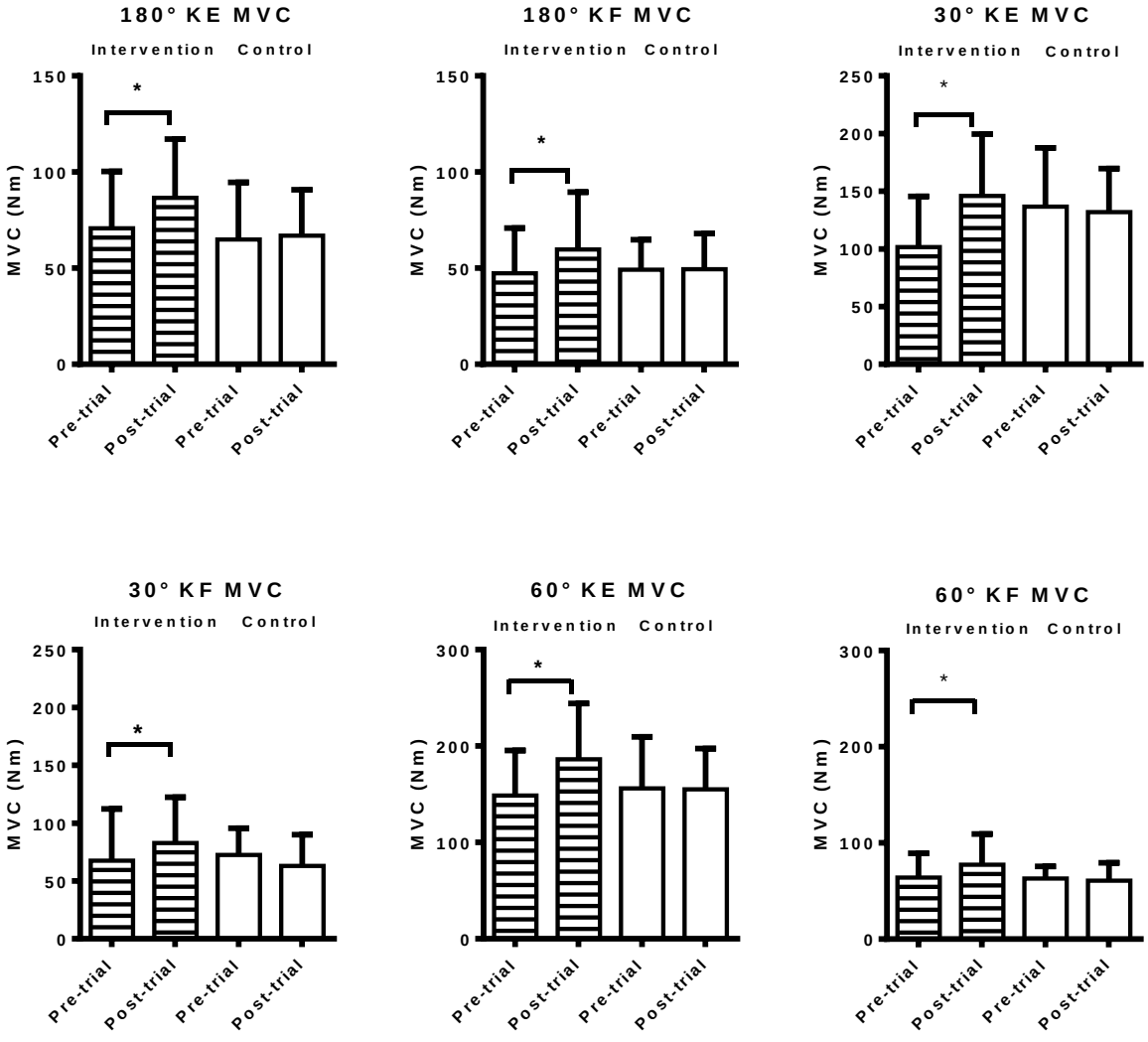

Figure 5.2 Changes in lower extremity muscle strength in individuals with manifest HD

The effects of nine months of multidisciplinary rehabilitation on changes in maximum voluntary contraction (MVC) muscle strength in the knee extensors (KE) and knee flexors (KF) of individuals with manifest HD. * Indicates significant differences in muscle strength between baseline and post-intervention.

Table 5.3 Changes (mean SD) in lean tissue mass, balance and mobility after nine months of multidisciplinary rehabilitation in the intervention and control group

	Intervention Group (n=9)			**Control Group (n=11)**		
	Pre-trial	**Post-trial**	***p* value**	**Pre-trial**	**Post-trial**	***p* value**
Lean tissue mass	49763.16 ± 11223.87	51034.46 ± 12210.80	0.066	53885.72 ± 10387.53	52248.34 ± 10387.53	0.060
BBS	46.88 ± 9.15	48.11 ± 8.76	0.326	44.9 ± 7.35	44.8 ± 6.35	0.484
CST	28.07 ± 13.16	27.33 ± 11.85	0.427	32.40 ± 12.55	32.00 ± 18.95	0.435
10 m TWT (SP)	8.37 ± 3.68	8.35 ± 4.06	0.472	8.02 ± 1.92	8.61 ± 1.72	0.111
10 m TWT (FP)	6.49 ± 4.38	7.10 ± 3.61	0.187	6.14 ± 1.36	7.09 ± 2.43	0.050*
4 m TWT	3.46 ± 2.53	2.97 ± 1.39	0.134	2.79 ± 0.86	3.35 ± 1.18	0.001*
6MWT	474.37 ± 169.59	449.37 ± 145.68	0.079	443.50 ± 101.62	391.50 ± 132.05	0.024*

BBS, Berg Balance Scale; CST, Chair Stand Test; TWT (SP), Timed Walk Test (self-paced), TWT (FP), Timed Walk Test (fast-paced), 4 m TWT, Four Meter Timed Walk Test, 6MWT, Six Minute Walk Test

5.5.1 Effects of multidisciplinary rehabilitation

Changes to lean tissue mass

Table 5.3 displays relative changes in lean tissue mass during the trial. There were no significant changes to lean tissue mass within each group after the nine month trial, however an examination of the relative changes in lean tissue mass between groups revealed that the intervention group had significantly greater lean tissue mass after the intervention than the control group (intervention group: 1271.30g ± 2275.05g; control group: -1637.38g ± 3024.08g; p=0.015).

Changes in maximal lower extremity muscle strength

Figure 5.2 displays changes in maximal lower extremity muscle strength. Knee extensor muscle strength increased significantly at slow (43.4% p=0.000) and fast velocities (22.3% p=0.040) in the intervention group, whereas it remained relatively unchanged in the control group (slow velocity, -3.5% p>0.05; fast velocity, 3.02% p>0.05). Individuals in the intervention group also displayed increases in knee flexor muscle strength at slow (22.7%; p=0.056) and fast velocities (26.19%; p=0.027). By contrast, knee flexor muscle strength decreased or remained unchanged at slow (-13.5%; p>0.05) and fast velocities (0.04%; p>0.05) in the control group. Increases in isometric muscle strength in the knee extensors (25.3%; p=0.000) and flexors (21.09%; p=0.025) were also found in the intervention group, while the control group displayed a slight decrease in isometric knee extensor (-0.07%; p>0.05) and flexor (-3.36%; p>0.05) muscle strength. An examination of changes in isokinetic and isometric knee extensor and flexor muscle strength between groups showed that the intervention group had significantly greater muscle strength than the control group after nine months of multidisciplinary rehabilitation [KE 180˚ (intervention group: 17.20 Nm ± 19.82 Nm) vs (control group: 1.95 Nm ± 11.23 Nm) p=0.025; KF 180˚ (intervention group:

12.00 Nm ± 16.10 Nm) vs (control group: 0.20 Nm ± 8.46 Nm) p=0.029; KE 30˚ (intervention group: 44.21 Nm ± 18.33 Nm) vs (control group: -4.66 Nm ± 21.17 Nm) p=0.000; KF 30˚ (intervention group: 20.65 Nm ± 21.35 Nm) vs (control group: -3.52 Nm ± 7.57 Nm) p=0.001; KE 60˚ (intervention group: 37.66 Nm ± 19.05 Nm) vs (control group: -1.17 Nm ± 22.79 Nm) p=0.000; KF 60˚ (intervention group: 17.92 Nm ± 18.32 Nm) vs (control group: -2.05 Nm ± 13.79 Nm) p=0.007].

Changes to mobility

Changes in mobility for both groups are displayed in Table 5.3. There were no significant changes in the 10 m Timed Walk Test, 4 m Timed Walk Test or 6 Minute Walk Test mobility measures in the intervention group during the trial period. In contrast, the control group displayed a significant deterioration on the 6 Minute Walk Test (13.2%), the fast-paced component of the 10 m Timed Walk Test (13.3%) and the 4 m Timed Walk Test (16.7%) after nine months. An analysis of the relative changes between groups revealed that the intervention group performed significantly better than the control group on the 4 Meter Timed Walk Test after nine months [(intervention group -0.49s ± 1.96s) vs (control group 0.56s ± 1.02s) p=0.011].

Changes to balance

Changes to balance for both groups are shown in Table 5.3. There were no significant changes in balance within or between groups throughout the study.

5.6 DISCUSSION

This study showed that multidisciplinary rehabilitation is useful for increasing muscular strength in the lower extremities. In addition this study showed that multidisciplinary

rehabilitation favourably impacts on lean tissue mass and mobility in individuals with manifest HD.

Previous studies have shown that muscular strength in the lower extremities is significantly reduced in individuals with manifest HD (Busse et al., 2008). Here we show that muscular strength is remediable to multidisciplinary rehabilitation. Specifically, we found that muscle strength in the knee flexors and extensors was significantly increased after multidisciplinary rehabilitation. The observed increases in lower extremity muscle strength are encouraging, especially considering that muscle weakness in the lower limbs contributes to balance and mobility problems in HD (Cruickshank et al., 2014). Increases in muscle strength may be attributed to the resistance exercise component of the intervention in this study. Studies of resistance exercise in other neurodegenerative disorders have consistently reported increases in muscle strength (Corcos et al., 2013; Dalgas et al., 2009; Dalgas et al., 2010b; Shulman et al., 2013). Taken together these results collectively suggest that interventions encompassing resistance exercise should be considered for improving muscle strength in individuals with HD and other neurodegenerative disorders.

Muscle wasting is a well-documented feature of HD that is not amenable to drug therapy (Aziz and Roos, 2013; van der Burg et al., 2009). In this study, multidisciplinary rehabilitation was found to favourably impact on lean tissue mass. Despite no baseline differences, the intervention group illustrated significantly greater lean tissue mass after the intervention when compared to the control group. This finding extends our previous work, where significant increases in body weight and fat mass were found following multidisciplinary rehabilitation (Thompson et al., 2013). The favourable effect of multidisciplinary rehabilitation on lean tissue is most likely attributable to the resistance exercise component of the intervention. Indeed there is some literature showing that resistance exercise increases muscle mass in the elderly (McCartney et al., 1995; Yarasheski

et al., 1999; Yarasheski et al., 1993) and in those with multiple sclerosis and Parkinson's disease (Dalgas et al., 2010b; Dibble et al., 2006). These results suggest that resistance exercise may be a useful therapeutic strategy for addressing muscle wasting in individuals with HD as well as for other neurodegenerative disorders.

Similar to earlier investigations, we found that multidisciplinary rehabilitation had a favourable effect on mobility in individuals with manifest HD (2013; Zinzi et al., 2007). In particular, we found that mobility was preserved in individuals in the intervention group, whereas it deteriorated in individuals in the control group. This finding confirms earlier exploratory findings by Piira et al (2013) and Zinzi et al (2007), who reported improvements in mobility after a twelve and twenty-four month intensive intermittent multidisciplinary rehabilitation intervention. Collectively, these findings suggest that multidisciplinary rehabilitation is a useful strategy for improving mobility in individuals with manifest HD.

In contrast to previous work (2013; Zinzi et al., 2007), we did not find any evidence to support the use of multidisciplinary rehabilitation for balance problems in individuals with manifest HD. Specifically, we found that balance was unchanged in the intervention group and the control group at the conclusion of the study. The short duration of the current intervention compared with previous studies may have accounted for our inability to find significant changes in balance in the current sample of individuals with HD. Moreover, the lack of formalised balance training in our intervention, unlike previous studies (2013; Zinzi et al., 2007), may have accounted for our inability to also see any such improvements. Formalised balance training may be necessary to improve balance in people with HD.

The present study is not without limitations. Our findings were collected from a relatively small sample of individuals with manifest HD. In addition, individuals remained on

medication throughout the study, which may have influenced some of the favourable effects associated with this multidisciplinary rehabilitation intervention.

5.7 CONCLUSIONS

This study provides preliminary evidence that multidisciplinary rehabilitation is an effective treatment strategy for increasing muscular strength in the lower extremities and favourably impacts on muscular mass and mobility in individuals with manifest HD. We recommend larger controlled trials to confirm the therapeutic utility of multidisciplinary rehabilitation as an adjunct treatment approach for reduced muscle strength, muscle wasting and mobility problems in individuals with HD.

5.8 ACKNOWLEDGEMENTS

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5.9 SUPPLEMENTARY DATA

Supplementary Table 5.4 Clinical exercise program

Exercise Mode	Exercises Utilised	Multi/Single Joint Exercises	Duration	Intensity	Progression
Active Warm Up	Walking (Treadmill) Cycling (Ergometer) Step ups	Not Applicable	3-5 minutes	40-60%	Increase warm up intensity Decrease recovery period
Aerobic Exercise	Walking (Treadmill) Cycling (Ergometer)	Not Applicable	8-10 minutes	60-80%	Increase intensity % (cadence/ resistance)
Resistance Exercise	Leg Press	Multi-joint	40 minutes	60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Knee Extension	Single-joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Knee Flexion	Single-joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Leg Abduction/ Adduction	Single-Joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Lat Pull Down	Multi-joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Supported Row	Multi-joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Chest Press	Multi-joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Abdominal Crunches	Single-Joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (additional weight)
Cool Down	Walking (Treadmill) Cycling (Ergometer)	Not Applicable	3-5 minutes	40-60%	Not Applicable

Abbreviations: Reps= Repetitions

Supplementary Table 5.5 Home-based exercise program

Exercise Mode	Exercises Utilised	Multi/Single Joint Exercise	Duration	Progression
Fine Motor	Laser tracing Button tying Speed/Accuracy trade-off	Not Applicable	15 minutes	Increase the difficulty of objects traced Increase the number and vary the size of the buttons tied Decrease shape size in the speed/accuracy trade-off tasks
Resistance Exercise	Knee Extension/Flexion	Single Joint	45 minutes	Increase resistance (Sanctbands)
	Wall Push	Multi-joint		Progress to push-ups on knees and then to full ROM push-ups
	Leg Abduction/ Adduction	Single-joint		Increase resistance (Sanctbands)
	Row	Multi-joint		Increase resistance (Sanctbands)
	Abdominal Crunches	Single-joint		Increase time in eccentric and concentric contraction phases

ROM, range of motion

Supplementary Table 5.6 Occupational therapy program

Exercise Modality	Tasks Utilised	Progression
Daily Activities	Cooking	Increase difficulty of cooking
	Laundry	Perform laundry without cues
	Gardening	Increased gardening to an independent state
	Eating	Improve the use and manipulation of eating utensils
Planning/Organisation	Utilisation of a diary (written or electronic)	Increase the number and difficulty of tasks throughout the day
	Planning social activities	
Memory	Facial Recognition	Increase the number of faces to be recognised
Problem Solving	Sudoku	Increase the difficulty of the Sudoku game
	Board Puzzles	Increased the difficulty and size of puzzle
	Boggle	Include time constraints
	Mastermind	Include time constraints

CHAPTER 6 - The Effect of Multidisciplinary Rehabilitation on Brain Structure and Cognition in Huntington's disease: an Exploratory Study

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6.1 ABSTRACT

Background

There is a wealth of evidence detailing grey matter degeneration and loss of cognitive function over time in individuals with Huntington's disease (HD). Efforts to attenuate disease-related brain and cognitive changes have been unsuccessful to date. Multidisciplinary rehabilitation, comprising motor and cognitive intervention, has been shown to positively impact on functional capacity, depression, quality of life and some aspects of cognition in individuals with HD. This exploratory study aimed to evaluate, for the first time, whether multidisciplinary rehabilitation can slow further deterioration of disease-related brain changes and related cognitive deficits in individuals with manifest HD.

Methods

Fifteen participants with manifest HD undertook a multidisciplinary rehabilitation intervention spanning nine months. The intervention consisted of once-weekly supervised clinical exercise, thrice weekly self-directed home based exercise and fortnightly occupational therapy. Participants were assessed using MR imaging and validated cognitive measures at baseline and after nine months.

Results

Participants displayed significantly increased grey matter volume in the right caudate and bilaterally in the dorsolateral prefrontal cortex after nine months of multidisciplinary rehabilitation. Volumetric increases in grey matter were accompanied by significant improvements in verbal learning and memory (Hopkins Verbal Learning-Test). A significant association was found between grey matter volume increases in the dorsolateral prefrontal cortex and performance on verbal learning and memory.

Conclusions

This study provides preliminary evidence that multidisciplinary rehabilitation positively impacts on grey matter changes and cognitive functions relating to verbal learning and memory in individuals with manifest HD. Larger controlled trials are required to confirm these preliminary findings.

Key Words

Cognition, executive function, Huntington's disease, neuropathology, rehabilitation

6.2 INTRODUCTION

Huntington's disease (HD) is a degenerative disorder of the nervous system caused by an unstable cytosine-adenine-guanine (CAG) expansion in exon 1 of the HTT gene (MacDonald et al., 1993). Despite progress, there is still no cure and available drug agents only provide partial relief of motor and psychiatric symptoms. There is, therefore, an urgent need to trial treatments that can impact on disease-related brain changes and clinical aspects of HD.

Over the last decade, parcellation and voxel based morphometry (VBM) imaging studies have shown evidence of grey matter (GM) degeneration in cortical and subcortical brain structures in HD (Dominguez et al., 2013; Georgiou-Karistianis et al., 2013a; Hobbs et al., 2011). Degeneration of GM is particularly pronounced in the striatum, commencing up to 20 years prior to clinical onset (Georgiou-Karistianis et al., 2013a; Tabrizi et al., 2013). Over the course of the disease, GM loss becomes more widespread, with atrophy also observed in frontal and occipital cortices (Dominguez et al., 2013; Tabrizi et al., 2013).

Deficits in cognitive function also arise in HD, even prior to diagnosis, presumably as a result of the neurodegenerative processes (Stout et al., 2012). In early HD, there are documented deficits in attention (Georgiou-Karistianis et al., 2012), psychomotor speed (Stout et al., 2012), working memory (Stout et al., 2012), planning and inhibition (Ho et al., 2003). In the absence of effective treatments, these deficits worsen over time, negatively impacting on functional independence and quality of life (Eddy and Rickards, 2013).

The loss of GM has been shown to correlate with a decline in cognitive performance in HD. Scahill et al (2013) have shown that loss of GM in cortical and subcortical structures significantly correlates with poorer performance on emotional recognition, working memory and odour identification tasks. Harrington et al (2014) have further shown that degeneration of fronto-striatal and fronto-parietal structures correlates with poorer performance on

attention, processing speed, verbal learning and memory and emotional recognition tasks.

Recent evidence suggests that lifestyle factors significantly influence disease-related brain and cognitive changes in HD. Bonner-Jackson et al (2013a) have shown that greater cognitive reserve (computed as the composite of innate intelligence and educational level) is associated with a slower rate of volume loss in the caudate nucleus and putamen and greater preservation of cognitive function in pre-manifest HD. Moreover, higher education status is significantly associated with a better cognitive outcome on the Unified Huntington's Disease Rating Scale (UHDRS) in manifest HD (López-Sendón et al., 2011). Finally, lifestyle passivity has been shown to significantly influence the onset of symptoms in HD (Trembath et al., 2010). Treatment strategies that enrich lifestyle may impact on disease-related brain changes and a loss of cognitive function in HD and warrant further investigation.

Previous studies have shown that environmental enrichment can preserve peristriatal structures and cognitive function in HD rodent models (van Dellen et al., 2000; Wood et al., 2010). Moreover, lifestyle interventions, such as multidisciplinary rehabilitation, have been shown to improve aspects of cognition, functional capacity, depression and quality of life (Piira et al., 2013; Thompson et al., 2013; Veenhuizen et al., 2011; Zinzi et al., 2007). When assessed separately, cognitive and motor interventions have also been reported to increase hippocampal, GM and white matter volume in the elderly and those with neurodegenerative disorders (Bonzano et al., 2014; Burciu et al., 2013; Erickson et al., 2011; Kühn et al., 2014).

The outlined findings informed our decision to evaluate the utility of multidisciplinary rehabilitation on disease-related brain changes and cognitive function in manifest HD. Specifically, we evaluated the effects of multidisciplinary rehabilitation on attenuating GM loss and associated declines in cognitive function. We hypothesised that multidisciplinary rehabilitation would increase GM volume in dorsolateral prefrontal cortex (DLPFC), striatum and hippocampus structures known to be functionally relevant to cognitive function. In

addition, we expected GM volume increases to be associated with better cognitive outcomes.

6.3 MATERIALS AND METHODS

6.3.1 Study design

The present investigation was a nine month exploratory study on the effects of multidisciplinary rehabilitation on brain structure and cognition in individuals with manifest HD. The duration of the intervention was chosen for two reasons: 1) structural changes can be detected in individuals with manifest HD after six months (Henley et al., 2006), and 2) evidence has shown that rehabilitation interventions can have favourable effects on brain structure after two weeks (Burciu et al., 2013).

6.3.2 Study approval, registration, and patient consent

Ethical approval was granted by the Edith Cowan University and North Metropolitan Area Mental Health Service (NMAMHS) Human Research Ethics Committees. Written informed consent was provided by all participants.

6.3.3 Participants

Fifteen participants with manifest HD were recruited using the North Metropolitan Area Mental Health Service Neuroscience Unit Database. Inclusion criteria included a family history of HD, a positive genetic test for the HD mutation (CAG >39), manifest disease (Unified Huntington's Disease Rating Scale-Total Motor Score [UHDRS-TMS] >5), the capacity to follow written or verbal instruction, the ability to perform sub-maximal aerobic and resistive exercise and aged 18 years or older. Participants were excluded if they suffered from recent drug or alcohol abuse, had a confounding neurological condition or concomitant physical, cardiovascular or respiratory condition which contraindicated exercise. Medication adjustments were recorded routinely throughout the trial (see Table 6.1).

Table 6.1 Participant demographics

No	Sex	CAG length	Age	Disease Duration (Years)	DBS	UHDRS-TMS	Medication (baseline)	Medication (during)
1	Male	46	57	7.6	596	45	Aripiprazole, Mirtazapine, Escitalopram	Aripiprazole Escitalopram
2	Male	42	71	9.5	461.5	59	Clonazepam, Olanzapine Amantadine, Mirtazapine	Clonazepam, Olanzapine Amantadine, Mirtazapine
3	Female	46	51	2.3	535.5	18	Venlafaxine, Mirtazapine, Olanzapine	Setraline, Creatine, CoQ10, Venlafaxine, Mirtazapine, Olanzapine
4	Male	45	47	1.8	446.5	52	Aripiprazole, Olanzapine, Mirtazapine, Escitalopram, Nitrazepam	Aripiprazole, Olanzapine, Mirtazapine, Escitalopram, Nitrazepam, Benzhexol
5	Female	46	45	4.2	472.5	36	Olanzapine, Escitalopram, CoQ10	Olanzapine, Escitalopram, CoQ10
6	Female	44	54	0.9	459	19	-	Olanzapine, Escitalopram
7	Female	41	50	0.6	275	25	Mirtazapine, Escitalopram, Aripiprazole, Lorazepam	Mirtazapine, Escitalopram, Aripiprazole, Lorazepam, Tetrabenazine, Propranolol
8	Male	44	48	1.4	408	58	Aripiprazole, Gabapentin, Escitalopram, Olanzapine	Amantadine, Clonazepam, Amantadine, Gabapentin, Pramipexole
9	Female	44	50	10.5	433.5	44	Tetrabenazine	Fluoxetine, Tetrabenazine, Actonel
10	Female	39	49	3.3	175	39	-	-
11	Male	41	61	0.9	335.5	13	-	-
12	Female	43	56	1.4	427.5	32	Haloperidol, Paroxetine	Haloperidol, Paroxetine
13	Male	41	53	17.3	297	5	CoQ10	CoQ10

14	Male	44	48	1	408	12	Escitalopram	Aripiprazole, Escitalopram
15	Male	40	68	6.7	310.5	17	Prazosin	Aripiprazole, Atenolol, Atorvastatin, Clonazepam, Clopidogrel, Quetiapine,
Summary	8M/7F	43.6 ± 2.2	52.5 ± 6.6	4.6 ± 4.8	402.7 ± 107.7	31.6 ± 17.5	NA	NA

DBS, Disease Burden Score (age × [CAG-35.5]), UHDRS-TMS, Unified Huntington's Disease Rating Scale-Total Motor Score

6.3.4 Multidisciplinary rehabilitation intervention

The intervention was designed after baseline assessment of the participants by an experienced interdisciplinary team consisting of physical therapists, exercise physiologists, occupational therapists and strength and conditioning specialists. The intervention consisted of a clinical exercise program, a home-based exercise program and fortnightly occupational therapy. The clinical exercise program consisted of supervised weekly aerobic and resistance exercises for an hour. The home-based exercise program involved thrice weekly self-directed muscle strengthening and fine motor exercises for an hour. Occupational therapy consisted of a variety of paper and pencil, verbal planning, memory and problem solving exercises designed to enhance cognition and executive function (see Supplementary Tables 6.3, 6.4 and 6.5). Adherence to clinical exercise and occupational therapy sessions were recorded by clinical exercise specialists and occupational therapists using a training diary. Adherence to the home based exercise sessions were recorded by patients using a provided training diary.

6.3.5 Outcome measures

Magnetic Resonance Imaging

Structural MR (magnetic resonance) images from 15 participants were acquired at baseline and 9-month follow-up using a 3T Philips Achieva Scanner and a Philips 8 - channel head coil (Philips Healthcare. Best, The Netherlands). Structural scans consisted of a T_1 3D Turbo Field Echo (TFE) scan (400x400, 130 slices, 1 × 1 × 1mm voxels, TR = 5.8 ms, TE = 2.7 ms).

Voxel-based morphometry (VBM) was performed on structural MR images to determine increases and decreases in GM volume between baseline and 9 months. As implemented in FSL-VBM Version 1.1, the VBM (Douaud et al., 2007), protocol included removal of non-

brain tissue from each participant's images, tissue segmentation into GM, spatial normalization (non-linearly to MNI 152) at 2 x 2 x 2 mm^3 resolution and (non-linear) registration to a right-left symmetric, study-specific GM template (average of all individual grey matter images). These images were modulated and then smoothed with a Gaussian kernel of ~4.6mm full width half maximum (FWHM).

Cognitive and Executive Function Measures

Cognitive performance was evaluated at baseline and at nine months using a variety of cognitive measures previously shown to be sensitive in HD (Stout et al., 2012; Tabrizi et al., 2013). The Colour Word Interference Test (CWIT) and Trail Making Test components of the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001; Delis et al., 2004) were used to examine response inhibition and cognitive flexibility. The Symbol Digit Modalities Test (SDMT) (Smith, 1982) was used to examine information processing speed and attention. Verbal learning and memory were examined used the Hopkins Verbal Learning Test-Revised (HVLT-R) (Brandt, 1991). All cognitive assessments were performed by cognitive raters blinded to the treatment condition.

6.4 STATISTICS

Demographic data are given as means and standard deviations. We used linear regression to estimate the increase or decrease in GM volume between baseline and 9 months. The regression model included separate explanatory variables for each participant (for each subject's mean effect) and age. Analysis was focused on regions of interest (ROIs) defined a *priori* based on previous studies in HD shown to be functionally relevant in terms of cognitive capacity (as reflected in episodic memory performance). ROIs included the striatum, hippocampus, and dorsolateral prefrontal cortex (DLPFC). Inferential statistics were carried out using a non-parametric permutation method (as implemented by FSL's randomise

tool). Only clusters with >10 contiguous voxels at a significance level of $p<0.05$ were considered to be indicative of significant longitudinal change. As we adopted an exploratory analysis strategy with ROIs clearly defined *a priori*, no correction for multiple comparisons was applied. GM volume change was also evaluated beyond the ROIs. In this case, maps were thresholded at $p<0.01$ (uncorrected) and voxels were considered significant within clusters of >10 contiguous voxels. The normality of cognitive data was assessed using the Schapiro-Wilk test. Changes in cognitive performance were assessed using mean values at baseline and at nine months with paired t-tests. Statistical significance was set at ($p\leq0.05$). All statistical analyses were performed using STATA 9.1 (Stata Corp, 4905 Lakeway Dr, Texas 77845 USA). We then investigated the functional relevance of change in GM volume in the ROIs, as reflected by associations between significant volume changes and significant change in performance measures from the HVLT-R (follow-up score minus baseline score): total recall, delayed recall, retention and the recognition discrimination index (RDI). The HVLT-R was chosen as dysfunction in recall and recognition memory is an important clinical feature of HD (Montoya et al., 2006). In order to quantify GM volume change, we created a single difference image for each participant by subtracting the follow-up from the baseline smoothed, modulated image generated by the VBM protocol. The relationship between volume change in ROIs and change in cognitive function was then assessed voxel-wise by means of FSL's randomise tool. Age was included as a covariate in all analyses.

6.5 RESULTS

6.5.1 Demographics

Table 6.1 displays demographic data and information on disease duration, disease burden and severity of motor abnormalities. Participants displayed high adherence to the supervised clinical program (84.2%), moderate adherence to the home-based program (58.6%) and high

adherence to occupational therapy sessions (79.2%).

6.5.2 Structural brain changes

Figure 6.1 shows significant volumetric increases in GM in the DLPFC bilaterally and in the tail of the right caudate nucleus after multidisciplinary rehabilitation. All remaining ROIs, including the right hippocampus, left putamen and accumbens showed GM volume loss. Beyond these ROIs, changes in GM volume were also observed. The superior thalami, left inferior temporal pole, right subcallosal cortex and parasagittal primary motor areas exhibited increases in GM volume. By contrast, the left anterior insula, right posterior cingulate/precuneus, left lateral occipital cortex, subcallosal cortex and focal areas in the temporal cortex bilaterally showed GM volume loss (Figure 6.2), consistent with previous neuroimaging studies in individuals with HD (Dominguez et al., 2013; Georgiou-Karistianis et al., 2013a; Tabrizi et al., 2012; Tabrizi et al., 2011a; Tabrizi et al., 2013).

6.5.3 Cognitive and executive function changes

Significant improvement was observed on the delayed recall (number of words recalled after delay) component of the HVLT-R after nine months of multidisciplinary rehabilitation (see Table 6.2). No significant changes were found for CWIT, TMT and SDMT outcomes after nine months of multidisciplinary rehabilitation (see Table 6.2).

6.5.4 Correlation analyses

Increased GM volume in the DLPFC (bilaterally) was found to be significantly associated with preserved performance on the RDI of the HVLT-R (see Figure 6.1).

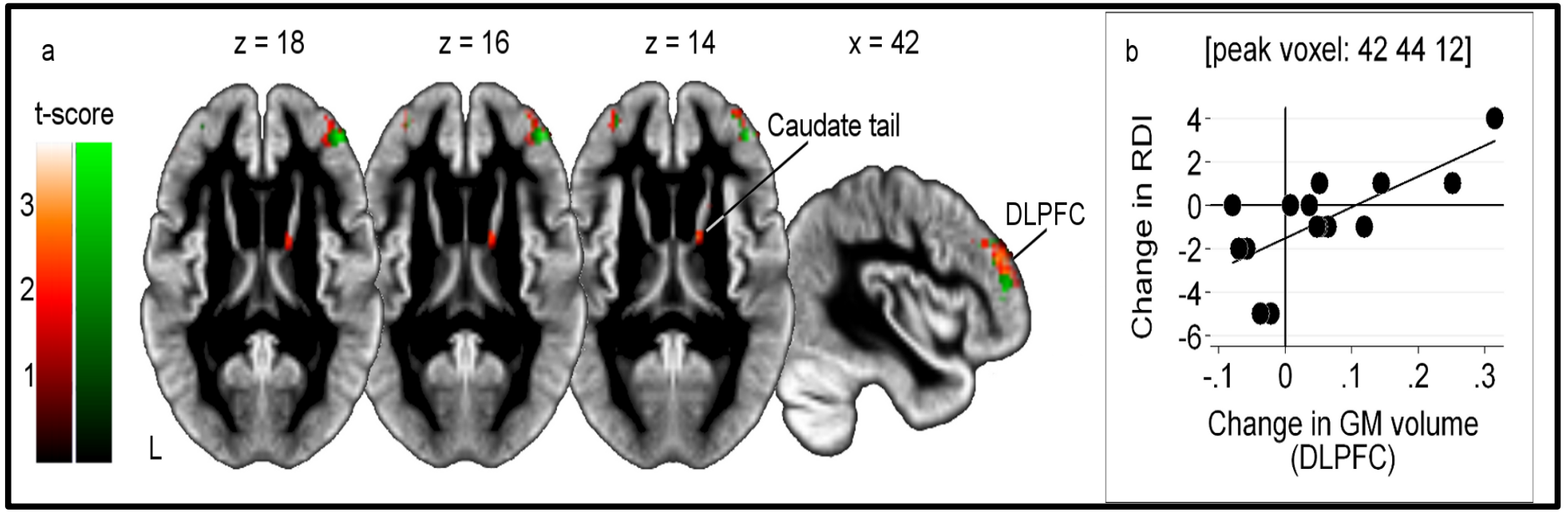

Figure 6.1 Significant GM volume changes after multidisciplinary rehabilitation in individuals with manifest HD

a) Significantly increased GM volume in the DLPFC and right caudate nucleus tail after nine months of multidisciplinary rehabilitation in individuals with HD (red-yellow), and a significant correlation between increased GM volume in DLPFC and preserved performance on the RDI task (green). Results are displayed on the study specific template normalized to MNI space ($p<0.05$, uncorrected). b) Scatterplot illustrating the correlation between increased DLPFC volume at the peak voxel and preserved performance on the RDI task

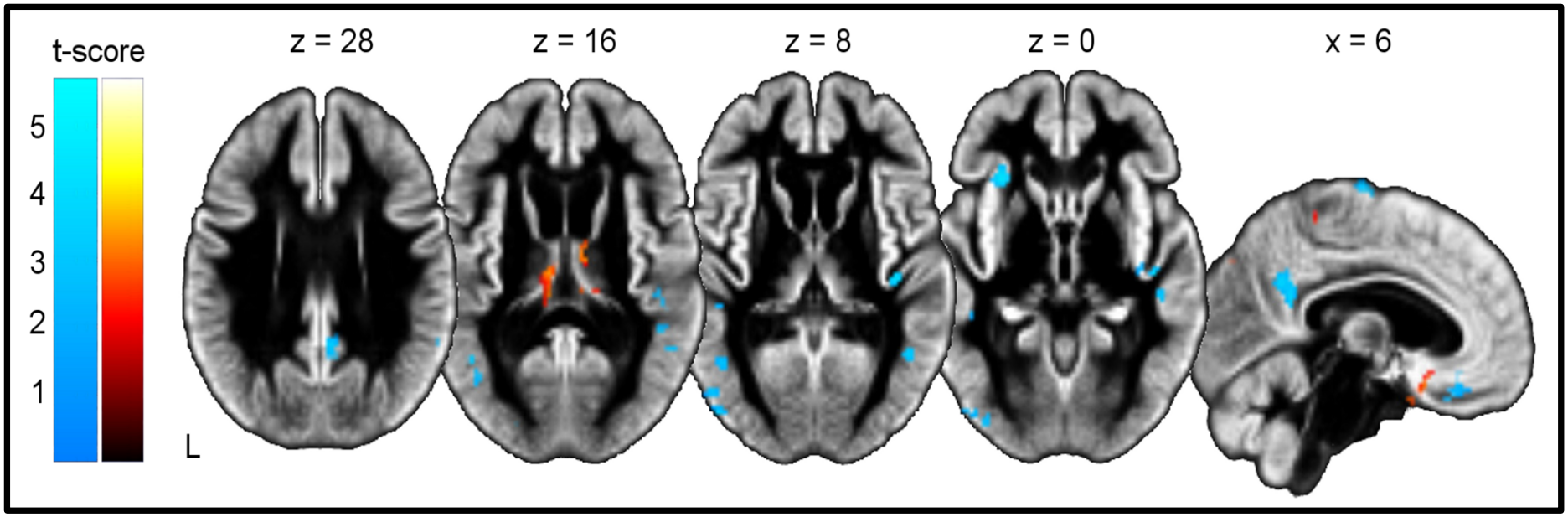

Figure 6.2 Whole brain GM volume changes in individuals with manifest HD

Results of the VBM analysis beyond the ROIs after nine months of multidisciplinary rehabilitation. GM volume loss in blue; GM volume increases in red-yellow. Results are displayed on the study specific template normalized to MNI space ($p<0.01$, uncorrected)

Table 6.2 Changes in cognitive function after nine months of multidisciplinary rehabilitation in individuals with manifest HD.

Outcome Measures	Baseline (n=15)	Post-trial (n=15)	p value
CWIT			
Colour naming	48.35 ± 18.86	52.35 ± 22.57	p=0.0999
Word reading	34.00 ± 10.97	35.35 ± 9.77	p=0.3249
Inhibition	91.00 ± 39.25	93.57 ± 41.39	p=0.4525
TMT			
Visual scanning	38.76 ± 15.76	43.52 ± 15.98	p=0.1149
Number sequencing	55.73 ± 19.87	61.80 ± 23.49	p=0.0507
Letter sequencing	61.92 ± 34.05	66.21 ± 30.77	p=0.1262
Motor speed	58.75 ± 27.39	62.31 ± 25.90	p=0.2433
HVLT-R			
Free recall	17.66 ± 5.56	16.73 ± 6.21	p=0.2019
Delayed recall	4.92 ± 2.36	6.28 ± 3.14	p=0.0130*
Retention	76.16 ± 29.21	81.22 ± 27.32	p=0.1866
Recognition	8.06 ± 3.08	8.93 ± 2.34	p=0.0793
SDMT			
Correct written	27.00 ± 10.25	26.78 ± 9.96	p=0.4525
Correct oral	31.00 ± 14.17	28.46 ± 15.59	p=0.1374

CWIT, Colour Word Interference Test; TMT, Trail Making Trials; HVLT-R, Hopkins Verbal Learning Test-Revised; SDMT, Symbol Digits Modalities Test. Significance was set at *$p<0.05$

6.6 DISCUSSION

This exploratory investigation has shown that multidisciplinary rehabilitation is capable of increasing GM volume and enhancing some aspects of cognitive function in HD. Specifically, we found evidence of increased GM volume in the right caudate and bilaterally in the DLPFC, as well as an improvement in verbal learning and memory after nine months of multidisciplinary rehabilitation. We also found a significant association between increased GM volume in the DLPFC and preserved performance in verbal learning and memory.

Similar to previous investigations in HD, we observed GM volume loss in most cortical and subcortical brain regions (Dominguez et al., 2013; Georgiou-Karistianis et al., 2013a; Hobbs et al., 2011; Kassubek et al., 2005; Kipps et al., 2005; Mühlau et al., 2007; Mühlau et al., 2009; Peinemann et al., 2005; Tabrizi et al., 2012; Tabrizi et al., 2011b; Tabrizi et al., 2013). In this study however, after multidisciplinary rehabilitation, we also observed increased GM volume in the DLPFC and in the right caudate nucleus in individuals with manifest HD. While this is the first study to report such a finding, recent work has shown that cognitive reserve (computed as the composite of intelligence and educational status) influences the rate of volume loss in caudate and putamen structures in individuals with pre-manifest HD (Bonner-Jackson et al., 2013b). Moreover, environmental enrichment has been shown to preserve peristriatal cerebral volume in the R6/1 HD mouse model (van Dellen et al., 2000). Motor and cognitive interventions have additionally been shown to increase hippocampal volume, white matter and grey matter volume as well as cortical thickness in the left middle frontal gyrus, inferior frontal gyrus, superior temporal gyrus in the elderly and those with other neurodegenerative disorders (Bonzano et al., 2014; Boyke et al., 2008; Burciu et al., 2013; Engvig et al., 2010; Engvig et al., 2012; Erickson et al., 2010; Erickson et al., 2011; Lövdén et al., 2012; Prosperini et al., 2014b; Sehm et al., 2014). These findings provide evidence to suggest that lifestyle factors play an important role in modulating the pathology

and clinical profile of HD.

The structural brain changes observed in the present study and others may reflect an increase in neurogenesis and/or favourable changes to neuronal morphology (Lazic et al., 2006; Nithianantharajah et al., 2009; Nithianantharajah and Hannan, 2013). This supposition stems from compelling evidence showing that environmental enrichment can increase markers of neurogenesis within the hippocampus (Lazic et al., 2006) as well as increase the diameter of dendritic spines in the R6/1 HD mouse model (Nithianantharajah et al., 2009). Molecular and cellular mechanisms that may have encouraged the surmised neurogenesis and/or alterations in neuronal morphology in response to multidisciplinary rehabilitation include an increased expression of neurotrophins like brain derived neurotrophic factor (BDNF), enhanced cerebral angiogenesis, and a decrease in elevated circulating glucocorticoids (i.e. cortisol) (Rothman and Mattson, 2013). BDNF enhances neurite outgrowth, synaptogenesis and cell survival, encouraging neurogenesis and experience-dependent synaptic plasticity (Rothman and Mattson, 2013). Recent preclinical data suggests that BDNF-dependent neurogenesis is tightly coupled with cerebral angiogenesis (Chen et al., 2013), and that both are dynamically modulated by changes in circulating glucocorticoid levels (Gray et al., 2013a; Shikatani et al., 2012; Weinstein et al., 2010). In particular, elevated glucocorticoid levels dampen cerebral angiogenesis and BDNF expression in healthy rodent's facilitating a decrease in neurogenesis (Gray et al., 2013a; Rothman and Mattson, 2013; Shikatani et al., 2012). It is possible that multidisciplinary rehabilitation facilitates an adaptive stress response that decreases circulating glucocorticoids, thereby enhancing cerebral angiogenesis and BDNF expression, encouraging neurogenesis and structural brain changes in HD patients.

There are currently no therapies that arrest or attenuate the progressive loss of cognitive function seen in individuals with HD. Here we found evidence of an improvement in verbal learning and memory after nine months of multidisciplinary rehabilitation. These findings

extend on our previous work, where task-specific improvements in processing speed measures were found after a nine month controlled investigation of multidisciplinary rehabilitation in individuals with manifest HD (Thompson et al., 2013). Moreover, these findings support experimental studies documenting improvements in cognitive performance in rodent models of HD after environmental enrichment (Wood et al., 2010; Wood et al., 2011). While evidence is limited in HD, an increasing number of studies are showing that motor and cognitive interventions positively impact on cognitive function in the elderly (Bherer et al., 2013; Erickson et al., 2011; Liu-Ambrose et al., 2010) and those suffering with MCI (Hampstead et al., 2011; Hampstead et al., 2012; Smith et al., 2013), MS (Flavia et al., 2010; Mattioli et al., 2010; Shatil et al., 2010; Solari et al., 2004) and PD (Calleo et al., 2011; París et al., 2011; Sammer et al., 2006). It is likely that the improvements in verbal learning and memory observed in this study resulted from the positive impact of multidisciplinary rehabilitation on caudate and DLPFC structures.

It is well known that degeneration of GM contributes to the development of cognitive deficits and progressive loss of cognitive function (Harrington et al., 2014; Scahill et al., 2013). In this study, we found a significant association between increases in GM volume in the DLPFC and preserved performance in verbal learning and memory. This finding is not unexpected given that memory retrieval and recognition is driven primarily by DLPFC connectivity in healthy individuals and in those with HD (Georgiou-Karistianis et al., 2013b).

A number of limitations must be taken into account when considering our findings. First, there was no control group, which limits our ability to derive definitive conclusions on the efficacy of multidisciplinary rehabilitation on disease pathology and clinical features in HD. Second, the small sample of HD participants in this study makes generalizability difficult. Lastly, participants remained on medication throughout the study, which may have influenced the therapeutic response to multidisciplinary rehabilitation.

Despite these limitations, our findings provide the very first evidence that multidisciplinary rehabilitation is effective in increasing regional GM volume in cortical and subcortical brain regions in HD. Results also show that multidisciplinary rehabilitation is capable of improving some aspects of cognition over a nine month period. Moreover, we found that increased GM volume in the DLPFC was associated with preservation of verbal learning and memory. These findings collectively indicate that neuroplasticity may still be present in HD and amenable to multidisciplinary rehabilitation. Future randomised controlled trials with larger sample sizes, longer duration interventions, more comprehensive imaging and cognitive outcomes and appropriate detraining periods are nevertheless required to confirm and expand on our preliminary findings.

6.7 ACKNOWLEDGMENTS

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6.8 CONFLICT OF INTEREST

Dr Thompson received payment via the Lotterwest Grant (grant number 107 / 20090827). All other authors declare no conflicts of interest.

6.8 SUPPLEMENTARY DATA

Supplementary Table 6.3 Exercises used in the clinical exercise program throughout the study

Exercise Mode	Exercises Utilised	Multi/Single Joint Exercises	Duration	Intensity	Progression
Active Warm Up	Walking (Treadmill) Cycling (Ergometer) Step ups	Not Applicable	3-5 minutes	40-60%	Increase warm up intensity Decrease recovery period
Aerobic Exercise	Walking (Treadmill) Cycling (Ergometer)	Not Applicable	8-10 minutes	60-80%	Increase intensity % (cadence/ resistance)
Resistance Exercise	Leg Press	Multi-joint	40 minutes	60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Knee Extension	Single-joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Knee Flexion	Single-joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Leg Abduction/ Adduction	Single-Joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Lat Pull Down	Multi-joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Supported Row	Multi-joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Chest Press	Multi-joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (kg)
	Abdominal Crunches	Single-Joint		60-80% 2-4 Sets 8-12 Reps	Increase training volume (additional weight)
Cool Down	Walking (Treadmill) Cycling (Ergometer)	Not Applicable	3-5 minutes	40-60%	Not Applicable

Reps, Repetitions, kg, kilograms

Supplementary Table 6.4 Exercises used in the home-based exercise program throughout the study

Exercise Mode	Exercises Utilised	Multi/Single Joint Exercise	Duration	Progression
Fine Motor	Laser tracing Button tying Speed/Accuracy trade-off	Not Applicable	15 minutes	Increase the difficulty of objects traced Increase the number and vary the size of the buttons tied Decrease shape size in the speed/accuracy trade-off tasks
Resistance Exercise	Knee Extension/Flexion	Single Joint	45 minutes	Increase resistance (Sanctbands)
	Wall Push	Multi-joint		Progress to push-ups on knees and then to full ROM push-ups
	Leg Abduction/ Adduction	Single-joint		Increase resistance (Sanctbands)
	Row	Multi-joint		Increase resistance (Sanctbands)
	Abdominal Crunches	Single-joint		Increase time in eccentric and concentric contraction phases

ROM, range of motion

Supplementary Table 6.5 Exercises used in occupational therapy sessions throughout the study

Exercise Modality	Tasks Utilised	Progression
Daily Activities	Cooking	Increase difficulty of cooking
	Laundry	Perform laundry without cues
	Gardening	Increased gardening to an independent state
	Eating	Improve the use and manipulation of eating utensils
Planning/Organisation	Utilisation of a diary (written or electronic)	Increase the number and difficulty of tasks throughout the day
	Planning social activities	
Memory	Facial Recognition	Increase the number of faces to be recognised
Problem Solving	Sudoku	Increase the difficulty of the Sudoku game
	Board Puzzles	Increased the difficulty and size of puzzle
	Boggle	Include time constraints
	Mastermind	Include time constraints

CHAPTER 7 – GENERAL DISCUSSION & FUTURE DIRECTIONS

Despite intense scientific efforts, there is still no cure or disease modifying strategy for HD, and available pharmaceutical agents only provide partial relief of psychiatric and involuntary motor features (Dominguez and Munoz-Sanjuan, 2014; Mason and Barker, 2009; Pidgeon and Rickards, 2013). Lifestyle factors are known to influence the structure of the brain as well as the onset and progression of clinical features in people living with HD (Bonner-Jackson et al., 2013b; Georgiou et al., 1999; Lopez-Sendon et al., 2011; Trembath et al., 2010; Wexler, 2004). Lifestyle enrichment strategies, particularly multidisciplinary rehabilitation may therefore have desirable effects on clinical and neuropathological aspects of HD. Currently, there is only a handful of exploratory studies that have evaluated the effects of multidisciplinary rehabilitation on clinical aspects of HD (Piira et al., 2013; Veenhuizen et al., 2011; Zinzi et al., 2007). Considering the potential benefits of multidisciplinary rehabilitation for patients, as well as the lack of inherent side effects and the necessity for a better multidisciplinary care model for HD, it is obvious that further investigations are warranted.

The work presented in this thesis is therefore timely. The central aim of this thesis was to determine the clinical utility of multidisciplinary rehabilitation on clinical and neuropathological aspects of HD (Chapters 4, 5 and 6). In order to design a comprehensive multidisciplinary rehabilitation intervention, and because balance and mobility are two of the most debilitating aspects of HD, the factors contributing to impairments in mobility and balance were investigated first of all (Chapter 2) (Cruickshank et al., 2014). Published rehabilitation strategies, with favourable effects on mobility and balance in other neurodegenerative disorders, were also investigated through a literature search (Chapter 3).

As a result of our investigations in study 1, lower extremity muscle weakness and the decline in specific cognitive abilities (processing speed, attention, cognitive flexibility, response

inhibition) were found to predict balance and mobility impairments in people with manifest HD (Cruickshank et al., 2014). Our findings were in line with previous reports in PD and MS (Broekmans et al., 2013b; D'Orio et al., 2012; Paul et al., 2013b; Sosnoff et al., 2013a). For example, Paul et al (2013b) reported that lower extremity muscle power significantly predicts balance and mobility performance in PD and more recent evidence has shown that cognitive deficits also contribute to mobility impairments in PD (Gurevich et al., 2014). Moreover, recent studies indicate that lower extremity strength is a significant predictor of mobility in patients with MS (Broekmans et al., 2013a). Deficits in processing speed and innate intelligence have also been documented to predict mobility outcomes in patients with MS (D'Orio et al., 2012). These findings collectively infer that some commonality exists between the outlined neurodegenerative disorders with respect to the clinical factors underpinning balance and mobility impairments. It is therefore likely that rehabilitation interventions with favourable effects on balance and mobility in neurodegenerative disorders like PD and MS will be beneficial for HD patients.

An emerging body of evidence indicates that resistance exercise is beneficial for people with neurodegenerative disorders (Corcos et al., 2013; Dalgas et al., 2013; Medina-Perez et al., 2014; Shulman et al., 2013). Consensus regarding the efficacy of resistance exercise for neurodegenerative populations nevertheless requires further elucidation. As part of this thesis, a systematic investigation of the effects of resistance exercise as a therapy for people with neurodegenerative disorders was performed. An intensive systematic literature search for studies of resistance exercise in neurodegenerative disorders only identified studies in PD and MS. A critical appraisal of the identified studies revealed that resistance exercise has favourable disease dependent effects on muscle strength, mobility, balance, clinical disease progression, fatigue, functional capacity, quality of life, disease biology, electromyography activity, mood, skeletal muscle mass and architecture (Bloomer et al., 2008; Broekmans et

al., 2011; Corcos et al., 2013; Dalgas et al., 2010a; Dalgas et al., 2009; Dalgas et al., 2010b; Dalgas et al., 2013; DeBolt and McCubbin, 2004; Dibble et al., 2006; Dibble et al., 2009; Dodd et al., 2011; Fimland et al., 2010; Hass et al., 2012; Medina-Perez et al., 2014; Paul et al., 2014; Sage et al., 2011; Schilling et al., 2010; Shulman et al., 2011). As expected, the most robust effects were found for muscle strength outcomes. Interestingly, a meta-analysis of changes in muscle strength revealed greater effects for people with PD. Different pathological mechanisms underpinning each neurodegenerative disorder likely account for the outlined discrepancy in the magnitude of muscle strength changes. Importantly, improvements in mobility were reported in a number of the included PD studies. Individuals suffering with HD display similar strength and mobility deficits. In line with our results in HD from study 1 and the results of our systematic review (study 2), it can be surmised that resistance exercise would have favourable effects on muscle strength and in turn mobility in people with HD.

The outlined findings from study 1 and 2 informed our decision to incorporate resistance exercise into our multidisciplinary rehabilitation intervention along with other rehabilitation components including aerobic exercise, physical therapy and cognitive rehabilitation. The latter rehabilitation components were selected given their favourable effects on brain structure and function, functional capacity and cognitive abilities in the elderly and individuals with neurodegenerative disorders (Colcombe et al., 2006; Erickson et al., 2010; Erickson, 2013; Erickson and Kramer, 2009; Erickson et al., 2012; Erickson et al., 2011; Filippi et al., 2012; Khalil et al., 2013; Nombela et al., 2011).

As previously outlined, the central aim of this thesis was to evaluate the clinical utility of multidisciplinary rehabilitation on clinical and neuropathological aspects of HD. To the best of our knowledge, this was the first controlled trial of multidisciplinary rehabilitation in people with HD. Data from this trial showed that multidisciplinary rehabilitation is safe, well

tolerated and well received by patients with HD. From a clinical standpoint, the data showed that multidisciplinary rehabilitation can improve muscle strength, self-perceived balance and body composition outcomes (Thompson et al., 2013). A preservation of mobility was also observed.

The significant improvements observed in muscle strength were somewhat expected given the large resistance exercise component of the multidisciplinary rehabilitation intervention. This finding is nevertheless of clinical importance, especially considering the wealth of data showing that muscle strength predicts functional capacity and falls in neurodegenerative disorders, including HD (Aziz and Roos, 2013; Cruickshank et al., 2014; Padilla et al., 2006; Paul et al., 2013a; Paul et al., 2013b). The improved muscle strength in the intervention participants contrasted strongly with a static level of muscle strength in the no intervention controls. Importantly, contrary to previous evidence declines in muscle strength were not observed in the control group (Busse et al., 2008). This indicates that declines in muscle strength may not be a universal feature of HD, but rather may reflect deconditioning that has taken place over many years as individuals become progressively immobilised.

An improvement in balance confidence accompanied increases in muscle strength in the intervention participants (Thompson et al., 2013). We did not however find favourable effects on other balance measures (Berg Balance Scale and dynamic computerised posturography). The Berg Balance Scale and dynamic computerised posturography have been shown to be reliable and valid measures of static and dynamic balance in patients with HD (Kloos et al., 2014; Quinn et al., 2013). These results indicate that patient perceived improvements in balance do not reflect actual balance improvements. This may in part be due to a lack of insight which has been previously documented in patients with HD. Our findings, at least in part, contrast with previous work. For example, Piira et al (2013) reported significant improvements in balance in patients with HD after intensive intermittent multidisciplinary

rehabilitation using the Berg Balance Scale. Methodological differences likely account for the outlined discrepancy in findings. In particular, Piira et al (2013) used a larger cohort of patients with HD and incorporated formalised balance training exercises into their intervention.

In contrast to previous work (Piira et al., 2013; Zinzi et al., 2007), we did not observe improvement on mobility outcomes. Instead, we found that patients randomised to the intervention group maintained their level of performance on mobility tasks, while those in the control showed deterioration on several mobility outcomes. This suggests that mobility may be preserved by multidisciplinary rehabilitation. In an earlier study, Zinzi et al (2007) found a significant improvement in mobility in a small sample of HD patients after an intensive intermittent multidisciplinary rehabilitation intervention. More recently, Piira et al (2013) reported a significant improvement on mobility outcomes in a larger sample of HD patients, using a similar intervention protocol. The outlined differences in findings may be attributed to differences in the intervention intensity. Piira et al (2013) and Zinzi et al (2007) used an intensive intermittent multidisciplinary rehabilitation intervention, whereas the current study used a longer duration moderate intensity multidisciplinary rehabilitation approach. Emerging evidence suggests that intensive rehabilitation interventions may produce more robust motor benefits in those with neurodegenerative disorders (Frazzitta et al., 2012a; Frazzitta et al., 2012b; Frazzitta et al., 2013).

Significant increases in body weight, lean tissu**e** and fat mass were also important findings of our study (Thompson et al., 2013). Weight loss, skeletal muscle atrophy (Farrer and Meaney, 1985; Farrer et al., 1985; Trejo et al., 2004; van der Burg et al., 2009) and adipose tissue alterations (van der Burg et al., 2009) are well reported features of HD. Weight loss is closely associated with a faster rate of disease progression (Aziz and Roos, 2013; Myers et al., 1991; van der Burg et al., 2009). The favourable changes to weight observed in this study

may therefore have a positive effect on disease progression, however this remains speculative, and subject to future investigation. Alterations in metabolic, endocrine signalling and immune pathways as well as a reduction in ghrelin-producing neurons in the stomach have all been implicated as pathological mediators of changes in body composition (van der Burg et al., 2008). Recent evidence indicates that elevated levels of stress may also mediate abnormal changes in body composition (Du et al., 2014). Multidisciplinary rehabilitation may positively impact on these mediators of weight loss, thereby improving or forestalling pathological changes in body composition. In line with this, exercise has been shown to upregulate ghrelin (Markofski et al., 2014), suppress leptin release (Ko and Choi, 2013; Lichtenstein et al., 2014; Rämson et al., 2012), exert anti-inflammatory effects (Gleeson et al., 2011) and reduce psychological stress (Greenwood and Fleshner, 2011; Puterman et al., 2010) in healthy adults.

Exploratory data additionally showed, for the first time, that multidisciplinary rehabilitation can increase GM volume in structures known to degenerate in people with HD. While structural increases in brain volume have not been reported previously in HD patients, preclinical studies have shown that environmental enrichment can preserve peristriatal structures in transgenic HD mice (van Dellen et al., 2000). Motor and cognitive interventions have additionally been shown to increase hippocampal volume as well as preserve white matter and grey matter volume in elderly people (Boyke et al., 2008; Engvig et al., 2010; Engvig et al., 2012; Erickson et al., 2010; Erickson et al., 2011). Exploratory findings from this study also showed that multidisciplinary rehabilitation can increase GM volume in a region dependent manner in patients with HD. Significant increases in GM volume were observed in the caudate nucleus and DLPFC of patients after multidisciplinary rehabilitation and were associated with verbal learning and memory. These findings are of clinical relevance for several reasons. First, the increases in GM volume were observed in structures

known to degenerate in people with HD (Dominguez et al., 2013; Georgiou-Karistianis et al., 2013a; Hobbs et al., 2011; Kipps et al., 2005; Tabrizi et al., 2013). Second, a significant improvement in verbal learning and memory has not been reported previously in patients with HD after any therapy (Mason and Barker, 2009; Piira et al., 2013; Venuto et al., 2012). Lastly, the significant association between increases in GM volume in the DLPFC and verbal learning and memory performance indicates that structural brain changes can occur in association with multidisciplinary rehabilitation with a clinically meaningful impact.

While multidisciplinary rehabilitation was found to improve some motor, body composition, cognitive and neuropathological outcomes, we found no improvement in mood, quality of life and bone mineral density. A number of cognitive outcomes also remained unchanged as did a number of brain structures that displayed GM volume losses. While unfavourable, this latter finding is in line with previous observational evidence reporting GM volume losses in cortical and subcortical structures (Georgiou-Karistianis et al., 2013a; Georgiou-Karistianis et al., 2013c; Tabrizi et al., 2012; Tabrizi et al., 2011a; Tabrizi et al., 2013). Our inability to find significant changes in mood was not surprising considering that BDI data showed no evidence of a depressive syndrome in study participants at baseline (Thompson et al., 2013).

A lack of changes on the SF-36 was somewhat unexpected. Previous studies have reported mixed findings with respect to the effects of rehabilitation on quality of life outcomes in manifest HD. Piira et al (2013) reported a significant improvement on the physical component, but not mental component of the SF-36 in a large cohort of HD patients after a one year intensive intermittent multidisciplinary rehabilitation intervention. In another study, Khalil et al (2013) reported no significant changes on the SF-36 in HD patients following a short physical therapy intervention. The small sample size used in this study coupled with the generic nature of the SF-36, likely accounts for our inability to find significant changes in quality of life. Studies with larger samples using an HD specific quality of life assessment are

required to appropriately assess the efficacy of multidisciplinary rehabilitation on quality of life in individuals with manifest HD.

The inability to find significant changes in bone mineral density in this study was also unexpected. However, it is important to note that no changes in bone mineral density were observed in the control group at the completion of the study. This suggests that bone mineral density is perhaps not an ideal biomarker, particularly given the duration of the current study. Previous work has shown that individuals with pre-manifest HD display lower bone mineral content relative to healthy age matched controls (Goodman and Barker, 2011). Moreover, preclinical studies have documented a lower bone mineral density in the R6/2 mouse model (Björkqvist et al., 2006). However, there is no data on longitudinal changes in bone mineral density in people with HD. It is possible that changes in bone mineral density manifest over many years as result of sedentary behaviour and taking medication (Bonelli et al., 2002) (or may in some way just relate to gene status). With this in mind, it may be possible to find favourable changes in bone mineral density using longer duration interventions. In support of this, recent evidence showed that high intensity resistance exercise interventions over twelve months increases bone mineral density in older adults (Kemmler et al., 2010) .

With the exception of verbal learning and memory, there was no evidence of performance improvements on other cognitive domains. However, it is important to note that significant deterioration on cognitive outcomes was not observed in the control group. These findings were not unexpected, especially considering the slow temporal profile of cognitive deterioration in people with HD, and the small sample of HD patients used in the current study. A recent study by Stout et al (2012), reported that only the SDMT, Circling Tracing Indirect and Stroop Word Reading assessments show robust evidence of cognitive deterioration over 12 months in early HD. However, for these assessments sample size estimates for a 50% effective treatment, 90% power and two tailed $p<0.05$ group

comparisons were estimated to be 150 (SDMT), 289 (Circling Tracing Indirect) and 337 (Stroop Word Reading). Evidence also indicates that these assessments are strongly influenced by motor control (handedness, speech and ocular control) and psychiatric symptom severity (Eddy and Rickards, 2014), limiting the validity of these measures for assessing cognitive capacity in HD. Future rehabilitation studies aimed at improving cognitive function require more careful methodological considerations, particularly with respect to the sample size, selection of cognitive assessments (minimise time dependent tasks) and duration of intervention utilised.

Beyond the caudate nucleus and DLPFC, GM volume loss was observed in the left anterior insula, right posterior cingulate/precuneus, left lateral occipital cortex, subcallosal cortex and focal areas in the temporal cortex. This is in line with findings from many prospective observational trials (Georgiou-Karistianis et al., 2013a; Georgiou-Karistianis et al., 2013c; Tabrizi et al., 2012; Tabrizi et al., 2011a; Tabrizi et al., 2013). These findings affirm the usefulness of structural imaging as a biomarker for prospective treatment trials. In addition, these results illuminate the possibility that multidisciplinary rehabilitation may exert region-dependent effects on the brain. Favourable region-dependent effects on hippocampal volume have been documented previously after a one year aerobic exercise intervention in older adults (Erickson et al., 2011). Combining rehabilitation strategies with different positive region-dependent effects may therefore provide more robust benefits for brain structures overall.

The work presented in this thesis is not without limitations. First, the sample size was small, therefore the findings from this study cannot be generalised to the wider HD community. Second, the work presented in this thesis only included individuals with mild to moderate HD. Individuals with advanced HD were not included in the present work owing to their inability to perform necessary outcome measures and many of the programmed

multidisciplinary rehabilitation exercises. As such, our findings are not reflective of nor can they generalised to the entire spectrum of manifest HD. Third, studies lacked a long term follow up period, which precludes the possibility of examining the duration of benefits from multidisciplinary rehabilitation. Fourth, study five did not include a control group limiting the significance of the reported findings. However, given that there is a wealth of evidence showing degeneration in the caudate nucleus and DLPFC, and no proven therapies with neurorestorative effects, our findings are of clinical significance and warrant further investigation.

7.1 Future Directions

Studies exploring the effects of multidisciplinary rehabilitation for people living with HD are only in their infancy (Piira et al., 2013; Thompson et al., 2013; Veenhuizen et al., 2011; Zinzi et al., 2007). The present research confirms and expands on previous reports documenting significant improvement in clinical aspects of HD (Piira et al., 2013; Thompson et al., 2013; Zinzi et al., 2007). This research also provides novel experimental evidence showing that multidisciplinary rehabilitation can increase GM volume in the caudate nucleus and DLPFC. Finally, this research shows that increases in GM volume are related to performance on verbal learning and memory tasks. More work is nevertheless required to explore the clinical, neurological and biological effects of multidisciplinary rehabilitation for people with HD. Additional research is also required to identify the most therapeutically effective rehabilitation components of multidisciplinary treatments for people living with HD. With this is mind, the following section outlines future directions that should be undertaken to improve the quality of evidence on multidisciplinary rehabilitation as a therapy for HD.

The work presented in this thesis and previous studies has shown that multidisciplinary rehabilitation can improve clinical aspects of HD (Piira et al., 2013; Thompson et al., 2013;

Veenhuizen and Tibben, 2009; Zinzi et al., 2007). In particular, significant improvements in motor function, body composition, mood, anxiety, physical quality of life and verbal learning and memory have been reported after multidisciplinary rehabilitation in patients with HD (Piira et al., 2013; Thompson et al., 2013; Zinzi et al., 2007). Methodologically robust studies with larger sample sizes, highly sensitive outcome measures, multiple assessment time points at baseline, more effective cognitive training exercises, longer duration interventions, and adequate follow up periods are nevertheless required to confirm and expand on this. Areas that warrant expansion include assessing the effects of multidisciplinary rehabilitation on sleep physiology, autonomic function, sexual behaviour, stress reactivity and cardiovascular function. These latter physiological and psychological processes are known to be perturbed in HD (Aziz et al., 2010a; Goodman et al., 2011; Jhanjee et al., 2011; Kobal et al., 2014; Mo et al., 2014; Morton, 2013; Zielonka et al., 2014), and can severely impact on quality of life.

Observational evidence together with our exploratory findings indicates that lifestyle factors influence structural brain changes in a region dependent manner in HD (Bonner-Jackson et al., 2013b). Similar findings have been observed in other neurodegenerative disorders after cognitive and motor training interventions (Bonzano et al., 2014; Prosperini et al., 2014a; Sehm et al., 2014). These findings have significant clinical implications regarding the selection and modulation of non-pharmacological treatments for individuals with neurodegenerative disorders, particularly those with HD. Future studies should use targeted multidisciplinary rehabilitation interventions, encompassing specific rehabilitation components, with known benefits on the clinical and/or biological outcomes of interest.

Significant volume loss can be observed in cortical and subcortical structures many years before clinical signs can be detected (Georgiou-Karistianis et al., 2013b; Georgiou-Karistianis et al., 2013c; Georgiou-Karistianis et al., 2013d). This disconnect between structural brain changes and clinical signs have led to the speculation that compensatory

neural processes may be present during the early stages of disease (Georgiou-Karistianis et al., 2013b). fMRI has the capacity to detect alterations in brain function and may enable neural compensation mechanisms to be probed in HD (Gray et al., 2013b; Poudel et al., 2014; Poudel et al., 2013). It would be interesting to explore the effects of multidisciplinary rehabilitation on compensatory neural processes in individuals with pre-manifest and manifest HD.

Longstanding evidence indicates that neuronal dysfunction precedes neuronal cell loss in HD (Georgiou-Karistianis et al., 2013c). Recent advances in imaging methods have enabled the quantification of neuronal dysfunction in pre-manifest and manifest HD, using fMRI (Georgiou-Karistianis et al., 2013b; Gray et al., 2013b; Poudel et al., 2014; Poudel et al., 2013). Emerging evidence in other neurodegenerative disorders has shown that cognitive and motor training can have profound effects on neuronal function (Bonavita et al., 2014; Cerasa et al., 2013; Chiaravalloti, 2012; Filippi et al., 2012; Nombela et al., 2011; Parisi et al., 2014; Sastre-Garriga et al., 2011; van Paasschen et al., 2013). Future studies exploring the effects of multidisciplinary rehabilitation on neuronal function in individuals at risk or with pre-manifest HD using fMRI methods would be of clinical interest.

Recent evidence by our group and others indicates that multidisciplinary rehabilitation exerts favourable clinical and neurological benefits in people living with manifest HD (Piira et al., 2013; Thompson et al., 2013; Veenhuizen et al., 2011; Zinzi et al., 2007). It is possible that multidisciplinary rehabilitation exerts these benefits by positively impacting on disease biology. Future studies investigating the effects of multidisciplinary rehabilitation on reliable biological markers of disease progression, clinical status and brain health are warranted. Candidate biological markers that could be utilised to assess the effects of multidisciplinary rehabilitation on disease biology include mhtt (Baldo et al., 2012; Weiss et al., 2012), BDNF (Zuccato et al., 2010), PGC-1α (Che et al., 2011; Taherzadeh-Fard et al., 2009), cortisol

(Shirbin et al., 2013a; Shirbin et al., 2013b; van Duijn et al., 2010), melatonin (Kalliolia et al., 2014; van Wamelen et al., 2013) and cholesterol (Karasinska and Hayden, 2011; Leoni and Caccia, 2014; Leoni et al., 2011).

Finally, it is important to identify which components of multidisciplinary rehabilitation interventions produce favourable effects in people with HD. From a methodological perspective this would involve examining the independent effects of each of the multidisciplinary rehabilitation components (exercise [aerobic and resistance], dual task training [cued motor training], cognitive training [computerised cognitive training, video game playing, paper and pencil cognitive training, bilingual training and sign language training], occupational therapy [cooking, planning and social organisation], speech and language therapy, respiratory muscle training [inspiratory muscle training and expiratory muscle training] and proprioceptive training) in people with HD. Data collected from such studies would help optimise multidisciplinary rehabilitation programs for people living with HD.

CHAPTER 8 – GENERAL CONCLUSION

The work presented in this thesis shows for the first time that multidisciplinary rehabilitation can increase GM volume in structures known to degenerate in HD. Moreover, the present work shows that multidisciplinary rehabilitation improves muscle strength as well as some aspects of motor control, cognitive function and body composition. These findings, while preliminary, have significant clinical implications with respect to the treatment of people with manifest HD. Multidisciplinary treatment approaches may represent a viable therapeutic avenue for people living with HD. Future studies are urgently required to confirm and expand on our findings showing that multidisciplinary rehabilitation can have neurorestorative effects and improve clinical aspects of HD.

APPENDICES

Appendix 1 Huntington's Disease Trangenic Mouse Models

Mouse Model (Strain)	Genetic Characteristics	Repeat Length	Behavioural Phenotype	Neurological Phenotype	Survival	Ref
R6/2	1kb sequence from exon 1 of the human HTT gene	~150	Week 4.5 (wheel running deficits) Weeks 4-6 (hypoactivity; open field testing) Week 5 (morris water maze deficits) Week 6 (rotarod deficits) 11-13 weeks (visual learning task deficits)	Decreased brain weight Lateral ventricular enlargement MSN dendrite diameter and spine density decreases NIIs appear by 4 weeks	10-13 weeks	(Mangiarini et al., 1996) (Carter et al., 1999) (Davies et al., 1997) (Turmaine et al., 2000)
R6/1	1kb sequence from exon 1 of the human HTT gene	116	Week 13 (horizontal rod deficits) Week 18 (rotarod deficits) Weeks 14-20 (clasping phenotype)	NIIs appear by 20 weeks 32 weeks dendritic spine atrophy	32-40 weeks	(Mangiarini et al., 1996) (Carter et al., 1999) (Davies et al., 1997) (Turmaine et al., 2000)
N171-82Q	N-terminal fragments of the first 171 AA of human HTT (exons 1, 2 and part of 3)	82	12 weeks (rotarod deficits)	17 weeks striatal degeneration ventricular enlargement	24-30 weeks	(Schilling et al., 1999) (Luthi-Carter et al., 2000)

HTT, Huntingtin gene, AA, amino acids, NIIs, neuronal intranuclear inclusion, MSN, medium spiny neuron

Appendix 2 Participant Information Sheet

Project: The Effects of Environmental Enrichment on Clinical Measures of Disease Progression and Quality of Life for Patients with Huntington's Disease.

Senior Investigators: Prof Mel Ziman, Dr Jennifer Thompson, Mr Travis Cruickshank, Prof Roger Barker, Dr Carmela Connor, Dr Joseph Lee, Prof Anthony Hannan, Dr Sonya Girdler, Professor Rob Newton, Dr Stanley Lazic.

Please take time to read the following information carefully and discuss it with your friends, family and clinician if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study and where will it be conducted?

This study is a joint collaboration between Huntington's WA (Inc.), Edith Cowan University, the Neurosciences Unit, the Howard Florey Institute (Melbourne), the Centre for Brain Repair at the University of Cambridge and the Brightwater Group, and it has been funded by Lotterywest. It will be conducted at Edith Cowan University.

Contact persons:

Should you have any questions about the study you may contact:

Dr Jennifer Thompson: Phone 6304 5635 Email jennifer.thompson@ecu.edu.au or

Associate Professor Mel Ziman: Phone 6304 5171 Email m.ziman@ecu.edu.au

All study participants will be provided with a copy of the Participant Information Sheet and Participant Consent Form for their personal records.

You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time or you may withdraw from any one procedure at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve. Whatever your decision, this decision will not lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

The following Information Sheet will explain the study and will include details such as:

- **What is the purpose of the study**
- **Why this trial might be suitable for you;**
- **The possible risks (side-effects) and benefits of the intervention;**
- **The nature of your participation;**
- **The type and frequency of any tests or procedures required by the trial;**
- **What are the costs to me;**
- **Your rights and responsibilities;**
- **What if something goes wrong;**
- **How will my safety be ensured;**
- **Will I find out the results of the study;**
- **Who is funding the study.**

What is the purpose of the study?

This study is a research project in which we are investigating the effects of mental and physical stimulation (environmental enrichment) on the progression of Huntington's disease.

This research project intends to implement a therapeutic intervention strategy for patients with Huntington's disease which is centred on mental and physical stimulation as a method for reducing symptoms of the disease and improving quality of life for patients.

Why is this study suitable for me?

You have been invited to participate in this study because you have been diagnosed with Huntington's disease, and you currently display symptoms of the disease.

What are the possible benefits of taking part in this research study?

The results of this study may be of interest to you and your family, and you may decide on whether or not the information may be disclosed to your family. You may experience an improvement in the symptoms of your disease. Also, your participation in this research study may assist researchers and health care providers to provide better treatment for people with Huntington's disease in the future.

How long will I be in this study and how will I participate?

If you agree to participate you will be randomly assigned to a research group with either a therapeutic intervention strategy or no therapeutic intervention strategy, and you will participate in a number of tests throughout the study to assess changes in the progression of the disease. You will be asked to wear an Actiwatch throughout the study which measures your physical activity, and provide blood/saliva samples at various stages of the research study. Instigation of the study: Tests such as clinical assessment, questionnaires and

MRI/DEXA (X-ray) scans will be performed at the beginning of the study as a baseline measure of the status of the disease. You will be asked to provide a blood/saliva sample at this stage.

6 months: You will be asked to undergo the same tests as above and provide a blood/saliva sample.

6-18 months: Depending on the research group to which you are assigned, you may or may not be treated for 12 months with an environmental enrichment intervention strategy which will entail performing a number of physical and mental stimulation strategies each week. At the end of a six month period, you will undergo clinical assessment and questionnaires. At the end of the full intervention/no intervention period of 12 months, you will be asked to undergo the final clinical assessment, questionnaires and MRI/DEXA (X-ray) scans, and provide a blood/saliva sample.

Overall, participants will be involved for a period of 18 months. Participation will require about 9 hours per week for the intervention strategy, and about 2 half days every six months for the assessments. If you have a carer, they will also be asked to participate in this research study.

What will happen if I decide to be in this study?

The study will be conducted over a 2 year period, with participants involved over 18 months. Participants who are assigned to the intervention group will perform mental and physical stimulation tasks over a 12 month period. These will be performed at Edith Cowan University and at home. During this time, you will receive phone calls or visits from a trained scientist to monitor your progress and participation in the research program.

As detailed above, you will take part in a variety of assessments throughout the study:-

- Clinical assessments will be performed by a neurologist to assess the status of the disease. These assessments will be conducted at 0, 6, 12 and 18 months. These assessments are mostly the same as the normal assessments you currently receive. These assessments may be videorecorded for further analysis.

- You will complete questionnaires assisted by a trained scientist at 0, 6, 12 and 18 months. These questionnaires are mostly the same as the normal questionnaires you currently participate in. If you have a carer, they will be asked to answer two questionnaires at these times.

- MRI and DEXA (X-ray) scans will be performed at 0, 6 and 18 months.

- You will perform balance tests at 0, 6 and 18 months.

- Blood/saliva samples will be taken at 0, 6 and 18 months for physiological assessment. The amount of blood taken will be small (20mls per visit). Blood will be drawn into two tubes. You will be required to chew swabs a couple of times throughout one day for saliva samples. Because your blood/saliva samples will only be identifiable by a coded number, the researchers performing the tests will not know which sample is yours. Samples will be analysed immediately and will not be stored during the research study.

You may choose to attend voluntary workshops to be updated on the progress of the study and to discuss with the research scientists any problems you or your family/carers may be experiencing with the research study. You may contact the researchers at any time during the study if you require any further general information.

Are there any reasons I should not be in this study?

The clinical staff collaborating in this research study will discuss these with you in detail and will ensure that this trial is both safe and appropriate for you.

What are the costs to me?

There will be no additional costs to you for participating in this research study. Blood samples will be taken at Edith Cowan University when you visit for your assessments. All transportation costs will be reimbursed by Edith Cowan University, or taxi vouchers will be provided for travel to and from the University where necessary.

What are the possible benefits of taking part in this research project?

The results of this study may be of interest to you as the carer of a person with Huntington's disease. By participating in this research, you may be assisting patients to obtain an improvement in the symptoms of their disease. Also, your participation in this research study may assist researchers and health care providers to provide better treatment for people with Huntington's disease in the future.

How will my safety be ensured?

In this study, the sample that you provide is a blood or saliva sample and there is very little risk to you in this procedure as only a small volume of blood or saliva is required for the test. Exercise treatments will be supervised by an experienced exercise physiologist, and you will be instructed on the correct warming up and cooling down procedures to minimise any discomfort from the exercise regime. All occupational therapy tasks will be supervised by an experienced occupational therapist. Scans will be performed by appropriately qualified health care professionals. However, please do not hesitate to contact the study co-ordinator or your

doctor in relation to any adverse effects you think you are experiencing. If the effects are severe enough, your doctor may stop your participation in the study.

What alternatives do I have to going on this study?

Your participation in this research study is voluntary. This study will not affect your treatment. Your treatment will continue in the same manner whether you decide to participate in the study or not.

You may wish to discuss with your doctor or the researchers how the test will benefit patient treatment in the future.

What are the possible side effects, risks and discomforts of taking part?

In this study, only a small volume of blood is taken (20 mls) at three different intervals throughout the study. There is very little risk to you in this procedure as only a small volume of blood is required. You may suffer a small amount of discomfort when you donate the blood sample, like the feeling of a pinprick. The likelihood of side effects from donating blood is small, around 1 in 100. However, should you suffer any side effects or experience any new or unusual symptoms, please tell your doctor immediately.

There are minor risks associated with MRI and DEXA scans; the use of appropriately qualified personnel reduces these risks. These risks will be discussed with you by a doctor.

You may experience minor discomfort during the performance of the physical exercises if you participate in the intervention strategy. Should you experience excessive discomfort during the performance of the physical exercises, or you do not feel comfortable, please inform the exercise physiologist immediately.

You may experience general body soreness if you participate in the exercise therapy. This is normal after performing physical exercises that you are not used to. Should you suffer excessive discomfort or experience any new or unusual symptoms, please tell your doctor immediately.

The researchers acknowledge that should this intervention therapy prove to be unsuccessful, or you do not experience as good a benefit as you anticipate you are going to achieve, that you may feel depressed or unhappy. Throughout this project, levels of depression will be assessed by a clinician and will be treated as the clinician deems necessary.

What if new information comes along during the study?

Sometimes, new information about an intervention or disease becomes available as a study progresses. You will be told about any information that could be important to you and to your decision to continue in the study. If you then want to continue in the trial, you may be asked to sign a revised consent form.

Stopping the study early:

Sometimes a trial needs to be stopped early because of safety concerns, because the trial is not effective enough, or for other reasons. If this occurs, the reasons will be explained to you and your treatment will continue as it would have without the test. Your treatment will not be influenced by participating in the research study in anyway.

What if something goes wrong?

You will receive the best medical care available during and after the intervention and/or tests. However, unexpected results may be obtained. In the unlikely event of risks to your health being identified, then you will be provided with the necessary care.

Medical treatment will be provided at no cost to you for research-related harm. The term "research-related harm" means both physical and mental injury caused by the product or procedures that are required by this trial.

Your participation in this study does not prejudice any right to compensation which you may have under statute or common law.

Will my taking part in this study be kept confidential?

The researchers will need to collect personal data about you, which may be sensitive, such as your relevant health information. The researchers may also need to get some of your health information from other health service providers, eg another hospital, pathology laboratory, radiographer, GP or other medical specialist.

Any personal or health information will be kept private and confidential. It will be stored securely and only authorised persons, who understand it must be kept confidential, will have access to it. Your study details will be given a number so that your identity will not be apparent. The trial records will be kept at the School of Exercise, Biomedical and Health Science at Edith Cowan University during the study and in a locked archive for at least 5 years and for a maximum of 15 years from the time the study is closed, and may be destroyed at any time thereafter.

Authorised representatives of the researchers, the investigating doctors, or University Human Research Ethics Committees, and other regulatory bodies may require access to your study records to verify study procedures and/or data. In all cases, when dealing with your information these people are required to comply with privacy laws that protect you.

The results of the research will be made available to other doctors through medical journals or meetings, but you will not be identifiable in these communications. By taking part in this

study, you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

Will I find out the results of the study?

The value of the research is not known at this time. You will be notified of the results of the research in general terms at your request and the outcomes of the research as a whole may be provided to you upon completion of the project.

What happens at the end of the study?

At the end of the study your visits to your doctor will continue and your treatment will not be compromised in any way by participating in this research study. Your doctor may adjust your medication as he/she feels appropriate depending on the outcome of the study.

Who has reviewed the study?

The Edith Cowan University Human Research Ethics Committee and the North Metropolitan Area Mental Health Service Human Research Ethics Committee have reviewed this study and have given approval for the conduct of this research trial. In doing so, this study conforms to the principles set out by the National Statement on Ethical Conduct in Human Research and according to the Good Clinical Practice Guidelines.

If you have any questions or require any further information about the research project, please contact:

Dr Jennifer Thompson: Phone 6304 5635 Email jennifer.thompson@ecu.edu.au or

Associate Professor Mel Ziman: Phone 6304 5171 Email m.ziman@ecu.ed.au

If you have any concerns or complaints about the research project and wish to talk to an independent person, you may contact:

Research Ethics Officer,

Edith Cowan University,

270 Joondalup Drive,

JOONDALUP WA 6027

Phone (08) 6304 2170

Email: research.ethics@ecu.edu.au

OR The Secretary,

North Metropolitan Area Mental Health Service Human Research Ethics Committee,

Private Bag No 1,

CLAREMONT WA 6910

Phone (08) 9347 6618

All study participants will be provided with a copy of the Participant Information Sheet and Participant Consent Form for their personal records.

Appendix 3: Participant Consent Form PLEASE TICK ✓

1. I have read and understood the 'Participant Information Sheet' for this study. Y ☐ ☐ N

2. The nature and possible effects of the study have been explained to me. Y ☐ ☐ N

3. I understand that the study involves the following procedures:

   a. I will be required to obtain medical approval to undertake the study before any measures or training can take place. Y ☐ ☐ N

   b. I will be randomly assigned to one of the following two groups:

      (1) Therapeutic intervention group (including occupational therapy and exercise tasks) or Y ☐ ☐ N

      (2) no therapeutic intervention group (no occupational therapy or exercise tasks). Y ☐ ☐ N

   c. I will be required to have my cerebral volume (MRI scan), height, weight, body composition (DEXA scan), and blood/saliva analysis (insulin/c-peptide, glucose, cortisol) assessed before, during and after the study period (at 0, 6 and 18 months). Y ☐ ☐ N

   d. I understand that as a measure of physical function, my balance ability will be assessed before, during and after the study (at 0, 6 and 18 months). Y ☐ ☐ N

   e. I will be required to complete quality of life questionnaires and undergo cognitive testing before, during and after the study period (at 0, 6, 12 and 18 months). I understand that most of these tests are performed as

part of my normal medical care, and if I participate in this research study without participating in the intervention, these tests will be undertaken as per my normal care regime. I understand that some of the cognitive tests may be videorecorded for analysis purposes. Y ☐ ☐ N

4. I understand that I will be required to wear an Actiwatch throughout the timeframe of the research study. Y ☐ ☐ N

5. I agree to my carer participating in this research project by completing questionnaires about my health status, and give permission for them to do so. Y ☐ ☐ N

This study has been approved by the Human Research Ethics Committees at Edith Cowan University and the North Metropolitan Area Mental Health Service. Should there be any concerns relating to the project, you can contact the Edith Cowan University Ethics Officer at (08) 6304 2170 or Email: research.ethics@ecu.edu.au or the Secretary, North Metropolitan Area Mental Health Service Human Research Ethics Committee at (08) 9347 6618 or by mail to Private Mail Bag No. 1, Clarement WA 6910.

Any questions concerning the project entitled "The effects of environmental enrichment on clinical measures of disease progression and quality of life for patients with Huntington's disease" can be directed to Dr Jennifer Thompson (Postdoctoral Research Fellow) Phone 6304 5635 or Email jennifer.thompson@ecu.edu.au, or Associate Professor Mel Ziman (Principal Investigator) Phone 6304 5171 or Email m.ziman@ecu.edu.au of the School of Exercise, Biomedical and Health Sciences, Edith Cowan University, Joondalup.

Appendix 4: Statement of Informed Consent

I (the participant) have read the information above and any questions I have asked have been answered to my satisfaction. I agree to participate in this activity, realizing that I may withdraw at any time. Y ☐ ☐ N

I agree the research data gathered for this study may be published provided my name is not used. Y ☐ ☐ N

I understand that the information I provide will be kept in the strictest confidence by the researchers, unless obliged to release by law. Y ☐ ☐ N

Name (please print) _____

Signed_____ Date_____

Participant or Authorised Representative

Contact Phone Number_____

Y ☐ ☐ N

Are you currently participating in any other research project?

Investigator (Name, please print)_____

Signed _____ Date _____

Appendix 5: Carer Information Sheet

Project: The Effects of Environmental Enrichment on Clinical Measures of Disease Progression and Quality of Life for Patients with Huntington's Disease.

Senior Investigators: Prof Mel Ziman, Dr Jennifer Thompson, Mr Travis Cruickshank, Prof Roger Barker, Dr Carmela Connor, Dr Joseph Lee, Prof Anthony Hannan, Dr Sonya Girdler, Professor Rob Newton, Dr Stanley Lazic.

Please take time to read the following information carefully and discuss it with your friends, family and clinician if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study and where will it be conducted?

This study is a joint collaboration between Huntington's WA (Inc.), Edith Cowan University, the Neurosciences Unit, the Howard Florey Institute (Melbourne), the Centre for Brain Repair at the University of Cambridge and the Brightwater Group, and it has been funded by Lotterywest. It will be conducted at Edith Cowan University.

Contact persons:

Should you have any questions about the study you may contact:

Dr Jennifer Thompson: Phone 6304 5635 Email jennifer.thompson@ecu.edu.au or

Associate Professor Mel Ziman: Phone 6304 5171 Email m.ziman@ecu.edu.au

All study participants will be provided with a copy of the Participant Information Sheet and Participant Consent Form for their personal records.

You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time or you may withdraw from any one procedure at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve. Whatever your decision, this decision will not lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

.**The following Information Sheet will explain the study and will include details such as:**

- **Why this trial might be suitable for you;**
- **The possible benefits of taking part in this research study;**
- **The nature of your participation;**
- **The type and frequency of any assistance you may be required to give;**
- **What are the costs to me;**
- **Your rights and responsibilities;**
- **Will I find out the results of the study;**
- **Will my taking part in this study be kept confidential;**
- **Who is funding the study;**

What is the purpose of the study?

This study is a research project in which we are investigating the effects of mental and physical stimulation (environmental enrichment) on the progression of Huntington's disease.

This research project intends to implement a therapeutic intervention strategy for patients with Huntington's disease which is centred on mental and physical stimulation as a method for reducing symptoms of the disease and improving quality of life for patients.

Why is this study suitable for me?

You have been invited to participate in this study because you are the carer of a patient that has been diagnosed with Huntington's disease that currently displays symptoms of the disease.

How long will I be in this study and how will I participate?

If you agree to participate, you will be asked to assist the research participant to take part in an intervention strategy (if they are assigned to the intervention group) by attending exercise and occupational therapy classes and assisting the participant to perform these tasks at home during the week. You may be asked to assist the research participant to attend a number of tests and scans throughout the study to assess changes in the progression of the disease. You will be asked to assist the participant to comply with wearing an Actiwatch throughout the study which measures their physical activity, and you will be asked to complete two questionnaires at each timeframe before, during and after the study. Instigation of the study: Tests such as clinical assessment, questionnaires, MRI/DEXA (X-ray) scans and blood/saliva tests will be performed at the beginning of the study as a baseline measure of the status of the disease. You will be asked to complete the questionnaires and assist the participant to attend appointments at this stage.

6 months: You will be asked to participate in the same manner as above.

6-18 months: If the participant is assigned to the intervention group, they will perform a number of physical and mental stimulation strategies each week for a 12 month period. At the end of a six month period (at 12 months), whether they have participated in the intervention strategy or not, the participant will undergo clinical assessment and questionnaires. At the end of the full period of 12 months (at 18 months), they will be asked to undergo the final clinical assessment, questionnaires, MRI/DEXA (X-ray) scans and blood/saliva tests. You will assist the participant in their performance of these tasks at home, and you may attend classes and appointments for tests and scans. You will also be required to complete two questionnaires each at 12 months and 18 months.

Overall, participants will be involved for a period of 18 months. Participation will require about 9 hours per week for the intervention strategy, and about 2 half days every six months for the assessments.

What are the possible benefits of taking part in this research study?

The results of this study may be of interest to you as the carer of a person with Huntington's disease. By participating in this research, you may be assisting patients to obtain an improvement in the symptoms of their disease. Also, your participation in this research study may assist researchers and health care providers to provide better treatment for people with Huntington's disease in the future.

What will happen if I decide to be in this study?

The study will be conducted over a 2 year period, with participants involved over 18 months.

Participants who are assigned to the intervention group will perform mental and physical stimulation tasks over a 12 month period. These will be performed at Edith Cowan University

and at home. During this time, you will assist the participant to perform these tasks and attend appointments and you will receive phone calls or visits from a trained scientist to monitor the progress and participation in the research program.

As detailed above, you will assist in a variety of assessments throughout the study:-

- Clinical assessments will be performed by a neurologist to assess the status of the disease. These assessments will be conducted at 0, 6, 12 and 18 months. These assessments are mostly the same as the normal assessments the participant currently receives. You may be required to assist the participant to attend these assessments.
- You will complete two questionnaires assisted by a trained scientist at 0, 6, 12 and 18 months.
- MRI and DEXA (X-ray) scans will be performed at 0, 6 and 18 months. You may assist the participant to attend these scans.
- The participant will perform balance tests and have blood/saliva samples taken at 0, 6 and 18 months. You may assist the participant to attend these tests.

You may choose to attend voluntary workshops to be updated on the progress of the study and to discuss with the research scientists any problems the participant or you may be experiencing with the research study. You may contact the researchers at any time during the study if you require any further general information.

What are the costs to me?

There will be no additional costs to you for participating in this research study. All transportation costs will be reimbursed by Edith Cowan University, or taxi vouchers will be provided for travel to and from the University where necessary.

What alternatives do I have to going on this study?

Your participation in this research study is voluntary. This study will not affect the participant's treatment, which will continue in the same manner whether you decide to participate in the study or not.

You may wish to discuss with your doctor or the researchers how the test will benefit patient treatment in the future.

What if new information comes along during the study?

Sometimes, new information about an intervention or disease becomes available as a study progresses. You will be told about any information that could be important to you and the participant, and to your decision to continue in the study. If you then want to continue in the trial, you may be asked to sign a revised consent form.

Stopping the study early:

Sometimes a trial needs to be stopped early because of safety concerns, because the trial is not effective enough, or for other reasons. If this occurs, the reasons will be explained to you and the participant's treatment will continue as it would have without the test. The treatment will not be influenced by the research study in anyway.

Will my taking part in this study be kept confidential?

Any information that you provide will be kept private and confidential. It will be stored securely and only authorised persons, who understand it must be kept confidential, will have access to it. The participant's details will be given a number so that their or your identity will not be apparent. The trial records will be kept at the School of Exercise, Biomedical and Health Science at Edith Cowan University during the study and in a locked archive for at

least 5 years and for a maximum of 15 years from the time the study is closed, and may be destroyed at any time thereafter.

Authorised representatives of the researchers, the investigating doctors, or University Human Research Ethics Committees, and other regulatory bodies may require access to the study records to verify study procedures and/or data. In all cases, when dealing with the information you provide, these people are required to comply with privacy laws that protect you.

The results of the research will be made available to other doctors through medical journals or meetings, but you or the participant will not be identifiable in these communications. By taking part in this study, you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

Will I find out the results of the study?

The value of the research is not known at this time. You will be notified of the results of the research in general terms at your request and the outcomes of the research as a whole may be provided to you upon completion of the project.

Who has reviewed the study?

The Edith Cowan University Human Research Ethics Committee and the North Metropolitan Area Mental Health Service Human Research Ethics Committee have reviewed this study and have given approval for the conduct of this research trial. In doing so, this study conforms to the principles set out by the National Statement on Ethical Conduct in Human Research and according to the Good Clinical Practice Guidelines.

If you have any questions or require any further information about the research project, please contact:

Dr Jennifer Thompson: Phone 6304 5635 Email jennifer.thompson@ecu.edu.au or

Associate Professor Mel Ziman: Phone 6304 5171 Email m.ziman@ecu.ed.au

If you have any concerns or complaints about the research project and wish to talk to an independent person, you may contact:

Research Ethics Officer,

Edith Cowan University,

270 Joondalup Drive,

JOONDALUP WA 6027

Phone (08) 6304 2170

Email: research.ethics@ecu.edu.au

OR The Secretary,

North Metropolitan Area Mental Health Service Human Research Ethics Committee,

Private Bag No 1,

CLAREMONT WA 6910

Phone (08) 9347 6618

All carer participants will be provided with a copy of the Carer Information Sheet and Carer Consent Form for their personal records.

Appendix 6: Carer Consent form PLEASE TICK✓

1. I have read and understood the 'Carer Information Sheet' for this study. Y ☐ ☐ N

2. The nature and possible effects of the study have been explained to me. Y ☐ ☐ N

3. I understand that the study involves the following procedures:

a. I will be required to complete quality of life questionnaires before, during and after the study period (at 0, 6, 12 and 18 months). Y ☐ ☐ N

b. I may be required to attend appointments for tests and scans with the participant before, during and after the study period (at 0, 6 and 18 months). Y ☐ ☐ N

c. If the participant is assigned to the intervention group, I may be required to attend the exercise and occupational therapy classes. Y ☐ ☐ N

d. If the participant is assigned to the intervention group, I will be required to assist the participant in performing exercise and occupational therapy task at home. I understand that I will be instructed on how to assist the participant. Y ☐ ☐ N

4. I understand that the participant will be required to wear an Actiwatch throughout the timeframe of the research study, and I may be required to assist with compliance in this regard. Y ☐ ☐ N

This study has been approved by the Human Research Ethics Committees at Edith Cowan University and the North Metropolitan Area Mental Health Service. Should there be any concerns relating to the project, you can contact the Edith Cowan University Ethics Officer at (08) 6304 2170 or Email: research.ethics@ecu.edu.au or the Secretary, North Metropolitan Area Mental

Health Service Human Research Ethics Committee at (08) 9347 6618 or by mail to Private Mail Bag No. 1, Clarement WA 6910.

Any questions concerning the project entitled “The effects of environmental enrichment on clinical measures of disease progression and quality of life for patients with Huntington’s disease” can be directed to Dr Jennifer Thompson (Postdoctoral Research Fellow) Phone 6304 5635 or Email jennifer.thompson@ecu.edu.au, or Associate Professor Mel Ziman (Principal Investigator) Phone 6304 5171 or Email m.ziman@ecu.edu.au of the School of Exercise, Biomedical and Health Sciences, Edith Cowan University, Joondalup.

Appendix 7: Statement of Informed Consent

I (the carer) have read the information above and any questions I have asked have been answered to my satisfaction. I agree to participate in this activity with the participant's consent, realizing that I may withdraw at any time. Y ☐ ☐ N

I understand that the information I provide will be kept in the strictest confidence by the researchers, unless obliged to release by law. Y ☐ ☐ N

I agree to participate in this research study by completing quality of life questionnaires and assisting the study participant to take part in this research project. Y ☐ ☐ N

Name of Carer (please print) _____

Signed _____ Date _____

Contact Phone Number _____

Investigator (Name, please print)_____

Signed _____ Date _____

Appendix 8 Example page of the exercise diary

Week **Date**	**Exercises**						**Comments**
Day	**Leg Extension**	**Leg Flexion**	**Calve Raise**	**Leg Abduction**	**Leg Adduction**	**Theraband Row**	**(e.g. experienced pain, fatiguing, easy to perform, hard to perform)**
Monday							
Tuesday							
Wednesday							
Thursday							
Friday							
Saturday							
Sunday							

Appendix 9 Statement of Contribution by Others (Study 2)

Statement of Contribution by Others

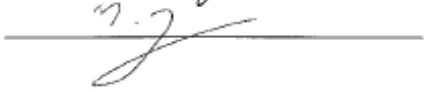
To Whom It May Concern,

I, Travis Miles Cruickshank, I contributed to the study design, search for research trials, analysis of the included trials, writing and editing of the manuscript entitled "A Systematic Review and Meta-Analysis of Resistance Exercise Trials in Individuals with Multiple Sclerosis or Parkinson's Disease".

(Signature of Candidate) 

I, as a Co-Author, endorse that this level of contribution by the Candidate indicated above is appropriate.

Mr Alvaro Reyes  Date 7 Nov 2014

Professor Mel Ziman  Date 11 Nov 2014

Appendix 10 Statement of Contribution by Others (Study 3)

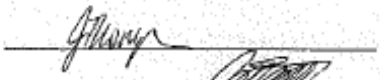
Statement of Contribution by Others

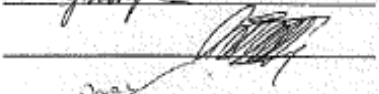
To Whom It May Concern,

I, Travis Miles Cruickshank, contributed to the study design, intervention delivery, data collection, data analysis, writing and editing of the manuscript entitled "The Effect of Multidisciplinary Rehabilitation in Patients with Early-to-Middle Stage Huntington's Disease: a Pilot Study.

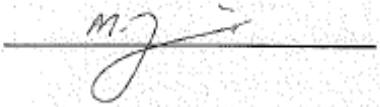
(Signature of Candidate) 

I, as a Co-Author, endorse that this level of contribution by the Candidate indicated above is appropriate.

Dr Jennifer A Thompson  Date 9/11/2014

Dr Luis E Penailillo  Date 07-NOV-2014

Professor Roger Barker  Date 07/11/2014

Professor Mel Ziman  Date 11/11/2014

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