THE UNIVERSITY OF HULL

Quality of life and physical outcomes following an exercise intervention in individuals with a traumatic brain injury: A pilot study

being a Thesis submitted for the Degree of

Doctor of Philosophy

In the University of Hull

by

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September 2019

Abstract

Traumatic brain injuries (TBI) are becoming one of the leading causes of long-term disability worldwide, with more than 200,000 people attending emergency departments in the UK each year following a head injury. This creates immense strain on the individual's life as well as the healthcare system. The long-term symptoms associated with TBI include depression, anxiety, headaches, dizziness, personality changes, increased aggression, and nausea. These symptoms can lead to job losses, relationship breakdowns and even homelessness. Traumatic brain injuries cannot always be avoided so evidence-based guidelines for suitable and effective rehabilitation interventions are important. The overall aim of this thesis was to pilot an original, multi-component exercise intervention on the mental and physical outcomes in individuals following a TBI. Secondly it aimed to identify disparities in the current rehabilitation guidelines and propose future changes. Finally it intended to lay foundations for a future larger RCT to be conducted across the UK with the implementation of exercise programmes within the community. A systematic review of the literature on the effects of exercise on the quality of life (QOL) in individuals with a TBI can be found in Chapter 3. It found limited conclusive data on the best exercise modality to illicit significant QOL improvements. Therefore, this highlighted the gap in the research and the need for more robust RCTs within this area.

Sixteen healthy adults (non-TBI) took part in the first empirical study (Chapter 5) investigating the effects of a 4-week multi-component exercise intervention on physical and health-related quality of life outcomes. The intervention consisted of circuit-based sessions 1x/week working on balance, strength, coordination, and dual-tasking with the second session per week involving aerobic, reaction time and agility exercises. The findings indicated significant improvements in sit-to-stand tests ($p = 0.04$, $g = 0.34$) and reaction time on the Fitlight Trainer ($p = 0.00$, $g = 2.94$) in the exercise group. This was also the case during the

15-minute cycling time-trial, where the exercise group demonstrated significant improvements in the total distance cycled and average power over the four weeks ($p = 0.008$, $g = 0.24$ and $p = 0.00$, $g = 0.28$, respectively). These results revealed the opportunity for physical improvements in a TBI population and justified the second empirical study (Chapter 6). The first part of this chapter looked at the TBI admissions into the Hull Royal Infirmary A&E department highlighting trends in patient and injury characteristics. In addition it demonstrated a wide range of potential participants and emphasised the rationale for an exercise rehabilitation programme. The findings from the audit informed the second part of this chapter, where seven participants (with a TBI) were recruited, with four individuals allocated into the novel exercise programme and three into the standard treatment (control) group. The exercise group attended two session a week for twelve weeks. Participants in the exercise group demonstrated significant improvements (decreased scores) in anxiety ($p = 0.05$) and depression ($p = 0.04$) compared to the control group as measured using the Hospital Anxiety and Depression Scale (HADS). Health-related QOL score as measured with the SF-36 revealed significant improvements for role-limited physical ($p = 0.02$) and vitality domains ($p = 0.03$) as a result of the exercise intervention. Significant improvements were also recorded for total distance covered during the cycling time trials ($p = 0.03$), number of sit-to-stands in 30 seconds ($p = 0.02$), resting heart rate ($p = 0.03$), and maximum workload during the aerobic fitness test ($p = 0.001$). An isokinetic dynamometer was used to measure lower limb average power at two angular speeds (60 deg/sec and 180 deg/sec). The exercise group demonstrated significant improvements during both leg extension ($p = 0.04$) and flexion ($p = 0.05$) at 180 deg/sec. In the final study (Chapter 7), a qualitative approach was used to understand the main facilitators to exercise following TBI. These included motivation, gaining an understanding of recovery, and improving physical fitness. The barriers to exercise were also explored, such as lack of confidence/ motivation and cost.

Overall this thesis demonstrated the potential benefits of a 12-week multi-component exercise intervention on QOL and physical well-being outcomes in a cohort of TBI individuals. It also identified disparities in the current TBI rehabilitation guidelines and proposed future recommendations for long-term support for TBI individuals.

Keywords: traumatic brain injury; quality of life; rehabilitation; exercise training; dual-tasking; psychological well-being; physical fitness.

Acknowledgements

This project could not have been possible without the advice and support of so many people, to whom I would like to express my upmost gratitude.

Firstly, I would like to thank Professor Natalie Vanicek, Dr John Perry, and Professor Sean Carroll for their continued supervisory support throughout this project. Their guidance and feedback has been invaluable.

Dr Abayomi Salawu, consultant in rehabilitation medicine, Hull and East Yorkshire NHS and the team at Hull Royal Infirmary, Hull and East Yorkshire NHS, for all their assistance in patient recruitment.

I would especially like to thank all of the participants who volunteered their time to take part in this project. Without them this study would not have been possible.

Last but not least, I would like to thank all of my family and friends who have continually supported and motivated me throughout this journey. To you all I am eternally grateful.

Dissemination

The work from this thesis has been presented at the following national conferences:

1st HYMS and HEY NHS Trust Rehabilitation Day Conference "Exercise/ physical activities and rehabilitation technology", Hull, UK, October 2018 (oral presentation).

British Association of Sport and Exercise Science (BASES), Harrogate, UK, November 2018 (oral presentation)

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1 Chapter One - Introduction

A Traumatic Brain Injury (TBI) occurs from an external force to the head causing temporary or long-lasting neurological dysfunction (McAllister, 2011). It can develop into a devastating condition inflicting serious physical, mental, social, and economic consequences to the individual patient, their families, and society as a whole (Kayani *et al.*, 2009). Much of the disability associated with TBI is concealed, with many survivors presenting no physical evidence of their injuries. However, the consequences of TBI can impact an individuals' life severely, resulting in personal relationship and family disruptions, employment issues, and in some cases homelessness (Cicerone *et al*., 2000; Oddy *et al*., 2006).

With more than 200,000 people attending emergency departments in England and Wales following a head injury each year (NICE, 2014), TBI presents a major health and socioeconomic problem. It is a leading cause of premature mortality and long-term disability, with TBI individuals tending to report higher rates of depression, anxiety and reduced quality of life following a TBI. In most cases of mild TBI the individual will recover within three months of their injury (Iverson, 2005), however a significant majority of these individuals will experience symptoms beyond three months and some even up to twelve months post-injury (Alves *et al*., 1986). Such symptoms include physical, cognitive and affective disturbances which are compatible with the development of chronic depression symptoms (Lepage *et al*., 2016). Cassidy *et al*. (2014) highlighted that poor recovery following a mild TBI was related to poor premorbid mental and physical health factors. Even though most individuals recover within one year of injury, prolonged recovery periods occur in those who present with more acute symptoms and greater emotional stress, therefore experiencing persistent symptoms. These findings highlight the importance of assessing post-injury symptoms as early as possible to guide diagnosis and inform the treatment and recovery process for each individual.

Regular participation in physical activity reduces the incidence of chronic health complications such as cancer, diabetes, stroke, hypertension and cardiovascular disease (Haskell *et al*., 2007). In addition to the physiological benefits, regular exercise enhances cognitive function which reduces anxiety and stress levels in both children and adult populations (McMillian *et al*., 2002). Age-related cognitive decline and neurodegenerative diseases are also attenuated with regular exercise (Kreber & Griesbach, 2016), suggesting that the protective benefits of exercise may also be observed following a TBI. Preliminary evidence has shown that individuals with a TBI who exercise regularly, experience health benefits such as improved learning abilities (Grealy *et al.*, 1999) and aerobic fitness (Mossberg *et al*., 2010), as well as enhanced balance, self-esteem, and social participation (Thornton *et al.*, 2005).

Traumatic brain injury research and rehabilitation is relatively early in its development and has only recently become a specialised area of interest within clinical care and rehabilitation research. Although TBI patients have shown to benefit from some level of specialised, interdisciplinary rehabilitation, (Semlyen, Summer & Barnes, 1998) there are no clear evidence-based guidelines to inform rehabilitation strategies following TBI compared to other clinical groups. There remains vast “grey areas” in the prescription of structured exercise as a rehabilitation tool following a TBI. The body of work presented in this thesis strives to examine and quantify both psychological and physical responses to a novel, multi-component exercise programme aimed to improve psychological wellbeing and quality of life (including physical aspects) following a TBI. The overall aim is to assist the development of evidence-base clinical recommendations for TBI rehabilitation to reduce the long-term implications of the injury on individuals’ wellbeing and to inform prospective guidelines on the benefits of structured, community-based exercise as a core rehabilitation tool. Ultimately, the findings of this pilot study will assist the development of larger, multi-centred, randomised controlled trials in the UK.

1.1 Thesis structure

A narrative review of the relevant literature was conducted in Chapter 2. This chapter begins with a brief introduction about the major regions of the brain and then explores the epidemiology, causes and characteristics associated with a TBI. This is then followed by a review of the current clinical guidelines in TBI diagnosis, discharge and rehabilitation. Following on from this, the structured exercise and physical training effects on rehabilitation are reviewed alongside an array of quality of life assessment tools. This chapter concludes with the specific study objectives and hypotheses of this thesis.

Chapter 3 presents a systematic review investigating the possible effects of structured exercise interventions for improving psychological wellbeing and quality of life in individuals with traumatic brain injury.

Chapter 4 presents the general methods that form this thesis. Here, the ethical review process, participant characteristics and inclusion/exclusion criteria are clarified. Specific procedural protocols are outlined in the individual chapters and will refer back to this general methods chapter.

Chapter 5 forms the first of three empirical studies in this thesis. This chapter is comprised of two parts, firstly outlining the rationale for the design and implementation of a novel, short-term, multi-component exercise intervention in a cohort of healthy individuals. The supervised and structured exercise intervention was designed within the overall context of exercise interventions within TBI rehabilitation settings. Notably, the structure of the exercise programming, incorporates the dual-tasking paradigm of performing two tasks simultaneously (motor task with cognitive task) in an exercise intervention. This was hypothesised as potentially being an important and unique component of the exercise intervention in the context of TBI rehabilitation. Both elements are used to inform the development of a similar exercise intervention for individuals with a TBI.

Chapter 6 forms the main study of this thesis, investigating the effects of a 12-week multi-component exercise intervention on psychological wellbeing and quality of life in individuals with a TBI. In the first part of this chapter, a comprehensive local audit of TBI admissions within the NHS and explains the rationale for recruitment in the Hull and East Yorkshire (HEY) area. The main findings and outcomes of the 12-week supervised, community-based empirical study of the exercise training intervention in post TBI, is presented within the second part of the chapter.

Chapter 7 addresses the qualitative aspect of the main study in which the individuals with TBI discuss the facilitators and barriers of exercise participation and compliance/ adherence and conveys their thoughts about the 12-week exercise intervention.

Chapter 8 focuses on the implications of the overall thesis, incorporating the individual chapter discussions and synthesising them together into the overall discussion and critical review of the literature in the context of TBI rehabilitation. It focuses on the clinical implications of the empirical findings, limitations to the empirical work, and future recommendations.

2 Chapter Two - Literature review

2.1 Introduction

This literature review will focus on areas related to the recovery process following a TBI. Firstly, a brief summary of the major regions of the brain will be outlined followed by the epidemiology, causes and symptoms of TBI. Thirdly, the clinical recommendations for TBI recovery will be reviewed including proposed methods, intensity and frequency of exercise. The chapter will conclude with an examination of four main QOL assessment tools to determine their suitability and an overview of the aims and objectives of the thesis.

2.2 A brief introduction to the major regions of the brain

The brain is composed of the cerebrum, cerebellum, and the brainstem (Martini, Nath & Bartholomew, 2012). The cerebrum makes up the majority of the brain and is where conscious thought processes and intellectual functions take place; it is divided into two cerebral hemispheres. Each cerebral hemisphere is comprised up of frontal, parietal, occipital, temporal, and limbic lobes (Figure 2.1).

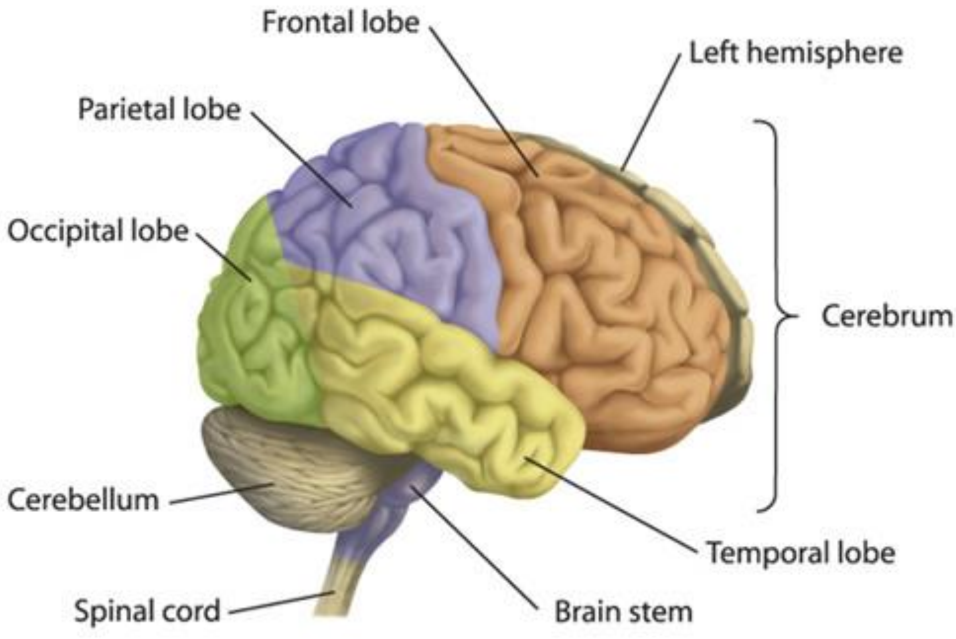

Figure 2.1. Major regions of the human brain

(image taken from: https://inside-the-brain.com/2013/03/07/what-is-attention-and-where-is-it-in-the-brain/)

The frontal lobe is functionally known as the primary motor cortex and is in control of voluntary, skilled movements. Immediately anteriorly to the primary motor cortex is the premotor cortex (Brodmann's area 6) whereby stimulation of this region induces movements involving groups of functionally related muscles. Lying on the medial surface of the premotor cortex is the supplementary motor cortex which tends to control posture related axial and proximal musculature. Lastly the region known as the prefrontal cortex, which lies anteriorly to the premotor area, dominates intellectual, judgmental and predictive faculties and the planning of behaviour (Crossmen, 2010).

Injuries to these lobes can cause disturbances in motor function, with loss of fine movements and reduced strength, speech difficulties, and behavioural changes (Martini, Nath & Bartholomew, 2012).

The temporal lobes are situated inferior to the frontal lobes and are involved in the processing of sensory inputs including visual, language, and emotional stimuli. They also play a major role in the formation of long-term memory and auditory interpretation (Wagner *et al.*, 2005). Trauma to the temporal lobes can cause disturbances of auditory sensation, perception, selective attention, auditory and visual input, visual perception, and altered personality. Similar to the frontal lobes, behavioural changes are common side effects when injury occurs to the temporal lobe. Language can be affected by temporal lobe damage with the lesions on the left disturbing the recognition of words, and right lobe damage causing loss of inhibition of talking. The temporal lobes play a key role in memory skills, left lesions can result in impaired verbal material memory, whereas damage to the right lobe can result in impaired non-material memory such as music and drawings.

The parietal lobes sit posteriorly to the frontal lobes and the central sulcus; their main function involves processing sensory information, understanding spatial orientation and codes motor actions (Fogassi *et al*., 2005). These lobes integrate sensory information including spatial sense and navigation, sense of touch, and the visual system. Language processing also occurs within the parietal lobes. Damage to the left lobe can result in right-left confusion, difficultly in writing and maths, language disorders (aphasia) and inability to perceive objects normally (agnosia). Right lobe damage can result in neglecting self-care skills such as dressing and washing, and denial of deficits, as well as visual attention and motor disorders. Left parietal-temporal lesions can effect verbal memory and ability to recall strings of digits. The right parietal-temporal lesions can produce significant changes in personality.

The most posterior lobes are the occipital lobes, sitting superior to the cerebellum. They oversee the receiving, processing, and interpreting of sensory information. This region of the brain is not particularly vulnerable to injury direct trauma due to its location (Kandel, Schwartz & Jessell, 1991). Deficits could occur to the visual-perceptual system such as visual field defects and scotomas (i.e. partial loss of vision). Damage to one side of the lobe causes homonymous loss of vision and could cause visual hallucinations and illusions. Lesions in the parietal-temporal-occipital association area can cause blindness with writing impairments.

The limbic lobe is a C-shaped region that crosses the temporal, parietal, and frontal lobes and is vital for learning, motivation, memory, and emotions. It plays a major role in the regulation of the endocrine system and regulates both conscious and unconscious functions (John, 2014). Damage to the limbic lobe can be related to temporal lobe epilepsy, hippocampal sclerosis (severe damage to neurones and glial cells), dementia, language deficits, personality disturbances, and psychiatric disorders (bipolar, PTSD, and anxiety). The prognosis of these deficits depends on the nature of the injury, time since the injury, quality of treatment, therapy, age, and overall health.

2.3 Epidemiology, causes, and characteristics

Traumatic brain injury is a major health and socioeconomic issue with a mortality rate of 15 per 100,000 people per year, with a case fatality rate of 2.7% in Europe (Tagliaferri *et al.*, 2006). The annual incidence of TBI (all severities) is approximately 262 per 100,000, with 150 per 100,000 people being admitted to hospital per year (Peeters *et al.*, 2015). The majority of individuals with mild brain injuries do not present themselves to hospital so these numbers may be an underestimation of the true incidence. However there exists great variability in studies investigating epidemiology of TBI cases with differences in data collection, coding variables, classification, and diagnostic errors. For example, the average incidence rates vary from 235 per 100,000/year (Tagliaferri *et al*., 2006) to 275 per 100,000/year (Peeters *et al.*, 2015). Both of these systematic reviews looked at studies (N=23 and N=28, respectively) in Europe. An explanation for this difference could be due to an increase in TBI incidences from 1980-2003 search (Tagliaferri *et al*., 2006) to 1990-2014 search (Peeters *et al*., 2015). Alternatively, there could have been an under registration of TBI cases in 1980-1990

In a review conducted by Chua *et al*. (2007) between 1974-2006 in the US, they outlined an average hospitalisation incidence rate of 200 per 100,000/year. This again differs with the results from Tagliaferri *et al*. (2006) and Peeters *et al*. (2015) but is only highlighting a single countries data and is conducted over a much longer period. The authors of the review (Chua *et al*., 2007) analysed average incidence rates in relation to injury severity showing 14 per 100,000/year for severe (33% average mortality), 15 per 100,000/year for moderate (2.5% mortality), and 131 per 100,000/year for mild cases. However, the authors did highlight that figures could be underestimated due to classification and diagnostic errors with mild cases being underreported due to treatment and discharge from primary healthcare centres that are not classified as hospitalisation.

According to a report by the National Institute for Health and Care Excellence (NICE), 1.4 million people attend emergency departments in England and Wales with a recent head injury and approximately 200,000 of these individuals are admitted to hospital for further monitoring (NICE, 2014). Following a TBI, cognitive, motor, and emotional deficits can persist for years. Individuals who have suffered a TBI are at higher risks of chronic complications and death (Langlois, Rutland-Brown & Wald, 2006). Traumatic brain injury is one of the major causes of death and disability especially in young adults. The World Health Organisation (WHO) have predicted that TBI will become the third most prevalent cause of global disease burden by 2020, surpassing many diseases (Edge, 2010). Majdan *et al*. (2015) conducted a study investigating the patterns of severity, causes and outcomes of TBI across five different countries (Austria, Slovakia, Croatia, Bosnia, and Macedonia) between 2001 and 2012 to identify populations at particular risk. Their results illustrated that the majority of the TBI incidents were as a result of motor vehicle accidents (32%), or occurred within the home or public places (26% and 21%, respectively). Approximately 14% of the incidents (252 out of 1818) occurred in an outdoor or sports facility. These findings show similar trends to the study by Jager *et al*. (2000) who reported the most frequent locations for incurring a TBI were in the home followed by motor vehicle accidents. Jager *et al*. (2000) investigated the incidence and patient characteristics following TBI in the U.S. between 1992 and 1994. These two reports have shown how trends have changed over the years with the most recent (Majdan *et al.*, 2015) study shifting towards more TBIs through road traffic collisions (RTC) than in the home. There is common agreement that individuals aged between 15 and 24 years are more likely to sustain a head injury (Jager *et al*., 2000; Majdan *et al*., 2015; Peeters *et al*., 2015) suggesting that this age group is more exposed to more risks and in some cases, poorer choices. Males are also more likely to sustain a brain injury than females with a ratio of 3:1 (male: female ratio). This may reflect the fact that some of the major causes of TBI, such as RTCs, violence, and sporting injuries, are related to more male-dominated activities. At the other end of the age spectrum, older adults are more likely to sustain head injuries at home due to falls (Jager *et al*., 2000; Andriessen *et al*., 2011). The study conducted by Andriessen *et al*. (2011) followed 508 moderate to severe TBI cases investigating relationships between epidemiological profiles, injury severity classification, and outcomes. Their results corroborated those of Majdan *et al*. (2015) with the incidence of injury being highest in public places or on roads, followed by injuries in the home.

Unlike Jager *et al*. (2000) and Andriessen *et al*. (2011), the Majden *et al*. (2015) study investigated more mild TBI cases by documenting TBI incidents that occurred outdoors and in sport facilities. In general, sport-related head injuries are associated with concussion and tend to be less severe than motor vehicle accidents. Adults aged between 30 – 60 years were more at risk of sport-related injuries. This has been refuted by other studies (Selassie *at el*., 2013; Sahler & Greenwald, 2012) who concluded that the most common age for sport-related injuries was 22.7 years or between 10 - 19 years of age, respectively. Mild TBIs are most commonly known as concussions, which involve temporary unconsciousness/confusion or any neurological dysfunction resulting from a force to the head (Giza & Hovda, 2001).

The initial effects of a trauma, known as the primary injuries, can come in the form of bruising, haematomas (blood clots), diffuse axonal injuries (disconnection of axons), or damages to the blood-brain barrier (BBB). The BBB is a semipermeable membrane separating the blood from the cerebrospinal fluid. These primary injuries can progress into secondary complications exacerbating the damage to the brain. These injuries are results of deficits with the autoregulation and pathophysiological changes within the brain, with hypoxia (deprivation of oxygen) and hypotension being most common (White & Venkatesh, 2016). Injuries can also be described in relation to how broad the damage is across the brain. Focal injuries occur in a specific location, whereas a diffuse injury occurs over a more widespread area. Focal injuries are commonly seen in the frontal and temporal lobes and can be identified with the use of computerised tomography (CT) scans from two days following the injury. If the incident is especially violent then deep intracerebral haemorrhages can occur resulting from arterial damage from either focal or diffuse damage. A diffuse injury refers to diffuse axonal injury (DAI) most commonly seen as punctate subcortical lesions around the corpus callosum and deep white matter (Khan, Baguley & Cameron, 2003) (Figure 2.2). The most common effect of DAI is the presence of altered consciousness, which can be used to diagnose the severity of TBI by observing the depth and duration of the unconscious state (Sandell, Bell & Michaud, 1998).

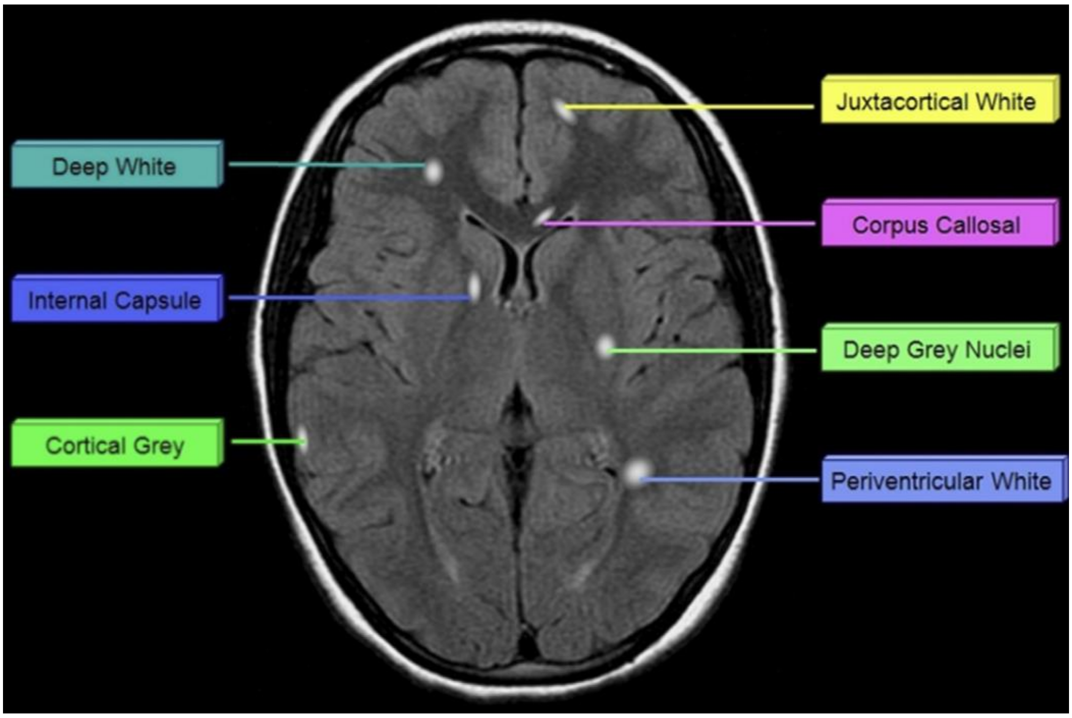

Figure 2.2. Potential locations of lesions following a DAI (Marin & Callen, 2013)

A TBI can be characterised as a closed or an open head injury. A closed head injury is when the contents of the skull are not exposed following the trauma, whereas during an open head injury the membrane that lines the inside of the skull is torn, exposing the contents of the skull (Richardson, 2013). When a closed head injury occurs, the brain can become compressed against the skull, and with only a limited amount of space to allow for swelling, the cerebral pressure will increase until treatment is provided. During a coup-countrecoup injury, whereby an impact accelerates the skull at which point the brain immediately subjacent to point of impact becomes impinged up on the moving skull (coup). Thereafter, as the skull stops, once again the brain impacts on the internal surface of the skull (countrecoup). This can lead to hematomas (brain bleeds), brain swelling, and issues with the flow of cerebrospinal fluid (surrounds and protects the brain). As the brain in being forcefully moved inside the skull during injury, twisting and shearing motions can result in microscopic lesions to nerve fibres. During a closed head injury, neurons about the affected regions may develop oedema (swelling causing them to retain fluid and swell up reducing their excitability (Richardson, 2013). Rapid movements can also result in the stretching of neuronal axons that can lead to interruptions in the functional communication between the brain and other parts of the body. Open head injuries are a result of either objects penetrating straight through the skull and into the brain or the objects causing fragments of the skull to penetrate the brain. In most cases, the individual will not lose consciousness, as the force transferred to the skull is very small in comparison to a blow to the head.

It has been estimated that 70-85% of TBI are categorised as mild, with the majority of these individuals making full recoveries within 3-6 months. This is not always the case, 10-15% remain symptomatic over longer periods of time with persistent post-concussion symptoms including: headaches, changes in hearing, taste, and mood, attention and memory deficits as well as sleep insomnia and irritability (Khan, Baguley & Cameron, 2003). These long-lasting symptoms can have negative effects on the individuals' quality of life and socioeconomic status and may present a burden on the healthcare system. The clinical guidelines following discharge are inconclusive whereby standard treatment does not make recommendations for exercise and/ or psychological support may be difficult to access. This highlights the importance of undertaking research into novel forms of treatment following TBI, and to inform guidelines, to ensure that individuals have access to appropriate treatment strategies and may overcome the debilitating after-effects of the injury.

2.4 Current clinical guidelines

Traumatic brain injuries cause physical, mental and often socioeconomic disruption to the lives of the individual, and their careers, such as family and friends, and can have lasting consequences. Access to effective and timely rehabilitation programmes can have a positive impact on rehabilitation goals (Rose & Johnson, 1996; Barnes, 1999) so guidelines, such as the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN), are in place to guide healthcare professionals in the management of TBI. The sections below will outline how these guidelines are used for diagnosis, in-patient and discharge care, and acute and long-term management.

2.4.1 Diagnosis

Both the NICE and SIGN guidelines agree in the diagnosis of TBI severity should be undertaken during the acute stage (within 15 minutes of arrival to the Accident and Emergency department). A consensus has been reached and the Glasgow Coma Scale (GCS) and Westmead Post-Traumatic Amnesia (PTA) scale are considered the most reliable tools in assessing TBI severity (NICE, 2014; SIGN, 2013). Injury severity is classified as mild, moderate or severe using the GCS (Table 2.1). This system describes the level of consciousness in patients with head injuries, by assessing eye opening movements, and verbal and motor responses. (Teasdale & Jennett, 1974).

Table 2.1. Classification of Glasgow Coma Scale

Score	Severity	Criteria
<3	Vegetative state	Patient showing no evidence of meaningful responsiveness
3-8	Severe	Patient is conscious but relies heavily on assistance with activities of daily living
9-12	Moderate	Patient is independent but disabled making some previous activities/tasks impossible to complete
13-15	Mild	Patient has capacity to resume normal occupational and social activities with minor deficits

Following initial assessment, acute management suggests a CT head scan should be done within the first hour for all individuals matching the criteria of GCS <13, and after two hours for patients with GCS <15, and/or who have an open/depressed fracture, basal skull fracture, seizures, focal deficit, or more than one episode of vomiting (NICE, 2014). Both the NICE (2014) and the SIGN (2013) guidelines are in agreement that if the CT scans showed abnormalities, a consultant should be called and the individual should be admitted into hospital and referred to the neurosurgeons. Following this, the patient is closely monitored and the GCS is re-assessed every 30 minutes for the first two hours, then hourly for the next four hours, and finally every two hours until their symptoms show improvements.

The Westmead PTA scale measures length of PTA in people with a TBI. It assesses amnesia, confusion, and disorientation when recalling and formulating new memories. This system was developed by Russell & Smith (1961) categorising injury severity into mild, moderate and severe. Jennett & Teasdale (1981) expanded the system to incorporate a more thorough breakdown (Table 2.2).

Table 2.2. Classification of PTA

Duration of PTA	**Severity**
< 5 minutes	Very mild
5 – 60 minutes	Mild
1-24 hours	Moderate
1 – 7 days	Severe
1 – 4 weeks	Very severe
> 4 weeks	Extremely severe

Using PTA as a method of classifying TBI severity has limitations however. Misclassification can occur by mistaking an individual's difficulty in recalling recent events and memories as PTA, when in fact they may have been under the influence of alcohol or drugs at the time of the injury (Friedland & Hutchinson, 2013). At the scene of the accident, medication such as morphine may be administered for pain relief which can cause memory gaps that again could be mistaken for PTA (Ruff *et al*., 2009).

2.4.2 In-patient and discharge care

According to the British Society of Rehabilitation Medicine (BSRM), if patients remain in hospital for more than 48 hours with impaired consciousness, they should be reviewed as soon as possible within hospital to advise appropriate management techniques to prevent secondary complications such as ischemia, cerebral hypoxia, hypertension, and cerebral oedema (Turner-Stokes, 2003). When the patient starts to recover in hospital, a more intensive rehabilitation programme could be prescribed to aid the transition from inpatient to community living. These programmes should address mobility and independent self-care in order to improve activity and reduce disability. Patients are only discharged when their GCS is equal to 15 and there is an absence of risk factors (NICE, 2014). The patient should be presented with discharge advice for reoccurring symptoms and guidance for family members.

2.4.3 Acute and long-term management

The NICE, SIGN and BSRM guidelines illustrate similar acute management methods (within the first 72 hours of arrival to hospital) for all severities of TBI. Participation in a rehabilitation programme should be a process that is guided and structured by all parties involved (healthcare professionals, patient, family, friends, and carers). The SIGN (SIGN, 2013) and BSRM (Turner-Stokes, 2003) guidelines state that early integration into a rehabilitation programme delivered by a multi-disciplinary team is more effective than standard treatment (no rehabilitation programme) and promotes positive physical and mental well-being outcomes to ensure the patient continues to function well within their environment. Both guidelines propose rehabilitation programmes that enhance activities of daily living, social integration, and return to work or education. Additionally, physical rehabilitation has been recommended to achieve independence and improve physical deficits such as impaired balance, coordination and sensation, muscle weakness, altered muscle tone, and impaired motor control. Repetitive task-orientated activities are recommended for improving functional ability, such as sit-to-stand and fine manual dexterity and should be incorporated into rehabilitation programmes (SIGN, 2013; Turner-Stokes, 2003). Relevant

The Concussion in Sport Group (CISG) provides global summaries of best practice in concussion prevention, diagnosis, and management (Patricios *et al.*, 2018). In their 2017 consensus statement, they documented guidelines for 10 different collision and contact sports (American football, Australian football, basketball, cricket, equestrian sports, football, ice hockey, rugby league, rugby union, and skiing). The aim was to gather the corresponding governing bodies of these chosen sports and harmonise current practice. Recognising and evaluating sport-related concussion (SRC) on the field is challenging and requires a rapid assessment of the athlete including side line evaluation looking at somatic, physical, emotional, balance, and cognitive impairments (McCrory *et al.*, 2017). According to the 2017 CISG consensus statement (Patricios *et al.*, 2018), the mandatory signs on concussion are: loss of consciousness, lying motionless for >5 seconds, confusion/disorientation, amnesia, vacant look, motor incoordination, tonic posturing, impact seizure, or ataxia. If an athlete demonstrates signs of concussion, they are temporarily removed from play for further neurological evaluations. If any doubt exists, then the athlete should not be allowed to resume play the same day of the injury.

It is important to remember that all individuals with a TBI are different and clinical outcomes depend on the rehabilitation programme, the individuals' personality, injury type and their social support network. Although these guidelines present similar recommendations, there are still unanswered questions such as when the best time is to start a rehabilitation programme and what are the recommended exercise frequency, intensity, time and type (FITT principles). Moreover, it is unclear which interventions deliver the most effective physical and mental well-being outcomes. This highlights the importance of ensuring rehabilitation programmes are individualised to the patient's needs and goals.

2.4.4 Glasgow Outcome Scale (GOS) vs. Glasgow Outcomes Scale Extended (GOSE)

The Glasgow Outcome Scale (Jennett & Bond, 1975) is a widely used questionnaire tool for assessing outcomes after TBI by classifying patients into different injury severity categories (death, persistent vegetative state, severe disability, moderate disability, and low disability). The GOS scale focusses on how the head injury affects functioning of daily activities rather than particular symptoms and deficits, and therefore it reflects disability (Wilson *et al*., 1998). Even though the GOS is not used to provide detailed information about specific difficulties, it implements a general index of overall outcomes and is recommended for use in clinical trials to measure functional outcomes (Clifton *et al*., 1992). However, the GOS has been criticised for its broad categories making it insensitive to the subtle changes in functional status, and suffering from a ceiling effect. For this reason the extended scale was developed (Glasgow Outcome Scale Extended - GOSE) to address these limitations by creating more specific categories and improving the structure of the questionnaire to enhance reliability. The extended version (GOSE) provides subdivisions for the three upper categories of the scale creating an alternative 8-point scale. The eight categories include: dead, vegetative state, lower severe disability, upper severe disability, lower moderate disability, upper moderate disability, lower good recovery and upper good recovery (Sander, 2002).

Levin and colleagues (2001) reported that the GOSE criterion validity was superior to that of the original GOS, using a sample of 87 patients with mild, moderate TBI or general trauma. The GOSE was also found to be more sensitive to changes in functioning from 3-month to the 6-month follow-ups. The GOSE has been designed for use with individuals aged 16 years and older, as the reliability when used with children is unknown and invalid with younger children (Wilson *et al*., 1998). The scale is intended to be administered after the individual is discharged from hospital when moderate disability and good recovery are assessable. An outcome category is then assigned for the individual (Table 2.3).

If the patient has minor disabilities, they are assigned to lower good recovery and those without head injury related disability placed in the upper good recovery band. Significant pre-injury disabilities will be screened and excluded from the study at recruitment so no additional information will be required during the assignment of the GOSE.

Table 2.3.Breakdown of category outcomes with descriptions of the GOSE.

Score	Category	Description
1	Dead	
2	Vegetative state	Only reflex responses with periods of spontaneous eye opening
3	Lower severe disability	Full dependent for all activities of daily living, requires constant available assistance and unable to be left alone at night.
4	Upper severe disability	Can be left at home alone for up to 8 hours but remains dependent and unable to use public transport or shop by themselves.
5	Lower moderate disability	Able to return to work (sheltered workshop or non-competitive job), rarely participates in social or leisure activities and ongoing daily psychological problems.
6	Upper moderate disability	Able to return back to work but at reduced capacity, participates in social and leisure activities less than half as often and experiences weekly psychological problems.
7	Lower good disability	Return to work, participates in social and leisure activities a little less than normal and has occasional psychological problems.
8	Upper good disability	Full recovery with no current problems relating to injury

2.5 Current practice in traumatic brain injury rehabilitation

The goal of any rehabilitation programme is to help the individual achieve the maximum recovery to their pre-injury level of functioning, comprising of acute inpatient management then long-term community management (Khan, Baguley & Cameron, 2003). Inpatient care is required for the more severe cases of TBI and occurs whilst the individual is still in hospital care. This phase focuses on post-traumatic amnesia (PTA) monitoring, pain management, cognitive and behavioural therapies, assistive technology, pharmacological management, as well as family education and counselling. After the individual has been discharged, community management aids in maximising that independence and reintegrating them back into the community (Turner-Strokes, 2003). These phases are extremely difficult as the cognitive and behavioural changes following a TBI tend to be long-term and an individuals' personality may change. This highlights the importance of education, family support and counselling as part of the rehabilitation, even for prolonged periods post-injury. These long-term community-based services can be costly, which affects the quality and availability to this population.

There is a limited amount of research investigating patient outcomes after TBI rehabilitation worldwide. This may be down to the intrinsic heterogeneity of TBI patients, impairments, pathologies, availability of services and differences in recovery (Chua *et al.*, 2007). The possible outcomes following rehabilitation are generally unclear among individuals with moderate and severe TBI, making it near impossible to predict the extent of recovery in the initial weeks post-injury. The first steps of rehabilitation, once individuals have been discharged from hospital, are to set patient-oriented goals with their healthcare team, by determining the combination of cognitive, behavioural and physical deficits (SIGN, 2013; Turner-Stokes, 2003).

Due to the vast differences between each TBI case, there still remains a lack of consensus about when to initiate a rehabilitation programme. However, there is a common agreement that rehabilitation should start as early as possible (Rose & Johnson, 1996; Barnes, 1999) with Rose & Johnson (1996) stating that effective rehabilitation should commence during the first six to nine months following a TBI. Barnes (1999) identified that the recovery curve is steepest in the first three months. Both of these studies referred to TBI as a singular injury without specifying severities, so these recommendations may differ slightly depending on the circumstances of each injury.

In sport-related concussion (SRC) cases, clinicians and coaches face the challenge of helping athletes return at an appropriate time without compromising their performance or health. According to the Concussion in Sport Group (CSG) consensus statement (Patricious *et al.*, 2018), concussed athletes should only return back to their sport when the following criteria have been met: concussion-relation symptoms have returned to baseline levels; cognitive testing has returned to baseline; and all neurological examinations are normal. This guideline is vague and is at the discretion of the athlete's coaching team to ensure safety of their athlete. Schneider *et al*. (2017) conducted a systematic review exploring the evidence for rest and rehabilitation in 28 studies. They concluded that following a brief period of complete (physical and cognitive) rest (24 - 48 hours) patients should be encouraged to increase activity gradually but the exact amount of rest needed before rehabilitation initiation still remains unclear. Uncertainty about when to initiate a TBI rehabilitation programme remains. Partaking in premature post-concussive exercise has been linked with an exacerbation of post-concussion symptoms (PCS) such as depressive and cognitive deficits (Griesbach, 2011).

More large-scale randomised control trials, across an array of exercise modalities and injury characteristics, are required in order to reach consensus for the most effective rehabilitation recommendations following TBI.

2.6 Physiological mechanisms of TBI

As research has demonstrated, recovery of brain function occurs following a head injury, with the time and efficiency of this recover being dependent on individual and injury characteristics (Teuber, 1975, Kertesz, 1979). Metcalfe (1998) documented a number of physiological mechanisms, which involved neurons and pathway restructuring. Swelling of the neurons can be reversed to a limited extent and the nervous system must adapt to the injury. A process called ‘axon sprouting’ (regeneration) occurs when then damaged neuron loses its synaptic input, causing a signal to be emitted and release of a nerve growth factor. These cause other axons and dendrites of nearby neurons to start sprouting extra branches that extend to the damaged neuron enabling synaptic connections. The extent to which this regeneration contributes to replacement of lost function remains unclear. Metcalfe (1998) also highlighted another factor known as the unmasking of silent synapses. A synapse is a modifiable point where a neuron passes on information to another, and is key for information storage in the brain. Some synapses are incapable of neurotransmission in resting conditions, becoming active only after activation during an action potential (Kerchner & Nicoll, 2008). These are known as silent synapses. Due to the active competition for synaptic space on neurons during the development of the micro-circuitry of the brain, active synapses may displace less active synapses to gain control. These less active synapses become dormant and render silent. Following an axonal injury, when the current synapse is damaged, these silenced synapses can be released and able to activate the targeted neuron. Neural stem cells are self-renewing cells that generate neurons during embryonic development. Following an injury, adult neural stem cells produce neuroblasts that migrate to lesion sites (Faiz *et al.*, 2015).

These findings raise hope for developing these cells to create therapies following TBIs to enhance repair and regeneration. It has been demonstrated that neural stem cells in the hippocampus retain the ability to generate neurons and glial (Gage *et al*., 1998), and replace and replenish old and damaged cells. This generation of neurons from stem cells is known as neurogenesis. Neurogenic responses are made up of three phases: 1) proliferation of new cells, 2) migration of the new cells to the targeted areas, and 3) differentiation into proper cell types (Halbergson *et al*. 2003). The degree of neurogenesis is affected by many factors including: biochemical, stress, environment and exercise (Kempermann & Gage, 2000). These processes occur naturally after a trauma in order to prevent further damage to the brain or aid restoration. Additional processes are present but they are stimulated by external factors such as medication or exercise.

2.7 Blood biomarkers

Biomarkers, such as brain derived neurotrophic factor (BDNF), are used as another tool to detect brain injury (Mondello *et al.*, 2011b). Some of the most studied potential biomarkers for TBI include S100B, Glial Fibrillary Acidic Protein (GFAP), Neurin-Specific Enolase (NSE) and BDNF. Giacoppo *et al.* (2012) proposed that S100B and NSE were two of the most promising biomarkers, with both presenting high correlations with TBI severity, along with Baker *et al.* (2012) demonstrating that high levels of S100B and NSE are indicative of poor neurological outcomes. This is also the case for GFAP, with Vos *et al.* (2004) suggesting that high levels of this protein were strongly predictive of a poor outcome or death. These biomarkers do hold some limitations though. S100B is not only expressed in brain tissue (it also appears in astrocytes, fat, bone marrow, skeletal muscles) and is affected by extra-cranial injuries, so may not be a true representation of the brain injury alone. In addition to this, it is only occasionally increased in mild TBI, so serves more as a predictor of more severe head injuries. NSE is also expressed in various tissues other than the central nervous system (platelets, red blood cells, and neuroendocrine cells).

Kaplan *et al*. (2010) proposed BDNF as a potential biomarker reflecting the neuro-regenerative response to TBI. It is the most abundant brain neurotrophin, involved in promoting neuron survival, differentiation, and outgrowth (Poo, 2001). It plays a prominent role in the repairing phases following a brain injury ~~when the levels of BDNF are increased~~, providing neuroprotective and repair functions, and restoring connectivity in disrupted areas. The inclusion of blood biomarkers for evaluating the prognostic factors, and effectiveness of an intervention, is a relatively novel approach among researchers and is becoming favoured for future studies.

Failla *et al.* (2016) investigated BDNF levels in mortality and outcome following severe TBI (n = 202, aged 16-74 years) compared with healthy participants (n = 30, aged 18-60 years). BDNF levels were measured in cerebral spinal fluid (CSF) and serum collected for one-week post injury. Compared to healthy controls, CSF BDNF levels increased, and serum levels were reduced one-week post injury. Average CSF BDNF levels were positively correlated with age ($r = .17$, $p = .045$). Serum levels were associated with acute mortality, with lower BDNF levels in participants who died 0-7 days post injury (130.75 ± 17.26 ng/mL) versus survivors (159.47 ± 60.57 ng/mL). However, attaining CSF samples are not always readily available in clinical trauma centres, so serum samples could be deemed a more accessible matrix.

Serum BDNF has shown to correlate with injury severity, whereby individuals with mild TBI (n = 10, 707 ± 72 pg/mL) demonstrated the highest levels compared with moderate (n = 10, 223 ± 29 pg/mL) and severe (n = 10, 51.1 ± 9.4 pg/mL TBI (Kalish & Philips, 2010). These three severity categories reflect the degree of tissue damage. Therefore, since BDNF plays a role in neuronal cell protection, the greater the tissue damage the lower the levels of present BDNF.

In most cases of mild TBI, individuals will recover to their pre-injury state within three months but a minority will not (Korley *et al*., 2016). The use of these prognostic biomarkers enables identification of individuals that are unlikely to make a full recovery, hence warranting the analysis of biomarkers in the rehabilitation process. Failla *et al.* (2016) proposed that the use of this biomarker should be evaluated in relation to therapies that stimulate BDNF signalling such as exercise interventions alike the current proposed pilot study. Brain derived neurotrophic factor synthesis is centrally mediated and dependent on activity (Rasmussen *et al.,* 2009).

Exercise has shown to increase an array of proteins associated with cognitive enhancement and neural plasticity, with the most associated protein being BDNF. Previous research has demonstrated the positive association between exercise and increased BDNF secretion amongst healthy individuals (Vega *et al*., 2006; Rasmussen *et al*., 2009; Ferris *et al.*, 2007; Seifert *et al*., 2010). These studies differed in exercise modality, from a ramp incremental exercise (Vega *et al*., 2006), short-term 30 minute cycling bouts (Ferris *et al.*, 2007), to a single 4 hour rowing session (Rasmussen *et al*., 2009) and a three month endurance training programme (Seifert *et al.*, 2010). This variance indicates that the mechanisms and threshold requirements for this increased concentration are not yet defined within human subjects. This is also the case amongst TBI cases, with the current literature investigating the effects of exercise on BDNF regulation following a TBI being very limited. As BDNF levels play a predominant role in neuronal plasticity, there is potential for peripheral exercise-induced upregulation of BDNF to aid the brain’s resistance to damage and neurodegeneration (Egan *et al*., 2003). Gold *et al*. (2003) assessed the effects of BDNF levels following short-term exercise amongst multiple Sclerosis patients (n = 25, 39.2 ± 1.8 years) and found that 30 minutes of moderate exercise (60% of $\dot{V}O_2max$) was enough to significantly increase BDNF levels ($p = 0.03$). There is the possibility that the positive effects of exercise on BDNF production amongst healthy individuals and in those with neurodegenerative diseases, could be mirrored amid TBI participants. For this though, robust RCTs need to be conducted.

2.8 Physical training for TBI recovery

The physical benefits of regular exercise are well researched amongst healthy populations (Haskell *et al*., 2007), as well as enhanced cognitive function with reductions in anxiety and stress levels (McMillian *et al*., 2002), along with declines in age-related cognitive impairments and neurodegenerative diseases (Kreber & Griesbach, 2016). Previous research has highlighted that exercise can enhance protective benefits following a TBI, by metabolic (Secher *et al.*, 2008), inflammatory (Piao *et al*., 2013) and neuroendocrine responses (Archer, 2012).

The brain is highly dependent on a steady supply of blood and the following mechanisms aid cerebral blood flow control; neurovascular coupling to increase flow in response to increased neuronal activity and metabolic demand, cerebral vasoreactivity to alter flow in response to changes in carbon dioxide levels, and cerebral autoregulation to maintain constant blood flow despite changing perfusion pressure (Tan *et al*., 2014). Unlike other organs, such as the liver or kidney which are more tolerant to fluctuations in blood flow and partial pressure changes, the compensatory mechanisms outlined above offset this limited autonomy and sure control of brain perfusion.

In cases where any of these mechanisms become impaired, cerebrovascular regulation may be compromised leading to some of the pathophysiologic heterogeneity associated with TBI. Some evidence indicates that aerobic exercise training can reduce persistent symptoms following a TBI by engaging the mechanisms above for cerebrovascular control. Such as sustained muscle contractions during exercise leads to cortical activation in the motor and sensorimotor areas of the brain, increasing cerebral metabolism, and hence engaging neurovascular coupling (Linkis *et al.*, 1995). The increased carbon dioxide production during aerobic exercise is also accompanied by greater cerebral vasoreactivity, regulating blood flow (Rasmussen *et al.*, 2006). In regard to effective cerebral autoregulation to regulate flow and prevent over perfusion (Brys *et al*., 2003), regular exercise could result in a 'training effect' on cerebrovascular regulation. In addition to this, deficits in cerebrovascular control have been shown during prolonged periods of inactivity (Kawai *et al*., 1993), emphasising the beneficial adaptations of exercise training to symptom reduction and improved cerebrovascular regulation. So, the physiological effects of exercise have been well-research amongst health populations, but a focus of this thesis is to determine if these same effects can be translated in TBI. Evidence of disturbed CBF volumes and cerebral autoregulation can be seen following an mTBI and in those with PCS which could explain why symptoms appear worsened during excessive physical exertion (Leddy & Willer, 2013) The abnormal CBF could be due to altered autonomic nervous system (ANS) function and/ or altered carbon dioxide regulation. Carbon dioxide tension in the blood is the primary regulator of CBF (Leddy *et al*., 2007).

During exercise, the percentage of total cardiac output to the brain is drastically reduced as blood is shunted from areas such as the brain, to the activated muscles (Ide & Secher, 2000). During maximal exercise, the brain receives approximately four times less blood volume per heartbeat, compared with the resting state (Rooks *et al*., 2010). So contrary to popular conceptions, there is no evidence to suggest that the brain is the recipient of additional metabolic resources during exercise (Dietrich, 2006). This leads onto suggest that exercise must place a severe strain upon the brain's information-processing capacity, becoming apparent by the decrease in neural activity in structures that are not directly essential to the maintenance of the exercise (Dietrich, 2006). This emphasises the fundamental principle that processes within the brain are competitive (Miller & Cohen, 2001). Even though there is preliminary evidence in the existing literature for the positive effects of exercise on the injured brain (Kreber & Griesbach, 2016; McMillian *et al*., 2002; Archer, 2012), it remains unclear how large that effect actually is.

Populations with neurological sequelae may not be able to perform the recommended exercise prescription and have decreased cardiorespiratory fitness compared to those without neurological dysfunctions (Pinto *et al.*, 2019). This is due to the pathophysiology of the disease-altering physical inactivity through prolonged sedentary behaviour (Block *et al*. 2016). Muscular dysfunctions related to spasticity are hyperactivity and hypertonicity, muscle weakness, and contractures (Nalysnyk *et al*., 2013). All of which can negatively effect on the individual causing impairments (e.g. pain, pressure sores), limit activity, increase dependency on caregivers, and decrease overall QOL (Nalysnyk *et al.*, 2013). There is also an increase in energy expenditure for performance of dynamic movements, increase in production of lactic acid and the use of muscle glycogen, and decrease in the synthesis of fatty acids (Das Neves *et al*., 2016). The application of aerobic training amongst individuals with neurological dysfunctions is increasing due to the benefits such as cognition improvement, cardiovascular conditioning, reduction in anxiety and depression symptoms, and increased oxygen consumption efficiency (Hassett *et al.*, 2017; Morawietz *et al*., 2013; Baert *et al*., 2012).

Many research studies have expressed the health and well-being benefits from participating in physical activity (Haskell *et al*., 2007; Warburton, *et al*., 2006; Pate *et al*., 1995). Such benefits include, but are not limited to: improved cardiovascular fitness (Macko *et al*., 2005), decreased incidence of colon cancer (Colditz *et al.*, 1997), reduced risk of osteoporosis and/or improved bone mineral density (Layne & Nelson, 1999), reduced depression (Dunn *et al*., 2005), decreased incidence of obesity (Warburton, *et al.*, 2006), and improved glucose tolerance and lipid profiles (American Diabetes Association, 2003). Increasingly, researchers have encouraged the use of exercise as an additional treatment following TBI due to the positive effects on PCS and comorbid conditions (Van-Praag, 2008). The optimal timing window for exercise is dependent on injury characteristics and symptom severity, and unfortunately still remains unclear.

2.8.1 Aerobic capacity

Aerobic capacity represents the capacity of the total oxygen delivery and its utilisation within the body. Individuals with TBI present with compromised resting pulmonary function with significant reductions in forced vital capacity and forced expiratory volume when compared with healthy, able-bodied controls (Wiercisiewski & McDeavitt, 1998).

The economy of ventilation is considered as the minute ventilation (V_E): oxygen uptake ($\dot{V}O_2$) ratio (V_E:$\dot{V}O_2$) measured during exercise. A higher ratio implies less efficiency, as greater ventilation is required per litre of oxygen consumed (Becker *et al*., 1977). Becker *et al*. (1977) reported a 30% higher V_E:$\dot{V}O_2$ ratio in individuals with TBI than in healthy controls during submaximal cycle exercise. Even though $\dot{V}O_2$ peak is a key indicator if aerobic fitness, it is rare that daily activities are performed at near peak intensity. Instead it is common for activities to require sustained submaximal efforts for prolonged period of times (Amonette & Mossberg, 2013). The evaluation of submaximal exercise responses may be more relevant as a measure of aerobic fitness without the variability associated with maximal effort exercise testing.

Exercise has shown to influence the CNS via several metabolic and neurochemical pathways that exist between the skeletal muscles, the spinal cord, and the brain (Dishman *et al*., 2006). In animal studies, it has emerged that learning capacity is mediated by the action of BDNF on synaptic plasticity, which has the potential to underlie cognition (Vaynman *et al*., 2003, Gómez-Pinilla *et al*., 2002, Molteni *et al*., 2002). For example, a week of voluntary wheel running can increase the capacity for learning and memory in rats (Vaynman *et al*., 2004). In addition, enhanced learning was present following chronic activity wheel running amongst mouse models of Alzheimer's disease (Adlard *et al*., 2005). Dietrich (2006) investigated the correlations between cognitive and affective responses during and after exercise. Following exercise, increased activation has been shown to occur in neural structure responsible for generating motor patterns, and within structures involved in sensory, autonomic, and memory function. However, there is very limited physiological research on human brain activity during exercise (Christensen *et al*., 2000), and the answer remains unclear as to how and to what extent exercise plays a role on cognitive function recovery following a TBI.

2.8.2 Aerobic training

The need to improve physical work capacity and endurance is often overlooked following a TBI due to the demands of physical therapies that concentrate on flexibility, muscle strength, balance, gait and functional skills (Mossberg, Amonette & Masel, 2010). The peak aerobic capacity of an individual with TBI is only 65 - 74% compared to a healthy control person (Bhambhani, Rowland & Farag, 2003). However, due to the variations in measuring techniques, exercise modalities, and physical impairments associated with TBIs, the true deficit is difficult to quantify. However, previous animal studies have outlined that aerobic exercise has a neuroprotective effect and activates growth hormones, increasing neural stem cell survival (Blackmore *et al*., 2009) and neurogenesis in the hippocampus by increasing blood flow to the dentate gyrus (Pereira *et al*., 2007).

If introduced at the right time, exercise could also lead to improved neuronal function. Animal experimental studies showing that premature voluntary exercise (within one week of injury) can delay recovery and impaired cognitive memory performance tasks (Griebach *et al*., 2004a). However, delaying aerobic exercise until 14 – 21 days post injury, has shown increased upregulation of BDNF in association with cognitive performance (Griebach *et al.*, 2004b). In human studies, it has been outlined that too much activity too soon could be detrimental to recovery, but that too little is also detrimental (Majerske *et al.*, 2008). This emphasises the variance in current research and the need to more robust studies to outline the appropriate times, type, intensity, and duration of exercise prescription following a TBI.

Increasing aerobic capacity can be challenging for both the individual and the healthcare team due to more serious cognitive, behavioural, and motor impairments associated with a TBI (Mossberg *et al.*, 2010). Special requirements may be required including: staff training, equipment, and changes to the exercising environment (parking, disabled accessibilities, and chaperones). Due to the lack of these adequate rehabilitation facilities, many individuals are unable to meet their full potential during recovery, which in turn can cause unnecessary physical and psychological burdens upon both the patient and their family. The benefits of aerobic training have been highlighted in previous research (Leddy *et al*., 2010; Schwandt *et al*., 2012; Wise *et al*., 2012; Chin *et al*., 2015).

Leddy *et al*. (2010) investigated the effects of a threshold exercise programme on participants with post-concussion syndrome in an athletic and non-athletic population. They enrolled 11 individuals (seven men, four female) with a mean age of 28 years, all with PCS symptoms and a mean time since injury of 19 weeks. Out of the eleven participants, six were athletes with the remaining five being non-athletes. The exercise programme included completing aerobic exercise at an intensity of 80% of their maximum heart rate during a treadmill test (at baseline) once daily for five to six days per week. They completed exercise tests every three weeks until their PCS symptoms were no longer exacerbated during exercise. The non-athlete group completed an average of 13 weeks whereas the athletes completed an average of four weeks. All of the participants reached the physiologic criterion for treatment success (exercised to exhaustion without symptom exacerbation) and returned to work/school and sporting activities. This study demonstrated that PCS symptoms could be improved from a controlled sub-symptom aerobic exercise programme and that the athlete's demonstrated reduced PCS symptoms at a quicker rate than non-athletes (4 Vs. 13 weeks). These improvements in PCS could be related to improved cerebral autoregulation following thee exercise programme. The brains ability to regulate blood flow when the blood pressure rose during exercise was enhanced. The participants all had PCS for ≥6 weeks and were not showing signs of improvement minimising the chances of the improvements being down to spontaneous recovery. However, it would have been informative to have a control PCS group to conclude if the improvements were in fact due to the exercise intervention alone. It was not surprising that the athletes responded to the exercise faster than the non-athletes, as they could have been more responsive to exercise and the non-athletes may demonstrate secondary gain issues.

Schwandt *et al*. (2012) investigated the feasibility of a 12-week aerobic exercise intervention in a cohort of moderate to severe TBI individuals (n = 4) with a mean age of 29 years. Time since injury varied from 11 months to 7.2 years across all four participants (mean of 2.6 years). The aerobic training (treadmill, cycle ergometer or recumbent step machine) involved participants working at an intensity of 60 - 75% of their age-predicted heart rate max for 30 minutes a day, three times a week. Following the programme, all participants improved on their Peak Power Output (PPO) and decreased maximum heart rate. There was also an improvement (lower scores) for the Hamilton rating scale for Depression (HAMD) and improved self-esteem on the Rosenberg self-esteem scale. Significant values were not available as descriptive statistics only were used to depict characteristics. In terms on the feasibility, all participants reached their target intensities without any adverse effects, with the view being that the exercises were challenging but achievable. Due to the absence of a control group, it is not possible to determine if the benefits were influenced by the exercise intervention or the increased attention and socialisation. The small sample size was also a limitation, but as the authors highlight, this was a pilot study to generate preliminary data.

Wise *et al*. (2012) investigated the qualitative effects of aerobic training on depression, quality of life and overall mental health in a cohort of 37 TBI individuals (mean age of 40 years). The TBI was not specified by a GCS but was severe enough to receive medical evaluation immediately following the injury. The mean time since injury was 2.1 years. The exercise intervention included 30 minutes of supervised aerobic exercises, once per week for 10 weeks. Individuals were also asked to perform 30 minutes of moderately intense aerobic exercise at home four times a week. The intensity of both the supervised and non-supervised sessions were based upon their heart rate goals. Following the 10-week intervention, there were significant improvements in the Becks Depression Inventory (BDI) and Short Form-12 (SF-12) mental scores with the exercise group reporting an average of 146.6 minutes of exercise per week. The BDI measures severity of depression and the SF-12 is a generic assessment of health-related quality of life (shortened from of the SF-36 health survey). These results support that potential benefit of exercise on QOL, depression and improved mental health in people with TBI. However, due to the intervention included unsupervised exercise sessions, it is not possible to determine whether improvements were due to the exercise or because of unmeasured factors. So, similarly to the studies by Leddy *et al*. (2010)

and Schwandt *et al*. (2012), the inclusion of a control group would help conclude the true outcomes of the intervention. It was also unclear as to whether the exercise led to improvements in mood and QOL or that increased mood and QOL led to an increase in exercise.

Chin *et al*. (2015) investigated the effects of a 12-week aerobic exercise programme on cognitive function in a cohort of mild to moderate TBI individuals (n = 7). The mean age was 33.3 years with a mean four years since injury. The intervention included 30 minutes of supervised aerobic treadmill exercises at an intensity of 70 - 80 % of heart rate reserve, three times a week. Following the 12-week intervention, participants significantly improved on the Trial Making Test (measures speed of information processing and select aspects of executive functioning) and for three out of the five domains (visuospatial/constructional, language, and delayed memory) of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). In addition to these improvements, cardiorespiratory fitness improved, indicated by increased $\dot{V}O_2$peak and peak work rate. Connections can be drawn between improved cognitive function and degree in which the cardiorespiratory system adapts to training. However, it is unclear as to the extent spontaneous recovery may have contributed to the cognitive function improvements due to the absence of a control group. In addition, the effects of social interaction were not measured which could have contributed towards the cognitive improvements. This could also have been the case for the other studies that did not measure social interactions, with either with other TBI individuals or with the fitness instructors, during their intervention sessions.

All four of these studies demonstrated that aerobic exercise promoted improvements on the individuals' physical and mental well-being following a TBI. The mean age of participants ranged from 28 to 40 years and all included both males and females. In terms of the time since injury, the studies by Leddy *et al.* (2010) and Schwandt *et al.* (2012), observed individuals within a shorter timeframe following injury (≤ 2 years) compared to those documented in Wise *et al.,* (2012) and Chin *et al.* (2015), (≥2 years). These differences highlighting again that more research should be conducted to determine the optimal time to start exercising following a TBI. Chin *et al.* (2015) and Schwandt *et al*. (2012) both implemented programmes incorporating vigorous intensity aerobic exercises (~70-85% HRmax) for 90 minutes per week for a total of 12 weeks. With Wise *et al*. (2012) featuring moderate intensity aerobic work (~50-70% HRmax) for 150 minutes per week. All three of these studies meet the minimum weekly recommendations, 150 minutes per week for moderate- intensity or 60 minutes per week for vigorous-intensity aerobic work (ACSM, 2010). However, in addition to this aerobic work, the guidelines also recommend performing activities that maintain or increase muscular strength and endurance (e.g. resistance training) for a minimum of two days each week (ACSM, 2010). Therefore, the above studies are still lacking to meeting the guidelines for exercise prescriptions.

2.8.3 Balance

Balance involves complex interactions between the sensory, motor, and musculoskeletal systems (Pickett *et al*., 2007). If there are any impairments to these interactions, or to the integration of this information, significant long-term disability could follow. Balance deficits can have negative repercussions on returning to work/education or leisure and vocational activities following a TBI.

Prangley *et al.* (2017) assessed balance control changes in six individuals, with a mean age of 39 years and who experienced persistent (symptomatic for > 26 days) PCS, following a vestibular training programme. The vestibular exercise programme consisted prescribed balance, visual, and of neck strengthening exercises, completed three times daily, seven days a week for four weeks. Previous research has shown that neck strength to be a predictor of concussion risk and that increasing neck strength may provide a protective factor (Toninato *et al*. 2018). The primary outcome was balance, which was assessed using a Nintendo Wii board with the participant completing four test conditions (eyes open, eyes closed, single leg eyes open, and single leg eyes closed). The authors demonstrated that the vestibular training elicited significant balance control (decrease in centre of pressure displacement and velocity) in the medial-lateral and the anterior-posterior directions when participants' eyes were closed.

Similar improvements were displayed by Damiano *et al.* (2016), who investigated the effects of an 8-week motor control training programme on individuals with TBI in comparison with non-TBI individuals (controls). The TBI group (n = 12) had a mean age of 31.3 years and were at least six months post-injury. Sessions lasted 30 minutes and were completed five days a week for 8 weeks. Postural responses were measured using a NeuroCom Smart Equitest system, which is a computerised assessment tool that aids diagnostic tests for the medical management of balance and mobility disorders. Two programmes were used: The Limits of Stability (LOS) test and the Motor Control Test (MCT). The LOS test quantifies the maximal distance the individual can displace their centre of gravity (CoG) in eight different directions (four cardinal and four diagonal) following a visual cue and maintain their stability in those positions for approximately 10 seconds, reaction time and movement excursion was measured. Latency of response was measures during the MCT, which assesses the participant's ability to recover their balance following an unexpected external postural disturbance with the use of their automatic motor system. The TBI group demonstrated limited endpoint excursions in the backwards and left directions compared with the non-TBI group (n = 12, mean age = 32.5 years) at the baseline assessment. Following the 8-week training programme, the TBI group presented significant improvements in the LOS reaction time ($p = 0.03$) and MCT composite scores ($p = 0.001$). This study highlighted the balance deficit in TBI individuals and that an exercise programme can illicit significant improvements on some balance outcomes. The TBI severity was not presented in terms of a GCS rating, but individuals were no longer receiving medical care and were all functioning well based on routine clinical tests.

Further improvements to balance were demonstrated by Ustinova *et al.* (2014) following a 20-session exercise programme consisting of a series of therapeutic exercises for training whole-body coordination, posture, and gait. They assessed a cohort of 22 TBI individuals (severity = mild and moderate) who were at least 6 months post-injury. Balance and gait were assessed using the Berg Balance Scale (BSS) and the Functional Gait Assessment (FGA), respectively. Following the programme, individuals demonstrated significant static and dynamic balance improvements on the BSS and significant gait improvements on the FGA. All three of these studies highlight the possibilities of exercise as a treatment for balance deficits in individuals with a mild to moderate TBI. Future directions in this area should cover large-scale clinical trials and investigate the possible relationships of balance with quality of life.

2.8.4 Dual-tasking exercise

Dual-tasking (DT) exercises can be incorporated as part of a multi-component rehabilitation programme. Dual-tasking can be described as the ability to attend to and perform two tasks at the same time (McCulloch *et al.*, 2009). These tasks can be motor or cognitive, or a mixture of both. However, DT can lead to diminished performance in one or both tasks (Rasmussen Jr *et al.*, 2008). This is known as dual-task interference. Pashler *et al.* (1994) highlighted three main theories behind DT interference: capacity sharing, bottleneck models, and cross-talk models. The theory of capacity sharing assumes that people share processing capacity amongst tasks, so when more than one task is performed at the same time there is less capacity for each individual task and the outcome performance is impaired. Alternatively, the bottleneck model (task-switching) is the idea that parallel processing may be impossible for specific mental tasks. Single tasks may only require a single mechanism to be dedicated to them, but when two tasks need the mechanism at the same time, one or both tasks will be delayed or impaired, thus creating a bottleneck. Finally, the cross-talk model refers to the content of the information being process-driven rather than the type of operation being carried out. It includes what sensory inputs are present, the responses being produced and the individual's thoughts. In theory, it should be easier to perform two tasks simultaneously when they involve similar inputs.

A number of measures have been suggested for measuring dual-task performance deficits in individuals with a TBI, for example the timed up and go cognitive test (Rachal *et al.*, 2018), walking and spoken sentence verification task (Evans *et al.,* 2009), walking and remembering test (McCulloch *et al.,* 2009), and the tandem walk with cognitive task (Weightman & McCulloch, 2014). In general, the assessment of dual-tasking consists of measuring a baseline performance on a single motor task (time taken to walk a pre-selected distance) then measuring the two tasks being performed simultaneously (walking whilst performing a cognitive task), (Weightman & McCulloch, 2014). The reduction in the dual-task condition performance is known as the dual-task cost (DTC) (Figure 2.3)

$$\text{Dual-Task Cost} = \frac{(\text{Dual-Task - Single Task})}{\text{Single Task}} \text{ x } 100$$

Figure 2.3.Calculation for DT cost (McCulloch, 2007).

Dual-tasking assessments have implications for real-life situations that require doing more than one thing at a time. Vallée *et al*. (2006) investigated the effects of environmental demands on dual-tasking abilities in people with TBI. They compared nine individuals' recovery from a moderate to severe TBI (mean GCS = 7.8) to healthy, age- and gender-matched controls whilst walking and stepping over obstructions with and without simultaneous Stroop task testing (cognitive task working with combination of colours and words). They demonstrated greater DTC for individuals with a TBI, who were significantly slower at the walking tasks.

In addition to changes in gait speed, postural sway and gait stability are also affected during dual-task conditions. Parker *et al*. (2005) assessed ten individuals with concussion (within 48 hours of injury) during two conditions: 1) walking (single task) and 2) walking whilst completing simple mental tasks (dual-task) and how they compared with age-, height-, weight-, and activity-matched controls (uninjured, n = 10). Their outcomes measures included gait velocity, stride length, stride time, step width, centre of mass (CoM), and centre of pressure (CoP). Both groups presented significant decrements in gait and CoM measurements during the dual-tasking exercises, with the TBI group demonstrating larger deficits in the CoM sway outcomes compared to the control group. These results mirrored the findings by the earlier study conducted by Geurts *et al*. (1999) who also found patients with mild TBI showed greater increases on CoP fluctuations during dual-task exercises (motor and cognitive) compared with uninjured subjects.

The use of DT training programmes have previously been used in healthy (Pellecchia, 2005), elderly (Silsupadol *et al*., 2009), chronic stroke (Yang *et al*. 2007), and Parkinson's disease (Yogev-Seligmann *et al*., 2012) populations and has shown to be feasible and to illicit significant improvements in walking speeds and DT ability. Pellecchia (2005) suggested that DT practise could improve DT performance. This short programme involved 18 healthy individuals (aged between 18-46 years) being randomised into three groups (no training, single task training, and DT training) with postural sway being the outcomes measure. The training groups performed three sessions over the course of one week incorporating of cognitive (counting backwards starting from a randomised 3-digit number) and postural (quiet standing on a compliant surface) tasks. Following the one-week training period, the no training and single task training groups demonstrated increased postural sway when performing the cognitive and postural task simultaneously, whereas the DT training group showed no increase in postural sway. All three other studies' implementation supervised DT training programmes over a four-week period (three times a week and lasting between 25-45 minutes per session). The two RCTs (Silsupadol *et al*., 2009; Yang *et al*. ,2007) had equally matched experimental groups in terms of sample number, age, and gender. The three studies all presented significant improvements in gait speed ($p<0.05$), with Silsupadol *et al.* (2009) showing additional significant improvements in balance ($p<0.001$) amongst the DT exercise groups.

In TBI populations, the effects of DT training programmes are sparse. Couillet *et al*. (2009) investigated the effects of a DT training programme amongst patients with severe TBI (>5 months post injury). Individuals were randomised into two groups AB (CON then EX, n=5, aged 23.8 years, 6.3 months since injury) and BA (EX then CON, n=7, aged 26.7 years, 16.1 months since injury). Individualised DT exercises were trained for one-hour session, four times a week for six weeks. These tasks were match as closely as possible to the daily needs of each individual (e.g. cooking tasks, shopping). During the CON phases, individuals performed tasks that did not tap on divided attention (e.g. simple problem solving, simple visual search tasks). During the specific divided attention measures (the divided attention subtest of the TAP and the go-no go and digit span dual-task test), a significant training-related effect was demonstrated ($p<0.001$). These results suggest that training had specific effects on divided attention and helped patients to deal more rapidly and more accurately with dual-task situations.

In addition, a case study by Fritz & Basso (2013) also highlighted the feasibility and possible functional improvements of incorporating cognitive-motor DTs to standard physical therapy in the inpatient rehabilitation settings amongst severe TBI populations. They included a seven-day directed intervention of DT training comprised of motor-motor and cognitive-motor dual tasks (yielding an average of 180 minutes over the seven days). However due to the sample number being one, it was not possible to determine the extent to which the DT training contributed to the improvements in the 'walking while talking' and the 'trail making' tests. Both studies demonstrated to possible positive effects of DT training on individuals with severe TBI. To gather a more generalised overlook of DT training, all severities of TBI should be acknowledged. However robust studies comparing the effects of DT training on different TBI severities are currently non-existent.

Damiano et al. (2016) assessed DT performance after an 8-week resistance (elliptical trainer) programme comparing TBI (n = 12) and non-TBI (n = 12) individuals. Similarly to previous research, the TBI group had poorer DT performance at baseline compared to the non-TBI group. No significant improvements in DT performance was presented after the 8-week programme. This lack of improvement has also been shown in previous literature whereby DT performance has only showed to improve if the intervention id specific to the testing paradigm (Evans *et al.*, 2009; Silsupadol *et al.*, 2009). However, in the study by Damiano et al., (2016) the poor DT performances in the TBI group showed a strong relationship with higher anxiety (r = 0.71, p = 0.02). This emphasises the importance of DT performance and the effects it can have on individuals following a TBI. For this reason, the inclusion of DT activities within an exercise-based rehabilitation programme is justified.

2.9 Quality of life

Following a TBI, it is not only the physical deficits that require treatment; psychological changes play an important role in recovery. Exercise has shown to enhance self-esteem and an individual's ability of coping with stressful situations that occur post-injury, making exercise an integral component of rehabilitation (Driver *et al*., 2006). Therefore, participating in an exercise programme could enhance overall health and well-being. This information should inform health professionals' rehabilitation strategies when working with individuals following TBI.

2.9.1 Depression

Mild to moderate depressive disorder is common following a TBI and has been ranked second in diseases for years lost due to disability or premature deaths, just behind ischemic heart disease (Murray & Lopez, 1997). In a study conducted by Bombardier *et al.* (2010), 53% of their 559 participants met the criteria for major depression at some point during the first year after TBI. They established that the risk of major depression following a TBI was associated with depression at the time of the injury, with these individuals more at risk of poorer health-related quality of life compared to healthy, non-inured controls.

Dikmen *et al*. (2004) investigated the rates and risk factors of depression over three to five years after a TBI. Participants (n = 283) had a mean age of 35.5 years with TBI severities ranging from mild to severe (mean GCS score of 12.4). Depressive symptoms were assessed using the Centre of Epidemiologic Studies Depression (CES-D) scale (rates the frequency of symptom occurrences). They documented overall high rates of depressive symptoms up to five years post injury with nearly half (46%) of participants presenting with a level of depression that would be considered clinically significant. Unfortunately, they were unable to show a reliable association between TBI severity and depressive symptoms. Both Bombardier *et al*. (2010) and Dikmen *et al.* (2004) highlighted the high prevalence of depressive symptoms following a TBI across all severities, emphasizing the need for more individualised treatment therapies with considerations towards the participants' pre-injury mental health status.

Detecting depression following a TBI is important, as left undetected or untreated it may affect functional recovery negatively, even heighten cognitive and behavioural difficulties. Deterioration of cognitive functioning (Chamelian & Feinstein, 2006), increased anxiety (Uomoto & Esselman, 1995) and aggressive behaviour (Jorge *et al*., 2004) are apparent in individuals with depression compared with others who have a TBI without depression. Individuals who experienced a mild TBI will often present signs of depression when they are admitted to emergency rooms (Levin *et al*., 2005) and post-injury referral services (Rapport *et al*., 2003).

Bateman *et al*. (2001) examined the impact of an aerobic exercise programme against relaxation therapy in a cohort of brain-injured individuals with a mean age of 42 years. Participants had an array of brain injuries including TBIs, strokes and haemorrhages all with a mean time since injury of 22.2 weeks. The severity of these injuries were not specified. Participants in the exercise group performed 30 minutes of aerobic cycling (cycling ergometer) three times a week for 12 weeks, working at an intensity of 60 - 80% of age-predicted maximum heart rate. Their outcomes measures included exercise capacity (work rate and heart rate), Berg Balance Scale (BSS), Rivermead Mobility Index (RMI), Barthel Index, FIM, Nottingham Extended Activities of Daily Living Index (NEADI) and the Hospital and Anxiety Scale (HADS). Participants in the exercise training group demonstrated significantly greater peak work rates compared to the relaxation group. They failed to demonstrate any significant improvements in the HADS for either group. However, it should be noted that only a few were significantly anxious or depressed at testing points, hence the little scope for change in any event. Therefore this non-significant results may not be a true representation of all TBI and baseline psychological measures should be taken into account.

2.10 Quality of life questionnaires

2.10.1 Short form-36 questionnaire (SF-36)

The SF-36 survey is an instrument for assessing the eight different domains of health-related quality of life and is applicable to many disease groups as well as the general population (Bullinger, 1995). These domains include: physical functioning (PF) role limitations related to physical health problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitations related to emotional problems (RE), and mental health (MH). Individuals are asked to complete the questionnaire by recalling the previous four weeks. All eight domains are scored separately on a scale of zero (negative health) to 100 (positive outcome).

Scholten *et al.* (2015) assessed functional outcome, health-related quality of life with the SF-36, in patients with mild (n = 797, mean age = 45 years), moderate (n = 50, mean age = 47 years) or severe (n = 149, mean age = 39 years) TBI. At both the 6- and 12-month follow-up assessments, the majority (>50%) of all the participants reported higher physical component scores (PCS) then mental component scores (MCS). In relation to TBI severity, participants with moderate or severe TBI had significantly lower outcomes on PCS, PF, RP, SF, and RE than those with mild TBI. They also illustrated that all of the eight domains of the questionnaire showed improvements for mild, moderate and severe TBI at 6- and 12-months post-injury, with the exception of mental health for severe TBI.

A study conducted by Findler *et al*. (2001) also assessed the relationships of SF-36 scores and injury severity in a cohort of 597 individuals. When compared to their control group, all individuals with TBI reported significantly lower health status. Unlike the report by Scholten *et al*. (2015), Findler *et al*. (2001) demonstrated significantly lower scores on all the domain scales when compared to moderate and severe cohorts, with the exception of physical function where there were no intragroup differences. Although these two studies reported different outcomes, they both concluded that the SF-36 was a reliable and valid measure for the use with persons with TBI.

The SF-36 has been used to evaluate quality of life changes following exercise interventions (Elsworth *et al*., 2011; Hoffman *et al*., 2010). Elsworth *et al*. (2011) investigated the feasibility of an individualised exercise intervention for people with long-term neurological conditions (Parkinson's, multiple sclerosis, motor neurone disease, neuromuscular disorders, cerebral palsy, TBI, transverse myelitis). The self-directed intervention ran over 12 weeks and participants were recommended to perform five aerobic and two strength sessions a week. There were no significant differences between the exercise (EX) and control (CON) group at pre-testing for the SF-36 mental ($p = 0.8$) and SF-36 physical ($p = 0.9$) components. Following the 12 weeks, the Ex group significantly improved on the SF-36 physical component scores ($p = 0.05$). However, there were no statistically differences in SF-36 scores between the EX and CON groups but the authors did highlight a moderate effect size for the SF-36 physical component (Cohen = 0.4).

In conjunction with this study, Hoffman *et al*. (2010) also demonstrated increased SF-36 scores (both PCS and MCS) following a exercise intervention (10-week) in a cohort of TBI individuals (severe enough to have required medical attention following injury). However, their results were also non-significant for the physical ($p = 0.2$) and mental ($p = 0.2$) components. The authors then decided to divide the entire sample into two groups. A 'high active' groups included participants who exercised for ≥ 90 minutes a week at baseline and the 'low active' group were those who exercised for < 90 minutes a week at baseline. This highlighted that the SF-36 mental component score was significantly higher in the active group ($p = 0.03$) compared to the low active group. The activity levels of individuals following a TBI could therefore affect their mental QOL.

Even though the SF-36 has been shown to be a reliable and valid quality of life measure for TBI individuals, more RCT trials need to be conducted to establish the effects of exercise interventions on quality of life. Additionally, there is a lack of SF-36 data following dual-task exercise interventions. This could highlight prospective relationships between the PCS and MCS subscales and the physical and mental components of dual-task programmes that could aid the development of more specific programmes in the future.

2.10.2 Rivermead Post-Concussion Symptoms Questionnaire (RPQ)

The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) is used to gauge the severity of Post-Concussion Symptoms (PCS) where the individual is asked to rate the severity of symptoms comparing them to pre-injury. The listed PCS used in this questionnaire are those that are most commonly reported in the literature, including headaches, feelings of dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, irritable, depressed, frustration, forgetfulness, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, and restlessness. King *at el.*, (1995) undertook a study investigating the reliability of the RPQ when used as a self-administered or as a clinically administered measure, either conducted early (7 - 10 days) or late (six months) post-injury. All 16 items were assessed individually, then were summed to find an overall score. The overall scores presented good inter-rater reliability, with ICC = 0.90 7 - 10 days post-injury and ICC = 0.87

at six months, using r_s Spearman rank correlation coefficient. When individual items were analysed, headaches, dizziness, forgetfulness, noise sensitivity and poor concentration were rated the highest reliability significance. They subdivided each symptom and found that fatigue was most commonly associated with irritability and frustration. Issues with headaches and sleep were found to become less common, along with nausea and disturbances with vision. These later complaints were shown to be less prevalent at 6 months post-injury. When looking at the reliability of individual PCS, King *et al*. (1995) established that headaches, dizziness, noise sensitivity, forgetfulness and poor concentration were among the most reliable symptoms. This was possibly because they were easier for the patients to identify and were the most constantly experienced symptoms. On the other hand, the least reliable PCS emerged as feeling depressed, frustration, restlessness and taking longer to think. Apart from the differences in the reliability ratings for individual symptoms, King *et al*. (1995) concluded that the RPQ was a reliable tool and its use by clinicians and researchers was strongly encouraged. The RPQ should be used for the assessment of progress and regression, rather than for actual diagnostic purposes for PCS.

Smith-Seemiller *et al.* (2003) subdivided the PCS of the RPQ into three groups: cognitive, somatic and emotional. They used this method to compare scores from individuals who had mild TBI against whose who suffered from chronic pain, concluding that both groups showed similar overall totals and somatic symptoms. Individuals with mild TBI reported higher rates in the cognitive sub-score hereby chronic pain sufferers presented a trend towards more emotional symptoms. Potter *et al*. (2006), supported the subdivision method in cognitive, somatic and emotional sub-scores, however, a high degree of co-variation was found between the different groups of symptoms. To combat these variations, a two-factor solution was generated that conjoined the somatic and emotional symptoms into one group. Potter *et al*. (2006) indicated that this use of the emotional-somatic group fitted reasonably well with their data. There is still limited significant evidence of the differences in effectiveness are for these two variations of the RPQ analysis. Eyres *et al*. (2005) are also in agreement that the 16 items of the RPQ should not be analysed and summated into a single score, but instead be split into two separate scales indicating RPQ-13 and RPQ-3. These two subdivisions are not corresponding to the somatic-emotional scale. The items for headaches, dizziness and nausea showed no relation to injury severity if analysed alongside the remaining 13 items (RPQ-13). On their own, Eyres *et al*. (2005) found that the sub-scores fitted well with their chosen statistical method (Rasch model) and could be summated to form a single scale. Therefore, the RPQ can be divided into the RPQ-13 and RPQ-3 which have been shown to demonstrate good test-retest reliability and adequate external construct validity (Eyres *et al*., 2005). Symptoms following a mild TBI can be clustered into two groups: early and late, drowsiness, headaches, dizziness and nausea typically presenting during the early stages. During the later stages (at least a few days or weeks post-injury) individuals will display symptoms consisting of physical, cognitive and emotional behaviours (Ryan & Warden, 2003). Even though these clusters were formulated, headaches and dizziness have been reported in both early and late stages of the injury (Eyres *et al.*, 2005).

2.10.3 Hospital Anxiety and Depression Scale (HADS)

The HADS was developed by Zigmond & Snaith (1983) with the hope to create a tool to identify the likelihood of anxiety disorders and depression among TBI patients. It is a self-report measure used as an assessment of the previous week. These two outcomes are measured by splitting the questionnaire into two sections: HADS-A for anxiety and HADS-D for depression. These disorders are common amongst TBIs, with up to 60% fitting the criteria for anxiety disorders and approximately 33% of individuals developing major depression (Driskell *et al.*, 2016). Depression and anxiety post-TBI are associated with poor cognitive, social and functional outcomes (Bombardier *et al*., 2010), highlighting the importance for early detection to increase the opportunity for improvements in long-term outcomes. Somatic symptoms have been removed from the HADS so that they do not interfere with the scores; questions relating to headaches, dizziness or insomnia are absent. Individuals rate each item on a 4-point scale ranging from zero (not at all) to three (very often). Scores for both HADS-A and HADS-D are summed up separately, with higher scores indicating greater levels of anxiety or depression. A score of 0-7is considered normal, 8-10 = borderline abnormal (mild), 11-14 abnormal (moderate) and 15-21 = abnormal (severe).

Van der Horn *et al*. (2013) investigated the relationship of post-concussive complaints, anxiety and depression in patients with minor, mild, moderate and severe TBIs. The minor TBI (GCS 15) group (n = 51) had a mean age was 42.1 years, the mild TBI (GCS 13 - 14) group (n = 121) had a mean age of 40.3 years and the moderate-severe TBI (3 - 12) group (n = 70) had a mean age of 35.2 years. There was a significant correlation between the presence of post-concussive complaints with the presence of anxiety ($r = 0.67$, $p < 0.01$) and depression ($r = 0.74$, $p < 0.01$). Surprisingly, they showed significantly ($p < 0.05$) higher frequencies for both anxiety and depression in the minor TBI group compared to the other two categories, even though they go on to suggest that the frequency of post-concussion complaints increased with severity of injury. This could be the result of negative perception and interpretation of injury, as these have shown to significantly influence post-concussion symptoms after mild TBI (Hou *et al*., 2012, Whittaker *et al*., 2007). Van der Horn at colleagues (2013) go on to express that it could be plausible that anxiety and depression amongst minor TBI, could be related to illness perception and self-awareness. In a more recent study, Van Der Horn *et al*. (2016) investigated the association between post-injury complaints and anxiety and depression following a mild TBI. The found significant correlations between increased frequency and severity of complaint to increased scores (unfavorable) in anxiety and depression from the HADS. Therefore, caution must be taken when analysing anxiety and depression outcomes across an array of TBI severities, but overall message is that increased post-concussion symptoms are related to increases in anxiety and depression. This highlights the potential benefits of using the RPQ and HADS questionnaire in conjunction when assessing changes to QOL following exercise-based rehabilitation programs.

2.11 Aim and Objectives

The overall aim of this thesis was to assist the clinical recommendations to improve TBI rehabilitation during the acute and long-term recovery phases. In order to achieve this aim, the following objectives were set:

1. To evaluate the effectiveness of exercise interventions for improving QOL in individuals with a TBI through a systematic review of the current literature. The outcomes of this review will inform evidence-based clinical guidelines for rehabilitation programmes for people who have suffered a TBI.
2. To assess the acceptability and feasibility of a 4-week, multi-component exercise intervention in healthy adults in order to inform the design and delivery of an exercise programme for individuals with a TBI.
3. To quantify the differences between single- and dual-tasks (motor and cognitive) in healthy adults, hypothesising that the motor task performance will decrease when performed simultaneously with a cognitive task, thus creating a dual-task cost (DTC). The DTC will be analysed weekly to establish it stabilises and reaches a plateau over a four week period.
4. To undertake a retrospective analysis of A&E admissions data to gain a greater understanding of the epidemiology of TBI in a major hospital in the North East of

England and to inform participant recruitment strategies and inclusion/exclusion criteria in a future study.

5. To evaluate a novel 12-week, multi-component exercise-based intervention on the mental and physical well-being of individuals with a mild to moderate TBI. The primary outcome will evaluate QOL through questionnaires. The secondary outcome will explore the effects of dual-tasking training, and finally the tertiary outcome will assess physical function over the 12-week period and will focus specifically on aerobic capacity, musculoskeletal function and physical mobility.
6. To gather a deeper understanding of the challenges that individuals with a TBI have to face during both acute care and long-term recovery through qualitative interviews. Identifying important issues for people who have had a TBI will inform patient-reported outcome measures for future studies.

3 Chapter Three - The possible effects of exercise on quality of life in individuals with traumatic brain injuries: A systematic review

3.1 Introduction

Traumatic brain injury (TBI) is a global health issue with at least 10 million annual cases, and a major cause of disability, morbidity and mortality (Langlois, Rutland-Brown & Wald, 2006; Corrigan, Selassie & Orman, 2010). Following a head injury, long term consequences can affect the physical, cognitive, behavioural, and emotional functions of the individual causing reduced motor control, sensation deficits, depression, and issues with speech (Langlois, Rutland-Brown & Wald, 2006). In addition, TBIs have been shown to increase the risk of developing other health conditions with individuals being 1.8 times more likely to report binge drinking (Horner *et al.*, 2005), 11 times more likely to develop epilepsy (Horner *et al.*, 2005), and more vulnerable to experiencing depression (Holsinger *et al.*, 2002) and developing Alzheimer's (Plassman *et al.*, 2000). These issues can result in relationship breakdowns (Hammond *et al.*, 2012), job losses (Gilworth *et al.*, 2006) and homelessness (Oddy *et al.*, 2006), leading to significant socioeconomic consequences, with financial burdens on the healthcare system and social stigma.

Regular physical activity is well known for promoting a variety of health benefits including improvements to cardiorespiratory fitness (Fletcher *et al.*, 2018), lower mortality rates (Owen *et al.*, 2010), reduced depressive symptoms (Conn, 2010), and enhancing overall psychological well-being (Guiney & Machado, 2013) in healthy individuals. Exercise, which is a planned, structured form of physical activity, has also been shown to enhance cognitive functioning and facilitate neuroplasticity (Cotman & Berchtold, 2002). For these reasons, exercise has been suggested to play a key role in the rehabilitation of individuals with a TBI. Mossberg and colleagues (2007) compared the aerobic capacity of TBI (n = 13, age range = 22-48 years, severity = mild to severe, mean time since injury = 10.4 months) and non-TBI age- and gender-matched individuals (n = 13, age range = 23-49 years). They demonstrated significantly lower peak responses in heart rate, oxygen consumption ($\dot{V}O_2$), minute ventilation (V_E), and oxygen pulse in the TBI cohort compared to the non-TBI individuals. However, another important outcome is the individuals' quality of life (QOL), (Koskinen, 1998; Kolakowsky-Hayner, Miner & Kreutzer, 2001).

Quality of life is subjective, taking into consideration the individuals' perception of their physical state, cognitive and affective state, interpersonal relationships and social roles in their lives (Whoqol Group, 1995). The World Health Organisation QOL questionnaire includes a spiritual dimension, which examines an individual's perception of 'meaning of life' and overarching personal beliefs (Whoqol Group, 1995). Quality of life is a very complex and broad-ranging concept affected by physical health, independence, psychological state of mind, beliefs, and social relationships. However, in broad terms, QOL has been defined as an "*individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*" (Whoqol Group, 1995, *p1405*). Bergquist and colleagues (1994) asked brain injured individuals to define their perceptions of QOL. Three major dimensions emerged: 1) achieving a sense of productivity; 2) establishing a sense of self-control, self-efficacy, and self-competency; 3) experiencing a sense of community among self, and others. Individuals with TBI report a lower QOL compared with the general population (Andelic *et al.*, 2009; Dijkers, 2004). Quality of life is a complex issue to discuss due to the many indicators including material living conditions, governance and basic rights. The current review will conceptualise QOL definitions by looking at the individuals' physical functioning, mental functioning, social and economic functioning as well as pain, vitality, and general health perceptions. A complete understanding of an individuals' QOL requires an understanding of their values and how objective measures influence their experiences.

Better physical functioning, and participation in fulfilling activities, such as social interactions and returning to employment, have previously indicated QOL improvements following a TBI (O'Neil *et al*., 1998; Webb *et al*., 1995). Additionally, physical activity is reportedly an effective treatment modality for reducing anxiety and somatic conditions in both healthy and TBI individuals (Ströhle, 2009). Due to the positive effects of exercise and physical activity on an individual's QOL, it has been considered a health-promoting self-care behaviour.

Regardless of the extensive research in TBI rehabilitation, there is still disagreement about the most effective exercise modality and general exercise principles in terms of frequency, intensity, time, and type (FITT). The overarching aim of this systematic review was to evaluate the possible effects of exercise interventions for improving QOL in individuals with a TBI. The first objective was to report on and compare the exercise intervention principles (FITT). Secondly, the different QOL tools used in relation to the exercise interventions were reviewed. Finally the effects of exercise interventions on aerobic fitness, balance and neuromuscular function were emphasised. The overall quality of the studies under review was also analysed. These objectives aim to inform future evidence-based guidelines for rehabilitation programmes for people following a TBI.

3.2 Methods

This systematic review was undertaken and reported in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher *et al*., 2009).

3.2.1 Search strategy

Database searches were conducted in PubMed, Web of Science, Scopus, Cochrane, and ProQuest. The specific search terms used were "traumatic brain injury", "TBI", "exercise", "physical activity", and "quality of life". The complete set of Boolean operators are explained in Table 3.1. There was no time restriction in the database search, which was conducted in March 2017 and again in April 2018 ensuring that that the review still displayed the most relevant studies.

Table 3.1. Search terms and phrases associated with each variable used in the search strategy. The Boolean operator OR was used between terms in each column and the term AND was used between columns.

Population	**Intervention**	**Outcome**
Traumatic brain injury	Physical therapy	Quality of life
Brain trauma	Exercise training	Psychometric
TBI	Physical activity	Depression
Brain injury	Dual-task	Health related quality of life
Concussion	Divided attention	QOL
Head injury	Rehabilitation	Life quality
Traumatic encephalopathy		

3.2.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria were formulated using the PICO methodology (Cherry *et al*., 2014).

Studies were included if:

- The population consisted of individuals aged ≥18 years with at least one group of TBI individuals (mild, moderate or severe).
- They incorporated interventions that included at least one form of physical activity defined as *"any bodily movement produced by the contraction of skeletal muscles that results in a substantial increase over resting energy expenditure"(*ACSM, 2013, *p2*)
- Comparisons were made between: intervention frequency, intensity, time and type (FITT principles); exercise and QOL outcomes; or TBI populations and healthy populations.
- Quality of life outcomes measures were reported relating to at least one of the following domains: physical function, mental function, socio-economic function, pain, vitality and/or general health perceptions. The FITT principles of the intervention were also included, focusing on how different interventions affect QOL outcome measures.

All forms of study designs were included apart from review articles and guideline papers in order to maximise available data.

Studies were excluded if:

- They only focused on non-TBI participants (e.g., stroke as this is classified as an acquired brain injury) without making any comparisons with individuals with TBI.
- They included interventions that were solely virtual reality or pharmaceutical.

- The outcomes measures did not incorporate QOL assessment tools that aligned with the inclusion criteria.
- They were not peer-reviewed.

3.2.3 Data extraction and synthesis

Following the database searches and the deletion of duplicates, initially the article titles were screened against the inclusion and exclusion criteria, followed by the abstracts and then a full-text review of potentially included articles against the specific criteria. The final selection of articles were analysed independently by two authors (GO, SK), no major disagreements were encountered and therefore a third reviewer was not required to act as an adjudicator. The data were extracted and organised by category: study identification, aim, participant characteristics and sample size, intervention characteristics, QOL outcome measures, and results.

3.2.4 Outcomes measures

The primary outcome measures compared the FITT principles of the exercise interventions, looking at participant characteristics and completion rates. Secondly, the outcomes from the QOL tools were analysed in relation to the exercise interventions. Quality of life assessment tools must have presented information related to at least one of the following domains: 1) physical functioning, 2) mental function, 3) social and economic function, 4) pain, 5) vitality, and 6) general health perceptions. This included (but not limited to) tools that measured depression, anxiety, stress, social interactions, sleep quality, and functional independence. Quality of life was quantified using validated questionnaires, including a mixture of generic or condition-specific scales developed to measure QOL especially. Finally, aerobic fitness, balance and neuromuscular function outcomes were analysed to highlight changes as a result of the exercise interventions where QOL had been measured.

3.2.5 Quality assessment

The methodological quality of the included studies was assessed using a checklist developed by Downs & Black (1998) which is suitable for both randomised and non-randomised studies. It consists of several components including: (1) Reporting (ten items): assessing whether the information provided is sufficient; (2) External Validity (three items): addressing the extent to which the findings could be generalised to the population; (3) Bias (seven items): addressing biases in the measurement of intervention and outcomes; (4) Confounding (six items): assessing bias in the selection of study subjects; and (5) Power (one item): assessing whether the negative findings could be due to chance. Answers were scored 0-1, except for one item in the Reporting component (scored 0-2) and the Power subscale (scored 0-5). The total maximum score was 33. Overall scoring can be categorised into good (>20), moderate (11-20) and poor (<11), (Downs & Black, 1998). The methodological quality was assessed by two independent reviewers with any disagreements being resolved before continuation of the analysis.

3.3 Results

3.3.1 Search results

The initial search returned 5128 articles (Web of Science: 1309, PubMed: 1804, Scopus: 1581, Cochrane: 238 and ProQuest: 196). The duplicate articles (2023) were identified and excluded leaving 3105 studies for the initial stage of the review (Figure 3.1). Most articles were excluded because they focused on interventions that did not include all three comparators (TBI, exercise and QOL); the main outcomes did not include QOL assessments; or the articles were animal studies. Both reviewers screened 43 full-text articles. Eleven papers were excluded because the details of the intervention were ambiguous. A further eight articles did not include QOL questionnaires that matched the inclusion criteria, so were also excluded from the review. Nine studies were included in the final analysis according to the unanimous decision of two authors.

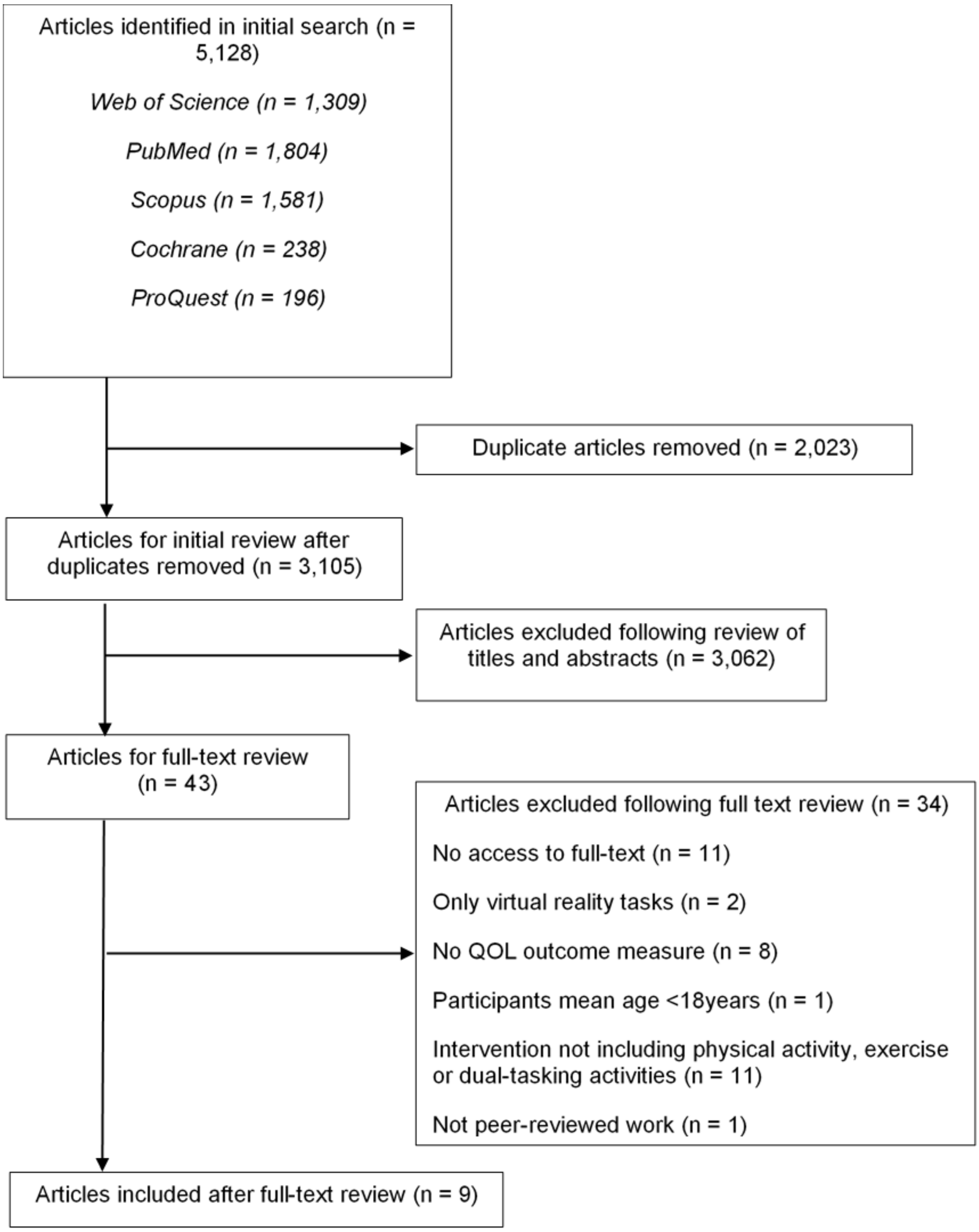

Figure 3.1.PRISMA flowchart of literature screening process.

3.3.2 Excluded studies

During the final search, 34 articles were excluded for at least one of the following reasons:

No access to full-text (n = 11); intervention only included virtual reality (n = 2); no clear

QOL tools were measured (n = 8); inclusion of participants aged <18 years (n = 1); intervention did not include physical activities, exercise or dual-tasking sessions (n = 11); the output was not peer-reviewed (n = 1).

3.3.3 Quality assessment

The total scores ranged between 18 (Kleffelgaard *et al*., 2016; Schwandt *et al*., 2012) and 29 (Hassett *et al*., 2009), (Table 3.2) with seven of the nine studies receiving a score of >20, categorised as 'good', and the remaining two both scoring 18 ('moderate'). All nine articles offered clear main outcomes, described the interventions in their methodology, and included participants that were representative of the TBI population described in the inclusion criteria. All presented adjustments for different lengths of follow-up for participants and exhibited valid and reliable outcome measures. The lowest ratings were for internal validity sub-sections measuring bias, with only three studies attempting to blind the researchers (Hassett *et al.*, 2009; Bateman *et al*., 2001; Elsworth *et al*., 2011). When the Downs and Black (1998) checklist was broken down into the individual questions, some limitations become apparent. Out of the nine studies included, five specified random allocations to treatment groups in their methods (Hassett *et al.*, 2009; Bateman *et al*., 2001; Elsworth *et al.*, 2011; Driver *et al.*, 2006; Hoffman *et al.*, 2010). Out of these five randomised papers, one did not include a description of the randomisation method (Hassett *et al.*, 2009), while only one other made adjustments for confounding in the analysis (Elsworth *et al*., 2011). All the studies scored zero (answering 'no') for blinding the participants to the intervention they received. This was inherently impossible as all of the interventions involved exercis

Table 3.2. Methodological quality assessment scoring using an assessment tool for randomised and non-randomised trials (Downs & Black, 1998).

	Reporting										**External validity**			**Internal Validity-Bias**							**Internal Validity-Confounding**							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
Study	Hypothesis/ Aims	Outcomes	Patient information	Interventions	Principle confounders	Findings	Variability Estimates	Adverse effects	Withdrawal	Exact probability	Represents Population Asked	Represents Population Included	Represents Facilities	Participant Blinding	Researcher Blinding	Data Dredging Clear	Follow up Adjustments	Appropriate Statistics	Intervention Compliance	Validity & Reliability	Participant Groups From Same Population	Recruitment Groups & Time Periods	Randomisation	Hidden Randomisation	Confounding Adjustment	Withdrawal Accounted for	Power	Total Score
Bateman (2001)	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	1	5	28
Chin (2015)	0	1	1	1	1	1	1	1	0	1	1	1	0	0	0	1	1	1	1	1	1	1	0	0	0	0	4	21
Damiano (2016)	0	1	1	1	1	1	1	1	0	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	0	5	23
Driver (2006)	1	1	1	1	1	1	1	0	0	1	1	1	1	0	0	1	1	1	0	1	1	1	1	0	0	0	5	23
Elsworth (2011)	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	0	1	1	5	27
Hassett (2009)	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	5	29
Hoffman (2010)	1	1	0	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	1	0	0	0	5	22
Kleffelgaard (2015)	1	1	1	1	1	1	0	1	1	0	1	1	0	0	0	0	1	0	1	1	1	1	0	0	0	1	2	18
Schwandt (2012)	1	1	1	1	0	1	0	1	1	0	1	1	0	0	0	1	1	0	1	1	1	1	0	0	0	1	2	18

3.3.4 Study characteristics

3.3.4.1 Participants

The number of participants that took part in the exercise sessions varied from 4 to 55 across all nine studies (Table 3.3). All nine reported on both female and male participants, across a varied age range between 24 and 65 years. Six out of the nine investigated the effects of exercise on people with TBI exclusively (Kleffelgaard *et al.*, 2016; Schwandt *et al.*, 2012; Hassett *et al*., 2009; Hoffman *et al*., 2010; Chin *et al*., 2015; Damiano *et al.*, 2016), while the remaining three articles grouped together a variety of brain related injuries that included TBI (Bateman *et al*., 2001; Elsworth *et al.*, 2011; Driver *et al.*, 2006). One study (Bateman *et al.*, 2001) included participants who had suffered strokes and haemorrhages, whereas another included people with Parkinson's disease, multiple sclerosis, motor neurone disorders, and cerebral palsy (Elsworth *et al*., 2011). One paper (Driver *et al*., 2006) did not specify how the brain-injured participants incurred their injuries. The severity of the TBI ranged from mild to severe (Glasgow Coma Score of 13-15 for mild, 9-12 for moderate and 3-8 for severe) across all nine studies. Five out of the nine, reported on cases where the time since injury was six months or longer (Schwandt *et al.*, 2012; Driver *et al.*, 2006; Hoffman *et al*., 2010; Chin *et al*., 2015; Damiano *et al.*, 2016), with two studies including participants who had sustained the injury in under six months (Hassett *et al.*, 2009; Bateman *et al*., 2001). Two papers did not specify the time since injury (Kleffelgaard *et al.*, 2016; Elsworth *et al*., 2011).

Table 3.3.Study characteristics and population data for included studies

Study								Population			
Author	**Study type**	**Country of origin**	**Total sample size (n)**	**EX group sample size (n)**	**Gender**	**Mean age (years)**		**Diagnosis**	**Severity (GCS)**	**Mean time since injury (months)**	
						EX	**CON**			**EX**	**CON**
Bateman (2001)	RCT	UK	157	55	M & F	41.7	44.7	TBI, stroke, haemorrhage, other	NR	5.1	5.9
Chin (2015)	Pre-post design	USA	7	7	M & F	33.3	n/a	TBI	Mild to moderate	48	NR
Damiano (2016)	Clinical trial	USA	24	10	M & F	31.3	32.5	TBI	NR	90	NR
Driver (2006)	RCT	USA	18	9	M & F	37.8	35.3	Brain injury	NR	40.3	41.2
Elsworth (2011)	RCT	UK	99	48	M & F	55	57	Parkinson's, multiple sclerosis, motor neurone disease, neuromuscular disorders, cerebral palsy, TBI, transverse myelitis	NR	NR	NR
Hassett (2009)	RCT	Australia	62	32	M & F	35.4	33	TBI	Severe to very severe	2.6	2.3
Hoffman (2010)	RCT	USA	80	37	M & F	39.7	37.1	TBI	NR	6-60	6-60
Kleffelgaard (2015)	Case study	Norway	4	4	M & F	36	n/a	TBI	Mild	NR	NR
Schwandt (2012)	Pilot study	USA	4	4	M & F	29	n/a	TBI	Moderate to severe	31.2	NR

3.3.4.2 Interventions

The duration of the exercise interventions varied from eight to twelve weeks (Table 3.4). Sessions ranged from 30 to 90 minutes with frequencies fluctuating widely from two to five times per week. The most common exercise plan involved exercise sessions lasting 30 minutes, performed three times weekly (Schwandt *et al*., 2012; Bateman *et al*., 2001; Chin *et al*., 2015).

Four studies demonstrated good completion rates of 77% (Hassett *et al*., 2009), 78% (Schwandt *et al*., 2012), 93% (Chin *et al*., 2015) and >80% (Damiano *et al*., 2016). In one case series (Kleffelgaard *et al*., 2016), the four participants attended between 8 and 15 sessions out of the maximum 16. Another documented the number of sessions performed per week, with 44% partaking in ≥1 session, 8% ≥2 sessions and 2% ≥3 sessions (Elsworth *et al*., 2011). During the supervised sessions in one study (Hoffman *et al*., 2010) only 5.9 sessions were attended over the 10 weeks out of a maximum of 10. The paper by Bateman and colleagues (2001) outlined that the average total minutes of exercise performed by the exercise group was 552 minutes, which was only 51% of the maximum 1,080 minutes. The average time spent exercising for each session was 23 minutes out of the maximum 30 minutes. Only one study did not present any adherence rates (Driver *et al*., 2006).

All of the papers delivered supervised exercise programmes with the exception of one, whereby it encouraged an unsupervised self-directed exercise intervention at the local gym (Elsworth *et al*., 2011). Three studies (Kleffelgaard *et al*., 2016; Hassett *et al*., 2009; Hoffman *et al*., 2010) included both supervised and un-supervised (home-based) exercise sessions. Six of the nine studies included aerobic exercises (aquatic aerobics, treadmill walking/running, stationary biking, stair-stepping, rowing, track running) as part of the intervention (Schwandt *et al*., 2012; Bateman *et al*., 2001; Elsworth *et al*., 2011; Driver et al., 2006; Hoffman *et al*., 2010; Chin *et al*., 2015), with two concentrating on motor control, balance, and strength and conditioning training(Kleffelgaard *et al.*, 2016; Damiano *et al.*, 2016). The study by Hassett et al. (2009) combined both strength and cardiovascular work in their exercise sessions. The intensity of the exercise sessions ranged from 50-80% of an individual's maximum heart rate. One article used revolutions per minute (RPM) to gauge intensity, where participants maintained 40-80 RPM on an elliptical trainer (Damiano *et al.*, 2016). Hassett et al. (2009) categorised their cardiovascular intensity as moderate (heavy breathing but could talk). Two studies did not report exercise intensities (Kleffelgaard *et al.*, 2016; Elsworth *et al.*, 2011). Six of the nine papers included a control group (Hassett *et al.*, 2009; Bateman *et al*., 2001; Elsworth *et al*., 2011; Driver et al., 2006; Hoffman *et al.*, 2010; Damiano *et al*., 2016) while the remaining three only presented findings for the intervention group (Kleffelgaard *et al*., 2016; Schwandt *et al*., 2012; Chin *et al.*, 2015).

Table 3.4.Intervention characteristics for included studies, detailing the exercise FITT principles (frequency, intensity, time, type), comparison groups, and the QOL outcome measures.

Study	Exercise modality – and equipment	Duration	Frequency (per week)	Intensity	Control/ comparison group	QOL outcome measures
Bateman (2001)	Aerobic – stationary cycling	12 weeks	3 x 30 minutes	60-80% HRmax	Relaxation exercises - TBI	BBS, RMI, Barthel index, FIM, NEADL, HADS
Chin (2015)	Aerobic – treadmill	12 weeks	3 x 30 minutes	70-80% HRR	NR	PSQI, BDI-II
Damiano (2016)	Motor control training – elliptical trainer	8 weeks	5 x 30 minutes	40-80 rpm	Continued daily routine - healthy	HAMD,PSQI, BAI, PTSD (PCL-C)
Driver (2006)	Aerobic and resistance – aquatics	8 weeks	3 x 60 minutes	50-70% HRmax	Vocational rehab classes - TBI	HPLP-II, PSDQ
Elsworth (2011)	Cardiovascular, strength and flexibility training – gym equipment	12 weeks	At least one session	NR	Standard treatment – TBI	SF-36, FSS,
Hassett (2009)	Cardiorespiratory and strength training – gym equipment	12 weeks	3 x 60 minutes	Moderate (heavy breathing but able to talk)	Home exercise programme - TBI	DASS, POMS, BICRO-39
Hoffman (2010)	Aerobic – treadmill, stair-stepper, rowing machine, stationary bike, track running	10 weeks	1 x 30 minutes (supervised) and 4 x 30 minutes (unsupervised)	60% HRmax	Continued daily routine - TBI	BDI, BPI, PSQI, Head injury symptom checklist, SF-36, PQOL.
Kleffelgaard (2015)	VR and strength and conditioning – circuit training	8 weeks	1 x 90 minutes and 1 x 60 minutes	NR	NR	RPQ, QOLIBRI, HADS
Schwandt (2012)	Aerobic – treadmill, stationary bike, stepping machine	12 weeks	3 x 30 minutes	60-75% HRmax	NR	HAMD, RSES

BAI = Beck Anxiety Inventory, BBS = Berg Balance Scale, BDI-II = Beck Depression Index version 2, BICRO-39 = Brain Injury Community Rehabilitation Outcome, BPI = Brief Pain Inventory, DASS = Depression Anxiety Stress Scale, FIM = Functional Independence Measure, FSS = Fatigue Severity Scale, HADS = Hospital and Anxiety Scale, HAMD = Hamilton Depression inventory, HRmax = Maximum Heart Rate, HRR = Heart Rate Reserve, NEADLI = Nottingham Extended Activities of Daily Living scale, NR = Not Reported, POMS = Profile of Mood States, PQOL = Perceived Quality Of Life scale, PSDQ = Physical Self-Description Questionnaire, PSQI = Pittsburg Sleep Quality Index, PTSD (PCL-C) = Post-Traumatic Stress Disorder (checklist-civilian version), QOLIBRI = Quality Of Life after Brain Injury, RMI = Rivermead mobility index, RPQ = Rivermead Post-concussion symptoms Questionnaire, RSES = Rosenburg Self-Esteem Scale, SF-36 = Short Form questionnaire 36, TBI = Traumatic Brain Injury, VR = Virtual Reality, NR = Not reported

3.3.4.3 Reported outcome measures

The primary outcomes were QOL assessment tools for seven (Kleffelgaard *et al*., 2016; Schwandt *et al*., 2012; Bateman *et al*., 2001; Driver et al., 2006; Hoffman *et al*., 2010; Chin *et al*., 2015; Damiano *et al*., 2016) of the nine studies, with the remaining two specifying QOL elements as their secondary outcomes (Hassett *et al*., 2009; Elsworth *et al*., 2011). Four of the articles also included outcomes related to aerobic fitness (Schwandt *et al*., 2012; Hassett *et al*., 2009; Bateman *et al*., 2001; Chin *et al*., 2015); three quantified balance outcomes (Kleffelgaard *et al*., 2016; Bateman *et al*., 2001; Hoffman *et al*., 2010); one measured strength and power (Elsworth *et al*., 2011), and one determined body composition (Hassett *et al*., 2009).

3.3.5 Effects of interventions

3.3.5.1 Quality of life

All nine studies used more than one QOL tool or QOL-related tool (Table 3.5). Twenty-three different instruments were used to assess QOL. The most frequently used QOL outcome tool was the Pittsburg Sleep Quality Index (PSQI) (n=3), (Hoffman *et al*., 2010; Chin *et al*., 2015; Damiano *et al*., 2016), followed by the Hospital Anxiety and Depression Scale (HADS) (n=2), (Kleffelgaard *et al*., 2016; Bateman *et al*., 2001), and the Becks Depression Index (BDI) (n=2), (Hoffman *et al*., 2010; Chin *et al*., 2015). The majority of the QOL assessments were measured at baseline and repeated post-intervention (two testing points). Two studies had an additional follow-up assessments that included QOL tools, (Hassett *et al*., 2009; Bateman *et al*., 2001).

Significant improvements in at least one QOL measure from baseline to post-intervention were reported in six of the nine papers. Measures included the Barthel index (BI) (Bateman *et al*., 2001), Pittsburgh Sleep Quality Index (PSQI) (Damiano *et al*., 2016), Health-Promoting

Lifestyle Profile II (HPLP-II) and the Physical Self-Description Questionnaire (PSDQ) (Driver et al., 2006), the Brief Pain Inventory (BPI) (Hoffman *et al*., 2010), the Rivermead Post-concussion Questionnaire (RPQ), the Quality Of Life after Brain Injury (QOLIBRI) questionnaire, the Hospital Anxiety and Depression Scale (HADS) (Kleffelgaard *et al*., 2016), and the Hamilton rating for Depression (HAMD) and the Rosenburg self-esteem scale (Schwandt *et al*., 2012). Three studies did not report any significant benefits in their QOL assessments following exercise (Hassett *et al*., 2009; Elsworth *et al*., 2011; Chin *et al*., 2015). The following QOL tools indicated improvements with lower scores: PSQI, RPQ, QOLIBRI, HADS, HAMD, and Rosenburg. Conversely, the BI, HPLP-II and BPI tools featured improvements with higher scores.

Table 3.5.The effects of the exercise interventions on QOL outcome measures for each study.

Study	QOL tool	Exercise			Control		
		Pre	Post	Change	Pre	Post	Change
Bateman (2001)	BSS	39.6	46.5	↑	37.7	44.7	↑
	RMI	8.2	10.9	↑	8.2	10.6	↑
	Barthel index	14.2	17.0	↑	13.8	17.3	↑
	FIM (total)	88.9	105.6	↑	85.7	101.4	↑
	NEADL	43.4	32.1	↓	44.1	32.5	↓
	HADS (anxiety)	5.6	5.0	↑	6.1	5.5	↑
	HADS (depression)	5.7	5.5	↑	6.6	5.8	↑
Chin (2015)	PSQI	4.6	3.7	↑	NA	NA	NA
	BDI-II	7.7	4.6	↑	NA	NA	NA
Damiano (2016)	HAMD	4.9	3.4	↑	1.1	NR	NR
	PSQI	5.2	3.5	↑	NR	NR	NR
	BAI	7.3	5.6	↑	NR	NR	NR
	PTSD (PCL-C)	30.1	25.5	↑	9.6	NR	NR
Driver (2006)	HPLP-II						
	-HR	3.4	2.9	↓	2.4	2.4	=
	-PA	2.3	2.9	↑	2.4	2.3	↓
	-Nutrition	2.4	0.6	↓	2.5	2.5	=
	-SG	2.5	2.9	↓	2.6	2.6	=
	-IPR	2.6	3.0	↑	2.6	2.6	=
	-SM	2.8	2.8	=	2.7	2.7	=
	PSDQ (self-esteem)	3.7	4.4	↑	3.8	3.8	=
Elsworth (2011)	SF-36						
	-Mental	51.4	5.3	↑	50.5	51.6	↑
	-Physical	28.9	33.0	↑	28.6	29.3	↑
	FSS	4.4	4.1	↑	4.4	4.2	↑
Hassett (2009)	DASS						
	-Depression	1	5	↓	1	1	=
	-Anxiety	2	2	=	2	1	↑
	-Stress	3	4	↓	3	2	↑
	POMS						

	-Vigour		58	56	↓	60	61	↑
	-Tension		37	38	↓	36	37	↓
	-Depression		40	41	↓	39	39	=
	-Anger		44	47	↓	43	43	=
	-Fatigue		46	47	↓	44	43	↑
	-Confusion		40	45	↓	41	41	=
	BICRO-39							
	-Socialising		14	14	=	12	14	↓
	-Psychological		7	10	↓	7	7	=
Hoffman (2010)	BDI		21.5	16.4	↑	24.7	21.2	↑
	BPI		3.8	3.1	↑	3.5	3.5	=
	PSQI		10.0	9.0	↑	10.6	10.9	↓
	HISC		11.0	11.8	↓	11.4	11.4	=
	SF-12							
	-Mental		31.8	38.3	↑	28.2	32.5	↑
	-Physical		41.6	42.0	↑	41.4	39.5	↓
	PQOL		54	58.0	↑	45	49	↑
Kleffelgaard (2015)	Patient 1	HADS	20	14.0	↑	NA	NA	NA
		RPQ-3	9	2.0	↑	NA	NA	NA
		RPQ-13	13	12.0	↑	NA	NA	NA
		QOLIBRI	40	43.0	↑	NA	NA	NA
	Patient 2	HADS	20	10.0	↑	NA	NA	NA
		RPQ-3	5	0.0	↑	NA	NA	NA
		RPQ-13	27	4.0	↑	NA	NA	NA
		QOLIBRI	41	67.0	↑	NA	NA	NA
	Patient 3	HADS	19	11.0	↑	NA	NA	NA
		RPQ-3	10	10.0	=	NA	NA	NA
		RPQ-13	36	24.0	↑	NA	NA	NA
		QOLIBRI	38	68.0	↑	NA	NA	NA
	Patient 4	HADS	20	23.0	↓	NA	NA	NA
		RPQ-3	5	5.0	=	NA	NA	NA
		RPQ-13	40	28.0	↑	NA	NA	NA
		QOLIBRI	43	54.0	↑	NA	NA	NA
	HAMD		23.8	12.5	↑	NA	NA	NA

Schwandt (2012)	RSES	13.3	21.3	↑	NA	NA	NA

Upward arrow indicates improvement, downward arrow indicates detriment, equal sign indicates no change

BAI = Beck Anxiety Inventory, BBS = Berg Balance Scale, BDI-II = Beck Depression Index version 2, BICRO = Brain Injury Community Rehabilitation Outcome, BPI = Brief Pain Inventory, DASS = Depression Anxiety Stress Scale, FIM = Functional Independence Measure, FSS = Fatigue Severity Scale, HADS = Hospital and Anxiety Scale, HAMD = Hamilton Depression inventory, HISC = Head Injury Symptoms Checklist, HR = Health Responsibility, HRmax = Maximum Heart Rate, HRR = Heart Rate Reserve, IPR = Inter-personal Relationships, NA = Not Applicable, NEADLI = Nottingham Extended Activities of Daily Living scale, NR = Not Reported, PA = Physcial Activity, POMS = Profile of Mood States, PQOL = Perceived Quality Of Life scale, PSDQ = Physical Self-Description Questionnaire, PSQI = Pittsburg Sleep Quality Index, PTSD (PCL-C) = Post-Traumatic Stress Disorder (checklist-civilian version), QOLIBRI = Quality Of Life after Brain Injury, RMI = Rivermead mobility index, RPQ = Rivermead Post-concussion symptoms Questionnaire, RSES = Rosenburg Self-Esteem Scale, SF-36 = Short Form questionnaire 36, SG = Spiritual Growth, SM = Stress Management, TBI = Traumatic Brain Injury, VR = Virtual Reality.

3.3.5.2 Aerobic fitness

Two articles presented increased peak work rates following their 12-week exercise programmes (Bateman *et al*., 2001: Chin *et al*., 2015), and one of these reported higher peak $\dot{V}O_2$ and improved $\dot{V}O_2$ at anaerobic threshold (Bateman *et al*., 2001). Another paper that reported aerobic fitness, demonstrated improved peak power output, decreased resting heart rate, and lower rate of perceived exertion (RPE) measured on the Borg scale after 12-weeks of aerobic training (Schwandt *et al*., 2012). One also quantified (resting) heart rate but did not note any significant changes (Bateman *et al*., 2001). The study by Hassett et al.(2009) described improved fitness by demonstrating an increased maximal velocity and distance covered during a modified 20 m shuttle test, but these changes were not statistically significant.

3.3.5.3 Balance and neuromuscular function

Two out of the three studies that reported balance outcomes presented significant improvements (Kleffelgaard *et al*., 2016; Damiano *et al*., 2016), (Table 3.6). Of these two, one reported improvements in the NeuroCom assessments using computerised dynamic posturography, specifically in the composite score of the Motor Control Test (MCT), and on reaction time and forward endpoint excursion during the Limits of Stability test (LOS), (Damiano *et al*., 2016). In the other study, assessments using the Balance Error Scoring System (BESS) were completed before and after their 8-week exercise programme and significant improvements were reported for three out of four of their participants (Kleffelgaard *et al*., 2016). The third study was unable to report significant changes in balance using the Berg Balance Scale (Bateman *et al*., 2001).

Table 3.6.Balance and neuromuscular outcomes measures for the exercise and control groups following an exercise intervention.

Study	Outcome		Exercise			Control		
			Pre	Post	Change	Pre	Post	Change
Bateman (2001)	Berg Balance Scale (/56)		39.6	46.5	↑	37.7	44.7	↑
	Walking velocity (m/s)		0.7	1.0	↑	0.7	1.0	↑
Damiano (2016)	LOS (reaction time - backwards) (s)		0.9	0.8	↑	NR	NR	NR
	LOS (reaction time - forwards) (s)		1.0	0.9	↑	NR	NR	NR
	LOS (movement velocity - forward) (deg/s)		4.0	4.4	↑	NR	NR	NR
	LOS (endpoint excursion - forward) (%)		66.5	70.3	↑	NR	NR	NR
	LOS (max excursion - forward) (%)		78.5	81.6	↑	NR	NR	NR
	MCT – composite score (m/s)		145.8	135.6	↑	NR	NR	NR
	HiMAT (/54)		35.7	34.3	↑	NR	NR	NR
	Walking cadence (steps/min)		111.6	113.1	↑	NR	NR	NR
	Walking velocity (m/s)		1.3	1.3	↑	NR	NR	NR
	Step length (m)		0.7	0.7	=	NR	NR	NR
Kleffelgaard (2016)	Patient 1	BESS (/60)	33	18	↑	NA	NA	NA
		HiMAT (/54)	53	53	=	NA	NA	NA
	Patient 2	BESS (/60)	34	12	↑	NA	NA	NA
		HiMAT (/54)	46	54	↑	NA	NA	NA
	Patient 3	BESS (/60)	29	11	↑	NA	NA	NA
		HiMAT (/54)	39	40	↑	NA	NA	NA
	Patient 4	BESS (/60)	30	25	↑	NA	NA	NA
		HiMAT (/54)	NR	NR	NR	NA	NA	NA

Shaded areas indicate statistically significant (p<0.05); upward arrow indicates improvement; equal sign indicates no change

BESS = Balance Error Scoring System, HiMAT = High Level Mobility and Assessment Tool, LOS = Limits of Stability, MCT = Motor Control Test, NA = Not Applicable, NR = Not Record

3.4 Discussion

This systematic review examined the possible effects of different exercise interventions on QOL in TBI. Due to the wide range of exercise protocols, frequency and duration, it was difficult to establish a clear, definitive exercise prescription that significantly improved QOL. This systematic review only identified nine suitable research articles, with a total of 460 participants, which fulfilled the inclusion/exclusion criteria. All the studies investigated the effects of an exercise intervention on QOL outcomes in individuals who had sustained a head injury. A variety of QOL assessment tools were used and a diverse array of exercise programmes were implemented.

Out of the nine included articles, six presented improvements in QOL outcomes following participation in an exercise intervention. However, these six used varying exercise modalities, emphasising the broad range of exercise delivery in terms of frequency, intensity, time, and type that may elicit significant changes. The effects of exercise following a TBI are widely researched (Sullivan, Hills & Iverson, 2018; Van Praag, 2008; Leddy *et al*., 2010, Wise *et al*., 2012; Prangley, Aggerholm & Cinelli, 2017) but there remains contrasting views on the most appropriate exercise modality and dose response, highlighting the complexity of prescribing an individualised exercise programme following a TBI.

Strohle and colleagues (2009) reported decreased cognitive impairments, including anxiety and depression, following exercise. However, their review reported on those with mental health disorders and not exclusively on TBI. In the current review, three of the nine studies (Schwandt *et al*., 2012; Hassett *et al*., 2009; Bateman *et al*., 2001; Hoffman *et al*., 2010) used forms of aerobic exercise training whereas one (Driver *et al*., 2006) examined aquatic exercises, evidencing that a range of exercise modalities can promote positive changes to an individual's QOL. Individuals who have suffered a TBI generally have a lower aerobic capacity compared with age- and gender-matched controls (Lew *et al.*, 2005; Becker *et al.*, 1977), therefore a targeted exercise programme that includes aerobic training could enhance cardiorespiratory outcomes (Mossberg *et al.*, 2007) and improve QOL concomitantly (Kleffelgaard *et al.*, 2016; Schwandt *et al.*, 2012; Bateman *et al.*, 2001; Driver *et al.*, 2006; Hoffman *et al.*, 2010; Damiano *et al.*, 2016). There was consistent evidence that aerobic exercise promoted positive changes in QOL when performed for 90 to 180 minutes per week working at an intensity of 50-80% of age-predicted maximum heart rate (Schwandt *et al.*, 2012; Bateman *et al.*, 2001; Driver *et al.*, 2006; Hoffman *et al.*, 2010; Chin *et al.*, 2015).

Resistance strength training and balance programmes also promoted QOL improvements when performed for 150 minutes a week for 8 weeks (Kleffelgaard *et al.*, 2016; Damiano *et al.*, 2016). The optimal intensity and mode of exercise were difficult to identify as both studies varied in their intervention design (Kleffelgaard *et al.*, 2016; Damiano *et al.*, 2016). One incorporated motor control training using an elliptical trainer during supervised sessions (Damiano *et al.*, 2016), whereas the other incorporated virtual reality and strength and conditioning training into their programme during supervised and un-supervised sessions (Kleffelgaard *et al.*, 2016). In addition to these differences, only one paper included a comparable healthy control group (Damiano *et al.*, 2016). Future research may focus on differentiating exercise types (e.g., aerobic, resistance/strength and balance training) to better understand whether selecting a preferred exercise modality may influence a participant's mental enjoyment, and thereby possibly improve QOL, as well as physical gains. This could be an important criterion to inform evidence-based recommendations for clinical guidelines. The selection criteria and sensitivity of the QOL assessment tools may also be subject to further investigations as only 10 out of the 23 tools used in the six studies (Kleffelgaard *et al.*, 2016; Schwandt *et al*., 2012; Bateman *et al*., 2001; Driver *et al*., 2006; Hoffman *et al*., 2010; Damiano *et al*., 2016) reported significant improvements. To the best of the authors' knowledge, all of these tools have been validated within a TBI population, with the exception of the HPLP-II. It may be that exercise is not wholly effective at improving QOL following TBI, however it should be acknowledged that the lack of change in QOL outcome measures may be due to the measures not being sensitive enough to detect meaningful differences. Looking to the future, more emphasis should be placed on the health and 'state of mind' elements that contribute to QOL. Analysing sub-groups of QOL, such as HRQOL, could outline more detailed improvements and underline specific exercise modalities that instigate progress.

We were unable to establish a single exercise modality that contributed to significant improvements in QOL as all the intervention designs varied. This supports the need for further research into specific exercise prescriptions. We would also suggest that participant preference for exercise modality should be considered, so that people are offered a programme that motivates them when possible. Moreover, attendance, adherence and completion rates should be reported consistently.

Most of the studies were disparate in terms of their methodology making it difficult to compare the outcomes across all of the trials. Three papers (Schwandt *et al*., 2012; Bateman *et al*., 2001; Chin *et al*., 2015) used aerobic-based interventions and followed similar exercise designs of 12 weeks, 30-minute sessions performed 3 times per week. All of these demonstrated enhanced cardiorespiratory fitness but only two reported QOL improvements (Schwandt *et al*., 2012; Bateman *et al*., 2001). This could reflect the wide range, and sensitivity, of QOL tools being used, making direct and accurate comparisons difficult. A consensus should be reached about the optimal QOL outcome measures for individuals who have sustained a TBI, so that the findings from different studies could be compared more easily.

Participant selection would also influence the results. Individuals were recruited from inpatient rehabilitation units (Hassett *et al*., 2009; Bateman *et al*., 2001), outpatient clinics (Kleffelgaard *et al*., 2016; Schwandt *et al*., 2012; Elsworth *et al*., 2011; Driver *et al*., 2006) and the local community via advertisements in newspapers and websites (Hoffman *et al*., 2010; Chin *et al*., 2015). The participants were unlikely to be offered different exercise modalities. Henceforth the amount of 'patient choice' could influence the QOL results. In future this should be considered, especially when QOL is the primary outcome.

The Downs and Black (1998) checklist presented 'good' overall scores for the majority of the studies. One issue that was identified was that only five articles specified random allocation to study groups (Hassett *et al*., 2009; Bateman *et al*., 2001; Elsworth *et al*., 2011; Driver *et al*., 2006; Hoffman *et al*., 2010). It is possible the outcome measures reported in the remaining four articles may have been influenced according to their participant allocation methods. These scores are important for establishing the robustness, integrity, and reliability of the articles included within this systematic review. Such factors should be considered, in order to establish true improvements, when drawing conclusions from previous research.

Many of the studies included a 'control' group as a comparison for the experimental groups. A range of controls were used including healthy, age- and gender-matched participants (Damiano *et al*., 2016) and controls with a TBI (Hassett *et al*., 2009; Bateman *et al*., 2001; Elsworth *et al*., 2011; Driver *et al*., 2006; Hoffman *et al*., 2010). Some control participants refrained from any involvement in exercise, whereas in two studies they were provided with alternative therapy programmes (Hassett *et al*., 2009; Bateman *et al*., 2001). The inclusion of a control group enables the evaluation of the effects of the intervention in the experimental group and is deemed an essential part of scientific research (Pithon, 2013). A limitation within this review was the heterogeneity of the control groups across the nine studies, which could affect the reported improvements when between-group analysis was conducted. It is important to match controls with the same characteristics as participants in the experimental group, especially when the control group has a TBI, on factors such as severity and time since injury.

With few papers looking specifically at the effects of exercise on QOL in people with TBI, it is problematic for clinicians to make evidence-based decisions when prescribing exercise programmes. The effectiveness of exercise on QOL needs to be evaluated with adequately powered randomised controlled trials and by measuring the feasibility of implementation, acceptability and effectiveness of a wide range of exercise on recognised QOL outcome measures. Future research should consider and address the methodological limitations of the published research to improve research quality. Specifically, estimating random variability when reporting methodology and ensuring that group allocations are randomised.

3.5 Conclusion

Analysing QOL as a single measure is a challenging task. In this systematic review, we were, able to establish some specific QOL elements that improved following an exercise intervention such as anxiety, depression, sleep quality, and pain in individuals with a TBI. Aerobic training was identified as the most common exercise modality that promoted these improvements. To gather a clearer understanding of how different exercise modalities affect an individual's recovery following a TBI, QOL could be broken down into sub-categories and analysed in this manner.

4 Chapter Four - General methods, equipment and outcome measures

4.1 Introduction

The current chapter outlines the ethical approval, inclusion and exclusion criteria, participants, and experimental procedures used in this thesis. The equipment and outcome measures are included within this chapter, along with references to scientific justifications for these procedures. Testing protocols are discussed, for anthropometric data, musculoskeletal and physical function, aerobic capacity and blood sampling. An overview of the novel exercise intervention and the psychometric instruments are also included in this chapter.

4.2 Ethical approval

This study was reviewed and approved by the Faculty of Science and Engineering ethics committee at the University of Hull (Reference FEC_40_2016_H) and the NHS Leeds West Research Ethics Committee (REC reference 16/YH/0210).

4.3 Inclusion and exclusion criteria

In chapter 5, healthy non-injured participants were recruited if they were aged 18-60 years, without current diagnosed health conditions (i.e. cardiovascular disease) or chronic musculoskeletal injuries (Reference FEC_40_2016_H). In chapters, 6 and 7, TBI participants were recruited as per the following inclusion/ exclusion criteria (REC reference 16/YH/0210). Individuals must have sustained a traumatic brain injury within the last 12 months with a severity of mild to moderate, rated on the Glasgow Coma Scale 9-12 for moderate and 13-15 for mild (Teasdale & Jennett, 1974). This scale was determined during the acute phase of injury when the individual was admitted to the Accident and Emergency department. The nursing staff observed these individuals every 30 minutes during the first 24 hours so a reliable severity scale could be determined (outlined in section 2.4.1). Inclusion criteria stipulated that participants were aged between 18-60 years of age and not currently participating in any other structured rehabilitation programme. In order to undertake the physical function and physiological assessments, participants must have been able to walk on level ground, up and down stairs unassisted, and cycle on a stationary bike (cycle ergometer) independently. Participants must not have had any non-lifestyle chronic diseases (e.g., cancer, Parkinsons, dementia), severe infections, cardiac complications, uncontrolled asthma or diabetes, or concurrent severe pain. Participants were excluded if they had recently suffered a stroke or were pregnant. At the point of recruitment participants must have provided informed consent either written or verbally. Prospective participants were required to understand verbal explanations or written information given in English (for the safety of the participants and researchers). If the prospective participants were unable to understand verbal English, then they were required to bring along a friend/family member who could translate and explain the instructions to them.

4.4 Recruitment

Prospective TBI participants were recruited via the Accident and Emergency services at Hull Royal Infirmary with the help a consultant in the A&E services and a clinical research nurse. Individuals were also signposted to this project with the help of a consultant in rehabilitation medicine located at Castle Hill Hospital. All prospective participants had to meet the strict inclusion and exclusion criteria outlined above. Prospective participants were also recruited from the local community by word of mouth and via leaflets placed around the A&E department at Hull Royal Infirmary.

4.5 Participants

4.5.1 General participant preparation

Prior to testing in chapters 5 and 6, participants were instructed to bring comfortable flat shows appropriate for performing mobility and aerobic tests. They were also asked to bring suitable light clothes for exercising. Water was provided on site along with access to showering facilities.

4.6 Experimental procedures

4.6.1 Anthropometric data

On arrival to the University of Hull, all participants had their height (cm) and body mass (kg) taken in the biomechanics laboratory using a free-standing stadiometer away from the wall on level ground (Seca, The Leicester Height Measure, Birmingham, UK) and weighing scales on an even surface (Seca, 7101021004, Hamburg, Germany), respectively. All participants were measured without shoes whilst wearing loose sports clothing. Resting blood pressure and heart rate were taken using an automatic upper arm blood pressure monitor (Omron, M6, Milton Keynes, UK) using a medium size cuff. For blood pressure, the normative range for a healthy adult is a reading of systolic 90-120mmHg and diastolic 60-80mmHg with recordings either lower or higher indicating low blood pressure or pre-/high blood pressure, respectively (American College of Sports Medicine, 2010). Participants were seated quietly for five minutes in a back-supporting chair with their feet flat on the floor and the examination arm and supported at the level with their heart in an extended position. The cuff was wrapped firmly around their arm ensuring the centre of the bladder of the cuff was directly above the brachial artery. The cuff was quickly inflated to a pressure of approximately 220mmHg, then slowly released to gather both the systolic and diastolic readings. At least two measurements were taken two minutes apart but if readings varied by more than 5mmHg, additional readings were taking until two consecutive readings were within 5mmHg (Brar and Ramesh, 2003). The average of the last two measurements were recorded.

4.6.2 Psychometric Questionnaires

In chapter 5, the Short Form 36 questionnaire (SF-36) was administered to healthy non-injured participants during baseline and post-testing visits to the University of Hull. In chapter 6, the SF-36 questionnaire, Hospital Anxiety and Depression Scale (HADS), Rivermead Post-Concussion Symptoms Questionnaire (RPQ), and the Glasgow Outcome Scale Extended (GOSE) were used to assess the effects of the exercise intervention on QOL in TBI individuals. These four questionnaires were completed during the baseline, post-testing and 6-month follow-up periods, allowing the researcher to gauge any changes in psychological outcomes.

4.6.2.1 Short Form-36 (SF-36)

The SF-36 was used to assess self-reported physical performance and health-related quality of life and has been administered as a generic measure of health status. Individuals in chapters 5 and 6 were all asked to complete this questionnaire to the best of their abilities, and recalling their answer over the past four weeks as truthfully as possible. It can be administered either via post, email or in person, allowing it to be widely accessible. The questionnaire is made up of 36 items divided into eight subgroups and a composite domain, also known as a transition question. The eight subgroups include: physical functioning (PF), role limitations due to physical problems (RP), general health perceptions (GH), vitality (V), social functioning (SF), role limitations due to emotional problems (RE), general mental health (MG) and bodily pain (BP). Analysis of the SF-36 begins with recording pre-coded numeric values using the set scoring keys so that each item is scored on a 0 (low) to 100 (high) scale with higher scores representing favourable health states. Scores represent the percentage of total possible score achieved. During the next step, items in the same scale are averaged together to create the eight scale scores. Items left black (missing data) are not included in calculating the scale scores. The scale score represent the average for all items in the scale. Question 2 in the questionnaire is used as the transition domain asking the individual, “compared to one year ago, how would you rate your health in general now?” Findler *et al*. (2001) investigated the internal consistency across all eight domains, with Cronbach’s alpha ranging from 0.68-0.87 (adequate to excellent) for the non-injured group, from 0.83-0.91 (excellent) for the mild TBI group, and from 0.79-0.92 (adequate to excellent) for the moderate to severe TBI group.

4.6.2.2 Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item scale commonly used by clinicians to determine a patient’s level of depression and anxiety according to seven items determining depression (HADS-D) and the remaining seven measuring anxiety (HADS-A) (Zigmond & Snaith, 1983). TBI participants were asked to complete this questionnaire by recalling the previous week. Each item was scored on a 4-point scale ranging from zero (not at all) to three (very often). The total anxiety and depression scores were calculated separately. Both scales of the HADS are outlined in table 4.1.

Table 4.1.HADS scores (Stern, 2014)

Score (/21)	**Severity category**
≤ 7	Non-cases
8 – 10	Mild
11 – 14	Moderate
15 - 21	Severe

Note: anxiety and depression scales scored separately

Dahm *et al*., (2013) demonstrated excellent internal consistency (Cronbach's alpha) for HADS-A (0.90), HADS-D (0.86) and total HADS (0.93) scores in a cohort of mild to severe TBI participants. The cut-off for anxiety or depression on the HADS was a score of ≥ 8 (Bjelland *et al*., 2002).

4.6.2.3 The Rivermead Post-Concussion Symptoms Questionnaire (RPQ)

The RPQ is a 16-item questionnaire used to determine the presence and the severity of Post-Concussion Symptoms (PCS) and informs on any changes over time. Participants were asked to rate the severity of their present symptoms, which are commonly found to occur following a traumatic brain injury, comparing them to their pre-injury status, using a 5-point scale. The items were scored and summed using a scale ranging from 0-4 (0= *not experienced*, 1= *no more of a problem*, 2= *a mild problem*, 3= *a moderate problem*, 4= *a severe problem*). The 16-item questionnaire was subdivided into two scales for analysis, with items for headaches, dizziness and nausea set aside from the remaining 13 items. This has shown to demonstrate the best test-retest reliability and external construct validity. King *et al*. (1995) tested the reliability of individual PCS and total symptom scores at 7-10 days after injury (self-administered) and six months post-injury (clinician-administered) using *Rs* Spearman rank correlation coefficient. The total PCS score at 7-10 days had a reliability score of .90, with a 6-month score of .87, overall presenting good inter-rater reliability with significant coefficients for all 16-items with headaches, dizziness, forgetfulness, noise sensitivity and poor concentration, being the highest.

4.6.2.4 Glasgow Outcome Scale Extended (GOSE)

The GOSE is a widely used questionnaire tool for measuring the outcomes following a traumatic brain injury and determining outcome groups of cases used by clinicians and researchers. This tool is versatile and can be administered over the phone or in person across a broad age range. It measures independence at home, independence outside the home, work, social and leisure activities and relationships with family and friends. Individuals are categorised into one of the eight categories after completion of all 19 questions scaled from one (minimum score) to eight (maximum score). The breakdown of the groups is as follows (from lowest to highest): dead, vegetative state, low severe disability, upper severe disability, low moderate disability, upper moderate disability, low good recovery and upper good recovery. Pettigrew *et al*., (2003) demonstrated excellent test/ retest reliability (weighted kappa coefficient), (0.92). When broken down into injury severity, they presented excellent interrater reliabilities for minor (K = 0.89) and severe (K = 0.92) brain injuries.

4.6.3 Postural control tests

Postural responses to dynamic perturbations were measured using the NeuroCom Smart Equitest system (SMART EquiTest, Oregon, USA) which is a computerised assessment tool that aids diagnostic tests for the medical management of balance and mobility disorders, first developed by Nashner & Peters (1990). The NeuroCom Equitest is able to analyse an individual's postural control accurately under a variety of sensory conditions in order to quantify the organisation of vestibular, somatosensory and visual responses to balance (Ray *et al*., 2008).

The system is composed of a dual force plate, capable of tilting up and down relative to the floor (rotating about the ankle joints) or translating in the anterior and posterior directions, integrated within a steel frame enclosure (Figure 4.1). Participants stood facing towards computer screen within the visual surround screens with their feet positioned on the base on the NeuroCom. Servomotors situated in the platform base control movements of the visual surround as well as the dual force plate, dependent on the exact testing condition. For example, both the support platform and visual surround can tilt during the Sensory Organisation Test (SOT) in response to the participant's sway (termed sway-referenced). The visual surround has a maximum angular velocity of 15°/s. The dual force plate is situated at the base of the platform where the individual stands facing the visual surround enclosure. The force plates comprise of five force transducers, one in each corner that measure vertical force and the fifth transducer in the middle measuring horizontal shear force. Each of the force plates are 23 x 46 cm and are connected by a pin joint. The rotation of the dual force plates and visual background is controlled by independent direct current servo motors enabling force plate rotation ± 10° around the ankle joint (maximum velocity of 50°/sec) and the visual surround to rotate ± 10° (maximum velocity of 15°/sec. The force plate sampling frequency was set at 100 Hz. The use of the NeuroCom system was used over the Biodex Balance system due to the moderate to high test-retest reliability (ICC [2,k] = 0.69-0.88) of dynamic postural stability in healthy individuals (Pickerill & Harter, 2011).

Figure 4.1. NeuroCom Smart Equitest system with sway-referenced moving visual surround and support surface. The participant is wearing a safety harness to prevent them from falling during the tests.

4.6.3.1 Participant set-up

Each individuals' information (age, height and body mass) was entered into the NeuroCom software (NeuroCom Pre Balance Master; NeuroCom International Inc.) on the computer in order for the results to be compared to an age-matched normative dataset for three age groups (20-59, 60-69, 70-79 years) with asymptomatic individuals with no balance disorders. Participants removed their shoes and were fitted with a safety harness connected to an overhead bar via two suspension straps and carbineers, as per the manufacturers' instructions. This was a safety precaution to prevent an actual fall if the participant lost balance. The harness was tight enough to prevent a fall from actually occurring, but loose enough to prevent restriction in their postural sway movements. The participant was then instructed to step onto the centre of the support surface facing the visual surround. The medial malleolus of each foot was centred directly over the bold stripe on the dual force plate, according to the manufacturer's guidelines (Figure 4.2). Participants were reminded to stay in this position on the force plates for each test. If a participant inadvertently moved their feet, they had to be correctly repositioned (and the test was repeated).

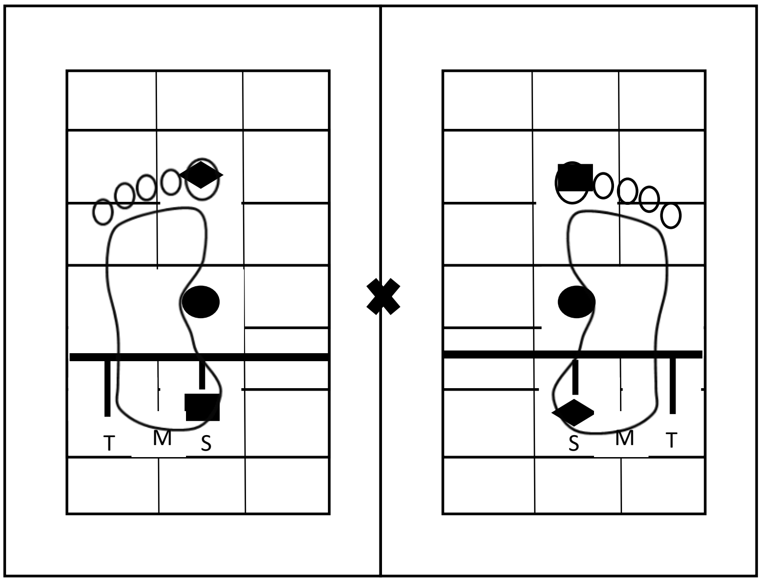

Figure 4.2. Correct foot placement on the force-plate surface on the NeuroCom EquiTest System.

4.6.3.2 Sensory Organisation Test (SOT)

The first test conducted using the NeuroCom was the SOT (Nashner & Peters 1990) whereby the participants responded to alterations to their somatosensory and visual input; these conditions were first measured in stable and then unstable conditions. During the SOT, the support surface, visual surround, or both were 'sway referenced' meaning that they moved in response to the individual's anteroposterior sway delivering inaccurate orientation information to the visual, vestibular and somatosensory systems. The SOT is comprised of six conditions (Figure 4.3) that assess visual, vestibular and somatosensory inputs. **Condition 1:** sway measured in stable neutral condition (eyes open, fixed surround, fixed support) in order to establish a baseline level. **Condition 2:** sway measured with fixed support, fixed surround and eyes closed (no vision). **Condition 3:** sway measured with eyes open, fixed support but inaccurate feedback from the visual surround (sway-referenced surround). The amount of postural sway is compensated for and mimicked by movement of the visual surround. The visual input will provide incorrect feedback relative to the participant's space. **Condition 4:** sway measured with an unstable support (sway-referenced support surface) with eyes open and fixed surround. In this condition the participant is receiving inaccurate somatosensory feedback. **Condition 5:** sway measured with eyes closed (visual cues removed) on an unstable support (sway-referenced moving support surface). In theory now, the participant's balance is dependent primarily on vestibular function as somatosensory input is inaccurate. **Condition 6:** sway measured with inaccurate visual and somatosensory cues (sway-referenced moving surround and support). During this condition, balance is determined by the intact vestibular system (overcoming inaccurate feedback from the visual and somatosensory systems). Each condition was completed over three, 20-second trials.

The SOT scores are based on the assumption that a normal individual can sway anteriorly and posteriorly over a total range of approximately 12.5 degrees without losing balance. The equilibrium score is calculated by comparing the angular difference between the individuals maximum anterior to posterior centre of gravity (COG) displacement to the theoretical 12.5-degree displacement. For each condition, equilibrium scores are expressed as a percentage between 0 ('fall') and 100 (perfect stability). In addition to the individual equilibrium scores, a composite equilibrium score is calculated. This is determined by independently averaging the equilibrium scores of conditions 1 and 2, adding these two scores to the scores from conditions 3, 4, 5 and 6, and dividing the sum by 14.

Intraclass correlation coefficients (ICC) for this test, averaging over all three trials, ranged from 0.26 in condition 3 to 0.68 in conditions 5 and 6. The composite score presented good reliability with an ICC of 0.66 with confidence intervals (CI) of 0.49, 0.79 (Ford-Smith *et al.*, 1995).

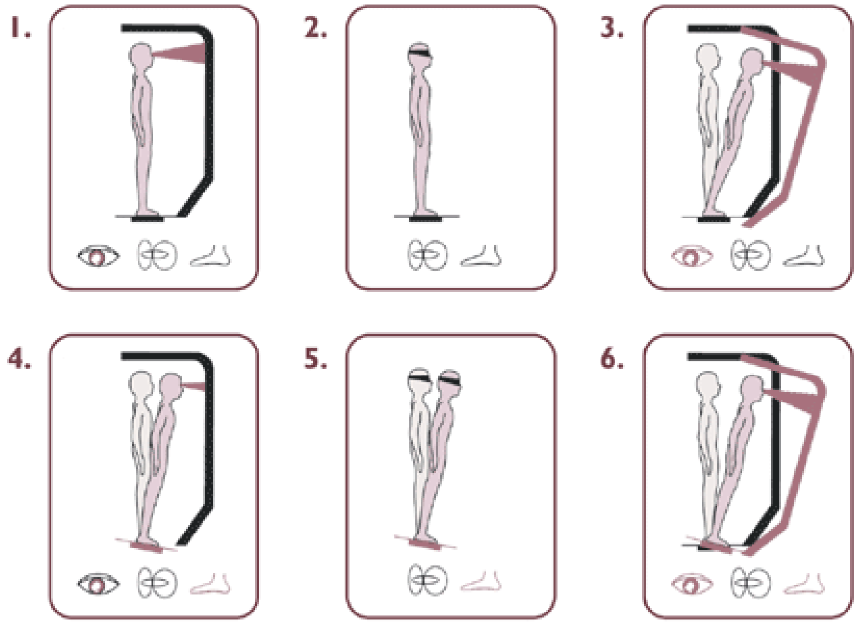

Figure 4.3. Sensory Organisation Test (SOT) six conditions. The items highlighted in black represent the sensory systems that remained intact during the testing condition. The red items indicated the sensory systems that were received inaccurate input as a result of sway-referenced moving surround and/or support surface. Image used courtesy of Natus Balance and Mobility *(Taken from: http://balanceandmobility.com/for-clinicians/computerised-dynamic-posturography/cdp-protocols/)*

4.6.3.3 Motor Control Test (MCT)

The MCT was performed to assess the participant's ability to recover their balance following an unexpected external postural disturbance with the use of their automatic motor system (Hale *et al.*, 2009). Sequences of unexpected backward then forward translations of the force plates were administered to the participant. The translations were scaled to the individual's height and progressed from small (threshold stimulus) to large movements (maximal response) with medium translations in between (Figure 4.4). The order of the translations was standardised (backwards then forwards, small progressing to large), and the participants feet were positioned as for the SOT, with their eyes open and looking forwards at the fixed surround. The MCT comprises of 6 conditions: 3 graded backward and 3 graded forward translations, which are scaled to the participant's height (Diever, Horak & Nashner 1998). The three graded translation durations were standardised for every individual; small (0.7° sway for 250ms), medium (1.8° sway for 300ms) and large (3.2° sway for 400ms).

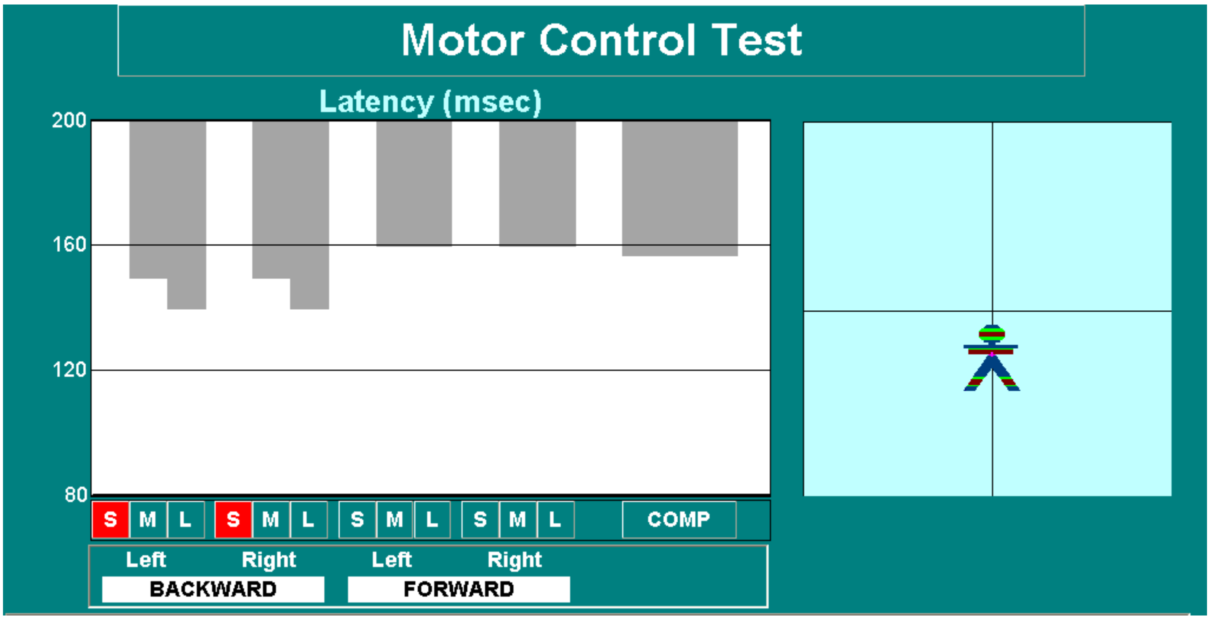

Figure 4.4. Screenshot of the MCT

Reaction time to response (latency) is the time (ms) between the onset of the force plate translation and initiation of the active force response in a leg (change in position of the centre of force asserted by the foot on the force plate). Figure 4.5 outlines an example of raw scores generated from the MCT. The numbers at the base of each bar indicate the number of search algorithms agreed on a single take-off point. These numbers range from 0 (no take-off points could be identified by any algorithms) to 4 (four of the algorithms agreed on the same take-off point). Scores during the small translations are used as a control and not presenting in results. The composite latency score is calculated by averaging the right and left legs, so there is a single score for each translation. All of these single scores are then averaged.

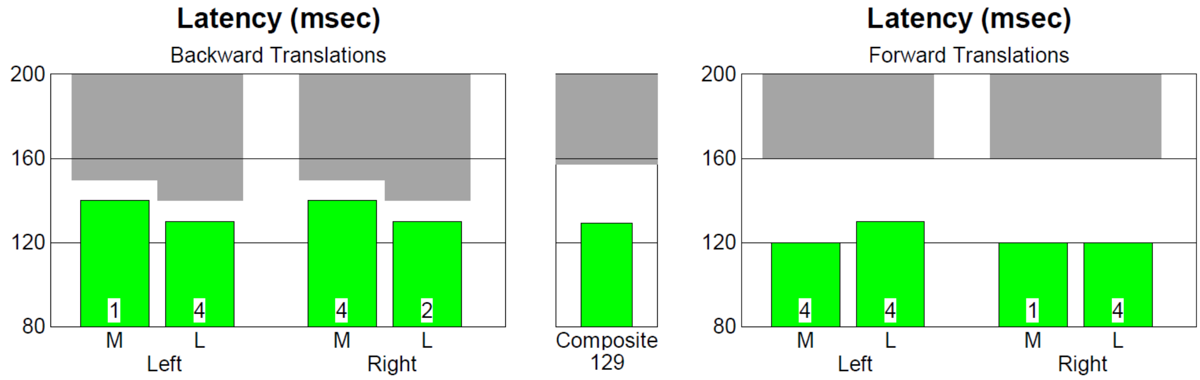

Figure 4.5. Raw MCT data

Excellent test/retest reliability (ICC = 0.92) has been demonstrated for MCT average latency scores in individuals with Parkinson's disease (n = 42, mean age = 66.2 years), highlighting that an increase in average latency of ≥7.4 ms represented the minimal detectable change (Harro et al., 2016).

4.6.3.4 Limits Of Stability (LOS) test

The LOS test quantifies the maximal distance the individual can displace their centre of gravity (CoG) in eight different directions (four cardinal and four diagonal) following a visual cue and maintain their stability in those positions for approximately 10 seconds. One trial was completed for each direction, but if a 'fall' occurred, the trial was repeated for that direction with a note added in the individual's records. In between each trial, the participant had to re-centre their CoG in the specified central yellow box indicated on the screen (Figure 4.6). A fall was recorded if the person took a step in any direction and/or touched the visual surround.

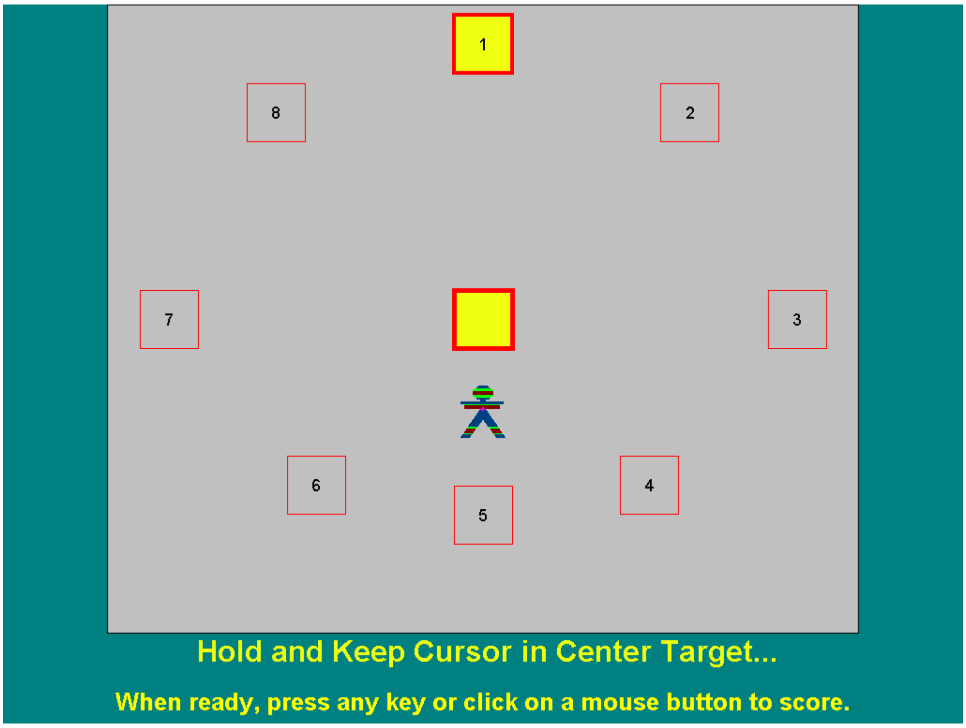

Figure 4.6. Screenshot of the LOS

Reaction time (RT) was measured at the time taken for the participant to voluntarily shift their CoG in an intended direction following a visual cue. Direction control (DCL) corresponds to the total angular distance travelled by the CoG toward the intended target compared to extraneous movement away from the intended target. This is express as a percentage. A score of 100% would indicate a straight line was produced from Cog to the intended target.

Moderate reliability (ICC [2,k] = 0.69, 95% CI = 0.40, 0.86) was expressed for DCL in a cohort of healthy, non-injured individuals (Pickerill & Harter 2011). In a cohort of mild to moderate Alzheimer's individuals, moderate retest reliability was presented for RT (ICC [3,1] = 0.52) and DCL (ICC [3,1] = 0.71), (Suttanon et al., 2011). Suttanon and colleagues also expressed minimal detectable changes (MDC) of 0.29 seconds for RT and 10.27% for DCL.

4.6.3.5 Star Excursion Balance Test (SEBT)

The SEBT measures motor control, neuromuscular efficiency, balance and active range of motion of the ankle, knee, hip and lumber spine. This test has been used to assess physical performance, screen deficits in dynamic postural control and identify individuals at greater risk for lower extremity injury in healthy active populations (Plisky *et al*., 2009). In addition, the SEBT can be used to assess improvements in dynamic balance following a training intervention in individuals with ankle instability (McKeon *et al.*, 2008).

The set-up included constructing an eight-point star on the biomechanics laboratory flooring, with each strip being two metres long with a 45° angle between each line (Figure 4.7). The aim of the SEBT was to maintain single leg stance on one leg while reaching as far as possible with the contralateral leg. Participants were asked to stand in the middle of the star, then whilst balancing on their right foot, they used their left foot to reach as far as possible in each direction on the star, making a light touch on the line, and returning the reaching leg back to the centre. Participants were instructed to make a light touch on the ground with the most distal part of the reaching leg and return to a double-leg stance back in the centre of the star. Progression to each point was performed in the clockwise direction starting from the anterior position following a standardised order (1-anterior, 2-anteromedial, 3-medial, 4-posteromedial, 5-posterior, 6-posterolateral, 7-lateral, 8-anterolateral). The distance from the centre of the star to the most distal reaching points were measured. Participant performed three trials using their right foot to balance and then asked to repeat the three trials using their left leg to balance. For familiarisation participants were allowed to have a maximum of two practice trials before testing commenced. The average distance in each direction (cm) was calculated on each leg by averaging the reaching distances over the three trials.

Kinzey & Armstrong (1998) were the first to test the reliability of the SEBT. They looked at left-anterior, left-posterior, right-anterior and right-posterior directions, and presented ICC reliabilities of 0.87, 0.87, 0.67 & 0.82 respectively. In a cohort of healthy non-injured individuals.

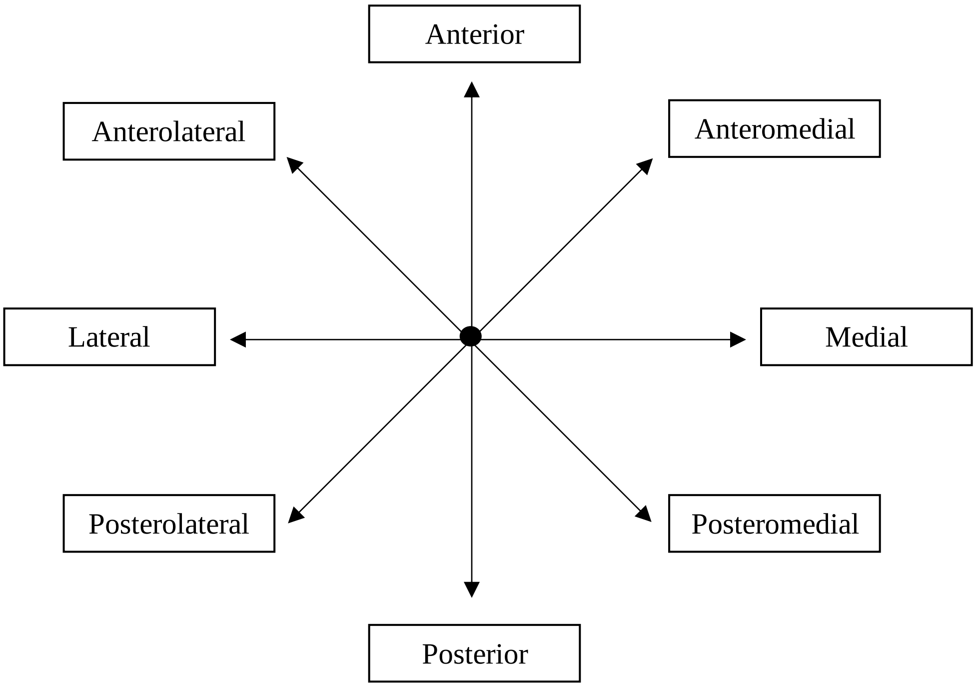

Figure 4.7. Directions of the Start Excursion Balance Test (SEBT) for the left support and right reaching leg. Note that the directions would be mirror images for the right support leg and left reaching leg.

4.6.3.6 Sit-to-stand test

The sit-to-stand test was used to assess functional lower extremity strength where the individual was required to move from the seated to the standing position, then resume a seated position, as many times as possible within a 30-second period. It was performed using a standard chair with a straight back and without support arms and the same chair was used for all participants. The seat was 42cm from the ground, and placed against a wall to prevent any movement from the chair during assessment. Participants wore their own comfortable footwear and were seated in the middle of the chair, back straight with their feet approximately shoulder width apart and placed on the floor at an angle slightly back from their knees. Arms remained crossed against the chest throughout the test, to minimise forward momentum from the upper extremities. Before the test commenced, the participants were encouraged to perform at least one practice trial for familiarisation. Upon the command 'go', individuals moved from the seated position on the chair to standing (body erect and straight), and returned to a seated position, as many times as possible within 30 seconds. The number of times the individual performed a STS movement over a 30 seconds period was recorded. The test was only performed once, so there was one score per individuals per visit. If the individual was unable to complete one stand or used their arms, they scored zero.

Test-retest reliability has shown to be excellent by Jones et al. (1999) with a value of r = 0.89 (95% Confidence interval 0.79-0.93) and an excellent inter-rater reliability of r = 0.95 (95% CI = 0.84-0.97) in a cohort of functionally independent individuals aged ≥60 years.

4.6.3.7 4.6.2.7 Timed-Up-Downs Stair (TUDS) test

The TUDS test is a measure of functional mobility in the lower extremities, involving many sensori-motor aspects including balance control, coordination and muscle strength. Individuals were required to ascend and descend a flight of stairs (nine steps) without running and the time was recorded from the first step until both feet were back at the base of the stairs. This method was adapted from Zaino et al. (2004) whereby they conducted the test using a 14-step flight of stairs and nine steps were used in the current study. The reason for this change was because of the accessibility to a staircase that was manageable for the participants, had handrails and was in a quiet location. Participant's wore comfortable footwear and started one foot from the bottom of the stairs. They were allowed one practice trial for familiarisation. On the command 'go' the participant was instructed to ascend the steps and turn around on the top step (landing) and descend back to their starting position. The time taken to ascend and descend were recorded (seconds) and combine to express an overall score with a shorter time indicating better functional ability. Only one trial was completed for each participant per visit.

The TUDS test demonstrated excellent intrarater, inter-rater and test-retest reliability (ICC 2,1 > or r = 0.94) during the study conducted by Zaino *et al*. (2004) in children (8-14 years) with cerebral palsy. A similar protocol (Flansbjer *et al.,* 2005) was examined that assessed the ascend and descend times separately (12 steps) in a cohort of stroke patients and presented strong interclass correlation coefficients for ascending (ICC [2,1] = 0.98) and descending (ICC [2,1] = 0.98).

4.6.3.8 Hand-grip strength

The hand-grip test was used to measure maximal isometric strength of the hand and forearm muscles using a portable hand-held dynamometer (Takei Scientific Instruments, TKK 5001 grip A/D, Shiba, Japan). Grip strength has been related to and predictive of multiple of health conditions such as bone mineral density and osteoporosis in women (Kärkkäinen *et al.*, 2008), cardiovascular disease and cancers in men (Gale *et al.,* 2006), and frailty and disability in later life (Syddall *et al*., 2003). Abnormalities in grip strength have been present in individuals following a mild TBI (Seo & Jang, 2015). Participants stood and held the dynamometer with their arms in full extension down the side of their body and, on the command 'go', held a maximal isometric contraction for three seconds. The force applied was shown via the scale on the front face of the dynamometer. Three trials were performed on each hand (dominant and non-dominant), interchanging after each trial to allow a brief rest period. Peak strength values were recorded for each trial in (N) for both hands and average values were calculated by averaging the trial scores. For analysis, only the dominant results were processed.

Excellent test-retest reliability was found for the hand-grip test in patients with neuromuscular and musculoskeletal dysfunction (ICC = 0.69 – 0.90) with an inter-rater reliability recorded as excellent for patients with spinal cord injuries (ICC = 0.85 – 0.95), (Schwartz *et al.*, 1992).

4.6.3.9 Isokinetic Dynamometry

Isokinetic dynamometry measures muscle power and torque using a constant angular velocity at a predetermined speed. Participants performed bilateral knee extension and flexion movement using the isokinetic dynamometer (Biodex, System 3, New York, USA).

Participant set-up

Participants were positioned in the seated position on the Biodex chair with seat and foot pedals positioned to fit each individual. Participants were strapped in across their trunk, pelvis, and the thigh of the moving leg, to minimise additional movement from other limbs that could affect the outcome of the test results (Figure 4.8). The dynamometer axis of rotation was aligned with the external femoral condyle of the knee and the second pad placed 2 cm above the upper edge of the malleolus. Once positioned correctly the participant was allowed to familiarise themselves with the equipment prior to testing and perform knee extension and flexion at the same speed as the protocol.

Figure 4.8. Isokinetic Dynamometer participant set-up with the right lateral femoral condyle aligned with the moving arm of the dynamometer. Image shows strappings across the chest, waist, upper leg and lower leg.

Test procedure

Once the participant was set-up, the anatomical reference angle was set to 90 degrees (angle of the knee) on the dynamometer and the range of motion (RoM) limits were set. The 'away' (full extension) and 'towards' (full flexion) values were set by moving the patient and the attachment to the desired limits for each direction. Finally, the weight of the limb is calibrated but positioning limb at full extension and getting the participant to relax fully (whilst attachment is locked in the extended position). The limb weight value will be used to negate gravity effect torque on collected data.

The test began, working with the right leg, with the participant performing five continuous concentric-concentric, knee flexion and extension cycles at an angular speed of 60 °/s followed by another five cycles at a speed of 180 °/s. In isokinetic mode, the individual will not feel resistance until meeting or exceeding the pre-selected speeds (60 °/s and 180 °/s). The resistance met will equal the participants' effort output. On completion of the two cycles with the right leg, the dynamometer arm was moved to the left side of the individuals' body and the set up procedure was repeated on the left leg. Throughout transition of the limbs, the participant remained sitting in the chair and no adjustments were made to the upper body harnesses. This order of test protocol was simulated for each individual during every visit to standardise the test. Before testing, the participants performed a three-minute warm-up in the form of gentle cycling gentle cycle on the stationary bike (Wattbike Ltd, Nottingham, United Kingdom) at 50 RPM. Once the test on the dynamometer was completed, a cool down was performed on the stationary bike to reduce the risk of injury and/or soreness. Peak torque (maximum amount of force angular force produced during the test - Nm), average power (average amount of power produced over the five cycles - watts) and total work (total energy transfer produced over the five cycles at each angular speed - J) were measured during extension (quadriceps as main muscle group) and flexion (hamstrings as main muscle group) during both speeds (60 °/s and 180 °/s) on both the right and left legs. For analysis the scores from the right and lefts legs were averaged.

Drouin *et al.,* (2004) conducted reliability and validity tests on the Biodex system 3 focusing on velocity, torque and joint angle. They observed near perfect trial (ICC 0.99-1.00) and day-to-day (ICC 0.99) reliability.

4.6.4 Aerobic capacity

To gather an understanding of participant's maximal oxygen uptake, an incremental maximal exercise test to exhaustion to determine peak oxygen uptake ($\dot{V}O_2$peak) was performed on a cycle ergometer (Lode Sport Excalibur, Medical Technology, Groningen, Netherlands) in the Human Physiology Laboratory at the University of Hull. This test was always performed last in the order of testing due to its exhaustive protocol that could hinder the performance of the other outcome measures.

4.6.4.1 Participant set-up

Participants were advised to wear comfortable sportswear and suitable shoes. Seat height and peddles were adjusted for each individual and a heart rate monitor (Polar A1 HRM, Polar Electro, OY, Finland) was fastened around the participant's chest. Once the participant was comfortable on the stationary bike, a face mask (Cranlea and Co. Birmingham, UK) was fitted snugly ensuring no air was able to escape, and then the turbine mouthpiece was connected onto the facemask. Relevant participant information was inputted on the computer system (ID number, height, body mass, gender and date of birth).

4.6.4.2 Equipment

The Excalibur Lode bike is the gold standard in ergometry for modern sports medicine and research with a workload range of 8-2500 watts and offers a wide variety of user interfaces (e.g., distance, RPM, HR, energy, torque). The Lode bike was used in conjunction with the

Oxycon machine (Oxycon Pro, Metabolic System, Jaegger, Hoechberg, Germany) to monitor pulmonary gas exchanges, heart rate and workloads. The Oxycon Pro is a favourable ergospirometry system allowing precise analyses, differentiation and quantifying of the functional cooperation of lungs, heart, metabolism and circulation. It recorded breath-by-breath data whilst participants performed a maximal exhaustion test on the Lode cycle ergometer. The Oxycon Pro consists of a transducer holder with a dead space of 30ml which is connected to either a mouthpiece or a face mask. For this study, a face mask was used for the exercise testing with a 40 ml dead space and was assessed for any leaks when placed on the participants face. Ventilation was measured by an optoelectrical segment that detects the rotation of the turbine (Viasys Healthcare, Warwick, UK) situated inside the transducer. During the test, expired oxygen and carbon dioxide were sampled through twin tubes (Viasys Healthcare, Warwick, UK) attached to the transducer holder in the face mask and controlled by the tidal flow. Oxygen concentrations were analysed by a paramagnetic analyser and an infra-red analyser measured the carbon dioxide. The Oxycon Pro had a ventilation ($\dot{V}E$) range of 0-300l/min, O_2 uptake ($\dot{V}O_2$) of 0-7l/min, CO_2 uptake ($\dot{V}CO_2$) of 0-7l/min and RER range of 0.6-2.0. The calculations were performed at a frequency of 100Hz enabling the system to analyse up to 80 breaths per minute taking oxygen samples every 10 seconds.

4.6.4.3 Calibration

Prior to testing, the temperature and barometric pressures were regulated into the Oxycon Pro, ensuring they remained constant, by considering the external environmental conditions. The oxygen and carbon dioxide analyses were calibrated using a gas of known concentration meanwhile a 3-l syringe (Cranlea and Co. Birmingham, UK) was used to calibrate the K4b2 turbine flow meter.

4.6.4.4 Test protocol

The test began with the participants sitting (without pedalling) at rest on the bike for five minutes whilst their baseline gas exchange analysis was measured. This was followed by a five-minute gentle warm-up at 50 watts cycling at 60 RPM. Once the warm-up was complete, the test began at a power output (PO) of 50 watts and increased gradually by 20 Watts every minute. During the test, participants were asked to maintain a speed of 60 RPM. This test was to voluntary exhaustion and the participant could have terminated the test at any point. If their RPM dropped below 60 and they were unable to increase their pedalling frequency, or if they showed any physiological signs of concern, the test was terminated by the researcher. The test could also have been terminated if heart rate (HR) reached >85% of age-predicted maximum heart rate (HRmax). A five-minute cool down period was allowed after the test had terminated at a PO of 50 watts. All visual feedback (e.g., computer, Oxycon screen and HR monitor) were hidden from the participant's view but verbal encouragement was given by the researcher. Participants were advised to remain in the laboratory until they felt fit to leave without the risk of fainting or becoming nauseous.

Pulmonary oxygen uptake ($\dot{V}O_2$), respiratory exchange ratio (RER) and heart rate (HR) were measured continuously throughout the rest, warm-up, testing and cool down stages. To determine $\dot{V}O_2$ and RER (CO_2 production/ O_2 uptake) the percentage of O_2 and CO_2 in inspired and expired air, as well as minute pulmonary ventilation, was measures via the Oxycon Pro gas analyser. $\dot{V}O_2$peak was determined if a plateau in oxygen uptake was never reached. If a plateau occurred, the point at which oxygen uptake no longer increased (or only marginally) with an increase in workload, would be classified as the individual's $\dot{V}O_2$max. More details are outlined in chapters 5 and 6. Rate of perceived exhaustion (RPE) was collected after each two-minute stage using the original Borg scale (Borg, 1982) in which the participants were asked to rate their exhaustion from a scale of 60 (no effort) to 120 (maximal effort), (Table 4.2).

Table 4.2. 15-graded scale for the rate of perceived excursion (Borg, 1982)

Borg rating	Description of exertion
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	

4.7 Exercise Intervention

In chapter 5, healthy non-injured participants that were allocated into the exercise group attended two group sessions a week for four weeks at the University of Hull. These sessions combined balance, coordination, agility, strength and dual-tasking activities and conducted by the principle investigator (GOC). The first session of the week was designed as circuit training, with participants completing a series of work stations made up by a combination of strength, balance, agility, coordination, and dual-task exercises (Table 4.3). The circuit training session designs alternated between A and B weeks to avoid boredom.

Table 4.3. Outline of the exercises during the circuit training sessions each week. A = schedule A, B = schedule B

Station	**Week**					
	A			**B**		
	Mode	**Description**	**Progression**	**Mode**	**Description**	**Progression**
1	Balance	Balancing on one leg for 30s then switching legs	Unstable surfaces	Agility	Agility ladder with both feet (X2)	Increase difficulty of step sequences
2	Dual-tasking	Walking heel-to-toe along a 20m walkway whilst completing the digit span recall task	Increased digit span	Balance	Balancing on one leg for 30s then switch legs	Unstable surfaces
3	Agility and aerobic	Step-ups for 1 minute to beat of metronome	Increased frequency of metronome	Strength and muscular endurance	Farmer's carries walking along a 20m walkway (X2)	Increase weights
4	Dual-tasking	Slalom movement around a 10m circuit of cones whilst counting backwards	Increased difficulty of counting backwards task	Dual-tasking	Walking heel-to-toe along a 20m walkway whilst completing the digit span recall task	Increased digit span
5	Strength and muscular endurance	Lunging along a 6m track (X2)	Include weights	Strength and muscular endurance	Squats for 2 minutes (30s on, 30s off)	Include weights
6	Coordination and strength	Throwing and catching a medicine ball	Incorporating unstable surfaces and balancing on one leg	Dual-tasking	Slalom movement around a 10m circuit of cones whilst counting backwards	Increased difficulty of counting backwards task
7	Coordination	Bouncing and catching tennis balls, 30s per arm	Incorporate 2 tennis balls simultaneously and rotating of the body	Balance and core strength	Balancing on unstable surface whilst holding a medicine ball out in front of chest (arms straight) for 1 min	Throwing and catching medicine ball with partner
8	Strength and muscular endurance	Squats for 2 minutes (30s on, 30s off)	Include weights	Coordination	Bouncing tennis balls with single and double arms whilst walking along a 6m walkway (X4)	Decrease size of walking surface (heel-to-toes walking)

For the second session of the week, participants performed three exercises incorporating reaction time, agility, and aerobic fitness. Reaction time was measured using a FitLight Trainer system (FITLIGHT Sports Corp, Risskov, Denmark), a wireless reaction system comprised of eight LED lights controlled by a portable tablet computer. The LED lights had inbuilt sensors which reacted to touch and deactivates the light. The layout of the FitLight Trainer is outlined in Figure 4.6. This layout required individuals to work at feet, trunk and head height and was standardised for all participants.

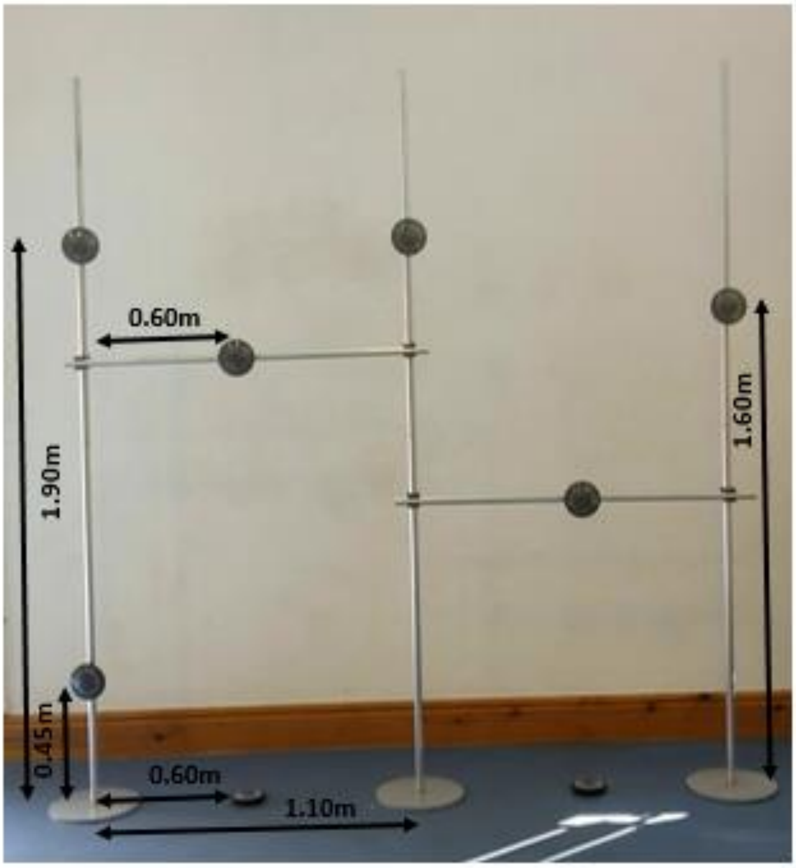

Figure 4.9. FitLight Trainer set up

Participants were positioned in the middle of the frame at arms' length from the centre vertical pole. After the presentation of each stimulus (randomised sequence) individuals were required to deactivate the LED light as fast as they could using their hands for the LED lights situated on the frames and with their feet for the floor LED lights. Each test lasted 60 seconds and was repeated three times. Reaction time (interval time between the presentation of the stimulus and the deactivation of the LED light) was recorded for each test, with the final reaction time score being averaged over the three tests.

The agility exercise included four different coloured cones set equal distance from a central spot. The researcher called out a colour and the participant had to run to the correct cone as fast as they could and return to the centre spot. Three trials were completed each session and progressed in difficultly by adding another cone and changing the command sequence.

Finally, the participants were asked to complete a 15-minute time trial on a stationary watt bike (Wattbike Ltd, Nottingham, United Kingdom). Average power (average power in watts over the 15 minutes) and distance (total distance in kilometres covered in 15 minutes) were recorded each week. The resistance on the Wattbike was implemented by the air brake levels ranging from one (minimum) to ten (maximum). Resistance levels are outlined in chapters 5 and 6. All participants performed a standardised warm-up starting with gentle jogging incorporating dynamic stretching and finishing off with static stretching working from the head downwards. Following every session, participants repeated these exercises as their cool-down. The exercise intervention in chapter 5 was used to inform an extended (12 weeks) intervention for participants with TBI (chapter 6). Progressions are outlined in the retrospective chapters.

4.8 Statistical analysis

A range of statistical analysis models were applied throughout this thesis and details of these models are presented in the methods sections of the relevant chapters. The assumptions of all statistical tests were checked to establish data normality using the appropriate test. In the instance of violation of normality, the appropriate non-parametric statistical tests were employed. SPSS V.23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) was used for all statistical analysis with $p < 0.05$ values considered significant.

5 Chapter Five – The effects of a 4-week multi-component circuit exercise intervention on mental and physical outcomes in healthy adults: Pilot study

5.1 Overview

This study consists of two elements, presented in two separate parts. Firstly, it will propose and outline the rationale of a novel, short-term multi-component exercise intervention in a cohort of healthy adults. This pilot study will monitor participant adherence levels to the exercise intervention and feasibility of the outcome measures selected. This will be used to inform the development of a similar exercise intervention for individuals following a traumatic brain injury. The second element will consider the aspect of dual-tasking (DT) exercises and determine the extent to which tasks have a DT cognitive attentional deficit and determine if the DT attentional deficits plateau. Similarly, to the first element, this information will be used to inform a dual-tasking programme for individuals with traumatic brain injury.

Part 1.

5.2 Introduction

Physical activity is also known as a preventative therapy for many health conditions for people of all ages. There is an array of physical fitness assessments that evaluate different components of health-related physical fitness, including aerobic fitness, body composition, and musculoskeletal fitness (Warburton, Nicol & Bredin, 2006). A multi-component exercise programme aims to incorporate structured circuit exercise-based activities that improve all these components of physical fitness and health and well-being. Previous studies that have incorporated different exercise modalities within one programme for individuals with neurological deficits, have highlighted significant improvements in cardiovascular fitness (Bhambhani *et al*., 2005; Hassett *et al*., 2009) muscular endurance (Jankowski & Sullivan, 1990), functional performance (Tiwari *et al*., 2018) and QOL (Driver *et al*., 2006; Elsworth *et al*., 2012; Kleffegaard *et al*., 2016). The study by Driver and colleagues (2006) investigated the effects of combined aerobic and resistance training in an 8-week programme and presented significant improvements ($p < 0.05$) and large effect sizes (ranging from 0.8 – 1.2) for health responsibility, physical activity, nutrition, spiritual growth, and inter-personal relationships. In addition, they found significant improvements in self-esteem, co-ordination, body fat, strength, flexibility, and endurance ($p <0.05$, $g = 0.8 – 2.7$). Kleffelgaard et al. (2016) also demonstrated meaningful improvements to QOL using the QOL In Brain Injury (QOLIBRI) questionnaire. Both these studies highlighted that desirable effects on QOL can be accomplished over an 8-week period.

In the current study, the exercise programme was designed as a group circuit training class as tasks are repetitive and tailored to the individuals' needs. Repetitive tasks of task-specific activity have shown to encourage neuroplastic changes within both healthy subjects and those with neurological injuries, which in turn promotes brain function recovery (Kimberley et al., 2010). In addition, class sessions require reduced staffing needs so can be ran with one researcher (Engligh & Hillier, 2011). Circuit training design allows the incorporation of a variety of exercises (e.g. strength, coordination, agility) but also the introduction of dual-tasking exercises that have shown to be beneficial to TBI recovery (outlined in part 2).

Prior to introducing a new exercise programme to individuals with TBI, firstly we aim to assess the feasibility and acceptability of the design and delivery in a cohort of healthy, non-injured individuals.

5.3 Aim

The aim of part one of this chapter was to assess the feasibility of conducting a dual-tasking multi-component exercise programme to assess mental and physical well-being. Primarily adherence rates were measured along with the acceptance to the exercise intervention design and delivery from both the participants and the researchers' perspectives. Secondly, QOL, balance, strength and functional test outcomes were measured to establish acceptability and highlight potential mental and physical improvements following a 4-week exercise programme. Finally, week on week changes in aerobic fitness (15-minute time trial), coordination and reaction time (FitLight Trainer) were measured to inform the TBI study. These findings will then be utilised to inform the design/structure of a multi-component exercise intervention for individuals following a traumatic brain injury. The pilot study will focus on participant exercise adherence and feasibility of the outcome measures.

5.4 Methods

5.4.1 Participants

Recruitment was conducted via University email and word of mouth with the potential participants first being screened against the inclusion criteria outlined in section 4.3. Participants were provided with a comprehensive participant information sheet and fully informed of the experimental aims and the study protocol before written consent was obtained.

A total of 16 individuals expressed interest and all fit the inclusion criteria deeming them eligible for the study. Written consent was obtained from all individuals after they had read through the information sheets and had a chance to ask any questions. Participants were allocated into either the exercise group or the control (no exercise) group based on their availability to attend two exercise sessions per week for four weeks.

5.4.2 Outcome measures

Baseline measures were obtained during the participant’s first visit to the University of Hull with post-testing measures obtained following the 4-week intervention period. The primary outcome measure was QOL followed by balance, mobility, strength and aerobic fitness.

5.4.2.1 Quality of life

Quality of life was assessed using the SF-36 questionnaire (Ware & Sherbourne, 1992), which is a generic, multipurpose health survey composed of 36 questions. Full outline of method and scoring is outlined in section 4.6.2.1. In brief, the questionnaire it is comprised of eight components (physical functioning, vitality, social functioning, mental health, role limiting physical, role limiting emotional, general health, bodily pain) whereby participants were asked to answer each question as truthfully as they could in relation to the past four weeks. This questionnaire was administered during the baseline and post-testing sessions.

5.4.2.2 Postural stability

Postural stability was assessed using the NeuroCom (SMART EquiTest, Oregon, USA). The first test performed was the sensory organisation test (SOT) which assesses dynamic posturography, isolating components of the vestibular, visual and somatosensory information in six test conditions. Each test condition, equilibrium scores were calculated expressed as a percentage between 0 (fall) and 100 (perfect stability). Using these equilibrium scores for the individual conditions, an overall composite score was calculated. For more details of outcome measure calculations for the SOT see section 4.6.3.3. Secondly, the Motor Control Test (MCT) was performed which produces sequences of platform translations of varied sizes in forward and backward directions to elicit automatic postural responses. Reaction time to response (latency)to the force plate translations were recorded and composite latency score was calculated by averaging the scores for each translation and legs (see section 4.6.3.3 for more details). The final test was the Limits of Stability (LOS) test, which quantifies the maximum distance an individual, could intentionally displace their centre of gravity in eight directions. Reaction time (time taken to shift COG to intended direction endpoint) and directional control (angular distance travelled by the COG towards the intended target compared to movement away from target) were measured during the LOS test. Full details on procedure and outcome variables are outlined in section 4.6.3.4.

5.4.2.3 Balance and mobility

The Star Excursion Balance Test (SEBT) (Gray, 1995) was performed with three repetitions on each leg and end reach distances were measured in all eight directions for both limbs. The average of the three trials were calculated (full details outlined in section 4.6.3.5). The next assessment was the 30 second sit-to-stand (STS) test (Jones *et al*., 1999) whereby the participants had to perform as many sitting to standing movements as possible in 30 seconds. A standard chair with a straight back and without support arms was used for all participants, and was placed up against a wall to reduce movement of the chair. One successful movement was counted when participants went from sitting, standing up straight, and then back to sitting fully in the chair (refer to section 4.6.3.6 for full procedure details). Timed-Up-Down Stairs (TUDS) test (adapted from Zaino *et al.* 2004) was performed next, involving the participant to ascend and descend a single flight of stairs (nine steps) as fast as they could without running. The total time to complete one repetition was recorded (full protocol is outlined in section 4.6.3.7).

5.4.2.4 Isokinetic strength

As an indicator of overall strength, the participants performed the hand-grip strength test (Schwartz *et al*., 1992) with each arm. Participants stood upright with their arms, fully straightened, by the side of their body. Three trials were performed for each arm and the average score were calculated (full description of protocol is described in section 4.6.3.8). According to importance of outcome measures, the next test assessed quadriceps and hamstrings strength using the Isokinetic Dynamometer (Biodex, System 3, New York, USA). Peak torque, total work, and average power (outcome measure calculations outlined in section 4.6.3.9) were measured for the quadriceps and hamstrings during concentric movements measured at two separate angular speeds (60°/s and 180°/s). Both limbs were tested, with an average of the two limbs being analysed. Before each assessment, the participants performed a gentle three-minute warm up on a stationary exercise bike without added resistance at 50 RPM (a full description of protocol is described in section 4.6.3.9).

5.4.2.5 Aerobic fitness

To measure aerobic fitness, participants underwent a voluntary maximal test performed on a stationary Lode cycle ergometer (Lode Sport Excalibur, Medical Technology, Groningen, Netherlands). Respiratory expired gasses were measured using an Oxycon metabolic cart with breath-by-breath analysis (Oxycon Pro, Metabolic System, Jaegger, Hoechberg, Germany). Following a five minute warm-up (at 50 RPM) the cycling resistance gradually increased by 20 watts/min (ramp protocol) and the participants had to maintain a minimum speed of 60 RPM for as long as they could. Heart rate (chest worn heart monitor - bpm) and RPE were collected during the test. Maximum oxygen consumption, maximum heart rate, and workload were calculated after the test was completed. A full description of protocol and outcome measures are outlined in section 4.6.4.

5.4.3 Study Design

This study was a pre-post study design with two groups. Individuals were assigned (non-randomised) into either the exercise or non-exercise (control) groups according to their willingness and availability to participate in the exercise intervention and were stratified according to gender.

5.4.3.1 Exercise Group

Participants in the exercise intervention group attended two supervised exercise sessions per week for four consecutive weeks. A detailed description of the exercise sessions are outlined in section 4.7. In brief, the first session of the week integrated strength, agility, coordination, involving dual-tasking exercises over an eight-station circuit. Each participant performed two laps of the circuit. These sessions lasted 60 minutes. Over the four weeks, individuals increased mental tasks, lifted heavier weights, and experienced adaptations to the balance activities to elicit exercise progression. The second session of the week encompassed agility and reaction time exercises, followed by a 15-minute cycling time trial performed each week. For a full description of the second exercise sessions and the measures, refer to section 4.7. The Fitlight trainer (FITLIGHT Sports Corp, Risskov, Denmark) was used to train the participant's reaction times. Eight LED lights were used and participants had to deactivate each light as quickly as they can when the lights lit up. Lights were placed so that participants had to use both arms with varying heights. Lights were also placed on the ground where the participants had to deactivate using their feet. With each trial lasting 60 seconds and performed three times. Reaction time was recorded each week so that difficulty could be increased (frequency of activated lights and decreased sensitivity of lights so increased accuracy was needed) when improvements were demonstrated. The cycling 15-minute time-trial was performed on a stationary bike (Wattbike Ltd, Nottingham, United Kingdom). A full description of the exercise protocol Distance covered (km) and peak power watts) were recorded over 15 minutes every week to evaluate improvements in cycling performance. For analysis the week to week and pre-post changes were established. Cycle ergometer air resistance was increased by increasing the air brake level (0 = minimum to 10 = maximum), increasing external workload, as the participants' cycling performance improved. These increases in air resistance were individualised to each participant depending on their own improvements with an average increase of two air brake levels over the four weeks. These 60-minute sessions included a 10-minute each warm-up and cool down involving gentle jogging with dynamic stretching and finishing off with static stretches for the whole body.

5.4.3.2 Control Group

During the four weeks, the control group were instructed to maintain their normal routine activities, and to refrain from engaging in any physical activity or exercise training programmes other than what they would normally do.

5.4.4 Statistical analysis

In order to establish changes between the pre- and post-exercise intervention results, pairwise comparisons between time and group and paired sample T-tests were performed, whereby statistical significant was recognised as $p < 0.05$. Effect sizes were calculated using Hedge's g formula, whereby a score of 0.2 = small effect, 0.5 = medium effect, and 0.8 = large effect. All statistical analyses were performed using SPSS v.23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp).

5.5 Results

5.5.1 Participant characteristics

A sample of convenience was recruited and a total of 16 individuals (8 females) were allocated into the exercise (EX, $n = 8$) or control (CON, $n = 8$) groups. Participants in the EX were aged between 22 and 40 years with a mean (SD) age of 28.8 ± 7 years and a mean body mass of 77.8 ± 15.5 kg. The CON group were aged between 24 and 51 years with a mean age of 35.8 ± 8.2 years and a mean weight of 77.9 ± 11.3 kg. There were no significant differences between the EX and CON group at baseline for age ($t_{14} = -1.83$, $p = 0.09$), height ($t_{14} = 0.351$, $p = 0.73$) or weight ($t_{14} = 0.00$, $p = 1.00$). Both the EX and CON groups had an equal male to female ratio (4:4) as defined by the stratified sampling method. There were no statistically significant changes in body mass over the four weeks in either the EX (mean change = 0.4kg, SD = 0.8) or the CON (mean change = 0.2kg, SD = 1.1) groups ($p > 0.05$).

5.5.2 Adherence to programme

All the individuals in the EX group met the target of attending all eight sessions over the four-week intervention periods (100% adherence). There were no major adverse reactions reported within the exercise intervention group apart from minor musculoskeletal discomfort experienced by some individuals following completion of the cycling time trial sessions. These effects subsided over a 24-hr period following the exercise.

5.5.3 Quality of life

All 16 individuals completed all parts of the questionnaire at both time points indicating a completion rate of 100%. There were no significant differences between the EX and CON group scores at pre-testing. The EX group did not show any statistically significant improvements (increases) across all eight domains of the SF-36 from pre- to post-testing (Table 5.1.) The CON however, showed a significant improvement, but a small effect size, in the general health domain ($t_7 = -3.052$, $p = 0.02$, $g = 0.3$) from pre- to post-testing. The domains that demonstrated the highest overall scores in the EX group were Role-Physical ($M = 100.0$, $SD = 0.0$) and Role-Emotional ($M = 100.0$, $SD = 0.0$) at baseline with Vitality ($M = 58.8$, $SD = 20.7$) being the lowest rated domain at baseline. Similarly, the CON group demonstrated the highest overall score for the Role-Physical ($M = 100.0$, $SD = 0.0$) and Role-Emotions ($M = 100.0$, $SD = 0.0$) domains, with Vitality ($M = 58.8$, $SD = 15.1$) being the lowest rated domain.

Table 5.1.SF-36 results highlighting all eight domain mean values from pre- to post-testing for the EX and CON groups.

Variable	Group	*n*	Pre	Post	Mean Diff	95% CI	Effect size (g)
Physical function	EX	8	95.6 (7.3)	96.3 (5.8)	0.6	-3.3, 2.1	0.1
	CON	8	95.0 (9.3)	96.3 (7.4)	1.3	-4.2, 1.7	0.15
Role limiting – physical	EX	8	100.0 (0.0)	96.9 (8.8)	3.1	-4.3, 10.5	0.47
	CON	8	100.0 (0.0)	100.0 (0.0)	0.0	0.0	0.0
Bodily pain	EX	8	89.3 (12.2)	87.8 (14.8)	1.5	-6.5, 9.5	0.10
	CON	8	84.6 (19.3)	87.8 (14.8)	3.1	-11.9, 5.6	0.18
General health	EX	8	72.1 (15.3)	70.3 (18.5)	1.9	-4.0, 7.8	0.10
	CON	8	66.6 (26.1)	74.8 (21.3)	8.1*	-14.4, -1.8	0.33
Vitality	EX	8	58.8 (20.7)	60.6 (19.2)	1.9	-9.6, 5.8	0.09
	CON	8	58.8 (15.1)	60.6 (18.8)	1.9	-9.6, 5.8	0.10
Social functioning	EX	8	89.1 (22.6)	96.9 (8.8)	7.8	-29.4, 13.8	0.43
	CON	8	90.6 (17.4)	95.3 (9.3)	4.7	-17.1, 7.7	0.32
Role limiting - emotional	EX	8	100.0 (0.0)	91.7 (15.4)	8.3	-4.6, 21.2	0.72
	CON	8	100.0 (0.0)	100.0 (0.0)	0.0	0.0	0.0
Mental health	EX	8	77.0 (16.4)	80.5 (12.7)	3.5	-18.3, 11.3	0.23
	CON	8	78.5 (16.3)	79.0 (10.4)	0.5	-7.1, 6.1	0.03

**Statistically significant at $p < 0.05$.*

5.5.4 Postural stability

For the SOT, there were no statistically significant improvements for the EX group, however the CON group demonstrated a significant increase for the composite score ($t_7 = 3.067$, $p = 0.02$, $g = 0.8$), (Figure 5.1). During the MCT and LOS test, there were no statistically significant improvements for the individuals' equilibrium or composite equilibrium scores for the EX and CON groups (Table 5.2).

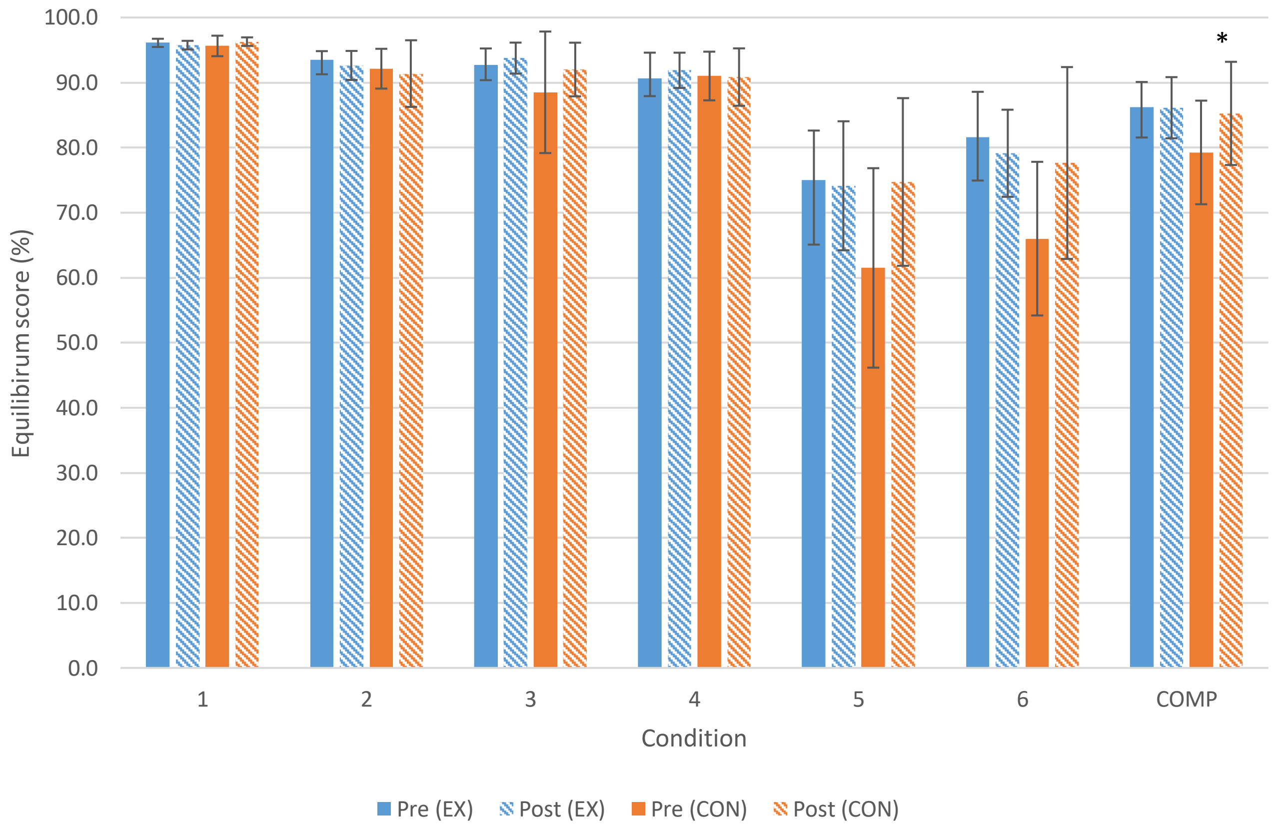

Figure 5.1.SOT equilibrium scores for each condition for the EX and CON groups

**Statistically significant at* $p < 0.05$.

1 = eyes open, fixed surround, fixed support, 2 = eyes closed, fixed surround, fixed support, 3 = eyes open, moving surround, fixed support, 4 = eyes open, fixed surround, moving support, 5 = eyes closed, fixed surround, moving support, 6 = eyes open, moving surround, moving support, COMP = composite score

Table 5.2.Postural stability in EX and CON groups at baseline and post-testing.

Variable	Group	n	Pre	Post	Mean Diff	% diff	95% CI	Effect size (g)
MCT latency (msec)	EX	8	110.3 (45.2)	127.4 (8.2)	17.1	15.5	-16.7, 51.0	0.50
	CON	8	130.1 (8.0)	113.9 (46.9)	-16.3	-12.5	-50.1, 17.6	0.46
LOS (RT)(s)	EX	8	0.7 (0.2)	0.7 (0.1)	-0.00	0.0	-0.2, 0.1	0.00
	CON	8	0.7 (0.4)	0.8 (0.4)	0.1	14.3	-0.1, 0.3	0.24
LOS (dc) (%)	EX	8	84.8 (5.1)	83.6 (5.0)	-1.1	-1.4	-17.1, 14.8	0.23
	CON	8	72.0 (29.3)	81.5 (6.7)	9.5	13.2	-6.4, 25.4	0.42

dc = directional control, LOS = limits of stability, MCT = motor control test, RT = reaction time

5.5.5 Balance and mobility

During the SEBT, the EX group demonstrated significantly greater reaching distance for the right leg in the lateral ($t_7 = -3.610$, $p = 0.01$) and medial ($t_7 = -3.565$, $p = 0.01$) directions (Table 5.3). The CON group presented a significant improvement in their reach distance on the left leg in the medial direction from pre- to post-testing ($t_7 = 4.389$, $p = 0.003$).

Table 5.3.SEBT average scores over all eight directions with right and left legs for the EX and CON groups at pre- and post-testing.

Direction	**Leg**	**Group**	**n**	**Pre**	**Post**	**Mean Diff**	**95% CI**	**Effect size (g)**
A	Right	EX	8	67.9 (7.8)	73.4 (4.5)	5.5	-11.2,0.2	0.8
		CON	8	71.1 (12.4)	69.6 (12.8)	1.5	-0.6,3.6	0.1
	Left	EX	8	70.4 (7.5)	73.7 (5.8)	3.3	-8.2,1.6	0.5
		CON	8	73.9 (13.5)	71.7 (13.4)	2.2	-1.5,5.8	0.2
AL	Right	EX	8	75.2 (6.9)	79.1 (5.9)	-3.9	-8.0,0.3	0.6
		CON	8	74.7 (11.1)	75.8 (9.5)	1.1	-4.6,2.3	0.1
	Left	EX	8	74.8 (9.5)	79.1 (4.8)	4.3	-10.0,1.5	0.5
		CON	8	76.8 (15.0)	75.2 (14.6)	1.6	-1.6,4.8	0.1
L	Right	EX	8	83.4 (7.7)	88.9 (6.8)	5.5*	-9.1,-1.9	0.7
		CON	8	83.1 (14.2)	82.1 (11.9)	1.1	-3.4,5.5	0.1
	Left	EX	8	82.9 (8.4)	86.9 (6.0)	4.0	-8.4,0.4	-0.5
		CON	8	81.9 (14.8)	83.1 (11.8)	1.3	-6.5,4.0	0.1
PL	Right	EX	8	96.7 (7.4)	99.4 (8.6)	2.7	-6.6,1.2	0.3
		CON	8	91.6 (15.4)	90.4 (15.0)	1.2	-6.3,8.6	0.1
	Left	EX	8	95.2 (10.4)	95.6 (8.6)	0.4	-4.8,4.1	0.04
		CON	8	91.4 (14.3)	91.3 (14.4)	0.2	-6.7,7.1	0.01
P	Right	EX	8	99.9 (9.6)	101.6 (10.1)	1.7	-6.1,2.7	0.2
		CON	8	94.9 (19.4)	93.1 (18.7)	1.7	-3.6,7.1	0.1
	Left	EX	8	97.6 (10.2)	99.1 (8.5)	1.5	-8.5,5.5	0.2
		CON	8	93.9 (18.9)	94.9 (16.9)	1.0	-5.5,3.5	0.1
PM	Right	EX	8	89.9 (10.2)	93.4 (6.2)	3.5	-8.5,1.5	0.4
		CON	8	84.6 (18.8)	85.7 (17.5)	1.1	-5.8,3.7	0.1
	Left	EX	8	90.8 (11.0)	92.3 (6.1)	1.5	-7.3,4.3	0.2
		CON	8	85.3 (17.7)	84.4 (19.8)	0.8	-4.3,5.9	0.05
M	Right	EX	8	71.3 (11.2)	78.8 (10.6)	7.4*	-12.4,-2.5	0.7
		CON	8	64.7 (20.1)	64.8 (18.5)	0.1	-4.5,4.4	0.01
	Left	EX	8	73.4 (11.8)	77.8 (8.2)	4.3	-9.8,1.2	0.4

		CON	8	62.9 (17.3)	67.1 (17.7)	4.3*	-6.5,-2.0	0.2
AM	Right	EX	8	63.4 (7.2)	64.9 (4.9)	1.4	-5.6,2.7	0.2
		CON	8	61.6 (7.6)	61.7 (8.7)	0.1	-2.9,2.7	0.01
	Left	EX	8	63.6 (9.2)	66.4 (8.7)	2.8	-6.7,1.0	0.3
		CON	8	67.2 (9.1)	63.9 (10.9)	3.3	0.1,6.5	0.3

*Statistically significant at $p < 0.05$.

A = anterior, AL = Anterolateral, AM = Anteromedial, L = Lateral, M = Medial, P = Posterior, PL = Posterolateral, PM = Posteromedial

No significant improvements were shown during the STS or TUDS tests for the EX group (Table 5.4). However, the CON group showed a significant improvement during the TUDS test from pre- to post-testing ($t_7 = 3.037$, $p = 0.02$).

Table 5.4.Mobility assessments for the EX and CON groups at pre- and post-testing.

Variable	Group	n	Pre	Post	Mean Diff	% diff	95% CI	Effect size (g)
STS (number in 30s	EX	8	16.1 (4.2)	17.5 (3.7)	1.4	8.7	0.1, 2.7	0.34
	CON	8	15.4 (3.6)	15.3 (3.2)	-0.1	-0.6	-1.4, 1.2	0.03
TUDS (s)	EX	8	6.9 (0.7)	6.7 (0.8)	-0.2	-2.9	-0.5, 0.1	0.25
	CON	8	7.2 (1.0)	6.7 (0.8)	-0.5*	-6.9	-0.8, 0.2	0.52

*Statistically significant at $p < 0.05$.

STS = Sit-To-Stand, TUDS = Timed Up and Down Stairs

5.5.6 Isokinetic strength

Grip strength was performed on both hands by only the mean right-hand results were used for analysis as this was the dominant hand across all participants. No significant improvements were found in the EX group ($t_7 = -1.096$, p = 0.3, 95% CI = -4.5 to 1.7, g = 0.14) or the CON group ($t_7 = 2.207$, p = 0.06, 95 % CI = -0.1 to 3.3, g = 0.12) (Figure 5.2).

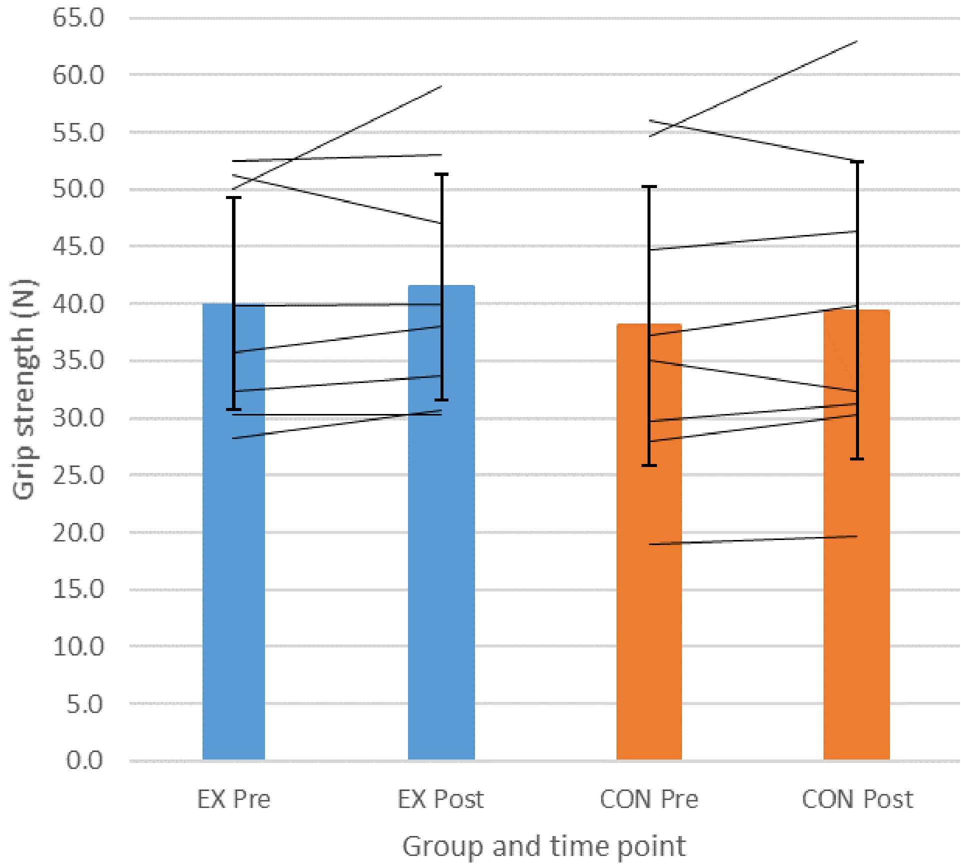

Figure 5.2.Hand grip strength on the dominant hand (right) for participants in the EX and CON groups from baseline to post-testing. The bar chart highlights the mean scores for each group. Individual's scores are illustrated as line graphs

There was a trend to significant increase ($0.05 > p < 0.1$) in peak torque during knee flexion at 180 °/s speed in the EX group (M = 4.0, $t_7 = 2.297$, $p = 0.06$,) but a small effect size ($g = 0.1$), (Figure 5.3 d.). No other statistically significant changes in peak toque were demonstrated and all presented with small effect sizes ($g < 0.2$), (Figures 5.3. a, b, c.). The total work during both speeds (60 °/s and 180 °/s) did not highlight any statistically significant improvements and small effect sizes ($g < 0.2$) for knee extension or flexion in either the EX or CON groups (Figures 5.4 a, b, c, d.). This was also the case for average power across all four conditions in both groups (Figures 5.5 a, b, c, d.)

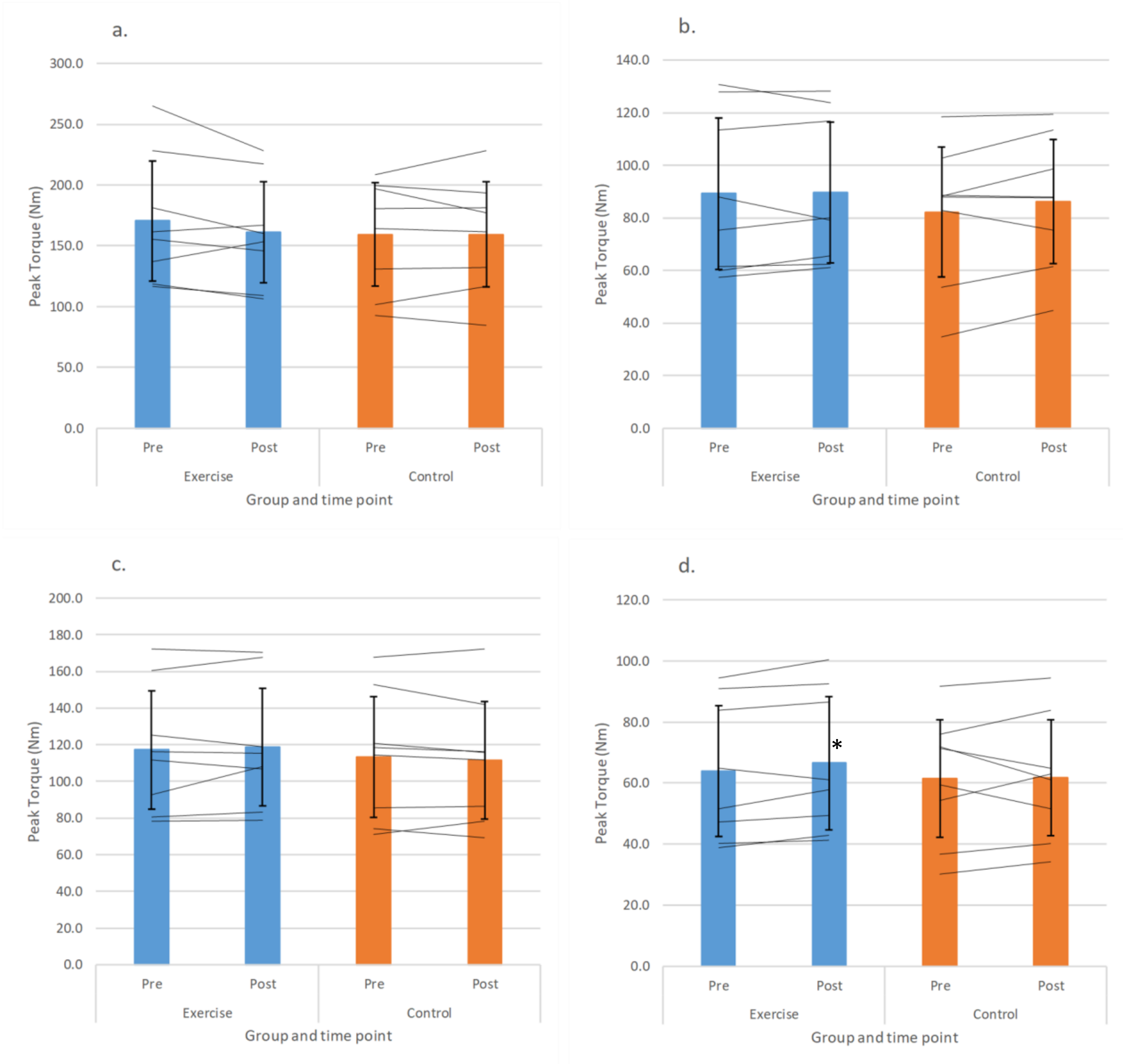

Figure 5.3. Peak Torque results for the EX and CON groups at baseline and post-testing. (a) 60 deg/sec during extension, (b) 60 deg/sec during flexion, (c) 180 deg/sec during extension, (d) 180 deg/sec duringflexion. Bar charts represent the mean scores and the line graphs indicate individuals' scores.

* = trend to significant change (0.05> *p* <0.01)

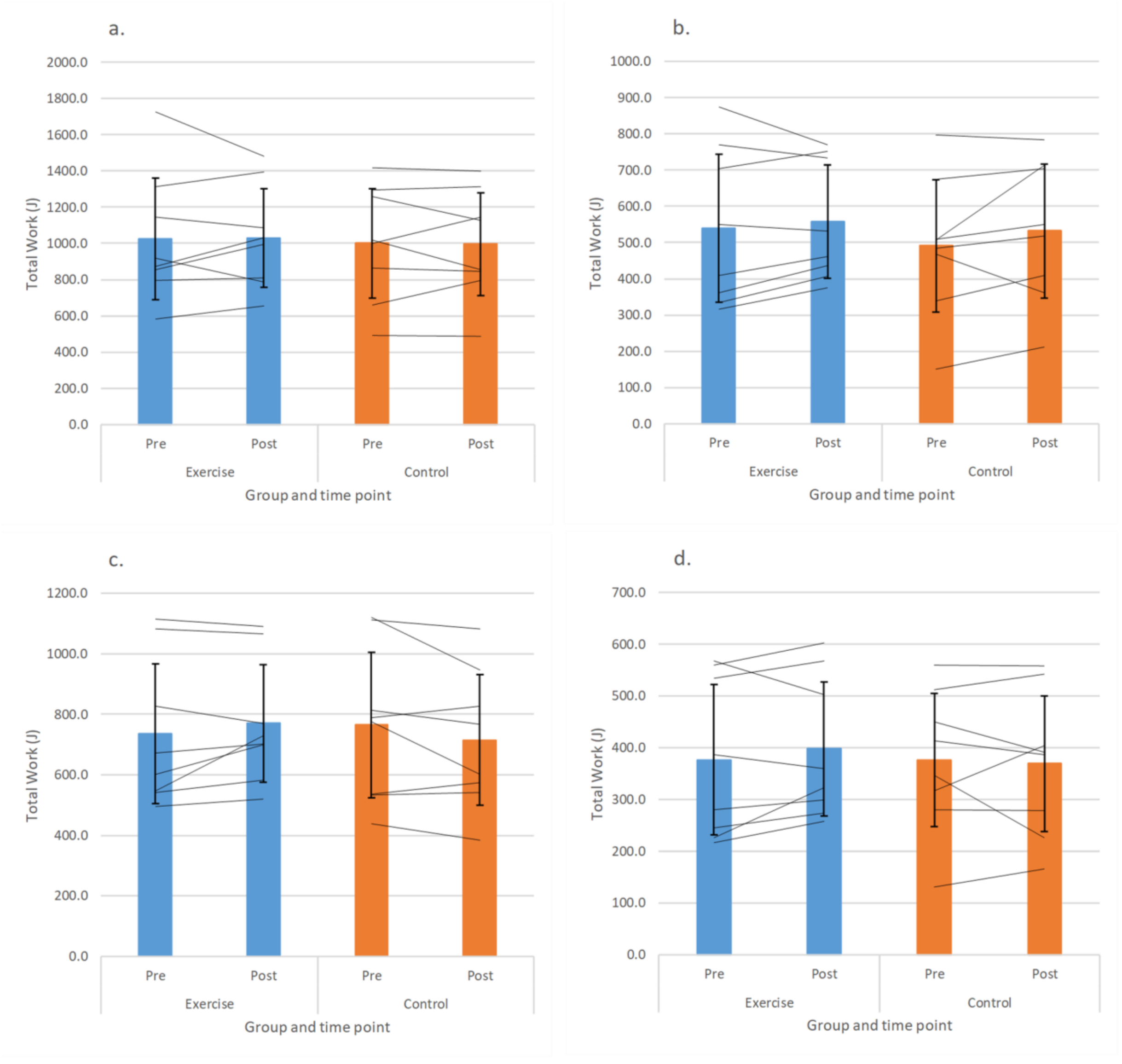

Figure 5.4.Total Work results for the EX and CON groups at baseline and post-testing. (a) 60 deg/sec during extension, (b) 60 deg/sec during flexion, (c) 180 deg/sec during extension, (d) 180 deg/sec during flexion. Bar charts represent the mean scores and the line graphs indicate individuals' scores.

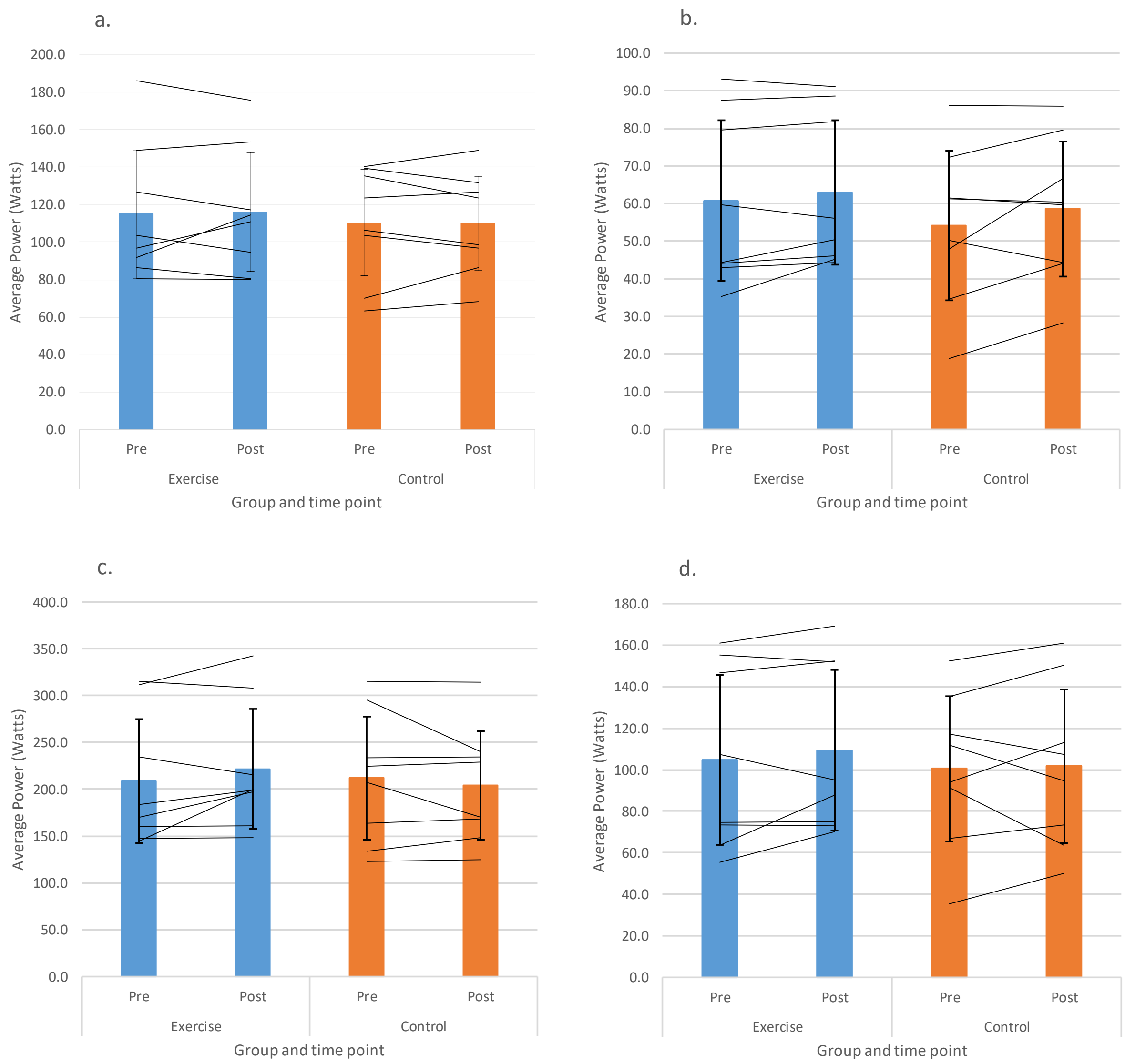

Figure 5.5.Average Power results for the EX and CON groups at baseline and post-testing. (a) 60 deg/sec during extension, (b) 60 deg/sec during flexion, (c) 180 deg/sec during extension, (d) 180 deg/sec during flexion. Bar charts represent the mean scores and the line graphs indicate individuals' scores.

5.5.7 Aerobic capacity

Participants in neither group showed any statistically significant improvements ($p > 0.05$) in peak cycle ergometer workload, resting heart rate, peak heart rate, or peak $\dot{V}O_2$ from pre- to post-testing (Figure 5.6).

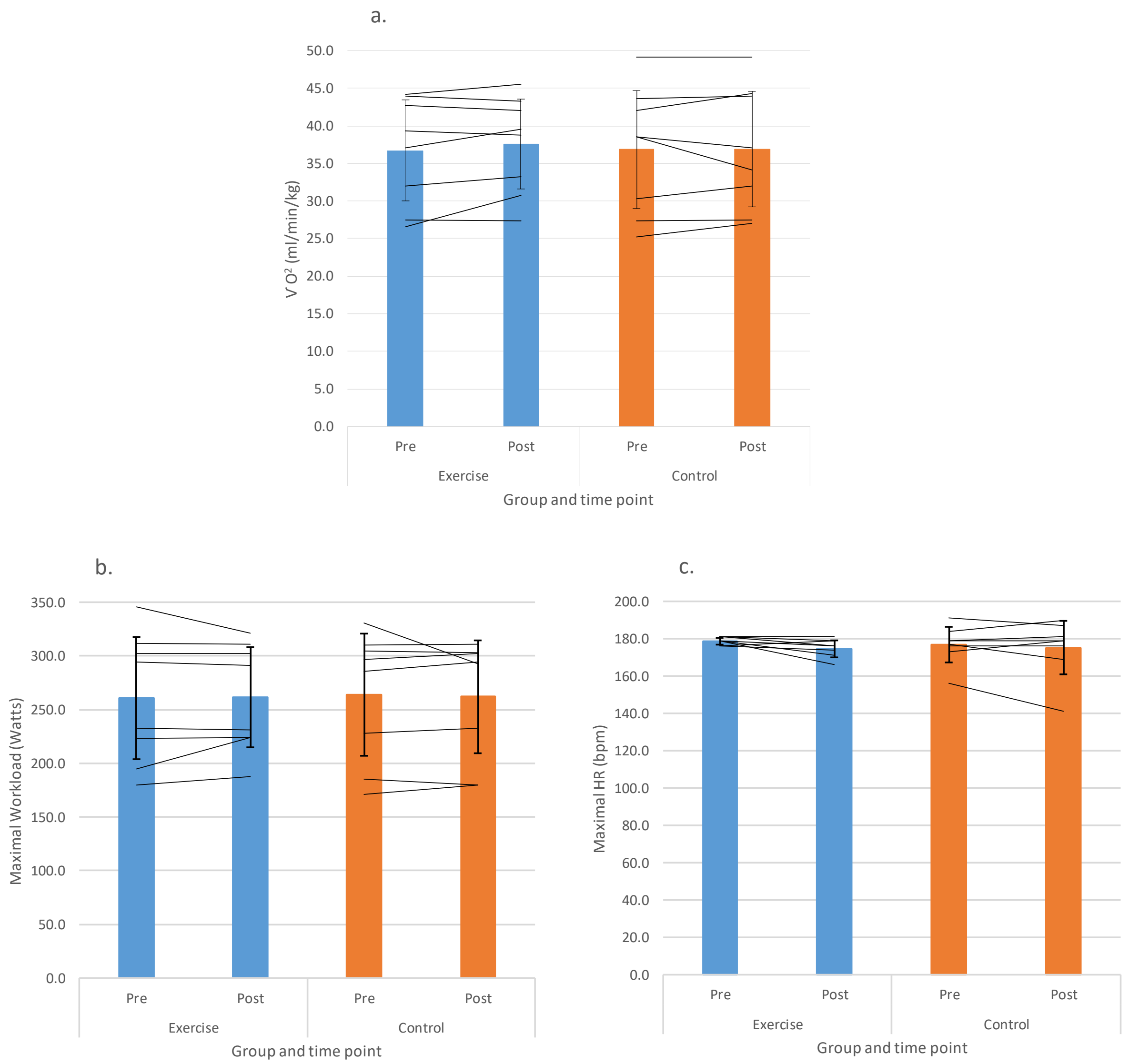

Figure 5.6.Aerobic capacity for EX and CON groups at pre- and post-testing. (a) Relative V̇O₂peak, (b) Maximal workload at V̇O₂peak, (c) Maximal HR at V̇O2peak. Bar charts represent the mean scores and the line graphs indicate individuals' scores.

5.5.8 Week by week time trial results for the EX group only

Distance and average power were monitored weekly during the time trial exercises in the EX group. There was a statistically significant increase in distance (km) covered from week one (*M* = 8.2, *SD* = 1.0) to week four (*M* = 8.5, *SD* = 0.9), (t_7 = -3.637, *p* = 0.008, *g* = 0.3) (Figure 5.7). There was also a statistically significant increase in average power (watts) from week one (*M* = 151.1, *SD* = 46.3) to week four (*M* = 165.1, *SD* = 44.5), (t_7 = -7.248, *p* = 0.00, *g* = 0.3) (Figure 5.8).

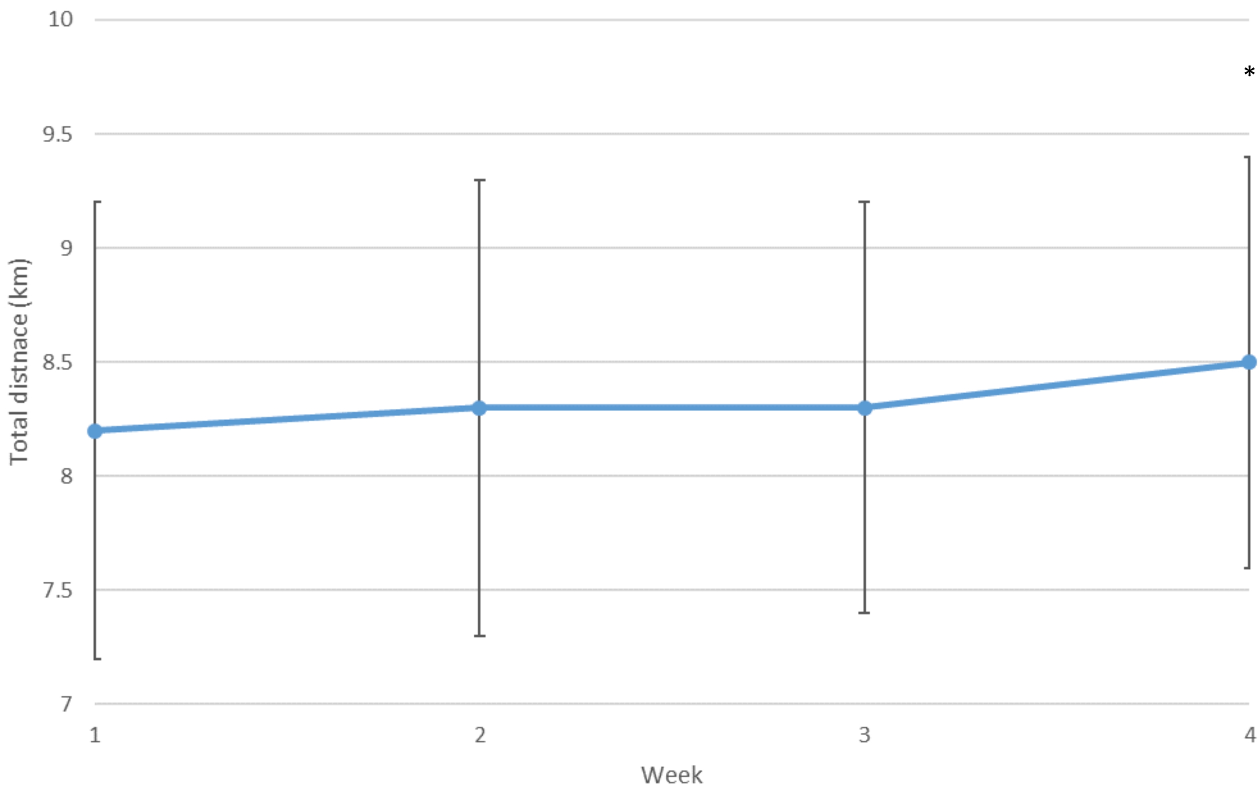

Figure 5.7.Total distance cover during the 15-minute time trial over the four weeks

**Statistically significant change from week one (p<0.05)*

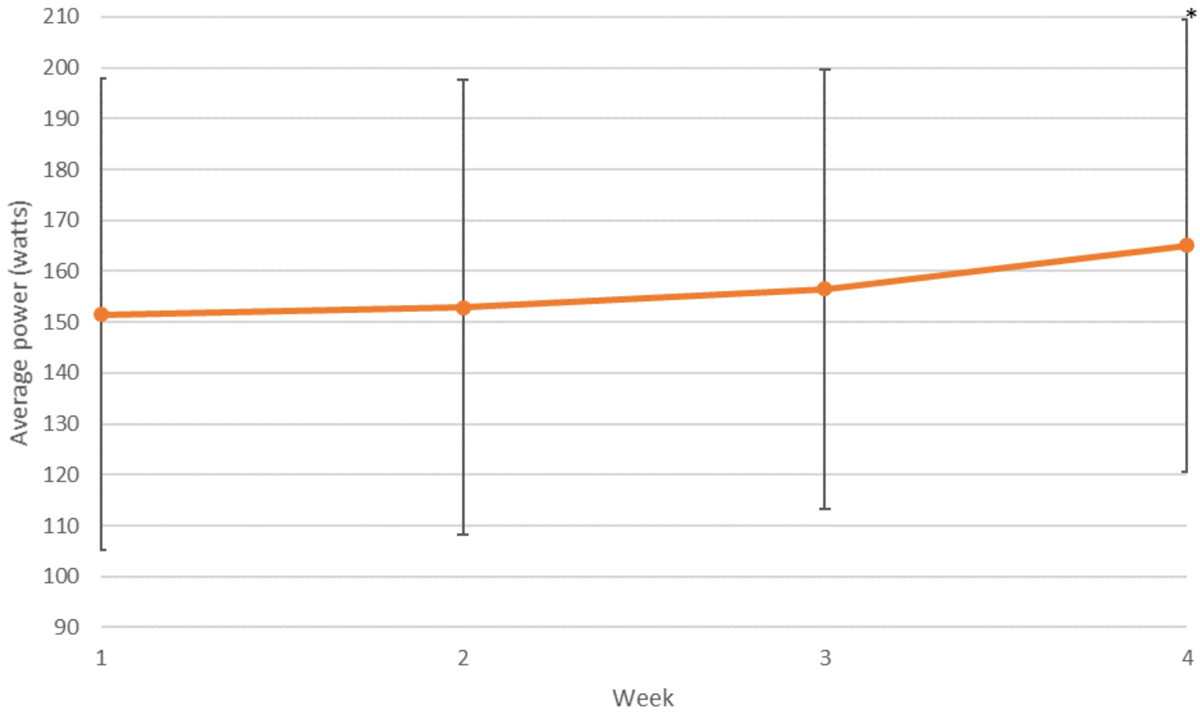

Figure 5.8.Average power during the 15-minute time trial over the four weeks.

**Statistically significant change from week one (p<0.05)*

5.5.9 Week by week FitLight Trainer results for the EX group only

Each week the participants in the EX group performed three trials on the Fitlight trainer, where their reaction time was measured (Figure 5.9). There was a statistically significant improvement in reaction time (sec) from week one (*M* = 0.8, *SD* = 0.1) and week four (*M* = 0.6, *SD* = 0.02), (t_7 = 7.887, *p* = 0.00, g = 1.2).

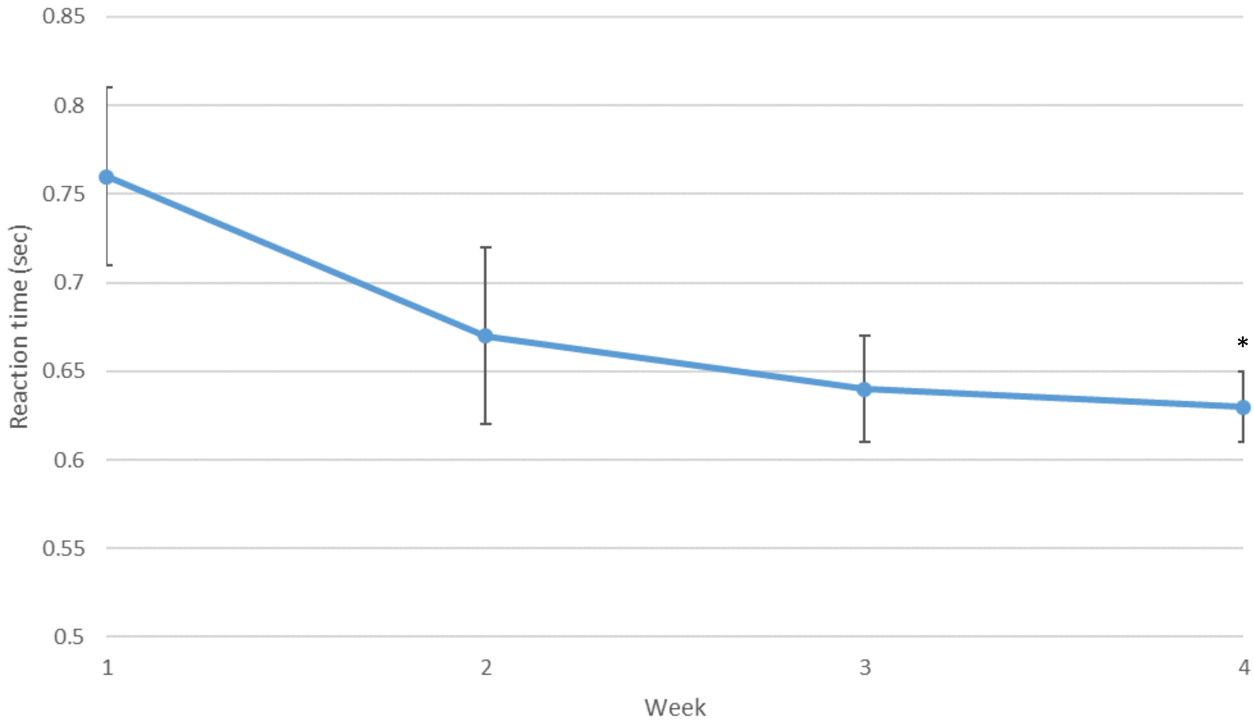

Figure 5.9.Reaction time during the Fitlight trainer exercises over the four weeks

**Statistically significant change from week one (p<0.05)*

5.6 Discussion

The aim of this study was to assess the acceptability and feasibility of the design and delivery of a novel multi-component exercise intervention.

There was 100% adherence to the supervised, structured exercise programme for all of the exercise intervention participants over the 4-week period and no serious adverse events were reported. This emphasises the feasibility of the programme in regards to the design and delivery with one researcher and two participants per session. Adherence rates were measured by the number of exercise sessions that each participant attended. The maximum number of sessions over the four weeks was eight. When interpreting adherence rates, individual's characteristics should also be taken into consideration, such as socio-demographic variables, motivation, social support, adherence history, illnesses, and environment (Bassett, 2003). This would allow researchers to determine if the adherence rates were down to individual characteristics or to the exercise intervention. In relation to the characteristics of the exercise intervention, previous literature has supported that the duration of the exercise sessions do not play a major role in determining adherence levels (Hansen *et al*., 2009; Medina-Mirapeix *et al*., 2009). On the other hand, lower adherence has been associated with higher exercise intensities amongst sedentary individuals. This decrease in adherence is believed to be related to higher rates of injury (Perri *et al*., 2002). The current study duration ran for a relatively short period of time (four weeks), which could be seen as an achievable commitment time for an exercise intervention, contributing to the 100% adherence rate. A systematic review looking at attrition and adherence rates of exercise interventions (duration ranging from 8-24 weeks) suggested shorter study lengths could contribute to lower attrition rates, however the patterns were difficult to reconcile due to varied data collection methods (Linke *et al*., 2011).

Regarding QOL, the current study failed to demonstrate significant changes in QOL (SF-36) for the exercise group. However, the SF-36 deemed a feasible questionnaire to include as part of the programme, demonstrating a 100% completion rate across both groups. To expand on this, it would have been useful to analyse the time it took to complete and subject evaluations (e.g. challenge level of task, quality of answers, feelings of boredom or irritation). Surprisingly, the current study showed signs of significant improvement for general health variable amongst the CON group. The CON group did have a lower baseline score for general health than the EX but this was not significant. A reason for this may be related to the CON group's daily routines, which may have included a high enough level of physical activity to endorse an improvement without the additional exercise intervention. This could therefore this could have implications on other measures. Ideally this would have been measured with the use of an exercise diary.

Previous research has shown that regular physical activity can elicit significant improvements in health-related QOL (Stewart *et al*., 1993; Acree *et al*., 2006; Belza *et al*., 2006) in healthy adults. However, these studies used participants who were over the age of 50 years, making it hard to compare against the current study's cohort of younger adults (aged between 22 and 51 years). Health-related QOL outcomes, such as the SF-36, have shown to significantly improve in TBI individuals following an exercise programme (Driver *et al.,* 2006; Kleffelgarred *et al.,* 2015; Elsworth *et al.,* 2011; Hoffman *et al.,* 2010). These studies also highlight additional HRQOL outcomes that improve with exercise such as the hospital anxiety and depression scale (HADS) and the Rivermead post-concussion symptoms questionnaire (RPQ). Therefore, in addition to the SF-36, these questionnaires will be carried forward to chapter 6 as outcome measures. The intervention durations for these studies ranged from 8-12 weeks, suggesting that the study duration should be increased >4 weeks in hope to illicit significant changes amongst a cohort of individuals with TBI. Even though the SF-36 did not show any significant improvements within this current study, TBI normative scores for the eight domains of the SF-36 have shown to be lower (poorer health) than those of the healthy individuals in the current study (Colantonio *et al.*, 1998; Emanuelson *et al.*, 2003). This leads to the impression that significant improvements in HRQOL could be seen in TBI individuals following this novel, multi-component exercise intervention.

No significant improvements were demonstrated in the NeuroCom tests for the EX group, which could due to the ceiling effect of the SOT in young/ middle-aged healthy individuals. It also could be a result of the programme lacking the correct balance exercise intensities to promote changes in healthy individuals. Balance training regimes have shown to endorse significant balance improvements in cohorts of healthy individuals with use of unstable surfaces (Emey *et al*., 2005; Balogun *et al*., 1992, Rothermal *et al*., 2004, Hoffman & Payne, 1995) and mixtures of flexibility and resistance training exercises (Bird *et al*., 2009). Despite the length of the exercise session being relatively short (four weeks), previous balance training programmes have shown a plateau in improvements after four weeks in healthy populations (Balogun *et al*., 1992). In addition, a systematic review by DiStefano *et al.* (2009) concluded that from an efficiency standpoint, four weeks of balance training is enough for improving both dynamic and static balances. However, few of the included studies measured compliance or incorporated supervised sessions, and a lack of randomised controls groups were presented. These could have influenced the evaluation of the effectiveness of an intervention program.

Even though no significant changes were present in this cohort of healthy individuals, it is hypothesised that significant improvements could be present in a cohort of individuals with traumatic brain injuries. Previous research has shown that TBI individuals have a significantly lower SOT composite score than healthy un-effected individuals (Basford *et al*., 2003; Kaufman *et al*., 2006) so a more meaningful change might be expected in a TBI group.

During the functional mobility assessments, the EX group did not present any statistically significant improvements in the STS test following the 4-week exercise intervention. Similarly, to the QOL, this could be down to the low intensity of the exercise programme or that a 4-week period was not enough to stimulate improvements in mobility. The STS test may be more suitable for a cohort of TBI individuals. Canning *et al.* (2003) highlighted regular difficulties in performing the STS action in moderate to severe TBI individuals due to motor impairments and deterioration of muscle function following their injury including weakness and poor motor control. With this in mind it is hypothesised that by extending the exercise programme time to 12-weeks should provoke significant changes in mobility. The TUDS and grip strength failed to present any statistically significant improvements in the EX group. There are limited studies that have obtained reference values for the TUDS in healthy adults meaning that direct comparisons of normative data could not be established. However, Flansbjer *et al*., (2005) assessed the TUDS test on 50 healthy adults aged 46 - 72 years highlight much slower scores (mean TUDS scores of 21 seconds) thank those in the current study. Zaino *et al*., (2004) looked at TUDS scores in healthy children (n = 27) aged 8-14 years and presented a mean score of 8.1 seconds (ranging from 6.3 seconds to 12.6 seconds). This could be due to the ceiling effect for TUDS with a young healthy sample, thereby not challenging enough to elicit a meaningful change over a short period. The lack of meaningful handgrip performance changes can be attributed to the fact that the exercise intervention did not contain any specific strength tasks that would elicit changes in the grip strength. For these reasons, the TUDS and the handgrip tests will not be measured with the TBI group.

During the exercise programme, participants performed a 15-minute cycling time trial each week on a cycle ergometer. There were small but significant improvements in the distance travelled and the average power during the cycling time trial. These improvements highlight that performing 15-minutes of aerobic exercise once a week could trigger positive improvements in performance (workload) for healthy individuals and have the potential to elicit these improvements amongst individuals following a TBI.

The factors responsible for training-induced improvements in exercise capacity are determined by several physiological (cardiovascular, neural, metabolic, respiratory) and psychological (mood, motivation, perceived effort) attributes. In terms of aerobic capacity changes, the current study did not show any statistically significant improvements in workload, heart rate, or peak $\dot{V}O_{2}$. This could be due to the short programme (four weeks) and the minimal amount of aerobic elements in the programme not being enough to elicit changes in healthy individuals. A previous study by Hsu *et al*. (2019) did show significant improvements in work rate, heart rate and peak $\dot{V}O_2$ following a four week exercise intervention (30 minutes stationary cycling, five times a week for four weeks) in a stroke population.

So, if the current exercise program were to remain at a four-week duration, the intensity of the aerobic exercises would have to increase. However, as this study was looking at the feasibility of the exercise programme, the main outcomes were looking at the practical, safety and adherence elements rather than significant improvements. Care should be taken with interpreting these improvements as there could have been a learning effect of repeating the same exercise for four weeks. Progressing this programme, to alleviate some of the learning effect that might be attributed to the testing protocol, participants should be given a familiarisation session to become accustomed with the exercise.

Reaction time was measured during the 4-week exercise programme with the FitLight trainer, whereby statistically significant improvements were seen from week one to week four. This improvement in reaction time presents an important and relevant change that could benefit TBI participants in the main trial. Combining exercise (balance, coordination, agility) with the FitLight Trainer is relatively novel and has the advantage of increasing visual stimulation and challenging reaction time, which could make the exercise session more engaging. Even though engagement wasn't measured directly during this study, adherence to the programme was 100% leading to the idea that participants were interacting well with the programme structure and design. Following a head injury, deterioration to central information processing has been evident by the slowing of reaction time (MacFlynn *et al.*, 1984). Decreased reaction time and cognitive processing is a common symptom following a traumatic brain injury, making every day activities a challenge. The significant improvement in reaction time from week one to week four, found in the current study, reveals the possibility of important benefits in a cohort of TBI individuals. As of yet, research on the FitLight Trainer within a healthy adult group of TBIs is sparse, so the introduction of these exercises is novel.

Therefore, the current results cannot be compared against any normative data (healthy or TBI). Previously, the FitLight has been used within other populations such as military, firefighters, and athletes (Fischer *et al*., 2015; Perroni *et al*., 2019; Slater *et al*., 2018; Jensen *et al*., 2014).

A limitation of this study is that the physical status of the participants was not recorded, so it was unclear if how physical or sedentary their lifestyles were. This may have affected the outcome measures and could highlight is pre-intervention physical fitness status influences the EX group outcomes.

5.7 Conclusion

This multi-component, structured exercise intervention delivered by one researcher, appears to be safe and feasible within a cohort of healthy individuals over a 4-week period, therefore confirming the design and delivery for the TBI study (chapter 6). The high adherence rates should hopefully be a good indication to the compliance of an extended programme in a cohort of TBI individuals. However, if the drop-out rates amongst TBI is high and the full 12 weeks are not completed, positive outcomes can be produced over four weeks so improvements may still be visible.

Part 2.

5.8 Introduction

In everyday life, we require the simultaneous performance of two or more tasks, such as walking and talking (motor:cognitive task), or walking whilst holding another object (motor:motor task). This is referred to as dual-tasking (DT). Dividing attention between these two tasks can result in a decrement of performance in one or both of the tasks (Rasmussen Jr *et al.*, 2008). The relative change between the single and the dual tasks is known as dual-task interference (Pashler, 1994; McCann & Johnston, 1992). Previous theories have been developed, which attempt to explain why this interference occurs. Firstly, there is the *serial bottleneck model* (Pashler, 1994) which suggests that this interference occurs because only one information system can process at a time. On the other hand Tombu & Jolicoer (2003) developed the idea of the *capacity sharing model*, which claims that two tasks can be simultaneously processed but this capacity is limited and may result in the allocation of one task over another to occur. According to Yogev-Seligmann *et al.* (2012) particular strategies for DT performance can be selected, known as the *model of task prioritisation*. Highlighting the idea that the individual must decide how to prioritise the two tasks, being determined by factors that minimise danger. This decision making hence affects the magnitude of the DT interference.

Dual-tasking interference can be expressed as the difference between the single- and dual-task performances, also known as dual-task cost (DTC). This cost has previously been associated with structural interference, limited capacity to attend to both task, and difficulty with allocating attention to both tasks (Baddeley & Della Salla, 1996). Attention allocation is perceived as an executive function task, which is thought to involve the dorsolateral prefrontal cortex to direct attention to specific tasks. The risk of damage to this area is very high in TBI due to its location (section 2.2). During a dual-tasking activity, the concentration of oxygenated haemoglobin (HbO_2) has shown to increase, representing increased prefrontal cortex activation (Chaparro *et al.*, 2017). The greater the dual-task demand is the greater the prefrontal cortex activations. However, there is a limit to this activation, so when this occurs a plateau may appear. This plateau could also be visible in the DTC data.

These directions are controlled by three major components in the brain: the central executor (main allocator of stimuli), the phonologic loop (auditory information), and the visuospatial sketch pad (visual and visuospatial information), (Baddeley & Della Salla, 1996). The phonological loop and the visuo-spatial sketch pad are also known as the two subsidiary slave systems which are coordinated by the central executive. Dual-task cost could occur as a result of the central executive having difficulty in coordinating both the slave systems simultaneously.

There is still a lot unknown about the brain-behaviour relationship in DT, but recent research (Yogev-Seligmann *et al*., 2012) has recognised the importance of the basal ganglia as playing a key role in the prioritisation model. This model proposes that well-practised and more automated tasks, which are mediated by the basal ganglia, govern task prioritisation when the individual is required to act quickly. Dual-tasking is one of the most prominent types of multi-tasking, which involves the temporal overlap of the execution of multiple tasks. The selective attention system of the brain supports this dual-tasking. With attentional training, the executive attention functions can be enhanced (Peterson & Posner, 2012). Dual-task performances have been shown to depend on the attentional control strategies, implying that training an optimal strategy can implement improvements (Bherer *et al*., 2005). Previous studies have demonstrated that training could substantially improve DT processing skills in older adults (Peterson & Posner, 2012; Bherer *et al*., 2005).

5.9 Aim

The aim of this study was to assess the feasibility to measure and quantify DTC week on week in order to inform the design of a dual-tasking programme for individuals with TBI. The primary objective was to quantify the differences between single and dual tasks with the hypothesis that by adding a cognitive task to a motor task, the motor task performance will decrease, thus highlighting DTCs. The second objective was to establish if the DTC stabilises and reaches a plateau over a four week period.

5.10 Methods

5.10.1 Participants

Participants aged between 18-55 years, with no previous head injuries, were recruited from the University of Hull. A full set of inclusion and exclusion criteria is described in section 4.3. The faculty ethic committee at the University of Hull approved the study protocol. Informed consent was obtained from all participants prior to testing (a full set of participant details can be found in section 5.5.1).

5.10.2 Study design

As previously described in section 5.4.3, this non-random allocation intervention study involved an exercise group (n=8) and control group (n=8). During the exercise sessions (see section 5.4.3.1), participants were asked to perform two separate dual-tasking activities during two weekly sessions for four weeks, including tandem walking and digit span recall and slalom walking and counting backwards from 100 in either 3s or 7s. These tasks were repeated during each session. All tasks included a single motor task followed by the introduction of a cognitive task. The primary outcome for all dual task conditions was the dual task cost (DTC) expressed as a percentage.

5.10.3 Tandem walking and digit span recall task - modified Walking and Remembering Test (McCulloch et al., 2009)

The tandem walking and digit span recall task began with the participants walking heel-to-toe at their own pace along a 20 m pathway. Participants were instructed to turn around at the last cone and make their way back to the staring position. Throughout the task, they were instructed to maintain heel-to-toe contact. During the first trial, the time to complete walking along the total 40 m was recorded (in seconds) and acted as the single task condition. During the second trial, which represented the dual-task condition, the participants were instructed to complete the same tandem-walking task but with the addition of repeating a sequence of single digits back to the instructor and the time required was recorded. The digit span recall involves progressively longer sequences of digits being presented to the individual, with the aim to successfully recall them in the correct order. During week one, the digit span started off with sequences of four digits. Another digit was incorporated when three successful sequences were recalled and this progression continued throughout the full four weeks.

If the participant had to stop walking to think of the next digit, they were instructed to start walking again as soon as they could. This cognitive task was chosen as it was easily performed whilst walking, did not require any special equipment, and did not present any bias against individuals with limited levels of literacy (McCulloch *et al.*, 2009). The digit span recall can be adjusted to match an individual's performance level. Walking in tandem was chosen for the motor task as it is a critical function for daily life that requires balance and independent mobility. The distance of 20m enabled the test to be administered in a variety of environments. The Walking and Remembering Test demonstrated excellent inter-rater (>0.97) and good test-retest reliability (0.79) in both young (college students >18 years) and older (>65 years) adults (McCulloch *et al.*, 2009).

5.10.4 Slalom walking and counting backwards from 100 in 3s and 7s – modified from Halvarsson, Dohrn & Stahle (2015).

The slalom and counting backwards dual task included participants walking in and out of a 10 m coned pathway, then turning around and walking back to the starting position at a self-selected pace (Figure 5.10). The time to cover the 20 m path while walking in and out of cones was timed (in seconds) and represented the single task condition. Participants were then asked to complete the walking motor task again while counting backwards from 100 in either 3s or 7s. The participant had to remain on the slalom pathway throughout, without missing a cone. As they became more comfortable with the task, they were asked to increase their walking pace and touch each cone during the slalom task. The slalom was used as the motor task as it simulated simple obstacle avoidance and could represent common daily tasks such as weaving in and out of people in a public busy place.

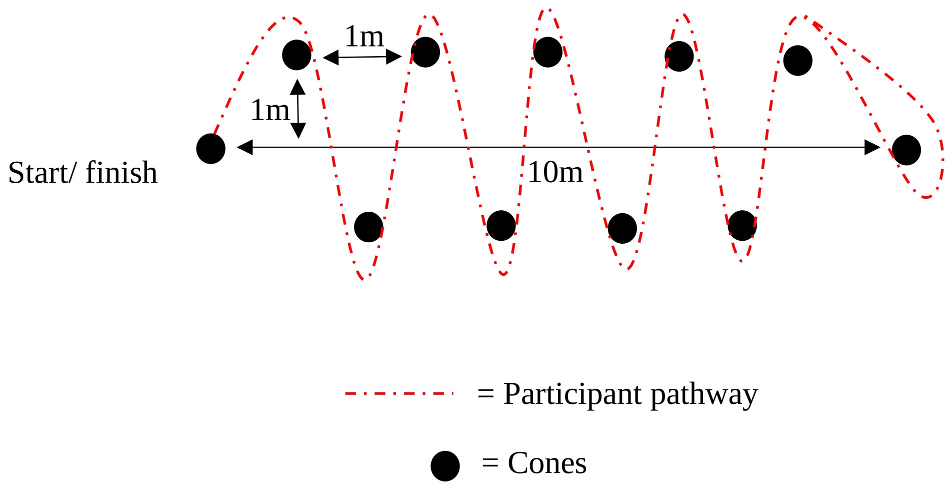

Figure 5.10.Slalom DT exercise set up

During all tasks, participants could rest when needed. The researcher avoided encouraging or advising participants during the tasks, apart from when individual safety was an issue. To quantify the changes in motor performances, dual-task decrements were calculated in seconds by subtracting the single task time from the dual-task time. The DTC was calculated as a percentage of this change between the single- and dual-tasks (refer to section 2.8.4 for calculation). The minimal detectable change for the DTCs are currently unknown as they may differ between motor DTC and cognitive DTC.

5.10.5 Statistical analysis

To gather an understanding of the effects of the dual-tasks on walking time, we applied models for repeated measures to evaluate within-group differences. Paired sample T-test were performed to evaluate associations with a p value < 0.05 considered statistically significant. Hedge's g was calculated as an indicator of standardised effect size, it was preferred over Cohen's *d* as Cohen's *d* can over-estimate effect size in small samples. All statistical analyses were performed using SPSS v.23.

5.11 Results

The eight participants from the EX group in part one completed the DT exercises (refer to section 5.5.1 for participant characteristics). The ratio of male to female participants was 4:4. All the participants in the exercise group had a 100% adherence to the intervention and no adverse effects were recorded.

Time taken to complete both the single and dual tasks were calculated for each task over the four weeks. For the tandem walking and digit span recall task, the single task performance was significantly quicker than the DT during weeks one (t_{15} = 2.654, p = 0.02), two (t_{15} = 3.049, p = 0.001), and three (t_{15} = 2.333, p = 0.03) (Table 5.5). This was also the case during the slalom DT (counting back in 3s) for weeks one (t_7 = 4.814, p = 0.002), two (t_7 = 2.670, p = 0.03), three (t_7 = 5.601, p = 0.001), and four (t_7 = 5.938, p = 0.001) (Table 5.6). Similarly, the slalom DT (counting back in 7s) also exhibited significantly faster performance for the single task compared to the DT in week one (t_7 = 5.031, p = 0.002) and weeks two (t_7 = 6.879, p = 0.000), three (t_7 = 9.054, p = 0.000) and four (t_7 = 6.700, p = 0.000), (Table 5.7).

Table 5.5.Single (motor) and DT (motor and cognitive) performances for the tandem walking and digit span recall task over the four weeks.

Week	Single task (s)	Dual task (s)	Mean diff. (s)	% change	95% CI	Effect size (g)
1	32.9 (6.6)	35.2 (7.5)	2.4*	7.0	-4.3, -0.5	0.3
2	30.4 (9.0)	33.2 (11.4)	2.8*	9.2	-4.8, -0.8	0.3
3	28.8 (7.1)	30.8 (8.6)	2.0*	6.9	-3.8, -0.2	0.2
4	26.5 (7.4)	28.0 (8.1)	1.5	5.7	-3.2, 0.3	0.2

**Statistically significant difference (P<0.05)*

Table 5.6.Single (motor) and DT (motor and cognitive) performances for the slalom walking and counting back in 3s task over the four weeks.

Week	Single task (s)	Dual task (s)	Mean diff. (s)	% change	95% CI	Effect size (g)
1	21.3 (1.9)	24.2 (2.0)	2.9*	13.6	-4.4, -1.5	1.4
2	20.1 (1.4)	22 (2.2)	1.9*	9.5	-3.6, -0.2	1.0
3	19.8 (1.7)	21.7 (1.7)	1.9*	9.6	-2.7, -1.1	1.1
4	18.8 (1.9)	20.4 (1.8)	1.6*	8.5	-2.2, -1.0	0.8

**Statistically significant difference (P<0.05)*

Table 5.7.Single (motor) and DT (motor and cognitive) performances for the slalom walking and counting back in 7s task over the four weeks.

Week	Single task (s)	Dual task (s)	Mean diff. (s)	% change	95% CI	Effect size (g)
1	20.8 (2.1)	23.8 (3.2)	3.0*	14.4	-4.4, -1.6	1.1
2	19.5 (1.4)	23.2 (2.6)	3.7*	19.0	-5.0, -2.4	1.7
3	19.2 (1.5)	22.3 (1.9)	3.1*	16.1	-3.9, -2.3	1.7
4	18.5 (1.8)	21.4 (2.3)	2.9*	15.7	-3.9, -1.8	1.3

**Statistically significant difference (P<0.05)*

The DTC were then calculated week on week over the four weeks. During the tandem walking and digit span recall task (Figure 5.11), there were no significant improvements (decreases in DTC) from week one (M = 7.3%, SD = 10.9) to week four (M = 8.3%, SD = 7.0), ($t_7 = -0.178$, $p = 0.9$, $g = 0.1$). The coefficient of variation (CV) decreased from week one (57.2%) to week four (46.0%), however this decrease was not statistically significant (p = 0.09).

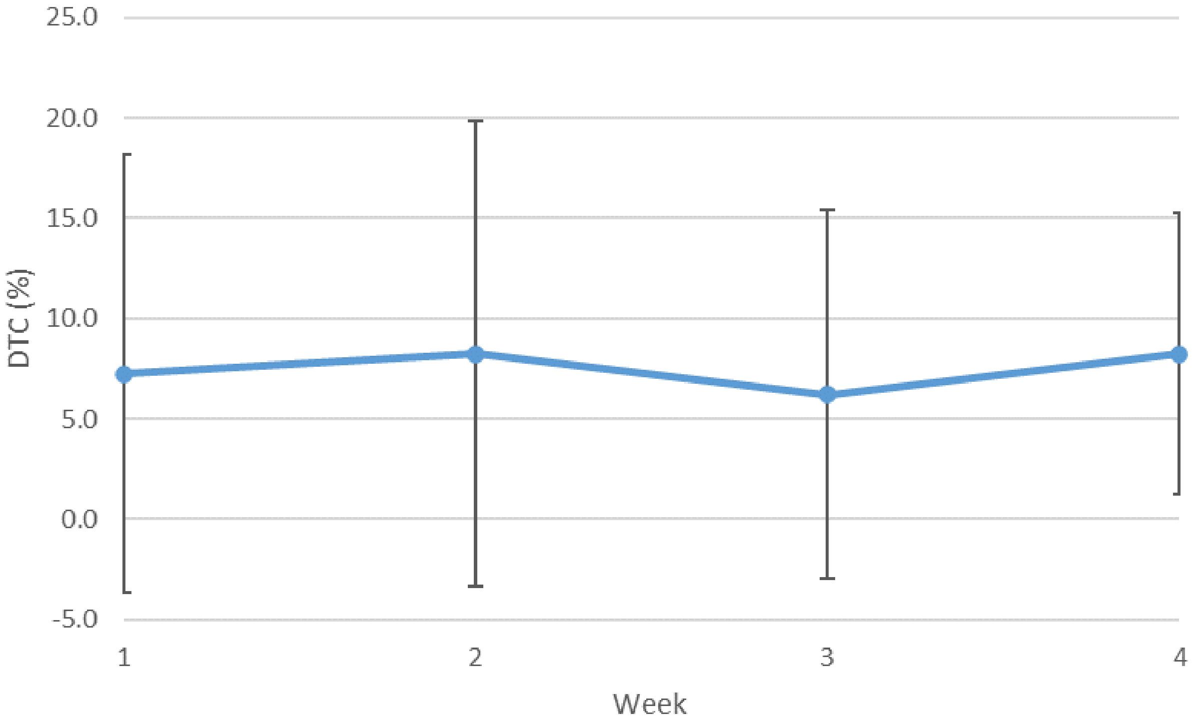

Figure 5.11.Mean DTCs during the 'tandem walking and digit span recall' task for the exercise group over four weeks.

There were no significant improvements in DTC present during the slalom walking and counting backwards in 3s (Figure 5.12) from week one (M = 14.2%, SD = 8.6) to week four (M = 8.7%, SD = 4.1), ($t_7 = 1.766$, $p = 0.8$) however a large effect size was demonstrated (g = 0.8).

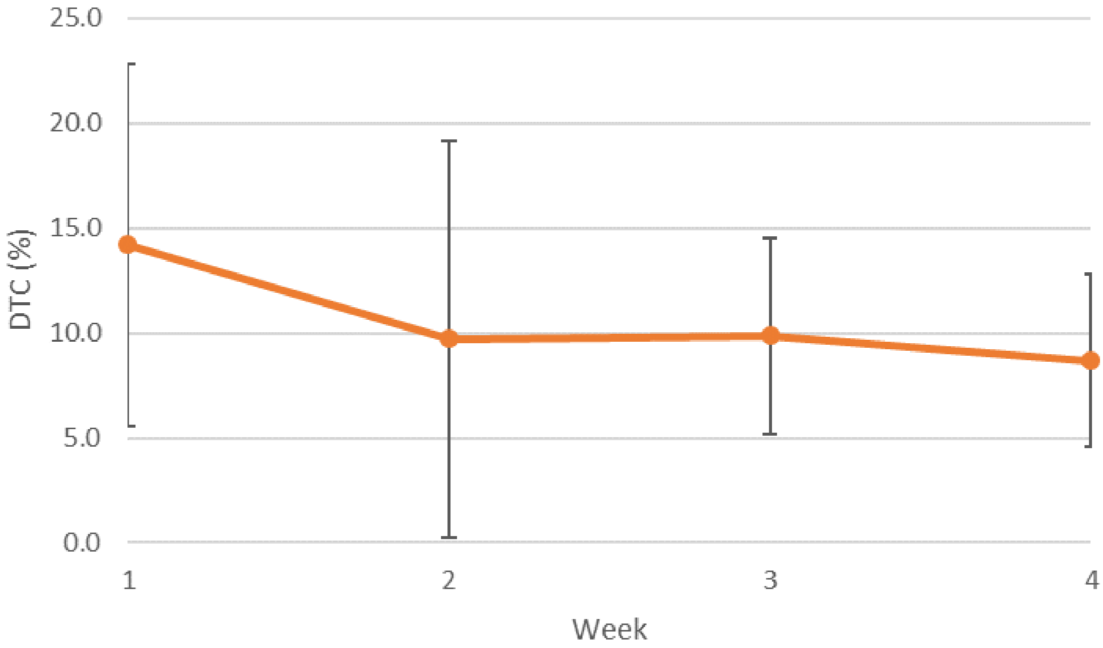

Figure 5.12.Mean DTCs during the ‘slalom walking and counting back from 100 in 3s’ task for the exercise group over four weeks.

Similarly, during the slalom walking and counting backwards in 7s task (Figure 5.13) there was no significant improvement in DTC from week one (M = 14.4%, SD = 7.1) to week four (M = 15.5%, SD = 5.8), (t_7 = 0.431, *p* = 0.7, *g* = 0.2). However, there was a significant decrease in performance (increase in DTC) from week one (M = 14.4%, SD = 7.1) to week two (M = 19.0%, SD = 6.4), (t_7 = 3.365, *p* = 0.01, *g* = 0.6).

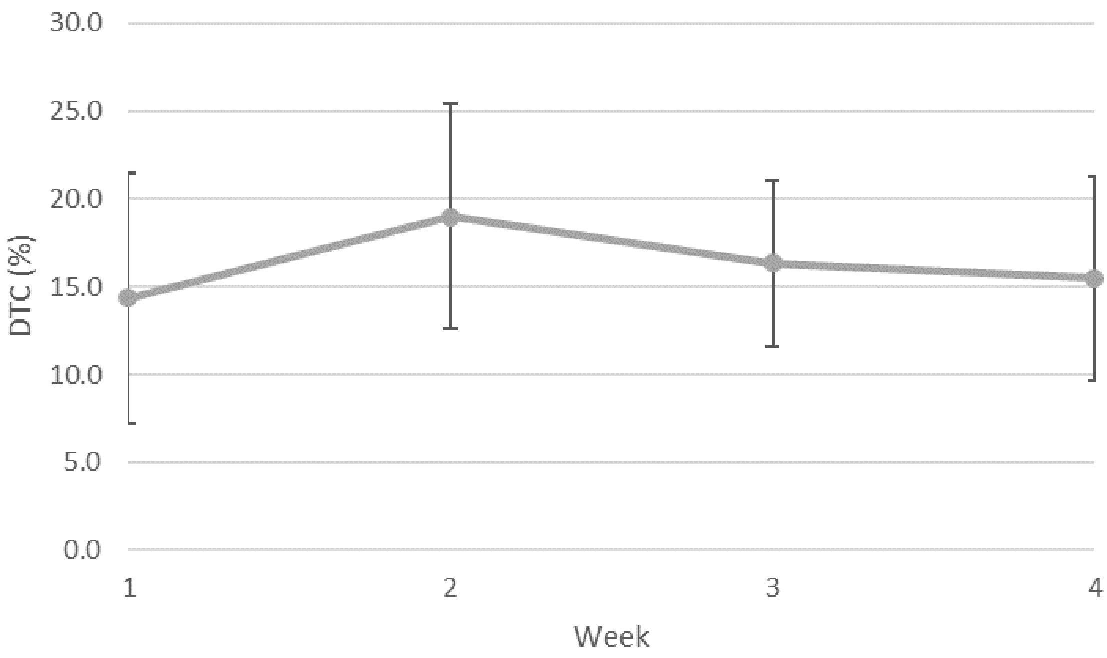

Figure 5.13.Mean DTCs during the ‘slalom walking and counting back from 100 in 7s’ task for the exercise group over four weeks

5.12 Discussion

The results of the current study show that, among a sample of both male and female healthy adults, completing a cognitive task whilst simultaneously executing a motor task, provoked some significant decrements in the performance of the motor task ($p < 0.05$) and evidence of DT interference. As expected, there was a significant decrease in walking speed (motor task) when a second task (cognitive) was introduced and performed simultaneously in all three tasks, presenting the dual-task cost (large effect sizes ranging from 0.8 – 1.7 for the slalom walking). Thus supporting the hypothesis of the primary objective. Previous research has presented similar trends in when combining a motor and cognitive task together simultaneously (Springer *et al.*, 2006; Beauchet *et al.*, 2005; Mirelman *et al.*, 2014). Springer *et al*. (2006) presented significant reductions in gait speed when a cognitive task, of counting back in 7s from 500, was introduced in a cohort of 19 young adults (aged between 18 - 35 years). Similarly, Beauchet *et al*. (2005) tested a cohort of 49 young, healthy individuals aged between 20 - 30 years, on walking and counting backwards from 50. They demonstrated a significant decrease in stride velocity and stride time when the counting task and walking where performed simultaneously. This was also the case in the study conducted by Mirelman *et al*. (2014) whereby there were significant decreases in gait speed and stride time when walking was combined with counting backwards in 7s from 3-digit numbers.

All three of these studies were cross-sectional designs (single time-point), whereas the data in the current chapter was measured longitudinally (multiple time points over a period of time), highlighting the novelty of the current programme. Longitudinal designs can show if DTCs persist even when the task is practised, which was revealed in the current study over a period of four weeks. The objective of this study was to inform a TBI exercise intervention, where adherence and retention rates were estimated to be low, so if changes in DTC occur over four weeks then the TBI cohort may also reap some benefits even if they do not adhere to the full programme.

The DTC between the single and DT activities could be explained by the theories of attention and capacity interferences, referred to previously in this chapter. According to Weerdesteyn *et al*. (2003) attention is a limited commodity and tasks that require attention, compete for this limited resource. Hence, if this capacity is exceeded, the performance of one or more of the tasks will be reduced. Looking at the DTC over the four weeks for all three tests, there were no significant decreases in DTC (increase of performance). This could indicate that a 4-week period is not long enough to illicit significant learning effects when performing a motor and cognitive task simultaneously (secondary objective). Hence alliterating the points from part one, that it would be suitable to extend the exercise programme to 12 weeks in a cohort of TBI, in the hope to illicit DT learning effects and significant improvements in DT ability.

Looking at the DTCs on a week to week basis highlighted an initial increase in DTC from week one to week two for the ‘tandem walking and digit span recall’ and the ‘slalom walking a counting backwards in 7s’ tasks. Conversely, the ‘slalom walking and counting backwards in 3s’ task showed a rapid decrease in DTC from week one to week two. This could indicate that counting backwards in 3s is a less demanding cognitive task when simultaneously performed whilst walking. Individuals with neurological deficits may be more susceptible to DT interference due to the increase in attentional demands in controlling the single motor task performance, leaving fewer resources to effectively cope with the secondary tasks (Weightman & McCulloch, 2014). So, a less demanding cognitive task would be suitable for a TBI cohort and should hence highlighting the justification for its inclusion into the exercise programme for chapter 6. Regarding the ‘slalom walking and counting backwards in 7s’ and the ‘tandem walking and digit span recall’ tasks, the initial increase in DTC could be exacerbated within a cohort of TBI. Compared with healthy individuals, people with a brain injury show significantly greater decrement in performance when partaking in two tasks simultaneously and strong correlations have been shown between this decrement and scores on the Barthel activities of daily living scale (Haggard *et al*, 2000).

Though there were no significant improvements in DT (decrease in DTC) over the four weeks during all exercises, increasing the training period from four to twelve weeks could introduce possible learning effects. Participants may become more comfortable and used to the DT exercises, thereby improving their DT performance disproportionally to their multi-tasking ability. In future studies, performance of a “familiarisation” DT session before testing may reduce the improvement in DT performance attributed to a learning effect. So, when implementing this programme with a TBI cohort (chapter 6) the initial week (week one) will be used as a familiarisation session. In addition to the possible learning effect of the DT exercises, the participants will be exposed to several other multi-tasking activities throughout the intervention. The whole exercise intervention will require participants to perform cognitive and motor task simultaneously. In particular, the Fitlight and agility cone exercises require the individual to process external stimuli (light activation/command from researcher) whilst simultaneously coordinating motor functions. By participating in the exercise programme, individuals will be required to multi-task which may contribute to the learning effect, therefore care must be taken in making conclusions of the direct effects of the DT exercises on DT improvements.

Testing DTCs on a weekly basis was practical for both the participants and the researcher. The participants were able to measure their performance week by week which increased their motivation and could have contributed to the 100% adherence rate for the exercise group. Regarding the researcher, it enabled a constant stream of recorded data which is important for predicting high dropout rates amongst TBIs. Due to the design of the exercise programme, the researcher was able to have two individuals participate at the same time. This allowed DTs to be closely monitored and recorded by the researcher whilst the other individuals performed tasks that did not need to full attention of the researcher.

A limitation of this study was the absence of recording the cognitive single task. This may have highlighted deficits in the cognitive task, as well as the motor task, when both tasks were performed simultaneously. Additionally, in future research the accuracy of the slalom DTs could be investigated to establish if the speed or the accuracy is affected the most with the incorporation of a cognitive task.

5.13 Conclusion

In conclusion, this study has demonstrated that dual-tasking activities may be delivered effectively as part of an exercise intervention and that it is feasible to quantify the weekly changes in DTC to monitor learning effects. Even though significant improvements were not demonstrated with the healthy individuals, it is hypothesised that by increasing the training period to 12 weeks will illicit significant performance improvements. These results have provided insightful data that can inform the implementation of DT activities into an exercise programme for individuals suffering from a TBI.

5.14 Overall conclusion

The overarching aim of this chapter was to assess the feasibility and acceptability of a four-week exercise programme in order to inform the design and delivery of a multi-component intervention for individuals with a TBI. It successfully highlighted the satisfactoriness of the current exercise design, highlighted by the 100% adherence rates. From a researcher's opinion, the circuit training set-up was suitable as it allowed attention to be focussed on the DT exercises whilst the other participants safely performed tasks that did not need the researcher's full attention. In addition, it enabled the researcher to quantify week on week changes to DT performances. Combining the findings from both elements of this chapter it highlighted components to take forward into an exercise programme for TBI individuals, such as extending the intervention period to 12 weeks and the continuation of week on week analysis for the aerobic fitness, reaction time and DT performances.

6 Chapter Six – The effects of a 12-week exercise intervention of mental and physical well-being in TBI individuals.

6.1 Overview

This chapter consists of two elements and will be presented in two separate parts. The first part follows on from the pilot study, which demonstrated that a novel exercise intervention could be designed and was feasible to deliver, and explores the incidence of TBI in the local region. This is important in order to identify the patient demographics and inclusion criteria of potential participants from the Hull area. The second part will investigate the effects of a novel, 12-week exercise intervention on individuals with a TBI, with the primary outcome looking at the changes in their quality of life.

Part 1.

6.2 Introduction

A Traumatic Brain Injury (TBI) is an alteration in brain functioning/ pathology caused by an external force through impact, blast waves, penetrating trauma, or an acceleration/ deceleration motion (Menon *et al*., 2010). These traumatic injuries evolve over time from primary to secondary injury. Primary injury refers to the brain damaged sustained at the time of the injury e.g. contusion, haematoma, and diffuse axonal injury. From the point of primary injury, secondary injuries, such as hypoxia and hypotension, can occur and can heighten brain damage further (White & Venkatesh, 2016). It is a major cause of disability, morbidity, and mortality with approximately 10 million people being affected annually worldwide, according to the World Health Organisation (WHO) (Harris *et al*., 2008).

In England during 2016-17, there were 23.4 million attendances recorded in Accident and Emergency (A&E) departments (NHS digital, 2017). Mondays were shown as the busiest day of the week and the months of May and July presented with the highest number of attendances per day. There was also an increased number of attendances for older patients aged between 65 - 79 years, from 10.2% of attendances in 2007-2008, to 11.9% in 2016-2017. These statistics account for all A&E attendances including Minor Injury Units and Walk-in Centres (without specifying TBI incidents) and provides an overview of the extent to which the A&E departments are utilised. Looking at the incidences of head injuries more specifically, around 1.4 million patients visit a hospital A&E department following a head injury in England and Wales every year (Lawrence *et al.*, 2016). When a patient arrives or is brought into the A&E department, diagnostic and management pathways are formed by determining the patient's level of consciousness and extent of the injury. If required, a CT scan is performed to understand the full extent of the injury. In the more severe head injuries, surgical treatment may be needed, and these patients are frequently admitted to the intensive care unit. For the mild injuries, patients generally get discharged and are provided with outpatient information about recurring symptoms they should look out for (Vos & Diaz-Arrastia, 2014). These symptoms could include persistent headaches, dizziness and nausea. Information about the TBI is vital, such as cause and severity, in order to correctly plan treatment methods in A&E. The findings of numerous previous studies, indicate that falls and road traffic collisions (RTC) are the most prevalent causes of TBI in the UK (Gabbe *et al*., 2011; Kehoe *et al.*, 2016; Hawley *et al*., 2017; Fountain *et al.*, 2017; Lawrence *et al*., 2016). Incidents of fall-related TBI are positively correlated to increasing age (Kehoe *et al.*, 2016; Hawley *et al*., 2017; Lawrence *et al*., 2016). To assess the severity of a patient's TBI, the Glasgow Coma Scale (GCS), (Teasdale *et al.*, 2014) is widely used assessing the responsiveness in three different domains; eye opening, motor and verbal responses to speech or stimulus (section 4.2.1).

Traumatic brain injury management is a key topic of interest in A&E departments across the country, attempting to gather unified guidelines for the most effective methods of treatment. A clear understanding of the epidemiology of TBI is required to attain these guidelines and rehabilitation. In order to assess the quality of care provided by the NHS, clinical audits are conducted. Audits were first introduced in Britain in 1989 (see *Working for Patient* (Department of Health, 1989)), with the aim to assess the reviewing and delivery of patient care and highlighting any shortcomings so they can be resolved. Their overall aims are to give patients better healthcare, to generate greater satisfaction and reward those working in the NHS responding to local needs and preferences. The number of retrospective audits for TBI admissions in the UK is limited (Lawrence *et al*., 2016; Hawley *et al*., 2017).

6.3 Aim

The aim was to complete a retrospective audit to gain a greater understanding of the epidemiology of TBI in an A&E department at a major hospital in Hull and East Yorkshire. The primary objective was to inform patient recruitment and inclusion/exclusion criteria for a future non-randomised controlled trial with an exercise intervention. To the author's knowledge, this would be the only recent audit at this hospital site specifically.

6.4 Methods

This local audit was conducted in the A&E department at Hull Royal Infirmary between July and August 2017. Permission to access patient case notes on site was approved by the Research and Development Department at Hull Royal Infirmary, adhering to the Good Clinical Practice (GCP) guidelines regarding patient confidentiality throughout. Data was anonymously coded and stored in password protected files. Access to data was limited to members of the research team only.

6.4.1 Patients

Patients were identified following their admission to A&E. Identified patients met the following inclusion criteria: aged 16 years and over and having sustained a brain injury related to trauma (all severity levels). Head injury was defined as any trauma to the head, excluding superficial injuries to the face. Patients were excluded from this audit if they sustained a brain injury that was classed as non-traumatic, for example: a non-traumatic haemorrhage, tumour, infectious disease, hypoxic injuries, or metabolic disorders.

6.4.2 Data collection

Requests for case reports were made to the A&E department for admission patients presenting with signs of a TBI. A proforma was developed, highlighting patient demographics and injury mechanisms. (see Appendix A for proforma). The data proforma also outlined admission day, method of arrival, intoxication on arrival and discharge methods (these results are outlined in Appendix B). All the data were extracted retrospectively on site at Hull Royal Infirmary, through patient clinical management systems and the ambulance sheets in A&E. The data extraction team comprised of a clinical research nurse and PhD student at the University of Hull who had an honorary contract with the local Trust and therefore full access to patient details.

6.4.3 Data analysis

SPSS V.23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) was used for the descriptive statistics. Age was categorised into five groups: 16 - 25 years, 26 - 45 years, 46 - 65 years, 66 - 85 years, and 86 - 105 years. Mechanism of injury was categorised into eight groups: sports, RTC, assault, deliberate self-harm, fall, others, and not available (n/a). The GCS was also categorised into four groups: mild, moderate, severe, and n/a. For the addition results (Appendix B), methods of arrival was classified into four groups: ambulance, self, other and not available (n/a). Discharge method was labelled into five groups: in-patient, discharged (follow-up), discharged (no follow-up), referred and n/a. All extracted data were collected and coded and then analysed in SPSS V.23.

6.5 Results

During the audit period of 66 days 293 patients (aged between 16-97 years) were admitted to the A&E department at Hull Royal Infirmary presenting signs/ symptoms of a traumatic brain injury. The mean (SD) age was 54.8 (25.8) years with 147 males (50.2%) and 146 females (49.8%) (Table 6.1). Some information was missing in the patient report files and was therefore categorised as N/A. The full set of results can be found in Appendix B.

Table 6.1.Patient characteristics of TBI admissions to the A&E department

	Male	**Female**
Number	147 (50.2%)	146 (49.8%)
Mean age (years)(SD)	48 (23)	62 (26)
Age range	16-91	16-97

Falls, assaults, and road traffic collisions (RTCs) were the most common mechanisms of injury (61.8%, 22.9%, and 10.2%, respectively) (Figure 6.1). Males presented with the majority of the sports-related head injuries (70%), RTCs (70%) and assaults (70.1%), whereas females presented with the majority of falls (61.3%) (Figure 6.1).

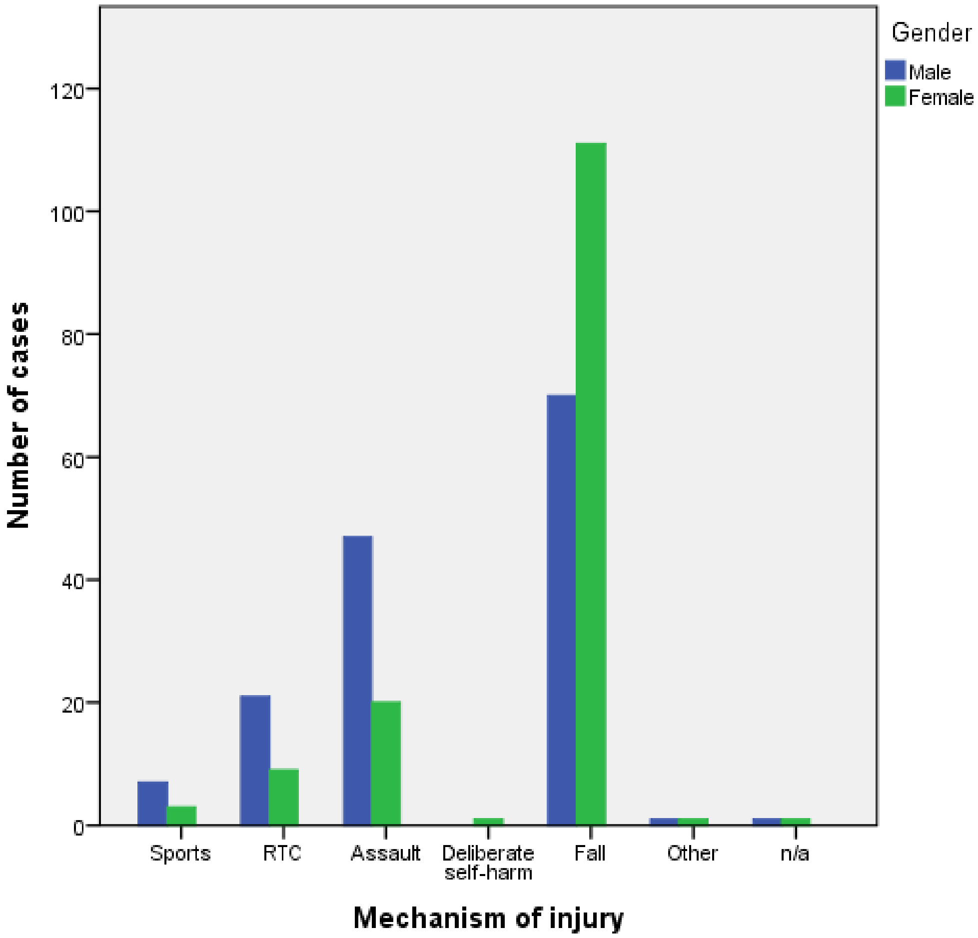

Figure 6.1.Mechanism of injury according to gender

In the groups aged 16-25 and 26-45 years, assaults were the most common mechanism of injury (40% and 43.5%, respectively). For patients in the groups aged 46-65, 66-85 and >86 years, falls were the most common form of injury (66%, 94.2%, and 100%, respectively) (Figure 6.2).

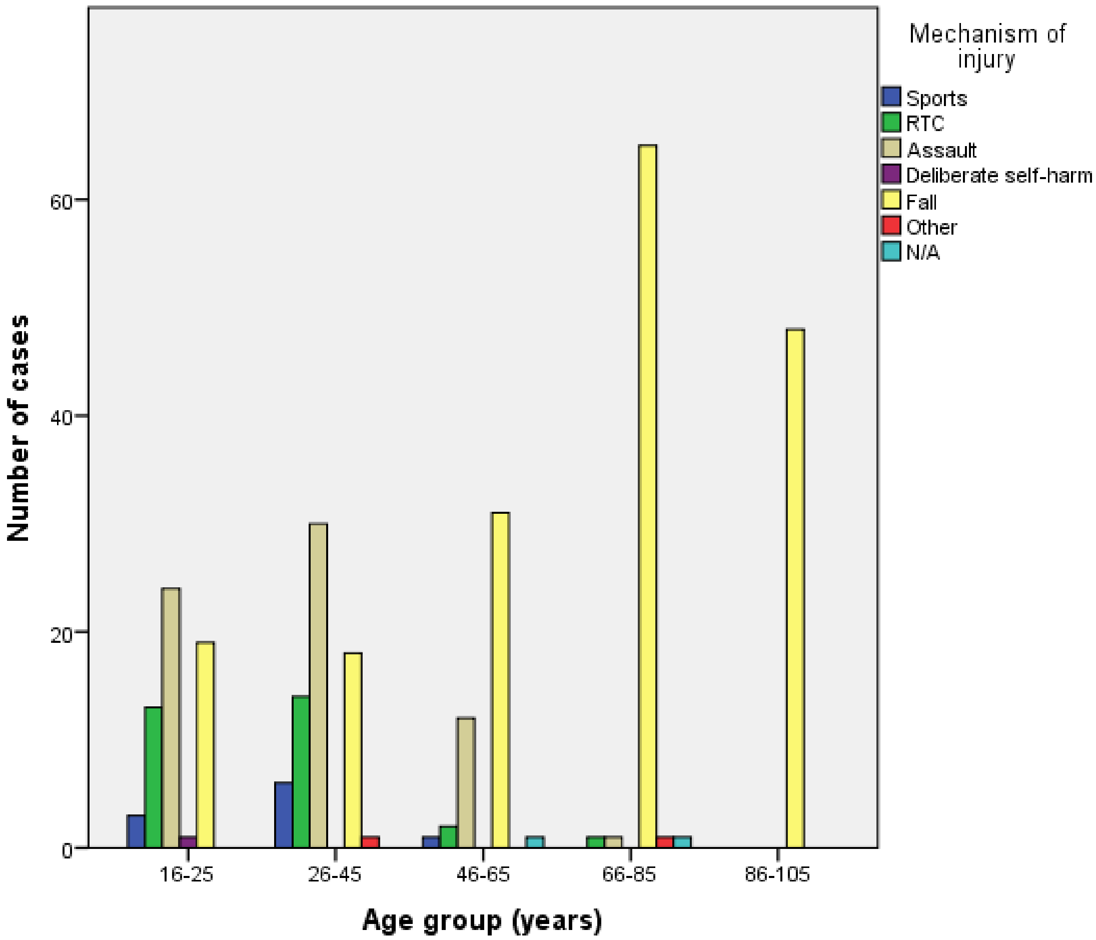

Figure 6.2.Mechanism of injuries according to age categories

The majority of the patients presented with mild GCS during their assessment in A&E (89.8%), compared with the moderate and severe scores (Table 6.2). Out of the 293 cases, 22 patients did not have their GCS in their patient notes.

Table 6.2.Glasgow Coma Scores upon initial assessment in A&E

Score	Frequency (n=)	Percent (%)
Mild	263	89.8
Moderate	5	1.7
Severe	3	1
n/a	22	7.4
Total	**293**	**100**

The majority of the mild and moderate severity TBIs were caused by falls (62.4% and 60%, respectively). Patients presenting with severe TBI, arrived following either an RTC (66.7%) or an assault (33.3%) (Figure 6.3).

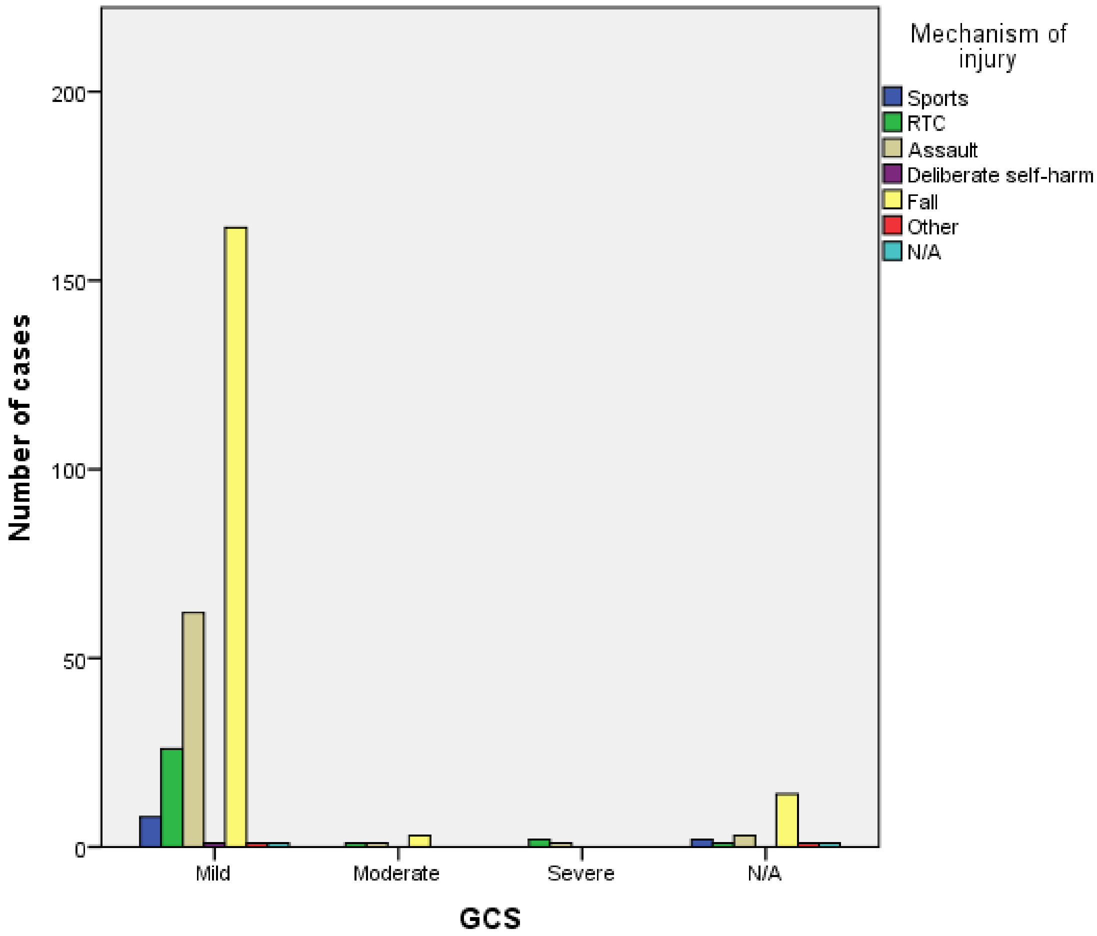

Figure 6.3.Mechanism of injury according to the GCS

The highest prevalence of mild TBIs occurred in patients aged between 66-85 years (24%), followed by 22.8% of cases for the 26-45 age category (Figure 6.4). Moderate TBIs were seen more in patients aged ≥86 years (40%) and severe TBIs being most prevalent in patients aged 26-45 years (66.7%).

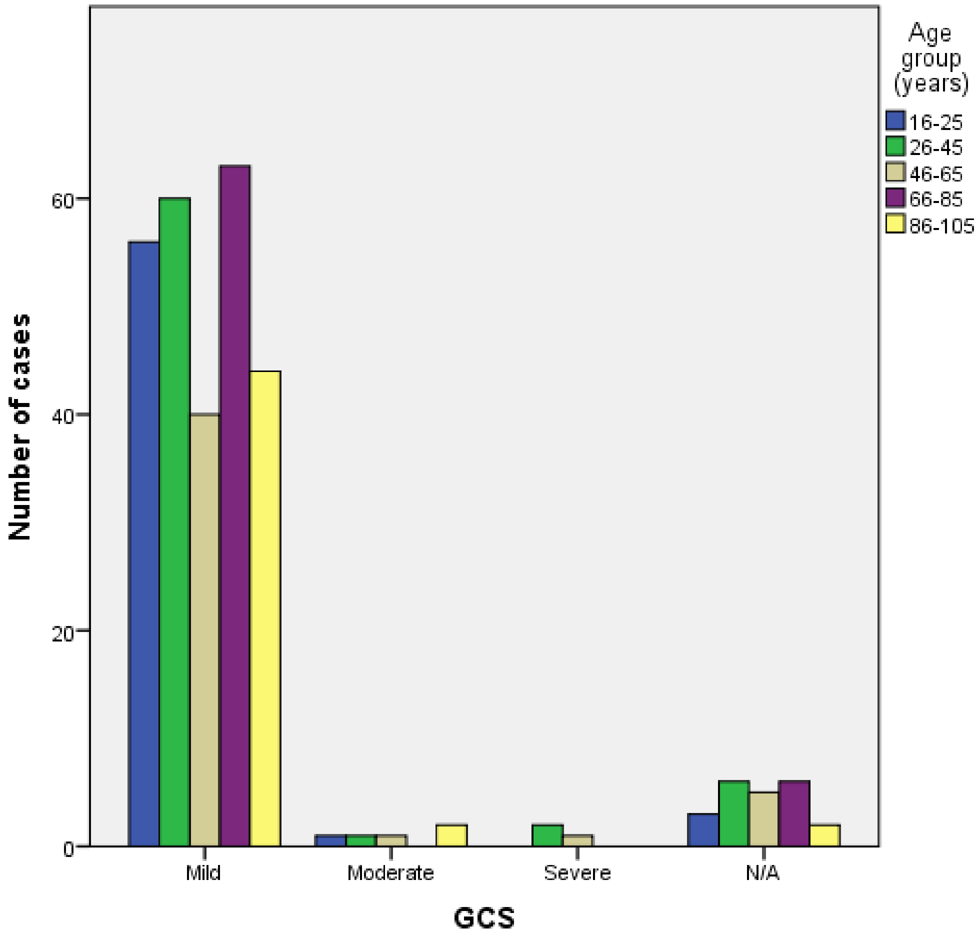

Figure 6.4.GCS according to age group

Additional results on admission day, methods of arrival, intoxication on arrival, and discharge methods are outlined in Appendix B. These were not included within the chapter as they did not inform specifically on patient recruitment and inclusion/exclusion criteria (primary objective).

6.6 Discussion

The aim of this study was to retrospectively assess the epidemiology of patients presenting with a TBI at an A&E department in Hull and East Yorkshire. Over a short period of time, many TBI cases were noted introducing a growing problem and targets lack of healthcare/social support in mild/moderate TBI severity. This therefore provides justification of the inclusion/exclusion criteria for part two of this chapter.

This study highlights trends in patient and injury characteristics that informs the epidemiology and the justification of the inclusion/exclusion criteria for part two of this chapter.

This study was conducted locally at only one A&E department in order to inform recruitment strategies for future research as part of this PhD thesis. The findings from this audit provide a more detailed overview of the incidence of TBI locally over a short time period in the summer.

6.6.1 Patient demographics and mechanism of injury

The current study gathered information from 293 patients who presented themselves to the A&E department at Hull Royal Infirmary following a TBI. The percentage of male and female patients presented no differences (50.2% and 49.8%, respectively). Falls were the most common mechanism of injury (61.8%) for all of the reviewed cases. Investigating this according to age groups, falls were more prevalent in patients aged 46 years and older. Previous research in the UK also presented increases in fall incidences as patient age increases (Lawrence *et al*., 2016; Hawley *et al*., 2017; Kehoe *et al*., 2016). Unlike the current study, Hawley *et al*. (2017) completed a retrospective analysis on primarily older adults (>65 years) but reported that falls-related injuries (<2m) were associated with patients in the oldest age category (>85 years). Kehoe *et al*. (2016) compared injury characteristics in younger (<65years) and older (≥65 years) patients in the UK over a 25-year period. Falls (<2m) were more prevalent in the older (70%) compared to the younger (20%) patients. The incidence of TBI caused by falls in older adults is a public health concern, which has been acknowledged in research related to falls prevention interventions (McClure *et al*., 2005).

In the current study, assaults (also known as intentional TBIs) were the most common cause of injury for patients aged between 16 - 45 years. These findings support Lawrence *et al.* (2016) who reported that younger patients (aged <50 years) had increased prevalence of assaults and RTC, and Shivaji *et al*. (2014) where assaults were the second most common cause of TBI (18%) and more prevalent in patients aged between 15 - 34 years of age. Cause of injury is related to gender as well as age, with the current study indicating that the majority of the falls were seen in females (61.3%) while more males presented with assaults (70.1%) and RTCs (70%). Hawley *et al*. (2017) found significant differences in causes of injury for men and women ($p<0.001$) with men presenting with more RTCs than females. They also demonstrated that males had more falls from a height (>2m).

6.6.2 Injury severity

In the current study, most injuries were categorised as mild severity (89.8%) and of these, 62.4% were caused by falls. This relates to the fact that the most common mechanism of injury was because of a fall. In the severe cases (GCS<8), the most prevalent cause of injury was an RTC (66.7%). More severe injuries have been associated with RTCs, with the addition of multiple of injuries, often leading to more unfavourable outcomes due to the need for intensive care (Kay & Teasdale, 2001). Injury severity also demonstrated patterns according to age group, with the highest prevalence of mild TBIs being presented in patients aged 66 - 85 years (24%). In the current study, the majority of the severe TBIs were seen in patients aged between 26 - 45 years (66.7%), as more RTC injuries occurred within this age group and RTCs presented the highest percentage of severe TBIs.

To expand on this, it would be beneficial to question the sedentary nature of the populations most effected by TBIs. This data could then be compared to the national guidelines for physical activity making it possible to identify what percentage of this population would likely to meet these guidelines. The importance of knowing this can relate to the true impact of aerobic training. It has already been established that TBI individuals have decreased cardiopulmonary fitness compared with nondisabled populations (Mossberg *et al*., 2007) and participate in levels of physical activity below the recommended guidelines (Hassett *et al*., 2009; Wise *et al*., 2012; Bombardier *et al.*, 2017). Establishing connections between physical activity participation and injury severity, may further highlight population groups that would benefit the most out of regular supervised exercise programs.

6.6.3 Limitations

It is important to acknowledge some limitations of the current study. The time period for data collection was small in comparison to previous studies that assessed trends over 10 - 12 year periods (Peeters *et al.,* 2015; Shivaji *et al*., 2014). This means that only a small scope of the patients were analysed. Data were only captured during the summer months, and there may be seasonal variations of the mechanisms for injuries (i.e. weather conditions, seasonal sports, more outdoor activities).

6.7 Conclusion

This study is the only current up to date audit to report TBI admissions into A&E at a major hospital in Hull and East Yorkshire. It highlights a wide range of potential participants that could be suitable for a novel exercise intervention study and informs the inclusion and exclusion criteria for a future study. The additional data (Appendix B) could also inform operational procedures at A&E relating to data about admission times/ dates and according to severity.

Part 2.

6.8 Introduction

Following a TBI, symptoms may persist for prolonged periods such as headaches, dizziness and nausea. These issues are often disabling and can have negative impacts for productivity, relationships, and overall quality of life (Azulay et al., 2013). Previous research has suggested that 60 - 90% of individuals with a mild TBI return to work or school within 6 months (Kristman *et al*., 2010), but symptoms have been known to persist even after one year post-injury (Cassidy *et al*., 2014). There is a growing body of evidence on the use of exercise training as treatment for people who have sustained a brain injury as it has been associated with reduced anxiety, depression, stress, and persistent post-concussion symptoms (Sullivan *et al*., 2018). Athletes with a recent concussion (mild TBI) presented with better outcomes (time from medical clearance to return to sport and post-concussion symptoms) following a multimodal physical therapy programme compared with athletes receiving the standard treatment (Schneider *et al*., 2014).

The use of exercise as a form of rehabilitation for individuals with a TBI is a widely studied topic now with attempts to establish the most effective modalities and dose response (Kleffelgarrd *et al.,* 2016; Driver *et al*., 2006; Elsworth *et al*., 2011; Hassett *et al*., 2009; Bateman *et al*., 2001; Chin *et al*., 2015; Schwandt *et al*., 2012) Previous research has investigated the effects of an aerobic exercise programme and found significant improvements in cardiorespiratory fitness (Bateman *et al*., 2001; Chin *et al*., 2015; Schwandt *et al*., 2012). All of these studies conducted their programme over a 12-week period which included 3 x 30 minutes session per week. Although we have a clearer understanding of the short-term benefits of aerobic exercise on cardiorespiratory fitness. There has been relatively limited information published on the effects of exercise training on other outcomes (health and wellbeing) in participants following a TBI.

Following a TBI, individuals are often left with lasting and serious adverse consequences for cognition, physical health, personality, behaviour, and mood, resulting in concomitant negative effects on their QOL (Azulay *et al*., 2013). Recovery from TBI may be a complex and lengthy process with both the physical and psychosocial domains of QOL changing over time (Pagulayan *et al*., 2006). Recent research has highlighted significant improvements to QOL following exercise interventions (Damiano *et al*., 2016; Driver *et al*., 2006, Kleffelgaard *et al*., 2015; Schwandt *et al*., 2012).

Balance and postural sway are generally compromised with previous research highlighting increased reliance on visual input and tendency to sway more in the anteroposterior and medio-lateral directions compared with individuals without neurological deficits (Geurts *et al*., 1999; Wade *et al*., 1997). Motor control training has shown to elicit significant improvements during the Motor Control Test (MCT) and Limits of Stability (LOS) test on the NeuroCom EquiTest following an 8-week elliptical trainer programme (30 minutes at 40-80 RPM, five days a week) training on an amongst TBI participants (n = 12, mean age = 31.1 years, time since injury ≥ 6 months), (Damianio *et al*., 2016). Significant improvements in balance have also been reported by Kleffelgaard *et al*. (2015) following an 8-week full-body strength and conditioning programme amongst individuals with a mild TBI (n = 4, aged between 24 – 45 years).

An area that has been less researched relates to the effects of Dual-Tasking (DT) tests and training. Individuals with cognitive impairments have shown significant reductions in motor performances during DT exercises compared with healthy adults (Vallée *et al*., 2006: Parker *et al*., 2005). Schwenk and colleagues, (2010) investigated the effects of a 12-week dual-task training programme in patients with mild to moderate dementia, demonstrating significant improvements to the DT performance during gait analysis and the combined motor:cognitive measures. These results highlight promising prospects for the use of exercise as a rehabilitation method for TBI individuals, including the addition of DT activities, but there is still a lack of consensus for the most effective exercise prescription primarily as a result of large-scale, robust study designs. In addition, physical activity participation is recognised to decrease following a TBI, when compared with preinjury levels (Fleming *et al*., 2011), emphasising the importance of re-engagement with more structured exercise programmes. The findings from the previous section of this chapter highlighted the large number of reported TBIs in the local Hull and East Yorkshire area, and partially informed the inclusion and exclusion criteria for the current study. The large numbers of patients admitted locally to A&E with a mild or moderate TBI suggests there is the potential demand for participation in a structured exercise programme.

6.9 Aim

The aim of this study was to evaluate a novel 12-week, multi-component exercise-based intervention on the mental and physical well-being of individuals with a mild to moderate TBI. The primary outcome will evaluate QOL through validated questionnaires. The secondary outcome will explore the effects of dual-tasking training by quantifying the dual task cost (DTC), and finally the tertiary outcomes will assess physical function following the exercise intervention by specifically investigating balance, mobility, strength, and aerobic capacity.

6.10 Methods

6.10.1 Participants

Individuals were recruited from the local Hull area including Hull royal Infirmary (HRI), Castle Hill Hospital (CHH) and the University of Hull. They were recruited through recommendations from consultants and via leaflets in HRI, CHH and the University of Hull. If interested, they were given a participants' information document outlining the study design and their role they would play if they wanted to participate. Next the prospective participants were screen against the following inclusion/ exclusion criteria (as previously described in section 4.3): a mild or moderate TBI, aged between 18 and 65 years, walk independently and could commit to the exercise intervention. Individuals were excluded if they had a current substance or alcohol abuse issues, pre-injury disabilities, known cardiovascular problems or taking medication that could interfere with mobility or cognitive functions. All participants provided written informed consent to take part. Once consent was obtained the participants were allocated into either an EX or a CON group by pragmatic randomisation (randomised in the order that they are recruited). Due to slow recruitment rates, participants that demonstrated a keen preference for exercise were allocated into the EX group to encourage retention rates as the drop-out rates were predicted to be relatively high. Pragmatic randomisation was chosen as is focusses on correlations between treatments and outcomes in real-world health system practices. This study was reviewed and approved by the NHS Leeds West Research Ethics Committee (REC reference 16/YH/0210).

6.10.2 Experimental protocol

For full methodological procedures, refer to methods section 4.0.

All participants attended testing sessions at baseline, mid-point (six weeks) and post-testing time points. Sessions included completing QOL questionnaires, postural stability, balance, mobility, and strength assessments, followed by a maximal aerobic capacity assessment. In addition, participants also had their blood taken at during the bassline and pots-testing sessions at the University of Hull. Quality of life questionnaires were sent (by post) to every participants during the follow-up period of 6-months post baseline. Participants were required to complete all four questionnaires and send back to the University in the pre-paid envelopes.

6.10.3 Experimental procedures

6.10.3.1 Quality of life (QOL)

Four questionnaires were used in this study: the Short From-36 (SF-36), Hospital Anxiety and Depression scale (HADS), Rivermead post-concussion symptoms (RPQ), and the Glasgow Outcomes Scale Extended (GOSE). All questionnaires were completed at baseline (in person), post-testing (in person) and at follow-up sessions (via post). The SF-36 assess self-reported physical performance and health-related QOL. Participants were asked to complete the questionnaire as truthfully as possible recalling their answers over the past four weeks. Each item is scored on a 0 (low) to 100 (high) scale, using pre-coded numeric values, with higher scores representing favourable health states. Items in the same scale are then averaged together to create the eight scale scores. Question 2 in the questionnaire is used as the transition domain asking the individual, "compared to one year ago, how would you rate your health in general now?" A full description of SF-36 and analysis is outlined in section 4.2.2.1. The HADS is a self-reporting questionnaire measuring anxiety and depression in the past week. Each question is rated from 0 (favourable) to 3 (unfavourable) and the anxiety and depression scores are added up separately presenting two total scores (full description in section 4.6.2.2). The RPQ measures the severity of 18 physical symptoms commonly seen following a TBI. The participants are asked to rate each symptom comparing with before their head injury, on a scale of 0 (not experienced at all) to 4 (a severe problem). The items are scored in two groups. The first group (RPQ-3) consists of the first three items (headache, feeling of dizziness and nausea) and the second group (RPQ-13) comprising of the next 13 items. Higher scores reflect greater severity (full description outlined in section 4.6.2.3). Glasgow Outcome Scale Extended (GOSE) assesses global functioning following a TBI with participants asked to answer each question relating to their current state. The grades are shown beside the responses for each question and the overall rating is based on the lowest outcome category. Overall rating is graded on an 8-point scale (1 = dead; 2 = vegetative state; 3 = lower severe disability; 4 = upper severe disability; 5 = lower moderate disability; 6 = upper moderate disability; 7 = lower good recovery; 8 = upper good recovery). The full description of the GOSE is outlined in section 4.6.2.4.

6.10.3.2 Postural stability

Postural responses were determined using the NeuroCom Smart EquiTest system (SMART EquiTest, Oregon, USA) quantifying the contribution of somatosensory, visual and vestibular responses to balance. Three tests were completed: Sensory Organisation Test (SOT), Motor Control Test (MCT), and Limits of Stability (LOS). The SOT measured participants' responses to alterations to the somatosensory and visual environments in six different conditions (refer to section 4.6.3.2). Individuals and composite equilibrium scores were calculated expressed as a percentage between 0 (fall) and 100 (perfect stability). The MCT assessed the participant's ability to recover following an unexpected external disturbance in six conditions: three graded backwards and three graded forward translations. Reaction time to response (latency) was recorded to each condition and averaged to produce a composite score (full description is outlined in section 4.6.3.3). Finally, the LOS test quantified the maximal distance the individuals can displace their COG in eight different directions (4 cardinal and 4 diagonal). All of the tests were scaled to the participant's height and age. Reaction time and directional control were recorded (refer to section 4.6.3.4 for full description).

6.10.3.3 Balance

The Star Excursion Balance Test (SEBT) measured motor control in eight directions (1-anterior, 2-anteromedial, 3-medial, 4-posteromedial, 5-posterior, 6-posterolateral, 7-lateral, 8-anterolateral), (refer to section 4.6.3.5 for full details). Participants were asked to stand in the middle of the star, balancing on one foot whilst reaching as far as possible, making a light touch on the line, in each direction on the star with the other and returning the reaching leg back to the centre. The distance between the centre of the star and the reaching point was measured (cm) for each trial on both legs and an overall score for each leg was determined by averaging the three trials.

6.10.3.4 Functional mobility

The sit-to-stand (STS) test was used to assess functional lower extremity strength (full description of test procedure in section 4.6.3.6). Participants were instructed to move from a seated to a standing position then back again as many times as they could in 30 seconds. The number (n) of complete sit to stand movements were recorded during one single trial.

6.10.3.5 Strength

Muscle power was measured using an isokinetic dynamometer. Participants performed five continuous concentric-concentric bilateral knee flexion and extension cycles at an angular speed of 60 °/s followed by another five cycles at 180 °/s (full description of set-up and protocol in section 4.6.3.9). The average power (watts) was recorded at each speed on both legs. For analysis the scores from the right and lefts legs were averaged.

6.10.3.6 Aerobic capacity

All participants completed a voluntary maximal exhaustion test at the baseline and the post-testing sessions on a cycle ergometer. A full description is outline in the section 4.6.4. In brief, participants were asked to perform a five minute gentle warm-up on the cycle ergometer cycling at 60 revolutions per minute (RPM). Following the warm-up, the participant continued to cycle but now with the added resistance of 50 Watts, which then continued to increase by 40 Watts gradually every two minutes throughout the test. Participants had to maintain a speed of over 60 RPM. Test was terminated when the speed dropped below 60 RPM without signs of increasing or if they demonstrated any signs of physiological concern. Once terminated, participants were asked to complete a five minute cool-down without any resistance and at their own conformable speed. Heart rate (bpm) was recorded throughout the test and participant were asked to rate their exhaustion from 6 (rest) to 20 (exhaustion) using the original Borg rate of perceived exhaustion (RPE) scale. Following the test, peak oxygen uptake ($\dot{V}O_2$peak) (ml/min/kg) and maximal workload (watts) were calculated (full description of outcome measures are outlined in section 4.6.4.4).

6.10.3.7 Bloods

Brain-Derived Neurotrophic Factor (BDNF) levels were measured in blood plasma via venepuncture at baseline and following the 12-week exercise intervention period. This biomarker is associated with providing neuro-protection and restoring connectivity after a TBI, playing a prominent role in the repairing phase (Kaplan *et al.*, 2010). Pre- and post-intervention samples were taken at the same time of day with participants refraining from vigorous exercise and alcohol consumption 24 hours prior to each test. Samples were taken by a trained phlebotomist at the University of Hull. The samples were taken intravenously from the median cubital vein. Standard infection control procedures were followed to reduce risk of infection to both participant and researcher: use of alcohol wipes to prepare the puncture site, use of sterile needle, protective clothing worn by the researcher and Hepatitis B inoculation. Three samples were taken from each participant at each time point in 10ml K2EDTA tubes and immediately centrifuged at 3500 rpm for 15 minutes at 4°C then stored at -80°C until analysis.

For biomarker analysis (conducted once participant had completed their post-testing session), the plasma samples were thawed at room temperature. BDNF was assayed by an enzyme-linked immunosorbent assay (ELISA) kit (Bio-Techne, Minneapolis, USA). Once thawed, the plasma samples were prepared by dilution with the calibrator diluent RD6P. All reagents were brought to room temperature. The wash buffer was prepared by adding 20 ml of the wash buffer concentrate to deionised water to prepare 500 ml of wash buffer. For the next reagent, the Human Free BDNF standard was reconstituted with calibrator diluent RD6P producing a stock solution on 4,000 pg/ml. 300 µL of the calibrator diluent RD6P was pipetted into polypropylene tubes. Addition of the stock solution was added to each tube to produce a dilution series with each tube being thoroughly mixed between transfers. The undiluted BDNF standard (4,000 pg/ml) served as the high standard. 100 µL of assay diluent RD1S and 50 µL of the plasma samples were added to each well and incubated for two hours at room temperature. The next step included adding 100 µL of the BDNF conjugate to each well and incubate for one hour at room temperature. Each well was aspirated and washed, repeating the process twice for a total of three washes. The substrate reagent was then prepared by mixing together the collar reagent A and B in equal volumes, and 200 µL was added to each well and incubated for 30 minutes at room temperature whilst being protected from light. The stop solution (50 µL) was then added to each well and the optical density of each well was determined within 30 minutes using a microplate reader set to 450 nm. Typical data for the average optical density for each diluent is shown in table 6.3.

Table 6.3.Typical optical density results for plasma assay concentrations

Human free BDNF concentration (pg/ml)	Average optical density
0	0.030
62.5	0.086
125	0.140
250	0.244
500	0.430
1000	0.770
2000	1.128
4000	1.961

(R&D systems, 2017) *https://resources.rndsystems.com/pdfs/datasheets/dbd00.pdf*

The minimal detectable dose of human free BDNF is typically <20 pg/ml. This biomarker has been carefully chosen as it has shown higher prognostic values among mild TBI compared with other markers that are only significantly susceptible for severe TBI. In addition to this, it has been shown to have a very strong association with TBI, excellent discriminative ability of 0.94-0.95. The association between TBI and BDNF is biologically plausible and has been demonstrated in diverse TBI models (Korely *et al*., 2016).

6.10.4 Exercise intervention

Individuals in the EX group attended two supervised, one-hour group sessions each week for 12 weeks, held at the University of Hull. Using the findings from chapter 5, the same exercise sessions were used within the TBI cohort as they demonstrated to be feasible in terms of design and delivery from both the participants and the researcher. The only difference was the length of the exercise intervention being extended to 12 weeks from four weeks. The first session of each week incorporated agility, coordination, balance, strength, and dual-tasking exercises set out as a circuit training, with eight different stations. Full intervention description in outlined in section 4.7. Participants repeated the circuit twice each session. Chapter 5 highlighted the feasibility of including DT activities into the exercise intervention amongst healthy individuals from both the participants and researcher point of view so the decision was to include them into the 12-week programme for TBI individuals. The same DT exercise were used in the same order as the programme in chapter 5. A full outline of DT exercise are described in section 5.10. In brief, each participant performed three dual-tasking activities as part of the circuit training exercise sessions. The first one included walking along a 20m pathway heel-to-toe and back again to the start. The time taken to complete this motor task was recorded. Participants were then asked to perform a digit span recall whilst performing the same motor task. The digit span recall involved progressively longer sequences of digits being presented to the individual, with the aim to recall them in the correct order successfully (during heel-to-toe walking, termed ‘heel-to-toe walking and digit span recall’). The other two tasks included participants walking in and out of cones set out over 10m and back to the starting position. Similarly to the first task, the time taken to walk the total 20 m distance was recorded. Participants were then asked to repeat the motor task again whilst performing an arithmetic task simultaneously. First they counted back from 100 in 3s (termed ‘slalom walking counting back in 3s’) then on the second circuit they counted back from 100 in 7s (termed ‘slalom walking counting back in 7s’). To quantify the changes in motor performances, dual-task costs (DTC) were calculated by subtracting the single task time from the DT time (section 2.8.4).

The second session involved reaction time, agility, and aerobic training, with the use of the Fitlight Trainer for reaction time, coloured cone exercises for agility, and a 15-minute cycling time-trial for aerobic fitness. These three exercises are all described in section 4.7. Exercise sessions were individualised so that each participant had their own goals and progressed at their own pace.

6.10.5 Control group

Participants allocated into the CON group received standard treatment by continuing with their daily routines without exercise intervention for the 12-weeks

6.10.6 Data analysis

Statistical analysis was performed on SPSS V.23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). To establish changes between the pre- and post-exercise intervention results, pairwise comparisons between time and group and paired sample T-tests were performed, whereby statistical significant was recognised as $p < 0.05$. For nominal or ordinal scale variables non-parametric measures were performed including Mann-Whitney and Wilcoxon Ranks tests were used, measuring between-subject and within-subject data, respectively. Effect sizes were calculated using Hedge's g formula for interval data variables (parametric tests), whereby a score of 0.2> small effect, 0.2-0.5 = medium effect, and >0.8 = large effect. It was not possible to examine interaction effect (mixed ANOVA) due to the small sample size.

6.11 Results

6.11.1 Participant characteristics

A total of 15 individuals were assessed against the inclusion/exclusion criteria but only nine participants provided with written consent (Figure 6.5). The participant characteristics of the nine individuals who provided informed consent out are outlined in table 6.4. Only the seven (unshaded sections of the Table 6.4) participants who had completed baseline testing were included in the analysis. They were allocated into either the exercise (EX) or the control (CON) group non-randomly by pragmatic design in relation to individuals' availability.

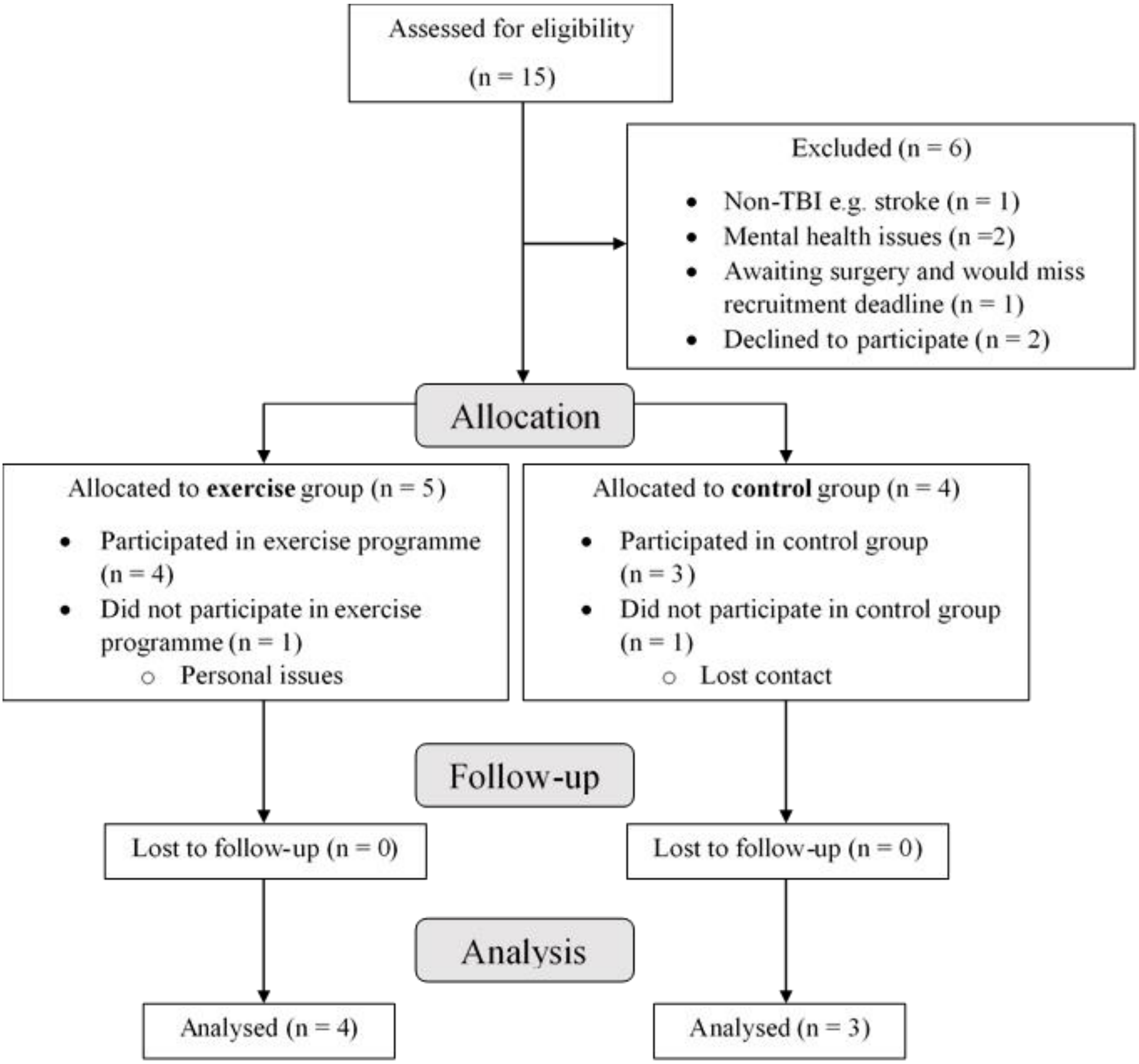

Figure 6.5.Recruitment consort flowchart

There were no statistically significant differences between the EX and CON group for age, height, body mass, or time since injury ($p > 0.05$). Participants in the EX group demonstrated a mean adherence rate to the exercise classes of 92.7% (ranging from 79.2-100%).

Table 6.4.Individual and injury characteristics for the EX and CON groups

Subject	Gender	Age (yrs)	Height (cm)	Body Mass (kg)	Injury mechanism	Time since injury (months)
EX						
1	M	52	179.6	71.9	Assault	3
2	M	58	179.2	98	Assault	18
3	M	43	178.5	119.8	Unexplained	22
4	M	46	168.2	83.3	Motor bike accident	11
5	F	53	161.5	47.1	Cycling accident	0.5
Mean (SD)		**49.8 (5.8)**	**176.4 (4.7)**	**93.3 (20.7)**		**13.5 (7.2)**
Mean (SD)		**50.4 (5.3)**	**173.4 (7.3)**	**84.0 (24.4)**		**10.9 (8.3)**
CON						
6	M	21	n/a	n/a	Assault	1
7	F	20	170.0	63.8	Sport concussion	1
8	M	28	173.0	71.5	Fall	2
9	F	48	159.0	54.9	Fall	15
Mean (SD)		**32.0 (11.3)**	**167.3 (6.0)**	**63.4 (8.3)**		**6.0 (6.4)**
Mean (SD)		**29.3 (11.3)**	**n/a**	**n/a**		**4.8 (5.9)**

Note: Shaded area indicate characteristics from participants who dropped out before taking part in their allocated groups and the mean results inclusive of their data. n/a = not applicable

6.11.2 Short Form-36 Questionnaire (SF-36)

Out of the eight domains, six showed no significant differences between the EX and CON group at the baseline measures. However, the EX group presented significantly lower scores for vitality (t_5 = -2.954, p = 0.03) and role limiting (emotional) (t_5 = -4.982, p = 0.004) domains than the CON at baseline. From pre- to post-testing, the EX group demonstrated a statistically significant improvement and large effect size for the role limiting – physical (t_3 = -4.371, p = 0.02, g = 3.03) and vitality (t_3 = -3.783, p = 0.03, g = 1.75) domains. Additionally, there was a trend to improvement (0.05 < p > 0.1) and large effect size for the role limiting – emotional domain in the EX group (t3 = -3.783, p = 0.06, g = 1.22). The CON group demonstrated a statistically significant improvement in the vitality domain from pre- to post-testing sessions (t_2 = 5.0, p = 0.04, g = 0.5), (Table 6.5).

The Mann Whitney test showed that the EX group demonstrated significantly greater changes over time in the vitality domain (U = 0.00, p = 0.03) compared to the CON group. The EX also ranked higher in all the other domains compared with the pre to post changes in the CON group, with the exception of the social functioning domain where CON demonstrated greater change. Figure 6.6 presents the SF-36 findings in comparison to normative data (Obidoa *et al*., 2010). The baseline scores for the EX group were all below normative data, with exception of bodily pain. As demonstrated, all of the EX group scores increased at post-testing and of these the PF and BP scores reached above the normative data. Overall, the CON group results were closer to the normative data at baseline compared to the EX group. No statistically significant changes were presented from pots-testing to the 6-month follow up for either groups over the eight domains.

Table 6.5.SF-36 results from pre- to post-testing for the EX and CON groups.

Variable	Group	Pre	Post	Follow-up	Pre - Post Mean Diff	95% CI	Effect size (g)
Physical function	EX	72.5 (28.4)	92.5 (6.5)	91.3 (14.4)	20.0	-63.1, 23.1	0.8
	CON	96.7 (5.8)	91.7 (7.6)	86.7 (18.9)	-5.0	-16.5, 26.5	0.6
Role limiting – physical	EX	12.5 (14.4)	81.3 (23.9)	75.0 (35.4)	68.8*	-118.8, -18.7	3.0
	CON	33.3 (57.7)	66.7 (57.7)	25.0 (43.3)	33.3	-176.8, 110.1	0.5
Bodily pain	EX	80.3 (27.8)	84 (22.6)	81.3 (27.9)	3.8	-12.0, 4.5	0.1
	CON	85.3 (14.0)	87.3 (21.9)	64.3 (40.1)	2.0	-34.6, 30.6	0.1
General health	EX	56 (14.3)	70.3 (18.9)	71.0 (24.4)	14.3	-41.0, 12.5	0.7
	CON	68.7 (28.4)	72.0 (13.2)	63.0 (9.6)	3.3	-47.0, 40.3	0.1
Vitality	EX	26.3 (16.0)≠	57.5 (15.0)	61.3 (14.9)	31.3*†	-57.5, -5.0	1.8
	CON	60.0 (13.2) ≠	51.7 (15.3)	58.3 (10.4)	-8.3*	1.2, 15.5	0.5
Social functioning	EX	69.0 (6.9)	72.0 (21.3)	81.3 (23.9)	3.0	-28.3, 22.3	0.2
	CON	79.3 (7.5)	96.0 (6.9)	87.5 (12.5)	16.7	-52.5, 19.2	1.9
Role limiting - emotional	EX	16.5 (19.1) ≠	66.8 (47.1)	75.0 (50.0)	50.3	-103.6, 3.1	1.2
	CON	89.0 (19.1) ≠	66.7 (57.7)	100.0 (0.0)	-22.3	-149.7, 194.4	0.4
Mental health	EX	61.0 (16.8)	69.0 (23.6)	75.0 (19.1)	8.0	-30.7, 14.7	0.3
	CON	85.3 (6.1)	86.7 (6.1)	85.3 (6.1)	1.3	-7.1, 4.4	0.2

**Statistically significant within subjects ($p < 0.05$)*

†Statistically significant between subjects ($p < 0.05$)

≠Statistically significant difference between subjects at baseline ($p < 0.05$)

Note: Shaded areas represent statistically significant changes.

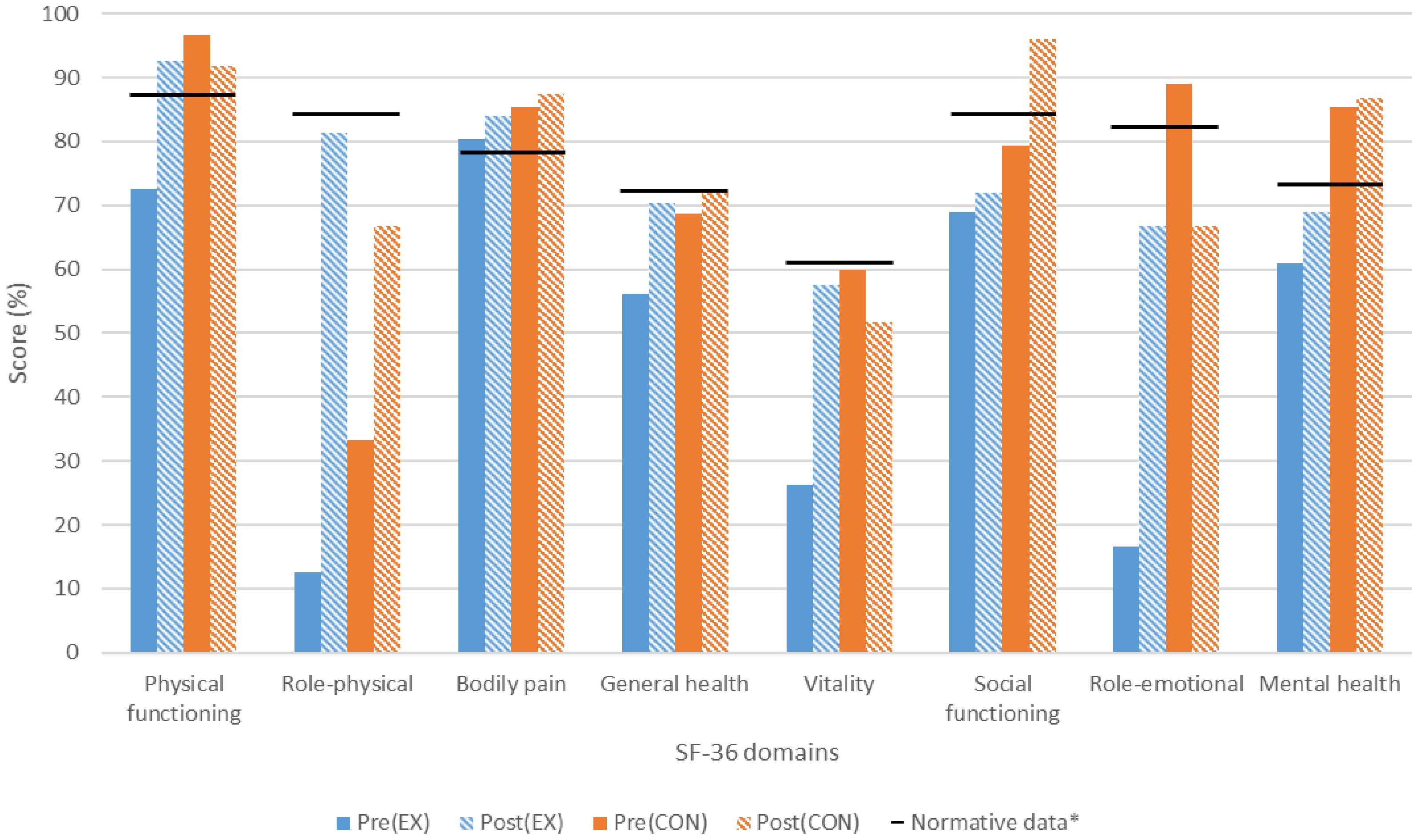

Figure 6.6.SF-36 results for EX and CON compared with normative data from healthy individuals.

* Normative data from Obidoa et al. (2010). This data was taken from 29,868 healthy individuals aged between 18 and 65 years and is based on the 0-100 scores.

6.11.3 Hospital Anxiety and Depression Scale (HADS)

At the baseline measures, there were no statistically significant differences between the EX and CON group for the anxiety scale. However, there was a significant difference for the depression scale ($t_{3.601}$ = 6.007, p = 0.01) with the CON presenting significantly lower baseline depression scores than the EX group. There was a statistically significant improvement (decrease in score) in the EX group for the anxiety (t_3 = 3.220, p = 0.05) and depression (t_3 = 3.656, p = 0.04) scales from baseline to post-testing (Table 6.6). No significant changes were found in the CON group. The change from baseline to post-testing for the EX group was statistically significantly greater than the change for the CON group for both scales (U = 0.00, p = 0.03). There were no significant changes from the post-testing to the 6-month follow-up sessions for both the EX and CON groups.

Table 6.6.HADS results from pre- to post-testing for the EX and CON groups

						Pre - Post		
Variable	Group	*n*	Pre	Post	Follow-up	Mean Diff	95% CI	Effect size (g)
HAD-A	EX	4	8.0 (4.8)	5.3 (4.1)	5.0 (3.7)	-2.8*†	0.03, 5.5	0.1
	CON	3	2.0 (2.6)	2.7 (2.1)	1.7 (1.5)	0.7	-3.5, 2.2	0.4
HAD-D	EX	4	8.3 (2.1)	4.8 (3.8)	4.3 (3.9)	-3.5*†	0.5, 6.5	0.1
	CON	3	1.7 (0.6)	2.7 (1.5)	1.7 (2.1)	1.0	-3.5, 1.5	0.4

**Statistically significant within subjects (p < 0.05)*

†Statistically significant between subjects (p < 0.05)

Note: a decrease in score indicates a favourable change in mood

HAD-A = anxiety domain, HAD-D = depression domain

6.11.4 Rivermead Post-Concussion Questionnaire (RPQ)

Analysis of all 16 individual symptoms presented no statistically significant differences at baseline for 14 out of the 16 symptoms between the EX and CON groups. The CON group showed significantly lower (favrourable) scores at pre-testing for 'poor concentration' (t_5 = 4.914, p = 0.004) and 'taking longer to think' (t_5 = 2.535, p = 0.05) symptoms compared to the EX group. There were no statistically significant changes from pre- to post-testing session for the EX or CON groups. The Mann Whitney test showed that the EX group demonstrated significantly greater improvements in the 'poor concentration' symptoms compared to the CON group (U = 0.5, p = 0.04) over time. Trends toward improvements ($0.05 < p > 0.1$) were indicated in the 'noise sensitivity' (U = 1.0, p = 0.06) and 'being irritable' (U = 1.0, p = 0.06) symptoms. When the 16-items were categorised into RPQ-3 and RPQ-13 (Table 6.6), there was a trend towards improvement ($0.05 < p > 0.1$) for the RPQ-13 score in the EX group (t_3 = -2.875, p = 0.06g = 0.6). There were no statistically significant changes from post-testing to the 6-month follow-up for either groups across both domains.

Table 6.7.RPQ results from pre- to post-testing for the EX and CON groups

					Pre - Post		
Variable	Group	Pre	Post	Follow-up	Mean Diff	95% CI	Effect size (g)
RPQ-3 (/12)	EX	0.9 (0.8)	0.6 (1.2)	0.5 (0.7)	-0.4	-0.6, 1.3	0.3
	CON	0.7 (0.9)	0.4 (0.2)	0.8 (0.6)	-0.3	-1.5, 1.9	0.4
RPQ-13 (/52)	EX	2.1 (0.6)	1.6 (0.9)	0.4 (0.5)	-0.5	-0.1, 1.0	0.6
	CON	0.7 (0.2)	0.9 (0.1)	0.3 (0.4)	0.2	-0.9, 0.5	1.0

RPQ = Rivermead Post-concussion Questionnaire

6.11.5 Glasgow Outcome Scale Extended (GOSE)

At baseline, there were no significant differences in the GOSE between the EX and CON groups ($t_2 = -2.0$, $p = 0.18$). All four participants (100%) demonstrated upper moderate disability at the baseline session in the EX group (Table 6.8). Following the 12-week exercise intervention one participant (25%) had upper severe disability, one (25%) had lower good recovery, and two (50%) had upper good recovery. There were no statistically significant changes from pre- to post-testing sessions in the EX or CON groups. No significant changes were presented from post-testing to the 6-month follow-up session.

Table 6.8.GOSE results from pre- to post-testing for the EX and CON groups

		Pre		**Post**		**Follow-up**	
Score	**Description**	**EX n (%)**	**CON n (%)**	**EX n (%)**	**CON n (%)**	**EX n (%)**	**CON n (%)**
1	Dead	0	0	0	0	0	0
2	Vegetative state	0	0	0	0	0	0
3	Lower severe disability	0	0	0	0	0	0
4	Upper severe disability	0	0	1 (25)	0	0	0
5	Lower moderate disability	0	0	0	0	0	0
6	Upper moderate disability	4 (100)	1 (33.3)	0	1 (33.3)	0	0
7	Lower good recovery	0	0	1 (25)	0	1 (25)	1 (33.3)
8	Upper good recovery	0	2 (66.7)	2 (50)	2 (66.7)	3 (75)	2 (66.7)

6.11.6 Postural stability

There were no statistically significant differences between the EX and CON group in the SOT equilibrium scores at pre-testing for five of the domains However, the CON group presented with significantly greater (better performance) SOT scores for conditions 2 (stable surface, eyes closed) (t_5 = -3.252, *p* = 0.02) and 4 (unstable surface, eyes open) (t_5 = -2.683, *p* = 0.04) that the EX group at pre-testing. There were no significant changes from pre- to post-testing session for the EX or CON across all domains. The EX group did demonstrate a statistically greater improvement change (from pre- to post-testing) than the CON group for condition 4 (*U* = 0.00, *p* = 0.03), (Figure 6.7).

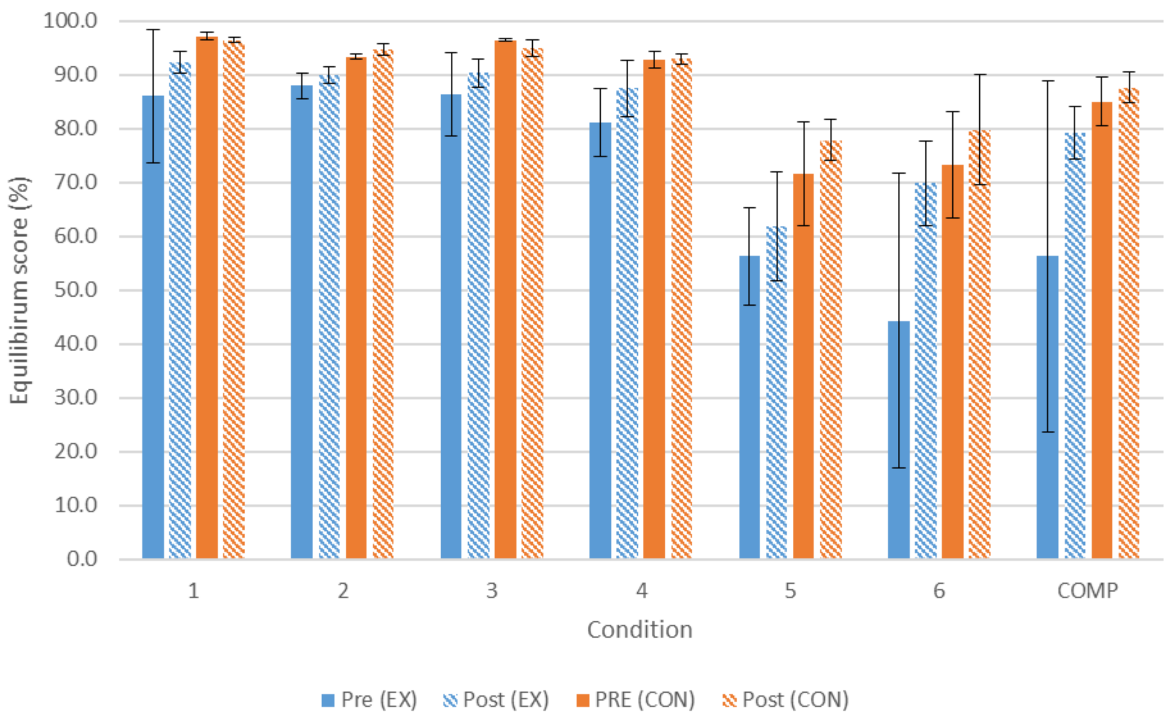

Figure 6.7.SOT for EX and CON groups at pre- and post-testing.

1 = eyes open on firm surface, 2 = eyes closed on firm surface, 3 = eyes open with sway referenced visual surround, 4 = eyes open on sway referenced support surface, 5 = eyes closed on sway referenced support surface, 6 = eyes open sway referenced support surface and surround, COMP = composite score.

At baseline, there were no significant differences between the EX and CON groups for latency on the MCT or the LOS-directional control (Table 6.9). However, there was a significant difference on the LOS-reaction time ($t_5 = 2.820$, $p = 0.04$) at pre-testing with the CON highlighted better (lower) reaction times compared to the EX group. No significant differences were found from the pre-to post-testing sessions for the EX or CON groups for MCT latency, LOS reaction time, or LOS directional control scores.

Table 6.9.MCT and LOS tests for both groups at pre- and post-testing.

Variable	Group	*n*	Pre	Post	Mean Diff	95% CI	Effect size (g)
MCT latency (msec)	EX	4	133.0 (7.8)	135.8 (6.2)	2.8	-8.5, 3.0	0.35
	CON	3	124.3 (4.7)	124.7 (5.5)	0.3	-4.2, 3.5	0.06
LOS - reaction time (sec)	EX	4	1.1 (0.3)	1.2 (0.5)	0.1	-0.5, 0.4	0.21
	CON	3	0.6(0.2)	0.8 (0.3)	0.2	-0.5, 0.2	0.63
LOS - directional control (%)	EX	4	82.0 (5.3)	79.5 (8.6)	-2.5	-7.6, 12.6	0.30
	CON	3	84.3 (5.0)	87.3 (0.6)	3.0	-14.4, 8.4	0.67

LOS = Limits of Stability, MCT = Motor Control Test

6.11.7 Balance

During the pre-testing measures of the SEBT, there were no statistically significant differences between the EX and CON groups (Table 6.10). Following the 12-week exercise programme, the EX group did not demonstrate any statistically significant improvements, however there was a trend to improvement ($0.05 < p > 0.1$) in the medial direction ($t_3 = -2.587$, $p = 0.08$, $g = 0.5$) with the right leg. Large effect sizes were demonstrated ($g = 1.0$) for the EX group in the anterolateral direction on the left leg ($t_3 = 1.527$, $p = 0.2$) and in the posteromedial direction on the right leg ($t_3 = -2.29$, $p = 0.1$). There were statistically significant increases for the CON group in the anterior ($t_2 = -4.612$, $p = 0.04$), posterolateral ($t_2 = -14.7$, $p = 0.01$), and posterior ($t_2 = -4.854$, $p = 0.04$) directions on the right leg. A trend to improvement was present for the CON in the anterior direction with the left leg ($t_2 = -3.781$, $p = 0.06$).

Table 6.10.SEBT results for all eight directions at pre- and post-testing sessions in the EX and CON groups

	Left	EX	73.6 (3.2)	72.5 (6.8)	1.1	-10.4, 12.7	0.2
		CON	66.2 (12.9)	73.8 (9.8)	7.6	-16.4, 1.1	0.5
AL	Right	EX	76.9 (7.9)	75.8 (7.1)	1.1	-11.7, 13.9	0.1
		CON	72.0 (17.1)	76.3 (5.8)	4.3	-33.6, 24.9	0.3
	Left	EX	81.6 (3.2)	77.3 (4.3)	4.4	-4.4, 13.1	1.0
		CON	69.2 (15.1)	81.5 (8.0)	12.3	-30.2, 5.5	0.8
L	Right	EX	78.0 (8.0)	77.4 (7.1)	0.6	-5.0, 6.3	0.1
		CON	71.0 (15.0)	82.5 (8.3)	11.5	-29.9, 6.9	0.8
	Left	EX	78.9 (7.4)	80.8 (5.9)	1.9	-11.6, 7.8	0.3
		CON	75.8 (17.3)	85.7 (9.0)	9.8	-30.7, 11.0	0.6
PL	Right	EX	80.4 (8.2)	79.9 (8.4)	0.5	-8.7, 9.7	0.1
		CON	75.3 (22.0)	84.2 (21.0)	8.8*	-11.4, -6.2	0.3
	Left	EX	85.4 (6.5)	85.5 (11.0)	0.1	-15.7, 15.4	0.01
		CON	77.0 (27.7)	88.5 (20.4)	11.5	-30.3, 7.3	0.4
P	Right	EX	78.0 (3.5)	80.3 (8.2)	2.3	-11.4, 6.9	0.3
		CON	76.0 (26.9)	87.7 (24.5)	11.7*	-22.0, -1.3	0.4
	Left	EX	79.8 (4.0)	82.3 (10.3)	2.5	-19.2, 14.2	0.3
		CON	79.5 (32.3)	93.0 (20.6)	13.5	-46.4, 19.4	0.4
PM	Right	EX	68.8 (4.7)	77.6 (9.9)	8.9	-21.2, 3.5	1.0
		CON	71.0 (21.5)	55.8 (44.7)	15.2	-106.3, 136.7	0.4
	Left	EX	67.8 (6.1)	71.9 (16.0)	4.1	-22.8, 14.6	0.3
		CON	74.8 (30.3)	86.3 (16.7)	11.5	-46.0, 23.0	0.4
M	Right	EX	55.0 (16.7)	63.8 (12.6)	8.8	-15.5, 2.0	0.5
		CON	58.3 (16.3)	69.7 (10.1)	11.3	-27.5, 4.8	0.7
	Left	EX	55.3 (16.8)	64.0 (10.8)	8.8	-31.2, 13.7	0.5
		CON	59.0 (23.0)	75.0 (14.6)	16.0	-41.5, 9.5	0.7
AM	Right	EX	67.9 (5.0)	64.8 (5.6)	3.1	-5.1, 11.3	0.5
		CON	57.5 (9.0)	63.7 (6.8)	6.2	-21.1, 8.8	0.6
	Left	EX	58.8 (18.6)	66.5 (4.7)	7.0	-38.6, 23.1	0.5
		CON	61.3 (10.0)	67.3 (2.1)	6.0	-31.8, 19.8	0.7

**Statistically significant (P < 0.05)*

A = anterior, AL = Anterolateral, AM = Anteromedial, L = Lateral, M = Medial, P = Posterior, PL = Posterolateral, PM = Posteromedial

6.11.8 Mobility

There were no statistically significant differences between the two groups for the STS test (t_5 = -2.244, p = 0.1) during the pre-testing session (Table 6.11). Following the 12-week exercise programme, the EX group demonstrated a statistically significant increase (improvements) in the number of STS performed in 30 seconds and large effect size (t_3 = -4.392, p = 0.02, g = 1.19). No significant changes were seen for the CON group.

Table 6.11.Mobility results for the EX and CON group from pre- to post-testing sessions.

Variable	Group	*n*	Pre	Post	Mean Diff	95% CI	Effect size (g)
STS (n)	EX	4	12.0 (1.8)	15.8 (3.4)	3.8*	-6.5, -1.0	1.19
	CON	3	17.7 (4.7)	18.7 (5.7)	1.0	-7.6, 5.6	0.15

**Statistically significant (P < 0.05)*

HR = heart rate, STS = Sit-To-Stand

6.11.9 Strength

One participant in the EX group was unable to perform this measure due to a personal issue. At pre-testing, there were no significant differences between the EX and CON group doe average power. The EX group demonstrated statistically significant improvements in average power during concentric knee extension (t_2 = -4.871, p = 0.04, g = 0.4) and flexion (t_2 = -4.350, p = 0.05, g = 0.9) at 180 °/s (Table 6.12). The improvements during flexion at both speeds (60 °/s and 180 °/s) were statistically significantly greater for the EX group compared to the CON (U = 0.00, p = 0.05). No significant changes were found in the CON group from pre- to post-testing.

Table 6.12.Average power (watts) results for knee extension and flexion a two angular speeds in both groups at pre- and post-testing.

Variable	Group	*n*	Pre	Post	Mean Diff	95% CI	Effect size (g)
Extension (60°/s)	EX	3	81.2 (18.3)	89.8 (11.0)	8.6	-28.9,11.6	0.46
	CON	3	101.8 (49.9)	99.7 (38.2)	-2.1	-39.1,43.3	0.04
Flexion (60°/s)	EX	3	38.0 (12.3)	48.3 (7.0)	10.3†	-24.0,3.3	0.82
	CON	3	57.2 (22.3)	52.4 (16.1)	-4.8	-16.6,26.2	0.2
Extension (180°/s)	EX	3	142.2 (40.6)	163.2 (42.3)	21.0*	-39.5,-2.5	0.41
	CON	3	173.8 (68.0)	176.0 (62.2)	2.2	-59.8,55.4	0.05
Flexion (180°/s)	EX	3	52.3 (24.1)	74.2 (15.5)	21.8*†	-43.4,-0.2	0.86
	CON	3	92.1 (28.6)	88.0 (24.2)	-4.1	-11.2,19.4	0.12

**Statistically significant ($P < 0.05$)*

†Statistically significant between subjects ($p < 0.05$)

Individual scores are outlined in figure 6.8. Visual inspection of the individuals' data implies that the participants in the EX group demonstrated increased average power during concentric flexion and extension at 60 °/s and 180 °/s. This however was not the case for the CON with some participants' demonstrating decreases in performance.

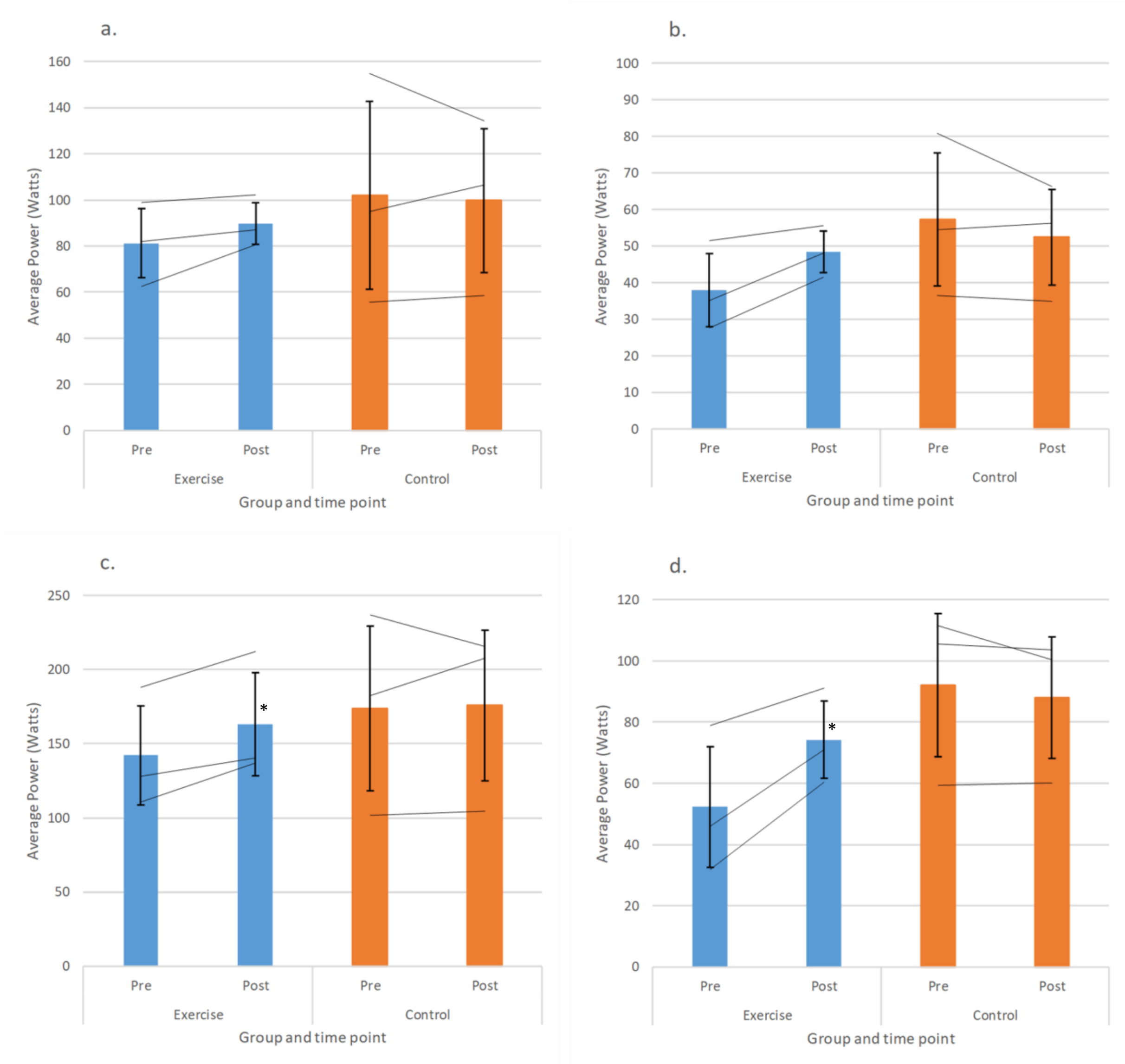

Figure 6.8.Average Power results for the EX and CON groups at baseline and post-testing. (a) 60 °/s during extension, (b) 60 °/s during flexion, (c) 180 °/s during extension, (d) 180 °/s during flexion. Bar charts represent the mean scores and the line graphs indicate individuals' scores.

**Statistically significant ($P < 0.05$)*

The EX group significantly increased their peak torque during knee flexion at 60 °/s (t_2 = -4.701, p = 0.04, g = 0.8) and 180 °/s (t_2 = -3.339, p = 0.08, g = 1.0) from pre-to post-testing demonstrating large effects sizes (Table 6.13).

Table 6.13.Peak Torque (Nm) results for knee extension and flexion a two angular speeds in both groups at pre- and post-testing.

Variable	Group	*n*	Pre	Post	Mean Diff	95% CI	Effect size (g)
Extension (60°/s)	EX	3	132.0 (35.0)	143.2 (13.2)	11.2	-68.5, 46.1	0.34
	CON	3	149.3 (69.7)	144.4 (57.4)	4.9	-52.9, 62.7	0.07
Flexion (60°/s)	EX	3	66.8 (11.7)	76.3 (8.3)	9.5*	-18.2, -0.8	0.84
	CON	3	81.0 (32.4)	77.4 (25.4)	3.7	-36.6, 43.9	0.10
Extension (180°/s)	EX	3	85.7 (18.5)	97.2 (21.3)	11.5	-36.0, 13.0	0.46
	CON	3	97.1 (40.4)	99.0 (38.3)	2.0	-31.2, 27.3	0.04
Flexion (180°/s)	EX	3	40.8 (10.8)	51.7 (5.3)	10.8*	-24.8, 3.1	1.03
	CON	3	54.6 (19.3)	54.2 (17.0)	0.4	-12.1, 12.9	0.02

**Statistically significant (P < 0.05)*

Figure 6.9 shows a visual representation of the individuals' data. All participants in the EX group either maintain or increase their peak torque scores from pre- to post-testing. The CON demonstrated some decreased individual scores, as well as greater variability between scores highlighted by larger standard deviations compared to the EX group.

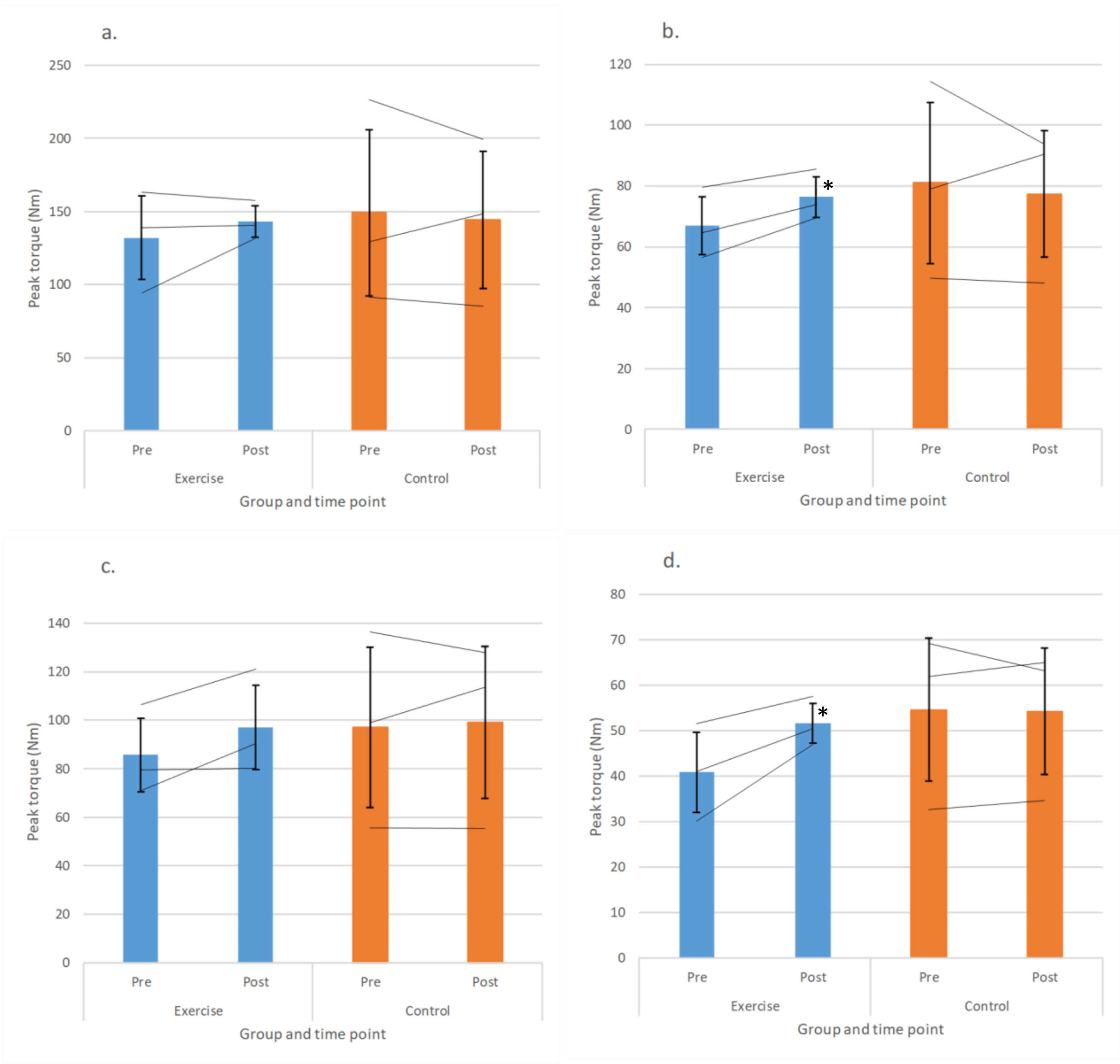

Figure 6.9 Peak Torque results for the EX and CON groups at pre- and post-testing. (a) 60 °/s during extension, (b) 60 °/s during flexion, (c) 180 °/s during extension, (d) 180 °/s during flexion. Bar charts represent the mean scores and the line graphs indicate individuals' scores.

**Statistically significant ($P < 0.05$)*

No statistically significant differences in total work were found in the EX group (Table 6.14), however there was a medium effect (*g* = 0.5) from pre- to post-testing during knee flexion at 60 °/s. No significant changes in the CON were shown.

Table 6.14.Total Work (J) results for knee extension and flexion a two angular speeds in both groups at pre- and post-testing.

Variable	Group	*n*	Pre	Post	Mean Diff	95% CI	Effect size (g)
Extension (60°/s)	EX	3	800.3 (205.3)	827.2 (122.2)	26.8	-234.3, 180.6	0.13
	CON	3	912.1 (458.3)	894.1 (381.3)	18.1	-197.2, 233.3	0.03
Flexion (60°/s)	EX	3	380.7 (144.3)	444.5 (73.3)	63.8	-249.7, 122.0	0.45
	CON	3	514.0 (199.9)	471.4 (162.0)	42.5	-53.9, 139.0	0.19
Extension (180°/s)	EX	3	564.0 (207.8)	603.0 (180.6)	39.0	-144.3, 36.3	0.16
	CON	3	625.6 (256.9)	606.8 (228.3)	18.8	-90.3, 127.9	0.06
Flexion (180°/s)	EX	3	222.8 (119.2)	272.7 (87.8)	49.8	-157.1, 57.5	0.38
	CON	3	343.6 (99.0)	318.3 (87.1)	25.3	-38.4, 89.0	0.22

Figure 6.10 shows the total work individual results for the Ex and CON groups. Similarly to the peak torque results, the EX group all either maintained of increased their total work from

pre- to post-testing sessions. The CON group showed greater variability for knee extension and flexion at 60 °/s (larger standard deviation) compared to the EX group.

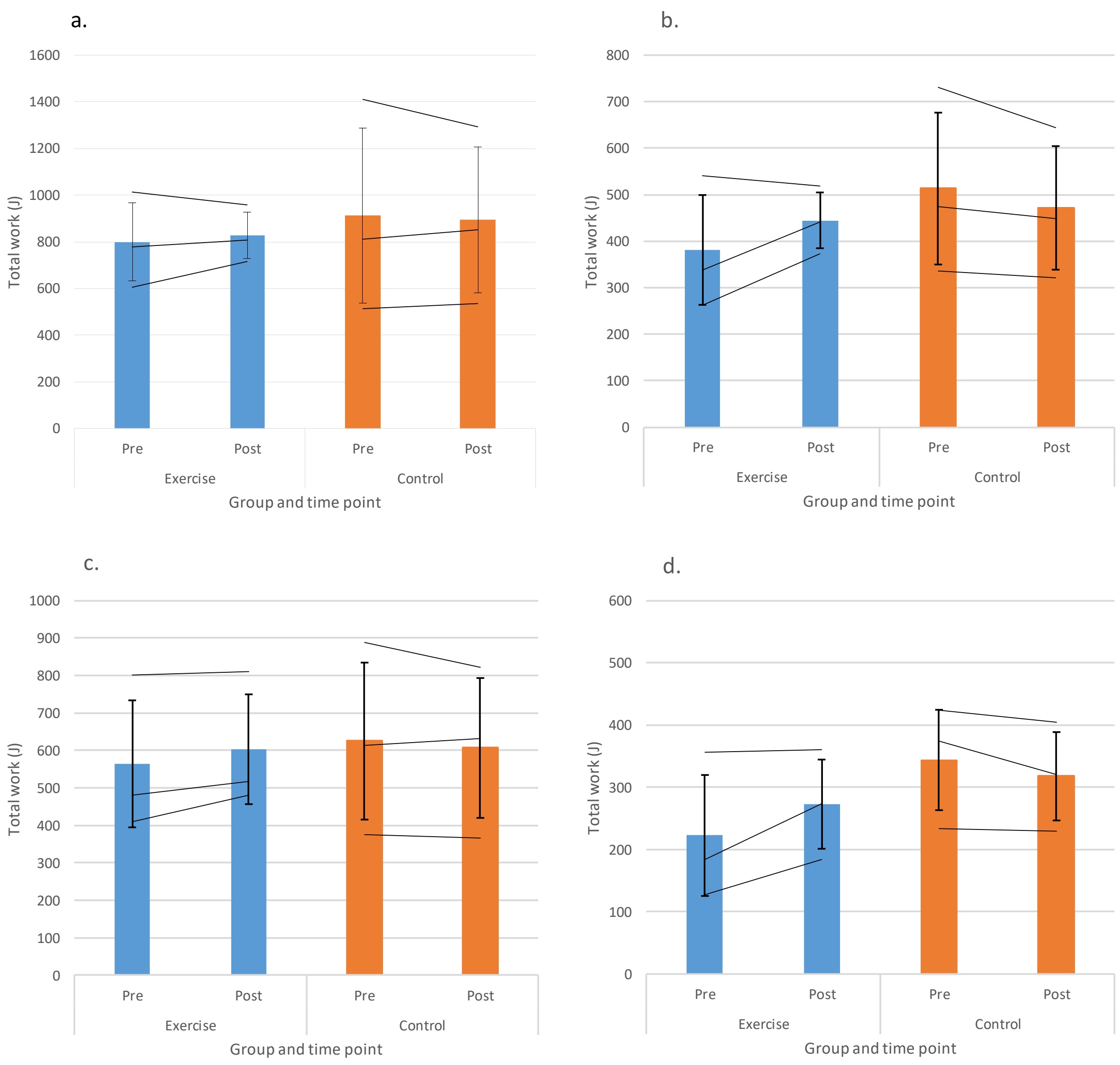

Figure 6.10 Total Work results for the EX and CON groups at pre- and post-testing. (a) 60 °/s during extension, (b) 60 °/s during flexion, (c) 180 °/s during extension, (d) 180 °/s during flexion. Bar charts represent the mean scores and the line graphs indicate individuals' scores.

6.11.10 Aerobic capacity and participant demographics

One participant in the CON group did not perform the aerobic capacity test due to personal reasons. Therefore, statistical analysis that compared the two groups was only performed on body mass and resting HR. There were no statistically significant differences between the EX and CON groups for body mass ($t_{2.299}$ = -0.101, p = 0.9) and resting HR (t_5 = 0.719, p = 0.5) at pre-testing. Following the 12-week intervention period, the EX group demonstrated a significant decrease (improvement) in resting HR (t_3 = 3.996, p = 0.03, g = 0.69) and increase (improvement) in workload (t_3 = -11.776, p = 0.001, g = 0.90) from pre- to post-testing (Table 6.15). No significant changes were shown for the CON group.

Table 6.15.Participant demographics and aerobic capacity for the EX and CON group from pre- to post-testing sessions.

Variable	Group	*n*	Pre	Post	Mean Diff	95% CI	Effect size (g)
Body mass (kg)	EX	4	93.3 (20.7)	93.4 (18.3)	0.15	-6.0, 5.7	0.01
	CON	3	97.2 (65.8)	97.6 (66.6)	0.4	-3.2, 2.4	0.01
Resting HR (bpm)	EX	4	78.8 (10.3)	71.1 (8.8)	-7.6*	1.6, 13.7	0.69
	CON	3	71.7 (16.0)	72.2 (9.0)	0.5	-19.1, 18.1	0.03
HR max (bpm)	EX	4	168.8 (22.1)	163.0 (22.7)	-5.8	-0.8, 12.3	0.23
	CON	2	195.0 (7.1)	191.5 (6.4)	-3.5	-2.9, 9.9	0.30
$\dot{V}O_2$peak – relative (ml/min/kg)	EX	4	28.1 (6.2)	30.3 (7.2)	2.1	-5.1, 0.8	0.28
	CON	2	44.9 (8.8)	43.5 (9.4)	-1.4	-3.7, 6.5	0.09
Workload (watts)	EX	4	214.3 (33.4)	249.3 (34.0)	35.0*	-44.5, -25.5	0.90
	CON	2	281.0 (75.0)	275.0 (77.8)	-6.0	-19.4, 31.4	0.04

**Statistically significant (P < 0.05)*

HR = heart rate

The individual results for aerobic capacity are outlined in figure 6.11. Visual inspection of the individuals' data suggests that most participants in the EX group either maintained or demonstrated increased peak O_2 consumption and decreased max HR, while the opposite was true for the CON group participants.

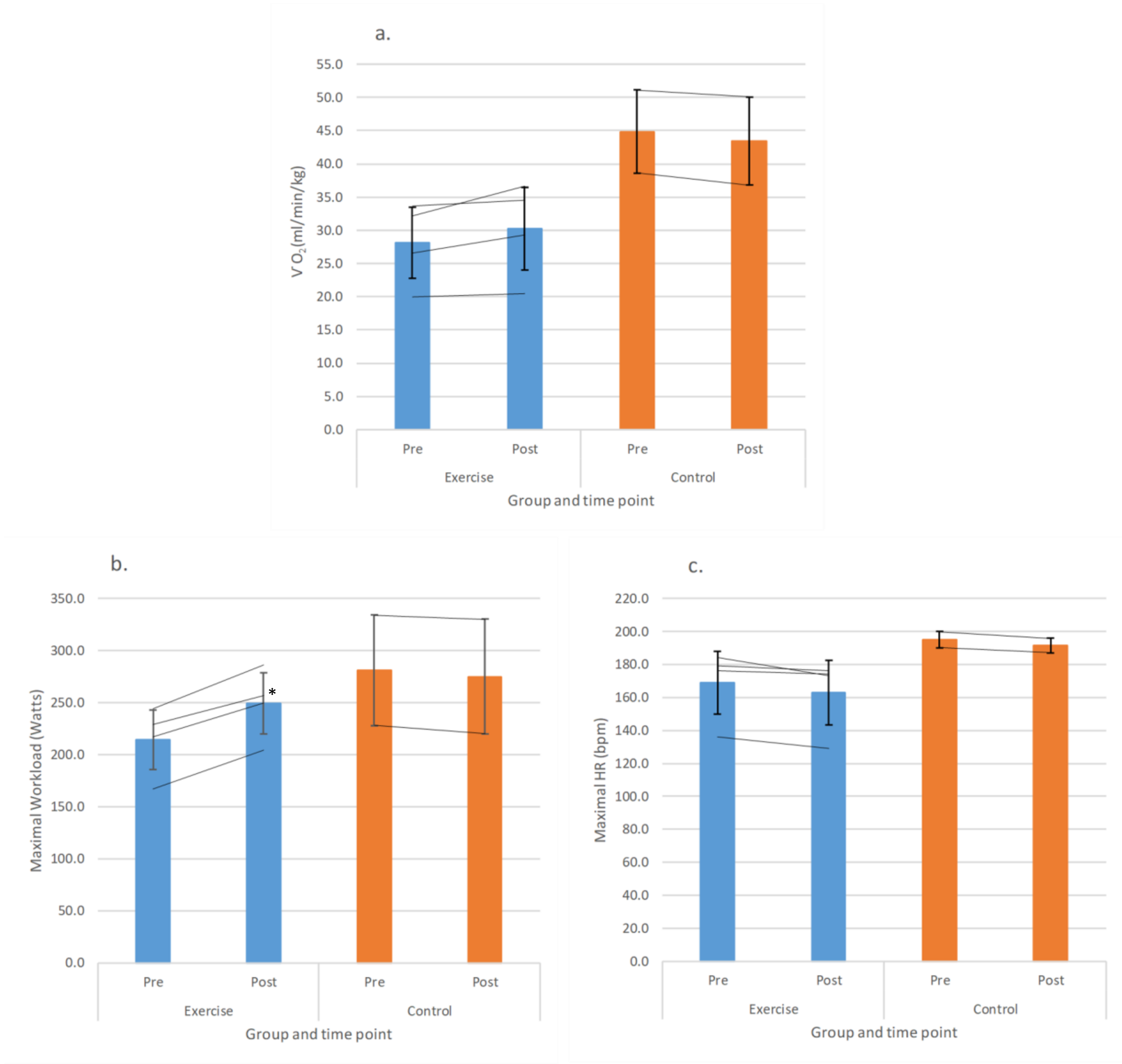

Figure 6.11 Aerobic capacity for the EX and CON groups at pre- and post-testing. (a) Relative V̇O2peak, (b) Maximal workload at V̇O2peak, (c) Maximal HR at V̇O2peak. Bar charts represent the mean scores and the line graphs indicate individuals' scores.

**Statistically significant ($P < 0.05$)*

6.11.11 BDNF blood biomarker

One participant from the CON was unable to have their blood taken due to personal reasons. There were no statistically significant differences between the EX and CON groups at pre-testing. No statistically significant changes were noted for either groups from pre- to post-testing. Mean BDNF concentrations increased in the EX group from pre- to post-testing by 59% (1766.67 to 2808.58 pg/ml). There was a decrease in the mean BDNF concentration for the CON group of 17% (2982.17 to 2476.83 pg/ml). On visual inspection of the individuals' data (Figure 6.12) in the EX group, two participants presenting with increased (unfavourable) concentrations whereas the other two showed decreased (favourable) results, whereas the both participants in the CON demonstrated decreased (favourable) concentrations from pre- to post-testing.

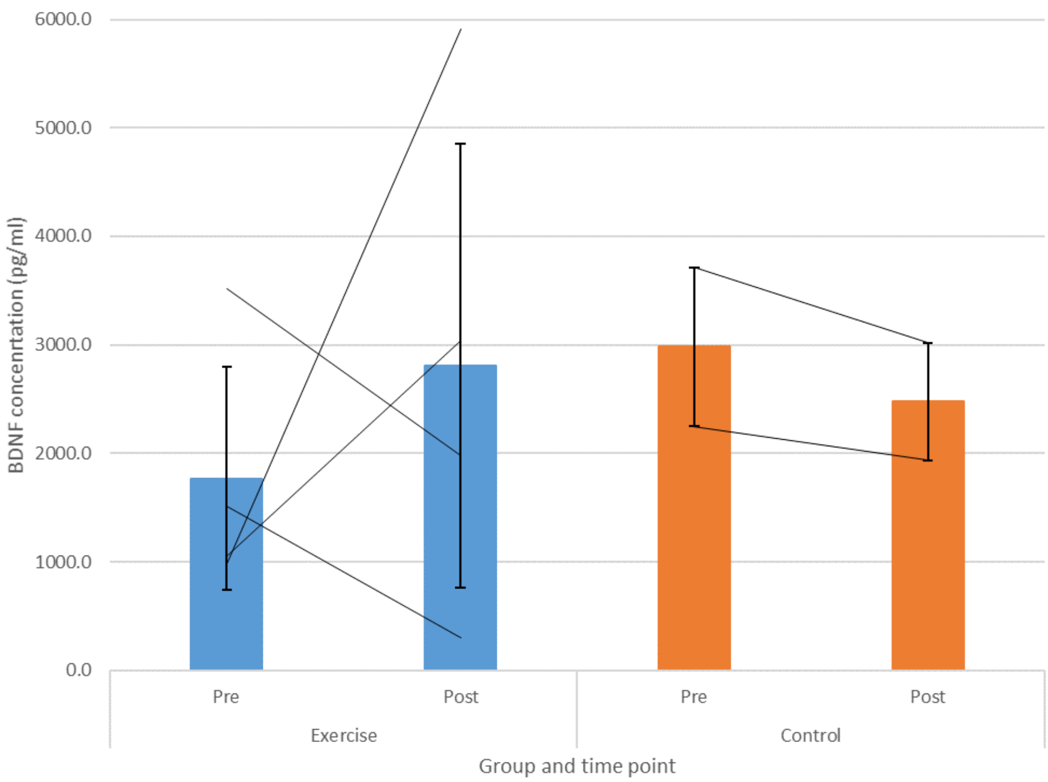

Figure 6.12 BDNF concentrations for the EX and CON groups at pre- and post-testing. Bar charts represent the mean scores and the line graphs indicate individuals' scores.

6.11.12 Week by week DTC for the EX group

Dual-task costs were calculated weekly, except for week one as this was the familiarisation sessions. The three different DT exercises are shown in Figures 6.13, 6.14 and 6.15. No statistically significant changes in DTC were demonstrated for either of the three exercises over the 12-weeks.

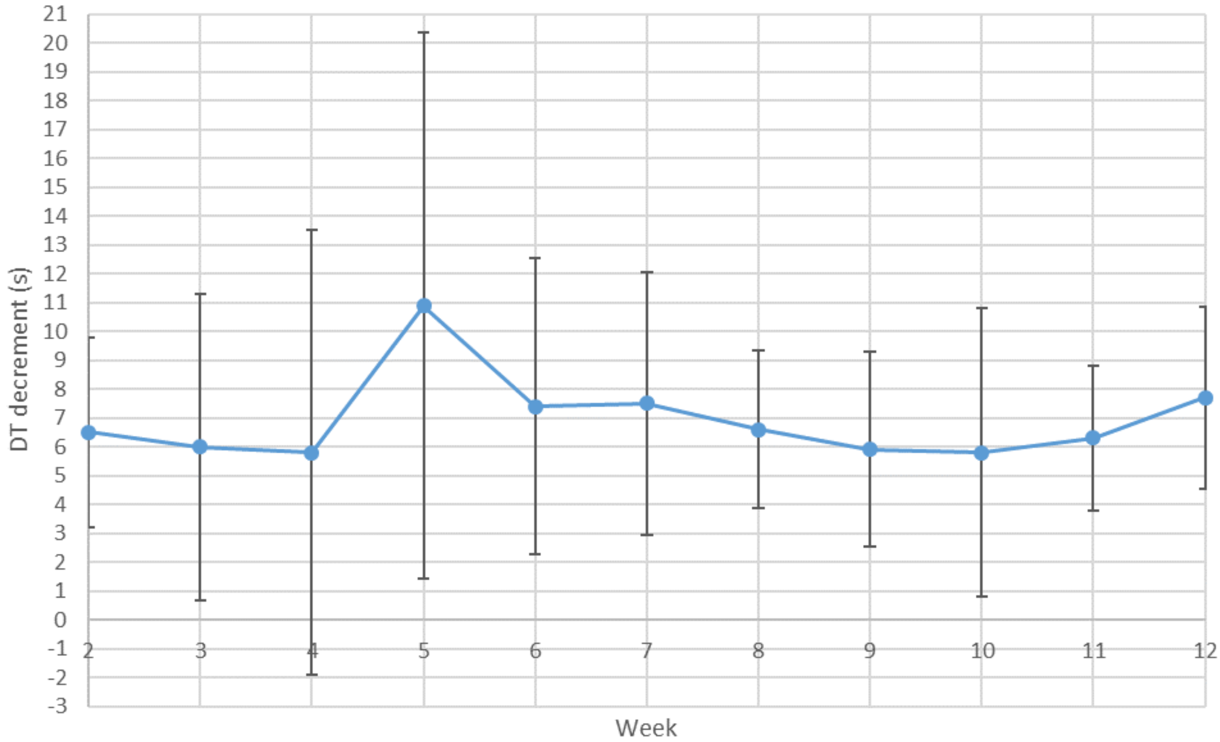

Figure 6.13 Tandem walking whilst performing a digit span recall DT decrement over the 11 weeks.

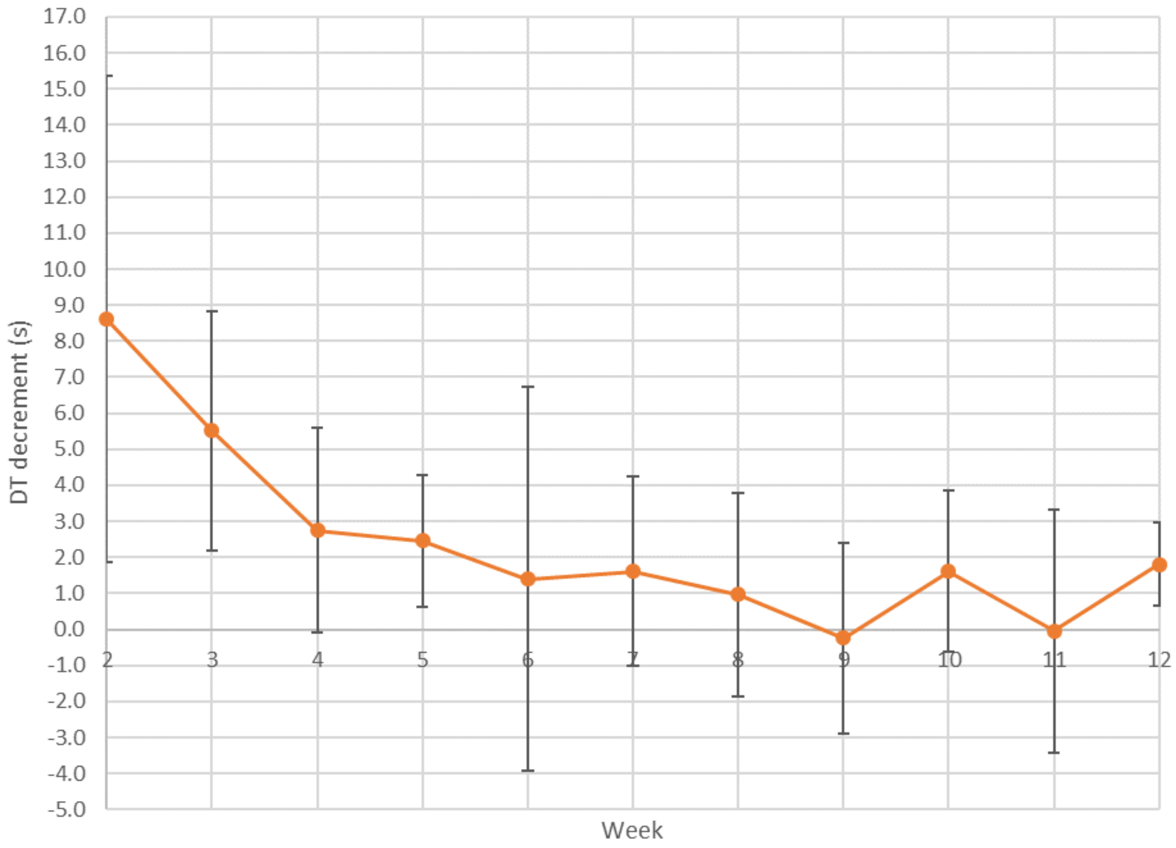

Figure 6.14 Slalom walking whilst counting back from 100 in 3s DT decrement over the 11 weeks.

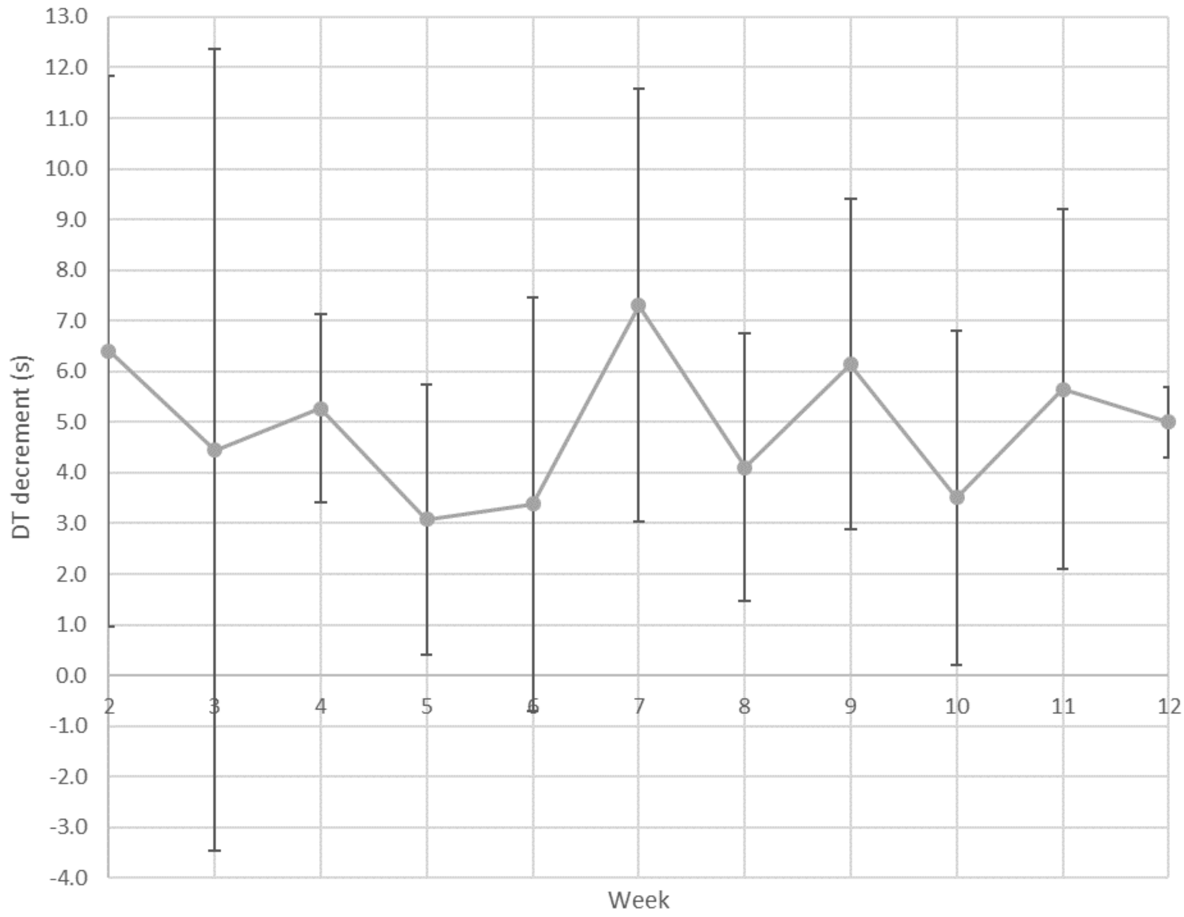

Figure 6.15 Slalom walking whilst counting back from 100 in 7s DT decrement over the 11 weeks

6.11.13 Week by week time-trial outcomes for the EX group

Distance and average power were calculated weekly, except for week one as this was the familiarisation sessions. Distance was measured in kilometres each week during the cycling time trials (Figure 6.16). There was a statistically significant increase from week two (M = 7.3, SD = 1.0) to week 12 (M = 8.0, SD = 0.9), ($t_2 = 5.965$, $p = 0.03$). No statistically significant improvements in average power (watts) was presented over the 12-weeks (Figure 6.17).

Both the distance and average power increased each week with both peak performances occurring during week nine (M = 8.9, SD = 0.6 and M = 168.5, SD = 48.8, respectively). From week ten to week 12, a plateau of performance starts to occur in average power.

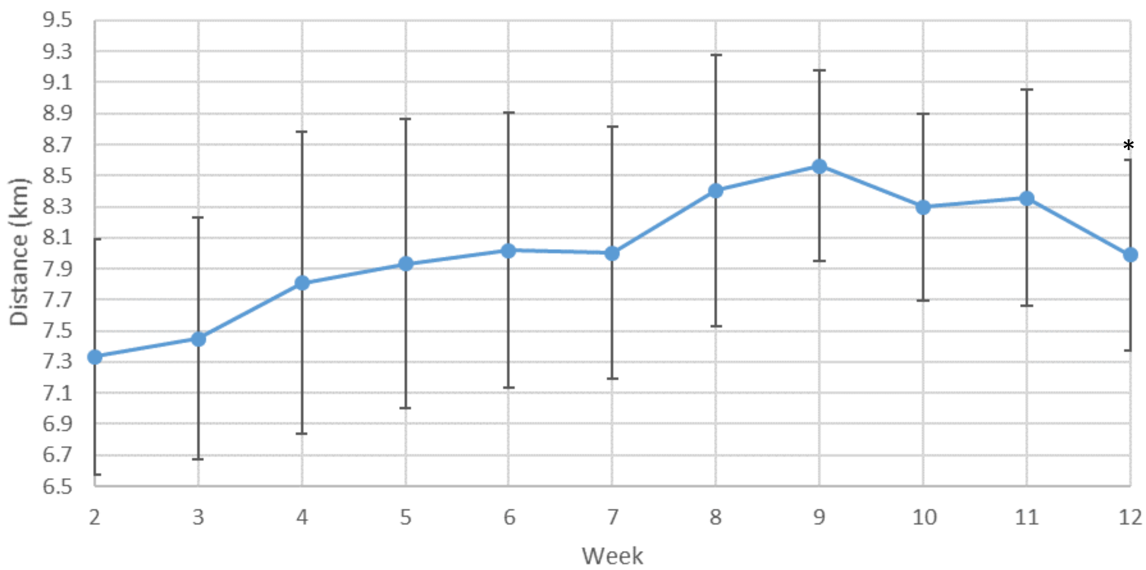

Figure 6.16 Distance covered during the 15-minute time trial over the 11 weeks.

**Statistically significant increase from week 2 to week 12 ($p < 0.05$)*

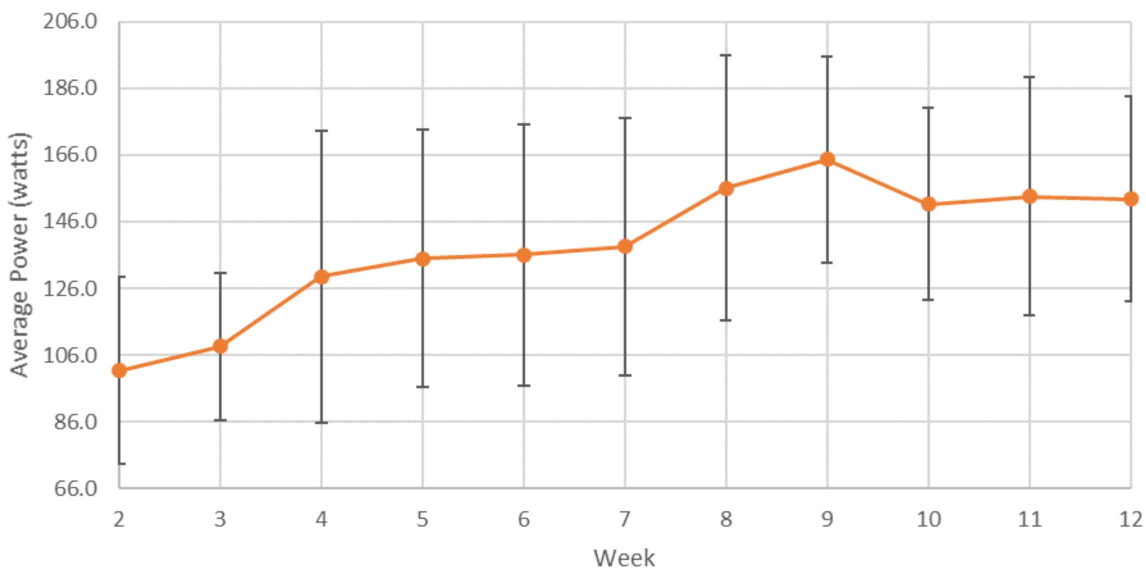

Figure 6.17 Average power during the 15-minute time trial over the 11 weeks.

6.12 Discussion

This study demonstrated some improvements to both mental and physical well-being in individuals with a TBI following a 12-week novel exercise programme.

6.12.1 Adherence

The mean adherence rate for the EX group was good (92.7%) with all participants attending at least 79% of the exercise sessions. Prior to completion of this chapter, high drop-out rates were anticipated, as previous literature has highlighted considerably lower physical activity participation among adults with disabilities compared with nondisabled populations (Driver *et al*., 2006; Carmona *et al.*, 2010).

Hence the inclusion of weekly assessments in DT and time trial tasks for the EX group. Fortunately, the high adherence surpasses these initial expectations. Adherence rates were measured to determine if the exercise programme was viable within the local community in individuals with a TBI, so these results show promising projections for future community-based programmes. It highlights that running a 12-week programme with two sessions a week was sustainable. However, these rates were taken from a small sample size so in future studies more participants would be needed to get a clearer understanding of the viability of the programme.

6.12.2 Quality of life

Significant improvements were also present for the role limiting-physical (68.8%) and vitality (31.3%) domains of the SF-36 in the EX group. The General Health, Vitality and Mental Health domains measure relatively wide score ranges, by measuring very favourable levels of those health score, setting the ceiling effect quite high (Ware & Kosinski, 2001). On the other hand, domains such as Physical Functioning and Role limiting-Physical assess a smaller range based on a lower ceiling. An effective exercise intervention is likely to influence many of these domains. The use of these health and well-being assessments are important in healthcare as they allow practitioners to consider the patient's total functioning when choosing therapies and monitoring the course of chronic diseases more accurately. Prior to this study, the SF-36 has been used within the TBI population to assess the effects of exercise on health-related QOL (Elsworth *et al*., 2011, Hoffman *et al*., 2010). The interventions in the study by Elsworth *et al.*, (2011) and Hoffman *et al.* (2010) were entirely or mostly unsupervised, respectively, which may affect adherence to the programme and/or reduce social interaction with others and which may explain why these studies did not report significant improvements. The current study was entirely supervised and participants were able to meet and interact with others. By conducting supervised sessions, training intensity and progression can be controlled throughout the programme, and instructors may provide motivational feedback and inspire individuals to attend and adhere to the programme.

This study highlighted that participating in a 12-week multi-component exercise programme can illicit significant improvements in anxiety (40.6%) and depression (53.4%) scales (HADS) when compared to standard treatment ($p = 0.03$). The HADS questionnaire has previously been used as an outcome measure by Bateman *et al*. (2001) who assessed the effect of exercise as rehabilitation in individuals with severe brain injuries. Both Bateman *et a*l., (2001) and the current study implemented a 12-week programme and used a cohort of individuals with similar mean ages (42.0 years compared to 49.8 years in the current study). However, Bateman *et al.*, (2001) did not present statistically significant improvements to either scales of the HADS. This could have been due to the fact that the pre-testing scores in their EX group for anxiety and depression were lower (better) than those in the current study. This could indicate that there was more scope for improvements within the current study hence the significant changes. Another possible reason for the significant improvements in anxiety and depression, observed in the current study, could be related to the multi-component nature of the exercise programme, whereas Bateman and colleagues (2001) included aerobic sessions exclusively. The current study includes a range of exercise modalities, including agility, balance, strength, aerobic and had the additional element of DT training.

Even though no significant improvements were presented in the EX for the RPQ-3 or RPQ-13, the mean change in ‘poor concentration’ symptom from pre- to post-testing was significantly greater for EX compared to that in CON. However, the EX group demonstrated significantly better scores on ‘poor concentration’ symptom during pre-testing so this may contribute to their better score change. Another influence in the significant change could be down to the group allocation method. As the participants were assigned to either the EX or CON group via pragmatic randomisation, so the participants that self-selected the CON group could have done so as they did not think they could cope with the exercise intervention because of their lack of concentration.

The decision to analysis each item individually was made to understand how specific symptoms were effected by a multi-component exercise intervention. Previous authors are in agreement that the RPQ should not be analysed and summated into a single score but either be sub-divided into cognitive and emotional elements or analysed individually according to item (Potter *et al*., 2006; Eyres *et al*., 2005). Adams & Moore (2017) also highlighted RPQ developments following their uncontrolled multi-model programme which combined vestibular rehabilitation, aerobic training, vision therapy, orthopaedic physical therapy, neuropsychology, and psychotherapy rehabilitation. The post TBI participants in that study were recruited during the chronic stages of recovery (>3 months post-concussion) with a mean time (SD) since injury of 19.8 (9.7) months. The positive changes reported in the current study and in the research by Adams & Moore (2017) suggest that benefits may be observed following a multi-component rehabilitation programme in individuals who have experienced a TBI. There still remains limited research on the effects of any short-term exercise programme on post-concussion symptoms using the RPQ.

Previous research from Sigurdardottir *et al.* (2009) examined post-concussion symptoms from 3-12 months post-TBI. Individuals were aged between 16-55 years and covered all severities (mild, moderate and severe). By using the RPQ and HADS (anxiety), they demonstrated decreased mean scores (improvement) in both scales from 3 to 12 months post-injury all across the severities. This highlights that without specific intervention, post-concussion symptoms can be prolonged and have negative effects on individuals' health and well-being, emphasising the potential importance of exercise as rehabilitation. However, this study suggests that these same improvements could be accomplished in a short period of time (12-weeks) by participating in a multi-component exercise programme.

In the current study, no statistically significant changes were apparent in the GOSE for either the EX or CON groups. There is a lack of research looking at GOSE scores following an exercise intervention similar to the one in the current study, but GOSE scores have shown to naturally increase (decrease of disability) over time (Haller *et al*., 2017). In their study, Haller et al. (2017) assessed a cohort of severe TBI patients, under the age of 65 years, over a 12-month period and found that the mean GOSE score increased from 5 to 7 (3 months and 12 months post-injury, respectively). Similar trends were found by Soberg and colleagues (2013) who demonstrated a significant increase in GOSE from 3 months to 12 months post-injury (5.2 to 6.1, respectively). Both studies indicate that following a TBI, disability is not static and can improve over time without the use of an exercise intervention. The injury severity was more severe at pre-testing in the Haller et al., (2017) study compared to the current study, so they had a greater scope for improvement following an exercise intervention. More future studies are required on TBI patients with a range of severity and longer follow-up periods.

6.12.3 Postural stability

In the current study, no statistically significant improvements were visible during the six SOT conditions from pre- to post-testing in either treatment groups. However, the pre- to post-testing change during condition four (unstable surface, eyes open) was significantly greater for the EX compared to the CON group. Highlighting that participating in the 12-week intervention encourages improvements in visual references (condition four) compared to those in standard treatment (control). However, the CON group did have a significantly better score during condition four at pre-testing compared to the EX group, so there the greater change in score for the EX group is expected as they have more scope for change. Condition four (unstable surface, eyes open) relies on the participants visual perception which refers to the ability of the brain to understand and interpret what they eyes see (Scheiman, 1997) and is integral to carrying out daily activities (Goodale and Milner, 2009; Jeannerod, 2006). Following a TBI, individuals are likely to experience a wide range of symptoms associated with vision such as headaches, vertigo, inability to focus, and difficultly with tracking and fixations (Padula et al. 2017) that can have negative effects on their QOL. Postural stability also relies on the vestibular system, whereby deficits in this system can characterised by dizziness and unsteadiness (Gottshall, 2011). In the current study, there were no significant changes shown for condition five whereby participants have to rely on vestibular cues when the visual ques are removed. This could be due to the exercise intervention not being specific enough to implement these changes. Previous research has been conducted on the effects of vestibular training programmes following TBI (Drijkongen *et al*., 2015; Alsalaheen *et al*., 2010). Alsalaheen *et al*. (2010) demonstrated significant increases in all six conditions during the SOT following treatment following a tailored vestibular programme relating to individuals' impairments and balance function. Significant improvements were also seen by Drijkongen et al. (2015) in the overall SOT composite score following an 8-week balance programme. The current study was unable to demonstrate any significant changes in MCT latency, LOS reaction time, or LOS directional control. The MCT provides information regarding automatic control of balance as a reaction to external disturbances whereas the LOS provides information on voluntary balance control. Significant changes in LOS reaction time ($p = 0.03$) and MCT composite latency score ($p = 0.001$) have been presented following an eight-week resistance-based exercise programme (Daminao et al., 2016).

In the current study, the participants did not highlight any significant vestibular deficits so the scope for improvement, highlighted by lack of significant improvements in postural stability, was smaller than those demonstrated in the studies by Drijkongen *et al*. (2015) and Alsalaheen *et al*. (2010). In addition, the current exercise-based intervention did not solely concentrate on vestibular training exercises, rather an array of training exercises (strength, aerobic, DT). So, the inclusion of more vestibular training elements to this exercise programme would be warranted in the future.

6.12.4 Balance

Following the 12-week exercise intervention there were trends towards improvement in balance indicated by the EX group in the medial direction on the right leg along with large effect size ($g = 1.0$) being present in the anterolateral and the posteromedial directions on the left and right legs, respectively. The SEBT requires strength and flexibility as well as proprioception which is the afferent feedback of the body's perception of motion and awareness of position. Following as TBI, proprioceptive feedback pathways, in regards to afferent input and central pattern generator, can be disturbed leading to movement disorders (Dietz, 2002). These movement disorders can have detrimental repercussions to the individuals QOL impeding on return to employment and recreation (Andelic *et al*., 2009) so should be a key focal point within rehabilitation. There is a limited amount of research investigating the SEBT performances in TBI so more studies are required.

6.12.5 Mobility

There was a significant increase in number of STS movements in 30 seconds for the EX group with large effect size (g = 1.2) following the 12-week intervention. The STS test assesses functional lower extremity strength and balance during a common everyday task. As mentioned previously, balance deficits are very common following a TBI leading to a decreased performance. A case study by (Zablotny & Nawoczenski, 2003) assessed the relationship between STS performance, COM velocities and joint angles in 24 year old male with a TBI. They highlighted that an unsuccessful (subject sat back down after attempting the STS transition without reaching upright position first) STS was primarily the results of insufficient knee extension angular velocity. Lower limb strength exercises therefore are integral to exercise programmes in order to illicit improvement performances in STS transitions, however more robust research is required in TBI cohorts to establish any statistically significant improvements. The STS test is easily accessible and cheap making it a feasible outcome measure for rehabilitation purposes.

6.12.6 Strength

Average power (extension and flexion at 180 °/s) and peak torque (flexion at 60 °/s and 180 °/s) significantly improved as a result of the 12-week exercise intervention in the EX group. As there were only three individuals per group during the isokinetic dynamometer measure, the statistical analysis was underpowered, so individual data was visually interpreted. The individuals within the EX either maintained or increased scores in both peak torque and average power over the 12-week period. Based on this, the strength elements within the circuit training sessions and the cycling time-trial, were enough to elicit meaningful improvements in lower limb strength. More research should be conducted to assess the direct relationship between the time-trial performance (peak power) and lower leg strength. There is limited research looking at the effects of exercise interventions on lower leg strength following a TBI (Walker et al., 1991).

6.12.7 Aerobic capacity

Maximum workload significantly increased in the EX group with significant decrease (improvement) in resting HR over the 12 weeks. Similar improvements were found by Chin *et al*. (2015) who examined the effects of a 12-week supervised aerobic training programme in individuals with a mild or moderate TBI. They also presented improvements work rate with the addition of increased $\dot{V}O_2$peak. Unlike the current study, the exercise intervention by Chin et al., (2015) was solely aerobic training. In order to illicit significant improvements in $\dot{V}O_2$peak more emphasis needs to be placed on aerobic-based exercises within a rehabilitation programme. Following a TBI, $\dot{V}O_2$peak has been shown to be significantly lower than that in age-gender matched healthy individuals (Mossberg *et al.*, 2007) with the majority of TBI patients being equal to or less than the 10th percentile of healthy normative data *(*Mossberg *et al*., 200*7)*. Individuals with a TBI tend to adopt more sedentary lifestyles for several of reasons (Bhambhani *et al*., 2003) and it is well documented of the negative effects this lifestyle can have on both health and mental well-being (refer back to section 2.8). Strong correlations (r = 0.831, p = 0.02) between improvements in $\dot{V}O_2$peak and cognitive function (Repeatable Battery for the Assessment of Neuropsychological Status) have been observed in patients with TBI (Chin *et al*., 2015). This highlights the added benefit of incorporating aerobic exercises into a multi-component intervention.

6.12.8 Blood

Following the 12-week interventions, the EX group demonstrated a trend to increase in BDNF concentrations compared to the CON, indicating the possible connection between non-exercise and decreasing (worsening) BNDF concentrations. An increase in BDNF concentration has been related to improvements in brain plasticity which can be triggered by exercise (Cotman & Berchtold, 2002). Henceforth, the results from the study present the possible positive relationship between a multi-component exercise intervention and enhanced BDNF concentrations. The cohort of participants was very small in the current programme, but it is possible that, with a larger cohort, the findings could reveal significant and clinically meaningful increases in BDNF which can accelerate brain recovery following TBI. Further investigation needs to take place to establish any correlations between BDNF levels and exercise. In future research, the blood analysis could be investigated as a prognostic tool in first instance, then establish if it could be used to aid the determination of recovery.

6.12.9 Dual-tasking

Following the 12-week intervention, dual-tasking ability improved (decrease in DTC) for the slalom walking and counting back from 100 tasks. As expected there was a decrease in walking speed (motor task) when a second task (cognitive) was introduced and performed simultaneously in all three tests, presenting the dual-task cost. This was predicted based on the findings from the previous pilot chapter which found a DTC existed in healthy, uninjured individuals when a motor and cognitive task were performed simultaneously. Improvements to DT performance have been demonstrated in previous literature across an array of neurological disorders of varying severities. Firstly Evans *et al.* (2009) investigated the effects of a 5-week cognitive-motor dual-tasking training programme in individuals with acquired brain injuries. Training involved two daily sessions of walking tasks combined with increasingly taxing cognitive demands. Following the intervention, the exercise group demonstrated significant performance improvements during the walking and sentence verification, walking and tone counting tasks suggesting that a cognitive-motor training programme may lead to improvements in walking and talking. Significant gait improvements were also presented by Yang *et al*. (2007) who examined the effects of a DT exercise programme on walking abilities in chronic stroke individuals. The intervention included 30 minutes of DT ball exercises three times a week for four weeks. They demonstrated a significant improvement in gait performances (speed, cadence, stride time and stride length). This emphasises that DT training over a short period of time (4 weeks) can have significant effects of everyday activities (gait). Fritz *et al*. (2009) examined the effects of a 14-day DT training programme on a female who had sustained a severe TBI. The individual improved her walking time during the single task, walking whilst talking (simple) and (complex) tasks. The three studies by Evans (2009), Yang (2007) and Fritz (2009) differ from the current study in terms of the participant and intervention characteristics but still emphasise the same findings that DT performance can be improved following DT training. This is highly beneficial for people following a TBI as executive function can become impaired, making it harder for the individual to perform two tasks simultaneously. A lot of everyday activities require dual attention (e.g. walking and talking) so extensive issues with DT could negatively affect QOL (e.g. decreased social interaction)

Balance control deficits can also be measured during DT conditions whereby dynamic balance control is assessed alongside a cognitive task. Previous research has outlined that differences in postural control exist between individuals with concussion (mild TBI) and uninjured healthy controls during the early stages of recovery (within 2 months) (Howell *et al*., 2013; Howell *et al.*, 2014; Howell *et al.*, 2015). In a more recent study by Howell *et al*. (2018), they demonstrated significantly greater medial-lateral centre of pressure displacement in a cohort of young adults (mean age 17.5 years) with a mild TBI compared with healthy, uninjured individuals during DT conditions (walking and auditory Stroop test). Even though DT training appears to be safe and effective in a cohort of people with neurological deficits (refs needed here), more research is needed to define specific DT interventions that look specifically at TBI across all severities.

6.12.10 Time Trial performance for participants in the EX group

Each week, distance and average power were measured during the 15-minute time trials in the exercise sessions. Over the 12-weeks both improved with distance presenting a statistically significant increase from week two to week 12. Stationary cycling was chosen as there were potential risks associated with treadmill running with individuals who may experience symptoms associated with vestibular- and physical-related impairments (headaches, dizziness, nausea). Exercise stimulates neurogenesis (the production of new neurons by the hippocampus and subventricular zone) and can increase baseline neuronal activity (Van Praag, 2008), which could aid in the recovery of a TBI. Thus emphasising the importance of this aerobic element within the current 12-week exercise intervention. In animal studies with induced stroke, exercise stimulation promoted stem cell migration to site of injuries and enhanced sensorimotor recovery (Hicks *et al*., 2007). Research investigating the neuroprotective effects of exercise in humans is scarce so more studies are needed to get a clearer picture on what healing effects exercise has on the brain. More research into the validity of this time-trial exercise needs to be conducted in order to highlight its true effect on physical fitness.

6.12.11 Limitations

The main limitation of the current study was the small sample sizes for the EX and CON groups. Recruitment rates were low despite the large number of individuals with a TBI in the local region that were highlighted in the audit (chapter 6 part 1). This may have been due to lack of communication between the recruitment sites, allowing potential participants to be missed for screening, so this would be a major area for improvement in the future. The small sample size meant that it was not possible to examine interaction effects via mixed ANOVAs. This would have been normal procedure for a RCT, but as this was an explanatory study with small samples sizes and qualitative data collection, t-tests were appropriate indicators.

As well as the low rates, the recruitment was relatively slow with individuals being recruited sporadically. This meant that some participants in the EX programme had to perform the sessions on their own before overlaps with the next recruitment. However this was only for a few weeks out of the full 12-weeks. The aim was to create an exercise intervention to improve QOL and a big element of that was expected to be through the social interaction amongst the TBI individuals. Another limitation was the group allocation method whereby a pragmatic approach was taken. By not undertaking randomisation, there is the possibility of bias towards a certain treatment. However, this was not deemed appropriate due to the recruitment issues, and the pragmatic approach allowed focusses to be on correlations between treatment and outcomes in real-world healthy systems.

Another limitation is during the time-trial activities. The increases in peak power each week could have indicated individuals became fitter, working harder, or that they were more familiar with the test, but this is unclear. In the future heart rate should be measured so that if the end time-trial heart rates were consistent or lower with higher average power, improved fitness would be demonstrated.

6.13 Conclusion

The aim of this study was to evaluate a novel 12-week, multi-component exercise intervention on the mental and physical outcomes in TBI individuals. The exercise intervention was effective in stimulating QOL improvements, particularly in anxiety, depression, patient-reported health statuses, with trends to improvement for post-concussion symptoms. The secondary outcome sought to quantify the DTCs on a week by week basis in the EX group, but unfortunately did not demonstrate any significant changes in mean DTC over the 12-weeks. Finally, the intervention promoted improvements in balance, mobility, lower extremity strength and aerobic capacity.

6.14 Overall conclusion

This chapter highlighted both the potential participants that could benefit from a novel exercise intervention, and the encouraging effects a 12-week multi-component exercise intervention can have on the mental and physical well-being of individuals with a TBI. There are indications that this small sample study could lay crucial foundations for a larger RCT, but as these are still initial findings, replications are warranted. As well as quantitative data, this research wanted to explore the acceptability of exercise to people who have had a TBI and gain an understanding of what recovery really means to them. Therefore, the following chapter will investigate their experiences towards their injury, recovery and exercise with the use of one-to-one interviews.

7 Chapter Seven – Facilitators and barriers associated with exercise for TBI individuals

7.1 Introduction

A growing amount of evidence supports the benefits of exercise in people with TBI. It has shown to have positive effects on post-concussion syndrome and comorbid conditions (Van-Praag, 2008; Leddy *et al.*, 2010; Hugentobler *et al.*, 2015) which are associated with TBI. Previous research has demonstrated improved cardiorespiratory with enhanced $\dot{V}O_2$peak and peak work rates (Chin *et al*., 2015), improved balance and coordination (Prangley *et al*., 2017; Damiano et al., 2016; Driver *et al*., 2006), and gait (Ustinova *et al*., 2014) in individuals with TBI. In addition to these physical benefits, studies have presented lowered depression levels (Bellon *et al*., 2015; Wise *et al*., 2012), decreased stress (Bellon *et al*., 2015) and increased self-esteem (Schwandt *et al*., 2012) following exercise.

Interviews and focus groups are the most common methods of data collection for qualitative research and are used with increasing frequency in clinical research. In order to gather an understanding of the individuals' views, experiences, beliefs and motivations, interviews are conducted. They are believed to provide a deeper understanding of social phenomena than that just retrieved from qualitative questionnaires, especially in areas that are unique and not fully understood (Gill *et al*., 2008). These one to one interviews allow individuals to explore sensitive topics and make them feel comfortable to share their experiences, which may be difficult in group situations. The researcher is then able to use this valuable information to acquire more in-depth knowledge about the topic, sometimes with the aim to complement evidence-based recommendations.

Exercise participation by individuals with disabilities is already known to be a multifaceted and complex issue (Van Der Ploeg *et al.*, 2004; Rogers *et al.*, 2008).). Previous research has investigated the barriers individuals with TBI have towards exercise and physical activity (Reavenall *et al*., 2010; Self *et al.*, 2013; Driver *et al.*, 2012). Reavenall *et al.* (2010) identified comon barriers associated with lack of motivation, poor underlying health, fatigue, transport issues, social aspects, and accessibility. Self *et al.* (2013) highlighted similar barriers, with the addition of busy lifestyles, work, and family commitments. The study by Driver *et al*. (2012) also highlighted similar limitations that incorporated a mixture of environmental and personal reasons.

7.2 Aim

The aim of this chapter is to gather a more personal understanding of the challenges individuals encounter during both acute care and long-term recovery following a TBI. Firstly, the facilitators and barriers towards exercise, following a TBI, will be highlighted. Secondly, the exercise group from chapter 6 will provide feedback on the exercise intervention emphasising the strengths and weaknesses of the design and delivery, so that the intervention can be tailored to meet individuals' needs in the future.

7.3 Methods

7.3.1 Participants

This study was reviewed and approved by the NHS Leeds West Research Ethics Committee (REC reference 16/YH/0210). All participants provided written informed consent.

The seven (4 EX, 3 CON) participants from chapter 6, part 2 were recruited to complete the one-to-one interviews. They all met the inclusion/ exclusion criteria referred to in section 4.3. A full set of participant characteristics are outlined in section 6.10.1.

7.3.2 One-to-one interviews

Individual, semi-structured interviews were conducted to capture the individuals' experiences of their injury and recovery progress. Individuals who met the criteria were asked to come into the University of Hull on two separate occasions. Interview commenced following a 12-week intervention period; for the EX group this was after a 12-week exercise structured exercise intervention (refer to section 4.7 for full description of the exercise programme) and a 12-week period of normal activities for the CON group. The semi-structured interviews focussed on their injuries, inpatient and outpatient experiences, pre-injury participation in physical activity, recovery progress, reasons for participating, and feelings about the 12-week programme. The interview questions differed slightly for the EX and CON groups (probing questions shown in Table 7.1.). Each post-programme interview lasted 30-60 minutes. Prior to each session, informed consent was gathered and the individuals were made aware that their responses were to be audio-recorded, and transcribed and that anonymised quotations may appear in published work. To warrant reliability and accuracy of the data collection, the same investigator (G.O.) conducted all of the interviews. This also ensured that there was a familiar face for the individuals to communicate with. All of the interviews were audio recorded (Olympus VN-732PC digital voice recorder, Olympus, Hamburg, Germany) and then transcribed verbatim into a word processing software (Word 2016, Microsoft, Inc; Redmond, WA, USA). One single investigator transcribed all of the audio files (G.O.).

Table 7.1.Probing questions for each focus group at post 12-week testing time point

Exercise intervention group	Control group
Available help	
• What support was provided to you once you were discharged from hospital? (i.e. physical, mental, home care). • Were you given any advice about exercising after your injury and the benefits of exercise? • If yes, then what type of exercises were you advised to do and the duration and frequency of these exercises? • What additional advice were you provided with, if any? • Were you signposted to any local help centres or charities?	
Physical activity	
• How would you compare your current level of physical fitness and health with before your injury? • Have you kept exercising during your participation in the study (either in EX or CON group)? If so, how often? What type of exercise? If not, why not? • What were the biggest challenges that keeps you from exercising?	
Feedback on exercise intervention	
• How did you come about finding information about this study? • What were the main reasons for taking part in this exercise programme? • What benefits (if any) did you feel you received from taking part in the programme (physically, socially, and mentally)? • Can you discuss any barriers (physical/psychological/social/environmental) that had made staying in the programme difficult? • Has the participation in this programme changed the way you think/feel about yourself as a person? • What did you like best about the programme? • What did you like least about the programme? • How do you think the programme could be made better in the future?	
Closing question: Do you want to add something, or do you feel that we missed something, related to this topic from the interview?	

7.3.3 Thematic analysis

Thematic analysis was used to systematically identify and offer an insight into the patterns and themes across all of the one-to-one interview datasets. It allows the researcher to make sense of the meanings and experiences of the individuals who took part in the study in a flexible manner and focus on the data in numerous different ways. The process of thematic analysis follows a six-phase approach (Braun & Clarke, 2006) (Table 7.2). Phase 1 was concerned with familiarisation with the data by reading and re-reading the textual data and re-listening to the audio files. During this phase, notes were made highlighting items of potential interest. Phase 2 is when the codes were generated, identifying and providing a label for a feature of the data that is potentially relevant to the overall research question. This phase was completed on hard copies of the transcripts clearly identifying the code name and highlighting the portion of text associated with that code. In the next phase, themes were generated from the text capturing meaningful information representing relatively patterned responses. At the end of this phase, a thematic map was generated to outline the themes and relevant data extracts. In phase 4, the potential themes were reviewed against the extracts of data and in relation to the entire dataset. This stage is essentially quality checking and by the end it is important that the themes capture the most important and relevant elements of the data, relating back to the research question. Phase 5 involves defining and naming the chosen themes, highlighting what is unique and specific about each one. Throughout this stage, it is essential that the meaning of the themes resonate with extracts from the data, other neighbouring themes, and the overall research question. Themes were named accordingly to highlight their content. The final phase is producing the report. This phase can be combined with the previous phase, as during qualitative research the write-up starts during note-taking and the overall report is expanded gradually.

Table 7.2.Six-phase thematic analysis approach adapted from Braun & Clarke (2006).

Phase	Description
1. Familiarisation with data	Reading and re-reading textual data and re-listening to audio files.
2. Initial coding	Identifying the initial codes that demonstrate interpretation of the data content.
3. Searching for themes	Generating and constructing themes that capture important information about the data in relation to the research question.
4. Revising themes	Developed themes reviewed in relation to the coded data and entire data set.
5. Defining and naming themes	Clearly stating that is unique and specific about each theme then create an informative and concise name.
6. Producing the report	Appropriate extracts and themes are assembled in a logically and meaningful way to tell a coherent story.

7.4 Results and discussion

The responses from the EX and CON groups are combined, with the exception of the responses concerning feedback on the intervention as this was just ask to those in the EX group. Analysis of the exercise group transcripts revealed three dominant themes contributing to the facilitating factors for participation in exercise: motivation; gaining an understanding of recovery; and increasing physical fitness (Figure 7.1). Two themes were identified as barriers to exercise participation: lack of motivation; and exercise related financial costs (Figure 7.1).

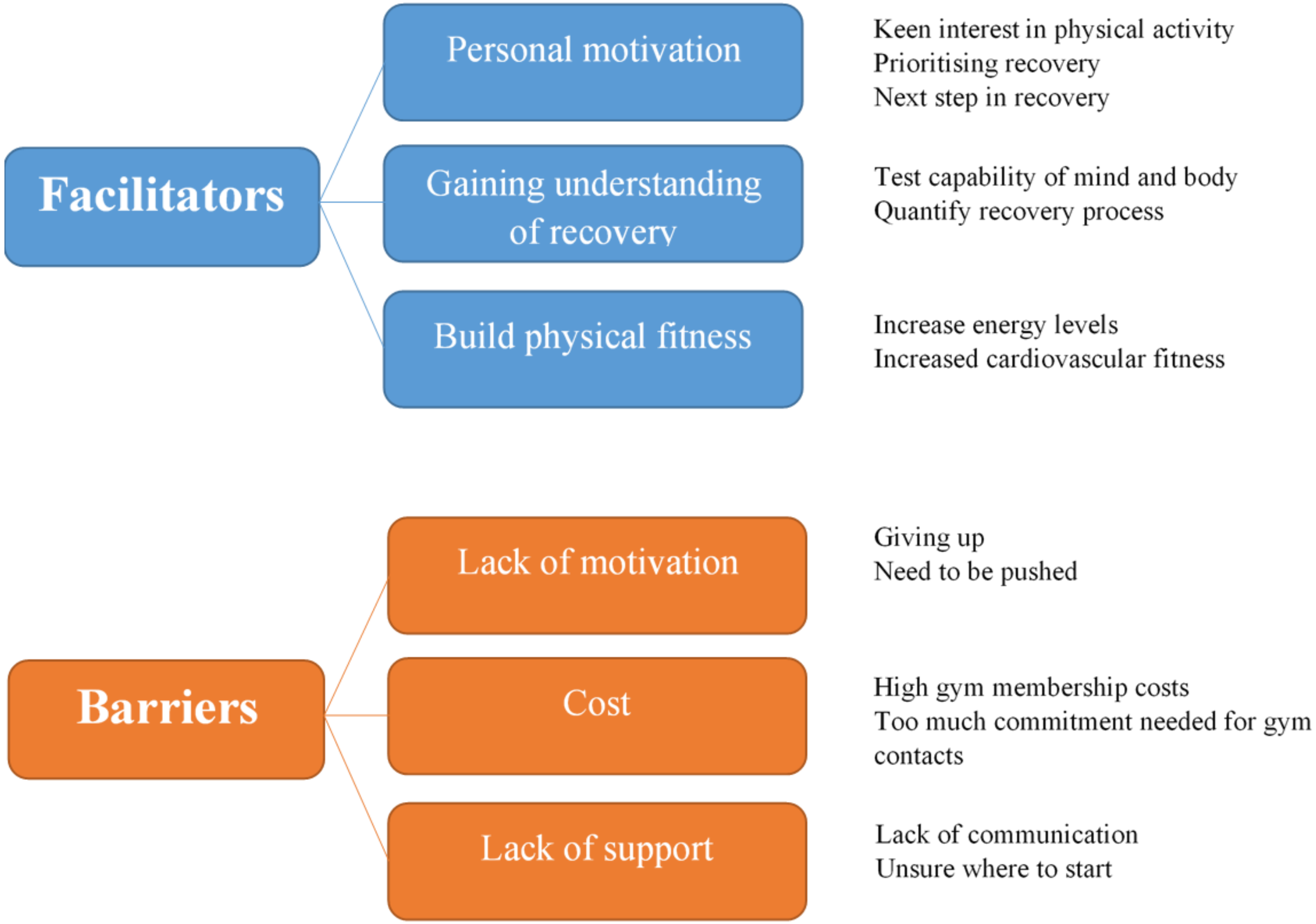

Figure 7.1.Perceived facilitators and barriers identified for the EX and CON groups in the one-to-one interviews

7.4.1 Facilitators of exercise

The theme of motivation to recover as a facilitator to participate in exercise following a TBI comprised of two key areas: keen interest in exercise and the feeling that exercise would be the next step to aid their recovery.

Facilitator: Motivation to recover

Motivation was defined as what sustained individuals wanting to improve/ or maintain their state of being (Lox *et al*., 2003). The American College of Sport Medicine recommendations suggest at least 30 minutes of moderate-intensity aerobic activity five days a week (150 minutes weekly) or vigorous-intensity for 20 minutes three times a week (ACSM, 2013). Participants emphasised that they wanted to get a better understanding of their physical limits and additional methods to increase their recovery.

> *"Anything that would aid my recovery I was interested in physical, mental anything"… "I was keen to prioritise* [recovery] *and make sure I stuck at it"* ***TS001***
>
> *"I did think it's got to help me understand* [injury]*"… "It was for me to find how capable or what I am able to do"* ***TS002***
>
> *"I wanted to do this, this was my next step. This for me came at a perfect opportunity"* ***TS003***

Motivation to recover is aided by clear goal setting at the beginning and throughout an individual's recovery and is integral to rehabilitation programmes especially when the primary goal is to improve quality of life (Dalton *et al*. 2012). Participants' responses in the current study were similar to those in Self *et al*. (2013) focus groups, whereby they highlighted main motivators as returning back to pre-injury lifestyles, enjoyment, social, and career influences.

Facilitators: Build up fitness

Another theme that became apparent was the need to build up general fitness and strength to aid recovery. This was emphasised more by the participants who were generally physcially active before their injury. The need to increase physical strength was associated with increase in confidence in order to perform everyday tasks and get back to work. One participant had a manual labouring job and was self-employed so this was a keen motivator.

> *"at the time I was beginning to think I need to start building some fitness up. So actually for me it came at a perfect time"…"there was a requirement for me for mental and physical stimulation"* ***TS003***

> *"a lot of it was to get my energy levels up and my fitness up again"…"so I can start exercising again and just motivating myself as well to start doing stuff"* ***TS004***

7.4.2 Barriers to exercise

Barriers were defined in this study as what prevented participants to take part in exercise or to maintain a physically active routine following their TBI. The main themes focussed on lack of motivation, cost and lack of support.

Barriers to exercise: Lack of motivation

A common theme for the barriers of exercising was the lack of motivation. Participants (EX and CON group) stated that without guidance or someone to motivate them, they gave up easily or were unable to push themselves to their full potential.

> *"that's what I need, to be pushed into things"…"it's a mental block to doing the hard stuff"* ***TS001***

One participant mentioned that they started going to the gymnasium for exercise during the exercise intervention but once the supervised programme finished they found it difficult to motivate themselves to attend gym sessions.

> *"somebody said that I would continue at the gym once it finished but I've given up"* ***TS002***

This participant also highlighted that they felt they were no longer progressing in their recovery once they had stopped coming to the University for exercise sessions.

> *"since I'm not coming I feel like I'm going a little bit backwards again"* ***TS002***

> *"I don't go to the University and I don't go to the gym anymore it's stopped, am I getting back out of improving* [statement]*"* ***TS002***

Participants mentioned that this lack of motivation caused them to get into a 'negative spiral' and the lack of exercise following the injury caused them to feel 'down'. This then led to decreased motivation spiralling out of control.

> *"my motivation was a bit low"…"it was hard at the beginning due to motivation"…"sometimes it let me down* [lack of motivation] *and then you get down and in some ways you feel sorry for yourself, and that puts you more down"* ***TS004***

Barriers to exercise: Cost

The cost of joining a gym was another major theme that appeared with participants highlighting their reluctance in signing a membership contract when they were unsure of their financial situation in the up and coming months.

> *"since programme* [ended] *I haven't been coming here and I haven't been going to the gym because of the cost"…"I can't afford to sign up for something for 6 months as I don't know what's going to happen in that 6 months"* ***TS002***

One participant emphasised that they were currently out of work and the gym prices were too expensive and they were wary of committing to a long-term contract.

> *"I have been very conscious of a lot of the gyms contract and this lot. Yeah quite a lot of money when I'm not in work"* ***TS003***

As well as cost, Self *et al.* (2013) also highlighted accessibility as a barrier for individuals following TBI, with participants not having access to local gyms or were unable to get transportation. Participants in the current study did not highlight accessibility as a major barrier, but this may have been different if individuals were from the surrounding villages where gyms are more scarce, rather than from the inner city.

Barriers to exercise: Lack of support

Two participants mentioned that a barrier to exercise was lack of guidance and help from either the gyms or from their healthcare teams.

> *"I tried to join the gym myself but I never heard anything back"****TS002***

> *"I think a lot of the problem with these type of things, you're unsure what the best thing to do is"* ***TS003***

> *"the fact that I didn't know anything about it* [recovery] *and they didn't tell me or anyone that was with me, anything about how to get back to normal."* ***TS007***

One participant mentioned that the received some information on discharge concerning exercise but was very vague.

> *"they* [hospital staff] *did say don't do any high intensity exercise for a few days. Urm but I don't think they went into too much detail with that."* ***TS008***

This participant felt totally left in the dark concerning her recovery pathway.

> *"it was a very isolated experience spending most of the day on my own"… "no one had explained to me that my nervous system was being bombarded by noise and light and that in itself was going to make struggle. So simple things like going to buy a loaf of bread, I might make the walk there but the process of dealing with the environment, choosing between all the options on the shelf, dealing with the transaction. By the time I get to the door I was completely exhausted and needed picking up and bringing home"* ***TS009***

Overall, there was the consensus that participants were 'in the dark' when it came to their injury and did not understand the best recovery methods. It can be disconcerting for an individual with no or little prior experience with physical activity to go into a gym setting and be expected to know what they are doing.

> *"It's alright saying that I'm going to go to the gym but its knowing what to do then I get there and what going to be beneficial and aid you in your recovery."* ***TS003***

Participants also went on to explain that they would benefit from a clearer understanding of their injuries from their care teams and what symptoms they may experience in the future. A participant in the control group went on to express the lack of awareness and advice they were provided by their care team.

> *"no one quantified rest, so I think like most people rest meant that stay on the horizontal and be quiet, but not literally do nothing"…"it's a thing* [awareness of head injuries and PCS] *that needs an awful lot of pushing for awareness and advice to patients and to therapist and medical practitioners and employers"* ***TS009***

Self *et al*. (2013) highlighted a lack of physical activity knowledge during their qualitative study with individuals with TBI. They reported that participants showed an uncertainty of what constitutes physical activity but expressed a belief that exercise was something that should be part of their outpatient rehabilitation. However, participants went on to convey they felt increased overall wellness as a benefit of physical activity and that it was a tool to prevent depression (Self *et al*., 2013).

Based on the participants' comments, greater flexibility with gym membership contracts (duration and prices), with the incorporation of short-term monthly contracts with the possibility of discount prices for individuals with disabilities, could facilitate more participation in physical activity following TBI. In regard to the lack of support/ knowledge as a barrier, more information should be implemented at the time of patient discharge with healthcare professionals providing guidance for physical activity either with information sheets or with signposting to local brain charities (e.g., Paul for Brain Recovery, MIND, Headway).

7.4.3 Effects of intervention

These responses are of those form the EX group and they were the only ones that could comment on the exercise intervention. Four main themes surfaced when the intervention group were ask to comment on the effects the exercise sessions had on them: increase in physical and mental fitness, regaining a routine and building up confidence. Participants were also asked how the exercise intervention could be improved.

Physical and mental fitness

Participants self-reported improvements in their coordination, balance, cardiovascular fitness and strength following the 12-week intervention.

> *"physically I got fitter"… "it definitely improved my coordination"… "I do think it has helped my recovery, certainly physically in terms of balance"* ***TS001***

> *"the main one is the physical aspect, my movement, my cardio, my strength in my legs, it's all increased exponentially from where I was 12 weeks ago"… "it has aided all aspect of my movement"****TS003***

One participant also revealed that they felt their mental improvements were as important as their physical development.

> *"It was good for the physical but I liked the mental, like the eye coordination, using my brain doing different, you know, brain exercises as well as fitness"* ***TS004***

Regaining a routine

Another common theme in the intervention group was getting back into a routine. One participant found that this routine was mentally beneficial.

> *"I think it has helped me mentally the fact I was doing something twice a week which I knew was benefiting me was actually mentally beneficial"****TS001***

One participant highlighted that the routine of coming into the University twice a week meant they had an activity to organise their life around. In addition to this, they mentioned that they found the social aspect of the exercise programme beneficial and knew that each week they were going to get social interaction outside of home-life.

"it's been the mental and social side, the having to set times, right I need to leave the house at so and so time because I wasn't driving, I was getting taxis, it was booking the taxis and sorting out organising things, organising my life around something" ***TS003***

Building up confidence

All participants in the exercise group emphasised improved confidence following the 12-week intervention. Some participants were nervous at the beginning but noticed improvements throughout the programme, including confidence with getting to the University on their own and the ability to deal with social situations during the sessions without worrying who was watching.

"I know when I first started I used to get you to meet me down there at the front as I was quite nervous about getting that wrong, finding where I was going, but once I done it I was fine" ***TS002***

"more relaxing for trying each one as I say when I first came I was a bit nervy who was going to be there, who was going to be looking. It was me who was looking around everywhere"… "it made me realise I was able to do things" ***TS002***

Participants also felt that this increased confidence enabled them to feel better about themselves in everyday life not just during exercise.

"there's definitely been a change in mind set from that as I feel more confident in myself to do things"…"I can go out and do things without thinking about it. That is probably the biggest aspect" ***TS003***

"it's given me a bit more confidence"…"if you look better you feel better, up in your head it makes you more confident as well and it makes you feel a lot better" ***TS004***

Future directions for the exercise intervention

Participants in the EX voiced the need for longer-term programmes to continue the positive effects of their recovery.

> *"I would have actually of liked to have done it for longer and continued doing it, because I have seen improvements and I think there would be further improvements for me to continue with for longer." **TS001***

> *"it's been good, good time I've enjoyed it, wish I could still be here* [in the programme] *but really enjoyed it." **TS002***

> *"I think it's been uh and very good course and obviously I would carry on with it a bit longer if I could you know." **TS003***

One participant even went on to mention that they felt they were regressing after finishing the programme as their routine had stopped.

> *"its since I'm not coming I feel like I'm going a little bit backwards again"… "I do worry a little bit now because I don't go to the university and I don't go to the gym anymore it's stopped, am I getting back out of improving."* **TS002**

When asked about how to improve the exercise intervention, participants wanted more of a group setting.

> *"For me personally, going back to the number of people that was involved. Possible if there was more people taking part" **TS002***

> *"More people would push you* [referring to themselves] *like competition wise. That would be better, instead of just having one on one maybe having another person or a*

couple more people. It motivates you [referring to themselves] *to work a bit harder and push yourself* [referring to themselves].” **TS004**

On participant recommended a next level to the programme so they could have continued support.

“do a next level course type of 12 weeks. Like a stage one stage two 12 weeks”… “A programme like there you here’s your level 2 programme for you to follow, you know. Something you can take away and do in the gym that type of thing. To increase from where you were to carry on”… “So maybe a little bit of help as a progression to the next level. Then that will be even better.” ***TS003***

This information is valuable, as this study was a pilot, these subjective insights allow further developments of the programme that can be incorporated into a larger scale study and to inform rehabilitation providers to the main needs of the individuals.

7.5 Conclusion

This study aimed to firstly, understand the facilitators and barriers to participate in exercise and physical activities for people with a TBI. Secondly, it then intended to highlight the positive aspects of the 12-week exercise programme.

Key perceived facilitators (personal motivation, understanding recovery and building physical fitness to aid recovery) and barriers (lack of motivation, cost and lack of support) to exercise surfaced. In addition the feedback on the intervention by the EX group highlighted areas for future development (increasing time period of intervention >12 weeks, developing follow-up programme for individuals to continue at home/ at the gym, and increasing number of participants in the exercise sessions to create more group interactions).

These one-to-one interviews allow a more personal insight into an individual's recovery process, their barriers and their goals. These qualitative data complement the previous quantitative data to provide us with an overall picture of this global epidemic and highlight areas for further improvement. Thinking ahead, it is important to increase patients' perceived competence and social support to facilitate participation in physical and social activities and the need for interventions that facilitate the adoption and maintenance of positive physical activity behaviours.

8 Chapter Eight – Overall Discussion

Traumatic brain injury is a major consequence of accidents and intentional behaviour with significant socioeconomic implications. Rates of TBI worldwide are described in epidemic proportions, with projections that it will soon become the third most prevalent case of global disease burden (Edge, 2010; Tagliaferri *et al.*, 2006; Peeters *et al.*, 2015; Chau *et al.*, 2007). The consequences of having a TBI can affect every aspect of the individuals' life such as physical health, mental well-being, social interactions, and financial situations (Langlois, Ritland-Brown & Wald, 2006; Cassidy *et al.*, 2004; Sullivan *et al.*, 2018). It can also incur heavy strains on friends and family members who may have to become careers or support households with on less income (Hammon *et al.*, 2012; Gilworth *et al.*, 2006). In terms of post-TBI rehabilitation, there is a growing amount of literature highlighting the positive effects of exercise on an individual's recovery (Mossberg *et al.*, 2007; Van-Praag, 2008; Leddy *et al.*, 2010; Wise *et al.*, 2012; Chin *et al.*, 2015). However, this thesis took a novel approach to TBI recovery by examining an original, multi-component exercise intervention on mental and physical outcomes. It also incorporates qualitative research exploring individual's experiences of their care, and facilitators and barriers to exercise.

The overarching aim of this thesis was to pilot an original, multi-component exercise intervention to assist future exercise recommendations for TBI rehabilitation. Chapter 3 investigated the possible effects of different exercise modalities on QOL in TBI. The systematic review uncovered some positive findings across several investigations, such as the inclusion of aerobic training into a recovery/rehabilitation programme prompted improvements in anxiety, depression, sleep quality, and pain with TBI populations. However, it was not possible to draw any definitive conclusions regarding the most effective exercise interventions to improve QOL due to the diversity of both the exercise-based interventions and outcome measures. This review highlighted the need for more structured RCTs within this research field. At this stage, it became apparent how broad the concept of QOL was and how it was measured in research studies. Applying the outcomes from the literature (Chapter 2) and systematic reviews (Chapter 3), it was feasible to develop a novel multi-component exercise programme that aimed to improve the QOL in TBI individuals. Firstly, the design and delivery of this intervention and the outcomes measures had to be assessed within a cohort of healthy individuals. Chapter 5 showed that a 4-week multi-component exercise intervention performed two times a week could induce meaningful improvements in overall mobility, aspects of muscular performance, and some aspects of cognitive functioning, reaction time, and dual-tasking interferences. It also highlighted the feasibility and acceptability of the design and delivery from both the participant and researchers' perspectives. It is has been reported that following a TBI, individuals have decreased aerobic (Wiercisiewski & McDeavitt, 1998; Becker *et al*., 1977; Lew *et al*., 2005), balance (Prangley *et al*., 2017; Damiano *et al.*, 2016; Ustinova *et al.*, 2014) and performance in dual-tasking abilities (Weightman & McCulloch, 2014; Robertson *et al.*, 1997; Haggard *et al.*, 2000). Adherence to the 4-week intervention was 100% with no serious adverse events in a healthy group of adults reported. These findings suggested that the programme was feasible to deliver in a small group, and some improvements in QOL were found, indicating the possibility that similar improvements could be elicited within a TBI cohort. Consistent with the systematic review literature (chapter 3) within short-term TBI interventions, the decision was made to extend the exercise-based intervention period to 12 weeks. In addition, the choice was made to remove some of the outcome measures (e.g. TUDS, grip strength) as they did not show improvements in the healthy population and there was a lack of previous literature indicating improvements in TBI. Chapter 6 part 1 presents the only up-to-date audit report of TBI admissions at HRI and was informative on the likely pool of eligible patients that could be potential study recruits and highlighted justification recruitment. Recruitment for part 2 of chapter 6 was expected to come from the Hull and East Yorkshire area and HRI, thus providing vital rationalisation that the main study recruitment could be feasible.

Within the timeframe of the final study, (part 2 of chapter 6) the investigator recruited and retained seven TBI individuals. It was notable that a proportion of the individuals had to be excluded due to mental health issues, declined to participate and personal issues. The notable findings from the exercise intervention in TBI patients showed significant improvements to QOL outcome measures and developments in dual-tasking ability and physical fitness were demonstrated. This investigation confirms the earlier randomised and non-randomised studies included with8n the SR that a 12-week exercise intervention can promote both mental and physical improvements following a TBI. Disability is not static and can improve over time without exercise interventions. However, chapter 6 demonstrated a decrease in disability following a 12-week exercise intervention with feedback suggesting decreased time scales for returning to pre-injury health statuses. This intervention included a range of different exercise modalities such as aerobic, strength, balance, and dual-tasking components. Exercise may expose individuals to a greater number of social interactions, increasing the likelihood of individuals developing inter-personal relationships. Previous research has highlighted the importance of increasing social interactions as part of an individual's rehabilitation (Fazio & Fralish, 1988). There is currently a lack of research looking at the effects of DT following a TBI and the effects exercise can have on an individual's ability to perform two tasks simultaneously.

These elements to recovery are important, as daily tasks necessitate dual-tasking without even realising it, such as walking around the shops whilst thinking about the shopping list or weaving in and out of other shoppers whilst controlling a trolley. Impairments in DT can cause anxiety for an individual and may lead to them becoming isolated, prolonging their impairments. Thus, this can lead to drastic consequences to an individuals' QOL. The quantitative results from chapter 6 are valuable to guide future developments in this area of investigations. Chapter 7 was designed to gather in-depth qualitative views of exercise-based rehabilitation and the specific intervention designed for the TBI participants. The main facilitators of exercise were motivation to recover pathway, and the perception derived from the improvements to physical fitness. With this exercise programmes, the aim was to highlight that mental well-being and physical improvements are equally essential for effective recovery. Conversely, even though patients understood the importance of exercise, barriers were apparent such as lack of motivation and financial costs related to exercise. (outlined in chapter 7). The transcripts of participants' opinion on the exercise intervention at the University of Hull, outlined that they benefited and enjoyed the social interactions with other TBI individuals. It provided them with a weekly routine and increased confidence to travel on public transport and exercising in front of others. Gathering qualitative data highlighted individuals concerns of their treatment and aftercare following discharge from hospital. By understanding the barriers that individuals face towards participating in exercise, clinicians may be in a better position to develop meaningful recovery promotion programs. In the first instance it could help the development an overarching guidance to rehabilitation programs, touching on elements such availability (multi-centred, variety of equipment), financially viable (pay per session, no long term contracts), and accessibility (transport service, showering facilities). Following on from this, more individualised programs can grow with specific sessions for varying severities and needs with specialised equipment and instructors. So, for example sessions could be ran in reduced light and noise environments for hypersensitive individuals and advanced sessions for the more abled individuals.

There seems to be a lack of information provided on the next steps of recovery and things to look out for. Every injury is different and depends on so many variables such as severity of injury, physical fitness pre-injury, mental well-being, and social support systems, so it is hard to provide exact time scales to recovery.

8.1 Clinical implications

The overall aim of this thesis was to assist the clinical recommendations for improving TBI rehabilitation with exercise, based on QOL and physical outcomes measures. Based on the findings of the systematic review and controlled empirical exercise- based interventions following TBI, and the supplementary qualitative TBI patient reports; the following recommendations are relevant:

Discharge care

- Information should be provided on the importance and benefits of regular exercising for physical, psychological well-being and QOL in patients following TBI.
- Patients should be signposted to local brain injury and related charities for further information and support (Headway, PAUL) on discharge.
- More emphasise needs to be placed on informing and educating patients on the long-term post-concussion symptoms (such as mood changes, fatigue, light and noise sensitivity, dizziness, and persistent headaches) that individuals may face in the future so that they are aware of medical complications and can seek appropriate help.

Rehabilitation interventions

- Ideally, supervised exercise-based rehabilitation should be initiated as soon as possible after acute TBI treatment (following acute care discharge) to illicit the optimum recovery.
- It is integral that goals are formulated between the individual, health care team and family members, so that everyone is sufficiently informed, and have regular tangible exercise-related targets to meet.
- Serial testing of physical, psychological and physical components during community-based rehabilitation are recommended. In the current thesis, it was apparent that individuals were more motivated when they saw regular improvements and made them feel more positive about their recovery.
- multi-component physical fitness elements should be key features of an exercise-based rehabilitation programme, this should include field-based assessments of functional tasks and physical capacities.
- Exercise-based rehabilitation programmes should be multi-component, incorporating a range of exercise modalities and including dual-tasking elements to specifically stimulate cognitive functioning. The dual-tasking exercises should be adaptable for everyday activities. Current issues within the rehabilitation process is transferring skills learned in rehabilitation settings to ‘real life’ situations

8.1.1 Limitations

Several limitations in this thesis should be acknowledged. The systematic review in chapter 3 uncovered difficulties in defining QOL so more specific elements should have been observed or the analysis should have been broken down into sub-categories, such as health-related QOL. The outcomes were quite broad and was difficult to compare the outcomes with varying values. Ideally, the included studies would have all used the same QOL tools allowing a more accurate comparison of interventions. At the time of the review search, there was a lack of studies that fit these criteria and there was no consensus on the most suitable QOL measurement tool for TBI individuals. Due to the studies under review not all being RTCs it was not possible to draw definitive conclusions on effectiveness, whereas instead it investigated the possible effects. It is however outlined in chapter 3 that the lack of RTCs in the specific area promoted recommendations for the future and highlights that this area of research is still young. In addition, it was not possible to draw out TBI data only in some of the studies in the review. Therefore, we were unable to distinguish between the sub-categories of brain injuries in the results in the review. Due to the diverse range of participant and intervention characteristics, outcome measures and QOL tools, these findings support the conclusion that no single exercise modality or single QOL outcome measure represent the most effective exercise to improve QOL following a TBI. This highlights the need for further research, including robust RCT study designs.

Chapter 5 highlighted some key findings that were essential for the main TBI chapter (chapter 6). The study included only one QOL outcomes measure within this cohort (SF-36) as it was assumed the healthy individuals may not exhibit the same QOL issues as TBI individuals and therefore would not show significant changes following the exercise. Unfortunately this lack of QOL outcome measures, meant that little was known of the effects the intervention would have on TBI individuals. The systematic review also highlighted this concern with the vast amount of QOL tools used within the nine primary studies.

The audit in chapter 6 (part 1) was conducted over a 2-month period in the summer season, so a true representation of the incidence rates could have been misjudged. It would ideally to undertaken over a longer period of time to gather a more accurate insight to the TBI incidents coming through the A&E department at HRI. However, from the large number of incidences in 2 months, it was presumed that the recruitment rates would be enough for the recruitment for the main TBI study. Unfortunately this was not the case with one of the main limitations of the thesis being the small sample size of TBI participants. This small sample size meant that the between-subject variability was large and individual participant data was included in order to highlight improvements. There are always challenges with recruitment in clinical studies. This may have been additionally adversely affected by the underlying clinical cohort, with brain-related pathology, retention to exercise-based interventions in the community settings has been reported as being problematic in both TBI and other neurological pathological conditions. These low numbers could be attributed to the general lack of interest in participating in a community-based exercise-based research project following a life-changing injury, where individuals may be more focussed on getting back to normality with work and rebuilding relationships. Another reason could be the complex demands of TBI patients in the acute setting, and the lower order of priority afforded to recruiting of lifestyle-based interventions. This however is a matter that should be addressed in the future and could be minimised within a clinical trial setting with a more structures' referral pathway established for clinical staff. Due to the small recruitment numbers, the participants in the exercise and control groups were not matched according to their cause of injury, time since injury, or age. Therefore caution must be taken when generalising the current findings top the wider TBI populations. In addition to this, the TBI individuals were not matched according to pre-injury (if available) and baseline depression and anxiety levels. Thus, vigilance must be used when generalising the QOL results to wider TBI cohorts.

The biggest limitation, however, is that it was not a randomised trial as in the participants were not randomly assigned to either the EX or the CON group. The main benefit of randomisation procedures is that it ensures the allocation of a participant to one or the other treatment can not be predicted, allowing the comparison groups to be equal in terms of both known and unknown baseline prognostic factors (Deeks *et al.*, 2003).

Another limitation that affected chapters 5 and 6 was that the dual-tasking exercises should have been analysed as single tasks separately then followed by the dual-task. This could have outlined if the decrements were also due to cognitive function as well as the motor tasks. The slalom and cognitive dual-tasks have not been assessed before in a TBI cohort, so caution should be taken when interpreting these results due to absence of reliability and normative data. This leads on to future research ideas needed to form concrete dual-task assessments in TBI populations.

8.2 Future directions

A future direction of this study could explore the effects of pre-injury mental and physical well-being on outcomes following a TBI and the effects if has on the recovery period. The same exercise intervention as used in the current study could be implemented but can explore the effects in different cohorts of individuals with carrying pre-injury status. Previous research demonstrated that chronic physical activity might preserve neurocognitive processes and increase physical health compared with those who live a more sedentary lifestyle (Zhao et al., 2016).

Moving forward, the secondary injury is the aspect we can realistically make a difference to. As mentioned in the introduction (chapter 1), the primary injury is the direct damage occurring at the time of the injury, whereas secondary injures occur at some time following the initial incident. Clear guidelines, advice and timely interventions can reduce the incidents of secondary injuries and promote an enhanced QOL.

More feasibility research should be conducted using the Fitlight Trainer within TBI groups to gather a more extensive understanding on the effects it has on coordination, reaction time and dual-tasking abilities. This also applies to the dual-tasking assessment methods. The hope is to use the findings from this thesis and merge it into a multi-centred RCT. Firstly, the feasibility of this exercise intervention within the community would have to be analysed. Then put forward to assess the effectiveness of the programme within a larger TBI populations around the country. More patient public involvement should be explored to refine the research question and to understand important patient-reported outcomes. This would in turn help amend and strengthen the structure of rehabilitation guidelines.

In regards to QOL, more robust research needs to be conducted specifically in TBI populations. This is a difficult area as QOL elements are perceived differently by individuals with many indicators such as material living conditions, governance and basic rights. So from this QOL should not be assessed as a single domain but rather categorised and analysed separately. This opens a whole new portion of research that should be explored before moving forward with rehabilitation guidelines.

There is a need to refine exercise and dual-task prescriptions on a clinical severity basis to design more mechanistic studies with components of the current exercise programme used within this thesis. These components (strength, balance, aerobic, dual-tasking) should be broken down and analyses amongst severity specific TBI populations so that we can establish the specific needs of a patient. Here both eh individual outcomes ad exercises would be piloted before a full intervention programme was established. To gather more individualised results, participants could be split up and analysed separately according to their physical fitness levels, mental status at time of injury, and if possible, stratify participants against their pre-injury physical levels. This would ask another question as to if pre-injury fitness levels effect recovery time and efficiency. From the qualitative study (chapter 7) and from talking to the participants each week, the social interaction seemed to play a major role in their commitment to the intervention. Therefore, future research should explore to what extent the social interaction between the researcher and/or the other participants, effected their recovery. To do this, we could introduce additional researcher to take the classes and interact with the participants as to establish if researcher's personality plays an important role. Additional treatment groups could be incorporated to compare no interaction (control group), phone interaction (control group with weekly phone calls), and face-to-face interaction (exercise group). Overall the aim of breaking down the elements of this exercise program would be to determine the variables that are affecting the outcomes e.g. the novel exercise programme, social interaction with researchers, social interaction with other TBI individuals, or establishing and maintaining a routine.

In terms of trial design, a crossover study whereby participants are allocated to different interventions (standard and novel treatment) could be implemented. An advantage of a crossover design is the removal of any biological and methodological variation and less participants are needed to be randomised to observe the intervention effects. However, crossover trials generally last longer which may inflate attrition rates and can potentially make it more challenging to determine causality. Another element to consider with this design would be the natural recovery from a TBI over a long time period, so with a longer trial period it may be hard to establish if the effects are from the intervention or by natural recovery. On the other hand, a parallel design is more versatile and easier to incorporate into meta-analyses, but larger sample sizes would be required. Further investigation would need to take place ad weigh up and advantages and disadvantages of using either of these designs.

8.3 Overall conclusion

This thesis contributes to a relatively new area of research that is fundamental for the guidelines in TBI rehabilitation. There was no scientific literature that specifically looked at the QOL outcomes following multi-component exercise intervention in individuals with a

TBI from the outset of this project in 2015. This thesis has demonstrated that exercise can illicit positive mental and physical improvements within a TBI population and overall QOL. Furthermore, this thesis has identified shortcomings and disparities in current TBI rehabilitation guidelines following discharge, proposed new exercise prescription guidelines and accentuated the critical need for more long-term support for TBI individuals within the community.

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Appendix A – Proforma for data collection during audit

AGE

GENDER

Male	Female	Not known

MONTH OF ARRIVAL

Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	N/A

DAY OF ARRIVAL

Mon	Tue	Wed	Thu	Fri	Sat	Sun	N/A

TIME OF ARRIVAL

0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12
12-13	13-14	14-15	15-16	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-0

ARRIVAL METHOD

Ambulance	Self	Other	Not Known

REFERRAL METHOD

Self-referral	999	GP	Work	Police
Social services	Educational services	111	Other	Not Known

PATIENT GROUP

Sports related	RTA related	Assault	Deliberate self-harm	Stroke	Fall	Other	N/A

DURATION IN DEPARTMENT (Hrs)

00:00-01:00	01:01-02:00	02:01-03:00	03:01-04:00	>04:00	N/A

DISCHARGE METHOD

In-patient	Discharged (follow-up)	Discharged (no follow-up)	Referred	Not Known

ATTENDANCE CATEGORY

First A&E attendance	Follow-up attendance (planned)	Follow-up attendance (unplanned)	No Known

GCS

Exclusion

Mental/cognitive	Cardiac	Respiratory	Musculoskeletal	Ca	Other

PREVIOUS HEAD INJURIES

First head injury	> 1 past head injury	N/A

Appendix B – Additional results from data collected during the audit

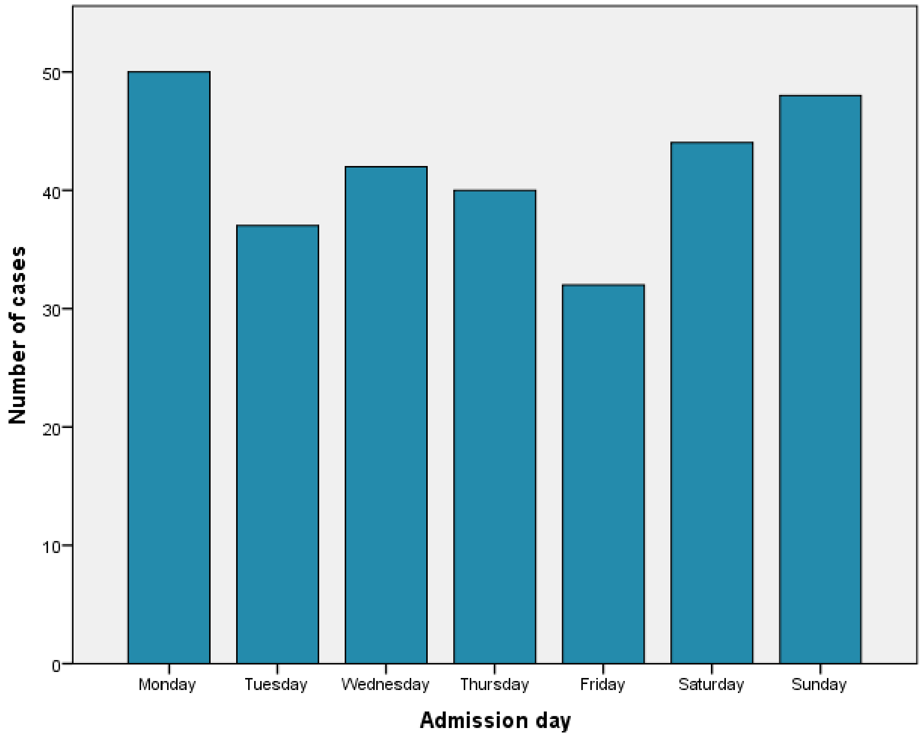

Figure 1. Day of admission to A&E

The majority of the TBI admissions arrived in A&E on Mondays and Sundays (17.1% and 16.4%, respectively). Friday was the quietest day (10.9%) (Figure 1).

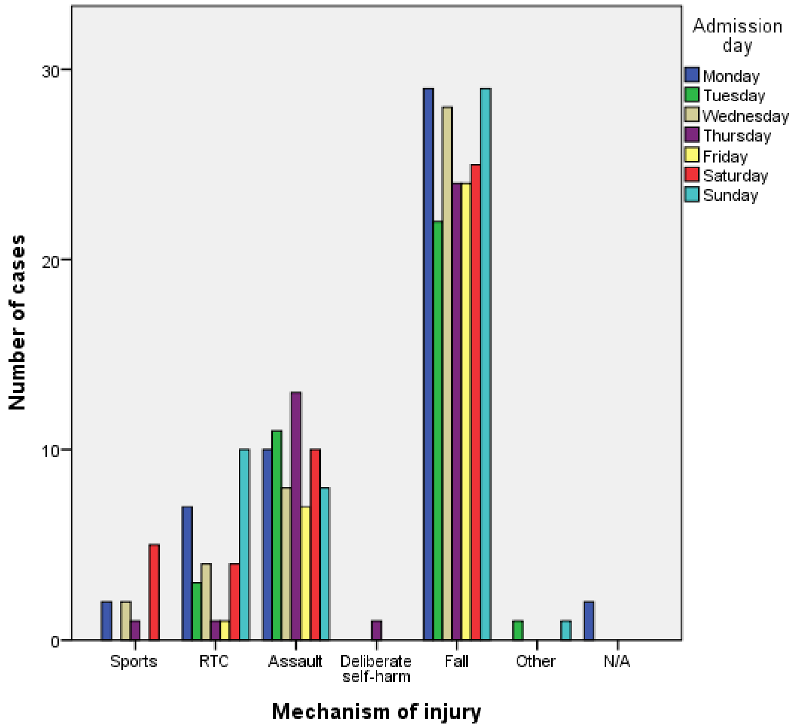

Figure 2. Mechanism of injuries according to admission day

By combining data of the admission days and mechanism of injuries, sports were more prevalent on Saturdays (50%), RTC on Sundays (33.3%), assault on Thursdays (19.4%), and falls on Mondays (16%) and Sundays (16%) (Figure 2).

Method of arrival

Looking at the full sample, 55.3% of patients were brought into A&E via the NHS ambulance service, 43.7% arrived via their own transportation (includes being brought in by a friend or family member). Incorporating admission day to method of arrival, 18.5% of the ambulance arrivals occurred on a Sunday, and Mondays were more popular with 'self-arrivals' (19.5%).

Intoxication on arrival

Intoxication was also noted when the patients arrived in A&E with 20.8% of patients demonstrated signs of being intoxicated, with 77.8% classified as sober. For the remaining 1.4%, intoxication levels were not available (N/A). The majority of the patients coming through A&E intoxicated were males (59%) compared to females (41%).

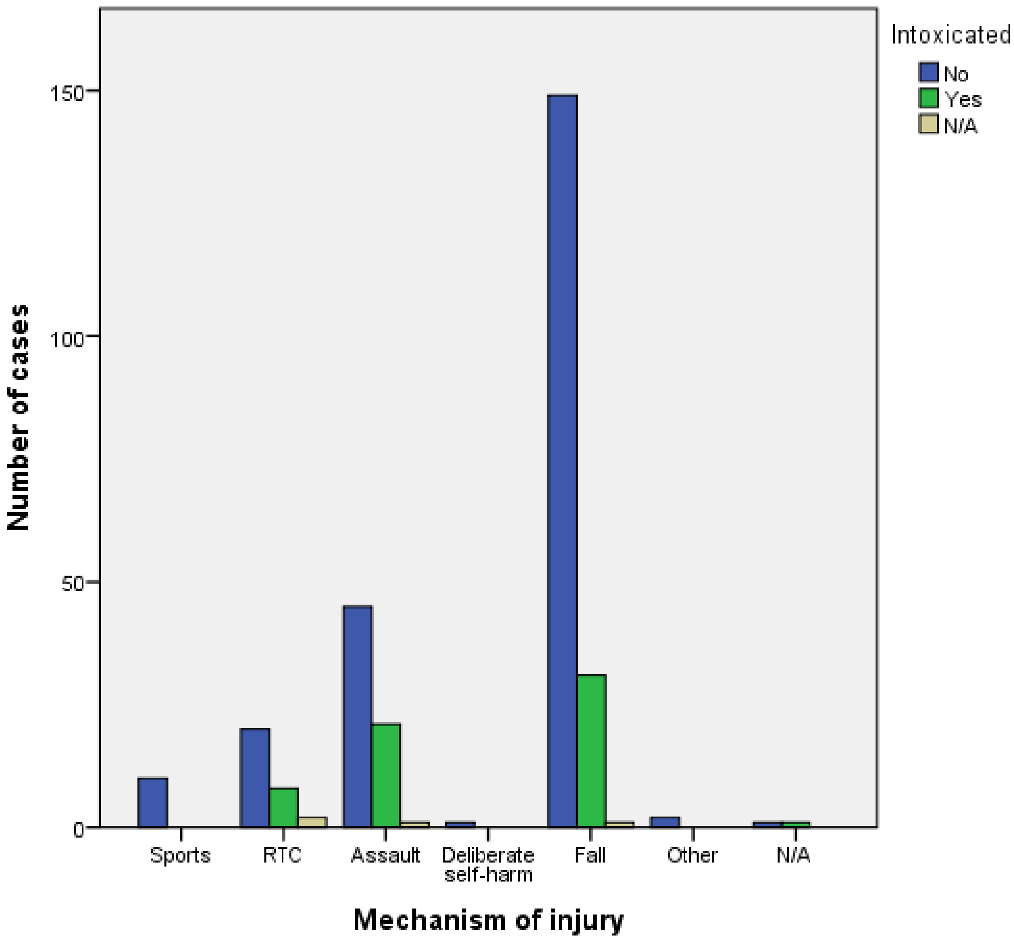

Figure 3. Mechanism of injury with levels of intoxication upon admittance to A&E

Of all the individuals attending the A&E department under the influence, 50.8% were due to a fall, 34.4% from assaults, and 13.1% from RTCs (Figure 3).

Discharge methods

The majority of patients were discharged following their initial assessments in A&E (76.1%), 14% of patients were admitted to the hospital wards for further observation, and two patients were referred to external centres. Combining this data with GCS, the majority of the discharge patients had mild TBIs (91.9%) with 1.3% having moderate severity injuries. For the patients who were admitted, the majority had a mild TBI (75.6%) with 4.9% presenting a moderate TBI and 7.3% having a severe TBI. The two patients who were referred to an external centre, both had mild TBIs.