The effects of person-centred active rehabilitation on symptoms of suspected Chronic Traumatic Encephalopathy: A mixed methods single case design.

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The effects of person-centred active rehabilitation on symptoms of suspected Chronic Traumatic Encephalopathy: A mixed methods single case design.

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“So let it be said that light will be shed when our world is led by leaders ahead of the headlines. These voices who are first on the front line, these women who stand up knowing the wind not by where it is, but by where it is blowing, leading worlds not by how society is, but by where change is going.”

- Amanda Gorman, *We Rise*

Abstract

Background: For almost a century, cases of former contact sport athletes who have developed cognitive impairments, changes in mood/behaviour, or motor dysfunction have been reported within scientific journals and major news outlets. In 2015, Chronic Traumatic Encephalopathy (CTE) was established as a unique neurodegenerative pathology linked to the repeated exposure to mild traumatic brain injury. Due to the observed long-term effects, multiple generations of former athletes are at-risk of developing symptoms of CTE. With no pathology-led intervention yet established, these athletes remain vulnerable and unsupported.

Aim: The aims of the thesis included (1) to establish the potential for active rehabilitation as an intervention strategy for the management of symptoms associated with suspected CTE, and (2) to equally consider evidence-based medicine (EBM) and person-centred care (PCC) when designing and evaluating a programme for the management of suspected CTE.

Methods: An umbrella review was carried out to examine the effect that active rehabilitation had on symptoms of tauopathies. Six mixed-method n-of-1 studies were carried out to assess the effect that a person-centred active rehabilitation programme had on symptoms of suspected CTE.

Results: The umbrella provided preliminary evidence to support the use of active rehabilitation in the management of tauopathies, with specific implications for the management of suspected CTE. A key observation was the positive effect of active rehabilitation on motor and cognitive symptoms in tauopathies. The mixed methods single case series provided preliminary evidence of a positive effect on some symptoms of suspected CTE. A positive effect was primarily seen in cognitive functioning, with mood and behavioural symptoms (e.g., anxiety, depression, loneliness, irritability, and insomnia) largely reporting a mix of positive and inconclusive effects.

Conclusions: For the first time, this thesis has offered preliminary evidence which suggests active rehabilitation may offer some benefit to individuals with symptoms of suspected CTE. This is supported by the findings of a one-year observational study which demonstrated positive effects across a range of symptoms utilising a person-

centred rehabilitation approach. Further, this thesis has illustrated the benefit of PCC in clinical research and practice.

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This thesis is dedicated to all my athletes and patients, past present and future, whose well-being I will always put first. Your friendship and your stories have always mattered to me.

List of abbreviations

Abbreviation	Definition
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognitive section
ADD	Attention-deficit disorder
ADS-6	Amsterdam Dementia Screening Test 6
ATC	Athletic Training Certified
AU	Arbitrary units
BBS	Berg Balance Scale
BDNF	Brain-derived neurotrophic factor
BNT	Boston Naming Test
BITe	Brief Irritability Test
CANTAB	The Cambridge Neuropsychological Test Automated Battery
CBD	Corticobasal degeneration
CBT	Cognitive behavioural therapy
CDT	Clock drawing test
CISG	Concussion in Sport Group
CTE	Chronic Traumatic Encephalopathy
EBM	Evidence-based medicine
ERFC	Rapid Evaluation of Cognitive Functions test
ESQ	Executive Skills Questionnaire
FACS	Functional Assessment of Communication Skills
FGA	Functional Gate Assessment
FoG	Freezing of Gait
FTD	Frontotemporal degeneration/dementia
GAD	Generalised anxiety disorder
GMHAT	Global Mental Health Assessment Tool
HAQ-DI	Health Assessment Questionnaire-Disability Index
HIIT	High-intensity interval training
HVLT	Hopkins Verbal Learning test
H&Y	Hoehn & Yahr scale
ICD-10	International Classification of Diseases-10
IGF-1	Insulin-like growth factor
JBI	Joanna Briggs Institute
LBD	Lewy Body dementia
MAAS	Mindful Attention Awareness Scale
MCI	Mild cognitive impairment
MMSCR	Mixed methods single case research
MMSE	Mini-Mental State Exam
MoCA	Montreal Cognitive Assessment
mTBI	Mild traumatic brain injury
NAP	Non-overlap of all pairs
NFL	National Football League
NFT	Neurofibrillary tangle
NHS	National Health Services
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NINDS	National Institute of Neurological Disorders and Stroke

PCC	Person-centred care
PCS	Post-concussion syndrome
PD	Parkinson’s disease
PDD	Persistent depressive disorder
PICO	Participant-Intervention-Comparison-Outcome
PIS	Participant
PPCS	Persistent post-concussive symptoms
PROMIS	Patient-reported outcomes measurement information system
PSS	Perceived Stress Scale
PTSD	Post-traumatic stress disorder
P-Tau	Phosphorylated microtubule-associated tau proteins
QCS	Qualitative case study
RPE	Ratings of perceived exertion
SCED	Single case experimental design
SMD	Standardised mean difference
SMT	Split-middle trend
SLUMS	Saint Louis University Mental Status
SPPB	Short Physical Performance Battery
TBI	Traumatic brain injury
TES	Traumatic Encephalopathy Syndrome
TUG	Timed Up and Go
UPDRS	Unified Parkinson's Disease Rating Score
WC-SMD	Within case standardised mean difference
6mWT	6-minute walk test

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1 Chapter 1: Introduction

1.1 Context of the thesis

1.1.1 Historical context: identifying the link between contact sport participation and neurodegeneration

Identifying and understanding the link between repeated head impacts (particularly within a contact sport setting) and long-term consequences to brain health has become a priority in the field of sports and exercise medicine. An association between repetitive head impacts linked with contact sport participation and an interruption of neurological processes leading to motor impairment, cognitive dysfunction, and changes in personality dates to at least 1928 when Dr. Harrison Martland published the findings from 23 cases of former boxers (Martland, 1928 cited in Changa et al., 2018; Smith et al. 2019; Solomon, 2018; Solomon and Zuckerman, 2015). He described a condition he termed ‘punch drunk syndrome’ in which boxers had developed:

> ‘Tremor, incoordination, extrapyramidal and other Parkinsonian symptoms’ and cognitive changes ranging from ‘slight mental confusion’ to ‘marked mental deterioration... requiring commitment to an asylum’ (Martland, 1928 cited in Solomon and Zuckerman, 2015:165).

In 1937, lieutenant J. A. Millspaugh published a description of ‘dementia puglistica’ where he presented his observations of a cohort of naval boxers. He noted cognitive dysfunction, dementia, and disorientation (Changa et al., 2018). In 1969, Dr. Anthony Herber Roberts published a book detailing the prevalence of a syndrome now termed Chronic Traumatic Encephalopathy (CTE) in 224 randomly selected retired boxers. He concluded that 17% of them exhibited the stereotypical clinical pattern associated with CTE (see subsection 2.3.2 for present day clinical patterns). Further, of the individuals who fought in over 150 fights during their career, 50% of them met the criteria (Changa et al., 2018; Smith et al. 2019). In 1973, Corsellis and colleagues presented neuropathological evidence of protein deposition and cerebral degeneration in 15 retired boxers. Alongside this neuropathological evidence, symptoms of motor impairment, cognitive dysfunction, and changes in personality were reported (Changa et al., 2018; Smith et al. 2019; Solomon, 2018). It wasn’t until

2005 that evidence of a potential link between exposure to repetitive head impacts and long-term brain impairment was presented in a sport other than boxing. This was established with Omalu's 2005 publication in which he identified CTE in a former National American Football League (NFL) player (Changa et al., 2018; Solomon, 2018). This discovery served as a primary catalyst for the modern-day research interest. In addition to American football, CTE has now been identified in former football, rugby, ice hockey, baseball, and wrestling athletes, as well as military personnel and domestic abuse victims (McKee et al., 2016; Smith et al., 2019; Stewart, 2021).

In 2015, CTE was established as a unique neurodegenerative condition linked to a repeated exposure to mild traumatic brain injury (mTBI) (see subsection 2.3.1 for definition) (McKee et al., 2016) by the National Institute of Neurological Disorders and Stroke/National Institute of Biomedical Imaging and Bioengineering (NINDS/NIBIB) consensus panel. This panel sought to provide evidence that CTE was a distinct neuropathological condition and to define its' pathological criteria (see subsection 2.3.1 for further information). Despite this established criterion, understanding of the observed association between exposure to repeated mTBI, contact sport participation, and development of impaired brain health remains limited and lacks consensus (LoBue et al., 2020; LoBue and Cullum, 2020; Smith et al., 2020; Stewart, 2021). As knowledge and understanding of the acute consequences of mTBI has grown, particularly within the context of sport, the interest in its' long-term implications has subsequently become a key focus. The advancements in research and understanding in this area have been slow, primarily due to a lack of comprehensive pathophysiological or epidemiological understanding of the causal link observed between exposure to repeated mTBI and the development of CTE. This means that while a causal relationship between exposure to repetitive mTBI, participation in contact sport, and the potential development of symptoms related to neurodegeneration has been observed, it has yet to be clearly and adequately defined (LoBue et al., 2020; LoBue and Cullum, 2020; Smith et al., 2020; Stewart, 2021). Subsequently, some research groups have called for caution when interpreting CTE research: while they acknowledge the presence of CTE as a distinct neuropathological condition linked to the exposure of mTBI, it is just one condition to

be considered within a much broader evaluation of the long-term consequences regarding a history of exposure to contact sport and mTBI (Smith et al., 2019; Stewart, 2021). Further, the idea that CTE is a progressive neuropathological condition leading to the eventual development of dementia has been called to question (Smith et al., 2019). It has been suggested that exposure to traumatic brain injury (TBI) serves as just one of many risk factors to be considered (LoBue et al., 2019; LoBue and Cullum, 2020; Stewart, 2021). It has been theorized that exposure to TBI or mTBI may simply increase the risk of developing dementia in populations already considered at-risk, or that the onset of neurodegenerative symptoms may be accelerated because of this exposure (LoBue et al., 2019; LoBue and Cullum, 2020).

Other groups, comprised of researchers and clinical experts, have proposed there is a lack of strong evidence available and therefore challenges the notion that motor impairment, cognitive dysfunction, or personality changes occur in former athletic populations at rates higher than those observed in the general population (Solomon, 2018). It should be noted that select researchers who promote this claim, at the time of writing, have been accused of plagiarism (Kemp and Davey, 2022) and clinical misconduct – specifically, accusations of downplaying the long-term effects of exposure to mTBI (Casper et al., 2021), withholding research results (Davey et al., 2022a), and influencing research publication (Davey et al., 2022b). Similar accusations of misconduct have been alleged against previous groups that published research contesting a need for more conservative protocols regarding the management of sports-related mTBI (Coates, 2013; Kaplan, 2020). Sports leagues and organizations (such as NFL, National Hockey League, World Rugby, Rugby Football Union, and Australian Football League) that have followed this less conservative advice have been involved, or are currently involved, in multi-million-dollar lawsuits (Magowan, 2020; McCann, 2016; McCann, 2018; Ingle, 2021; Kemp, 2021). Any references by these authors did not have a significant effect on the synthesis of this study. Any publications written by this research group, or by authors associated with this research group, that were included in this thesis were used as a secondary source of information or to present and discuss the concussion in sport consensus statements that have been widely and globally adopted across multiple sporting leagues (Bull, 2020a).

1.1.2 Modern context: present-day cases of CTE

Despite the lack of consensus regarding the consequences of participation in contact sport and its effect on long-term brain health, nearly a century after the punch-drunk syndrome was first described cases continue to be documented. Reporting of some cases have now moved from the pages of research publications and into the headlines of major news outlets (Bilyk, 2016; Burke, 2021; Conway, 2014; Conway, 2015; Graziano, 2016; ESPN E60: Hilinski's Hope, 2020; 30 for 30: Seau, 2018). The death of former NFL player Tiaina Baul 'Junior' Seau in 2012 marked a major turning point in the societal understanding and attitude towards contact sport and mTBI in the United States. While there had been some awareness of a potential link between American football and neurodegeneration over the preceding decade, nothing shocked the United States quite like the death of Seau.

Seau was universally beloved. He was *THE* commercial darling. Often described as the greatest line-backer in the history of the NFL, Seau transcended the game and became a pop culture icon (Burke, 2021). This was largely thanks to his warm, friendly, and energetic demeanour. Every teammate, every coach, and every fan was met with, "Hey buddieee!" and that huge, infectious smile. Everybody adored him, he made it impossible not to (30 for 30: Seau, 2018).

A fan sign honouring the late Junior Seau at a San Diego Chargers game.

Source: Stephen Dunn/Getty Images

Following his retirement, things went downhill. Seau began to withdraw from his family and businesses – completely uncharacteristic of the formerly known hard-working and hyper-involved Seau. He became violent, aggressive, and easily provoked. At one point, he was charged with domestic abuse against his then girlfriend. He started making reckless business and financial decisions, was gambling heavily, and became dependent on alcohol (30 for 30: Seau, 2018). There is speculation that Seau attempted suicide once before, driving his car off a cliff. Then, on 2 May 2012, Junior Seau was found dead in his home. He shot himself in the chest, believed by others to indicate the desire for his brain to be investigated (as was stated in a note left by Dave Duerson, another former NFL player who shot himself in the chest). A post-mortem examination confirmed the presence of CTE (Burke, 2021; 30 for 30: Seau, 2018).

The story of Junior Seau is complex and heart-breaking; however, it should be understood that while his story stands out, it's certainly not unique. The same year as

Seau's suicide, former NFL players Jovan Belcher (age 25 years) murdered his girlfriend and the mother of his three-month-old daughter before taking his own life at his team's training facility. He did so in front of both the Kansas City Chiefs coach and the general manager (Conway, 2014). In the years that followed, other American football players were in the news: in 2013 Paul Oliver, who reportedly struggled with chronic headaches and depression, died by suicide. He shot himself in front of his family (Bilyk, 2016). Adrian Robinson took his own life in 2015 (Conway, 2015), and Tyler Sash died by accidental overdose following a history of substance abuse (Graziano, 2016). In 2017, the staggering story involving Aaron Hernandez, the New England Patriots player who was dropped from the team following his arrest and eventual conviction of double homicide, took his own life at the beginning of his jail sentence (Boston Globe Spotlight Team, 2018). And in 2018, Tyler Hilinski, the 21-year-old quarter back from Washington State University, took his own life following months of abnormal and erratic behaviour (ESPN E60: Hilinski's Hope, 2020). At the time, society appeared numb to the news of former NFL players, but this was different. He was so young.

Tyler Hilinski, quarterback for the Washington State Cougars.

Source: Chris Williams/Icon Sportswire/Getty Images

Concerns regarding the long-term risks associated with contact sport participation is not unique to the United States either. Better known as ‘the King’ by West Brom supporters, Jeffery Astle led the club to its last ever FA Cup victory. Thirty-four years later, in 2002, he died not knowing he had ever even been a footballer. According to the coroner's report, Astle’s death was caused by industrial disease: his brain damaged by years of heading a tough and heavy leather football (Bull, 2021). There had been decades of anecdotal evidence suggesting such a link, but Astle served as the first tangible case of such consequences within the United Kingdom.

Jeff Astle goal celebration during the 1968 FA Cup Final.

Source: Mike McLaren/Central Press/Hulton Archive/Getty Images

Once again, the story of Jeffrey Astle is not unique, and this concern has only continued to spread globally in recent years. Other English football ‘greats’ who are suffering with or have died from early onset or mixed dementia believed to be linked to the repetitive exposure to mTBI as a result of participation in contact sport include Bobby Charlton, Jack Charlton, Nobby Stiles, Ray Wilson, and Denis Law (PA Sport Staff, 2021). Steve Thompson, former Rugby Union World Cup winner, doesn’t remember any of the 2003 World Cup games. At age 43 years, he has been diagnosed with early onset dementia and has been placed on suicide watch on at least one occasion (Al-Samarrai, 2022). And finally, Australia has been the latest country forced to address the long-term consequences of contact sport. Andrew Macpherson, a former amateur Australian football player, took his own life in February of 2022. His family reported that for at least two years prior, they had noticed obvious changes in his behaviour and personality. He was gambling heavily, struggled with

alcohol abuse, and became socially isolated. This comes after a string of professional Australian athletes have begun preparing for their own litigation battles to seek post-career medical assistance (Kemp and Davey, 2022).

1.1.3 Personal context: a word from the author

In 2018, the same year Tyler Hilinksi died, I was working with my first American football team as a certified athletic trainer (ATC): an allied healthcare professional qualified to prevent, examine, diagnose, treat, and rehabilitate emergency, acute or chronic injuries and medical conditions. Prior to this, I spent five years as a student working with three different American football teams. I have always had a deep-seeded passion for American football and its' athletes. It has always been, and will always be, my preferred work setting.

Some of the athletes I have previously worked with are now playing for high level university teams, like Tyler Hilinski did. Others are in the NFL, like Junior Seau was. And every day I fear that one of their names will be the next headline. When I took on the qualification of an ATC, I promised to advocate for the best interests of my athletes. I promised to provide thoughtful, compassionate, and high-quality health care. Now, here is a pathology which my athletes are at high risk for, and I had no answers for them. I felt an innate need and tremendous responsibility to change that. So, just like any other evidence-based approach to prevention and intervention, I went to the literature to see what potential answers might exist that fell within the scope of my practice. Those ideas served as the foundation and inspiration for the conception of this thesis.

1.2 Thesis overview

1.2.1 Aims and objectives

The aims of the thesis are:

1. To establish the potential for active rehabilitation as an intervention strategy for the management of symptoms associated with suspected CTE

2. To equally consider evidence-based medicine (EBM) and person-centred care (PCC) when designing and evaluating a programme for the management of suspected CTE

To achieve the aims outlined above, the following objectives were set:

1. To examine the existing evidence of the effect that active rehabilitation has on the recovery from mTBI, a review of the literature was presented (Chapter 2)
2. To examine the existing evidence on the effect that active rehabilitation has on symptoms associated with suspected CTE in other tauopathies, an umbrella review was carried out (Chapter 3)
3. To observe the effect that a person-centred active rehabilitation programme had on participant symptoms associated with the development of suspected CTE, an n-of-1 study was conducted (Chapter 5)
4. To provide an element of PCC within the intervention and the research design, mixed methods single case research (MMSCR) was conducted (Chapter 5)

1.3 Chapter summaries

1.3.1 Chapter 2

The aim of chapter two is to define what a tau pathology is before discussing the neuropathology of CTE. A present understanding of mTBI and how this links to the development of long-term brain impairment is also discussed. The identification and symptomatology of CTE is then presented. Finally, a summary of the current management options for CTE and mTBI is presented.

1.3.2 Chapter 3

The aim of chapter three is to examine the evidence regarding the directionality and magnitude of the effect that active rehabilitation has on symptoms of suspected CTE observed in other tauopathies. The effect of active rehabilitation on symptoms of cognitive function, motor function, functional mobility, gait speed/velocity, and balance are presented. The implications for CTE management are then discussed.

1.3.3 Chapter 4

The aim of chapter four is to outline the methodology for a series of n-of-1 studies investigating the effect that active rehabilitation has on the symptoms of individuals with suspected CTE. Methodology rooted in pragmatism and person-centred care (PCC) is discussed. Further, methods for visual and statistical analysis are presented. Finally, methods for qualitative analyses and integration of semi-structured interviews are presented.

1.3.4 Chapter 5

The aim of chapter five is to present the results of a series of single case studies. The effect that a person-centred active rehabilitation programme had on symptoms of cognitive function, executive function, attention, anxiety, depression, loneliness, irritability, and sleep quality across six cases was presented. Attention to contextual information and intervention prescription was given when interpreting and presenting the results.

1.3.5 Chapter 6

The aim of chapter six is to discuss the results across the entire thesis with a specific focus on the effect that active rehabilitation had on symptoms associated with suspected CTE, consideration of the various active rehabilitation modes, consideration of the various outcome measures included, and the usefulness of understanding the contextual factors that influenced the results of the mixed methods single case research (MMSCR) study were presented. The implications of these results for clinical practice as well as implications for future research were also discussed.

2 Chapter 2: Literature review

2.1 Chapter overview

Chapter one laid out the context for this study and established the reported effect that CTE has had on former contact sport athletes for almost a century. Chapter one also noted the lack of consensus regarding a pathophysiological understanding between exposure to contact sport, repetitive brain injury, and the later development of a neurodegenerative pathology. Chapter two first seeks to define tau, accompanied by discussion of tau pathology. Following this, the neuropathology of CTE is presented with discussion of how this links to the present understanding of mTBI. Identification and symptomatology of CTE is then presented. Finally, a summary of the current management options for CTE and mTBI is presented.

2.2 Tau pathology

Phosphorylated microtubule-associated tau proteins (p-tau) are a group of proteins that contribute to neural health and normal functioning. Tau stabilizes microtubules which provide shape and structure to neural axons, dendrites, and synapses (Imbimbo et al., 2022; Orr et al., 2017). It has also been found to aid in axonal transport, synaptic transmission, cytoskeletal regulation, and proteostasis (Imbimbo et al., 2022; Kneynsberg et al., 2017). Tau has a reversible hyperphosphorylation capability which provides neural protection and regulation; however, this capability can also serve as a catalyst for neurodegeneration in a group of pathologies collectively termed tauopathies (Orr et al., 2017; Kneynsberg et al., 2017).

The development of pathogenic tau formulation has been associated with irreversible hyperphosphorylation and the disruption of microtubule stability as illustrated in Figure 1 (Imbimbo et al., 2021). It remains unclear in what order this occurs or what the specific pathophysiology is (Imbimbo et al., 2021), but factors such as genetics, metabolic syndromes, or exposure to brain injury are believed to trigger the formation of this pathogenic tau (Imbimbo et al., 2022; Kneynsberg et al., 2017; Orr et al., 2017). As hyperphosphorylation continues, tau may be released and relocate to neural synapses (Tracy et al., 2022). This translocation allows for the further spread

and eventual accumulation of pathogenic tau, eventually leading to neural cell death and atrophy of several brain regions characteristic of diseases such as Alzheimer's disease (AD), Corticobasal degeneration (CBD), Frontotemporal degeneration/dementia (FTD) Lewy Body disease (LBD) and Parkinson's disease (PD) (Orr et al., 2017; Tracy et al., 2022).

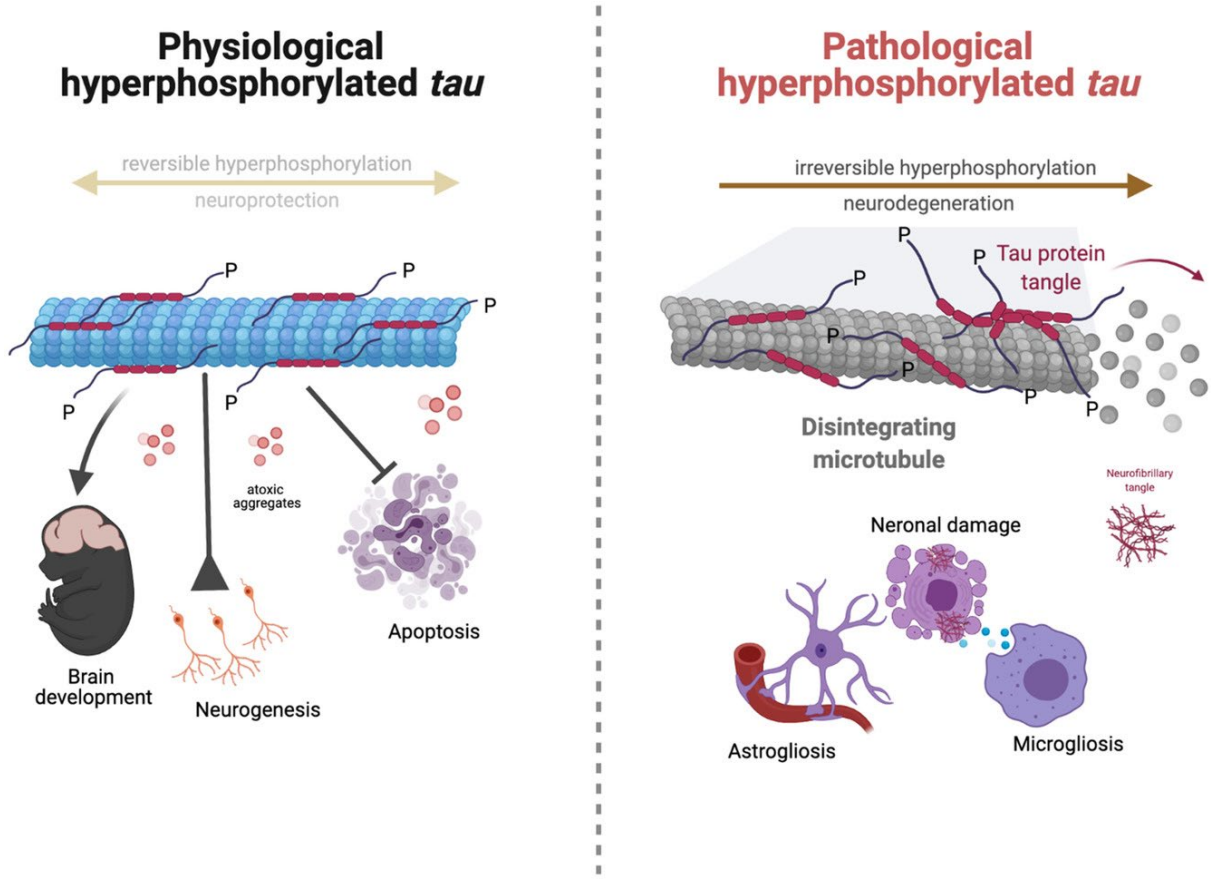


Figure 1. Physiological versus pathological tau protein.

Source: Imbimbo et al., 2022:1012.

2.3 Chronic Traumatic Encephalopathy

2.3.1 Neuropathology of CTE

CTE is a neuropathology defined by a unique, irregular pattern of tau protein accumulation in neurons, and sometimes in astrocytes, around small blood vessels at the base of the cortical sulci. These aggregates are found mainly in the superficial

layers of the frontal, temporal, and parietal cortices, but typically spread through the cerebral cortex, medial temporal lobe, amygdala, hypothalamus, thalamus, and brain stem in later stages of development (Bieniek et al., 2021; McKee et al., 2016). Figure 2 illustrates the brain of a former American football player whose autopsy identified CTE compared to that of a healthy brain. Additional features of CTE examined with autopsy include (Bieniek et al., 2021; McKee et al., 2016):

- Neurofibrillary tangles (NFT) in gyral side, gyral crest, superficial cortical laminae, hippocampus, entorhinal cortex, amygdala, thalamus, mammillary body, and cerebellar dentate nucleus
- Macroscopic features: disproportionate dilatation of the third ventricle, septal abnormalities, mammillary body atrophy, and contusions or other signs of previous traumatic injury
- TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex. and amygdala

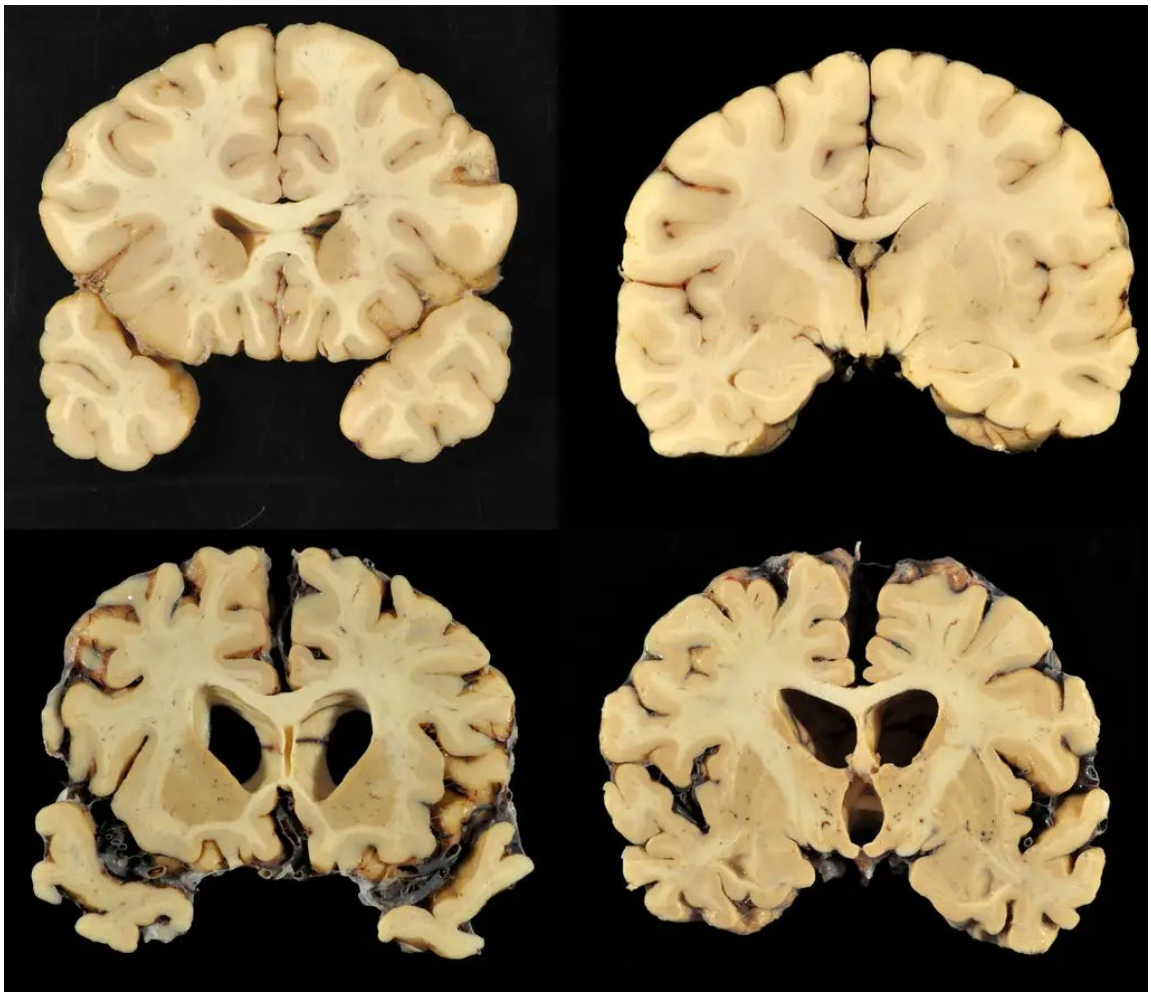


Figure 2 Healthy brain (top) versus brain with CTE (bottom)

Source: Ann McKee/Boston University.

There is no consensus on the pathophysiology of CTE, but there is agreement that exposure to TBI, including mTBI, is a major risk factor (Bieniek et al., 2021; Cantu and Budson, 2019; Katz et al., 2021; McKee et al., 2016; Montenigro et al., 2014; Pierre et al., 2021). MTBI's are the consequence of impacts to the head which result in acceleration-deceleration forces (forces may be linear or rotational in nature). These forces are subsequently transferred to surrounding brain tissues (Carter et al., 2021; Dech et al., 2019). Acutely, mTBI causes shearing and stretching of cytoskeletal structures including neurons, glia, vasculature and extracellular matrix which may lead to an 'acute neurometabolic cascade' of disruption to neuroanatomic, neurotransmitter, neurometabolic, inflammatory, and vascular processes (Carter et

al., 2021; Dech et al., 2019). It is suggested that this cascade may then lead to impaired cerebral blood flow, disruption of energy production, promotion of neuroinflammation, and impaired neurotransmission (Carter et al., 2021; Dech et al., 2019) resulting in physical symptoms (headaches, dizziness, etc.), emotional symptoms (anger, depression, etc.), cognitive impairment (memory, concentration, etc.), and sleep disturbance (sleeping too much, too little, etc.) (Carter et al., 2021).

2.3.2 Identification of CTE

Currently, CTE can only be diagnosed post-mortem (Cantu and Budson, 2019; Katz et al., 2021; Montenigro et al., 2014; Pierre et al., 2021); therefore, much work has been done to establish a set of clinical features to aid in identifying potential CTE in people at risk. Table 1 illustrates signs and symptoms of CTE that have been reported in the literature.

Table 1. Symptoms reported in the literature to be associated with Chronic Traumatic Encephalopathy (CTE)

Cognitive	Mood	Behaviour	Motor	Vestibular
• Dementia • Impaired memory • Impaired attention • Impaired concentration • Executive dysfunction • General cognitive impairment • Dysgraphia • Alogia	• Depression • Hopelessness • Loss of interest • Anxiety • Fearfulness • Aggression • Irritability • Mood swings • Apathy • Fatigue • Insomnia • Suicidality	• Physical violence • Verbal violence • Inappropriate behaviour • Explosivity • Short fuse • Loss of control • Disinhibition • Impulsivity • Personality changes • Paranoid delusions • Social isolation	• Dysarthria • Ataxia • Gait disturbance • Parkinsonism • Muscle tremor • Clonus • Muscle rigidity • Muscle weakness • Muscle spasticity • Masked facies	• Balance impairments • Visuospatial difficulty • Blurred vision • Double vision • Dizziness

Sources: Cantu and Budson, 2019; Montenigro et al., 2014.

Traumatic Encephalopathy Syndrome (TES), first established by Montenigro and colleagues (2014), is the clinical criteria widely used for research purposes. The criteria outlined by Montenigro et al. (2014) does not result in a diagnosis of CTE, but failure to meet these criteria indicates the presence of CTE is highly unlikely (Cantu and Budson, 2019). It was not until 2021 that this criterion was updated, presented by Katz and colleagues (2021). The updated criterion further defined cognitive impairment and now specifies the need for evidence of impairment to episodic memory or executive functioning. Neurobehavioral dysregulation was also further defined and now includes symptoms of rage, emotional lability, or mood swings as core clinical features. Finally, symptoms must demonstrate a progressive worsening over a 12-month period (Katz et al., 2021). Depression is now considered a supportive feature rather than a core clinical feature. Other supportive features include anxiety, apathy, paranoia. In this updated criterion, motor features were more clearly defined and include Parkinsonism (bradykinesia, rigidity, rest tremor, and parkinsonian gait disorder), signs of motor neuron disease (weakness, dysphagia, fasciculations, muscle atrophy, spasticity, hyperreflexia, extensor plantar response, and spastic dysarthria), dysarthria, ataxia, and imbalance. Finally, delayed onset is a requirement in the updated criterion rather than a supportive feature (Katz et al., 2021). Table 2 outlines the five criteria for demonstrating the presence of TES as presented by both Montenigro and colleagues (2014) and Katz and colleagues (2021).

Table 2. Traumatic Encephalopathy Syndrome

Broad Criteria	**Montenigro et al., 2014**	**Katz and colleagues, 2021**
History of multiple head impacts (direct or indirect)	Four mTBI (concussion) Two moderate/severe TBI Six or more years of exposure to subconcussive trauma (contact sport, military service, domestic abuse)	Five or more years of participation in contact or collision sport American football requires at least two years at high school level* Military service or other sources of multiple head impacts (e.g., domestic abuse, head banging, vocational activities) for extended period of time (threshold not established)
No other neurological disorder present that likely account for all clinical features Can have comorbid diagnosis of substance abuse, post-traumatic stress disorder (PTSD), mood/anxiety disorders, or other neurodegenerative diseases		
Timeline of 12 months	Signs/symptoms must be present for a minimum of 12 months	Evidence of progressive worsening over at least 12 months
Presence of at least one core clinical feature	**Cognitive:** self-reported and difficulties in cognition substantiated by impairment on standardized tests **Behaviour:** explosive, short fuse, out of control, physically and/or verbally violent, intermittent explosive disorder **Mood:** feeling overly sad, depressed, hopeless, persistent depressive disorder	**Cognitive:** self-reported (or clinician's report) and difficulties in cognition substantiated by impairment on standardized tests; deficits in episodic memory or executive functioning must be reported **Neurobehavioral dysregulation:** self-reported (or clinician's report); poor regulation or control of emotions/behaviour (explosiveness, impulsivity, rage, violent outbursts, short fuse, emotional lability)

Supportive features	*Presence of at least two supportive features* Impulsivity Anxiety: anxious mood, agitation, excessive fears, obsessive or compulsive behaviour Apathy: loss of interest in usual activities, loss of motivation, loss of emotions Paranoia Suicidality Headache: Significant and chronic headache; one episode per month for minimum of six consecutive months Motor features: Dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, Parkinsonism Progressive, documented decline of at least 12 months Delayed onset of core feature after significant head impact exposure, usually two or more years	*Presence of at least three supportive features* **Delayed onset** **Motor signs:** • Parkinsonism, bradykinesia, rigidity, rest tremor, parkinsonian gait, disorder, dysarthria, ataxia, imbalance, Weakness, dysphagia, other lower motor neuron signs, diagnosis of amyotrophic lateral sclerosis **Psychiatric features** • Anxiety: pervasive worries, excessive fears, agitation, obsessive or compulsive behaviour • Apathy: loss of interest in usual activities and loss of motivation or drive • Depression: overly sad, dysphoric, hopeless; with or without suicidal thoughts or attempts • Paranoia: delusional beliefs of suspicion, persecution, or unwarranted jealousy

TBI: traumatic brain injury; mTBI: mild TBI.

*Based on clinical judgement with minimal evidence Sources: Cantu and Budson, 2019; Katz and colleagues, 2021; Montenigro et al., 2014.

2.3.3 Management of CTE

Currently, treatment options for CTE are supportive in nature (Cantu and Budson, 2019; Pierre et al., 2021) meaning therapies and medication are prescribed with the intention of increasing patient quality of life and decreasing patient discomfort. While tauopathy specific intervention and treatment options are still under investigation, Khanna and colleagues (2016) have provided a review of target strategies, many of which include the use of pharmacology. These include identifying inhibitors of the kinases which catalyse tau phosphorylation, inhibition of tau acetylation, proteolytic processing, fibrillization of tau, improving cellular proteostasis, modulating tau expression, decreasing microtubule dynamics, and using tau immunotherapy (Khanna et al., 2016). However, which enzymes to target and what adverse effects may occur have yet to be fully understood.

To the author's knowledge, no primary level research has been conducted to investigate the effects that an intervention has on populations of suspected or probable CTE. Recommended supportive therapies include cognitive rehabilitation therapy, mood and behaviour therapy, mindfulness, and attention to diet (particularly a Mediterranean diet). Motor therapy, vestibular rehabilitative therapy, occupational-ocular therapy has also been recommended (Cantu and Budson, 2019; Pierre et al., 2021). Finally, exercise has been recommended due to its success with treating memory disorders, stroke, post-concussion syndrome (PCS), and moderate-severe TBI (Cantu and Budson, 2019; Pierre et al., 2021).

2.4 Recovery guidelines for mild traumatic brain injury

As mentioned previously, mTBI is considered a major risk factor in development of CTE. In sport, for many decades, total rest was considered the best practice for managing mTBI, suggesting it promoted recovery from symptoms while simultaneously reducing the risk for further head injury (Carter et al., 2021; Reid et al., 2021). Recent research has challenged this notion, with consensus and best practice guidelines now beginning to promote the idea that low levels of physical and cognitive activity are more beneficial for the recovery from acute mTBI compared to complete

rest. Several literature reviews and large scale randomised controlled trials have provided evidence indicating that both adult and adolescent populations who experienced mTBI and received active rehabilitation (including aerobic and multimodal activities) as a treatment option consistently reported a significant positive effect on symptom levels (Carter et al., 2021; Langevin et al., 2020; Leddy et al., 2018a; Leddy et al., 2018b; Reid et al., 2021). Further, the incidence of developing post-concussion symptoms (PCS) (those symptoms which do not resolve within a 'normal time frame', usually one month post injury) was significantly lower (Carter et al., 2021; Leddy et al., 2018a; Leddy et al., 2018b). There is some preliminary evidence to suggest that active rehabilitation can shorten the duration of returning to sport (Leddy et al., 2018a; Leddy et al., 2018b); however, further research needs to be done in this area to better establish that effect.

A full profile of the physiological effects from exercise which directly benefits the recovery from mTBI has yet to be established (Dech et al., 2019); however, there is evidence which suggests exercise has a general positive effect on the structural integrity and functional capacity of the brain. Structurally, increased volume or decreased atrophy have been observed in structures including the basal ganglion, hippocampus, white matter, and grey matter (Calverley et al., 2020). Exercise has a positive functional effect on the brain as well. Specifically, an extracellular effect of angiogenesis and an intracellular effect of neurogenesis is noted (Vorkapic et al., 2021). Cerebral blood flow is enhanced through the provocation of angiogenesis, increased cerebral perfusion, and enhanced vasoreactivity (Calverley et al., 2020). Increased cerebral blood flow subsequently increases the upregulation of neurotransmitters and synthesis of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1) (Calverley et al., 2020; Vorkapic et al., 2021). This enhances neurogenesis and neuroplasticity, promoting new cell growth which can successfully integrate into established neural networks. Neural communication and connectivity are improved as well. This is achieved through the promotion of synaptogenesis, as well as the enhancement of neuromodulation and neurotransmission (Calverley et al., 2020; Vorkapic et al., 2021).

Consensus statements and best practice guidelines have now begun to shift following evidence indicating that inactivity is, in fact, not the best treatment for individuals recovering from mTBI. Clinical guidelines established by the American Physical Therapy Association (APTA) and the American College of Sports Medicine (ACSM) Clinical Sports Medicine Leadership committee now recommend an initial period of rest (first 24-48 hours) followed by gradual return to activity based on tolerance (avoiding activities considered high risk for second impact) (Herring et al., 2021; Quatman-Yates et al., 2020). Other organizations are awaiting the highly anticipated consensus statement to be published after the International Consensus Conference on Concussion (CISG) in Sport due to take place in October 2022, which has not been updated since 2016. The current consensus statement acknowledges the potential for rehabilitation but refrained from providing any specific guidance and instead called for further research (McCrory et al., 2017).

The ACSM consensus statement does not offer specific methodology to indicate the types of articles considered in determining such recommendations, but it does indicate that the expert panel had unanimous agreement (Herring et al., 2021). Studies referenced in the consensus statement are not explicitly reported, but do include clinical guidelines and consensus statements, systematic reviews, randomised controlled trials, secondary analysis, and case studies (Herring et al., 2021). The APTA used a two-step approach in creating their consensus statement. The first stage was a preliminary search to determine what evidence was available. The second stage of the literature review indicated that any article peer-reviewed, deemed highly relevant, and considered of high-quality by independent experts in the field were considered for eligibility (Quatman-Yates et al., 2020). This consensus statement considered a wide range of studies, including but not limited to clinical guidelines and consensus statements, protocols, systematic reviews, observational studies, descriptive studies, randomized controlled trials, secondary analysis, and expert opinion (Quatman-Yates et al., 2020). Like the ACSM consensus statement, the CISG consensus statement utilised multiple expert panels to determine that relevance and eligibility of included research (Herring et al., 2021; Meeuwisse et al., 2017). In total, 202 abstracts were accepted for the conference and were considered for the consensus statements. Studies included randomised controlled trails,

observational studies, secondary analysis, and systematic reviews (Meeuwisse et al., 2017). As indicated by the three consensus statements which were referenced, future consensus statements will likely continue to consider a wide variety of research areas and methods as this area further develops.

3 Chapter 3: Umbrella Review

3.1 Chapter overview

Chapter two defined tauopathy and how the development of pathogenic tau can disrupt normal brain functioning. Chapter two also presented CTE, a tauopathy linked to the exposure to contact sport. Chapter three seeks to examine the evidence regarding the effect that active rehabilitation has on symptoms of suspected CTE observed in other tauopathies. The effect of active rehabilitation on symptoms of cognitive function, motor function, functional mobility, gait speed/velocity, and balance are presented. The implications for CTE management are then discussed.

3.2 Study rationale and aims

To the best of the authors' knowledge, no review to date has been conducted to determine if active rehabilitation is a management tool that can be applied broadly to patients suffering from tau pathology. Further, no studies have been published that establish an evidence-based intervention strategy precisely intended for the symptoms or processes of suspected CTE. Therefore, the purpose of this study is to establish the potential for active rehabilitation as an intervention strategy for the management of suspected CTE by performing an umbrella review, evaluating and appraising the evidence regarding the effect that active rehabilitation has on other tauopathies. The term 'active rehabilitation' is used here to differentiate between other forms of rehabilitation such as cognitive rehabilitation, vestibular rehabilitation, and neurorehabilitation. Rather than using terms such as 'exercise' and 'physical activity' solely, the term active rehabilitation indicates that an exercise-based programme has been designed with the intention of increasing levels of function in an individual. This is a term that has been referenced in other concussion and mTBI research articles, including Carter et al., 2021, Gauvin-Lepage et al., 2019, and Imhoff et al., 2016.

Undertaking an umbrella review will establish whether active rehabilitation is a successful management strategy across a range of tauopathies, subsequently addressing an evidence gap within the field of CTE interventions. The aims of the study were:

1. To examine the existing evidence on the effect that active rehabilitation has on symptoms associated with suspected CTE in other tauopathies.
2. To assess the potential for active rehabilitation as an intervention strategy for the management of symptoms in tauopathies, with specific implications for the management of suspected CTE.

Research objectives:

1. To achieve aims 1 and 2, an umbrella review was performed and evidence from systematic reviews and meta-analysis were evaluated for consistency and magnitude of effect.
2. To provide evidence of the implications for suspected CTE, the similarities across tauopathies as well as the underpinning physiological mechanisms that active rehabilitation may elicit were discussed.

3.3 Methods

To establish sound justification to explore a new intervention within an emerging field, a literature review design that employs a broad scope approach while still maintaining scientific rigor was necessary. An umbrella review includes, exclusively, systematic reviews and meta-analyses for analysis and seeks to provide evidence on effectiveness of an intervention by performing a complete appraisal of all available evidence and comparing findings across the reviews (Aromataris et al., 2015; Aromataris et al., 2020). Features such as the magnitude of the effect, consistency, and quality are considered (Aromataris et al., 2020). Analysis can be performed across a broad range of conditions, interventions, and outcomes (Aromataris et al., 2015; Fusar-Poli and Radua, 2018). The objective of an umbrella review is not to resynthesize the information presented in a systematic review nor to reanalyse the data available from primary sources. Rather, an umbrella review highlights whether the evidence within a body of literature is consistent and seeks to explore how or why the intervention does, or does not, work (Aromataris et al., 2015; Aromataris et al., 2020). This lends itself not only to broad eligibility criteria, but also broad

interpretation of the findings (analysis/discussion) (Aromataris et al., 2015; Aromataris et al., 2020).

This umbrella review was performed following guidelines set out by Aromataris and colleagues (2020) in association with the Joanna Briggs Institute (JBI). The guidelines recommend the following actions:

- Clearly state the objectives of the umbrella review
- Clearly define, a priori, eligibility criteria
- For those umbrella reviews seeking to assess the effectiveness of an intervention, provide a clearly stated Population-Intervention-Comparator-Outcome (PICO) element
- Comprehensively report search strategies
- Use a two-step screening process completed by two independent reviewers: i) examination based on title and abstract and ii) examination based on full text
- Provide relevant context of included studies
- Clearly define types of studies included
- Assess methodological quality off included studies, completed by two independent reviewers
- Extract data using standardised data extraction tool, completed by two independent reviewers
- Disagreements between independent reviewers are resolved by consensus or by the decision of a third reviewer
- Present results in a narrative format accompanied by a flowchart and a table of findings

3.3.1 Search strategy

A computerized systematic search of CINAHL, Medline, Cochrane, Web of Science, PubMed, and SPORTDiscus was completed using a database-specific search syntax as outlined in Table 3 for CINAHL, Medline, PubMed, and SPORTDiscus (see Appendix 1 for the search syntax of remaining databases). The search included sources from inception until October 2020.

Table 3. Information on literature search and selection criteria

Search and PICO	
Search syntax	(disease OR disorder OR symptom* OR dementia OR *degenerat*) AND (Alzheimer OR Parkinson OR “Lewy body” OR frontotemporal OR corticobasal) AND (therapy OR intervention OR treatment OR rehabilitation) AND (exercise OR "physical activity" OR "resistance training" OR "aerobic exercise" OR "balance training" OR walking OR sport OR yoga OR pilates) AND ("systematic review")
Population	Men and women diagnosed with Alzheimer’s disease, Parkinson’s disease, Lewy Body dementia, Frontotemporal degeneration/dementia, and/or Corticobasal degeneration
Intervention	Active rehabilitation of any type. Interventions that combined active rehabilitation with other techniques (e.g., pharmacological treatment + exercise) were excluded.
Comparator	Usual care, no intervention, light-intensity physical activity*
Outcome	Common symptoms associated with CTE (See Table 1, subsection 2.3.2)

*Light-intensity physical activity refers to activity that falls within 2-4 on a 0-10 rating of perceived exertion (RPE) chart and do not result in a substantial increase in heart rate or breathing rate (Bull et al., 2020).

The tauopathies AD, PD, LBD, CBD, and CBD were selected as the more commonly known tauopathies where tau is a primary feature. CTE was not included in the review as there is currently no primary level research for potential interventions on populations of suspected or probable CTE (see subsection 2.3.3). MTBI was not included as mTBI is not chronic in nature nor considered a tauopathy.

3.3.2 Eligibility criteria

Studies were included if the full-text was available and were peer-reviewed systematic reviews and/or meta-analyses that examined the efficacy of active rehabilitation in the management of common neurodegenerative diseases with tau aggregation. Only reviews written in English and with data presented in a way that could be extracted by the authors were included. Further inclusion criteria were defined according to the PICO process, included in Table 3.

The author and a supervisor independently screened the title, abstract, and full text for eligibility. If disagreement between reviewers occurred, a consensus eligibility method was used. A third reviewer was not needed as there was no circumstance in which a consensus could not be reached.

3.3.3 Quality evaluation

The author and a supervisor independently assessed the methodological quality of the included systematic reviews and meta-analyses using the JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses (Aromataris et al., 2020). Eleven factors were assessed for appropriateness or adequacy in relation to objectives, such as inclusion criteria, search strategy, appraisal strategies, analysis strategies, and conclusions drawn. A point was given for each component addressed, where the minimum and maximum of the total possible score was 0 and 11, respectively. Higher scores indicated higher levels of methodological quality. Discrepancies between reviewers were resolved through discussion and a consensus was reached without the need of a third reviewer.

3.3.4 Data extraction

Data was extracted independently by the author (RH) using the JBI Data Extraction Form for Review for Systematic Reviews and Research Syntheses (Aromataris et al., 2020). This included recording information on author, year of publication, country of origin, objectives, results, appraisal, appraisal instruments, appraisal rating, and other

relevant information on the primary level studies included in the review. The extracted data was checked by a supervisor for accuracy.

In addition to completing the JBI extraction checklist for each included review, for all eligible meta-analyses the SMD, 95%CI, and number of studies included were extracted. If a pooled effect was not available for a given study, a random effects model was run to calculate the missing values using the available mean, standard deviation, and number of participants for the intervention and control groups. This model was conducted using metagen in the metafor package in R (R Studio, Version 1.2.1335). This was done to reduce the number of excluded studies and maximise included data for subsequent analysis.

3.3.5 Statistical analysis

The results of the data syntheses were grouped by clinical features, as illustrated in Table 2 (see subsection 2.3.2). The magnitude of the effect of the intervention across all reviews was assessed as a pooled SMD, more precisely: Hedges *g* $=\frac{M_1-M_2}{SD*_{pooled}}$.

SMDs were classified according to Cohen's definition, with effect values interpreted as: 0.20-0.50, small; 0.51-0.80, moderate; >0.80, large (Cohen, 1988).

Variability of the intervention effect was assessed by 95%CI and a 95% prediction interval (95%PI). The 95%PI was calculated using the following formula: $\hat{\mu} \pm z_1 - \alpha/2 \sqrt{SE[\hat{\mu}]^2 + \hat{\tau}^2}$, where $\hat{\mu}$ is the estimated average true outcome, $z_1 - \alpha/2$ is the 100 x (1-a/2)th percentile of a standard normal distribution, $SE[\hat{\mu}]$ is the standard error of $\hat{\mu}$, and $\hat{\tau}^2$ is the estimated amount of heterogeneity. While the 95%CI presents the variation in the reported effect sizes accounting for the number of data points included in the random effects model, the 95%PI presents the range of the true effect size in a future study accounting for both uncertainty and random error (IntHout et al., 2016). As such, the 95%PI provides a more stable estimate in the SMD that clinicians and researchers can use accounting for possible uncertainly in the estimate due to sample sizes, population, and exercise modality as well the random error.

For each group (outcome measures), a pooled SMD (Hedges *g*) and 95% CI was calculated using a metagen random effects model in the metafor package in R (R Studio, Version 1.2.1335). Heterogeneity (I^2) was classified according to the Cochrane's definition (Deeks et al., 2021), with 0-40% considered likely not important, 30-60% representing a moderate level of heterogeneity, 50-90% representing a substantial heterogeneity, and 75-100% indicating considerable levels. A decision on whether heterogeneity was significant or not was based on the Cochrane Q statistic.

3.4 Results

3.4.1 Search results

The search identified 1,303 potential articles (Figure 3). After duplicates were removed, 774 titles were screened and 629 were excluded based on relevance or access to the article, leaving 145 abstracts to be screened for eligibility. Fifty-one abstracts did not indicate relevant outcome measures and/or intervention techniques as defined by the criteria set out in Table 3, leaving ninety-four articles. Eighty-two articles did not include extractable data and/or an appropriate control group as defined by the eligibility criteria in Table 3 (see subsection 3.3.1); therefore, a total of twelve articles were included for quality evaluation and data synthesis.

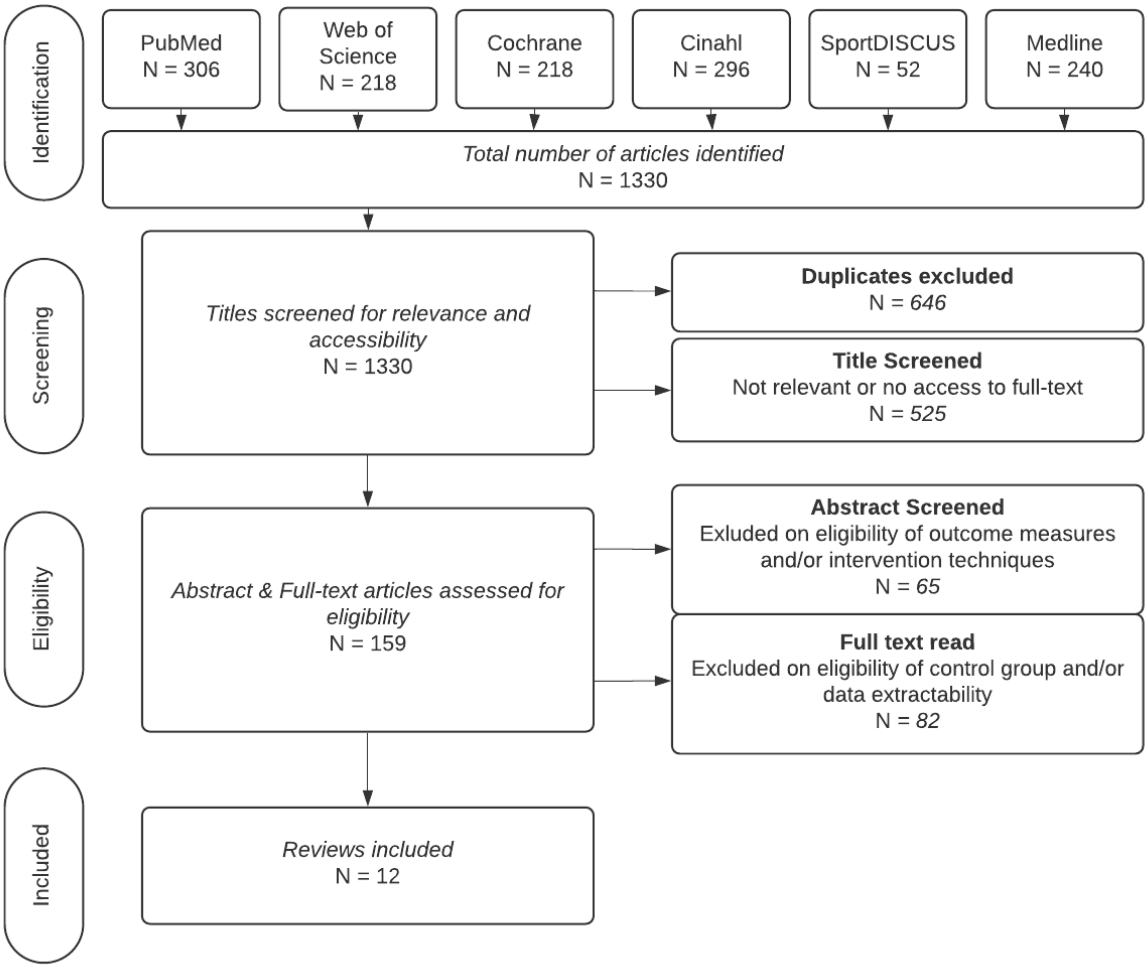


Figure 3. PRISMA flowchart indicating the study selection process.

Characteristics of each included study can be found in Table 4. Information included number and type of primary level studies included ('primary studies'); the sample size, the diagnosed tauopathy, and the disease severity ('population'); a list of included active rehabilitation techniques utilised and what the control group was defined as ('intervention & control'); the outcome measures utilised, grouped by clinical features ('outcomes'); the significance of the results as reported by the study accompanied by the reported heterogeneity ('significance'); and the appraisal of the primary level studies as reported by the study ('appraisal').

Table 4. Summary of the methods, results and appraisals used in each study

Study	Primary Studies	Population	Intervention & Control	Outcomes	Significance	Appraisal
Allen (2011)	16 RCT, qRCT	*n* = 747 PD Mild-moderate severity Mean age range: 62.9 ± 11.9 years to 75.8 ± 4.2 years	Intervention: exercise (aerobic, resistance, Tai Chi, dance) Control: no intervention, TAU, education classes, flexibility exercise	**Balance** (BBS, single leg stand time, tandem stance) **Functional mobility** (TUG, sit to stand time, turning time, step length, cadence **Gait** (gait time, gait velocity)	Significant positive effect on balance. Non-significant positive effect on functional mobility and gait. Heterogeneity: Balance: 0-72% Turning time: 0% Functional mobility: 0-37% Gait: 6% (Dependent on outcome measure)	Cochrane risk of bias tool Mod-high quality: 7 Insufficient info: 8
Alves Da Rocha (2015)*	2 RCT	*n* NR PD Age NR	Intervention: dance Control: no intervention	**Balance** (BBS) **Motor function** (UPDRS III) **Gait** (6mWT)	Positive effect on gait, balance and motor function Heterogeneity: Balance: NA Motor function: 97%	PEDro scale Good: 1 Fair: 1

					Gait: 91%	
Sharp & Hewitt (2014)*	2 RCT	*n* = 137 PD H&Y mean: 2.1, 2.6 Mean ages reported: 66.6, 69.9	<u>Intervention:</u> dance <u>Control:</u> no intervention	**Balance** (BBS) **Motor function** (UPDRS III) **Functional mobility** (FoG) **Gait** (6mWT, gait velocity)	Significant positive effect on motor function, balance, gait velocity. No effect on functional mobility. <u>Heterogeneity</u> Balance: 0% Motor function: 0% Functional mobility: 0% Gait: 0-45% (Dependent on outcome measure)	Cochrane Collaborations risk of bias assessment tool Individual reports not available.
Winser (2018)*	2 RCT	*n* = 96 PD Age NR	<u>Intervention:</u> Tai Chi <u>Control:</u> no intervention, other active treatments	**Functional mobility** (TUG)	Significant positive effect Heterogeneity NR	PEDro: High GRADE: High

Ströhle (2015)*	4 RCT	*n* = 119 AD MMSE scores: 13-22 Age NR	<u>Intervention:</u> exercise treatment <u>Control:</u> TAU, daily organized activities, home safety assessment sessions	**Global cognitive function** (ADAS-cog, ERFC, MMSE)	Moderate to strong effects <u>Heterogeneity:</u> 61.6%	Cochrane Collaboration's tool for assessing risk of bias Synthesis NR
Cai (2017)*	13 RCT	*n* = 958 AD MMSE scores 5.8-22 (2 NR) Mean age range: 72.4-81.8	<u>Intervention:</u> aerobic, resistance, combined <u>Control:</u> no exercise	**Global cognitive function** (MMSE, CDT, FACS)	Positive overall random effect on cognitive function <u>Heterogeneity:</u> 77%	Downs and Black Quality Index 5: good 7: moderate 1: poor
dos Santos	2 RCT	*n* = 83	<u>Intervention:</u> dance classes	**Motor function** (UPDRS III)	Significant positive effect on motor function. Non-	Cochrane criteria

Delabary (2017)*		PD H&Y stages 1-4 Mean age range: 66.5± 2.8 to 69.3±1.9	<u>Control:</u> no intervention	**Functional mobility** (FoG) **Gait** (6mWT, gait velocity – forward, backward)	significant positive effect on gait and functional mobility. <u>Heterogeneity:</u> Motor function: 0% Functional mobility: 0% Gait: 0%	Synthesis NR
Kwok et al (2016)	6 RCT, 4 CCT	*n* = 344 Range: 13-80 PD Severity: mild-moderate Mean age range: 60.8-74.9	<u>Intervention:</u> Mind & body, yoga, Tai Chi, dance <u>Control:</u> no intervention, placebo, waitlist, usual care, non-exercise control	**Balance** (BBS) **Motor function** (UPDRS III) **Functional mobility** (TUG) **Gait** (6mWT)	Large significant effect on motor symptoms, balance and postural instability. Moderate significant effect on functional mobility <u>Heterogeneity</u> Balance: 0%-89% Motor function: 0-60% Functional mobility: NA-95% Gait: NA-0% (dependent on intervention mode)	Effective Public Health Practice Project 1: strong 5: moderate 4: weak
Flynn (2019)*	11 RCT, 1 qRCT	*n* = 1,496	<u>Intervention:</u> home-based exercise	**Balance** (SPPB, BBS, miniBESTest)	Positive effect on balance and gait speed <u>Heterogeneity:</u>	PEDro

		PD Mild-moderate severity Age range: 60-72	<u>Control:</u> TAU, placebo	**Gait** (time taken to walk, preferred gait speed, fast gait speed, TUG, FGA, 180 deg. turn test)	Balance: 0% Gait: 0%	10: good 2: fair
Tomlinson (2012)*	20 RCT	*n* = 1,455 PD H&Y stages 2.1-2.6 Age range: 65-69	<u>Intervention:</u> physiotherapy, exercise, treadmill, dance, martial arts <u>Control:</u> no intervention, placebo	**Balance** (BBS) **Motor function** (UPDRS III) **Gait** (speed, TUG)	Significant positive effect on balance, gait and motor function. <u>Heterogeneity</u> Balance: NA-75% Motor function: 0%-87% Functional mobility: 0%-48% Gait: 0%-34% (dependent on intervention mode)	Synthesis NR
Yang (2014)*	4 RCT, 1 nRCT	*n* = 190 PD	<u>Intervention:</u> Tai Chi <u>Control:</u>	**Balance** (BBS, 1 leg stance, tandem stance) **Motor function** (UPDRS III)	Significant positive effect on balance, motor function and functional mobility. Insufficient evidence of effect on gait.	Cochrane Collaboration tools Synthesis NR

		H&Y stages 1.5-4 Age range: 63-69	placebo, no intervention, other therapies	**Functional mobility** (TUG) **Gait** (gait velocity, 6mWT)	<u>Heterogeneity</u> Balance: 0-68% Motor function: 57% Functional mobility: 0% Gait: 0% (Dependent on outcome measure)	
Farina (2014)	6 RCT	*n* = 171 AD MMSE scores 5-29 Age NR	<u>Intervention:</u> exercise <u>Control:</u> no exercise, home safety assessment, daily activity, organized conversation, TAU, support group	**Cognitive function** (ERFC, MMSE, ADAS-cog, ADS-6, BNT, HVLT, CANTAB-Expedio)	Significant positive effect <u>Heterogeneity:</u> 69%	Quality Assessment tool for Quantitative Studies: Moderate-strong

AD=Alzheimer's disease; ADAS-Cog=Alzheimer's Disease Assessment Scale Cognitive section; ADS-6=Amsterdam Dementia Screening Test 6; BBS=Bergs Balance Scale; BNT=Boston Naming Test; CANTAB=The Cambridge Neuropsychological Test Automated Battery; CCT=controlled clinical trial; CDT=Clock drawing test; ERFC=Rapid Evaluation of Cognitive Functions test; FACS=Functional Assessment of Communication Skills; FGA=Functional Gate Assessment; FoG=Freezing of Gait; HVLT=Hopkins Verbal Learning test; H&Y=Hoehn & Yahr scale; MMSE=Mini-Mental State Exam; PD=Parkinson's disease; NR=not reported; NRCT=non-RCT; qRCT=quasi-RCT; RCT=randomized controlled trial; SPPB=Short Physical

Performance Battery; TAU=treatment as usual; TUG=Timed Up and Go; UPDRS=Unified Parkinson's Disease Rating Score; 6mWT=6 minute Walk Test.

*All data presented in study did not meet eligibility criteria so only relevant data was extracted.

3.4.2 Methodological quality assessment

The overall methodological quality of the systematic reviews and meta-analyses are presented in Figure 4. Methodological quality can be considered high due to most components being adequately addressed within the systematic reviews and meta-analyses. The primary component which negatively impacted the level of quality was publication bias, where assessment was not clearly reported through a visual check of a funnel plot or statistical tests (Alves Da Rocha et al., 2015; Cai et al., 2017; Flynn et al., 2019; Kwok et al., 2016; dos Santos Delabary et al., 2018; Sharp & Hewitt, 2014; Ströhle et al., 2015; Tomlinson et al., 2012) or publication bias was not explicitly mentioned (Winser et al., 2018).

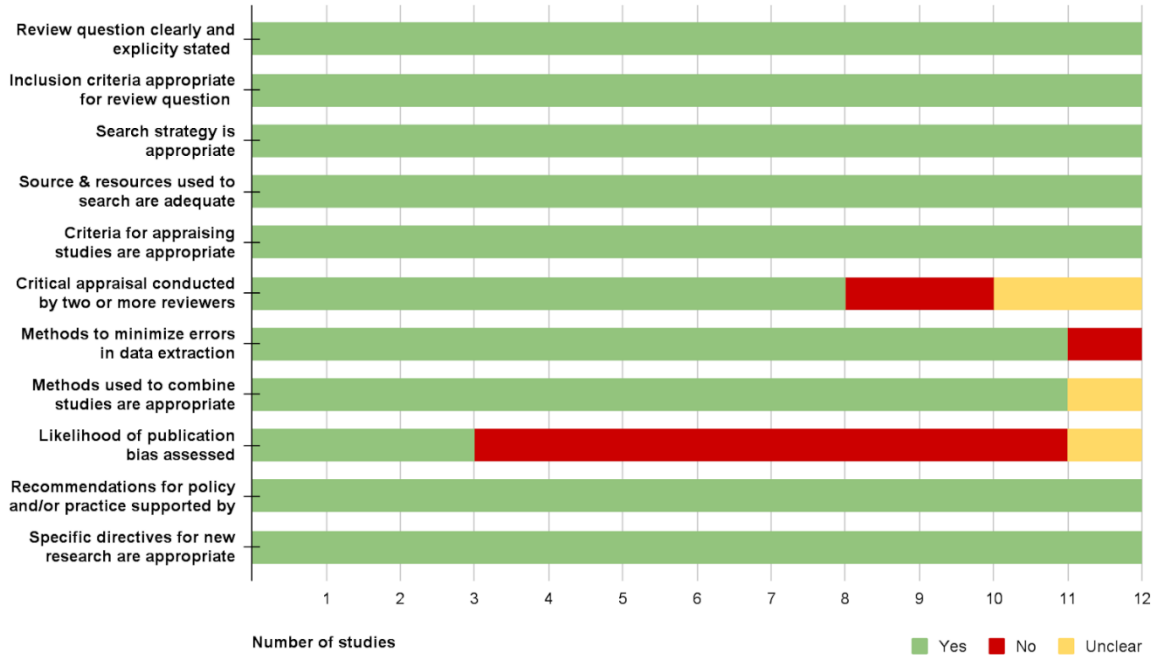


Figure 4. Bar graph highlighting the quality components of included systematic reviews/meta-analyses to report methodological quality

3.4.3 Population

The population included in this review was largely homogeneous with most being diagnosed with mild-moderate stages of PD. Three studies included data that observed the effect of active rehabilitation on the cognitive function of participants

with AD (Cai et al., 2017; Farina et al., 2014; Ströhle et al., 2015) with no other pathologies (i.e., LBD, FTD, and CBD) included.

3.4.4 Cognitive function

Studies assessing the effectiveness of active rehabilitation on global cognitive symptoms (*n* = 3) result in a moderate pooled SMD (SMD = 0.66, 95% CI -0.40 to 1.71, P = 0.116) but a prediction interval ranging from -1.34 to 2.39. A considerable level of heterogeneity was also evident (I^2 = 89.4%, Q = 18.79, P < 0.001) (Figure 5).

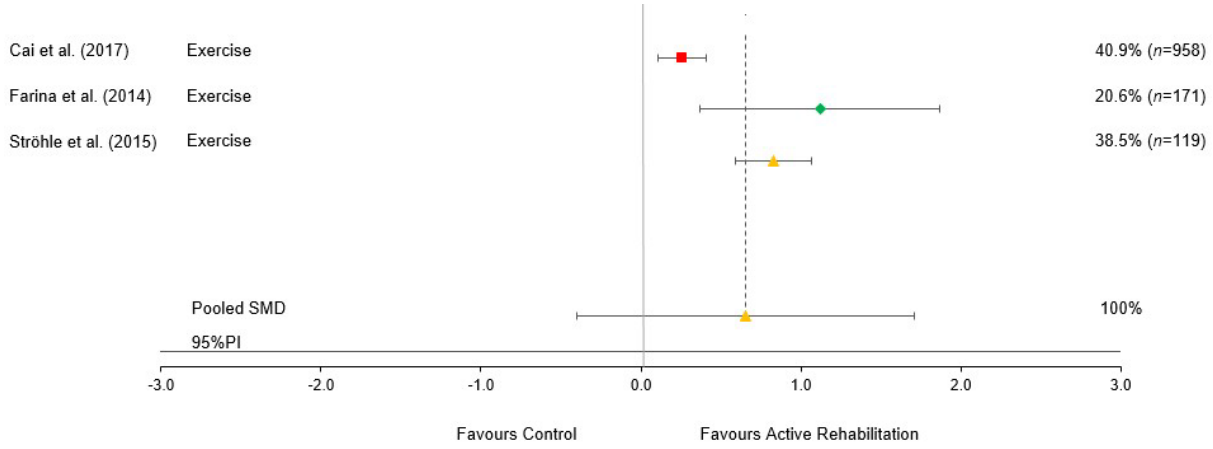


Figure 5. Forest plot to illustrate the SMD ± 95% CI for studies evaluating the effect that active rehabilitation has on measures of cognitive function

3.4.5 Mood/Behaviour

No eligible reviews provided information on symptoms of mood and/or behaviour; therefore, analysis on associated outcome measures was not possible.

3.4.6 Motor function measures

Due to most of the included data involving different types of motor function measures, this section was broken into three subsections: motor function health (Figure 6), functional mobility (Figure 7), and gait speed/velocity (Figure 8). Motor function (*n* = 6), mainly consisting of UPDRS III outcome scores, observed a large pooled SMD

(SMD = 0.83, 95% CI 0.43 to 1.22, P < 0.001). The prediction interval ranged from -0.79 to 2.43 and level of heterogeneity was substantial (I^2 = 76.8%, Q = 51.75, P < 0.001) (Figure 6). Functional mobility (*n* = 7), consisting of measures such as freezing of gait, timed up and go, sit to stand, step length, cadence, and turning time, observed a small SMD (SMD = 0.45, 95% CI 0.19 to 0.71, P = 0.002). The prediction interval ranged from –0.52 to 1.42 and a substantial level of heterogeneity was observed (I^2 = 74.3%, Q = 62.29, P < 0.001) (Figure 7). Gait speed/velocity (*n* = 8), consisting of measures such as gait velocity/time, speed and the 6-minute walk test, observed a trivial SMD (SMD = 0.11, 95% CI -0.14 to 0.36, P = 0.372). The prediction interval ranged from -0.94 to 1.15 and a substantial level of heterogeneity was observed (I^2 = 79.8%, Q = 84, P < 0.001) (Figure 8).

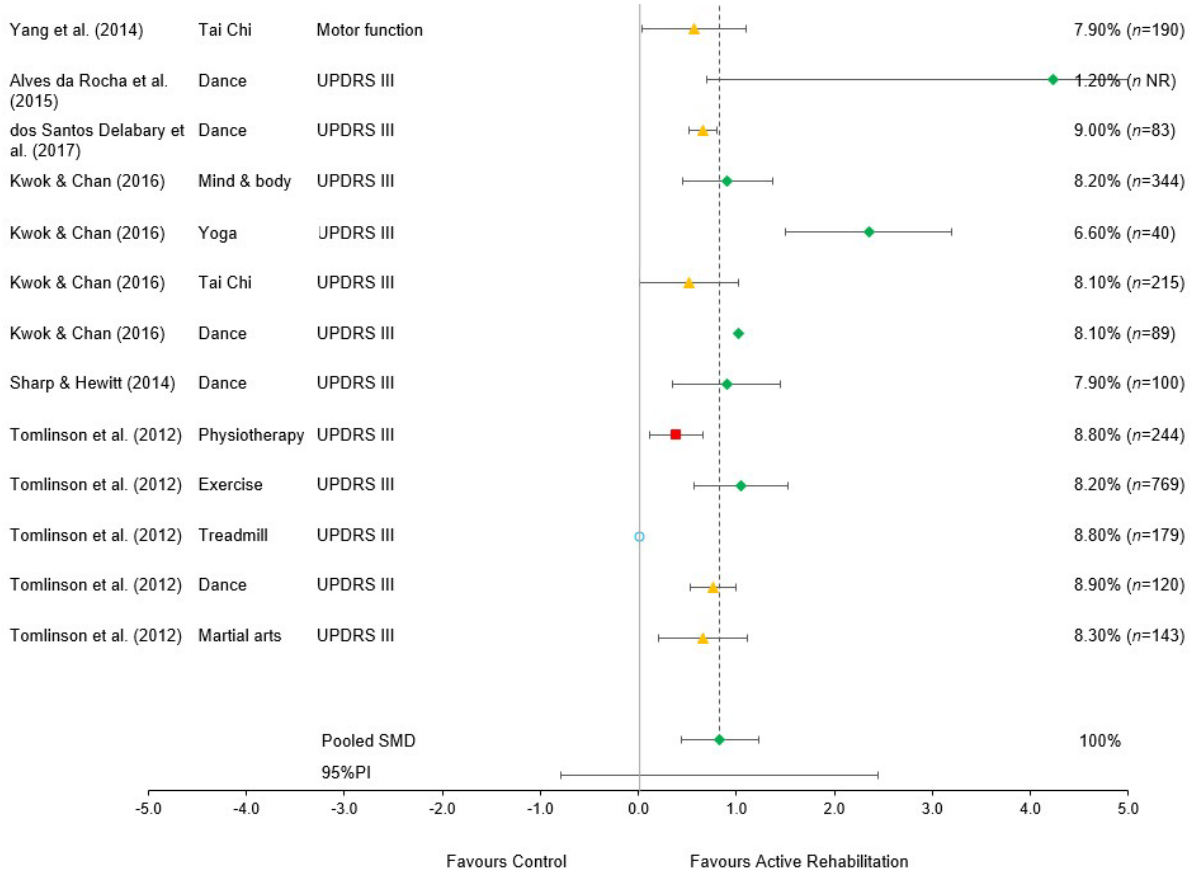


Figure 6. Forest plot to illustrate the SMD ± 95%CI for studies evaluating the effect that active rehabilitation has on measures of motor function.

UPDRS III: Unified Parkinson's Disease Rating Score Part III (motor)

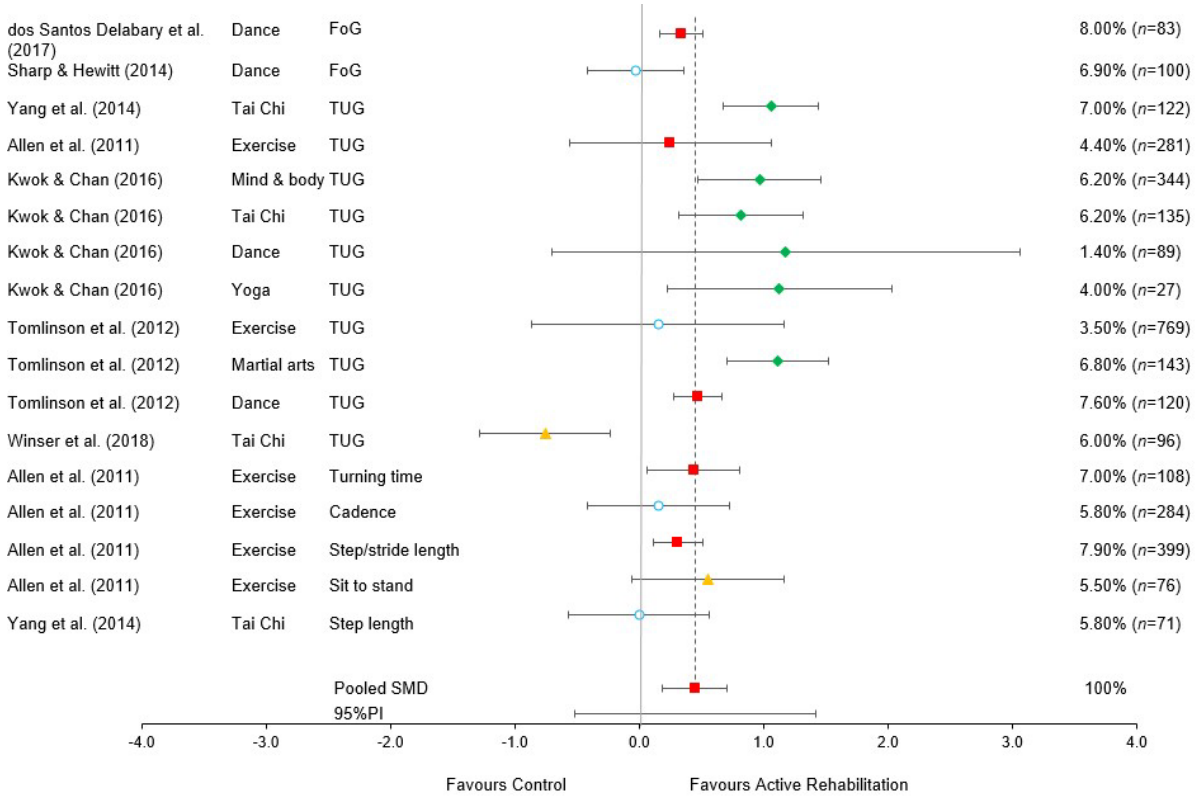


Figure 7. Forest plot to illustrate the SMD ± 95%CI for studies evaluating the effect that active rehabilitation has on measures of functional mobility.

FoG: Freezing of gait; TUG: timed up and go test

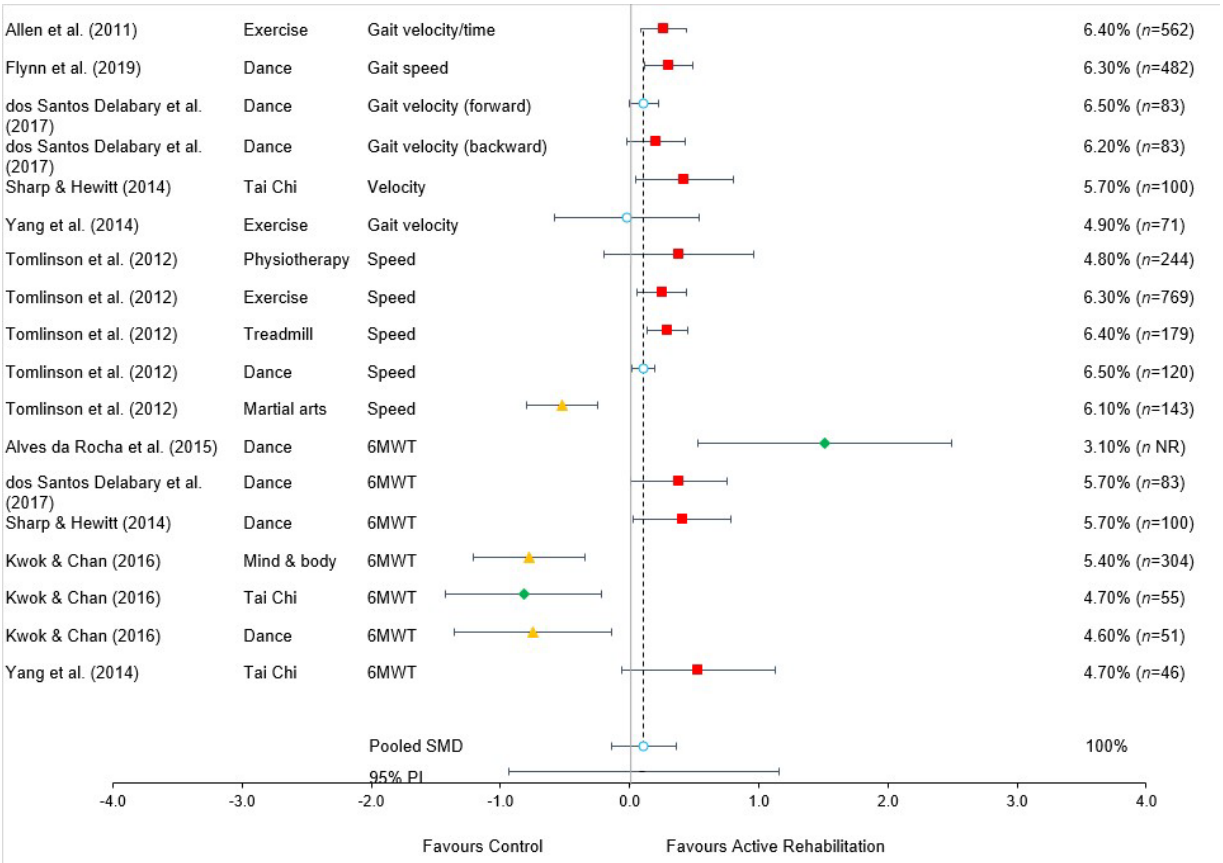


Figure 8. Forest plot to illustrate the SMD ± 95%CI for studies evaluating the effect that active rehabilitation has on measures of gait speed/velocity.

6mWT: Six-minute walk test

3.4.7 Vestibular/Ocular (Balance)

Assessing the effectiveness of active rehabilitation on vestibular and/or ocular symptoms (*n* = 7) resulted in the inclusion of balance measures only, primarily using the Berg Balance Scale (BBS) or a component of the BBS such as single leg or tandem stance. A large pooled SMD was observed (SMD = 0.88, 95% CI 0.56 to 1.21, P <0.001) with a prediction interval ranging from -0.38 to 2.15, and heterogeneity deemed to be considerable (I2 = 91.9%, Q = 196.77, P < 0.001) (Figure 9).

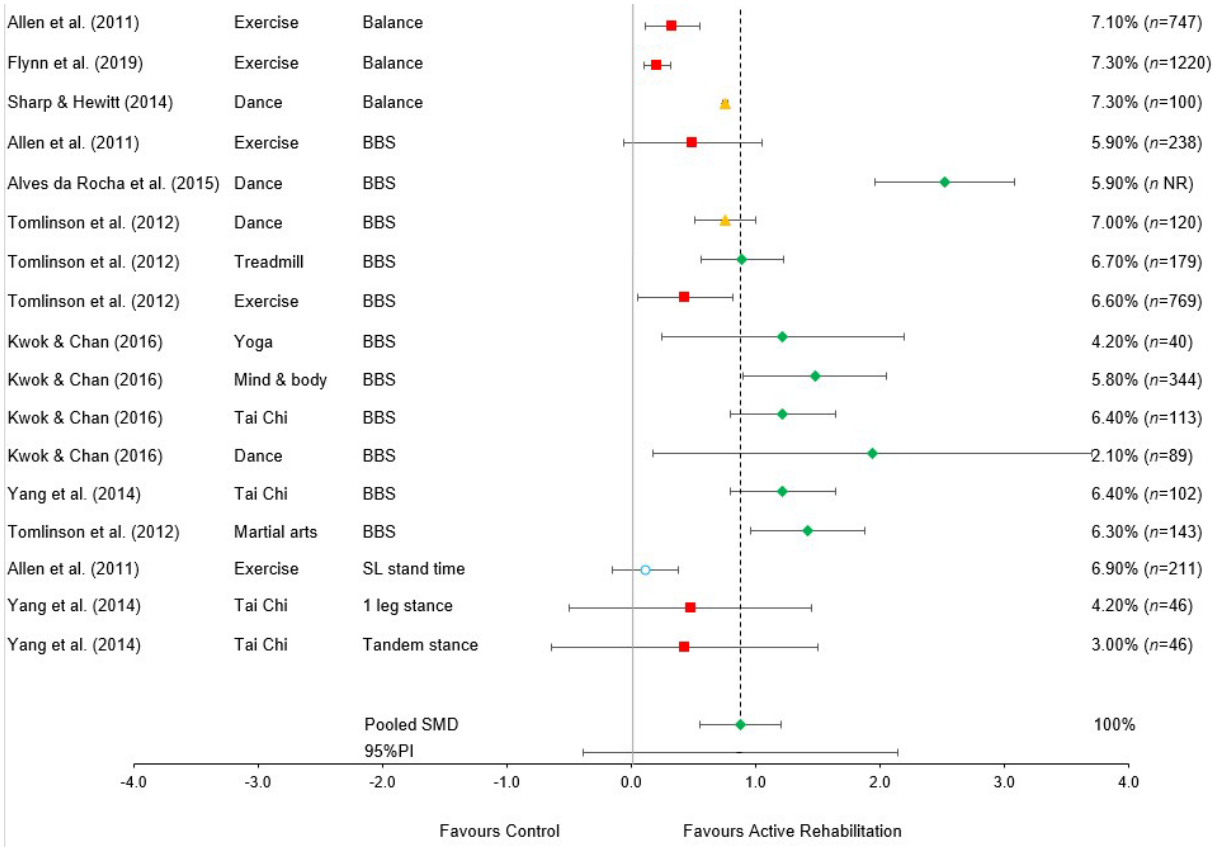


Figure 9. Forest plot to illustrate the SMD ± 95%CI for studies evaluating the effect that active rehabilitation has on measures of balance.

BBS: Berg Balance Scale

3.5 Discussion

The aim of this umbrella review was:

1. To examine the existing evidence on the effect that active rehabilitation has on symptoms associated with suspected CTE in other tauopathies.
2. To assess the potential for active rehabilitation as an intervention strategy for the management of symptoms in tauopathies, with specific implications for the management of suspected CTE.

The aims of this umbrella have been met. Determined by the size and consistency of the measured effect as well as the quality of the evidence, this study found that active rehabilitation has a large effect on balance and motor function, a moderate pooled

effect on cognitive function and a small effect on mobility in populations suffering from tauopathies. Results should be interpreted with caution as all measures demonstrated substantial to considerable levels of heterogeneity and wide 95%PI; however, when considering the SMD, 95%CI, and 95%PI, there is little to no likelihood of a negative or null effect. This provides evidence of a consistently positive effect, thus supporting the use of active rehabilitation as a management tool for symptoms associated with tauopathies. This study has addressed a gap in the evidence regarding potential intervention strategies for CTE and provides a basis for the use of active rehabilitation in future CTE research.

3.5.1 Quality

The methodological quality of included systematic reviews and/or meta-analyses was found to be high (Figure 4) with a lack of insight into publication bias being the only common error.

The quality of evidence from studies looking at cognitive function was moderate to strong (Cai et al., 2017; Farina et al., 2014); however, there were potential sources of bias that were not clearly reported by the primary studies. These included allocation concealment, rating of biometric quality, and selective reporting. Blinding was again a commonly noted issue. There was no evidence of publication bias reported with this group of reviews.

When evaluating the quality of evidence for the analysis of motor function: i) five studies did not provide specific information that could be effectively extracted (dos Santos Delabary et al., 2018; Flynn et al., 2019; Sharp & Hewitt, 2014; Tomlinson et al., 2012; Yang et al., 2014), ii) of those studies which reported quality of evidence, most were considered high quality (Allen et al., 2011; Flynn et al., 2019; Winser et al., 2018); common issues included selection bias, blinding, and global rating.

The quality of evidence gathered to analyse the effect that active rehabilitation has on measures of balance was inconclusive. Multiple studies did not provide the factors of interest outlined in subsection 3.4.3 (Flynn et al., 2019; Sharp & Hewitt, 2014; Tomlinson et al., 2012; Yang et al., 2014). When these factors were reported, the

quality was inconsistent: i) three studies provided good to strong levels of quality (Allen et al., 2011; Alves da Roch et al., 2015; Flynn et al., 2019) with missing components largely concerning intention to treat and blinding; these factors are difficult to achieve in studies interested in evaluating the effect of an exercise programme, ii) two studies demonstrated weak levels of quality (Alves da Rocha et al., 2015; Kwok et al., 2016) reporting issues of selection bias, blinding, and global rating, and iii) one study (Allen et al., 2011) noted a possibility of publication bias due to small sample size studies and large positive effects.

While the findings are promising, the assessment of the quality of evidence across the meta-analyses included in this review calls for caution.

3.5.2 Efficacy

Cognitive dysfunction is one of the core clinical features for identifying potential CTE pathology (Cantu and Budson, 2019; Katz et al., 2021; Montinegro et al., 2014), with executive function, episodic memory, mental flexibility, semantic verbal fluency, and attention and processing speed being some of the more notable impairments. Evidence suggests that active rehabilitation has a moderate effect on cognitive symptoms in AD populations, the only population included in the meta-analyses of cognitive function assessed in this umbrella review. The lack of inclusion of other tauopathies and the small number of studies assessed indicates that findings should be interpreted with caution when extrapolating to other populations. Given the small number of studies, the 95%PI offers little information; however, preliminary findings are positive. Despite the 95%CI suggesting a small chance of null or negative findings, all included studies observed a positive effect ranging from small to large. Farina et al., 2014 found a large effect with a larger number of studies and participants included. Heterogeneity in this analysis reported substantial to considerable levels and is likely explained by disease severity and intervention prescriptions. Despite all studies including AD patients, the study with the lowest level of heterogeneity had a smaller sample size with a smaller range of severity scores (Ströhle et al., 2015), meaning greater certainty can be provided by this analysis (moderate SMD). The variability of outcome measures used could also introduce high

levels of heterogeneity, with nine different tools included. Despite a wide 95%PI and considerable levels of heterogeneity creating uncertainty in the expected size of the effect, the evidence reviewed suggests that patients with tau pathology will experience a positive effect on cognitive symptoms with active rehabilitation. This effect was observed across general exercise programmes (Farina et al., 2014; Ströhle et al., 2015), cardiovascular programs, resistance training, and multi-modal training programmes (cardiovascular + resistance training) (Cai et al. 2017).

While not a core clinical feature, motor impairment is a supportive feature noted in suspected CTE. As seen in Table 1 (see subsection 2.3.2), potential symptoms can include Parkinsonism (gait disturbances, bradykinesia, etc.), muscle rigidity, muscle tremors, and vestibular/ocular impairment (balance, dizziness, double vision, etc.) (Cantu and Budson, 2019; Montinegro et al., 2014). This umbrella review indicates that active rehabilitation has a positive effect on motor function and functional mobility; though it is worth noting that the only meta-analyses included in this review that assessed motor function and mobility included patients with mild to severe PD. Although the 95%PI indicates there is a small chance that a future study may produce null or negative results, the pooled SMD suggests a likely improvement in UPDRS III scores, a scale that measures the motor function abilities of those living with PD. Interestingly, the more successful interventions were mostly those that fall under the category of mind and body, including yoga, tai chi, dance and martial arts. These interventions put a great deal of focus on mind-body coordination, spatial awareness (Kwok et al., 2016; Winser et al., 2018; Yang et al., 2014) and smooth movements (Winser et al., 2018). The variation in intervention mode delivered (treadmill, tai chi, strength training, etc.) and the large range of sample sizes included likely contributed to the substantial level of heterogeneity reported. Regardless, this umbrella review illustrates that active rehabilitation produces a positive effect on motor function symptoms; however, the size of the effect is uncertain due to the wide 95%PI and substantial level of heterogeneity.

Clinicians can also expect small to moderate improvements in timed up and go tests, a commonly used measure of functional mobility. There were multiple data points that observed a large effect; however, these were largely from the same study (Kwok et

al., 2016). Only two other studies observed a large effect (Tomlinson et al., 2012; Yang et al., 2014) with the rest of the data reporting trivial (Tomlinson et al., 2012) to small (Tomlinson et al., 2012; Allen et al., 2011) positive effects, and one moderate negative effect (Winser et al., 2018). Regardless, the 95%CI and 95%PI illustrate a likely small positive effect. Other measures, such as freezing of gait and gait analysis, were inconsistent with some data points demonstrating a null effect (Sharp and Hewitt, 2014; Yang et al., 2014; Allen et al., 2011) and others demonstrating a small to moderate positive effect (dos Santos Delabary et al., 2018; Yang et al., 2014; Allen et al., 2011). Again, the presence of multiple intervention programmes likely contributed to a substantial level of heterogeneity. No intervention type seemed to be more successful than others, with observed modes including general exercise (cardiovascular, resistance training, combination) (Allen et al., 2011; Tomlinson et al., 2012), tai chi (Kwok et al., 2016; Winser et al., 2018; Yang et al., 2014), yoga (Kwok et al., 2016), martial arts (Tomlinson et al., 2012), and dance (Kwok et al., 2016; dos Santos Delebary et al. 2017; Sharp and Hewitt, 2014; Tomlinson et al., 2012). Evidence from this umbrella review suggests that active rehabilitation has a positive effect on measures of functional mobility in tau pathology; however, the expected effect size varies as indicated by the varying pooled effect sizes, wide 95%PI measures, and substantial levels of heterogeneity.

The effect that active rehabilitation has on symptoms of gait speed/velocity is inconclusive due to the observed trivial effect along with both 95%PI and 95%CI showing a high likelihood of negative, null/trivial, and positive effects. While many of the reviews showed a small to moderate positive effect, those that produced negative results had a larger effect (Kwok et al., 2016; Tomlinson et al., 2012). Only one study produced a large positive effect (Flynn et al., 2019), accompanied by wide a 95%CI. Heterogeneity was substantial, likely from the various interventions and outcome measures used. Dance and Tai Chi produced both positive and negative effects, with exercise and physiotherapy producing modest improvements. This review did not provide conclusive evidence on the effect that active rehabilitation has on symptoms of gait speed/velocity in patients with tau pathology.

Evidence suggests that active rehabilitation has beneficial effects on vestibular/ocular symptoms. Specifically, this umbrella review found a positive effect on balance in patients suffering from mild to moderate PD, with only one study including participants with severe levels of PD (Yang et al., 2014). Despite an observed large effect, it should be noted that the majority of data points that provided a large effect came from the same study (Kwok et al., 2016) and these had wide 95%CI. In addition, heterogeneity was considerable. Clinicians can still expect to see small to large improvements in balance based on the 95%CI and 95%PI. This effect was observed regardless of the type of intervention prescribed, one of the likely contributors of a considerable amount of heterogeneity. Reviews included interventions such as general exercise (cardiovascular, resistance training, combination) (Flynn et al., 2019; Tomlinson et al., 2012; Allen et al., 2011), tai chi (Kwok et al., 2016; Yang et al., 2014), yoga (Kwok et al., 2016), martial arts (Tomlinson et al., 2012), and dance (Alves da Rocha et al., 2015; Kwok et al., 2016; Sharp and Hewitt, 2014; Ströhle et al., 2015). The most common outcome measure used was the BBS. Three (Yang et al., 2014; Allen et al., 2011) of the four studies which used a single component of the BBS, the single-leg stance, reported a null or negative effect which suggests the interventions used might have a more rounded effect than that reflected in a single measure. Still, the evidence indicates that active rehabilitation will produce a positive effect on measures of balance in populations suffering from tau pathology; however, the expected effect size is less certain due to the considerable level of heterogeneity and a wide 95%PI.

When considering the consistency of positive findings and reported pooled effect sizes across systematic reviews or meta-analyses that investigate the impact of active rehabilitation on various tauopathies, this umbrella review has provided evidence to support the use of active rehabilitation as a management tool for suspected CTE – a condition where currently no experimental intervention studies have been published. Despite the heterogeneity observed across this umbrella review, likely due to different tauopathies, different levels of disease severity, different intervention modes, and different outcomes, the reported effects are largely positive. Only the effect on measures of gait speed/variability remains inconclusive with the likelihood of a positive, null or negative seemingly equal.

However, it must be noted that the effect of active rehabilitation on symptoms of cognitive and motor function should be interpreted with caution. The calculated confidence and prediction intervals suggest a small likelihood of null or negative findings; nevertheless, the pooled moderate and large point estimates suggest a generally beneficial effect. Furthermore, the effectiveness of active rehabilitation on measures of functional mobility appears to depend on the assessment utilized. A positive effect is more consistent in studies that utilize the timed up and go test. The overall size of the effect on measures of functional mobility is small as indicated by the pooled effect. Measures of balance provide the strongest and most consistent positive effect in this review, accompanied by a large pooled SMD.

The degree of effectiveness for motor function, cognitive function, and balance remains to be determined, as indicated by large variability in 95% confidence and prediction intervals. Regardless, this review has provided preliminary evidence to support the use of active rehabilitation as a therapeutic option for management of clinical symptoms and health outcomes of common tauopathies, including CTE.

3.5.3 Future research

There are two gaps that emerged within this review. The first is the lack of systematic reviews or meta-analyses addressing the effect that active rehabilitation has on tauopathies other than PD and AD. This includes LBD, FTD, and CBD. The addition of such systematic reviews or meta-analyses would create a more robust evidence base which better supports the reliability and applicability of this umbrella review. The other gap is the effect that active rehabilitation has on mood/behaviour symptoms of tauopathies. Mood and behaviour symptoms make up the other two core clinical features for identifying suspected CTE (Cantu and Budson, 2019; Montinegro et al., 2014).

One contributing factor which may explain the gaps identified in this study is related to the methodology employed in primary level studies and the eligibility criteria employed at the secondary levels of research (systematic reviews and meta-analyses). More information on AD, LBD, and mood/behaviour impairments would

have been included in this analysis had inactive/treatment as usual control groups and extractable data been presented. Indeed, more than 82 systematic reviews and meta-analyses were excluded at this stage in the screening process which included both AD and LBD populations as well as cognitive, motor and mood/behaviour outcome measures. Due to the increased heterogeneity and variability that is expected in an umbrella review, a non-active rehabilitation control group was necessary to effectively evaluate whether active rehabilitation affects symptoms associated with tauopathies. Future systematic reviews and meta-analyses should consider following those reporting guidelines based on the Equator Network to enhance their usefulness for further umbrella reviews. Specifically, they should consider data transparency and the use of control groups that receive no additional treatment.

The other contributing factor which may explain the gaps identified by this umbrella review is the overall lack of studies observing the effect that active rehabilitation has on populations suffering from CBD and FTD. Case studies have been performed and note improvements in balance, walking, gait, executive function, attention, and depressive symptoms (Borba-Pinheiro et al., 2013; Steffen et al., 2007; Steffen et al., 2014); however, no further research could be identified. The lack of studies observing CBD can be explained by the rarity of the disease which has caused a general lack of knowledge regarding identification and treatment options (Constantinides et al., 2019). FTD is also in its research infancy (Rascovsky et al., 2011) where current efforts are largely concerned with identification techniques and epidemiology.

3.5.4 Conclusions

Despite the limitations, the results of this umbrella review report positive effects of active rehabilitation on the following measures that appear important in the management of tauopathies:

- Cognitive function
- Motor function
- Functional mobility

- Balance

Applicability of the findings of the umbrella review to CTE is supported by the underpinning physiological mechanisms that active rehabilitation may elicit on these similar tauopathies. While the mechanisms and areas affected may differ between tauopathies, the progressive neural degeneration and associated clinical symptoms are attributed to synaptic dysfunction and impairments to neural connectivity which accumulated p-tau creates. With no intervention, the process leads to neural cell death and subsequent atrophy of affected regions (Imbimbo et al., 2021; Kneynsberg et al., 2017). As presented in subsection 2.4, active rehabilitation can decrease brain atrophy and enhance brain function by promoting neurogenesis and improving cerebral blood flow (Calverley et al., 2020). Whilst it is not within the scope of this thesis to determine whether there is a direct effect on the development of tau, such effects may prove to slow, or even prevent, further progression of tauopathy related degeneration.

Within these broad areas, specific activities have emerged as potential candidates for inclusion in active rehabilitation programmes for CTE patients. These include:

- General exercise or physiotherapy
- Cardiovascular (e.g., treadmill training)
- Resistance training
- Multimodal (e.g., cardiovascular + resistance training)
- Mind & body (e.g., tai chi, yoga, martial arts)
- Dance

There is further evidence which does not fall within the scope of this review which supports the use of active rehabilitation in other tauopathies (LBD, CBD and FTD) and for mood and behaviour symptoms, but more high-quality research is needed (see subsection 3.5.3). Further, there are likely other suitable rehabilitation strategies which did not fall within the scope of this review that could be considered, such as cognitive rehabilitation. Regardless, this review provides preliminary evidence to support future research which seeks to investigate the effect that active rehabilitation has on patients with suspected CTE.

4 Chapter 4: Methods

4.1 Overview, study rationale, aims, and objectives

Thus far, this thesis has presented the real-world consequences of CTE (Chapter one), the neurodegenerative disease linked to repeated exposure to mTBI. Chapter two outlined what these consequences are and included symptoms such as executive dysfunction, behavioural dysregulation, and motor impairment. These consequences have been documented in contact sport athletes for almost a century and, to the best of the author's knowledge, no studies have been published that establish an evidence-based intervention strategy precisely intended for the symptoms or processes of suspected CTE. Chapter three provided preliminary evidence to present active rehabilitation as an effective intervention for the management of tauopathies. The implications that this has for the management of suspected CTE were also discussed. Chapter four outlines the methodology for a case series that investigated the effect that active rehabilitation has on the symptoms of individuals with suspected CTE, the first known experimental study seeking to establish an appropriate intervention tool for suspected CTE.

Therefore, the purpose of this study was to investigate the effectiveness of active rehabilitation on symptoms associated with suspected CTE. The aims of the mixed methods single case experimental design included:

1. To assess the effect that a person-centred active rehabilitation programme had on participant symptoms suspected to be associated with the development of CTE.
2. To understand how contextual factors (both proximal and distal) affected the participants' experience of an active rehabilitation programme and the perceived effectiveness.

To achieve the aims outlined above, the following objectives were met:

1. To establish whether a participant met the criteria for Traumatic Encephalopathy Syndrome (TES) and to define a participant's unique symptom set, an initial interview and baseline data collection phase were carried out.

2. To create a person-centred research environment, semi-structured follow-up interviews took place at every data collection point.
3. To determine the effect that a person-centred active rehabilitation programme had on symptoms of suspected CTE, a visual analysis of n-of-1 quantitative data was performed.
4. To provide evidence of the expected size of the intervention effect, a within-case standardized mean difference (WC-SMD) and non-overlap of all pairs (NAP) were calculated.
5. To gather information of contextual factors, participants completed a daily log of activity and were interviewed at different timepoints using semi-structured interviews.
6. To integrate the n-of-1 results with the qualitative data, an explanation building qualitative analysis was performed.

4.2 Methodological approach, ontological and epistemological perspective

4.2.1 Evidence-based medicine and person-centred care

This thesis adopted the notion presented by Price and colleagues (2015): that evidence-based medicine (EBM) and person-centred care (PCC) should be viewed like two wheels on a bike, where both are equally necessary for the creation of an adequate and effective treatment plan. In healthcare, PCC is characterized by a framework which asserts the patient as a person rather than the disease or condition they bear. Factors such as context (values, feelings, will, circumstances), family, history (medical, personal), needs, and preferences should be considered when determining appropriate care. In addition, the person is encouraged to become an active agent in the decision-making process (Jacobs et al., 2017; Ekman et al., 2011; Martin and Félix-Bortolotti, 2014). In 2011, the Gothenburg Centre for Person-Centred Care (GPCC) presented three ‘routines’ for implementing PCC into clinical practice (Ekman et al., 2011; Ekman et al., 2021):

1. Initiating a patient-clinician partnership by inviting (and listening to) a patients’ narrative regarding their disease experience, symptoms, and impact on daily

life. This narrative shifts the focus away from epidemiology and focuses on the patient as a unique individual.

2. Implementing the patient-clinician partnership to reach a shared understanding of the patients' experiences, feelings, beliefs, needs, and preferences. This shared understanding serves as the foundation for an appropriate and meaningful treatment programme. It also encourages active patient involvement and responsibility in the development of this treatment programme.
3. Safeguarding the patient-clinician partnership through adequate documentation. This includes documentation of the patient narrative and the mutually agreed treatment plan.

If undertaken through a lens of PCC, clinical research should place the person as the lead – not the researcher, not the clinician, not the disease. Table 5 outlines common characteristics that should be considered when designing and carrying out clinical research which values PCC.

Table 5. Characteristics of PCC research

Broad characteristic	Points to consider
Person-centred research environment	Researchers are aware of contextual influences: • Which are complex, layered and constructed by people • That can influence a person's perception and being Researchers seek to contribute to a safe, critical, and creative communicative space: • With shared-power and psychological safety • Which encourages participant authenticity • That leads participant and researcher to learn about one another as distinct persons
Prerequisites of person-centred research	Researchers should have an interest and belief in: • Person-centred values: respect, self-determination, mutuality and reciprocity • Research designs that encourage participant sharing

	• Developing relational connectedness with participant • Understanding the participant within their own life context and roles • Participant (and own) well-being • Facilitation and co-production of participant emancipation and transformation • Multiple forms of knowledge
Person-centred research processes	Processes should allow for: • An invitation to share lived experiences • A level of respect regarding participant engagement, self-determination, mutuality and reciprocity • Methods that bring multiple forms of knowledge • Shared decisions on the degree of open-endedness and structuredness of data gathering • Non-judgmental interactions and sympathetic presence between researcher and participant • Methods that lead to critical and creative analysis of lived experiences • Researchers influence on data gathering and analysis process
Person-centred outcomes	Outcomes should: • Focus on participant (and researcher) well-being • Encourage commitment to and sustained involvement in person-centred research • Create a person-centred research culture

Sources: adapted from Titchen et al., 2017 with further information sourced from Jacobs et al., 2017; McCormack and McCance, 2006.

4.2.2 Theoretical perspective

Classic EBM considers high-quality evidence to come from those studies which contribute significant value and retain reliability (Brass, 2010; Sheridan and Julian, 2016). This belief, whether directly or indirectly, places emphasis on the idea of ‘efficacy’: does the intervention work in ideal conditions? When controlling for all other external factors (i.e., ideal conditions), an observed effect would indicate a strong likelihood this change was a direct result of the applied intervention and suggests, with confidence, the proposed intervention does influence the outcomes of interest

(Brass, 2010; Streiner, 2002). While informative, relying solely on efficacy trials to inform statements and guidelines can lead to an ‘oversimplified and restricted view of evidence’ (Sheridan and Julian, 2016: 207). Limitations in age, comorbidities, concomitant factors (therapies, conditions, drug use, etc.) and even resource accessibility may sacrifice external validity for internal integrity, leaving evidence of efficacy reliable but difficult to integrate into a treatment programme for the complex and unique individuals which make up the patient population (Price et al., 2015; Sheridan and Julian, 2016).

Pragmatic clinical trials sacrifice some reliability to offer increased generalizability instead, providing an opportunity to bridge the gap between classic clinical trials and clinical practice (Brass, 2010). Pragmatic research encourages effectiveness trials: research which seeks to address whether an intervention works in real-world conditions (Brass, 2010; Streiner, 2002). Broader evidence regarding demographics, comorbidities, interventions, and even outcome measures, all ‘real-world’ factors which are considered in daily clinical practice, can be provided with the use of pragmatic research (Brass, 2010; Martin and Félix-Bortolotti, 2014). This makes the evidence more generalizable even if the effect is less reliable than results provided by efficacy trials.

Inspired by the by the underpinnings of pragmatic clinical trials as presented by Brass (2010), this thesis has adopted the epistemological and ontological framework of pragmatism. Research rooted in pragmatism offers a framework for researchers who wish to provide rigorous evidence that simultaneously maintains a PCC approach. Pragmatism elects to emphasise the need for methods that are best suited to answer the research questions and places the focus on the consequences of the research rather than the methodology; therefore, pragmatism embraces plurality and abductive logic (Kaushik and Walsh, 2019; Onghena et al., 2019; Van Ness et al., 2017). While not without a potential for the production of false claims, pragmatic research does not seek to establish an absolute truth, even challenging the very notion of such a need when considering the realities of human nature (Elder-Vass, 2022).

4.2.3 Research design

A mixed methods single case research (MMSCR) design was employed for this thesis. MMSCR is a type of single-case experimental design (SCED) (see subsection 4.2.3.1) which seeks to integrate a qualitative component to the case (Onghena et al., 2019; Van Ness et al., 2017;). It is important to note here that integration in the context of this thesis refers to equal representation of both qualitative and quantitative components. It implies that the different measures are taken in sync rather than subsequently, and neither is deemed to have more value than the other (Onghena et al., 2019). The integration of a SCED and qualitative case study (QCS) (see subsection 4.2.3.2) allows for the rigorous and systematic investigation of a phenomenon (i.e., the causal relationship between the dependent and independent variables) within a case's own context (e.g., the patient and their various contextual factors) (Onghena et al., 2019; Van Ness et al., 2017).

4.2.3.1 n-of-1 study

SCED is a methodological framework which may be used for effectiveness trials. Further, such designs support PCC and EBM approaches (Selker et al., 2021). SCEDs are a specific group of single-case methodologies which utilize a within-subject paradigm to establish a causal relationship between an independent and dependent variable. Rather than simply observing a single participant, an independent variable (i.e., intervention) is systematically manipulated according to a predetermined schedule, and the responses measured frequently and subsequently analysed to establish a cause-and-effect relationship (causal relationship) with the dependent variables (i.e., the target behaviours) (Tate and Perdices, 2020). SCED study designs, the participant serves as their own control (Tate and Perdices, 2020), and analysis visually compares the participant response under two or more 'conditions' (referred to as phases) (Byiers et al., 2012). Rather than a traditional single pre-post treatment comparison, utilizing a within-subject paradigm like that used in SCEDs allows for multiple demonstrations of effect within the same subject (Kazdin, 2021). Table 6 outlines the various types of SCEDs.

Table 6. Single case experimental design types and focus

Case study type	Study focus
Withdrawal/ reversal	• Intervention is introduced and withdrawn (A-B-A-B) • Provides at least three demonstrations of experimental effect
n-of-1	• Sub-type of withdrawal/reversal design • Largely used for intervention studies • Paired sequences of A-B phases are randomised and evaluated for treatment effect
Multiple baseline	• Onset of intervention is staggered across multiple participants (at least three)
Alternating-treatments	• Compares two or more interventions or procedures • Phases are rapidly and randomly alternated
Changing-criterion	• Operant conditioning paradigm seeking to gradually alter behaviour • Intervention is introduced in steps until an a priori-established criterion is achieved • A second, third, and so-forth set of criterion is established • Meeting the defined criterion serves as a demonstration of experimental effect (requires at least three)

Source: adapted from Tate and Perdices, 2020. A = non-intervention/baseline phase; B = intervention phase

SCEDs have been linked to PCC, or components of PCC, by multiple authors (Kazdin, 2021; Kravitz et al., 2014; Selker et al., 2021). According to Kravitz and colleagues (2014), the success of an n-of-1 depends on the effective collaboration between researcher and participant to determine appropriate interventions and outcome measures. The research group also notes the pragmatic value of conducting an n-of-1 study (Kravitz et al., 2014). The outcomes of this collaboration can then be used to inform a general knowledge base. Due to the rigorous and systematic methods that are followed, the Oxford Levels of Evidence Working Group (OCEBM Levels of Evidence Working Group, 2011) has labelled those n-of-1 trials which aim to investigate treatment benefits as providing Level 1 evidence. With a multi-crossover design trial, where evidence from multiple trials is combined, the knowledge base has even more potential for gain (Selker et al., 2021). A 5-3-20 threshold has been

proposed: if at least five different SCED studies are published by three independent research groups from different institutions, with a combined twenty participant sample size, then an intervention can be established as ‘evidence-based’ (Tate and Perdices, 2020).

4.2.3.2 Qualitative case study

QCS is another methodology which can be used to provide an evidence-based exploration of the effect an intervention has on a specific case. Like SCED research, a QCS systematically investigates a phenomenon (e.g., what effect the presence of an intervention has on a participant) within its’ own context (Baxter and Jack, 2008; Yin, 2018). Further, this research design can be used to develop and evaluate the effect of an intervention while providing context of the case itself (Baxter and Jack, 2008). Table 7 outlines the various types of QCS.

Table 7. Qualitative case study types and focus

Case study type	Study focus
Explanatory	• To explain a presumed causal link • To link programme implementation with programme effects
Exploratory	• To explore situations in which the intervention does not have a clearly defined set of outcomes
Descriptive	• To describe an intervention or phenomenon within the real-life context of which it occurred
Multiple-case studies /Collective	• To explore differences within and between cases • To replicate findings across multiple cases
Intrinsic	• To better understand a case • Purpose is not to understand a construct of phenomenon, but to study the case itself
Instrumental	• To accomplish something other than understanding a particular situation • Provides insight into an issue • Helps to refine theory

• Case is of secondary interest

Source: adapted from Baxter and Jack, 2008

Where QCS adds value is its ability to facilitate an in-depth exploration of a participant's perspectives. While providing an in-depth description of a defined phenomenon (i.e., the introduction of an intervention), QCS research may also seek to understand 'how' or 'why' such an event occurred (Baxter and Jack, 2008; Yin, 2018). Qualitative data can provide rich information about a topic by exploring a host of factors influencing a case, typically informed by multiple sources of data (such as documents, interviews, direct observations, or participant-observation) (Baxter and Jack, 2008; Hancock and Algozzine, 2006). This capability is particularly useful when little is known about a topic (such as a new intervention within an emerging field) (Hancock and Algozzine, 2006). Further, QCS research encourages active participation of and collaboration with the participant (Baxter and Jack, 2008), necessary components for SCED research and PCC research.

4.2.3.2 Mixed methods single case research

While the theory of utilizing qualitative data to add contextual 'meat on bones' is presented in the literature (Onghena et al., 2019), few MMSCR studies could be found that truly integrate the two data types within the study protocol itself. Of those studies that utilized mixed methods within a SCED setting, the design typically employed a pre- or post-intervention interview to provide case context, investigate appropriate interventions, provide insight into general feasibility of the intervention, or to determine altered behaviour (Onghena et al., 2019; Van Ness et al., 2017). No study could be identified which effectively integrated the qualitative and quantitative data to explain the causal-link demonstrated by the SCED component within the real-world context in which it occurred.

The ontological and epistemological frameworks for which qualitative and quantitative data are typically grounded in may provide one explanation for why few examples of MMSCR with integration of data could be identified. Generally, quantitative research is underpinned by positivism (the belief that reality is true in nature and can be known

or measured objectively) and qualitative research by interpretivism (the belief that reality is created through the individuals' perceptions, feeling and beliefs; therefore, 'truth' cannot be known or quantified objectively') (Kaushik and Walsh, 2019; Martin and Félix-Bortolotti, 2014). As directed by the aims and objectives outlined in see subsection 4.1, this study seeks to: i) assess the effect that active rehabilitation has on suspected CTE and ii) how contextual factors influence the study experience and perceived effectiveness. Further, this thesis seeks to answer such questions within a framework that equally values both EBM and PCC (see subsection 4.2.1). Such aims require an ideology which allows for the equal representation of a measurable reality and a perceived reality, further emphasizing why pragmatism was elected for this thesis (see subsection 4.2.2). Pragmatism acknowledges the potential for an objective reality, but this objective reality cannot be separated from, or encountered without, human experience (Kaushik and Walsh, 2019). Supported by such, this thesis elected to integrate the methodologies of a withdrawal n-of-1 study and an explanatory QCS. A withdrawal n-of-1 SCED allows for the visual and statistical analysis of an intervention effect to establish a causal effect (Tate and Perdices, 2020). An explanatory QCS allows for the explanation of the presumed causal effect between an intervention and an observed phenomena, further linking the programme implementation with programme effects. This is effectively achieved with the use of multiple data sources (Baxter and Jack, 2008; Yin. 2018).

A withdrawal design begins with a baseline phase (A phase; non-intervention phase) where target behaviours can be measured prior to the introduction of the intervention. The intervention is then introduced (B phase; intervention phase), withdrawn (A phase), and introduced again (B phase) (Byiers et al., 2012; Kazdin, 2021; Tate and Perdices, 2020). With this more traditional withdrawal design (A-B-A-B), there are three opportunities to demonstrate a causal relationship (A to B, B to A, A to B) (Tate and Perdices, 2020). This design can be altered by randomizing the phase order or phase onset, counterbalancing paired phases (referring to a matched A-B block), or introducing a second (third, fourth, etc...) intervention (Kazdin, 2021; Kravitz et al., 2014; Tate and Perdices, 2020). An n-of-1 trial is a specific subset of a withdrawal study design where these paired phases (A-B) are randomized and the treatment effect is evaluated (Tate and Perdices, 2020). Analysis of SCED is strongly rooted in

visual analysis (Byiers et al., 2012; Kazdin, 2021; Kravitz et al., 2014; Tate and Perdices, 2020); however, this can be further supported through statistical analysis (Byiers et al., 2012; Brossart et al., 2014; Manolov and Solanas, 2017; Pustejovsky and colleagues, 2020; Tate and Perdices, 2020).

As presented by Yin (2018), the steps for an explanation-building analytical process are as follows:

Step one: Define initial explanatory proposition

Step two: Compare case data to the initial proposition

Step three: Revise the initial proposition

Step four: Compare other details of the case against this revision

Step five: Repeat across all included cases

This approach allows for an initial analysis of the qualitative data (steps 2 and 3), followed by the integration of all available data (step 4), which can then be presented in a narrative format (Baxter and Jack, 2008; Yin. 2018).

4.3 Participants

4.3.1 Recruitment, eligibility, and sample

The population sample goal was five to ten participants. This number of participants would serve as 25-50% of the total sample size needed to establish active rehabilitation as an evidence-based intervention for the management of CTE symptoms as suggested by the 5-3-20 threshold outlined in section 4.2.3.1

Potential participants were approached through several gatekeepers and personal networks of the researcher, including various sports teams, individuals working within the field of sports journalism, and the Manchester Movement Unit (the educational physiotherapy clinic at Manchester Metropolitan University). These gatekeepers were given a project poster (Appendix 2) to distribute to potential participants. Individuals with a history of involvement in contact sports (e.g., boxing, American football, wrestling, rugby, football [soccer], karate, hockey, lacrosse) or sports known to

frequently produce concussions (e.g., skiing, horseback riding, parachuting) were approached. If interested, these individuals were given a participant information sheet (Appendix 3) which outlined study details, inclusion/exclusion criteria, expectations, benefits, and risks. Potential participants were encouraged to ask questions via email or web-based phone call before agreeing. If participants agreed to participate, they were asked to fill out and sign a participant consent form (Appendix 4).

Individuals between the age 20 and 60 years who met the 2014 TES criteria (see Table 2, subsection 2.3.2), spoke/read English, and were at least one year post-retired from professional or university level sport were eligible for inclusion. The 2014 criteria was followed because the updated criteria offered by Katz and colleagues (2021) was not yet available prior to the start of the study. An age range of 20 to 60 years allowed for sufficient exposure to mTBI/contact sport while controlling for potential concomitant neurodegenerative disease, presence of dementia, and other neurological disorders that may account for symptoms. Appendix 6 outlines further criteria used to determine the presence of potential neurological disorders. Participants reportedly suffering from dementia were excluded.

At any time during data collection, withdrawal could be explicitly expressed by the participant. Withdrawal could also be assumed if the participant (1) missed more than two follow-up interviews in a row, or (2) did not respond to at least two contact attempts made by the researcher seeking to schedule a follow-up interview. In the event of participant withdrawal, any data where a full data collection cycle had been completed (A-B matched pair) was kept for analysis.

4.3.2 Ethical considerations

Ethical approval was gained from the Manchester Metropolitan University Faculty of Health, Psychology and Social Care Research Ethics and Governance Committee (Ethos No. 11822) (Appendix 5). Research was conducted in accordance with the University's Data Protection Policy. Results in Chapter 5 were presented using pseudonyms to ensure anonymity.

No adverse reactions to the implementation of an active rehabilitation programme were anticipated beyond the standard risks associated with physical activity, including delayed onset muscle soreness (DOMS) and the possibility of musculoskeletal injury. Due to the progressive nature of the disease, there was a possibility for symptoms to worsen. It was explained to participants in the participant information sheet (Appendix 3) as well as in preliminary discussions that participants would be removed from the study and referred to their GP if they exhibited concerning levels of symptoms as indicated by provided outcome measure ranges (see Table 9, subsection 4.4.3). No participant exhibited such concerning levels throughout the study.

One anticipated adverse reaction to participation in the study was the participants response to meeting eligibility criteria (I.e., TES criteria). During preliminary discussions, it was explicitly expressed to potential participants that the purpose of this study was not to diagnose anyone with CTE. This is supported by the fact that there are currently no diagnostic criteria for CTE (see subsection 2.3.2). Instead, the eligibility criteria for this study participation included meeting the 2014 TES criteria (see subsection 4.3.1). Participants were then informed whether they met the study eligibility criteria or not. They never received any diagnosis. For this reason, phrases such as ‘meeting TES criteria’ and ‘symptoms associated with suspected CTE’ have been used throughout this thesis. Such phrases were echoed throughout the recruitment and study processes as well. The project poster (Appendix 2) does not mention CTE at all, instead focusing on recruiting anyone with a history of concussion and/or participation in contact sport. The participant information sheet (Appendix 3) does not indicate that participants will receive any diagnosis, only that interviews and a screening process will take place to determine eligibility and identify any relevant symptoms. No participant refused to participate based on this information, nor did anyone ask for a formal diagnosis. All participants understood the scope of this study and the eligibility criteria.

The burden of participation was another consideration taken into account when designing the study procedures. A five-assessment limit was implemented, meaning the follow-up surveys could not exceed five different outcomes of interest. This limit intended to minimise participant burden, prevent dropout, decrease the number of

incomplete surveys, and increase the quality of data by ensuring time taken to complete the survey was not excessive. Evidence suggests there is an inverse relationship between length of time to complete a web-based survey and the number of completed responses as well as the quality of the responses (Galesic and Bosnjak, 2009). Limiting the number of surveys to five attempted to keep the estimated time to complete between ten and twenty minutes. A final list of outcome measures for each participant were determined at the end of the baseline phase and prior to the start of the first study phase (A1 or B1). In four cases (Niall, Luigi, Gemma, Simon), impairment was not observed in one outcome measure during the baseline phase and therefore was removed from the list of outcome measures. Only in one case (Luigi) was this outcome measures replaced with another. Niall did not show impairment in two outcome measures, with two additional outcome measures added prior to the start of the first study phase. Kristen demonstrated an impairment in all five selected outcome measures during the baseline phase; therefore, all of her outcome measures were retained.

4.4 Materials and procedures

4.4.1 General procedure

The study was designed and reported in line with the Consolidated Standards of Reporting Trials (CONSORT) extension for N-of-1 trials (CENT) 2015 statement (Shamseer et al., 2015; Vohra et al., 2015) (Appendix 7).

Each case was anticipated to take 51 weeks to complete. The study began with an initial interview, followed by a three-week baseline phase (details regarding the initial interview and baseline phase can be found in subsections 4.4.2 and 4.4.3). Following the baseline phase, participants were randomly allocated to one of two systematic counterbalanced withdrawal study designs, the first being A-B, B-A, B-A, A-B and the second option being B-A, A-B, A-B, B-A where ‘A’ indicates a non-intervention phase and ‘B’ indicates an intervention phase (details regarding phase A, phase B, and intervention delivery can be found in subsections 4.4.4 and 4.4.5). Participants were randomly allocated using a coin flip, where tails indicated the participant to begin with

phase A (inactive) and heads indicated participant to begin with phase B (active). Each paired phase (A-B or B-A) lasted twelve weeks and consisted of three follow-ups which took place every two weeks. A brief study scheduled is illustrated in Figure 10.

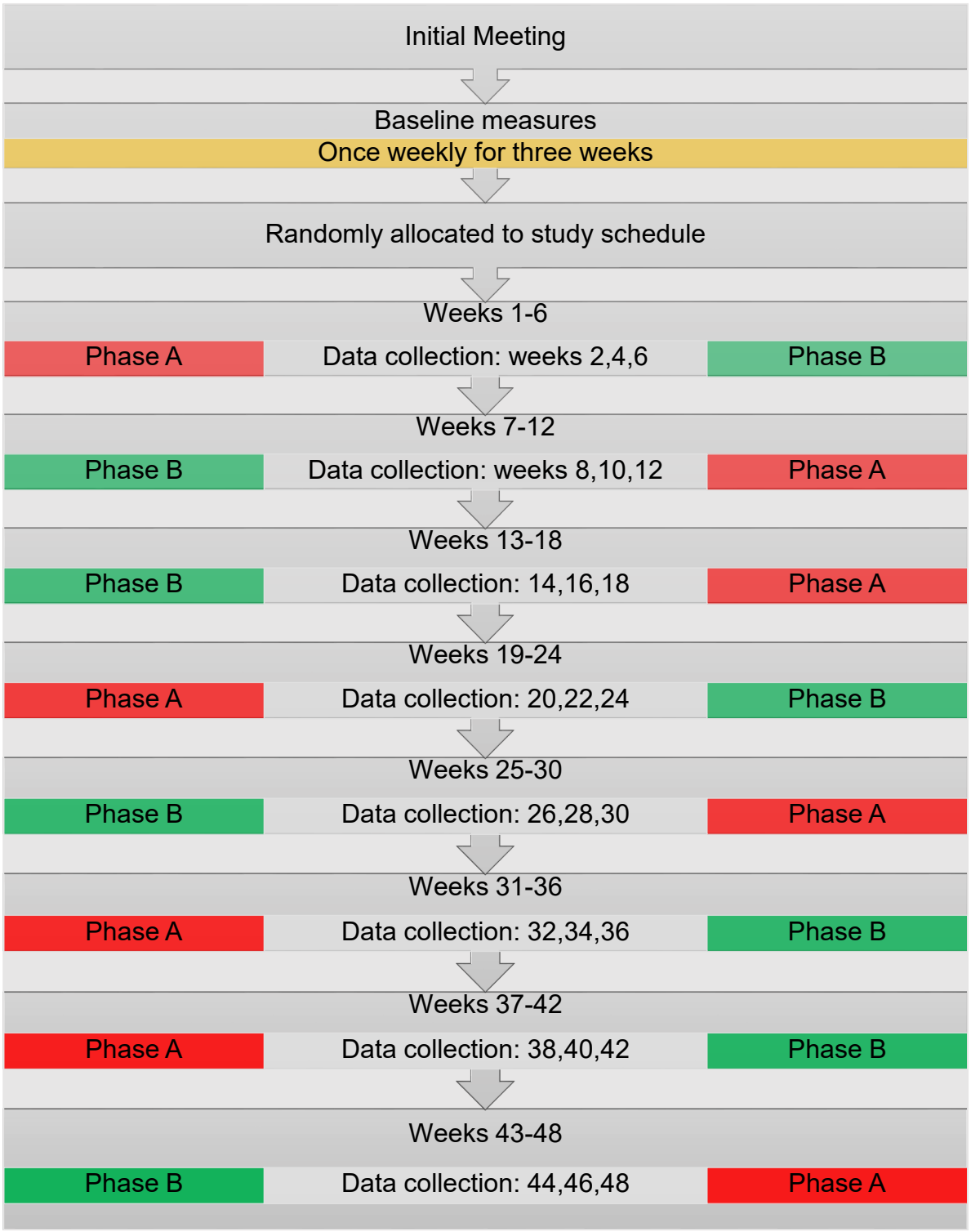


Figure 10. General study schedule

A = non-intervention phase; B = intervention phase.

The setting of the study was entirely online. Any outcome assessments used were delivered using Qualtrics XM. All interviews were conducted using either a web-based video or phone call depending on participant preference and comfort. With the agreement of the participants, the interview was audio recorded and deleted once transcribed. Intervention programmes were delivered via email and accompanied by access to an online folder which held tutorial videos on specific exercises for participant reference (Appendix 8).

4.4.2 Initial interview and screening assessments

An initial interview was conducted in order to (1) screen the participant for study eligibility, ensuring they met clinical criteria for the presence of TES (see Table 2, subsection 2.3.2) and (2) to screen the participant for evidence of potential cognitive impairment, changes in mood/behaviour, or motor impairment associated with CTE (see Table 1, subsection 2.3.2) which could be assessed during the baseline period. To date, there is no established battery of assessments relevant to the specific population included in this study. This is supported by a lack of any results when searching for core outcome sets for TES/CTE on the Comet Initiative website (https://www.comet-initiative.org/). A general approach was adopted instead. The initial interview began with three screening assessments which included:

- Saint Louis University Mental Status (SLUMS)
- Global Mental Health Assessment (GMHAT)
- Patient-Reported Outcomes Measurement Information System Health Assessment Questionnaire - Physical Function 24a (PROMIS – Physical Function 24a)

Details of the screening assessments can be found in Table 8. The initial meeting concluded with a semi-structured interview which sought to elicit further information related to eligibility criteria, as well as provide the participant with an opportunity to share information on topics such as relevant sporting history, medical history, family medical history, and any other further symptoms or concerns the participant wanted to express (Appendix 9).

Table 8. Screening Assessments

Assessment	Description
Saint Louis University Mental Status (SLUMS)	• 11-item cognitive screening assessment • Total possible score: 30 AU • Optimal MCI cut-off: 25 AU • Higher scores indicate higher levels of cognitive function
Global Mental Health Assessment Tool (GMHAT)	• Global mental health screening assessment • Total possible score: N/A • Impairment cut-off: N/A • Higher scores indicate higher levels of mood/behaviour impairment (e.g., higher levels of anxiety, higher levels of depression)
PROMIS bank v2.0-Physical Function 24a	• 24-item physical function screening assessment • Total possible score: 102 AU • Cut-off for impairment: 98 AU • Higher scores indicate higher levels of motor function

MCI: mild cognitive impairment; PROMIS: Patient-reported outcomes measurement information system. N/A: not applicable due to multiple subscales used. Sources: HealthMeasures, 2021; Sharma et al., 2004; Shwartz et al., 2019)

The SLUMS assessment is an 11-item cognitive screening assessment which assesses orientation, attention, numeric calculation, immediate and delayed verbal recall, verbal fluency, executive functions, figure recognition/size differentiation and immediate recall of contextual verbal information (Shwartz et al., 2019). SLUMS has a reported sensitivity of 0.81 and specificity of 0.68 (MCI vs. no diagnosis) (Shwartz et al., 2019). An assessment with clear cut-off points and strong detection abilities was needed to determine if participants met the TES criteria, as it states cognitive impairment must be both self-reported and validated by assessment.

GMHAT is a clinical assessment tool developed by the Home Office and Public Health England which seeks to ‘assess and identify a wide range of mental health problems’ (Sharma et al., 2004:114). Though there are some global mental health screening questionnaires available, they often focus on one or a subset of related disorders. The GMHAT was the most expansive mental health screening tool

available. It includes 20 different areas of enquiry, with each component consisting of one to three different questions. Questions were designed around the International Classification of Diseases 10 (ICD-10) (Sharma et al., 2004). It assesses various symptoms/disorders that are also associated with CTE, including anxiety, impaired concentration, depression, hopelessness, suicidality, insomnia, paranoid delusions, and personality changes. It also enquires about information considered relevant to CTE including PTSD, alcohol abuse, and drug abuse. Due to the nature of the assessment, a total score and cut-off score was not available. This assessment does not seek to provide one global mental health score, rather it rates the severity of each component assessed.

The PROMIS Physical Function 24a assessment investigates self-reported impairments in activities of daily living which may be impacted by present physical dysfunction (HealthMeasures, 2021). The purpose of this assessment was not to identify a specific diagnosis, but rather to lead the researcher through questions which may identify motor symptoms associated with CTE (see Table 1, subsection 2.3.2). Relevant specificity and sensitivity measures for the PROMIS Physical Function 24a assessment could not be found, including the database of measures provided by the Shirley Ryan Ability Lab (www.sralab.org/rehabilitation-measures).

Following the screening assessments, a semi-structured interview was conducted in order to (1) further ensure participants met clinical criteria for the presence of TES (see Table 2, subsection 2.3.2) and (2) to screen the participant for any further evidence of cognitive impairment, changes in mood/behaviour, or motor impairment associated with CTE (see Table 1, subsection 2.3.2).

4.4.3 Baseline phase and outcome assessments

The baseline phase sought to further establish the presence of a functional impairment to meet TES criterion (see Table 2, subsection 2.3.2). In line with PCC, assessments used in the baseline phase were individually selected for each participant based on relevance to the participant and their disease experience. Any symptom associated with the development of CTE had the potential for inclusion (see

Table 1, subsection 2.3.2). Details of the potential outcome measures that were included can be found in Table 9.

Table 9. Outcome assessments

Area of assessment	Scale	Description
Cognitive function	PROMIS Short Form v2.0 - Cognitive function 8a	• 8-item cognitive function self-report assessment • Highest possible t-score: 63.5 AU • Cut-off for impairment: 45 AU • Assessed components of global cognitive function • Higher scores indicate higher levels of cognitive function
	Executive Skills Questionnaire (ESQ)	• 12-item executive function assessment • Total possible score: 252 AU • Cut-off for impairment: N/A • Assessed 12 components of executive function such as sustained attention, working memory, and metacognition • Higher scores indicate higher levels of executive function
	Mindful Attention Awareness Scale (MAAS)	• 15-item mindful attention assessment • Total possible score: 90 AU • Population average: 58 ± 10 AU • Assessed objective experiential awareness and attention • Higher scores indicate higher levels of attention
Mood/ behavioural changes	PROMIS Short Form v1.0 - Anxiety 8a	• 8-item anxiety self-report assessment • Highest possible t-score: 83 AU • Cut-off for impairment: 55 AU • Assessed components of anxiety such as worry, fear, and feeling on edge • Higher scores indicate higher levels of anxiety
	PROMIS Short Form v1.0 - Depression 8b	• 8-item depression self-report assessment • Highest possible t-score: 81 AU • Cut-off for impairment: 55 AU

	• Assessed components of depression such as hopelessness and distress • Higher scores indicate higher levels of depression
Brief Irritability Test (BITe)	• 5-item irritability assessment • Total possible score: 25 AU • Population average: 13 ± 5.5 AU • Assessed components of irritability such as anger, hostility, and neuroticism • Higher scores indicate higher levels of irritability
UCLA Loneliness Scale	• 20-item loneliness assessment • Total possible score: 60 AU • Population average: 33 ± 7.5 AU • Assessed components of loneliness such as social isolation, depression, and interpersonal relationships • Higher scores indicate higher levels of loneliness
Pittsburgh Sleep Quality Index (PSQI)	• 7-item sleep quality assessment • Total possible score: 21 AU • Cut-off for impairment: < 5 AU • Assessed components of sleep quality such as latency, efficiency and disturbances • Higher scores indicate worse sleep quality

Sources: Bellaert et al., 2022; Brown and Ryan, 2003; Buysse et al., 1989; Cohen et al., 1983; Dawson and Guare, 2012; HealthMeasures, 2021; Holtzman et al., 2014; MacKillop and Anderson, 2007; Osman et al., 2016; Russell et al., 1978; Russell, 1996.

Due to the five-assessment limit implemented (see subsection 4.3.2), a baseline assessment which showed no impairment as defined by assessment cut-off scores was replaced with an outcome measure assessing another symptom of interest which was discussed in the initial interview (if enough symptoms were discussed). TES criterion was still met in these instances.

As was stated in subsection 4.2.1, research conducted with a PCC lens should utilize outcome measures which assess outcomes considered meaningful by the participant (Briseid and Skatvedt, 2017; Martin and Félix-Bortolotti, 2014). Further, authors who

promote the use of PCC within a SCED have also advocated for consideration of self-report measures to be used in such settings (Byiers et al., 2012; Kazdin, 2021; Kravitz et al., 2014).

PROMIS assessments, funded by the National Institutes of Health, were a desirable self-report tool. PROMIS assessments were developed with clinicians and researchers in mind and have many useful components, including score interpretation guides and multiple cut-off points to consider. These assessments were developed, calibrated and validated using multiple quantitative, qualitative, and mixed method approaches (HealthMeasures, 2021).

The Executive Skills Questionnaire (ESQ) was included due to its break-down of the twelve different components that it measures (e.g., sustained attention, working memory, and metacognition) (Dawson and Guare, 2012). Despite the lack of available population norms or cut-off range, this assessment was still preferable due to its ability to identify changes in specific components that the participants may have expressed concern over.

The Mindful Attention Awareness Scale (MAAS) was utilized to measure objective awareness and attention. As there are few self-report scales that measure solely attention, this scale was able to measure the participants attention and awareness of their present surroundings (Brown and Ryan, 2003; MacKillop and Anderson, 2007; 2014Osman et al., 2016).

The Brief Irritability Test (BITe) sought to measure dimensions of irritability that included not only anger but hostility, aggression, and neuroticism (Bellart et al., 2022; Holtzman et al., 2014).

The UCLA Loneliness Scale was used to measure feelings of depression and social isolation. (Russell et al., 1978; Russell, 1996). It is one of very few self-report assessments available that measures levels of loneliness.

The Sleep Quality Index (PSQI) was used to measure sleep quality and insomnia. It is easily used by clinicians and researchers and provides a clear cut-off value to identify poor versus good sleepers (Buysse et al., 1989).

4.4.4 Phase A and phase B, bi-weekly follow-ups, and daily activity log

Follow-ups took place every two weeks for the duration of the study. These follow-ups consisted of completing self-report assessments, providing an updated daily log, and completing a semi-structured interview. Table 10 illustrates the participant tasks to be completed for each phase type.

Table 10. Completion of tasks during Phase A and Phase B

Phase A (non-intervention)	Phase B (intervention)

• Bi-weekly semi-structured follow up interview
• Qualtrics survey:
  • Self-report symptom assessments
  • Daily log - physical activity & other contextual information
	• Bi-weekly semi-structured follow up interview
	• Qualtrics survey:
	  • Self-report symptom assessments
	  • Daily log - physical activity & other contextual information
	• One weekly resistance training programme
	• One weekly cardiovascular programme

In addition to these self-report measures discussed in subsection 4.5.3, the Perceived Stress Scale (PSS) was included in some of the Qualtrics surveys. PSS is a 10-item assessment which seeks to perceived stress. The total possible score is 40 AU, with a population average of 13 ± 8.5 AU (Cohen et al., 1983). A higher score indicates higher levels of perceived stress. This assessment was added to give further support to the contextual information gathered during the follow-up interviews. Careful considerations regarding the time for the sessions were prioritised as a pre-requisite for a successful completion of the study, and therefore, PSS was only added to the assessments on those cases when possible (i.e., cases with four or less assessments).

Study participant did not require participants to cease normal activity. Rather, the intervention programmes were developed in a way that sought to increase the activity

load and intensity compared to a participant's normal activity levels. In addition, participants were asked to provide a daily log of activity. A record of daily activity provided context and insight into a participant's activity levels outside of the active rehabilitation programme. Participants were encouraged, but not required, to include any other contextual information they felt was relevant in these daily activity logs (e.g., effect of activity on symptoms, dietary changes, changes in medication).

Finally, a semi-structured interview took place at every data collection point. A list of questions which served as an outline for discussion can be found in Appendix 9. The semi-structured interviews primarily sought to create a PCC environment (see Table 5, subsection 4.2.1), promoting factors such as understanding the participant as a person and encouraging participant involvement. These interviews also sought to investigate i) how the presence of the person-centred active rehabilitation programme affected the symptoms of interest, ii) how the participant described their experience with the rehabilitation programme and prescription, iii) how contextual factors (both proximal and distal) may have influenced the participants symptom levels, and iv) how contextual factors may have influenced their experience with or effect of the programme.

4.4.5 Intervention delivery

The study was designed to be available globally and conducted entirely online; therefore, the intervention needed to have the capacity to be delivered online as well. Further, as the study was being conducted through a PCC framework, the intervention needed to be easily adaptable to the participants' needs, preferences, and abilities. Chapters 2 and 3 provided evidence of a positive effect observed in individuals recovering from mTBI and tauopathies as a result of resistance training, cardiovascular activity, or a multimodal approach (a combination of the two). In particular, Chapter 3 reported a positive effect of general exercise (which included both resistance training and cardiovascular activity) on symptoms of cognitive function, a core feature of TES. Although Chapter 3 also provided evidence of a positive effect as a result of mind and body activities (e.g., yoga, Tai Chi, martial arts) and dance, these were not areas that the researcher has appropriate training in, nor

are they modes of activity that could be easily modified or delivered online. Resistance training and cardiovascular activity are two active rehabilitation techniques that fall within the researchers' scope of practice as an ATC, they can be easily modified to suit individual participants, and the programmes could be adapted to an online delivery system; therefore, this study adopted a multimodal approach with each participant completing one resistance training programme and one cardiovascular programme each week during intervention phases.

The training programmes were tailored by mode, duration, and intensity based on participant needs, preferences, and abilities. Intensities for the resistance training programmes were prescribed utilizing a modified Borg Rate of Perceived Exertion (RPE) chart (Borg, 1998) (Appendix 10). The higher the prescribed the number, the closer to a one rep max the exercise should feel. A prescription of ten would indicate no further repetitions could be completed after the prescribed rep range was achieved, whereas a prescription of one would indicate twelve additional reps could be completed with ease. The intensities of the cardiovascular training programmes were prescribed utilizing the Borg 6-20 chart (Borg, 1998) given its linear relationship with heart rate (Appendix 10). A six on the scale reflected complete rest whilst twenty reflected maximal intensity. Participants could adjust the speed, load, incline, or any other variable to reflect the prescribed intensity ensuring their perception of the intensity corresponded with the anchor given (e.g., “somewhat hard”).

Resistance training programme prescriptions were based on participant experience and strength. Cardiovascular programme prescriptions were based on participant abilities and cardiovascular capacity. Due to the context of the study and also in line with PPC, participant experience and abilities were determined by the participant. This was first established prior to the onset of the study and was monitored throughout the study using relevant follow-up interviews (that is, any interview which proceeded an intervention phase). Here, any necessary modifications or progressions for the rehabilitation programme were discussed and subsequently implemented.

Programmes were emailed to the participants after each relevant follow-up interview. Programmes where specific exercises were prescribed were supplemented with demonstration videos and accompanied by a written description. An example can be

found in (Appendix 8). One aim of conducting the follow-up interviews every two weeks was to discuss with the participant how they were feeling with the present programme. Modifications were made to the programme if, for example, they wished to change the intervention mode, or they felt the programme was causing concern (e.g., it was too difficult). If applicable, progressions of the programme or individual exercises were offered to address any participant adaptation. This ensured an appropriate intensity was maintained throughout the study. Information regarding intervention variation specific to the participants are detailed in Chapter 5.

4.5 Data analysis

4.5.1 Quantitative data

There is little guidance or consensus available on how to conduct visual analysis of SCED or MMSCR systematically (Wolfe at al., 2019). This thesis modified the framework offered by Wolfe and colleagues (2019) and was created in accordance with The What Works Clearinghouse (WWC) Single-Case Design Standards (Kratochwill et al., 2010, 2013). To begin, a predictable pattern of measures was established for each of the paired non-intervention and intervention phases using a split middle trend (SMT) line (Manolov and Solanas, 2017). The SMT line was then used to predict outcome measures for the subsequent phase. Level, trend, and variability were considered here (see Table 11 for definitions). These predicted outcome measures were then compared to the reported outcome measures. If the manipulation of the independent variable was associated with a change in the pattern of behaviour (i.e., change in level, trend, or variability) compared to these predicted measures, a basic effect was established.

Table 11. Potential outcome assessments

Term	Definition
Basic effect	Change in level, trend, or variability
Causal effect	At least three basic effects are demonstrated

Level	Self-reported symptom levels
Trend	Direction and slope of data over time
Variability	Spread/fluctuation of data around trend line
Immediacy of effect	Change occurred between last 3-5 data points of initial phase and first 3-5 data points of subsequent phase
Overlap	Less than 30% of data points overlap with highest/lowest (depending on desired effect) data point of initial phase
Consistency	Similarity in patterns of level, trend, or variability across all intervention/non-intervention phases

Sources: Kratochwill et al., 2010, 2013; Wolfe et al., 2019

If a basic effect was established, the immediacy of the effect and the overlap of data were then considered. After all phases were compared, the consistency of the data patterns between all A and all B phases were considered. Figure 11 illustrates an example of how to determine a basic effect. When the SMT line for phase A1 is extended into the double phase B1 + B2 (as illustrated by the blue arrow), the reported outcome measures do not greatly differ from those predicted by the SMT line. The trend direction did not change either; however, the variability in phase B1 + B2 is significantly reduced compared to that observed in phase A1 (as illustrated by the dotted purple line). This would indicate a basic effect. When the SMT line for B3 is extended into the double phase A3 + A4 (as illustrated by the blue arrow), the variability immediately decreases before then increasing (as illustrated by the dotted purple line). Further, the trend changes direction and the levels are markedly lower than those predicted by the B3 SMT line.

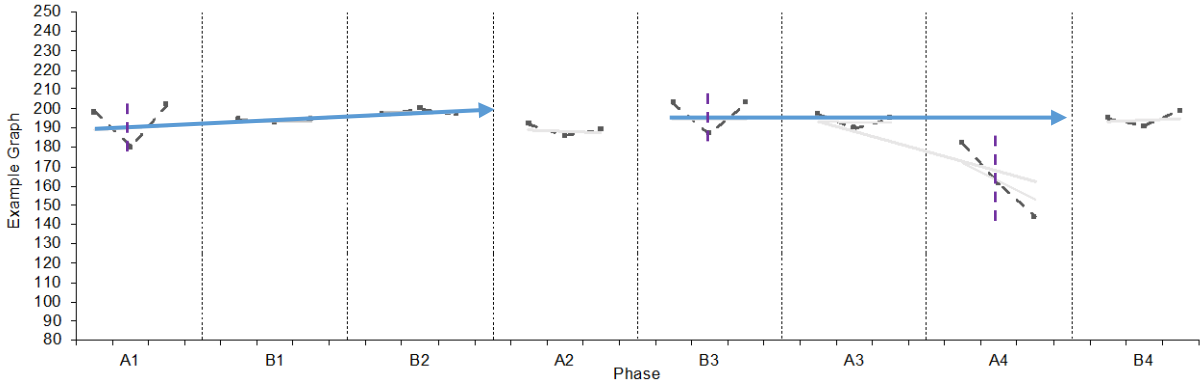


Figure 11. Example of SCED visual analysis.

A = non-intervention phase; B = intervention phase.

If three basic effects were established, then a causal relationship between the intervention and the outcome measures can then be established.

Following the proposed framework for visual analysis provided by Wolfe and colleagues (2019), the size of the effect was estimated using a point system. 1.0 point was awarded for evidence of change in level, trend and/or variability. 0.25 points were awarded if the change was immediate, there was less than 30% of data overlap, or there was evidence of consistency between phase-types (intervention/non-intervention). The proposed framework is based on a classic four phase SCED (i.e., A-B-A-B). This classic design provides three opportunities to demonstrate an intervention effect with possible scores ranging 0-5; however, this thesis has adopted a design which provides five opportunities to demonstrate an intervention effect. The rating scale was therefore modified to suit the design of this thesis and is presented in Table 12.

Table 12. Visual analysis rating scale

Score	Anchor
0	No basic effects; does not demonstrate a causal relationship
1	One basic effect; does not demonstrate a causal relationship
2	Two basic effects; does not demonstrate a causal relationship
3 - 4	Demonstrates a causal relationship with small behavioural change
5 - 6	Demonstrates a causal relationship with moderate behavioural change
7 - 8	Demonstrates a causal relationship with large behavioural change

Source: adapted from Wolfe et al., 2019. Must demonstrate a minimum of three basic effects.

In addition to visual analysis, within-case standardized mean difference (WC-SMD) and non-overlap of all pairs (NAP) were calculated using the shiny app SingleCaseES: single case effect size calculator provided by Pustejovsky and colleagues (2022). Raw scores were presented with mean ± standard deviation. SMDs were classified according to Cohen's definition, with effect values interpreted as: 0.20-0.50, small; 0.51-0.80, moderate; >0.80, large (Cohen, 1988). A decision on whether NAP was significant or not was based on how close it was to .50, where NAP = 0.50 suggests equal data overlap between matched pairs. This indicates the probability of a randomly selected data point in phase B being greater (or lower depending on the desired effect) than phase A is, on average, 50% (Pustejovsky et al., 2022).

These statistics capture global differences observed across the twelve-month study span. This complements the phase-by-phase approach of the visual analysis detailed above. Statistics were employed to inform and reinforce the broader findings of the causal effect by commenting on the size of the effect measured during intervention phases against non-intervention phases as well as the probability that an outcome measure taken during an intervention phase would overlap with levels observed during non-intervention phases (Brossart et al., 2014).

If one data point was missing from a phase, the mean of the other two data points was taken. If two or more data points were missing from a double intervention phase

(e.g., B1 + B2), the single data point was plotted, and the missing data was explicitly reported to add caution to the interpretation of results. If the missing data occurred in a single intervention phase (e.g., B1), this phase was removed from visual analysis. Statistical analysis was still carried out with missing data.

4.5.2 Qualitative data

Analysis followed the explanation building approach outlined in subsection 4.2.3. Considering the research aims outlined in subsection 4.1, the following propositions were initially determined:

1. The presence of the person-centred active rehabilitation programme had a positive effect on the participant's symptoms of interest
2. The needs and preferences of the participant regarding the rehabilitation mode and prescription were met
3. Proximal and distal factors influenced i) the participant's reported symptom levels, ii) the participant's experience with the active rehabilitation programme, and iii) the effect of the active rehabilitation programme

While a total of twenty-four follow-up interviews were available, a pragmatic approach for qualitative analysis was adopted (Braun and Clarke, 2021). Instead, a sample of interviews was included for analysis. This sample consisted of interviews that took place at the end of each A-B paired phase (e.g., A1.3, B2.3, B3.3, and A4.3). This allowed for the time constraints of PhD research to be addressed, but further, selecting the interviews which took place at the end of a paired phase provided a more global view of the participant perspective as it related to the phase (whether A or B) and present contextual factors.

Interviews were first transcribed using an intelligent verbatim transcription approach, with 'unrelated dialogue' removed from the transcripts. This 'unrelated dialogue' consisted of personal conversation that may have taken place between the researcher and the participant. Such conversation creates a person-centred environment by encouraging the participant and researcher to learn about one another as a distinct person. It also encourages participant authenticity. These are essential components for creating the safe, critical, and creative communicative

space characteristic of PCC research (see Table 5, characteristics of PCC research); however, this dialogue was not considered relevant to the overall analysis of outcomes of the study. Once transcribed, the transcriptions were read and re-read (at minimum three times) looking for discussion related to the topics of interest defined by the above propositions. Additional topics were permitted to emerge as well. After coding all selected transcripts across all participants, the following themes emerged: disease experience, patient as person, COVID-19, and treatment plan. A table of themes, subthemes, and representative quotes were compiled for each participant and sent to all supervisors. This was accompanied by a random selection of nine transcripts. Each supervisor checked three of the transcripts for accuracy (against the provided table) as to increase trustworthiness and decrease risk of bias. Feedback was considered and the transcripts were read again before the final propositions were determined. These propositions were then compared against other sources of information (quantitative analysis, daily activity logs, prescribed active rehabilitation programmes) and a narrative summary was provided in the following case subsections:

- Subsections titled ‘participant perspective’ present information regarding the effect that the intervention had on symptoms of interest (proposition 1)
- Subsections titled ‘intervention schedule and physical activity’ present information concerning needs and preferences of the participant as it relates to the active rehabilitation programme (proposition 2)
- Subsections titled ‘study schedule and context’ presented information regarding contextual factors and what influence they may have had on symptom levels, participant experience, and the potential effect of the active rehabilitation programme (proposition 3)

A summary of the results, which included the integration of all data sources, was then provided at the end of each case. Here, all components of the case and how they interacted were presented. Sources of additional data included the quantitative analysis of the self-report measures (the n-of-1 component), daily activity logs, and the prescribed active rehabilitation programmes. Summaries were shared with supervisors who again checked for accuracy to increase trustworthiness and decrease risk of bias.

To maintain scientific rigour while integrating qualitative data to this study, consideration for credibility, transferability, dependability, and confirmability was undertaken as follows:

1). Credibility is a fundamental principle in qualitative research that seeks to ensure the data presented and interpreted in such a way that confidence this reflected the participants truth is maximised. In this study, credibility was maximised by t taking several steps. Firstly, the extended period of participation with multiple interviews taking place allowing the research to check for consistency of information (i.e., response validation), build trust, and allowed topics to be revisited. Secondly, multiple types of data were collected during the study allowing for a degree of triangulation of the findings (e.g., depression score and interview data). Thirdly, a degree of debriefing was completed with the project supervisors. Finally, a think description of the topics was extracted and interpreted before being presented.

2). Transferability indicates the degree to which an observed response would be expected when applied to other contexts or similar conditions (Watkins, 2012). The qualitative data in this study sought to provide a detailed understanding of the context in which the observed responses occurred. This includes not only detailed information on the rehabilitation programme and activity levels, but also a detailed understanding of the surrounding context for which the intervention was taking place in. When synthesizing the results of all cases together, such detail allows others to make a judgment about the possible transferability to a context relevant to them.

3). Dependability ensures that research processes are consistent and carried out with careful attention (Watkins, 2012). While this study followed a semi-structured approach, the same questions were asked (see Appendix 9) and the same areas of interest were probed every two weeks for 48 weeks total. Further, transcripts and analyses were checked by supervisors to ensure accuracy. Finally, supervisors had an overview of the entire research process including all consent forms, data storage, notes, and any issues that might have arisen.

4). Confirmability implies that influence by the observer was minimised (Watkins, 2012). While the methods of this study did not allow for a great deal of distance

between the observer and the observed, analysis of qualitative or quantitative data was not carried out for any participants until the final case was concluded. Further, supervisors checked key documents (i.e., transcript, analyses) for accuracy and potential confirmation bias.

5 Chapter 5: Case results

5.1 Chapter overview

Chapter four outlined the methodology for a mixed methods single case research (MMSCR) design rooted in pragmatism and PCC was discussed. Methods for visual, statistical, and qualitative analysis were then presented. Chapter five presents the results of a series of single case studies. The effect that a person-centred active rehabilitation program had on symptoms suspected to be related to CTE on six cases was presented with attention given to contextual information and intervention prescription when presenting the results.

5.2 Initial interview and baseline period

Ten participants were recruited for the study. Two participants did not demonstrate a measurable impairment during the screening or baseline phase in one of the three core clinical features and therefore did not meet eligibility criteria (see subsection 4.4.1 for eligibility criteria). A further two participants withdrew from the study before they completed an entire AB matched phase; therefore, their data was excluded from the study. A cause for withdrawal was not given in either case.

Participant information to be considered as informed by the initial semi-structured interview for included participants (n = 6) can be found in Table 13 (see subsection 4.4.2 for initial interview and baseline methods). Figure 12 illustrates a complete study timeline across all participants and includes contextual information regarding the COVID-19 pandemic regulations in place at the time of data collection.

Table 13. General participant information.

PTP (age, sex, nationality)	History of head impacts	SLUMS*	GMHAT	PROMIS*	Additional participant history**
Niall (20/M/UK)	> 6 years: field hockey, basketball, rugby	27/30 AU WNL	**Cognitive:** concentration **Mood/behaviour:** worry, anxiety, loss of interest	100/102 AU No motor impairment	**Cognitive:** memory impairment, executive dysfunction **Mood/behaviour:** history of depression, suicidal tendencies, social isolation
Luigi (38/M/ Canada)	> 6 years ice hockey	25/30 AU MCI	**Cognitive:** concentration **Mood/behaviour:** worry, anxiety, depression, loss of interest	100/102 AU No motor impairment	**Cognitive:** memory impairment, concentration and attention impairment, executive dysfunction **Mood/behaviour:** irritability, short fuse, explosivity, history of panic attack, history of suicidal ideation Persistent headaches

Kristen (29/F/US)	> 6 years: rugby, softball	30/30 AU WNL	**Cognitive:** concentration **Mood/behaviour:** worry, anxiety, depression, loss of interest, hopelessness, sleep disruption	98/102 AU Mild signs of motor impairment - result of recent surgeries	**Cognitive:** memory impairment, concentration and attention impairment, executive dysfunction. Diagnosed with ADHD and currently on medication. **Mood/behaviour:** anxiety, depression history of panic attack, history of suicidal ideation. Diagnosed with GAD and PDD and currently on medication. Persistent headaches
Abel (24/M/US)	> 6 years: American football, football, rugby	27/30 AU WNL	**Cognitive:** concentration **Mood/behaviour:** worry, anxiety, depression, loss of interest	101/102 AU No motor impairment	**Cognitive:** attention impairment, executive dysfunction **Mood/behaviour:** anxiety, depression
Gemma (29/F/US-Italy)	> 6 years: karate, basketball, softball, volleyball	30/30 AU WNL	**Cognitive:** concentration	102/102 AU No motor impairment	**Cognitive:** executive dysfunction **Mood/behaviour:** history of panic attack

			Mood/behaviour: worry, anxiety		
Simon (35/M/UK)	> 6 years rugby	23/30 AU MCI	**Cognitive:** concentration **Mood/behaviour:** worry, anxiety, depression	100/102 AU No motor impairment	**Cognitive:** cognitive impairment, executive dysfunction **Mood/behaviour:** mood disturbances Persistent headaches

Participant pseudonyms, duration, and type of sport played when exposed to head impacts, outcomes from screening assessments, and additional relevant individual symptom reported during initial interview details are presented.

*Measured score/total score of assessment. ** informed from semi-structured interview

F: female, GAD: Generalised anxiety disorder; GMHAT: Global Mental Health Assessment; M: male, MCI: mild cognitive impairment (according to assessment cut-off); PROMIS: Patient-Reported Outcomes Measurement Information System Health Assessment Questionnaire - Physical Function 24a; PDD: Persistent depressive disorder; PTP: Participant; SLUMS: Saint Louis University Mental Status; WNL: within normal limits (according to assessment cut-off).

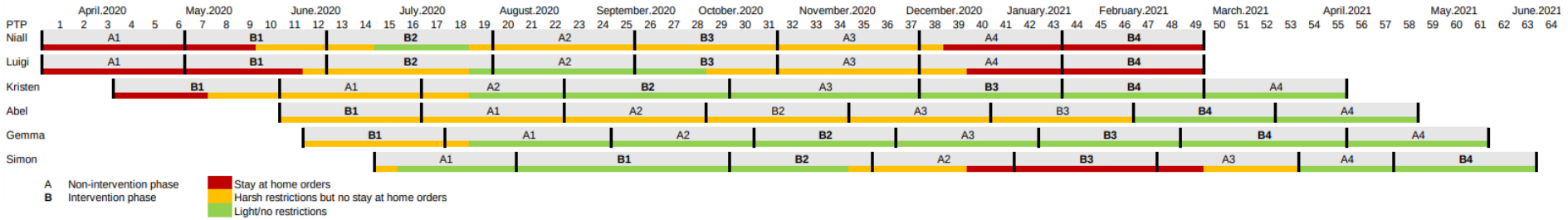


Figure 12. Participant characteristics and study timeline.

Includes contextual information concerning the COVID-19. A = non-intervention phase; B = intervention phase.

5.3 Niall

5.3.1 Participant history, screening, and baseline assessment

Niall was a 20-year-old male student apprentice from England (United Kingdom). He was single and living at home with his mother and sister. Niall reported a long history of participation in various contact sports, including field hockey, basketball, and rugby. At the time of starting the study, he was participating in recreational field hockey. Table 14 presents the results from the initial interview and baseline assessments which directed the list of outcome measures.

Table 14. Niall: Traumatic Encephalopathy Syndrome criterion, study eligibility, and outcome measures of interest

Criteria	Results from initial interview & baseline measures
History of multiple head impacts (direct or indirect)	No history of TBI Over 6 years of exposure to subconcussive trauma
No other neurological disorder present that likely account for all clinical features	None identified
Signs/symptoms must be present for a minimum of 12 months	First noted ~2.5 years ago
Presence of at least one core clinical feature	**Cognitive:** • Concerns of impaired memory, concentration • Signs of executive dysfunction • SLUMS score 27/30 AU - score 'within normal limits' • PROMIS Short Form v2.0 - Cognitive function 8a - scores between 'within normal limits' and 'mild' cut-off **Mood:** • Reported history of depression PROMIS Short Form v1.0 - Depression 8b - scores 'within normal limits'
Presence of at least two supportive features	Anxiety, history of suicidality, delayed onset • PROMIS Short Form v1.0 - Anxiety 8a - scores 'within normal limits'
Additional symptoms to consider	Social isolation

Table informed by TES criteria (see Table 2, subsection 2.3.2). Additional symptoms informed by list of symptoms associated with CTE (see Table 1, subsection 2.3.2). Cut-off measures determined by assessment used (see Table 9, subsection 4.3.4)

PROMIS: Patient-Reported Outcomes Measurement Information System; SLUMS: SLUMS: Saint Louis University Mental Status; TBI: traumatic brain injury.

Measures of cognitive function displayed impairment on self-report scores; however, it should be noted that this impairment was not observed across all baseline data points. When considering those questions which Niall did display consistently lower scores (indicating lower levels of cognitive function), impairments in memory and executive function were apparent. This was also observed in Niall's assessment of anxiety, in which those questions with consistently higher scores (indicating higher levels of anxiety) were symptoms of executive dysfunction (e.g., attention impairment, indecisiveness, fidgeting). Therefore, outcome assessments measuring cognitive function and executive function were included. Niall did not demonstrate elevated levels of anxiety or depression; however, those questions which consistently observed higher scores during the baseline phase (indicating higher levels of anxiety or depression) were primarily to do with feelings as expressed through loneliness or social isolation. This was something that Niall had also expressed in his initial interview. Therefore, an outcome assessment measuring loneliness was included in order to measure levels of social isolation.

As a result, Niall's outcomes of interest included:

- Cognitive function (global cognitive function, executive function, memory, concentration), assessed with PROMIS Short Form v2.0 - Cognitive function 8a and Executive Skills Questionnaire (ESQ)
- Social isolation (loneliness), measured with UCLA Loneliness Scale

In addition, PSS was included to gather further information regarding stress levels experienced throughout the study (see subsection 4.4.4).

5.3.2 Intervention schedule and physical activity

Niall was a healthy and active young adult. He reported enjoying gym-based workouts and continued to participate in recreational field hockey when able. There were no reported precautions or contraindications to be considered when developing Niall's programmes. A summary of his exercise prescription, activity levels as reported from the daily activity logs, and any contextual information extracted from the follow-up interviews are presented in Figure 13.

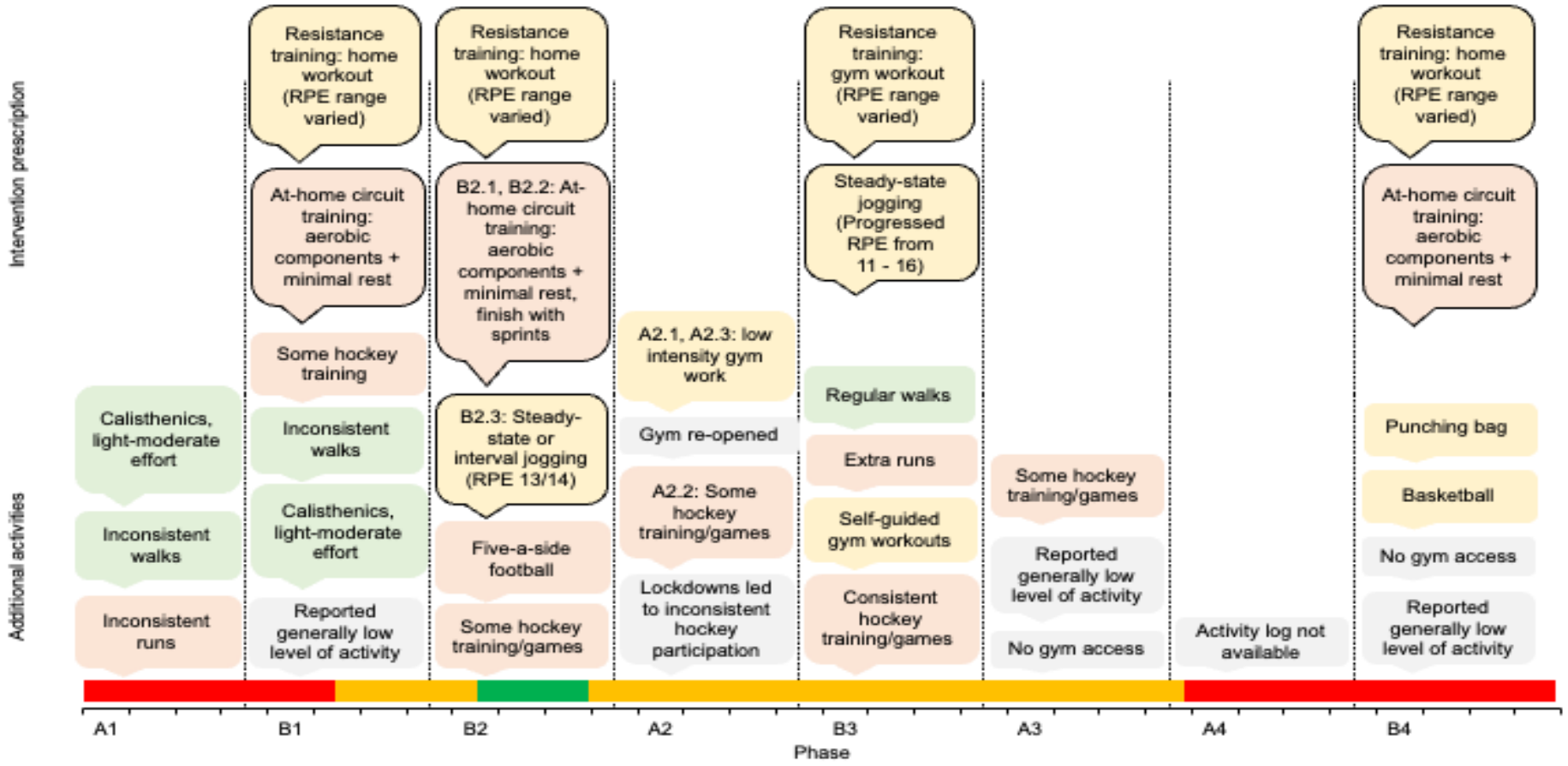


Figure 13. Niall's intervention schedule and reported activity levels

Prescribed activity outlined in black. Additional activities were informed by daily activity log or included follow-up interviews (B1.3, A2.3, A3.3, B4.3). Activities characterised in accordance with recommendations from Ainsworth et al. (2011) and Bull et al. (2020b): Light intensity. Moderate intensity. Vigorous intensity. Distal context. General state of Covid-19 lockdown responses as informed by local news sources: — stay-at-home orders. — Strict restrictions (no stay-at-home orders). — Light/no restrictions. A = non-intervention phase; B = intervention phase.

The needs and preferences of the participant regarding the strength training programmes changed throughout the study and depended primarily on Niall's accessibility to a gym, which was impacted by the COVID-19 lockdown measures and his comfort-level with returning to gyms. As such, only one phase (B3) was completed in a gym setting despite that being Niall's preferred environment. B1, B2 and B4 programmes consisted of home-based workouts utilising body-weight exercises. Niall's view of these home workout programmes was summarised by the following being stated in B1.3:

> Honestly, I've gotten to the point now, even with my general daily exercises. I'm thinking just, I cannot be bothered with these [home workouts] anymore. Just let me go to a gym.

Effort was made to make these workouts as engaging as possible for Niall despite the circumstances. Generally, exercises were progressed by using household objects as weights or by modifying the exercises to alter the intensity (such as a timed hold, tempo, or variations in form). He stated that he was happy with changing some of the exercises to introduce variety but did express his preference for the 'too failure' exercises. He stated in his B1.3 follow-up interview,

> ...you know how it was keep going till failure? I think that was good because like, at least that way you could gauge improvements...

These exercises were kept for the remainder of any programmes intended to be completed at home as being able to gauge improvement seemed important for buy-in to the programme.

The needs and preferences of the participant regarding the cardiovascular training programmes also changed throughout the study and were largely dependent on the season (i.e., warm and dry versus cold and rain). They were also influenced by the COVID-19 pandemic and his access to the gym. In the initial introduction of the intervention (B1), Niall preferred doing circuit training to satisfy the cardiovascular requirement. The circuit training programmes were progressed by manipulating the number of reps or rounds completed. To increase intensity further, sprints were added to the end of the circuits in phase B2. This also allowed Niall to get outside

more, something he expressed wanting as the weather was improving. This continued until B2.3 where Niall reported he would prefer to run outside for the whole cardiovascular programme, as opposed to just sprints at the end. He was given the option to choose between steady-state jogging or interval running. In B3, Niall preferred steady state running as he could do this outside or at the gym. His prescription was increased each week by manipulating either the intensity or the duration of activity. In B4, Niall returned to circuit training due to the weather (which turned cold and rainy) and the continued presence of the COVID-19 pandemic (which restricted his access to the gym). He felt this programme was intense; therefore, no progressions or changes were made in this phase.

5.3.3 Cognitive function

5.3.3.1 PROMIS Short Form v2.0 - Cognitive function 8a

There was a positive effect of the programme on Niall's cognitive function (Figure 14). A complete visual analysis report can be found in Appendix 11.1.

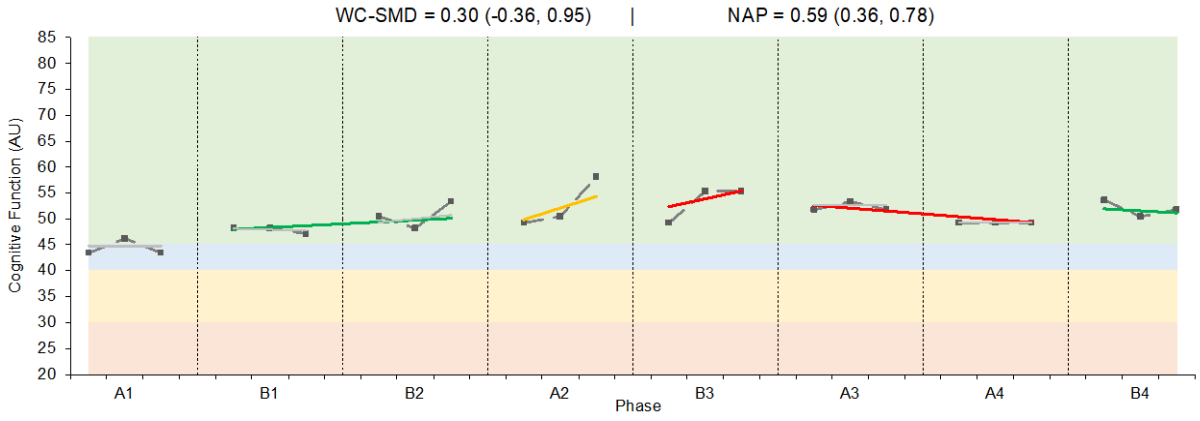


Figure 14. Niall's self-report scores from PROMIS Short Form v2.0 - Cognitive Function 8 assessment

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. Population norms: — Normal. — Mild levels. — Moderate levels. — Severe levels. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Four basic effects were observed on measures of cognitive function (visual analysis rating = 4.75, small behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Two of these basic effects were positive (B1 + B2, B4), and two of them were negative (B3, A3 + A4). See subsection 4.5.1, Table 11 and Table 12 for terms associated with visual analysis of n-of-1 studies.

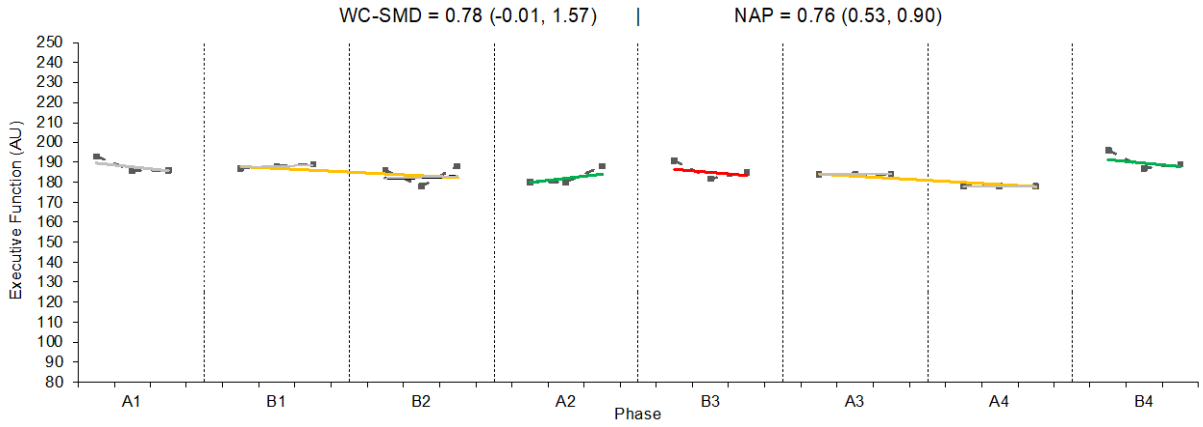
The initial introduction of the intervention (B1 + B2) demonstrated an immediate increase in levels of cognitive function (indicating improving levels) with little to no overlap; however, the direction of the trend line and variability did not change. When removed (A2), no basic effect was observed; that is, the trend direction, levels, and variability did not differ from those predicted by the SMT line in B1 + B2. When the intervention was re-introduced (B3), the levels of cognitive function were lower than those predicted by the A2 SMT line (indicating worsening symptoms); however, the trend direction and variability were unchanged. Further, the effect was not immediate, and overlap was present. When removed (A3 + A4), levels of cognitive function were lower (indicating worsening symptoms) and the trend changed to a negative direction. The variability decreased. The effects were not immediate, and overlap was present. It should be noted here that two data points were missing from this set; therefore, results should be interpreted with caution. The final introduction of the intervention (B4) resulted in an increase in levels of cognitive function (indicating improving levels); however, variability increased. Further, the trend direction remained unchanged and in a negative direction. These effects were immediate, but overlap was present. There were no consistent patterns observed across either phase types.

Analysis of data across the entire study period indicated a small positive, within-case effect of the intervention on measures of cognitive function (WC-SMD = 0.30, 95% CI -0.36 to 0.95) with scores recorded during intervention phases (40.9 ± 2.9 AU) 1.30 points higher than those recorded during non-intervention phases (49.6 ± 4.1 AU). NAP (NAP = 0.59, 95%CI 0.36 to 0.78) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being greater than a randomly selected data point in phase A is, on average, 59%

5.3.3.2 Executive Skills Questionnaire

There was a positive effect of the programme on Niall's executive function (Figure 15). A complete visual analysis report can be found in Appendix 11.1.

Figure 15. Niall's self-report scores from Executive Skills Questionnaire



▪Raw data. — Split middle trend (SMT). — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Three basic effects were observed on measures of executive function (visual analysis rating = 4.00, small behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in executive skills. Two of these basic effects were positive (A2, B4), and one was negative (B3).

There was no basic effect demonstrated with the initial introduction of the intervention (B1 + B2). The removal of the intervention in A2 resulted in a positive change in trend direction; however, the levels of executive function were not different from those predicted by the B1 + B2 SMT line, nor was the change immediate. In addition, variability was unchanged and data overlap was present. The re-introduction of the intervention (B3) also demonstrated no change in levels or variability, but the trend turned negative. Again, this effect was not immediate, and overlap was present. No basic effect was demonstrated with the removal of the intervention (A3 + A4). It should be noted here that two data points were missing from this set; therefore, results should be interpreted with caution. Finally, the last intervention phase (B4)

observed an immediate improvement in executive function compared to levels predicted by the previous SMT line (A3 + A4) (indicating improving levels); however, the trend continued to decline, and the variability was unchanged. There was little to no overlap observed. The variability appeared unchanged across all phases. There was no consistent pattern of trend direction or levels in either phase types.

Overall, a moderate positive, within-case effect of the intervention on measures of executive function (WC-SMD = 0.78, 95% CI -0.01 to 1.57) with scores recorded during intervention phases (187.2 ± 4.5 AU) 3.92 points higher than those recorded during non-intervention phases (183.3 ± 4.7 AU). NAP (NAP = 0.76, 95%CI 0.53 to 0.90) suggests a low level of data overlap between matched pairs where the probability of a randomly selected data point in phase B being greater than a randomly selected data point phase A is, on average, 76%.

When analysing specific components of executive function (Table 15), active rehabilitation demonstrated a large effect on measures of response inhibition and a moderate effect on metacognition. A small effect was observed on measures of emotional control, flexibility, goal-directed persistence, and task initiation. A small negative effect was observed on measures of time management and working memory. All other measures reported a trivial effect.

Table 15. Niall's individual components of executive function

Executive skill	Mean A ± SD	Mean B ± SD	WC-SMD (95%CI)	NAP (95%CI)
Emotional control AU	16.60 ± 0.70	16.83 ± 1.85	0.24 (-1.35, 1.83)	0.52 (0.31, 0.73)
Flexibility AU	13.30 ± 1.70	14.3 ± 1.23	0.42 (-0.26, 1.09)	0.62 (0.39, 0.80)
Goal-directed persistence AU	15.60 ± 0.84	15.67 ± 1.30	0.31 (-0.57, 1.20)	0.54 (0.32, 0.74)
Metacognition AU	15.50 ± 0.53	15.83 ± 0.83	0.75 (-0.29, 1.80)	0.68 (0.44, 0.84)
Organization AU	16.20 ± 1.40	16.00 ± 0.85	0.10 (-0.50, 0.71)	0.57 (0.34, 0.76)
Planning/ prioritization AU	15.70 ± 1.64	15.50 ± 0.90	0.05 (-0.56, 0.65)	0.60 (0.37, 0.78)
Response inhibition AU	14.60 ± 1.17	16.17 ± 1.19	1.43 (0.47, 2.38)	0.85 (0.62, 0.95)
Stress tolerance AU	16.10 ± 1.29	15.92 ± 1.00	0.00 (0.68, -0.68)	0.53 (0.32, 0.73)
Sustained attention AU	15.70 ± 1.06	15.58 ± 0.79	0.00 (-0.67, 0.67)	0.56 (0.34, 0.76)
Task initiation AU	13.40 ± 1.58	13.92 ± 1.00	0.38 (-0.28, 1.04)	0.66 (0.43, 0.83)
Time management AU	17.60 ± 1.17	17.50 ± 0.67	-0.22 (-0.88, 0.44)	0.40 (0.21, 0.63)
Working memory AU	13.80 ± 1.14	13.83 ± 1.11	-0.27 (-0.80, 0.27)	0.49 (0.28, 0.70)

Range of potential scores: 0-21 AU. Desired effect. Undesired effect. Trivial effect/Overlap. A = non-intervention phase; B = intervention phase; NAP = non-overlap of all pairs; WC-SMD = within case standardized mean difference.

5.3.4 Mood/behaviour

5.3.4.1 UCLA Loneliness Scale

A positive effect was observed on Niall's symptoms of social isolation and depression (Figure 16); however, statistical analysis calls into question whether this was a result of the active rehabilitation programme. A complete visual analysis report can be found in Appendix 11.1.

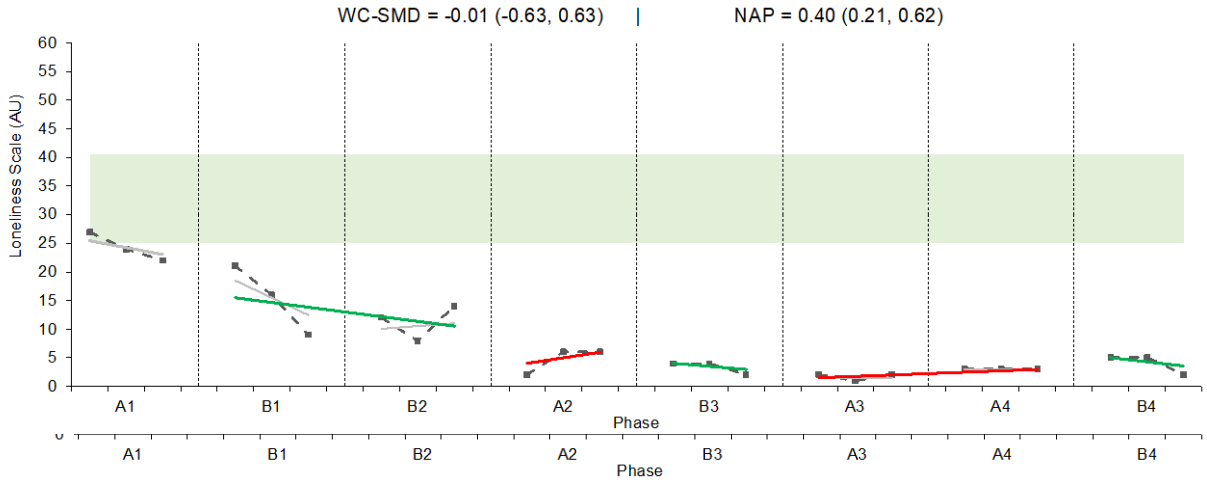


Figure 16. Niall's self-report scores from UCLA Loneliness Scale

■Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. Population norms: — Population average. — Above population average. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Five basic effects were observed on measures of loneliness (visual analysis rating = 6.50, moderate behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and levels of loneliness. Three of these basic effects were positive (B1 + B2, B3, and B4), and two were negative (A3, A3 + A4).

The initial introduction of the intervention (B1 + B2) observed an immediate improvement in levels of loneliness when compared to the A1 SMT line; however, variability was increased. The trend direction was unchanged, but little to no overlap was observed. When the intervention was removed (A2), the trend immediately changed to indicate a worsening of symptoms; however, variability decreased. Levels

did not differ from those predicted by the previous SMT line (B1 + B2) and there was little to no overlap present. When the intervention was re-introduced (B3), the trend direction observed an immediate improvement in levels of loneliness and were lower than those predicted by the previous SMT line (A2). Variability was unchanged, and overlap was present. When removed (A3 + A4), the trend direction indicated a worsening of symptoms and levels were higher than those predicted by the previous SMT line (B3); however, this change was not immediate, and overlap was present. Variability was unchanged. It should be noted here that two data points were missing from this set. The final introduction of the intervention (B4) observed only a change in the trend direction, indicating an improvement in symptoms. Levels and variability did not differ from those predicted. The effect was not immediate, and overlap was present. The low levels of variability were consistent across all non-intervention phases. Intervention phases consistently saw a negatively trending SMT. No other patterns were observed consistently across either phase types.

Analysis across the study duration reported a trivial negative, within-case effect of the intervention on measures of loneliness (WC-SMD = -0.01, 95%CI –0.63 to 0.61) with scores recorded during intervention phases (8.50 ± 6.07 AU) 1.00 points lower than those recorded during non-intervention phases (9.50 ± 10.44 AU). NAP (NAP = 0.40, 95%CI 0.21 to 0.62) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being lower than phase A is, on average, 40%.

5.3.5 Participant perspective

In those follow-up interviews which were included (B1.3, A2.3, A3.3 and B4.3), Niall did not talk about his cognitive and executive function in relation to the intervention. Most of the discussions were related to how the symptoms were affected by the COVID-19 pandemic (see subsection 5.3.6 for further details). Only in phase A3.3 did he discuss his symptoms outside of the context of the pandemic, stating,

> Memory- I’ve not really been listening to that many people, so I guess it’s not necessarily a memory issue, more of a listening issue.

When asked specifically about the overall effect that he believes the study had on his cognitive function (phase B4.3), Niall reported,

> I feel like over time my memory- I've gotten more focused.

Niall attributed some of this improvement to the implementation of some coping mechanisms such as writing lists which he learned when receiving CBT throughout phase B4. He stated (B4.3),

> I've started writing things in lists. But I feel like in time, that has helped me....My notes pages on- my lists have gotten a lot more vague.

However, when asked which symptom he felt most benefit from participating in the study, he answered (B4.3),

> I'd definitely say memory.

This indicated that the intervention, in addition to the coping mechanisms, resulted in a perceived improvement in memory and cognitive functioning.

Based on the included follow-up interviews which were included (B1.3, A2.3, A3.3 and B4.3), it was difficult to determine what effect the intervention had on Niall's symptoms of social isolation and depression.

In phase B1, Niall expressed,

> I've got people to talk to it's just nice to have- it's like in the survey, one the questions is companionship. I know this isn't companionship, but personally I don't think I need companionship necessarily right now, but more just a sense of having people that want to talk to me...

And in phase A2, Niall reported continuing to see his family for weekly get-togethers on Sundays. Further, in phase A3, Niall was relaxed and refreshed, stating,

> I've had nothing to be anxious about...I am very chilled at the moment...

When asked about the overall effect that he believes the study had on his symptoms of social isolation and depression, Niall stated (B4.3),

> ...as the year has gone on, depression has very much become a thing of the past. And I know we spoke before, at the start of the study, there's a quite significant time in my history where there's a lot of depression. And I feel like the more time that goes between that, the less it's even there.

This statement would indicate that he did experience an improvement in feelings of loneliness and social isolation, but it is difficult to determine whether the intervention was solely responsible for such an improvement.

5.3.6 Study schedule and context

Niall began the study in March 2020, amidst the beginning of the COVID-19 pandemic. Figure 17 illustrates an estimated timeline of the government pandemic response in Niall's area and his PSS scores. Figure 17 also includes additional distal contextual information that may have influenced the study experience, as informed by the included follow-up interviews (B1.3, A2.3, A3.3, B4.3) and general news sources.

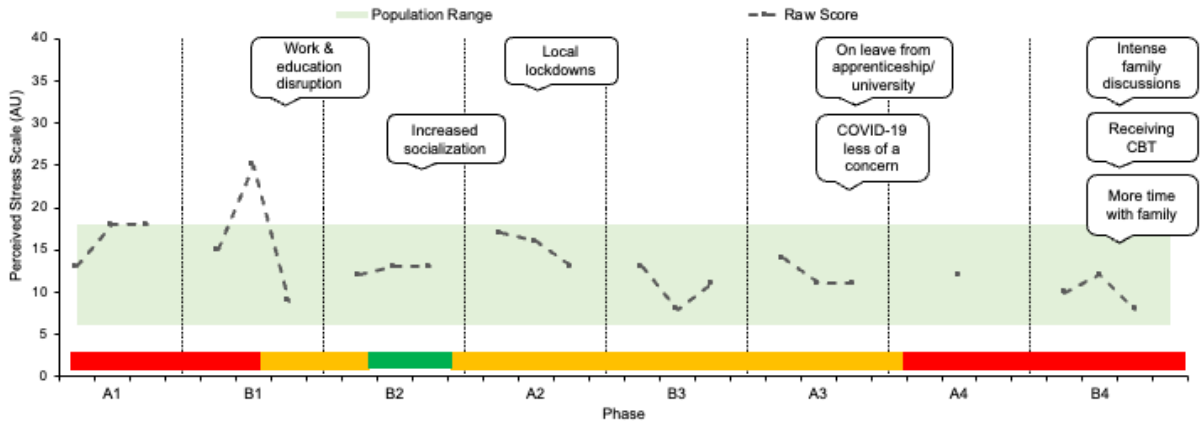


Figure 17. Niall's PSS scores at each data collection point

A higher score indicates higher levels of perceived stress. Population norms: — Population average. The general state of Covid-19 lockdown responses as informed by news sources are represented as: — stay-at-home orders, — strict restrictions (no stay-at-home orders) and — light/no restrictions. A = non-intervention phase; AU= arbitrary unit; B = intervention phase. CBT: cognitive behavioural therapy.

Niall discussed how the pandemic disrupted his work and university environment. Not only did this cause some irritability for Niall, but he mentioned it was having a negative impact on his cognitive and executive functioning. In B1.3, he stated,

> ...the only thing that I noticed that I can't really do at the moment, I'm really struggling to do, is just multitasking. I, for the life of me, cannot multitask at the moment.

When asked if this was normal for him, he responded,

> Generally speaking, I'd say no. I think this might be to do with just being cooped up more so than anything.

He went on to say,

> ...and I'm still doing the work, I'm just doing it at a slower pace....I don't have any pressured work at the moment.

This lack of pressure was caused by the disruption in his apprenticeship, where he was having to now work and learn from home. This caused a general reduction in workload and programme demands. Niall had general difficulty adjusting to this new environment at first and it appeared to have an influence on his cognitive and executive functioning scores; however, the global pandemic did not appear to have a significant influence throughout the entire study. In A3, Niall was stating,

> ...COVID, for the most part, hasn't really been a concern...the only mild concern we've had is in relation to me and whether I can or can't go to hockey this last week. Which, if I can't, it's not the world's worst situation...

This idea was re-iterated in B4, when Niall stated,

> I think, for me, this is just going to be my general life now at this point. Like, the whole working from home thing. Apprentices are going to be the last to return to work anyway, so this is probably going to be me for at least another year.

It should be noted that throughout the study, Niall had sensitive family circumstances going on which may have influenced his overall health and well-being. It was not a topic that was discussed at length during the follow-interviews; however, Niall did

report in A4 that he started receiving CBT from the National Health Services (NHS) to help process the events. Niall described himself as feeling level-headed about the circumstances. Niall did not explicitly report whether CBT was having any effect on present symptoms.

5.3.7 Results summary

A person-centred active rehabilitation programme demonstrated a positive effect on Niall's symptoms of cognitive dysfunction (global cognitive function, executive function, memory, concentration) and social isolation (loneliness). Table 16 illustrates a summary of results across the study.

Table 16 Niall's summary of results

Area of assessment & *symptoms of interest*	Outcome measure	(+)	(=)	(-)
Cognitive function • *Global cognitive function* • *Executive function* • *Memory* • *Concentration*	Cognitive function 8a Executive Skills Questionnaire Participant perspective			
Mood/behaviour • *Social isolation*	UCLA Loneliness Scale Participant perspective			

Desired effect. Undesired effect. Trivial effect/inconclusive.

While a causal effect of active rehabilitation on measures of cognitive function, executive function, and loneliness was demonstrated by visual analysis, external factors should be considered when interpreting these results. Evidence suggests that Niall's levels of socialisation, and subsequently his response to the programme, was impacted by the presence of the COVID-19 pandemic. Further, the level of activities which provided a social element appeared to have an influence on Niall's outcome measures. Niall was able to return to hockey training in phase B1, with the frequency

of that training increasing in phase B2. In addition, he was able to take part in other social activities such as five-a-side football or going to the gym with friends as lockdown restrictions continued to ease (B2, B3). In A2, gyms were re-opened; however, a local lockdown was implemented in the middle of the phase. This temporarily disrupted his ability to go to hockey training and games. Levels of loneliness were on a steady decline regardless of the presence of the intervention programme and appear to be associated with the easing of lockdown restrictions and an increase in social physical activities described above. This continued until midway through phase A2 where there was a slight increase in levels of loneliness, corresponding with the implementation of a local lockdown for Niall's area. While the observed influence is less obvious, a drop in cognitive function and executive function was reported in B1 and A2 despite positive trend lines (indicating improving symptoms). This effect could be explained by the local lockdown, as PSS scores were elevated here. This is compared to phase B2, where PSS scores were lower, and levels of activity were the highest. Subsequently, levels of cognitive and executive function were both trending in a positive direction here.

Despite the influence of the pandemic, there is still evidence to suggest that active rehabilitation had a positive effect on measures of cognitive function, executive function, and loneliness. The latter half of the study in particular gives clearer evidence of this. Despite a return to red level national lockdown restrictions in phases A4 and B4, PSS scores were largely stable from B3 onward, suggesting Niall had adjusted to the new environment as best as he could. Only executive function demonstrated an entirely negative effect in phase B3, with levels of executive function lower than expected and demonstrating a negative trend (indicating worsening symptoms). In this same phase, cognitive function also demonstrated levels lower than what was predicted from the previous SMT line; however, the trend was positive (indicating improving levels). Levels of loneliness were low and demonstrated a negative trend (indicating continued improvement). In phase B4, all outcome measures demonstrated a negative trend line (indicating worsening symptoms); however, levels were immediately higher than what was predicted by the previous SMT line. It should be noted here that due to lockdown restrictions Niall did not have access to the gym or hockey during this phase. This is further evidence to suggest

Niall needs a social component for the most effective person-centred active rehabilitation programme. A positive or null effect illustrated across all outcome measures suggests that the social aspect is not the only influencing factor and that the presence of an active rehabilitation programme did have an effect as well.

It can be inferred that despite a lack of activity restriction, there was a consistent difference in activity levels between the intervention and non-intervention phases as determined by an observed difference in reported activity intensities and frequencies. Niall was most active in phase B2. His activity frequency was more consistent in these phases and the intensity of the activities were generally higher. The mode or intensity of the activities did not appear to have a significant effect on Niall's response. This is illustrated by those phases with the highest activity levels (B2, B3) not having an increased effect on outcome measures compared to other intervention phases. In addition, a six-week versus twelve-week intervention (back-to-back intervention phases) did not appear to have a strong effect on the outcomes; nor did a longer non-intervention phase.

5.4 Luigi

5.4.1 Participant history, screening, and baseline assessment

Luigi was a 38-year-old male from Ontario (Canada). He was married with two children and working full-time as an operations manager in the healthcare system. Luigi has a long history of participation in ice hockey (> 6 years), having played in university as well as in a high-level league following his time in university. During his career, Luigi suffered multiple concussions (> 4), mentioning at least one instance where he sustained three concussions in the span of a month. Due to injury, Luigi was advised to retire from university level hockey. He continued playing in men's leagues until 2012. Table 17 presents the results from the initial interview and baseline assessments which directed the final list of outcome measures.

Table 17. Luigi: Traumatic Encephalopathy Syndrome criterion, study eligibility, and outcome measures of interest

Criteria	Results from initial interview & baseline measures
History of multiple head impacts (direct or indirect)	Multiple mTBI (> 4), some within short periods of time Over 6 years of exposure to subconcussive trauma
No other neurological disorder present that likely account for all clinical features	None identified
Signs/symptoms must be present for a minimum of 12 months	Became apparent around 2012
Presence of at least one core clinical feature	**Cognitive** • Concerns of impaired memory, concentration, and attention • Signs of executive dysfunction • SLUMS score 25/30 AU - score meets assessment cut-off for 'mild cognitive impairment' • PROMIS Short Form v2.0 - Cognitive function 8a - scores 'within normal limits' **Mood** • Reported history of depression • PROMIS Short Form v1.0 - Depression 8b – scores within 'mild' cut-off **Behaviour** • Explosive, short fuse • BITe – scores above population average
Presence of at least two supportive features	Anxiety, history of suicidality, delayed onset • PROMIS Short Form v1.0 - Anxiety 8a - scores between 'within normal limits' and 'moderate' cut-off
Additional symptoms to consider	Irritability

Table informed by TES criteria (see Table 2, subsection 2.3.2). Additional symptoms informed by list of symptoms associated with CTE (see Table 1, subsection 2.3.2). Cut-off measures determined by assessment used (see Table 9, subsection 4.3.4)

PROMIS: Patient-Reported Outcomes Measurement Information System; SLUMS: SLUMS: Saint Louis University Mental Status; TBI: traumatic brain injury.

Despite meeting the cut-off for MCI during the screening process, Luigi did not display an impairment when measuring global cognitive function using the PROMIS Short Form v2.0 - Cognitive function 8a. When considering questions which he consistently displayed lower scores (indicating lower levels of cognitive function), impairments in memory and executive function were observed; therefore, measures of executive function were included. Luigi reported higher levels of anxiety, depression, and irritability during the baseline phase; therefore, all three of these outcome measures were included.

As a result, Luigi's outcomes of interest included:

- Cognitive function (executive function, memory, attention, concentration), assessed with Executive Skills Questionnaire (ESQ)
- Anxiety, measured with PROMIS Short Form v1.0 - Anxiety 8a
- Depression, measured with PROMIS Short Form v1.0 - Depression 8b
- Irritability (short fuse, explosivity), measured with Brief Irritability Test (BITe)

In addition, PSS was included to gather further information regarding stress levels experienced throughout the study (see subsection 4.4.4).

5.4.2 Intervention schedule and physical activity

Luigi was healthy and active with no reported precautions or contraindications to be considered. He enjoyed gym-based workouts and outdoor activities. A summary of his rehabilitation prescription, activity levels as reported from the daily activity logs, and any contextual information extracted from the follow-up interviews can be found in Figure 18.

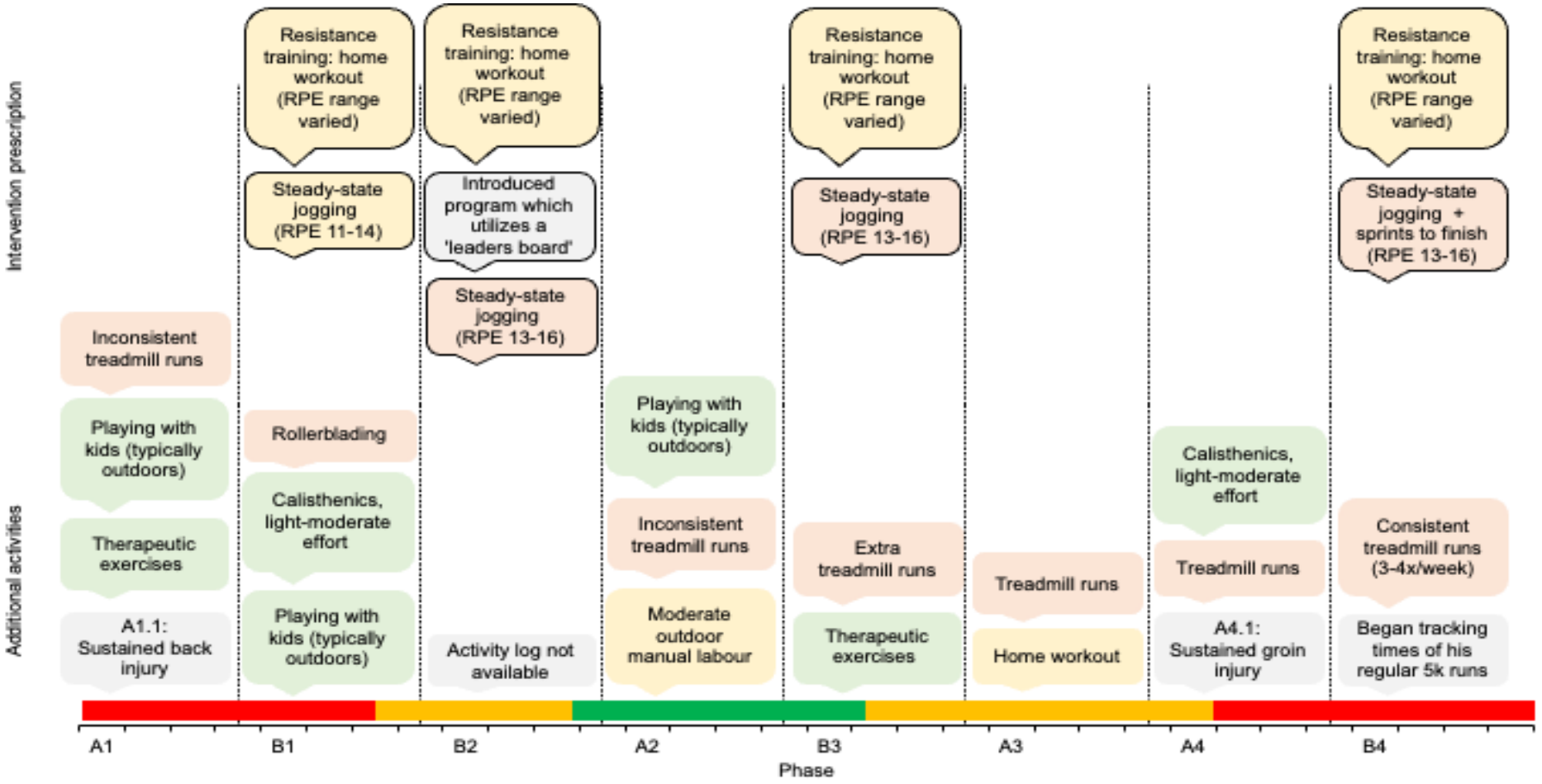


Figure 18. Luigi's intervention schedule and activity levels
Prescribed activities outlined in black. Additional activities were informed by daily activity log or included follow-up interviews (B1.3, A2.3, A3.3, B4.3). Activities characterised in accordance with recommendations from Ainsworth et al. (2011) and Bull et al. (2020b): — Light-intensity. — Moderate intensity. — Vigorous intensity. — Distal context. General state of Covid-19 lockdown responses as informed by local news sources: — stay-at-home orders. — Strict restrictions (no stay-at-home orders). — Light/no restrictions. A = non-intervention phase; B = intervention phase.

Participation in the study resulted in Luigi learning about his own needs and preferences; therefore, the needs and preferences regarding the resistance training programme changed throughout the study as he experienced that learning process. Some of the adjustments made were a direct consequence of the COVID-19 lockdowns. Despite his preference for the gym, he did not have access to or did not feel comfortable going to his normal gym at any point in the study. This meant no phases were completed in a gym setting, and programmes instead consisted of home-based workouts utilising body-weight exercises. Luigi found it difficult to workout in this kind of environment and admitted it was a learning experience for him, stating in his final interview,

> ...I know me, [I'm] headphones in, hoodie on, sweatshirt, sweatpants – if I'm at the gym, don't talk to me. That's how I am...it was kind of a learning experience on how to function with them [his children] being up and having to get a workout in.

Through participating in the study, Luigi also learned that to increase his motivation to exercise, he needed some sort of competitive aspect or goal to pursue. In his B1.3 follow-up, he stated,

> There was a tangible goal, like you could see it when I completed it, right?...So maybe that's where I started thinking about how I was getting more out of the day to day [manual labour tasks] than just putting a couple hours in doing a workout...I think if there was, you know, like a leader's board, let's say...

This inspired a change in format of the strength training programme in B2, where the prescribed exercises were decreased and a CrossFit Workout of the Day with associated leader board was provided as part of the programme.

The needs and preferences regarding the cardiovascular programme were largely met throughout the study. The mode of activity stayed the same and consisted of steady-state jogging mostly on a treadmill. Progressions in intensity and time were made throughout the programme as necessary. Luigi was much more motivated and consistent with his treadmill runs towards the end of the study, which started in the New Year (middle of phase A4). He stated,

> I think I just re-adjusted to saying I need to move every other day...whether it be one of your workouts or if I'm not feeling a workout then I run. So, I think I've been able to commit to that...I can't think of a day that I haven't hit my goal in terms of every other day since 2021 turned over.

When reflecting on the entire study experience, Luigi expressed a positive one. In his final interview he stated,

> I liked having direction for the exercise, I think that was good. I think the only big pain, honestly it wasn't even a pain, it was just kind of finding the time or, like, taking the time out because I knew the importance of it, was the journaling [daily activity log].

5.4.3 Cognitive function

5.4.3.1 Executive Skills Questionnaire

There was a positive effect of the programme on Luigi's executive function (Figure 19). A complete visual analysis report can be found in Appendix 11.2.

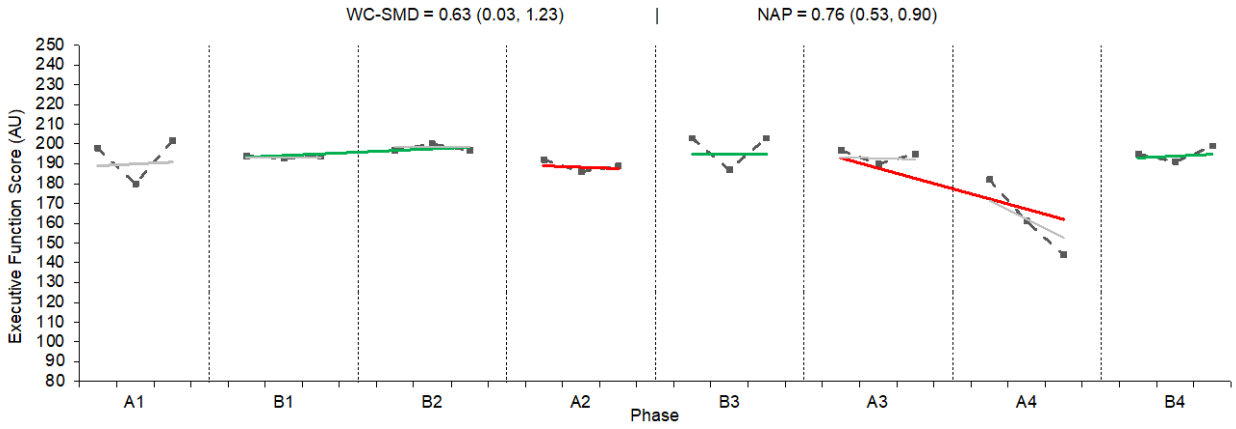


Figure 19. Luigi's self-report scores from Executive Skills Questionnaire

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMDzxx – within case standardized mean difference.

Five basic effects were observed on measures of executive function (systematic visual analysis rating = 7.00, large behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in executive skills. Three of these basic effects were positive (B1 + B2, B3, B4), and two of them were negative (A2, A3 + A4).

The initial introduction of the intervention (B1 + B2) did not change the reported levels or direction of the trendline when compared to the A1 SMT line; however, variability did immediately decrease. Overlap was present here. When the intervention was removed in A2, there was an immediate negative effect on levels of executive skills, which were lower than those predicted by the B1 + B2 SMT line. Further, the trend direction turned negative. In addition, variability was unchanged, and overlap was present here. The re-introduction of the intervention in B3 resulted in an immediate increase in levels of executive function with little to no overlap. The trend direction changed to a positive direction, and variability increased as well. The removal of the intervention (A3 + A4) resulted in a negative effect on the trend line direction and levels of variability. Further, reported levels were lower than those predicted from the B3 SMT line. These effects were not immediate, and overlap was present. The final introduction of the intervention (B4) saw an immediate positive effect on effect on the trend line direction and levels of variability. Further, reported levels were higher than those predicted from the A3 + A4 SMT line, and little to no overlap was present. The only consistent pattern reported across phase types was the reported levels observed during intervention phases (around 190-200). It should be noted these levels were consistently higher than all non-intervention phases. There was no consistent pattern observed across all non-intervention phases.

Analysis of data across the study duration indicated a moderate positive, within-case effect of the intervention on measures of executive function (WC-SMD = 0.63, 95% CI 0.03 to 1.23) with scores recorded during intervention phases (196.08 ± 4.76 AU) 11.41 points higher than those recorded during non-intervention phases (184.67 ± 16.74 AU). NAP (NAP = 0.63, 95%CI 0.03 to 1.23) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being greater than phase A is, on average, 63%.

A positive effect was observed on all components of executive function (Table 18). Active rehabilitation demonstrated a large effect on measures of working memory and metacognition. A moderate effect was demonstrated on measures of emotional control, task initiation. All others demonstrated a small effect.

Table 18 Luigi's individual components of executive function

Executive skill	Mean A ± SD	Mean B ± SD	WC-SMD (95%CI)	NAP (95%CI)
Emotional control (AU)	14.08 ± 2.02	15.17 ± 1.95	0.50 (-0.26, 1.25)	0.64 (0.41, 0.82)
Flexibility (AU)	13.59 ± 1.68	14.25 ± 1.48	0.37 (-0.35, 1.09)	0.65 (0.41, 0.82)
Goal-directed persistence (AU)	16.75 ± 1.96	17.83 ± 0.58	0.20 (-0.46, 0.86)	0.55 (0.33, 0.75)
Metacognition (AU)	15.92 ± 1.78	17.50 ± 0.67	0.83 (0.18, 1.47)	0.80 (0.56, 0.92)
Organization (AU)	17.33 ± 1.92	18.00 ± 0.00	0.32 (-0.22, 0.86)	0.58 (0.36, 0.77)
Planning/ prioritization (AU)	16.00 ± 1.95	16.67 ± 0.98	0.32 (-0.28, 0.92)	0.57 (0.35, 0.76)
Response inhibition (AU)	14.67 ± 1.44	15.00 ± 0.74	0.22 (-0.38, 0.81)	0.57 (0.35, 0.77)
Stress tolerance (AU)	13.08 ± 1.56	13.92 ± 1.08	0.41 (-0.65, 1.47)	0.66 (0.41, 0.84)
Sustained attention (AU)	16.33 ± 2.15	17.25 ± 1.14	0.40 (-0.22, 1.01)	0.64 (0.41, 0.81)
Task initiation (AU)	15.75 ± 2.22	17.58 ± 1.24	0.73 (0.07, 1.39)	0.72 (0.48, 0.87)
Time management (AU)	17.83 ± 2.25	18.33 ± 1.15	0.21 (-0.39, 0.80)	0.53 (0.31, 0.73)
Working memory (AU)	13.25 ± 1.14	14.50 ± 1.38	1.02 (0.10, 1.94)	0.74 (0.51, 0.88)

Range of potential scores: 0-21. Desired effect. Undesired effect. Trivial effect/Overlap. A = non-intervention phase; B = intervention phase; NAP = non-overlap of all pairs; WC-SMD = within case standardized mean difference.

5.4.4 Mood/behaviour

5.4.4.1 PROMIS short form v1.0 - Anxiety 8a

There was a positive effect of the programme on Luigi's levels of anxiety (Figure 20). A complete visual analysis report can be found in Appendix 11.2.

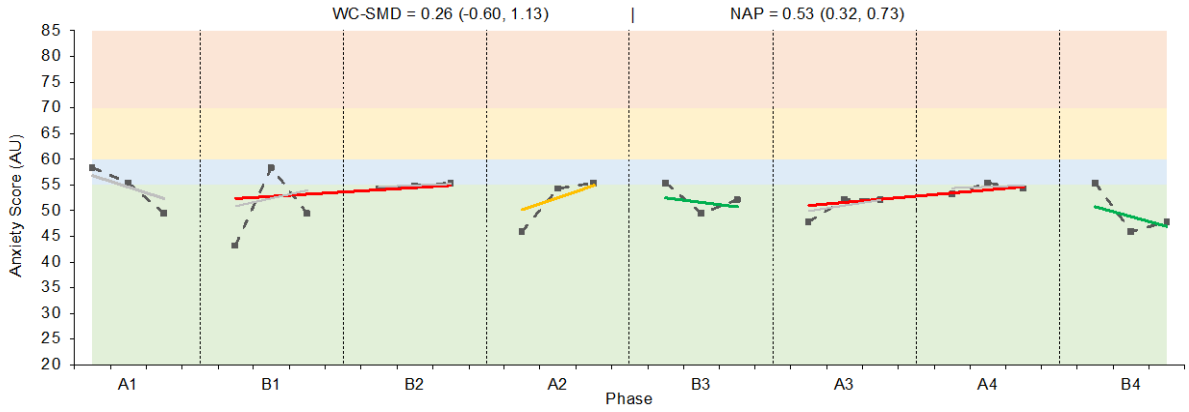


Figure 20. Luigi's self-report scores from PROMIS short form v1.0 - Anxiety 8a assessment

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Four basic effects were observed (systematic visual analysis rating = 5.00, moderate behavioural change). Two of these basic effects were positive (B3, B4) and two of them were negative (B1 + B2, A3 + A4).

When the intervention was first introduced (B1 + B2), symptom levels increased, and the trend direction changed to a positive direction (indicating a worsening of symptoms). Variability also immediately increased, particularly in phase B1. Overlap was present. When removed (A2), no basic effect was observed; that is, the trend direction, levels, and variability did not differ from those predicted by the SMT line in B1 + B2. When the intervention was re-introduced in B3, symptom levels decreased, and the trend direction immediately changed to a negative direction (indicating symptom improvement). Variability was unchanged, and overlap was present. When the intervention was removed (A3 + A4), symptom levels higher than predicted by the previous SMT line (B3) and the trend direction again turned positive (indicating

worsening symptoms). Variability decreased here. These changes were immediate; however, overlap was present. When the intervention was introduced in B4, symptom levels were lower than those predicted by the previous SMT line (A3 + A4) and the trend direction changed to a negative direction (indicating symptom improvement). Variability increased, but little to no overlap was present. There were no consistent patterns of levels, trend direction, or variability observed across either phase types.

Analysis of data across the study period indicated a small positive, within-case effect of the intervention on measures of executive function (WC-SMD = 0.26, 95% CI -0.60 to 1.13) with scores recorded during intervention phases (51.8 ± 4.62 AU) 1.0 points lower than those recorded during non-intervention phases (52.8 ± 3.58 AU). NAP (NAP = 0.53, 95%CI 0.32 to 0.73) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being lower than phase A is, on average, 53%.

5.4.4.2 PROMIS short form v1.0 - Depression 8b

There was a positive effect of the programme on Luigi's levels of depression (Figure 21). A complete visual analysis report can be found in Appendix 11.2.

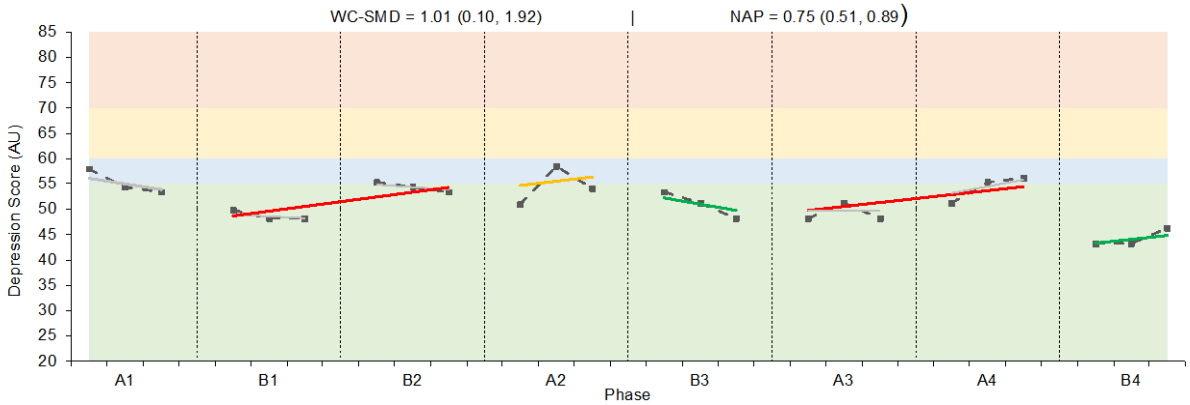


Figure 21. Luigi's self-report scores from PROMIS short form v1.0 - Depression 8b assessment

■Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Four basic effects were observed (systematic visual analysis rating = 4.75, small behavioural change). Two of these basic effects were positive (B3, B4) and two of them were negative (B1 + B2, A3 + A4).

When the intervention was introduced, the trend direction changed to a positive direction (indicating worsening symptoms), though the effect was not immediate. Only symptom levels in B2 were higher than those predicted by the previous SMT line (A1). Variability was unchanged, and overlap was present. When removed (A2), no basic effect was observed; that is, the trend direction, levels, and variability did not differ from those predicted by the SMT line in B1 + B2. When re-introduced in phase B3, symptom levels were lower than those predicted by the previous SMT line (A2), and the trend direction turned negative (indicating improving symptoms). Variability also decreased, though the effect was not immediate and overlap was present. When removed (A3 + A4), and levels were higher than those predicted by the previous SMT lines (B3), and the trend direction turned positive (indicating worsening symptoms). There was no change in variability, and overlap was present.

When the intervention was introduced in B4, symptom levels were immediately lower than those predicted by the previous SMT line (A3 + A4), but the trend direction and variability remained unchanged. No overlap was present. There were no consistent patterns in levels, trend direction, or variability observed across either phase types.

Analysis across the study duration indicated a large positive, within-case effect of the intervention on measures of executive function (WC-SMD = 1.01, 95% CI 0.10 to 1.92) with scores recorded during intervention phases (49.57 ± 4.08 AU) 3.71 points lower than those recorded during non-intervention phases (53.28 ± 3.42 AU). NAP (NAP = 0.75, 95%CI 0.51 to 0.89) suggests a low level of data overlap between matched pairs where the probability of a randomly selected data point in phase B being lower than phase A is, on average, 75%.

5.4.4.3 Brief Irritability Test

The effect of the programme on Luigi's symptoms of irritability, explosivity, and short fuse was inconclusive (Figure 22). A complete visual analysis report can be found in Appendix 11.2.

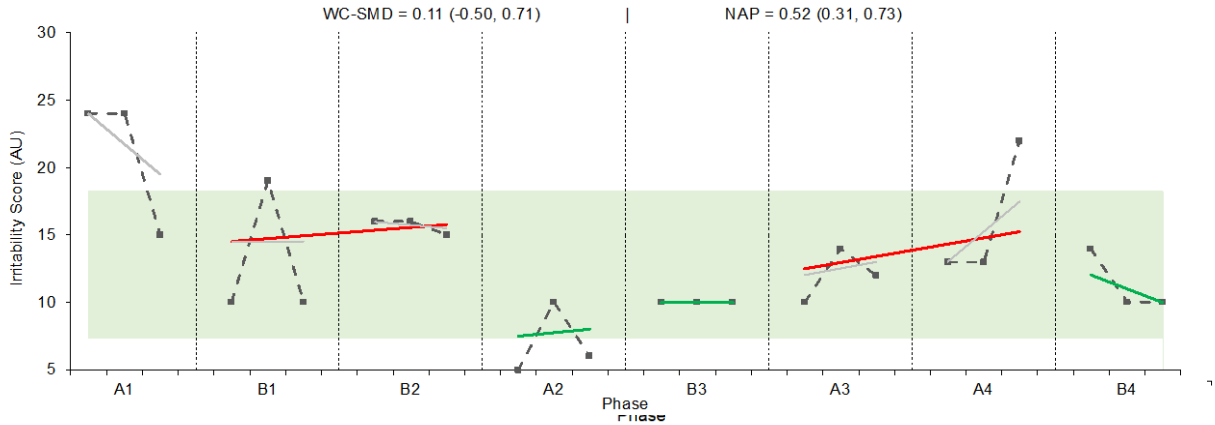


Figure 22. Luigi's self-report scores from Brief Irritability Test (BITe) assessment

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Five basic effects were observed on measures of irritability (visual analysis rating = 7.00, large behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Three of these basic effects were positive (A2, B3, B4), and two of them were negative (B1 + B2, A3 + A4).

With the initial introduction of the intervention (B1 + B2), levels of irritability were increased compared to those predicted by the previous SMT line (A1) and the trend direction turned positive (indicating worsening symptoms). These effects were not immediate and occurred primarily in B2. Overlap was also present here. When the intervention was removed (A2), levels of irritability immediately decreased and with little to no overlap. The trend direction and variability were unchanged. When the intervention was re-introduced (B3), the levels of irritability did not differ from those predicted by the previous SMT line (A2); however, the variability immediately

decreased. The trend direction was neutral here, and overlap was present. When removed (A3 + A4), variability immediately increased. Further, levels were higher than predicted by the previous SMT line (B3), and the trend direction turned positive (indicating worsening symptoms). Little to no overlap was present. Finally, the presence of the intervention in B4 resulted in levels of irritability lower than those predicted by the previous SMT line (A3 + A4), and with little to no overlap. A change in trend direction to negative was also observed (indicating improving symptoms). Across phase types, variability was consistently high in all non-intervention phases. There was no consistent pattern observed across all intervention phases.

Analysis across the study indicated a trivial positive, within-case effect of the intervention on levels of irritability (WC-SMD = 0.11, 95% CI -0.50 to 0.71) with scores recorded during intervention phases (12.5 ± 3.29 AU) 1.50 points lower than those recorded during non-intervention phases (14.00 ± 3.58 AU). NAP (NAP = 0.52, 95%CI 0.31 to 0.73) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being lower than phase A is, on average, 52%.

5.4.5 Participant perspective

In those follow-up interviews which were included (B1.3, A2.3, A3.3 and B4.3), only in phase A2.3 did Luigi discuss his symptoms of executive function, memory, attention, and concentration. He reported,

> ...I'm not really paying close enough attention to what's- not even what's going on at home, it just sems like I'm having trouble remembering.

He did not discuss these symptoms in the other included interviews which made it difficult to determine a clear difference between the phase types. Upon reflection in his final interview, Luigi stated,

> I think, overall, symptoms have improved. I think being able to identify a lot of the areas in which I was struggling with. Maybe with the headaches and the memory gaps and things have been a learning process in terms of what I've been able to learn and how to deal with them.

In those follow-up interviews which were included (B1.3, A2.3, A3.3 and B4.3), there was not enough evidence to suggest a clear difference between Luigi's symptoms of anxiety, depression, and irritability (short fuse, explosivity) in intervention and non-intervention phases; however, there was evidence suggesting that Luigi has successfully learned to use physical activity as a coping mechanism for these symptoms. In A3, he stated,

> I think on the days I'm pissed off, like I was yesterday, it helped...I think the angrier you are at the day or at people, it seems to motivate me more and I get a better sweat...

This was repeated in B4.3, where he stated,

> I haven't been as explosive, I guess. It's still there, like it's still manifests and whatever, but I think that the staying consistent with working out every other day or back-to-back days has been a huge relief of that.

This would indicate that the symptoms of irritability, short fuse, and explosivity were still present, but Luigi felt he had more control over these emotions when he was more active. Regarding anxiety and depression, Luigi did not discuss these symptoms during the selected intervention phases (B1.3, B4.3); however, he adopted a more neutral mood in the non-intervention phases (A2.3, A3.3), stating things like (A2),

> I feel pretty good. I don't- I'm not, like, totally upbeat. But I'm not depressed. I'm just tired.

This would suggest a potential positive effect of the intervention on symptoms of anxiety and depression.

5.4.6 Study schedule and context

Luigi began the study in March 2020, at the beginning of the COVID-19 global pandemic. Figure 23 illustrates an estimated timeline of the government pandemic response in Luigi's area and his PSS scores. Figure 23 also includes additional distal

contextual information that may have influenced the study experience, as informed by the included follow-up interviews (B1.3, A2.3, A3.3, B4.3) and general news sources.

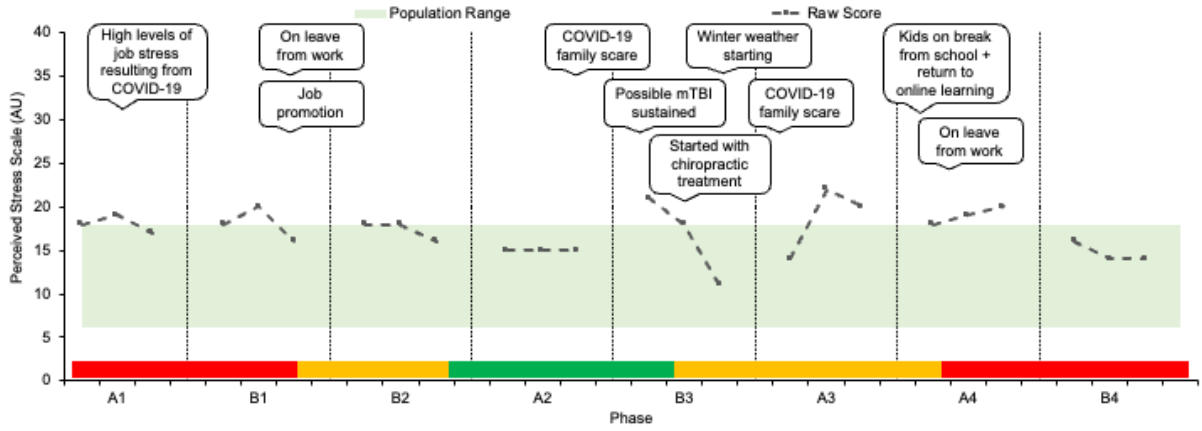


Figure 23. Luigi's PSS scores at each data collection point

A higher score indicates higher levels of perceived stress. Population norms: — Population average. The general state of Covid-19 lockdown responses as informed by news sources are represented as: — stay-at-home orders, — strict restrictions (no stay-at-home orders) and — light/no restrictions. A = non-intervention phase; AU= arbitrary unit; B = intervention phase.

The presence of the COVID-19 pandemic and subsequent government response restrictions had an evident effect on Luigi's study participation and symptom levels. When reflecting on the effect of the pandemic in his final interview, Luigi stated,

> I think there was too much noise during COVID, if I'm being honest. I think there was a lot of distraction, a lot of, you know, mental health challenges to be honest.

He acknowledged that he did believe it had a negative effect on the outcomes of the study.

It was evident that having children during the pandemic was especially difficult for Luigi. As a father of two young children, Luigi was already struggling with parenthood. This was something he expressed during his initial interview. Due to government pandemic responses, Luigi found himself having to work from home while accommodating to children who were having to learn from home as well.

Circumstances were much easier for Luigi when the lockdown responses were looser, and he could get help from extended family. In B1, Luigi stated,

> Since they expanded to, we could open up to people now and have some help, my in-laws have started- well, they watched the kids yesterday for like half a day. So that was a huge help...

Generally, living through a global pandemic as a small, young family was difficult for everyone. Luigi demonstrated feelings of general frustration and sympathy for his family (wife and children). Early in the pandemic, the family had seemed to adjust. In B1, Luigi stated,

> Everyone's gotten used to home life, so we kind of know what sets each other off and when to let the kids be kids.

However, as the pandemic prolonged, it became more difficult for Luigi to maintain that level of optimism and stability. He was missing normal holidays and the activities that the children typically did for fun (e.g., birthday celebrations and after school activities). Towards the end of the study, Luigi simply expressed,

> ...we're bored of being bored.

He also found participating in the study and completing home-workouts during such circumstances difficult. He stated in his final interview,

> ...finding the time for yourself without people around, people bugging you...it was kind of a learning experience on how to function with them being up and having to get a workout in.

A final component to be considered is Luigi's decision to pursue chiropractic care. Following persistent neck pain and headaches that developed, Luigi was receiving chiropractic care, particularly for the cervical region. He believed this made a difference with the frequency and intensity of the headaches. He reported in A3,

> Headaches have kind of, they're still there but they've subsided- they're not as often. Or if they are there, they're not lasting as long.

Luigi did not persist with this treatment through the entire study, nor did he mention any effect on the study symptoms of interest; however, he did express feeling a physical benefit from the chiropractic treatment.

5.4.7 Results summary

A person-centred active rehabilitation programme demonstrated a positive effect on Luigi's symptoms of cognitive dysfunction executive function, memory, attention, concentration), anxiety and depression. The effect that person-centred active rehabilitation had on Luigi's symptoms of irritability, short fuse, and explosivity was inconclusive. Table 19 illustrates a summary of results across the study.

Table 19 Luigi's summary of results

Area of assessment & *symptoms of interest*	Outcome measure	(+)	(=)	(-)
Cognitive function • *Executive function* • *Memory* • *Attention* • *Concentration*	Executive Skills Questionnaire			
	Participant perspective			
Mood/behaviour • *Anxiety* • *Depression* • *Irritability* • *Short fuse* • *Explosivity*	PROMIS Short Form v1.0 – Anxiety 8a			
	PROMIS Short Form v1.0 – Depression 8b			
	Brief Irritability Test			
	Participant perspective			

Desired effect. Undesired effect. Trivial effect/inconclusive.

Despite some potential for data overlap across many of the outcome measures, the introduction of the rehabilitation programme consistently demonstrated a positive basic effect on levels of executive function (B1, B2, B3, B4). This is irrespective of any potential contextual influence. This is supported by a moderate WC-SMD and 95%CI that suggests minimal probability of a negative or null effect. Components of

executive function that demonstrated the strong positive effect were meta-cognition, flexibility, stress tolerance, task initiation, and working memory. As there was little difference in the levels of executive function reported across intervention phases, it appears that the intensity, mode, or frequency of the programme prescription did not have a strong influence on the effectiveness. The duration of the programme (six versus twelve weeks) did not appear to have an effect either.

The person-centred active rehabilitation programme had similar patterns of effect (regarding outcome levels and trend directions) across all three mood/behaviour outcomes of interest across the entire study. PSS scores seem to also follow the same patterns of outcome measure levels and trend directions. When considered this along with Luigi's comments about the programme providing a coping mechanism, this suggests that whether there is evidence of physiological benefit or not, the presence of a person-centred active rehabilitation programme provided a way for Luigi to effectively manage his symptoms of suspected CTE. The size of this effect is inconclusive. Evidence suggests that person-centred active rehabilitation had a large effect on levels of depression, with little to no probability of a null or negative effect; however, the effect that the programme had on anxiety and irritability is less conclusive. WC-SMD suggests a moderate effect on anxiety, but 95%CI and overlap suggest a possibility for a null or negative effect. Analysis of irritability suggests an equal likelihood of a null, negative, or positive effect.

While contextual factors were present, they did not appear to distract from the effectiveness of the person-centred rehabilitation programme. There is a possibility that the size of the effect was disrupted; however, PSS scores were relatively stable with only two phases (A2, B4) reporting relatively lower measures compared to the rest of the study measures. These phases reported little information about contextual information; however, A2 occurred during a period of green lockdown restrictions and B4 occurred during a period of red restrictions. These two phases reported general enjoyment with activity compared to some of the other phases. Despite not restricting activity levels, there still remained an observable difference between the activity frequency and intensities when the active rehabilitation programmes were

implemented. A2 is the only exception, where Luigi was spending a lot of time outdoors either playing with his kids or doing manual labour.

5.5 Kristen

5.5.1 Participant history, screening, and baseline assessment

Kristen was a 29-year-old female from New York (United States). Kristen lived with her fiancée. She had no children at the start of the study but was actively trying to start a family towards the end. Kristen reported two moderate TBI's, one sustained during a rugby match and one because of a car crash. The car crash also resulted in multiple wrist and forearm surgeries. As a result of these injuries and surgeries, Kristen was not working. In addition to the more severe TBI's discussed above, Kristen also reported suffering from multiple mTBI's (estimated six to seven per year, across two to three years) which were sustained in rugby. Kristen reported a long history of participation in sports (>6 years), primarily rugby but also including softball during adolescence. She stopped all physical activity (excluding physiotherapy) following the injuries described above. In addition to the extensive history of TBI, Kristen also has a history of carbon monoxide poisoning, multiple ankle fractures, post-concussion syndrome (PCS), generalized anxiety disorder (GAD), persistent depressive disorder (PDD) and attention-deficit disorder (ADD). Table 20 presents the results from the initial interview and baseline assessments which directed the final list of outcome measures.

Table 20. Kristen: Traumatic Encephalopathy Syndrome criterion, study eligibility, and outcome measures of interest

Criteria	Results from initial interview & baseline measures
History of multiple head impacts (direct or indirect)	Multiple mTBI (> 4), some within short periods of time Two moderate TBI Over 6 years of exposure to subconcussive trauma
No other neurological disorder present that likely account for all clinical features	Post-concussion syndrome diagnosis was in 2012/2013. Second-degree family history of Parkinson's disease. No other potential disorders identified.
Signs/symptoms must be present for a minimum of 12 months	Present since 2012
Presence of at least one core clinical feature	**Cognitive** • Concern of impaired memory, concentration, and attention • SLUMS score 30/30 AU - scores 'within normal limits' • PROMIS Short Form v2.0 - Cognitive function 8a - scores between 'within normal limits' and 'mild' cut-off **Mood** • Diagnosed PDD • PROMIS Short Form v1.0 - Depression 8b - scores within 'mild' cut-off
Presence of at least two supportive features	Anxiety, history of suicidality, persistent headaches • PROMIS Short Form v1.0 - Anxiety 8a - scores between 'mild' and 'moderate' cut-off
Additional symptoms to consider	Executive dysfunction, insomnia • PSQI – scores meet assessment cut-off for poor sleep

Table informed by TES criteria (see Table 2, subsection 2.3.2). Additional symptoms informed by list of symptoms associated with CTE (see Table 1, subsection 2.3.2). Cut-off measures determined by assessment used (see Table 9, subsection 4.3.4)

PROMIS: Patient-Reported Outcomes Measurement Information System; SLUMS: SLUMS: Saint Louis University Mental Status; TBI: traumatic brain injury.

Kristen displayed an impairment in all selected outcome measures; therefore, they were all included for the remainder of the study. As a result, Kristen's outcomes of interest included:

- Cognitive function (executive function, memory, attention, concentration), assessed with PROMIS Short Form v2.0 - Cognitive function 8a, and Executive Skills Questionnaire (ESQ)
- Anxiety, as measured with PROMIS Short Form v1.0 - Anxiety 8a
- Depression, as measured with PROMIS Short Form v1.0 - Depression 8b
- Insomnia, as measured with Pittsburgh Sleep Quality Index (PSQI)

Because Kristen had already reached the five-assessment limit intended to control for participant load (see subsection 4.4.2), PSS scores were not collected.

5.5.2 Intervention schedule and physical activity

Kristen reported some exercise intolerance due to her previous TBI's, explaining when she does too much activity or completes certain exercises, she experiences symptoms such as headaches, nausea, executive dysfunction (particularly with language). For example, in her initial interview she stated,

> Yesterday I was walking around with my sister-in-law and my nephew, and we probably walked for like 45 minutes. And when I had to make conversation, I was constantly switching up my words and just kind of, like, spacey and having a hard time focusing.

In addition, Kristen has had multiple surgeries in previous years as a result of her car crash, some of which occurred just prior to the start of the study, and another happened during the study (B2). Because of this, she was limited in what upper body exercises she could do; therefore, Kristen's programmes were kept at low to moderate intensities and only lower body activities were prescribed. A summary of her rehabilitation prescription, activity levels as reported from the daily activity logs and any contextual information extracted from the follow-up interviews can be found in Figure 24.

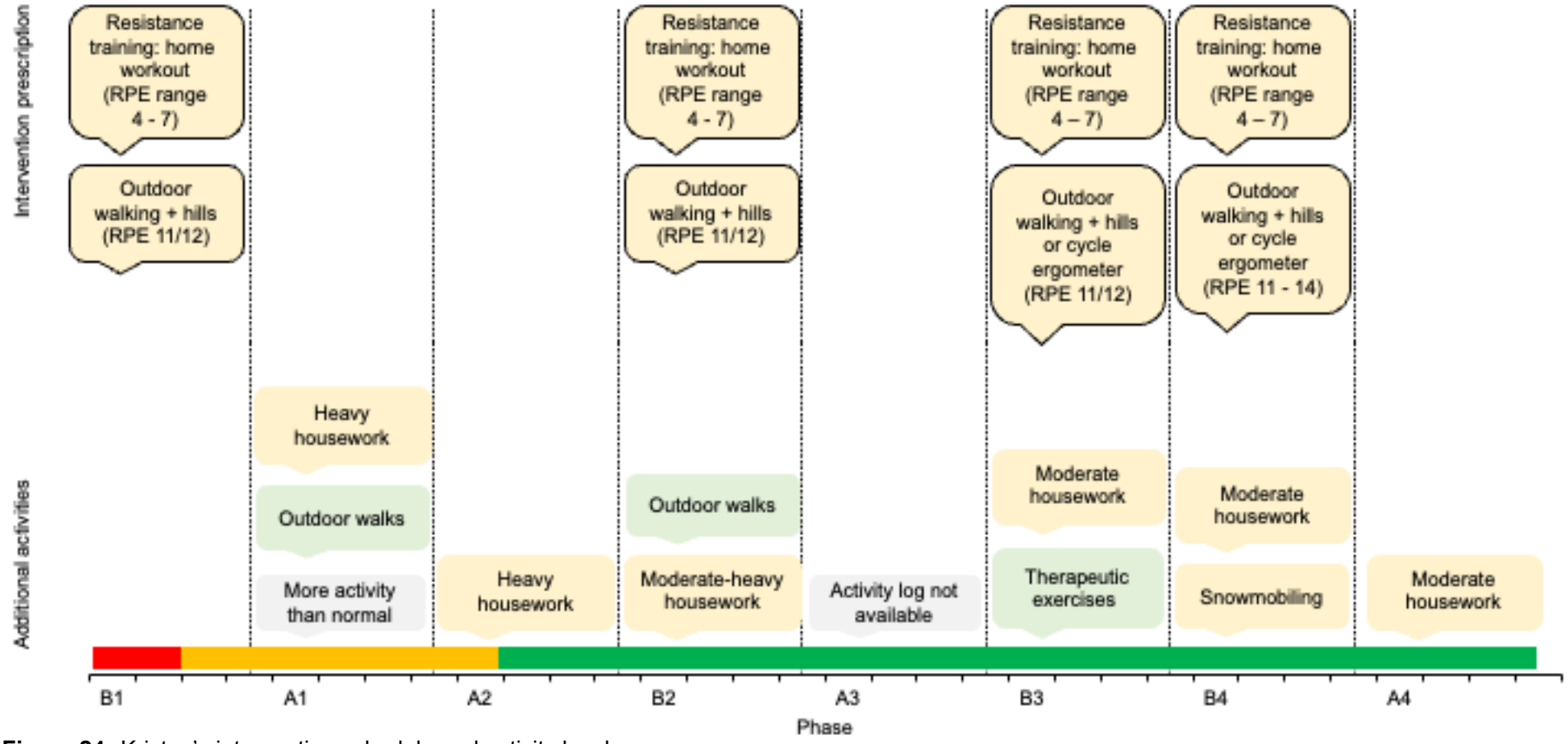


Figure 24. Kristen's intervention schedule and activity levels

Prescribed activities outlined in black. Additional activities were informed by daily activity log or included follow-up interviews (A1.3, B2.3, B3.3, A4.3. Activities characterised in accordance with recommendations from Ainsworth et al. (2011) and Bull et al. (2020): — Light-intensity. — Moderate-to-vigorous intensity. — Vigorous-intensity. — Distal context. General state of Covid-19 lockdown responses as informed by local news sources: — stay-at-home orders. — Strict restrictions (no stay-at-home orders). — Light/no restrictions. A = non-intervention phase; B = intervention phase.

Exercise intolerance continued to be a challenge for developing a programme that met Kristen's needs and preferences. Throughout the study, resistance training and cardiovascular programmes were adapted only to introduce variation in exercises or to progress the intensity prescriptions. These progressions were slow. Even so, phases B1, B3, and B4 resulted in symptoms of headache, dizziness, and nausea as a result of the programmes. In phases B2 and B3, she reported a negative effect on her insomnia as a result of the programmes. Kristen expressed a great deal of frustration regarding these adverse reactions. In her final interview (A4), she stated,

> I feel guilty that I couldn't put in the full effort I wanted to. That was tough...[It felt like] in another six weeks it'll get better, it'll go better. And it's- sometimes it did, sometimes it didn't, sometimes no matter what I did it didn't make a difference...

Despite the adverse reactions, Kristen did state,

> ...but it gave me the groundwork to kind of, okay- this is what we worked on. This worked with it, this didn't, so certain exercises this way I could do, that I can't. And I could almost start to see where the threshold might be. I started to kind of understand these triggers.

Kristen expressed that attention to load and intensity was necessary for her to complete activities. She reported in B2,

> If I can do stuff throughout the day or sometimes if it's a longer duration of doing lesser stuff, it's not always as bad for the strengthening. I think when it's higher intensity, and a shorter time.

This was re-iterated in her final interview, where she expressed,

> I think it just really made it- if it's an activity that I'm doing throughout the day and I don't force myself or try to get into, like, I'm out of breath- anytime I think I got out of breath or just really exhausted a normal workout is when I have the problem, but if I can extend it, where it doesn't have the entire intensity, it was okay.

Paying attention to these details helped with her exercise intolerance to a degree.

5.5.3 Cognitive function

5.5.3.1 PROMIS Short Form v2.0 - Cognitive Function 8 assessment

The effect of the programme on Kristen's cognitive function was inconclusive (Figure 25). A complete visual analysis report can be found in Appendix 11.3.

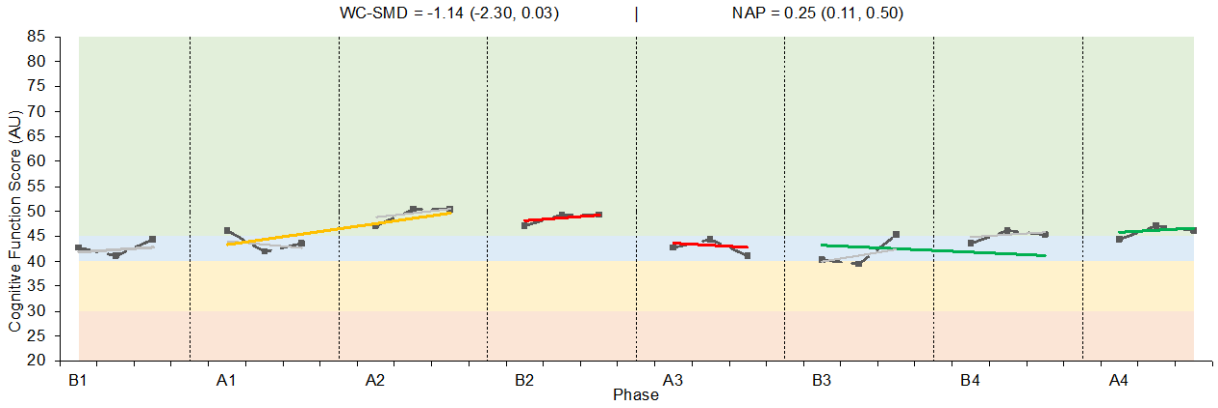


Figure 25. Kristen's self-report scores from PROMIS Short Form v2.0 - Cognitive Function 8 assessment

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Four basic effects were observed on measures of cognitive function (visual analysis rating = 4.5, small behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Two of these basic effects were positive (B3 + B4, A4), and two of them were negative (B2, A3).

There was no basic effect demonstrated with the removal of the intervention in A1 + A2; that is, levels of cognitive function, trend direction, or variability did not differ from those predicted by the B1 SMT line. The re-introduction of the intervention in B2 resulted in an immediate decrease in levels of cognitive function compared to those predicted by the previous SMT line (A1 + A2). The direction of the trend and variability were unchanged, and overlap was present. When removed (A3), there was an immediate decrease in levels of cognitive function and the trend direction turned

negative (indicating worsening cognitive function). Variability was unchanged, and overlap was present. When re-introduced (B3 + B4), levels were higher than those predicted by the previous SMT line (A3). This is most prevalent in phase B4; however, the trend direction and variability were unchanged. Further, this effect was not immediate, and overlap was present. Lastly, the removal of the intervention in A4 resulted in increased levels of cognitive function compared to those predicted by the previous SMT line (B3 + B4), and the trend direction turned positive (indicated improving levels of cognitive function); however, this effect was not immediate and overlap was present. Variability was unchanged. No consistent patterns of cognitive function levels, trend direction, or variability were noted across either phase type.

Analysis across the study duration indicated a large negative, within-case effect of the intervention on measures of cognitive function (WC-SMD = -1.14, 95% CI -2.30 to 0.03) with scores recorded during intervention phases (44.51 ± 3.23 AU) 0.98 points lower than those recorded during non-intervention phases (45.49 ± 3.04 AU). NAP (NAP = 0.25, 95%CI 0.11 to 0.50) suggests a low level of data overlap between matched pairs where the probability of a randomly selected data point in phase B being greater than phase A is, on average, 25%.

5.5.3.2 Executive Skills Questionnaire

There was a negative effect of the programme on Kristen's executive function (Figure 26. A complete visual analysis report can be found in Appendix 11.3.

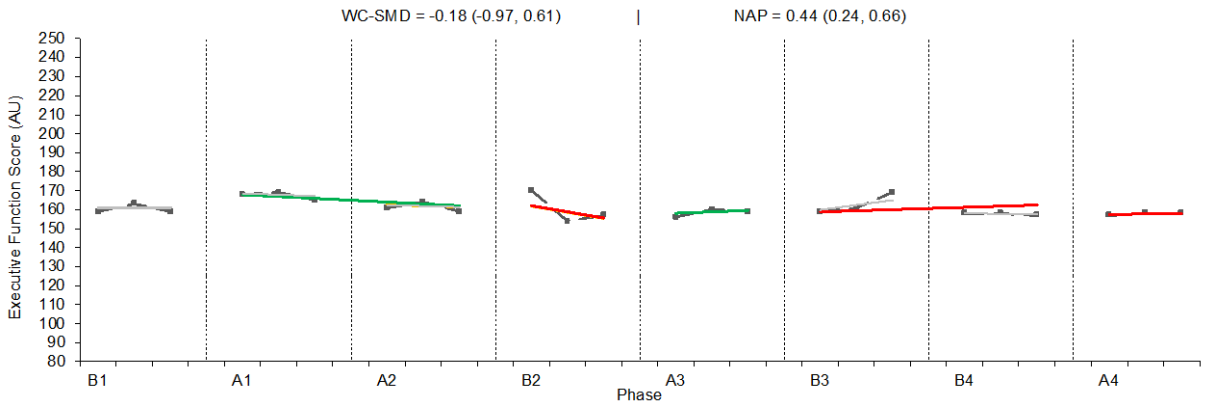


Figure 26. Kristen's self-report scores from Executive Skills Questionnaire

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Five basic effects were observed (systematic visual analysis rating = 5.5, moderate behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Two of these basic effects were positive (A1 + A2, A3), and three of them were negative (B2, B3 + B4, A4.

The removal of the intervention in A1 + A2 did not change the trend direction or the variability; however, it did cause an immediate increase in the levels of executive function when compared to the SMT calculated in B1. Overlap was present here. When re-introduced in B2, levels of executive function and trend direction were not changed; however, variability was higher. This effect was not immediate, and overlap was present. When the intervention was removed (A3), levels of executive function were higher than those predicted by the previous SMT line (B1 + B2), variability decreased and the trend direction reversed towards a positive direction (indicating increasing executive function); however, this effect was not immediate, and overlap was present. The re-introduction of the intervention (B3 + B4) demonstrated only an increase in variability. This effect was not immediate. Further, levels of executive function did not differ from those predicted by the previous SMT line (A2), and the trend direction was unchanged. Overlap was also present here. With the final removal of the intervention, levels of executive function were lower than those predicted by the

previous SMT line (B3 + B4); however, variability decreased. These effects were not immediate, and the trend direction remained unchanged. Further, overlap was present. The only consistent pattern reported across phase types was the low levels of variability observed among all non-intervention phases. There was no consistent pattern regarding levels of executive function, trend direction, or variability observed across all intervention phases.

Analysis across the duration of the study indicated a trivial negative, within-case effect of the intervention on measures of executive function (WC-SMD = -0.18, 95% CI -0.97 to 0.61) with scores recorded during intervention phases (161.17 ± 4.32 AU) 0.84 points lower than those recorded during non-intervention phases (160.33 ± 4.81 AU). NAP (NAP = 0.44, 95%CI 0.24 to 0.66) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being greater than a randomly selected data point in phase A is, on average, 44%.

When analysing specific components of executive function (Table 21), active rehabilitation demonstrated only one positive effect – a moderate effect on task initiation. A small negative effect was observed on measures of emotional control, flexibility, organization, planning/prioritization, stress tolerance and working memory. All other measures demonstrated a trivial effect.

Table 21 Kristen's individual components of executive function

Executive skill	Mean A ± SD	Mean B ± SD	WC-SMD (95%CI)	NAP (95%CI)
Emotional control (AU)	12.67 ± 0.78	12.50 ± 1.00	-0.20 (-1.06, 0.66)	0.40 (0.22, 0.63)
Flexibility (AU)	15.17 ± 0.39	15.08 ± 0.29	-0.20 (-0.86, 0.46)	0.46 (0.26, 0.68)
Goal-directed persistence (AU)	13.92 ± 0.51	13.82 ± 0.39	-0.15 (-0.81, 0.51)	0.47 (0.26, 0.68)
Metacognition (AU)	13.83 ± 0.72	13.75 ± 0.45	-0.11 (-0.73, 0.52)	0.44 (0.24, 0.66)
Organization (AU)	12.58 ± 0.51	12.42 ± 0.67	-0.30 (-1.17, 0.57)	0.40 (0.21, 0.63)
Planning/ prioritization (AU)	13.08 ± 1.16	12.67 ± 1.15	-0.33 (-1.09, 0.42)	0.38 (0.20, 0.61)
Response inhibition (AU)	14.33 ± 0.98	14.25 ± 0.97	-0.08 (-0.82, 0.66)	0.47 (0.26, 0.68)
Stress tolerance (AU)	14.92 ± 0.79	14.67 ± 0.65	-0.29 (-0.98, 0.40)	0.46 (0.26, 0.68)
Sustained attention (AU)	12.25 ± 0.75	12.33 ± 0.89	0.10 (-0.71, 0.92)	0.50 (0.29, 0.71)
Task initiation (AU)	12.08 ± 0.29	12.25 ± 1.14	0.54 (-1.61, 2.69)	0.55 (0.33, 0.75)
Time management (AU)	13.42 ± 0.67	13.50 ± 0.90	0.12 (-0.77, 1.00)	0.54 (0.32, 0.74)
Working memory (AU)	13.08 ± 1.08	12.75 ± 0.75	-0.29 (-0.94, 0.36)	0.43 (0.23, 0.65)

Range of potential scores: 0-21. Desired effect. Undesired effect. Trivial effect/Overlap. A = non-intervention phase; B = intervention phase; NAP = non-overlap of all pairs; WC-SMD = within case standardized mean difference.

5.5.4 Mood/behaviour

5.5.4.1 PROMIS short form v1.0 - Anxiety 8a assessment

There was a negative effect of the programme on Kristen's levels of anxiety (Figure 27). A complete visual analysis report can be found in Appendix 11.3.

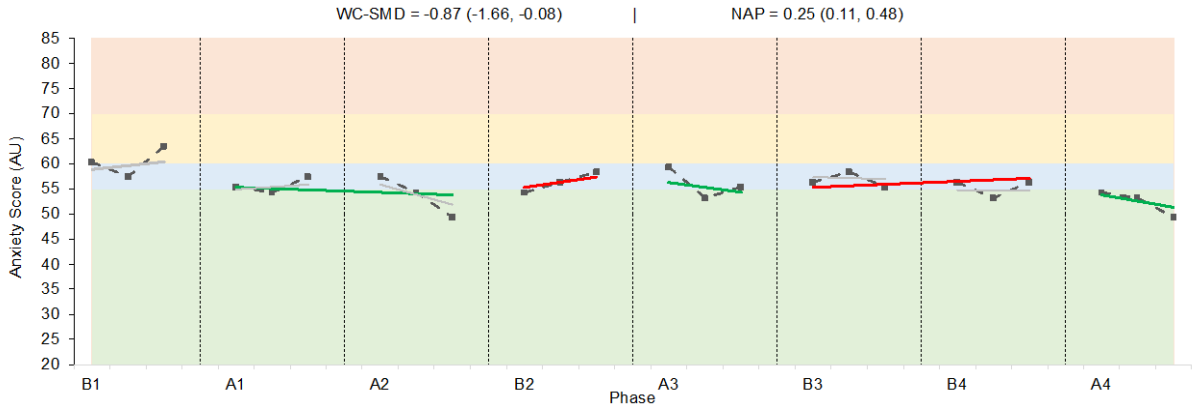


Figure 27. Kristen's self-report scores from PROMIS short form v1.0 - Anxiety 8a assessment

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Five basic effects were observed on measures of cognitive function (visual analysis rating = 6.0, moderate behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and levels of anxiety. Three of these basic effects were positive (A1 + A2, A3,A4), and two of them were negative (B2, B3 + B4).

The removal of the intervention in A1 + A2 resulted in an immediate decrease in levels of anxiety and change of trend direction to a negative direction (indicating an improving symptoms). Variability was unchanged, and overlap was present. When re-introduced (B2), levels of anxiety were higher than those predicted by the previous SMT line (A1 + A2), and the trend direction immediately turned positive (indicating worsening symptoms). Variability did not differ from the previous phase, and overlap was present. When the intervention was removed (A3), levels of anxiety were lower than those predicted by the previous SMT line (B2), and the trend direction

immediately turned negative (indicating improving symptoms). Variability increased in this phase, and overlap was present. When the intervention was re-introduced (B3 + B4), levels of anxiety were higher than those predicted by the previous SMT line (A3), and the trend direction turned positive (indicating worsening symptoms). Variability was unchanged, and overlap was present. Finally, when removed in A4, levels were immediately lower than those predicted by the previous SMT line (B3 + B4), and the trend direction turned negative (indicating improving symptoms). Variability also decreased, although overlap was present. There were no consistent patterns of symptom levels, trend direction, or variability observed across either phase type.

Analysis of data across the study duration indicated a large negative, within-case effect of the intervention on measures of cognitive function (WC-SMD = -0.87, 95% CI –1.66 to -0.08) with scores recorded during intervention phases (57.22 ± 2.75 AU) 2.79 points higher than those recorded during non-intervention phases (54.43 ± 2.98 AU). NAP (NAP = 0.25, 95%CI 0.11 to 0.48) suggests a low level of data overlap between matched pairs where the probability of a randomly selected data point in phase B being lower than a randomly selected data point in phase A is, on average, 25%.

5.5.4.2 PROMIS short form v1.0 - Depression 8b assessment

There was a negative effect of the programme on Kristen’s levels of depression (Figure 28). A complete visual analysis report can be found in Appendix 11.3.

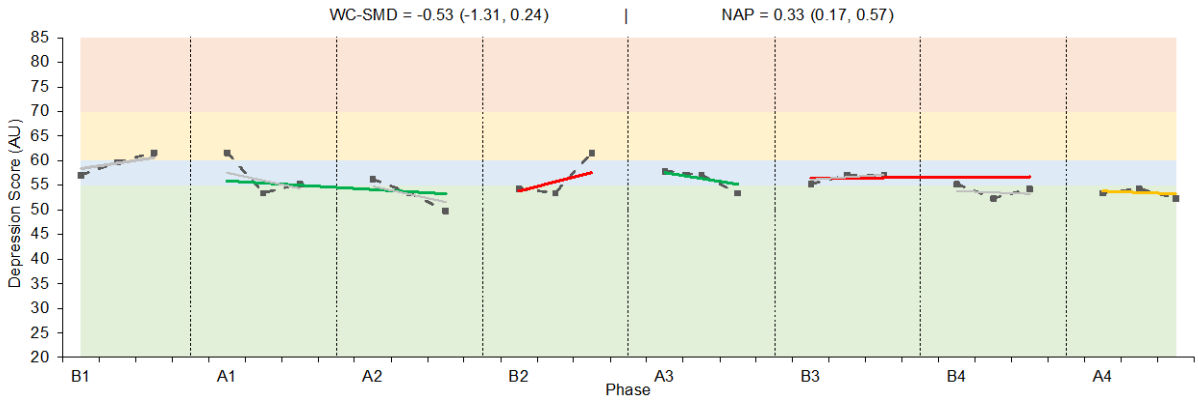


Figure 28. Kristen's self-report scores from PROMIS short form v1.0 - Depression 8b assessment ▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Four basic effects were observed on measures of depression (visual analysis rating = 4.75, small behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Two of these basic effects were positive (A1 + A2, A3), and two of them were negative (B2, B3 + B4).

The removal of the intervention in A1 + A2 resulted in an immediate decrease in levels of anxiety and a change in trend direction to negative (indicating improving symptoms). Variability also increased. Further, little to no overlap was present. When re-introduced (B2), levels of depression were higher than those predicted by the previous SMT line (A1 + A2), and the trend direction turned positive (indicating worsening symptoms). These effects were not immediate. Further, variability was unchanged, and overlap was present. When the intervention was removed in A3, levels of depression were lower than predicted by the previous SMT line (B2), and the trend direction immediately turned negative (indicating improving symptoms). Variability also decreased; however, overlap was present. When the intervention was re-introduced in B3 + B4, levels of depression did not differ from those predicted by the previous SMT line (A3); however, the trend direction immediately turned positive (indicating worsening symptoms) and variability was increased. Overlap was present in this phase. Finally, the removal of the intervention in A4 did not demonstrate a basic effect; that is, the trend direction, levels, and variability did not differ from those

predicted by the SMT line in B3 + B4. There were no consistent patterns of symptom levels, trend direction, or variability observed across either phase type.

Analysis across the study indicated a moderate negative, within-case effect of the intervention on measures of cognitive function (WC-SMD = -0.53, 95% CI -1.31 to 0.24) with scores recorded during intervention phases (56.59 ± 3.06 AU) 1.75 points higher than those recorded during non-intervention phases (54.48 ± 3.06 AU). NAP (NAP = 0.33, 95%CI 0.17 to 0.57) suggests a low level of data overlap between matched pairs where the probability of a randomly selected data point in phase B being lower than a randomly selected data point in phase A is, on average, 33%.

5.5.4.3 Pittsburgh Sleep Quality Index

Due to only two basic effects being observed, a causal relationship could not be established between the presence of active rehabilitation and the subsequent effect on Kristen's quality of sleep (Figure 29). A complete visual analysis report can be found in Appendix 11.3.

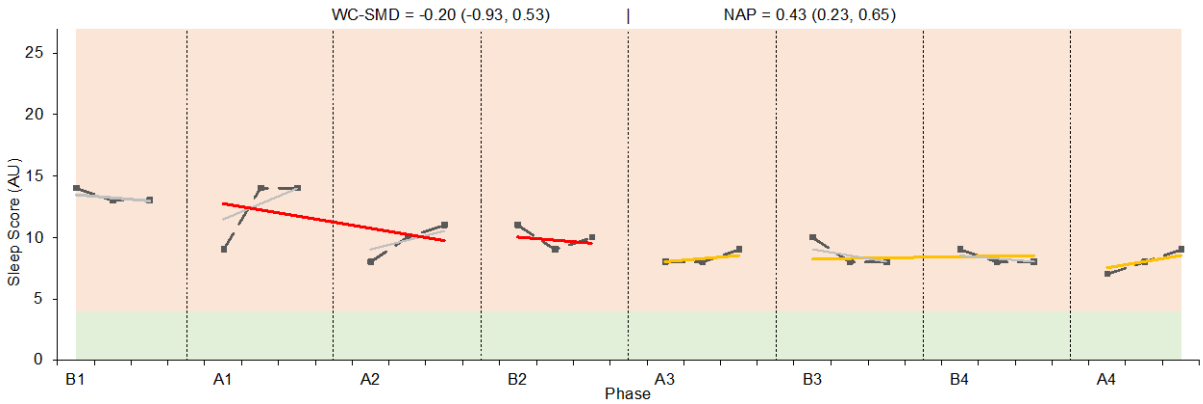


Figure 29. Kristen's self-report scores from Pittsburgh Sleep Quality Index (PSQI)

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Statistical analysis indicated a small negative, within-case effect of the intervention on measures of sleep quality (WC-SMD = -0.20, 95% CI -0.93 to 0.53) with scores

recorded during intervention phases (10.08 ± 2.19 AU) 0.50 points lower than those recorded during non-intervention phases (9.58 ± 2.31 AU). NAP (NAP = 0.43, 95%CI 0.23 to 0.65) suggests data overlap between matched pairs the probability of a randomly selected data point in phase B being lower than a randomly selected data point in phase A is, on average, 43%.

5.5.5 Participant perspective

In those follow-up interviews which were included (A1.3, B2.3, B3.3 and A4.3), there was not a clear difference between the intervention and non-intervention phases regarding Kristen's symptoms of cognitive function (executive function, memory, attention, concentration). Kristen only mentioned her cognitive symptoms in B3.3, where she reported increasing her medication levels back to normal after a period of lower levels. This had a positive effect on her cognitive symptoms, where she reported,

> I was a little more ambitious, able to do stuff...I feel like my memory on certain things, it's hard to keep time in place, but I feel a little better.

Kristen did not offer any further comment on her cognitive symptoms in the included interviews.

In those follow-up interviews which were included (A1.3, B2.3, B3.3 and A4.3), there appeared to be a negative effect of active rehabilitation on symptoms of anxiety and depression. In phase B2, Kristen stated,

> I've had a lot more anxiety, the depression...I have no desire to do anything.

In phase B3, Kristen reported,

> I feel a little better. I've gotten the moments of anxiety and depression where I just feel like it's not as bad as it was.

But she reported still feeling quiet and disengaged from other people at this time. Kristen did not mention these symptoms during the included non-intervention follow-up interviews (A1, A4). Further, it did not appear that the active rehabilitation

programme had any effect on Kristen's insomnia, as she reported struggles with sleep and fatigue throughout three of the four included interviews (A1, B3, A4).

5.5.6 Study schedule and context

Kristen began the study in April 2020, amidst the COVID-19 global pandemic. Figure 30 illustrates an estimated timeline of the government pandemic response in Kristen's area. Because Kristen had already reached the five-assessment limit intended to control for participant burden, PSS scores were not recorded. Figure 30 also includes additional distal contextual information that may have influenced the study experience, as informed by the included follow-up interviews (A1.3, B2.3, B3.3, A4.3) and general news sources.

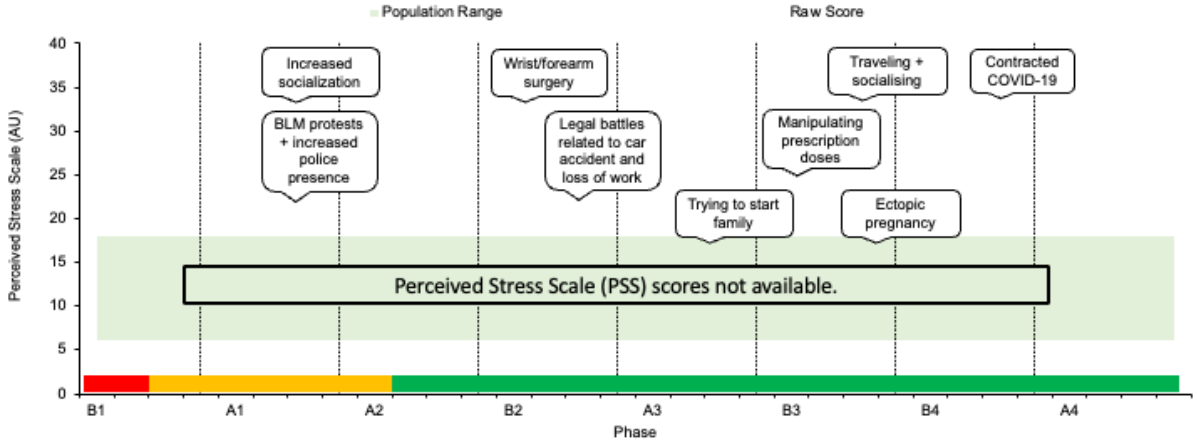


Figure 30. Kristen's contextual factors

A higher score indicates higher levels of perceived stress. Population norms: — Population average. The general state of Covid-19 lockdown responses as informed by news sources are represented as: — stay-at-home orders, — strict restrictions (no stay-at-home orders) and — light/no restrictions. A = non-intervention phase; AU= arbitrary unit; B = intervention phase.

Aside from the acute adverse reactions to the intervention programme, there were other themes of interest which Kristen spoke about in her follow-up interviews that likely influenced the success of the intervention. Two apparent and connected themes were the presence of the COVID-19 pandemic and the civil unrest (Black Lives Matter protests, 2020 Presidential election) which was present in the United States during

the time of this study. The COVID-19 pandemic was already causing disruption in her day-to-day life and feelings of isolation, having to be cautious of where she went and who she was around. The addition of the civil unrest caused even further isolation, where Kristen expressed (A4),

> ...we are more secluded. And there's definitely some friends we don't talk to as much. We don't talk politics and we just *know*...

During the study, Kristen and her partner decided to try for a baby which impacted her symptoms due to adjusting her medication levels. The apparent effect this had was discussed briefly in subsection 5.4.3.3; however, Kristen also suffered from an ectopic pregnancy during the study.

5.5.7 Results summary

A person-centred active rehabilitation programme demonstrated a largely negative effect on Kristen's symptoms of cognitive function (executive function, memory, attention, concentration), anxiety, and depression. There was no effect observed on Kristen's insomnia. Table 22 illustrates a summary of results across the study.

Table 22 Kristen's summary of results

Area of assessment & *symptoms of interest*	Outcome measure	(+)	(=)	(-)
Cognitive function • *Global cognitive function* • *Executive function* • *Memory* • *Attention* • *Concentration*	Cognitive function 8a			
	Executive Skills Questionnaire			
	Participant perspective			
Mood/behaviour • *Anxiety* • *Depression* • *Insomnia*	PROMIS Short Form v1.0 - Anxiety 8a			
	PROMIS Short Form v1.0 – Depression 8b			
	Pittsburgh Sleep Quality Index			
	Participant perspective			

Desired effect. Undesired effect. Trivial effect/inconclusive.

The effect that the intervention had on Kristen's cognitive function was negative; however, this effect was likely influenced by other contextual factors. Despite a large WC-SMD reported for measures of global cognitive function, there were negative effects observed across both phase types (intervention and non-intervention) and there were positive effects observed across both phase types. The NAP calculated for measures of cognitive function suggests the intervention had a negative effect on measures of cognitive function independent of these contextual factors; however, the size of this negative effect is difficult to determine. When considering measures of executive function, the intervention may not have had a significant negative effect independent of these contextual factors. This is supported by the WC-SMD and NAP values reported. The effect that the intervention had on Kristen's mood/behavioural symptoms (anxiety, depression) was also negative. This is supported by visual, statistical, and qualitative analysis. While a negative effect was observed, the size of this negative effect was difficult to determine due to the apparent influence of contextual factors.

More than the COVID-19 pandemic and the political discourse which took place in the first half of the study, proximal contextual factors seemed to have a bigger influence on Kristen's symptoms. The first half of the study where lockdown measures were in place and political discourse had a heavier presence, Kristen's symptoms were somewhat stable. Unfortunately, there are no PSS scores available to better support this claim. However, the latter half of the study is where more of the negative effects were observed. The manipulation of her medication as a result of trying to start a family, as well as the lingering physical and legal stressors which resulted from her car crash discussed in the initial interview, were likely the biggest contributing contextual factors and may have influenced the effectiveness of the intervention programme. In phases B2 and A3, her medications were lowered, and she was having to address new legal challenges. Further, Kristen suffered an ectopic pregnancy which had a significant influence on how Kristen was feeling. These factors had an apparent impact on Kristen's overall health and well-being. This was expressed through interviews but can also been observed across all outcome measures.

Despite the measured negative effects, Kristen still felt that future programmes may still be beneficial for her. She felt that her progress was impeded by all the contextual factors that were occurring throughout the study duration, and therefore, an accurate measure of its effect could not be determined. She expressed learning what worked for her and what didn't and further, she expressed a desire to continue trying to find an active rehabilitation programme that works for her. Based on this in combination with discussions regarding the intervention prescription, Kristen may have had more benefit with a programme that was more closely monitored than what this study allowed for. She may have benefit from a face-to-face approach where her programme intensity could have been more closely monitored and the programme could have been better adjusted for her needs.

5.6 Abel

5.6.1 Participant history, screening, and baseline assessment

Abel was a 24-year-old male British-American living between Massachusetts and New Jersey, United States. He was single and freelancing as a sportswriter. Throughout the study, Abel held various other jobs in addition to his freelancing. Some of these jobs required him to relocate, resulting in Abel moving every few months for the duration of the study. Abel has a long history of participation in contact sport (> 6 years), including American football, football, youth basketball and youth rugby. Table 23 presents the results from the initial interview and baseline assessments which directed the final list of outcome measures.

Table 23. Abel: Traumatic Encephalopathy Syndrome criterion, study eligibility, and outcome measures of interest

Criteria	Results from initial interview & baseline measures
History of multiple head impacts (direct or indirect)	No documented TBI Over 6 years of exposure to subconcussive trauma
No other neurological disorder present that likely account for all clinical features	None identified
Signs/symptoms must be present for a minimum of 12 months	Present for 3+ years
Presence of at least one core clinical feature	**Cognitive** • Concern of impaired memory, concentration, and attention • SLUMS score 27/30 AU - scores 'within normal limits' • PROMIS Short Form v2.0 - Cognitive function 8a - scores between 'within normal limits' and 'mild' cut-off • MAAS – scores below and bordering population average **Mood** • Symptoms of depression • PROMIS Short Form v1.0 - Depression 8b – scores between 'within normal limits' and 'moderate' cut-off
Presence of at least two supportive features	Anxiety, delayed onset • PROMIS Short Form v1.0 - Anxiety 8a - scores between 'within normal limits' and 'moderate' cut-off
Additional symptoms to consider	Executive dysfunction

Table informed by TES criteria (see Table 2, subsection 2.3.2). Additional symptoms informed by list of symptoms associated with CTE (see Table 1, subsection 2.3.2). Cut-off measures determined by assessment used (see Table 9, subsection 4.3.4)

PROMIS: Patient-Reported Outcomes Measurement Information System; SLUMS: SLUMS: Saint Louis University Mental Status; TBI: traumatic brain injury.

While Abel did not reach the cut-off for MCI in the screening protocol, he did report some mild levels of cognitive dysfunction in the baseline phase. This impairment was not consistent, but those questions reporting consistently lower levels were questions related to executive function, attention, and concentration. Further, some of the questions from the assessment of anxiety which Abel consistently reported higher levels were related to executive function and attention as well. Assessments of anxiety and depression observed scores ranging from ‘within normal limits’ to ‘moderate levels’ indicating some impairment, but this impairment was inconsistent.

As a result, Abel’s outcomes of interest included:

- Cognitive function (executive function, attention, concentration), assessed with Executive Skills Questionnaire (ESQ) and Mindful Attention Awareness Scale (MAAS)
- Anxiety, measured with PROMIS Short Form v1.0 - Anxiety 8a
- Depression, measured with PROMIS Short Form v1.0 - Depression 8b

In addition, PSS was included to gather further information regarding stress levels experienced throughout the study (see subsection 4.4.4).

5.6.2 Intervention schedule and physical activity

Abel was healthy and active with no reported precautions or contraindications to exercise to be considered. He enjoyed outdoor activities and occasionally played flag football (non-contact version of American football). A summary of his active rehabilitation programme, activity levels as reported from the daily activity logs, and any contextual information extracted from the follow-up interviews can be found in Figure 31.

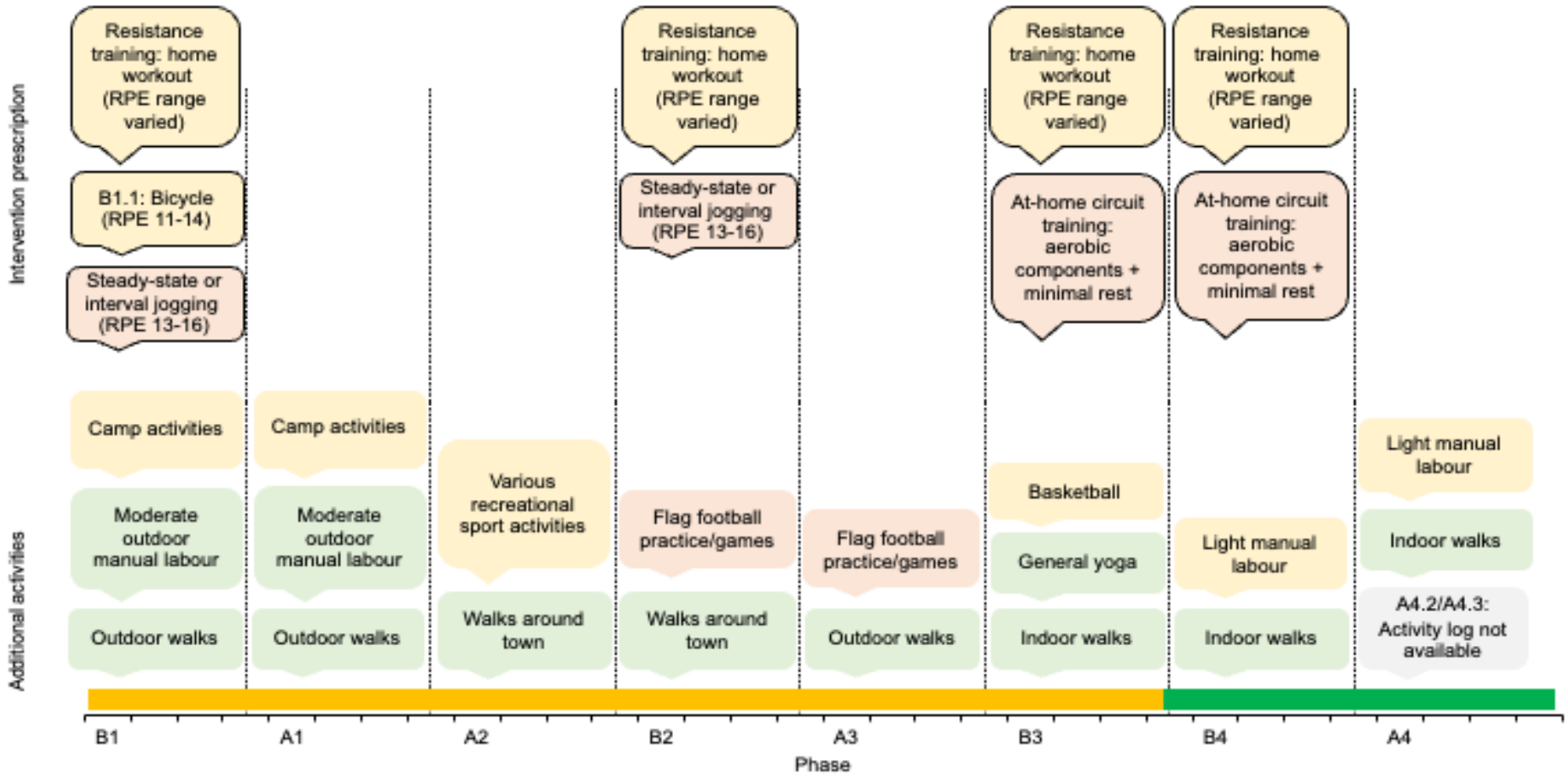


Figure 31. Abel's intervention schedule and activity levels.

Prescribed activities outlined in black. Additional activities were informed by daily activity log or included follow-up interviews (A1.3, B2.3, B3.3, A4.3). Activities characterised in accordance with recommendations from Ainsworth et al. (2011) and Bull et al. (2020b): — Light-intensity. — Moderate-to-vigorous intensity. — Vigorous-intensity. — Distal context. General state of Covid-19 lockdown responses as informed by local news sources: — stay-at-home orders. — Strict restrictions (no stay-at-home orders). — Light/no restrictions. A = non-intervention phase; B = intervention phase.

From the selected follow-up interviews (A1.3, B2.3, B3.3 and A4.3), Abel offered no specific comments on whether the rehabilitation programme was meeting his needs or preferences. Throughout the study, strength training programmes were adapted simply to introduce variation in exercises or to progress the intensity prescriptions. The setting of the workouts depended on Abel's accessibility to a gym, which was dependent on where he was living at the time or the COVID-19 lockdown measures in place. Therefore, prescribed programmes were created in a way that was adaptable to whatever setting was available. The modes of cardiovascular activity changed midway through the study and were simply determined by Abel's preference. This change in preference was largely to do with the season. B3 and B4 took place from December to March, which resulted in Abel preferring to be indoors rather than running outside.

5.6.3 Cognitive function

5.6.3.1 Executive Skills Questionnaire

There was a positive effect of the programme on Abel's executive function (Figure 32). A complete visual analysis report can be found in Appendix 11.4.

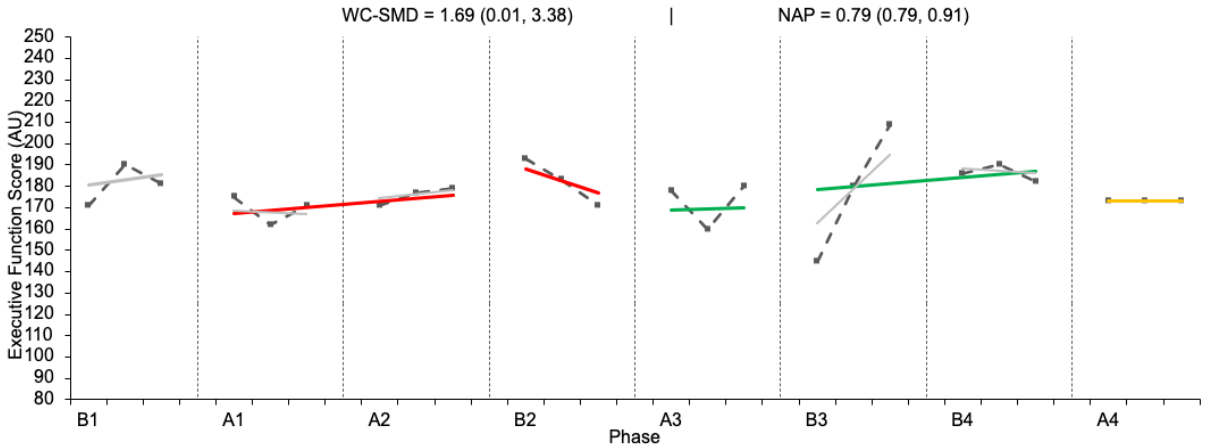


Figure 32. Abel's self-report scores from Executive Skills Questionnaire

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — (+) basic effect. — (-) basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Four basic effects were observed on measures of executive skills (visual analysis rating = 4.75, small behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Two of these basic effects were positive (A3, B3 + B4) and two of them were negative (A1 + A2, B2).

The removal of the intervention in A1 + A2 observed an immediate decrease in levels of executive function compared to the SMT line calculated in B1; however, the trend direction did not change. Variability was unchanged, and overlap was present. The re-introduction of the interval in B2 resulted in an immediate negative trend line (indicating worsening symptoms); however, when considering that variability unchanged, the symptom levels did not differ from those predicted by the SMT line calculated in the previous phase (A1 + A2). Overlap was present. The removal in A3 resulted in a change of trend direction towards positive (indicating improving symptoms). This effect was not immediate. Again, with the variability unchanged, the symptoms levels did not differ from those predicted by the previous SMT line (B2). The final introduction of the intervention introduction (B3 + B4) resulted in an immediate increase in variability (B3) before decreasing (B4). Further, levels of executive function were higher than those predicted by the A3 SMT. The trend direction was unchanged, and overlap was present. A basic effect could not be demonstrated in the final phase due to missing data (see subsection 4.5.1 for handling of missing data). There were no consistent patterns of symptom levels, trend direction, or variability observed across either phase type.

Analysis of data across the study duration indicated a large positive, within-case effect of the intervention on measures of executive function (WC-SMD = 1.69, 95% CI 0.01 to 3.38) with scores recorded during intervention phases (172.67 ± 6.23 AU) 9.15 points higher than those recorded during non-intervention phases (181.75 ± 15.40 AU). NAP (NAP = 0.79, 95%CI 0.67 to 0.91) suggests a low level of data overlap between matched pairs where the probability of a randomly selected data point in phase B being greater than a randomly selected data point in phase A is, on average, 79%.

When analysing specific components of executive function (Table 24), active rehabilitation demonstrated a large effect on measures of sustained attention and task initiation. A moderate effect was demonstrated on emotional control, and a small effect was demonstrated on goal-directed persistence, time management and working memory. A small, negative effect was observed on measures of flexibility, organization, and response inhibition. All other measures reported a trivial effect.

Table 24 Abel's individual components of executive function

Executive skill	Mean A ± SD	Mean B ± SD	WC-SMD (95%CI)	NAP (95%CI)
Emotional control (AU)	14.08 ± 2.07	15.67 ± 2.10	0.71 (-0.09, 1.51)	0.77 (0.54, 0.90)
Flexibility (AU)	17.75 ± 0.97	17.42 ± 1.24	-0.32 (-1.19, 0.54)	0.43 (0.24, 0.65)
Goal-directed persistence (AU)	12.00 ± 1.13	12.50 ± 2.58	0.41 (-0.91, 1.73)	0.64 (0.40, 0.88)
Metacognition (AU)	15.42 ± 1.51	15.17 ± 2.12	-0.15 (-1.07, 0.76)	0.47 (0.27, 0.68)
Organization (AU)	15.92 ± 1.56	15.42 ± 2.50	-0.30 (-1.30, 0.70)	0.49 (0.28, 0.70)
Planning/ prioritization (AU)	13.33 ± 1.50	13.58 ± 1.62	0.16 (-0.62, 0.93)	0.54 (0.32, 0.74)
Response inhibition (AU)	17.58 ± 1.00	17.08 ± 1.51	-0.47 (-1.44, 0.50)	0.41 (0.22, 0.64)
Stress tolerance (AU)	18.00 ± 0.43	18.08 ± 1.08	0.18 (-1.26, 1.62)	0.47 (0.26, 0.68)
Sustained attention (AU)	9.33 ± 2.19	12.33 ± 2.90	1.28 (0.27, 2.28)	0.78 (0.55, 0.91)
Task initiation (AU)	9.25 ± 1.71	12.17 ± 2.69	1.58 (0.43, 2.74)	0.81 (0.58, 0.92)
Time management (AU)	12.92 (2.02)	14.75 (1.96)	0.37 (-0.31, 1.05)	0.60 (0.37, 0.78)
Working memory (AU)	17.00 (1.21)	17.42 (1.08)	0.32 (-0.40, 1.04)	0.59 (0.36, 0.78)

Range of potential scores: 0-21. Desired effect. Undesired effect. Trivial effect/Overlap. A = non-intervention phase; B = intervention phase; NAP = non-overlap of all pairs; WC-SMD = within case standardized mean difference.

5.6.3.2 Mindful Attention Awareness Scale

There was a trivial effect of the programme on Abel's levels of attention (Figure 33). A complete visual analysis report can be found in Appendix 11.4.

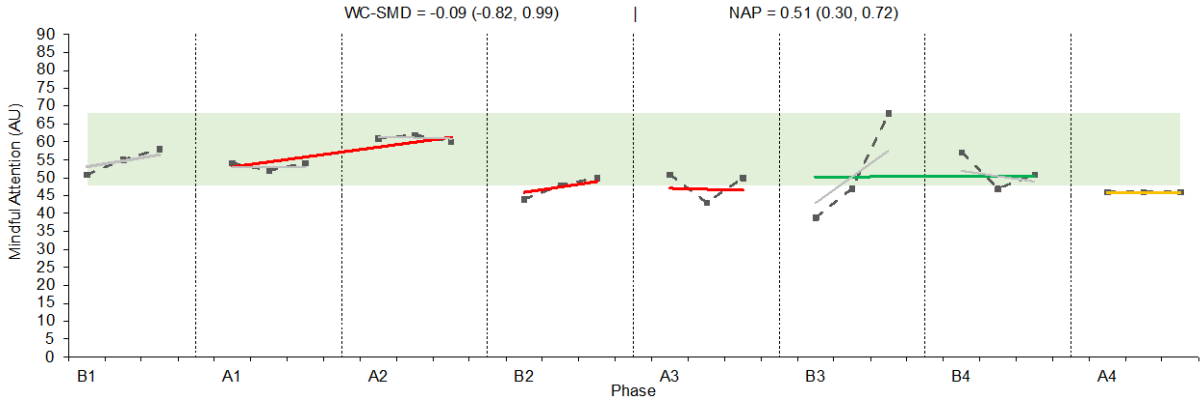


Figure 33. Abel's self-report scores from Mindful Attention Awareness Scale (MAAS)

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Four basic effects were observed on measures of mindful attention (visual analysis rating = 4.75, small behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Only one of these basic effects was positive (B3 + B4), with three of them demonstrating a negative effect (A1 + A2, B2, A3).

The removal of the intervention in A1 + A2 resulted in an immediate decrease in levels of mindful attention when compared to levels which were predicted by the previous SMT line (B1). Variability and trend direction did not change, and overlap was present. When re-introduced (B2), the levels of attention were again immediately lower than those predicted by the previous SMT line (A1 + A2). Trend direction and variability did not change, and overlap was present. When the intervention was removed in A3, levels of attention were lower than those predicted by the previous SMT line (B2), and the trend direction moved to a negative direction (indicating worsening symptoms). Further, the variability increased, and overlap was present. These effects were not immediate. When re-introduced (B3 + B4), levels of attention

were higher than those predicted by the previous SMT line (A3), and the trend direction changed to a positive direction (indicating improving symptoms). Variability also increased, and overlap was present. These effects were not immediate. A basic effect could not be demonstrated in the final phase due to missing data (see subsection 4.5.1 for handling of missing data). There were no consistent patterns of symptom levels, trend direction, or variability observed across either phase type.

Analysis across the study indicated a trivial positive, within-case effect of the intervention on measures of executive function (WC-SMD = 0.09, 95% CI -0.82 to 0.99) with scores recorded during intervention phases (51.25 ± 7.53 AU) 2.05 points lower than those recorded during non-intervention phases (53.30 ± 6.31 AU). NAP (NAP = 0.51, 95%CI 0.30 to 0.72) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being greater than a randomly selected data point in phase A is, on average, 51%.

5.6.4 Mood/behaviour

5.6.4.1 PROMIS short form v1.0 - Anxiety 8a assessment

There was a negative effect of the programme on Abel's levels of anxiety (Figure 34). A complete visual analysis report can be found in Appendix 11.4.

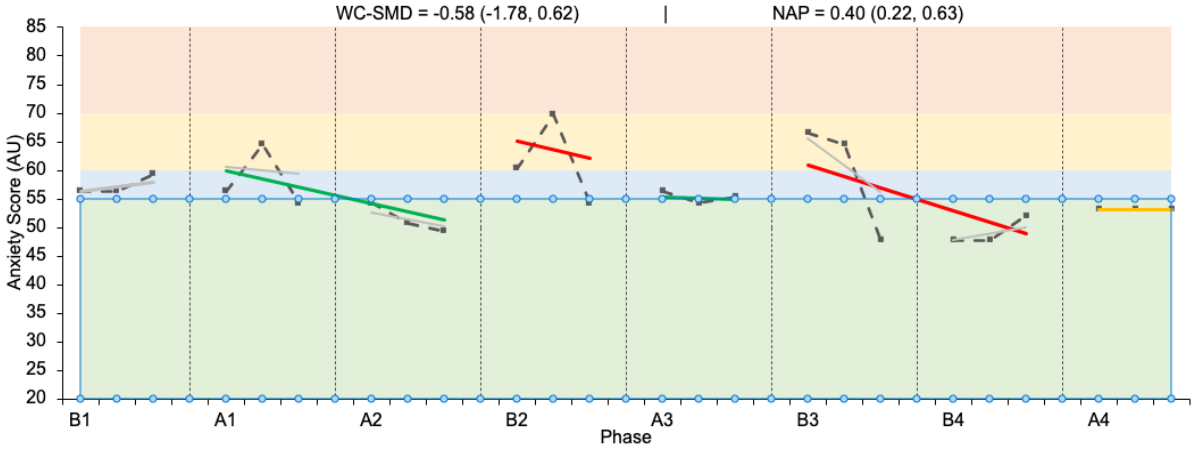


Figure 34. Abel's self-report scores from PROMIS short form v1.0 - Anxiety 8a assessment

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Four basic effects were observed on measures of anxiety (visual analysis rating = 5.00, moderate behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Two of these basic effects were positive (A1 + A2, A3), and two of them were negative (B2, B3 + B4).

The removal of the intervention in A1 + A2 resulted in a decrease in levels of anxiety compared to those predicted by the previous SMT line (A1); although, it should be noticed this effect didn't occur until A2. There was also a change in trend direction towards negative (indicating improving symptoms). Variability initially increased (B1), and overlap was present. When the intervention was re-introduced (B2), levels of anxiety immediately increased. Variability and trend direction were unchanged. Overlap was also present. When removed in A3, variability immediately decreased; however, levels of anxiety did not differ from those predicted by the previous SMT line (B2), and the trend direction remained negative (indicating worsening symptoms). Overlap was present. When the intervention was re-introduced in B3 + B4, levels were initially higher than those predicted by the previous SMT line (A3). In B4, levels did not greatly differ from those predicted by the A3 SMT line. Variability also increased. The trend direction was unchanged, and overlap was present. A basic effect could not be demonstrated in the final phase due to missing data (see subsection 4.5.1 for handling of missing data). There were no consistent patterns of symptom levels, trend direction, or variability observed across either phase type.

Analysis across the study duration indicated a moderate negative, within-case effect of the intervention on measures of executive function (WC-SMD = -0.58, 95% CI -1.78 to 0.62) with scores recorded during intervention phases (56.94 ± 7.48 AU) 2.04 points higher than those recorded during non-intervention phases (55.90 ± 4.05 AU). NAP (NAP = 0.40, 95%CI 0.22 to 0.63) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being lower than a randomly selected data point in phase A is, on average, 40%.

5.6.4.2 PROMIS short form v1.0 - Depression 8b assessment

There was a negative effect of the programme on Abel's levels of depression (Figure 35. A complete visual analysis report can be found in Appendix 11.4.

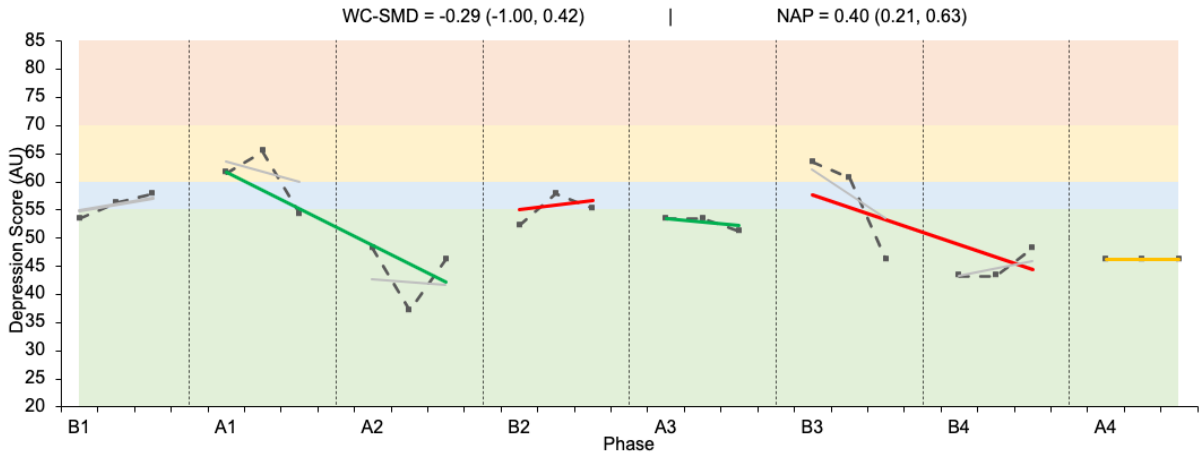


Figure 35. Abel's self-report scores from PROMIS short form v1.0 - Depression 8b assessment

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Four basic effects were observed on measures of depression (visual analysis rating = 4.25, small behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Two of these basic effects were positive (A1 + A2, A3), and two of them were negative (B2, B3 + B4).

The initial removal of the intervention (A1 + A2) resulted in levels of depression lower than those predicted by the previous SMT line (B1) and a change in trend direction towards negative (indicating improving symptoms). Variability also increased. These changes were not immediate, and overlap was present. When the intervention was re-introduced (B2), levels of depression were higher than those predicted by the previous SMT line (A1 + A2) and the trend direction turned positive (indicating worsening symptoms). These changes were not immediate. Further, variability was unchanged, and overlap was present. When the intervention was removed (A3), levels of depression were lower than those predicted by the previous SMT line (B3)

and the trend direction turned negative (indicating improving symptoms). Variability also decreased. These changes were not immediate, and overlap was present. When the intervention was introduced for the final time (B3 + B4), levels did not differ from those predicted by the previous SMT line (A3) and the trend direction was unchanged; however, variability was immediately increased. Overlap was present. A basic effect could not be demonstrated in the final phase due to missing data (see subsection 4.5.1 for handling of missing data). There was no consistent pattern observed across either phase types.

Analysis of across the entire study period indicated a small negative, within-case effect of the intervention on measures of executive function (WC-SMD = -0.29, 95% CI –1.00 to 0.42) with scores recorded during intervention phases (53.18 ± 6.68 AU) 2.4 points higher than those recorded during non-intervention phases (50.78 ± 7.60 AU). NAP (NAP = 0.40, 95%CI 0.21 to 0.63) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being lower than a randomly selected data point in phase A is, on average, 40%.

5.6.5 Participant perspective

In those follow-up interviews which were included (A1.3, B2.3, B3.3 and A4.3), there was not a clear difference between intervention and non-intervention phases regarding Abel's symptoms of executive function or attention as Abel did not offer any comment on his executive function or attention in those interviews which were included. There was not a clear difference between intervention and non-intervention phases regarding Abel's symptoms of anxiety or depression either. In A1, he stated,

> I've not really had any- I've not not bad at all, really. So no anxiety, no.

And in B3, he reported,

> There haven't really- I don't think there have been really any moments where any of the symptoms felt overwhelming or anything...

Despite a lack of apparent difference between the phase types, when reflecting on his study experience, Abel reported,

> But it's been really good. There have been a lot of other inputs that have definitely made significant changes, helped me mentally. But this really helped me identify things and actually kind of tune in to how I feel and knowing what I feel like and knowing what it feels like. And this has really helped me. Like I feel like a completely different person.... I feel so much more positive.

When asked what he thought most benefit from the study, he answered,

> Probably more on the depression side of things. Obviously throughout our various points I really struggled. I was in a really tough spot...And I'm, overall, in such a better place mentally. I'm so much better at making sure it doesn't turn into this thing that debilitates me in some form, whether it's just not wanting to leave my room, or just mentally being switched off. I'm not freaking out.

Abel believed the effect to be a cumulative one, which is why differences between individual phases were less obvious. He stated (A4),

> I didn't necessarily feel it initially. Especially- kind of in the middle of the study, I was kind of thinking I don't know if I feel a difference here. But I do think it was definitely cumulative...I feel that there's a sense of it is definitely looking back, I can definitely see. It's definitely easier to kind of feel some motion.

5.6.6 Study schedule and context

Abel began the study in May 2020, towards the end of the first COVID-19 wave in the United States. Figure 36 illustrates an estimated timeline of the government pandemic response in Abel's area and his PSS scores. Figure 36 also includes additional distal contextual information that may have influenced the study experience, as informed by the included follow-up interviews (A1.3, B2.3, B3.3, A4.3) and general news sources.

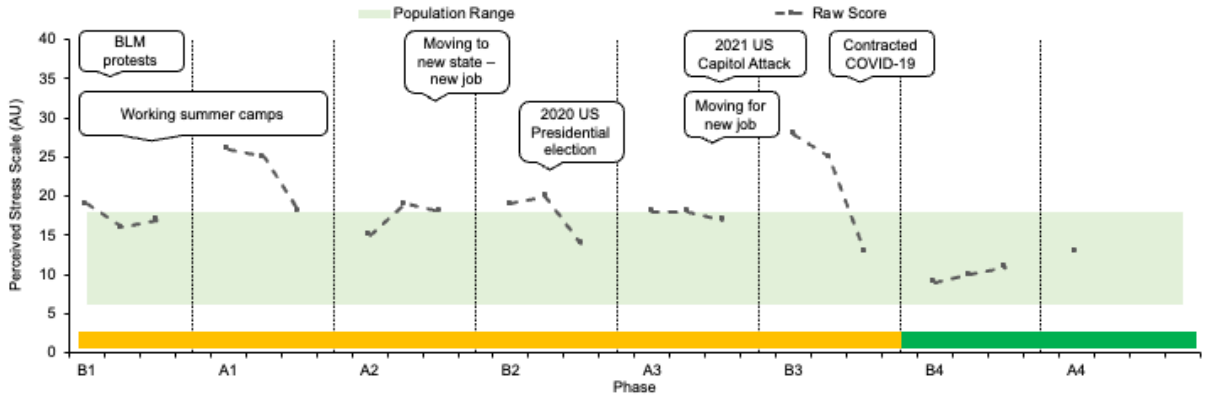


Figure 36. Abel's PSS scores at each data collection point

A higher score indicates higher levels of perceived stress. Population norms: — Population average. The general state of Covid-19 lockdown responses as informed by news sources are represented as: — stay-at-home orders, — strict restrictions (no stay-at-home orders) and — light/no restrictions. A = non-intervention phase; AU= arbitrary unit; B = intervention phase.

The COVID-19 pandemic and the civil unrest (Black Lives Matter protests, 2020 Presidential election, US Capitol Attack) present in the United States were two factors present which may have impacted Abel's study experience. By the middle of the study, the civil unrest appeared to have less of an influence. In B2, he reported,

> I stopped paying attention to is as keenly because it just wasn't gonna help me.

He went on to say,

> For the most part, this two weeks has been a lot more positive than before. I think that's a lot to do with friends and the outside climate.

When given the opportunity to reflect on potential influencing factors in his final interview, Abel answered,

> Social and political hasn't been, you know, the best. That was, uh, until November. So for the first half, really third, of it. That was definitely an enormous contribution to a lot of the more negative feelings, and rarely, well probably never really offered any relief.

However, the consequences of the COVID-19 were present throughout. At the start of the study, Abel appeared well-adjusted. He reported in B1,

> I've seen- well socially distanced with a few of my friends.

He went on to say,

> The times I've gone out in Boston, it's pretty much everybody wears a mask. I've had to take public transport everywhere, but when I do, people don't sit next to you and people do a good job of keeping their distance.

Despite this, the pandemic continued to cause disruption with work and socialisation.

Another influencing factor, which was consistently changing, was Abel's work and living circumstances. While working as a freelance writer, Abel also worked as a camp director, with the department of camp coordination, and as a live-in nanny. Each of these jobs were located in different locations in the Northeast of the US. Some of the jobs brought Abel great satisfaction. When getting ready for his nannying position, he reported (B1),

> I'm quite nervous, but I'm really excited...I thought it's a fairly good opportunity to kind of just- it's like a fresh start.

While in his camp coordination position waiting for another season to start, he described himself as,

> ...defeated and done. I just can't get into the mindset to work.

5.6.7 Results summary

The effect that a person-centred active rehabilitation programme demonstrated on Abel's symptoms of cognitive function (executive function, attention, concentration), depression, and anxiety was mixed and therefore inconclusive. Table 25 illustrates a summary of results across the study.

Table 25 Abel's summary of results

Area of assessment & *symptoms of interest*	Outcome measure	(+)	(=)	(-)
Cognitive function • *Global cognitive function* • *Executive function* • *Attention* • *Concentration*	Executive function			
	Mindful Attention Awareness Scale			
	Participant perspective			
Mood/behaviour • *Anxiety* • *Depression*	PROMIS Short Form v1.0 - Anxiety 8a			
	PROMIS Short Form v1.0 – Depression 8b			
	Participant perspective			

Desired effect. Undesired effect. Trivial effect/inconclusive.

The effect that the intervention had on Abel's executive function was positive. This is supported by the visual, statistical, and qualitative analysis. The effect that the intervention had on Abel's attention was trivial; however, there is evidence to suggest that contextual factors negatively influenced the effectiveness of the intervention. The intervention demonstrated an inconsistent positive effect; however, removal of the intervention consistently observed a negative basic effect. The effect that the intervention had on Abel's mood and behavioural symptoms was negative. This is supported by the visual analysis, statistical analysis, and qualitative analysis. Statistical analysis across the study indicates this effect was small, suggesting that contextual factors may have influenced the effectiveness of the intervention. This is particularly evident in the first half of the study. There were still some restrictions as a result of the COVID-19 pandemic; however, the political discourse and the 2020 Presidential election also had a significant effect. PSS scores were elevated through phase B2, where scores ultimately dropped afterwards. This may be associated with the end of the 2020 Presidential election. Following phase B2, all outcome measures indicated a small improvement in symptoms. There was also a spike in PSS scores observed in phase B3. This could be explained by the aftermath of the US Capitol

attack, or it could also be explained by Abel's expressed frustration with work around this time. Either way, this spike in PSS scores was also observed across measures of depression and anxiety. This indicates that the intervention may not have been the only contributing factor to the worsening of symptom levels, as there was an observed improvement in cognitive functioning and mindful attention here.

There is evidence to suggest the intensity of the activity should be considered. While Abel's additional activity did not largely differ between the phase types (indicating a clear difference between intervention and non-intervention scores), it should be noted that the intensity of these additional activities was lower in the latter half of the study. This is where the most improvement was observed.

5.7 Gemma

5.7.1 Participant history, screening, and baseline assessment

Gemma was a 29-year-old female living between New York, United States and Lombardy, Italy. During the study, she was in a long-distance relationship which had her traveling often. Gemma was in-between jobs as a paediatric physical therapist and was mostly working 'per diem' throughout the study. Gemma reported a long history of participation in various contact sports (> 6 years). She mostly focused on karate, but also played basketball, softball, and volleyball. Table 26 presents the results from the initial interview and baseline assessments which directed the final list of outcome measures.

Table 26. Gemma: Traumatic Encephalopathy Syndrome criterion, study eligibility, and outcome measures of interest

Criteria	Results from initial interview & baseline measures
History of multiple head impacts (direct or indirect)	No documented TBI Over 6 years of exposure to subconcussive trauma
No other neurological disorder present that likely account for all clinical features	None identified
Signs/symptoms must be present for a minimum of 12 months	Present for at least 2 years
Presence of at least one core clinical feature	**Cognitive** • Signs of executive dysfunction • SLUMS score 30/30 AU - score 'within normal limits' • PROMIS Short Form v2.0 - Cognitive function 8a - scores 'within normal limits'
Presence of at least two supportive features	Anxiety, delayed onset • PROMIS Short Form v1.0 - Anxiety 8a - scores between 'within normal limits' and 'moderate' cut-off

Table informed by TES criteria (see Table 2, subsection 2.3.2). Additional symptoms informed by list of symptoms associated with CTE (see Table 1, subsection 2.3.2). Cut-off measures determined by assessment used (see Table 9, subsection 4.3.4)

PROMIS: Patient-Reported Outcomes Measurement Information System; SLUMS: SLUMS: Saint Louis University Mental Status; TBI: traumatic brain injury.

Despite no impairment measured using the SLUMS or PROMIS Short Form v2.0 - Cognitive function 8a assessments, the ESQ assessment observed consistently lower levels of executive functions with some components, specifically response inhibition, emotional control, time management, and stress tolerance. Measures of anxiety ranged from ‘within normal limits’ to ‘moderate levels’ indicating some impairment, but this impairment was inconsistent.

As a result, Gemma’s outcomes of interest included:

- Cognitive function (executive function), assessed with Executive Skills Questionnaire (ESQ)
- Anxiety, measured with PROMIS Short Form v1.0 - Anxiety 8a

In addition, PSS was included to gather further information regarding stress levels experienced throughout the study (see subsection 4.4.4).

5.7.2 Intervention schedule and physical activity

Gemma was healthy and active with no reported precautions or contraindications to exercise to be considered. She enjoyed resistance circuit training and outdoor activities, particularly running. A summary of her active rehabilitation pogramme, activity levels as reported from the daily activity logs and any contextual information extracted from the follow-up interviews can be found in Figure 37.

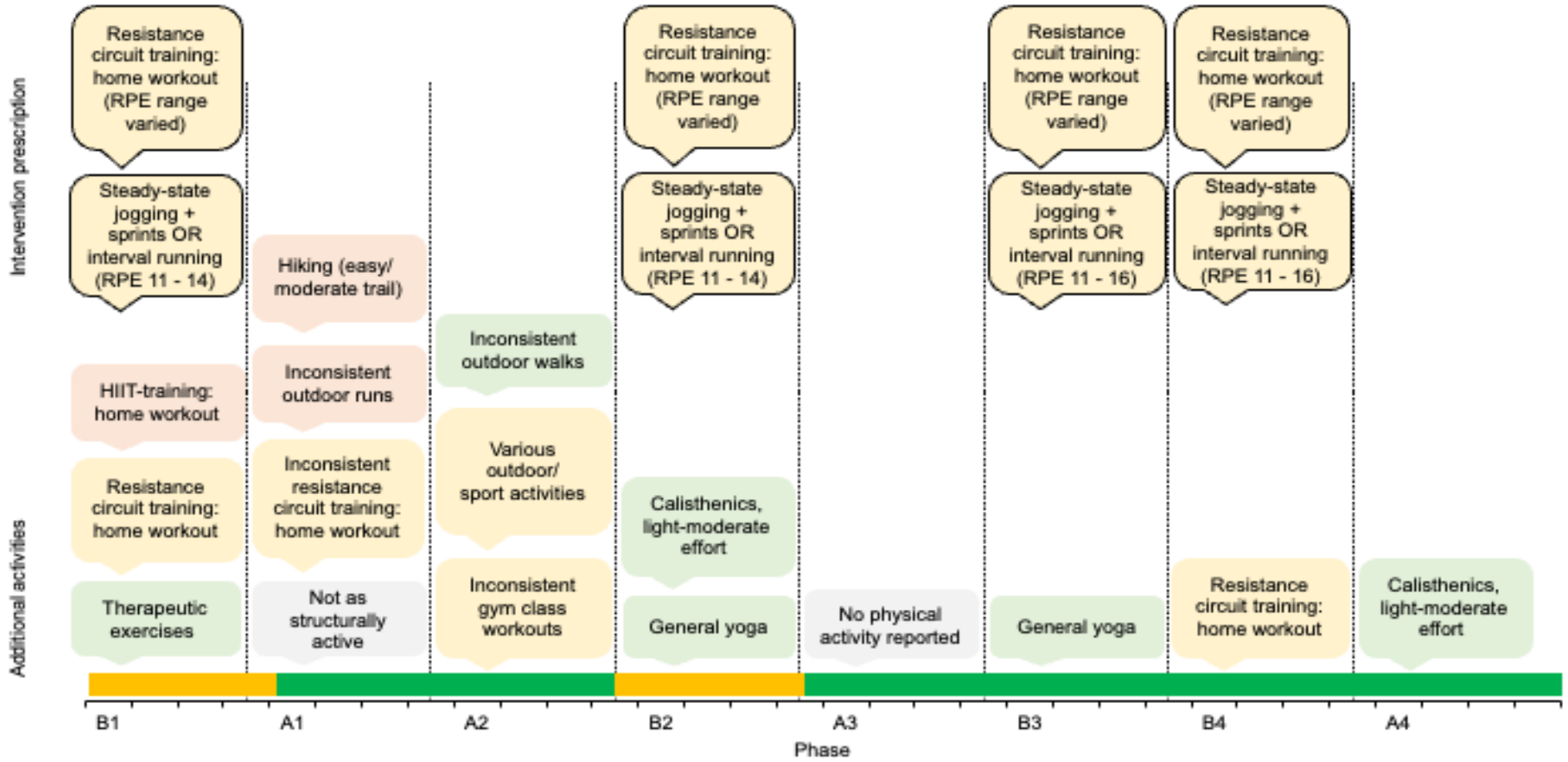


Figure 37. Gemma's intervention schedule and activity levels.

Prescribed activities outlined in black. Additional activities were informed by daily activity log or included follow-up interviews (A1.3, B2.3, B3.3, A4.3). Activities characterised in accordance with recommendations from Ainsworth et al. (2011) and Bull et al. (2020b): Light-intensity. Moderate-to-vigorous intensity. Vigorous-intensity. Distal context. General state of Covid-19 lockdown responses as informed by local news sources: stay-at-home orders. Strict restrictions (no stay-at-home orders). Light/no restrictions. A = non-intervention phase; B = intervention phase.

From the selected follow-up interviews (A1.3, B2.3, B3.3 and A4.3), Gemma offered no specific comments on whether the rehabilitation programme was meeting her needs or preferences. Throughout the study, Gemma's resistance training programmes consisted of resistance circuit training programmes where exercises were completed as a circuit rather than the more traditional one exercise at a time until the prescribed number of sets are completed. An aerobic component was not added to these programmes, differentiating it from other high-intensity interval training (HIIT) programmes. Gemma's cardiovascular activity allowed her to choose between steady-state jogging or interval training. This interval training could be done outside, on a treadmill or a rowing machine. This gave Gemma some variety to choose from during the study, while still maintaining a consistent intensity progression.

Overall, Gemma was satisfied with the programme prescription and delivery. When reflecting on her study experience in the final interview (A4), she stated,

> I feel like the workouts were definitely easy to maintain. And like I said, it was- because they were pretty long, like it could easily take me over an hour to do them sometimes, but because it was just twice a week, that was manageable...I could easily perform the home exercises at home, nothing required - like a ton of space or equipment or prescription. I felt it was appropriate for my intensity goals and I was able to, you know, make it easier or harder if I needed to, easily. And having all those descriptors allowed it to be fluid so that I didn't have to stop and like ask you questions and then maybe delay doing them myself.

5.7.3 Cognitive function

5.7.3.1 Executive Skills Questionnaire

Due to only two basic effects being observed, a causal relationship could not be established between the presence of active rehabilitation and the subsequent effect on measures of executive function (Figure 38). A complete visual analysis report can be found in Appendix 11.5.

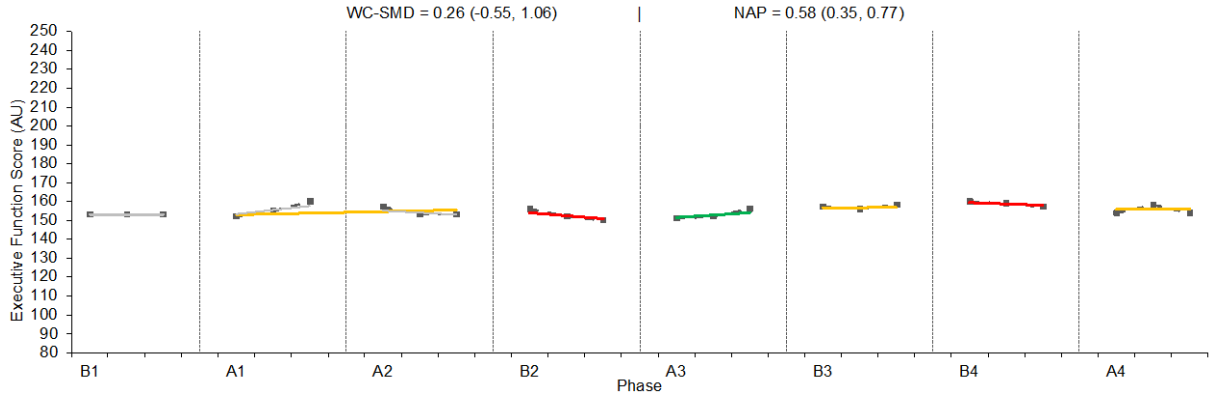


Figure 38. Gemma's self-report scores from Executive Skills Questionnaire

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Analysis across the entire study period indicated a small positive, within-case effect of the intervention on measures of executive function (WC-SMD = 0.26, 95% CI -0.55 to 1.06) with scores recorded during intervention phases (155.33 ± 3.08 AU) 0.75 points higher than those recorded during non-intervention phases (154.58 ± 2.71 AU). NAP (NAP = 0.58, 95%CI 0.35 to 0.77) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being greater than phase A is, on average, 58%.

When analysing specific components of executive function (Table 27), active rehabilitation demonstrated a large effect on measures of flexibility and a moderate effect on measures of stress tolerance. A small effect was demonstrated on measures of time management and working memory. A moderate negative effect was observed on measures of goal-directed persistence and a small negative effect was observed on measures of metacognition. A small negative effect was observed on measures of time management and working memory. All other measures reported a trivial effect.

Table 27 Gemma's individual components of executive function

Executive skill	Mean A ± SD	Mean B ± SD	WC-SMD (95%CI)	NAP (95%CI)
Emotional control (AU)	10.58 ± 0.90	10.42 ± 0.51	-0.17 (-0.78, 0.44)	0.45 (0.25, 0.67)
Flexibility (AU)	13.00 ± 0.74	14.00 ± 0.95	1.26 (0.27, 2.25)	0.79 (0.56, 0.91)
Goal-directed persistence (AU)	13.50 ± 0.67	13.08 ± 0.29	-0.57 (-1.19, 0.04)	0.33 (0.16, 0.56)
Metacognition (AU)	14.75 ± 0.75	14.58 ± 0.67	-0.21 (-0.91, 0.50)	0.43 (0.24, 0.66)
Organization (AU)	15.00 ± 0.00	15.00 ± 0.00	0.00 (0.00, 0.00)	0.50 (0.29, 0.71)
Planning/ prioritization (AU)	14.50 ± 0.52	14.42 ± 0.51	-0.15 (-0.89, 0.59)	0.46 (0.26, 0.68)
Response inhibition (AU)	11.58 ± 0.90	11.58 ± 0.51	0.00 (-0.61, 0.61)	0.51 (0.30, 0.72)
Stress tolerance (AU)	11.92 ± 0.29	12.08 ± 0.67	0.54 (-0.81, 1.88)	0.57 (0.35, 0.77)
Sustained attention (AU)	12.33 ± 0.65	12.33 ± 0.65	0.00 (-0.74, 0.74)	0.50 (0.29, 0.71)
Task initiation (AU)	12.00 ± 0.00	12.00 ± 0.00	0.00 (0.00, 0.00)	0.50 (0.29, 0.71)
Time management (AU)	13.33 ± 0.78	13.67 ± 0.65	0.40 (-0.31, 1.10)	0.62 (0.40, 0.80)
Working memory (AU)	12.08 ± 0.90	12.42 ± 0.90	0.34 (-0.41, 1.10)	0.61 (0.39, 0.80)

Range of potential scores: 0-21. Desired effect. Undesired effect. Trivial effect/Overlap. A = non-intervention phase; B = intervention phase; NAP = non-overlap of all pairs; WC-SMD = within case standardized mean difference.

5.7.4 Mood/behaviour

5.7.4.1 PROMIS short form v1.0 - Anxiety 8a assessment

The effect that a person-centred active rehabilitation programme on Gemma's levels of anxiety was inconclusive (Figure 39). A complete visual analysis report can be found in Appendix 11.5.

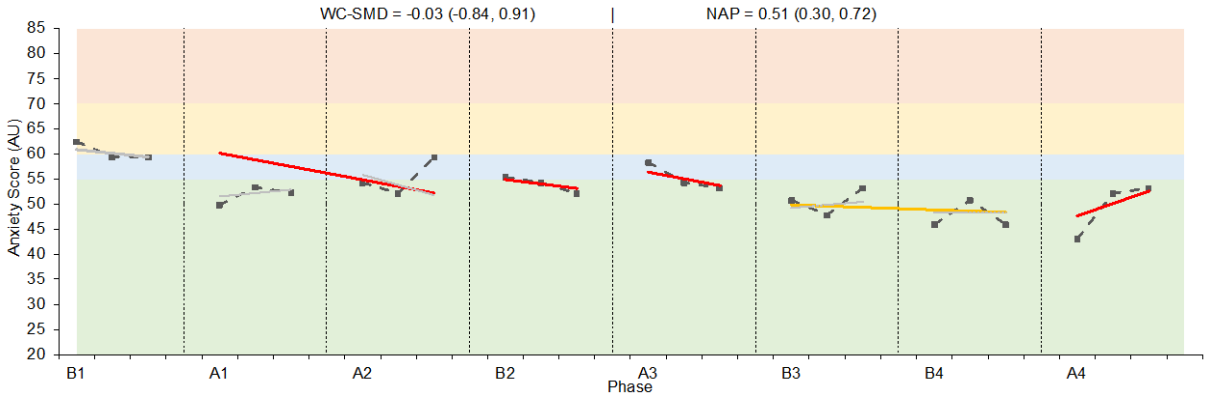


Figure 39. Gemma's self-report scores from PROMIS short form v1.0 - Anxiety 8a assessment

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Four basic effects were observed on measures of anxiety (visual analysis rating = 5.25, small behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. All basic effects overserved were negative (A1 + A2, B2, A3, A4).

When the intervention was removed in A1 + A2, levels of anxiety did initially decrease (A1); however, in A2 they returned to those predicted by the previous SMT line (B1). The trend direction was unchanged, but variability immediately increased. Little to no overlap was present. When the intervention was re-introduced (B2), levels of anxiety were higher than those predicted by the previous SMT line (A1 + A2), but the trend direction was unchanged. Variability immediately decreased, and overlap was present. When removed (A3), levels of anxiety were immediately higher than those predicted by the previous SMT line (B2). The trend direction and variability remained unchanged, and overlap was present. No basic effect was demonstrated with the re-

introduction of the intervention (B3 + B4) that is, the trend direction, levels, and variability did not differ from those predicted by the SMT line in A3. When removed (A4), levels of anxiety were higher than those predicted by the previous SMT line (B3 + B4) and the direction of the trend turned positive (indicating worsening symptoms). The variability was unchanged, and this effect was not immediate. Further, overlap was present. Across all intervention phases, the trend direction was consistently negative (demonstrating an improvement in symptom levels across the study duration). There were no consistent patterns of symptom levels, trend direction, or variability observed across either phase type.

Analysis across the study duration indicated a trivial, within-case effect of the intervention on measures of anxiety (WC-SMD = -0.03, 95% CI -0.84 to 0.91) with scores recorded during intervention phases (53.13 ± 5.38 AU) 0.13 points higher than those recorded during non-intervention phases (52.98 ± 4.07 AU). NAP (NAP = 0.51, 95%CI 0.30 to 0.72) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being lower than a randomly selected data point in phase A is, on average, 51%.

5.7.5 Participant perspective

In those follow-up interviews which were included (A1.3, B2.3, B3.3 and A4.3), there did not appear to be a difference between how Gemma was feeling during intervention and non-intervention regarding executive function. In fact, Gemma hardly discussed components of executive function. Of the interviews that were included, she only mentioned her cognitive function once. In phase A1, she stated,

> ...clarity seems pretty fine. Mental clarity kind of comes and goes.

Even in the final interview, Gemma did not offer any opinion on how her executive skills had been impacted by participating in the study.

There did not appear to be an obvious difference between how Gemma was feeling during intervention and non-intervention regarding her levels of anxiety either. She spoke about her anxiety in every included interview; however, there did not appear to

be a significant difference in her perceived experiences. For example, in A1 Gemma stated,

> I'm not as anxious in terms of, like, frequency and severity...I haven't really felt anxious-anxious in a while, but definitely in my head.

And in B3, Gemma stated,

> ...but I still don't think I've been like, anxious. So- I feel like overall, definitely moments of, like, stress but normal, tolerable amounts. I don't think I've really had anxiety.

This idea was re-iterated by Gemma in her final interview, where she stated,

> I can't really say for certain if I noticed like any specific changes in my symptoms, based on like active versus inactive.

Gemma did offer an acknowledgement of improvement in symptoms overall compared to when she first began, reporting in her final interview,

> I definitely feel like- I felt when we started the study I was way more anxious. Now, I haven't had, like, really anxiety, badly, in a really long time. Like, I'll have a 30-minute bout here or there, but then it clears up...[I'm] not, like, lying in bed at night crazy anxious. So, I do feel like it's gotten less frequent, and definitely less intense.

5.7.6 Study schedule and context

Gemma began the study in May 2020, towards the end of the first Covid-19 wave in the United States. Figure 40 illustrates an estimated timeline of the government pandemic response in Gemma's area and her PSS scores. Figure 40 also includes additional distal contextual information that may have influenced the study experience, as informed by the included follow-up interviews (A1.3, B2.3, B3.3, A4.3) and general news sources.

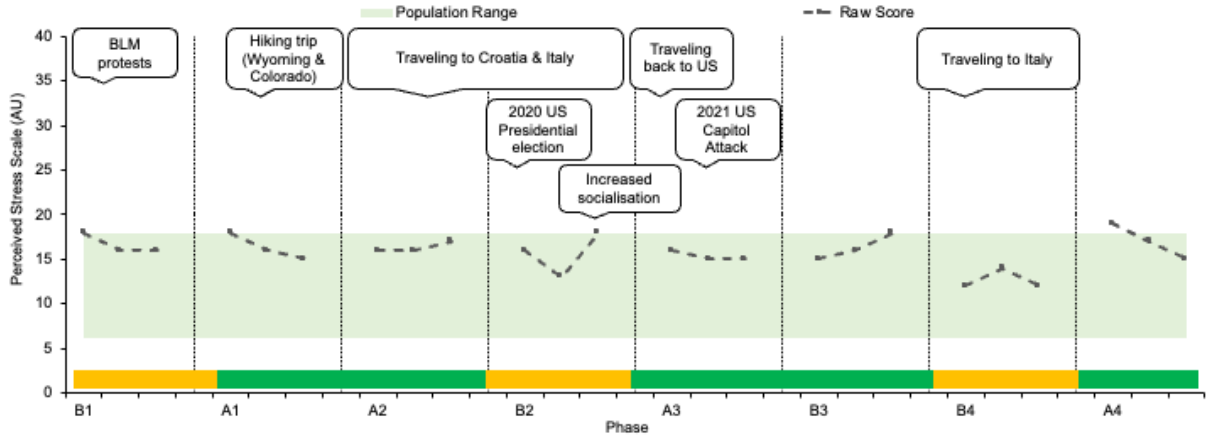


Figure 40. Gemma's PSS scores at each data collection point

A higher score indicates higher levels of perceived stress. Population norms: — Population average. The general state of Covid-19 lockdown responses as informed by news sources are represented as: — stay-at-home orders, — strict restrictions (no stay-at-home orders) and — light/no restrictions. A = non-intervention phase; AU= arbitrary unit; B = intervention phase.

There were various topics which were discussed during Gemma's follow-up interviews that may have impacted her symptom levels and subsequently impacted the success of the intervention. The most evident topic was the presence of the COVID-19 pandemic. This had multiple influences on Gemma's study experience and symptom levels. The virus itself created some anxiety and stress regarding her family members, particularly her grandparents and her new-born niece. In B1, she expressed fear and concern over spreading the virus to her family following her travels, stating,

> But still, now that I'm home I'm like, my grandparents live here. I'm like, am I exposing them?...You always worry it's going to be you, you know?

And in B3, she reported,

> ...I've definitely been stressed with stuff like trying to get vaccines for my grandparents get one for myself, trying to figure out, like, planning, scheduling.

The isolation caused by the government pandemic responses was another factor that had an evident impact on Gemma's study experience. Gemma described herself as quite social and needing regular interaction. This coupled with time differences when

traveling caused some difficulty for Gemma. In B2 when asked about potential sources of anxiety, Gemma answered,

> I think just the fact that I'm here [in Italy], and, like, basically I don't really- I only see one person, my boyfriend...we're not going to his parents anymore, I'm not working, you can't do any sort of socialising, I don't have my Italian lessons.

She went on to say,

> But I am like very much your social person, so, I'm like, yeah, like, I'm very social. I like to just interact with other humans, so it's like, that's what's definitely getting to me. And the time difference is hard.

Another major contributing factor that served as a source of anxiety was the evident civil unrest that was present in the United States through much of 2020/2021. Between the 2020 Presidential election, the eruption of the Black Lives Matter protests and the attack on the US Capitol, Gemma stated,

> ...there's such a divide...and I feel it.

At times, Gemma felt irritated and exhausted by the constant presence. She had to take herself off of social media at one point. Early in the study, Gemma felt it was the only thing that people were interested in discussing, reporting (B1)

> ...every conversation you have with anyone ever is always about either COVID or the political climate...It makes me feel ignorant because I don't want to talk about it anymore.

There were personal circumstances that may also have negatively impacted Gemma's symptom levels. Gemma was in a long-distance relationship, the source of many of her travels. This consistent planning was stressful at times and navigating the pandemic responses of various other countries was a source of stress and anxiety at times as well. In addition, Gemma's work had been impacted by the COVID-19 pandemic prior to the start of this study; therefore, she took on various jobs and per diem work throughout the year. She reflected in her final interview on these factors, stating,

> ...I feel like there were so many factors for me personally that influenced how I was feeling – with COVID, with politics, with my long-distance relationship. There was no definitive end to when I got stuck here in quarantine and was not going to be able to see my boyfriend, and [then] I saw him and it was weird. Not being able to work, then when I got laid off work. I'm constantly stressed that I've been out of the workforce for too long. Not having a home base and, like, constantly moving.

She felt like each of these factors contributed to her inability to really determine the true effect of the intervention.

5.7.7 Results summary

A person-centred active rehabilitation programme did not demonstrate a strong effect on Gemma's symptom of cognitive function (executive function) or anxiety. Table 28 illustrates a summary of results across the study.

Table 28 Gemma's summary of results

Area of assessment & *symptoms of interest*	Outcome measure	(+)	(=)	(-)
Cognitive function • *Executive function*	Executive Skills Questionnaire Participant perspective			
Mood/behaviour • *Anxiety*	PROMIS Short Form v1.0 - Anxiety 8a Participant perspective			

Desired effect. Undesired effect. Trivial effect/inconclusive.

There was not enough evidence to determine what, if any, effect the active rehabilitation programme had on Gemma's levels of cognitive function or anxiety. Gemma's levels of cognitive function did not appear to have any change. This is supported by the similar measures taken throughout the study, a lack of demonstrating a causal effect, and the presence of overlap. There was an observed

improvement in levels of anxiety when comparing the start to the end of the study; however, this improvement appears independent of the presence of any intervention. This is supported by the trivial effect reported for measures of anxiety.

5.8 Simon

5.8.1 Participant history, screening, and baseline assessment

Simon was a 35-year-old male living in Bristol, United Kingdom. Simon lived with his long-term girlfriend. He was not working when he began the study but he did return to full-time work for the first time since his severe TBI during the study. Simon reported a long history of playing rugby (> 6 years) which ended due to a moderate TBI sustained during a match. This injury had a significant impact on Simon's quality of life and ability to work. During his rugby career, Simon suffered from multiple diagnosed and undiagnosed concussions, some of which were consecutive within a condensed timeframe. Simon also has a history of anterior cruciate ligament (ACL) rupture as a result of rugby. Table 29 presents the results from the initial interview and baseline assessments which directed the final list of outcome measures.

Table 29. Simon: Traumatic Encephalopathy Syndrome criterion, study eligibility, and outcome measures of interest

Criteria	Results from initial interview & baseline measures
History of multiple head impacts (direct or indirect)	Multiple mTBI (> 4), some within short periods of time 1 severe TBI, resulting in loss of consciousness Over 6 years of exposure to subconcussive trauma
No other neurological disorder present that likely account for all clinical features	None identified.
Signs/symptoms must be present for a minimum of 12 months	Present since ~2007
Presence of at least one core clinical feature	**Cognitive** • Concerns of impaired memory, concentration, and attention • Signs of executive dysfunction • SLUMS score 26/30 AU - score meet assessment cut-off for 'mild cognitive impairment' • PROMIS Short Form v2.0 - Cognitive function 8a - scores between 'within normal limits' and 'mild' cut-off • MAAS – scores below population average **Mood** • Reported history of depression • PROMIS Short Form v1.0 - Depression 8b - scores between 'within normal limits' and 'mild' cut-off
Presence of at least two supportive features	Anxiety, delayed onset • PROMIS Short Form v1.0 - Anxiety 8a - scores 'within normal limits'

Table informed by TES criteria (see Table 2, subsection 2.3.2). Additional symptoms informed by list of symptoms associated with CTE (see Table 1, subsection 2.3.2). Cut-off measures determined by assessment used (see Table 9, subsection 4.3.4)

PROMIS: Patient-Reported Outcomes Measurement Information System; SLUMS: SLUMS: Saint Louis University Mental Status; TBI: traumatic brain injury.

Though the impairment was not consistent, Simon did exhibit mild levels of cognitive impairment. Further, components of memory, task initiation, attention, concentration, and organization were consistently lower across various assessments (ESQ, PROMIS Short Form v2.0 - Cognitive function 8a, MAAS). Simon reported an inconsistent impairment in levels of depression, and levels of anxiety were considered normal.

As a result, Simon's outcomes of interest included:

- Cognitive function (global cognitive function, executive function, memory, attention, concentration), assessed with PROMIS Short Form v2.0 - Cognitive function 8a, Executive Skills Questionnaire (ESQ), and Mindful Attention Awareness Scale (MAAS)
- Depression, measured with U PROMIS short form v1.0 - Depression 8b

In addition, PSS was included to gather further information regarding stress levels experienced throughout the study (see subsection 4.4.4).

5.8.2 Intervention schedule and physical activity

Simon reported some exercise intolerance due to previous TBI's. In his initial interview he stated,

> I get headaches when I'm straining or bending down and picking stuff up. So I've got no problem physically doing it...but I get, not always, but sometimes I get quite a strong headache.

To address this, Simon's programme minimised the use of exercise that involved straining or bending down. A summary of Simon's active rehabilitation programme, activity levels as reported from the daily activity logs, and any contextual information extracted from the follow-up interviews can be found in Figure 41.

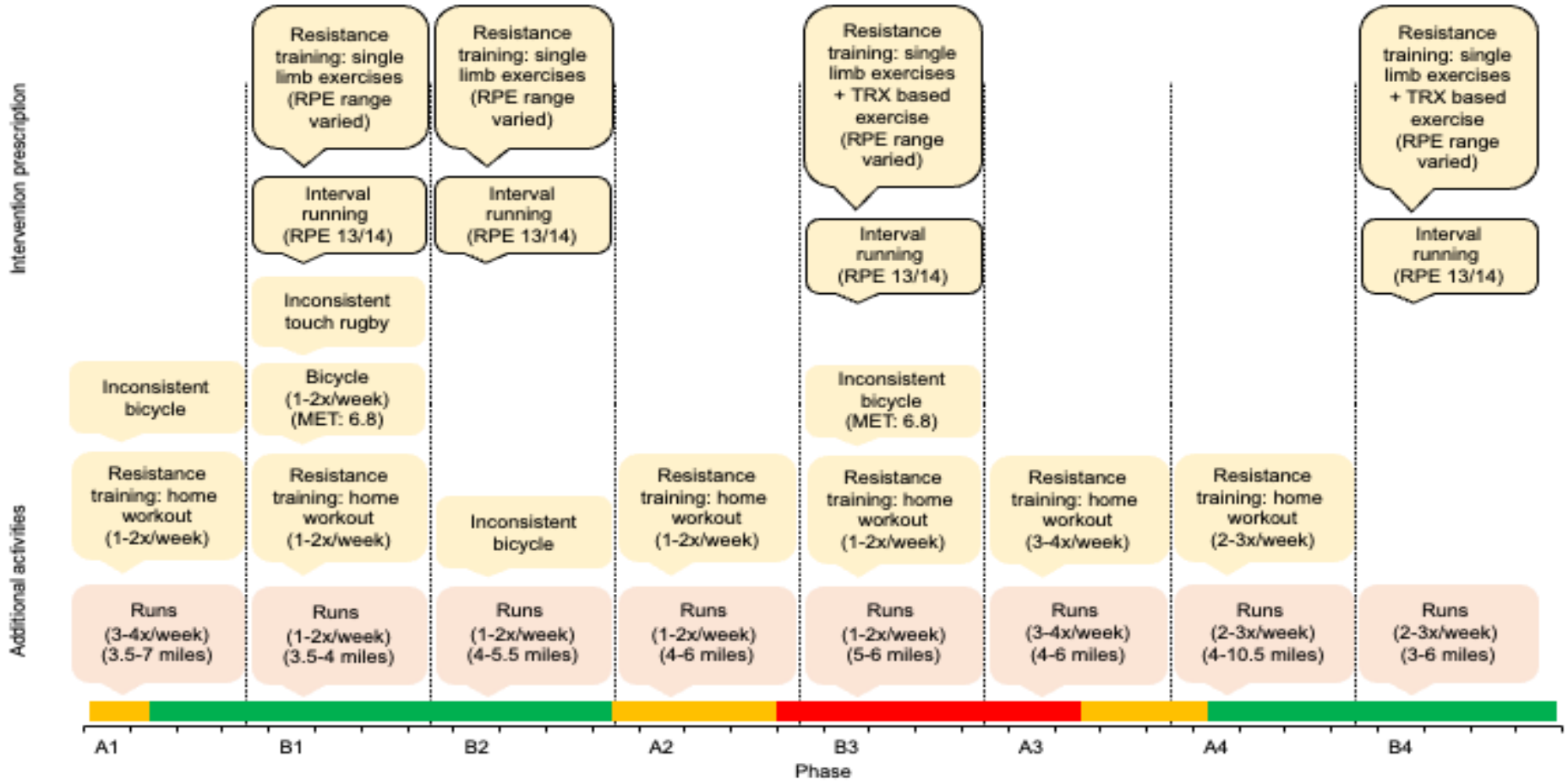


Figure 41. Simon's intervention schedule and activity levels.

Prescribed activities outlined in black. Additional activities were informed by daily activity log or included follow-up interviews (B1.3, A2.3, A3.3, B4.3). Activities characterised in accordance with recommendations from Ainsworth et al. (2011) and Bull et al. (2020b): Light-intensity. Moderate-to-vigorous intensity. Vigorous-intensity. Distal context. General state of Covid-19 lockdown responses as informed by local news sources: stay-at-home orders. Strict restrictions (no stay-at-home orders). Light/no restrictions. A = non-intervention phase; B = intervention phase.

Addressing Simon's needs and preferences was a consistent challenge throughout the study. Simon was reluctant to give up his normal physical activity routine; therefore, programmes during intervention phases utilised single limb exercises to differentiate intensity levels and exercise type from the non-intervention phases where Simon was still consistently active. Further, cardiovascular programmes introduced interval running to differentiate from the steady-state running the Simon was doing during non-intervention programmes. Throughout the study, strength training programmes were adapted only to introduce variation in exercises or to progress the intensity prescriptions. The setting of the workouts depended on Simon's accessibility to a gym, which was impacted by the COVID-19 lockdown measures. In addition, the programmes maintained a degree of consistency so that Simon could easily adjust to them during intervention phases.

Still, Simon had difficulty adjusting to the programmes. In B1, Simon stated,

> I have been finding that exercise is probably less of a stress buster and more of a sort of chore sometimes at the moment. Which, you know, always sort of worries me a bit, because it's usually a great stress buster for me...I could probably do with it being a little bit less routinely. I think that's the way I tend to play it.

In the same interview (B1) he also stated,

> I think we've just got to try and adjust how I do things...I quite like having a little routine and just being able to get in and do it.

In the final interview, Simon again reflected on this theme. He stated,

> I actually needed to work out what was going on in myself. I really felt like I wasn't enjoying going to the gym anymore. I was finding the gym, rather than being a pleasurable thing to do, [it was] becoming a bit of a drag. I guess it took me sort of talking to myself and thinking about it to work out why and it was, obviously, you know, you have to explore a little bit and I thought actually this is not reasonable. It's because I'm putting more effort into running and there's only so much of me to go around.

He also went on to state,

> It's quite nice for me to know what's going on and be able to concentrate and focus on something, which was trying to try to enjoy or do better at the endurance run.

This suggests a need for some sort of tangible goal to increase his motivation and enjoyment of physical activity.

5.8.3 Cognitive function

5.8.3.1 PROMIS Short Form v2.0 - Cognitive Function 8 assessment

The effect of the programme on Simon's cognitive function was inconclusive (Figure 42). A complete visual analysis report can be found in Appendix 11.6.

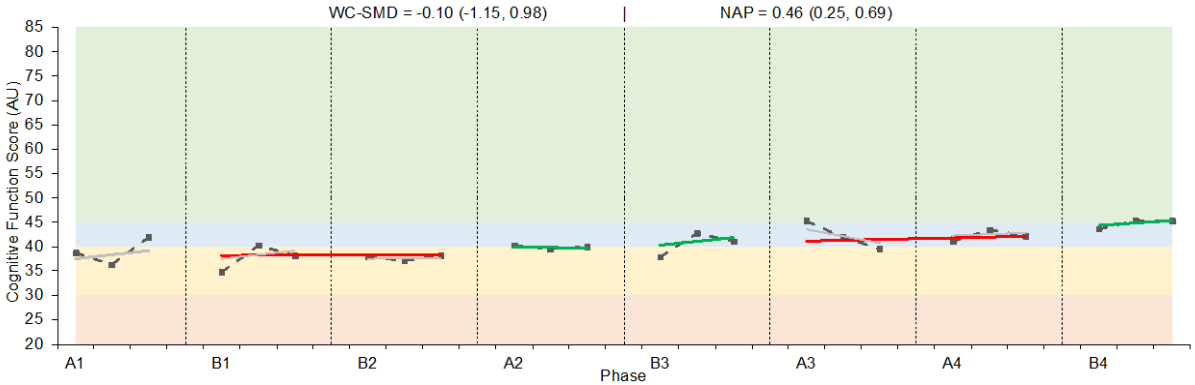


Figure 42. Simon's self-report scores from PROMIS Short Form v2.0 - Cognitive Function 8 assessment

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Five basic effects were observed on measures of cognitive function (visual analysis rating = 5.75, moderate behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Three of these basic effects were positive (A2, B3, B4), and two of them were negative (B1 + B2, A3 + A4).

The initial introduction of the intervention (B1 + B2) resulted in an immediate decrease in levels of cognitive function compared to those predicted by the A1 SMT line. There was also a delayed decrease in variability noted in phase B2. The trend direction was unchanged, and overlap was present. When removed (A2), levels of cognitive function were immediately increased compared to those predicted by the previous SMT line (B1 + B2). The trend direction and variability were unchanged, and overlap was present. Re-introduction of the intervention in phase B3 resulted in increased levels of cognitive function compared to those predicted by the previous SMT line (A2); however, variability was also increased. The trend direction was unchanged, and these effects were not immediate. Further, overlap was present. When removed (A3 + A4), there was a decrease in levels of cognitive function; however, this effect was not immediate and there was no change in trend direction or variability. Overlap was also present. The final introduction of the intervention (B4) resulted in a decrease in variability; however, levels of cognitive function did not differ from those predicted by the previous SMT line (A3 + A4). Further, the trend direction did not change, and overlap was present. The only consistent pattern across phase types was the consistent positive trend (indicating improving symptoms) observed in all intervention phases. Non-intervention phases either observed a positive or a neutral trend line. No other patterns (considering levels or variability) were observed.

Analysis of the data across the entire study period indicated a trivial negative, within-case effect of the intervention on measures of cognitive function (WC-SMD = -0.10, 95% CI -0.36 to 0.95) with scores recorded during intervention phases (40.20 ± 3.41 AU) 0.65 points lower than those recorded during non-intervention phases (40.85 ± 2.35 AU). NAP (NAP = 0.46, 95%CI 0.25 to 0.69) suggests data overlap between matched pairs where the probability of a randomly selected data point in phase B being greater than a randomly selected data point in phase A is, on average, 46%.

5.8.3.2 Executive Skills Questionnaire

There was a positive effect of the programme on Simon's executive function (Figure 43). A complete visual analysis report can be found in Appendix 11.6.

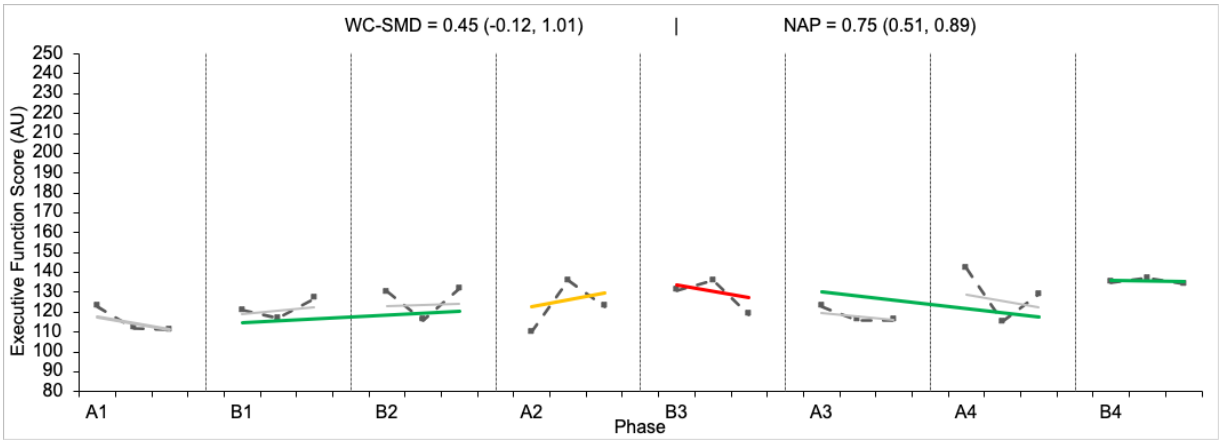


Figure 43. Simon's self-report scores from Executive Skills Questionnaire

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Four basic effects were observed on measures of executive skills (visual analysis rating = 4.5, small behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Three of these basic effects were positive (B1 + B2, A3 + A4, B4), and one was negative (B3).

The initial introduction of the intervention (B1 + B2) resulted in an immediate increase in levels of executive function compared to those predicted by the previous SMT line (A1), as well as a change to a positive trend direction (indicating increasing symptoms). Further, variability increased, and overlap was present. No basic effect was observed with the removal of the intervention (A2); that is, the trend direction, levels, and variability did not differ from those predicted by the SMT line in (B1 + B2). The re-introduction of the intervention in B3 resulted in a negative trend line (indicating worsening symptoms); however, the levels and variability were not different from those predicted by the previous SMT line (A2). This change was no immediate, and overlap was present. The removal of the intervention (A3 + A4) resulted in levels higher than those predicted by the previous SMT line (B3). This effect was not immediate and mainly occurred in phase A4. Further, the trend direction and variability were unchanged. Overlap was also present. The final introduction of the intervention (B4) demonstrated an immediate increase in levels of

executive function higher than those predicted by the previous SMT line (A3 + A4). Variability also decreased. The trend direction was unchanged, and overlap was present. There were no consistent patterns of symptom levels, trend direction, or variability observed across either phase type.

Analysis indicated a small positive, within-case effect of the intervention on measures of executive function (WC-SMD = 0.45, 95% CI -0.12 to 1.01) with scores recorded during intervention phases (127.92 ± 7.72 AU) 6.59 points higher than those recorded during non-intervention phases (121.33 ± 10.13 AU). NAP (NAP = 0.75, 95%CI 0.51 to 0.89) suggests a low level of data overlap between matched pairs where the probability of a randomly selected data point in phase B being greater than a randomly selected data point in phase A is, on average, 75%.

When analysing specific components of executive function (Table 30), active rehabilitation demonstrated a large effect on measures of metacognition and a moderate effect on measures of planning/prioritization and working memory. A small effect was observed on measures of flexibility, organization, response inhibition and sustained attention. A small negative effect was observed on measures of stress tolerance and time management. All other measures reported a trivial effect.

Table 30 Simon's individual components of executive function

Executive skill	Mean A ± SD	Mean B ± SD	WC-SMD (95%CI)	NAP (95%CI)
Emotional control (AU)	7.33 ± 2.15	7.58 ± 1.98	0.11 (-0.61, 0.82)	0.53 (0.31, 0.73)
Flexibility (AU)	6.83 ± 2.55	7.42 ± 1.93	0.21 (-0.45, 0.88)	0.59 (0.36, 0.78)
Goal-directed persistence (AU)	19.25 ± 2.01	19.58 ± 1.73	0.15 (-0.54, 0.85)	0.56 (0.34, 0.75)
Metacognition (AU)	8.50 ± 1.88	10.50 ± 1.24	0.99 (0.25, 1.73)	0.82 (0.58, 0.93)
Organization (AU)	13.92 ± 1.88	14.50 ± 1.45	0.29 (-0.38, 0.96)	0.59 (0.36, 0.78)
Planning/ prioritization (AU)	9.17 ± 2.29	10.67 ± 2.06	0.61 (-0.14, 1.36)	0.69 (0.46, 0.85)
Response inhibition (AU)	10.92 ± 2.47	11.75 ± 2.56	0.31 (-0.45, 1.08)	0.61 (0.38, 0.79)
Stress tolerance (AU)	8.17 ± 2.41	7.42 ± 2.19	-0.29 (-1.01, 0.43)	0.40 (0.22, 0.63)
Sustained attention (AU)	6.42 ± 2.27	7.17 ± 1.99	0.31 (-0.40, 1.02)	0.60 (0.37, 0.79)
Task initiation (AU)	8.50 ± 1.68	8.25 ± 1.66	-0.14 (-0.88, 0.60)	0.44 (0.25, 0.66)
Time management (AU)	13.17 ± 2.04	12.00 ± 1.48	-0.53 (-1.21, 0.15)	0.28 (0.13, 0.52)
Working memory (AU)	9.50 ± 2.84	11.42 ± 1.83	0.63 (-0.04, 1.30)	0.71 (0.48, 0.94)

Range of potential scores: 0-21. Desired effect. Undesired effect. Trivial effect/Overlap. (see subsection. A = non-intervention phase; B = intervention phase; NAP = non-overlap of all pairs; WC-SMD = within case standardized mean difference.

5.8.3.3 Mindful Attention Awareness Scale (MAAS)

The effect of the programme on Simon's levels of attention was inconclusive (Figure 44). A complete visual analysis report can be found in Appendix 11.6.

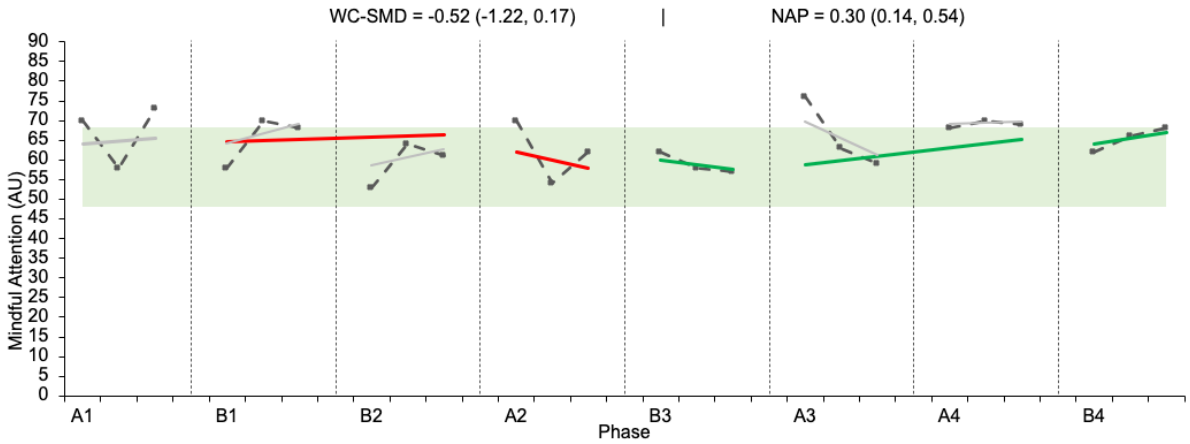


Figure 44. Simon's self-report scores from Mindful Attention Awareness Scale (MAAS)

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Five basic effects were observed on measures of mindful attention (visual analysis rating = 6.00, moderate behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in cognitive function measures. Three of these basic effects were positive (B3, A3 + A4, B4), and two of them were negative (B1 + B2, A2).

The initial introduction of the intervention (B1 + B2) resulted in levels of attention lower than those predicted by the previous SMT line (A1); however, this effect was delayed and only occurred in phase B2. Variability and trend direction were unchanged, and overlap was present. When removed (A2), there was an immediate decrease in levels of mindful attention accompanied by a change in trend direction to negative (indicating worsening symptoms). The variability was unchanged, and overlap was present. When re-introduced (B3), levels of attention were immediately higher than those predicted by the previous SMT line (A2) and variability decreased. The trend direction did not change, and overlap was present. When removed (A3 +

A4), levels of attention were immediately higher than those predicted by the previous SMT line (B3) and the trend direction changed to a positive direction (indicating improving symptoms). Variability also increased, and little to no overlap was present. The final introduction of the intervention (B4) resulted in decreased variability; however, levels of attention did not differ from those predicted by the previous SMT line (A3 + A4) and the trend direction was unchanged. Further, overlap was present. There were no consistent patterns of symptom levels, trend direction, or variability observed across either phase type.

Analysis across the study duration indicated a moderate negative, within-case effect of the intervention on measures of mindful attention (WC-SMD = -0.52, 95% CI -1.22 to 0.17) with scores recorded during intervention phases (62.25 ± 5.17 AU) 3.75 points lower than those recorded during non-intervention phases (66.0 ± 6.69 AU). NAP (NAP = 0.30, 95%CI 0.14 to 0.54) suggests a low level of data overlap between matched pairs where the probability of a randomly selected data point in phase B being greater than a randomly selected data point in phase A is, on average, 30%.

5.8.4 Mood/behaviour

5.8.4.1 PROMIS short form v1.0 - Depression 8b assessment.

The effect of the programme on Simon's levels of depression was inconclusive (Figure 45). A complete visual analysis report can be found in Appendix 11.6.

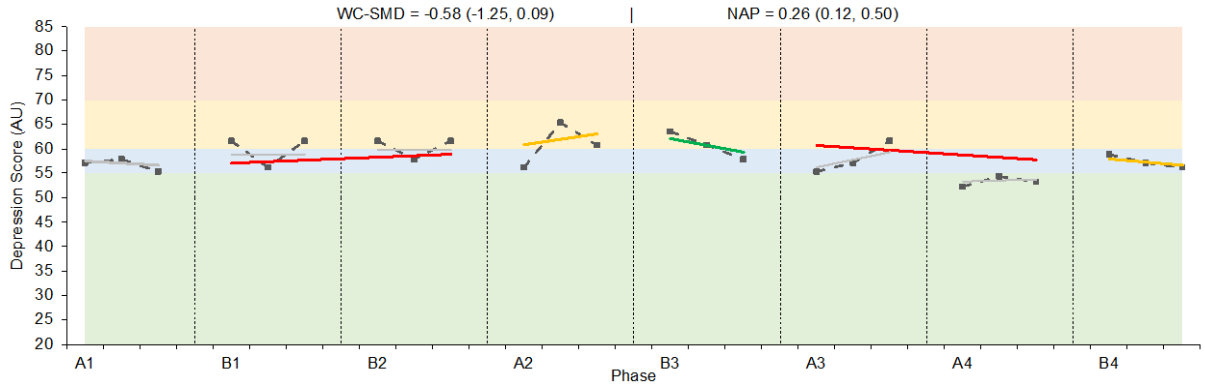


Figure 45. Simon's self-report scores from PROMIS short form v1.0 - Depression 8b assessment

▪Raw data. — Split middle trend (SMT). Basic effect of SMT: — No basic effect. — +ve basic effect. — -ve basic effect. AU = arbitrary unit. A = non-intervention phase. B = intervention phase. NAP = non-overlap of all pairs. WC-SMD – within case standardized mean difference.

Three basic effects were observed on measures of depression (visual analysis rating = 3.5, small behavioural change), demonstrating evidence of a causal effect between the active rehabilitation programme and changes in measures of depression. One of the basic effects was positive (B3), and two of them were negative (B1 + B2, A3 + A4).

The initial introduction of the intervention resulted in increased variability and levels higher than those predicted by the previous SMT line (A1). The direction of the trend line turned positive (indicating worsening symptoms). This effect was not immediate, and overlap was present. When removed (A2), no basic effect was observed. When the intervention was re-introduced in B3, the direction of the trend immediately turned negative (indicating improving symptom levels), and levels were lower than those predicted by the previous SMT line (A2). Variability also decreased. Overlap was present. When the intervention was removed, the trend direction was unchanged and levels did not differ from those predicted by the previous SMT line; however, variability increased. This effect was not immediate, and overlap was present. No basic effect was observed with the re-introduction of the intervention in B4. There was no consistent pattern observed across either phase types.

Statistical analysis indicated a moderate negative, within-case effect of the intervention on measures of mindful attention (WC-SMD = -0.58, 95% CI -1.25 to 0.09) with scores recorded during intervention phases (59.56 ± 2.49 AU) 2.34 points higher than those recorded during non-intervention phases (57.22 ± 3.76 AU). NAP (NAP = 0.26, 95%CI 0.12 to 0.50) suggests a low level of data overlap between matched pairs where the probability of a randomly selected data point in phase B being lower than phase A is, on average, 26%.

5.8.5 Participant perspective

In those follow-up interviews which were included (A1.3, B2.3, B3.3 and A4.3), it was unclear the effect that active rehabilitation had on Simon's levels of cognitive function, executive function memory, attention, or concentration. Simon did not offer any specific comments on these symptoms. The effect that the intervention had on Simon's levels of depression was also unclear. In all included interviews, Simon reported feeling negative or neutral feelings, and no further comments were offered.

5.8.6 Study schedule and context

Simon began the study in June 2020, at the end of the first Covid-19 wave in the UK. Figure 46 illustrates an estimated timeline of the pandemic response in Simon's area with his subsequent stress response. This figure also includes additional distal contextual information that may have influenced the study experience, as informed by the included follow-up interviews (A1.3, B2.3, B3.3 and A4.3) and general news sources.

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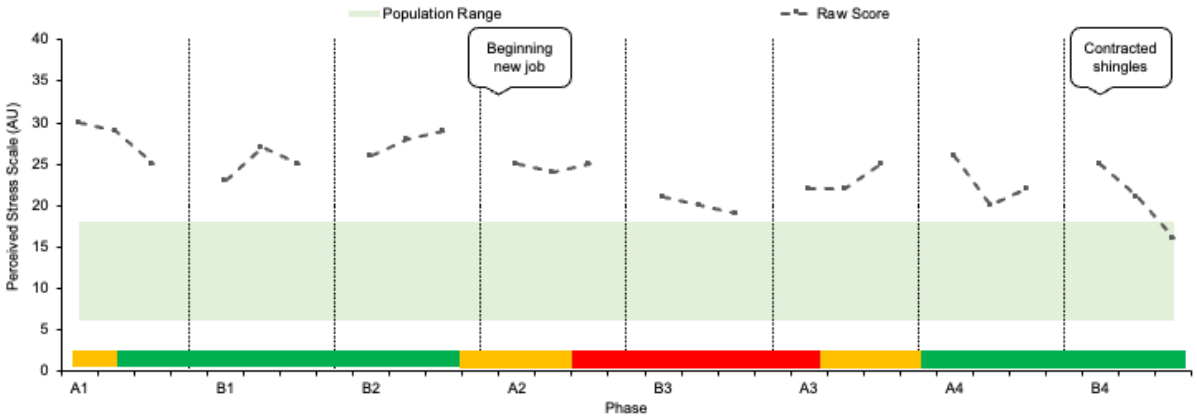

Figure 46. Simon's PSS scores at data collection point

A higher score indicates higher levels of perceived stress. Population norms: — Population average. The general state of Covid-19 lockdown responses as informed by news sources are represented as: — stay-at-home orders, — strict restrictions (no stay-at-home orders) and — light/no restrictions. A = non-intervention phase; AU= arbitrary unit; B = intervention phase.

Simon did not offer a great deal of insight into contextual factors that may have influenced his study experience. COVID-19 had a particular effect on Simon. He reported in A2,

> I just seem to be a little overwhelmed by everything, just everything in general. That seems to be everyone right now.

And in A3 he stated,

> ...just ready for it to be over. Ready for being able to have a bit more freedom and get in the gym...Change usually sort of knocks me for a little bit.

The other main contextual factor was that Simon returned to full-time work for the first time since his moderate TBI. When reflecting on this impact in his final interview, Simon stated,

> So that's been a big change. It's certainly been a big change to how much time you have available for training and how you have to fit that in around what you do in a different way. Although, yes, of course, you have to sort of add to that certainly been a positive experience for me.

5.8.7 Results summary

There was not enough evidence to recommend what effect that a person-centred active rehabilitation programme demonstrated on Simon's symptoms of cognitive function (global cognitive function, executive function, memory, attention, concentration) and depression. Table 31 illustrates a summary of results across the study.

Table 31 Simon's summary of results

Area of assessment & *symptoms of interest*	Outcome measure	(+)	(=)	(-)
Cognitive function • *Global cognitive function* • *Executive function* • *Memory* • *Attention* • *Concentration*	Cognitive function 8a			
	Executive Skills Questionnaire			
	Mindful Attention Awareness Scale			
	Participant perspective			
Mood/behaviour • *Depression*	PROMIS Short Form v1.0 - Depression 8b Participant perspective			

Desired effect. Undesired effect. Trivial effect/inconclusive.

There is evidence to suggest that a person-centred active rehabilitation programme had a positive effect on Simon's executive function. This is supported by visual and statistical analysis. There was not enough evidence to determine what, if any, effect the active rehabilitation programme had on Simon's levels of cognitive function, attention, or depression. Despite a causal effect being established for both measures of cognitive function, attention, and depression, a negative or positive effect was equally likely with either phase type. This is supported by a calculated trivial WC-SMD and NAP suggesting overlap for measures of cognitive function. Measures of attention and depression both suggest a potential negative effect; however, the observed negative effects were not strong and could be explained by contextual factors.

Simon had difficulty adjusting to participation in the study, and this may explain some of the negative effects that were noted with the presence of the study. Simon was given the opportunity to withdraw from the study if he felt that the expected tasks were too overwhelming for him; however, he chose to remain in the study. The biggest adjustment that Simon had was changing his workout routines. He was very particular about his activity modes and levels, and therefore it cannot be determined that a clear difference between intervention and non-intervention phases was present.

5.9 Chapter summary

The aim of chapter five was to present the results of a series of single case studies. The aim of the MMSCR was:

1. To assess the effect that a person-centred active rehabilitation programme had on participant symptoms suspected to be associated with the development of CTE.
2. To understand how contextual factors (both proximal and distal) affected the participants' experience of an active rehabilitation programme and the perceived effectiveness.

The aims of this chapter have been met. The effect that a person-centred active rehabilitation program had on symptoms suspected to be related to CTE on six cases was presented with attention given to contextual information and intervention prescription when presenting the results.

6 Chapter 6: Discussion

6.1 Chapter overview

Chapter five presented the results of a series of six case studies. The effect that a person-centred active rehabilitation programme had on a variety of symptoms including cognitive function, executive function, attention, anxiety, depression, loneliness, irritability, and sleep quality was presented. Chapter six discusses the results across the entire thesis with a specific focus on the effect that active rehabilitation had on symptoms associated with suspected CTE, consideration of the various active rehabilitation modes, the various outcome measures included, and the usefulness of understanding the contextual factors that influenced the results of the MMSCR study were presented. The implications of these results for clinical practice as well as implications for future research are also discussed.

6.2 Summary of findings

6.2.1 Symptoms

This thesis has provided evidence to suggest that active rehabilitation is a promising intervention therapy for those suffering from symptoms related to suspected CTE. This is based on the available evidence showing a positive effect on management of mTBI (see subsection 2.4), a positive preliminary effect on tauopathies (see Chapter 3), and a positive or inconclusive preliminary effect observed across a case series of individuals with suspected CTE (see Chapter 5).

A review of the literature on mTBI indicates a positive effect of active rehabilitation strategies on acute and persistent levels of cognitive dysfunction, mood and behavioural symptoms, and motor impairment (see subsection 2.4). Further, there is evidence to suggest that active rehabilitation reduces the risk of PCS, and that it may reduce the time to return to play/competition (Carter et al., 2021; Langevin et al., 2020; Leddy et al., 2018a; Leddy et al., 2018b; Reid et al., 2021). An umbrella review seeking to establish the effect that active rehabilitation had on cognitive dysfunction and motor impairment in tauopathies (Chapter 3) reported a positive effect, although further research is needed to corroborate these findings. Regardless, when considering the SMD, 95%CI, and 95%PI, a minimal likelihood of a negative or null

effect was reported with most findings favouring active rehabilitation. The effect that active rehabilitation had on symptoms of mood/behaviour in tauopathies was not available as no study included in the review provided information on mood/behaviour symptoms.

Finally, a series of n-of-1 experiments observing the effect that active rehabilitation had on cognitive dysfunction and mood/behaviour symptoms (Chapter 5) reported an almost equal number of positive and trivial/inconclusive effects. Further research is needed to sufficiently establish the effect. Importantly, only one case (Kristen) reported a negative effect across both cognitive function (global cognitive function, executive function) and mood/behavioural symptoms. Contextual factors such as exercise intolerance, previous medical history, and medication adjustments appeared to play a significant role in this observed negative effect; therefore, these factors should be considered in future research and clinical practice. Table 32 provides a summary of the cases across each symptom of interest. The effect that active rehabilitation had on symptoms of motor function was not reported as no participants included in the study had any motor impairments.

Table 32. Number of participants that demonstrated a desired, inconclusive, or undesired result from the case series

Area of assessment	Symptom	(+)	(=)	(-)
Cognitive function	Global cognitive function	1	2	
	Executive function	4	1	1
	Attention		2	
	Participant perspective	2	4	
Total number of effects		7	9	1
Mood/behaviour	Anxiety	1	1	2
	Depression	1	1	2
	Loneliness	1		
	Irritability		1	
	Insomnia		1	
	Participant perspective	3	3	
Total number of effects		6	7	4

Desired effect. Undesired effect. Trivial effect/inconclusive.

The only impairment observed across all participants was executive dysfunction. Interestingly, executive function demonstrated the most consistent positive effect across the intervention, with four out of the six participants reporting a positive effect. One participant demonstrated a trivial/inconclusive effect (Gemma), and one demonstrated a negative effect (Kristen). Flexibility (Luigi, Gemma), meta-cognition (Niall, Luigi, Simon), task-initiation (Niall, Luigi, Abel), and working memory (Luigi, Simon) saw positive effects across multiple cases. Only two components of executive function saw a negative effect with low levels of overlap (goal-directed persistence, time management), and these effects were only observed in two cases (Gemma, Simon). The effect of active rehabilitation on other measures of cognitive function (global cognitive function, attention) were largely trivial/inconclusive. This pattern was also expressed during the interviews, with only two participants (Niall, Luigi) expressing they felt that the intervention had a positive effect on cognitive function. No participants expressed feeling as though the intervention had a negative effect.

Anxiety and depression were evident at baseline for four participants, though the effect of active rehabilitation on these symptoms was inconclusive overall. Luigi demonstrated a positive effect on both measures of anxiety and depression. Gemma demonstrated a trivial/inconclusive effect on measures of anxiety and Simon demonstrated a trivial/inconclusive effect on measures of depression. Finally, Kristen and Abel demonstrated a negative effect on both measures of anxiety and depression. The effect of active rehabilitation on other measures of mood/behaviour demonstrated a positive effect (irritability) or trivial/inconclusive (loneliness, sleep) effects. It should be noted that these symptoms were only measured for one participant; therefore, results can only be interpreted effectively within their context and warrants further investigation. According to the qualitative data, the effectiveness varied between positive (Niall, Luigi, Abel) and limited/inconclusive (Kristen, Gemma, Simon). Luigi suggested that the intervention may not have directly impacted his symptoms, but it did provide a way to help him manage his symptoms. This was particularly apparent with his symptoms of irritability, short fuse, and explosivity. Abel reported he felt as though a positive effect was cumulative. While comparing measures at individual points may not have offered a strong indication of a positive

effect, comparing where he started to where he ended did offer evidence of a positive effect.

6.2.2 Outcome measures

Several outcome measures were reported throughout this thesis to determine the potential effect of active rehabilitation on symptoms of suspected CTE. A summary of outcomes included from the umbrella review (Chapter 3) and the MMSCR series (Chapter 5) can be found in Table 33. Research regarding the management of mTBI consistently used outcome measures which combine all areas of interest (cognitive function, mood/behaviour, motor function), and included the following:

- Sports Concussion Assessment Tools 2/3
- Graded Symptom Checklist
- 22-item Postconcussion Symptom Scale (PCSS) questionnaire
- 19-item Postconcussion Symptom Scale (PCSS) questionnaire
- IMPACT test
- Postconcussion symptom inventory
- Rivermead PCS Questionnaire
- PCS scale found in the Immediate Post-Concussion Assessment and Cognitive Testing
- Health Behaviour Inventory
- BBS

Table 33. List of outcome measures included across thesis

Area of assessment	Condition	Symptom	Outcome measure
Cognitive function	Tauopathy	Global cognitive function	Alzheimer's Disease Assessment Scale Cognitive section (ADAS-Cog)
			Amsterdam Dementia Screening Test 6 (ADS-6)
			Boston Naming Test (BNT)
			The Cambridge Neuropsychological Test Automated Battery (CANTAB)
			Clock drawing test (CDT)
			Functional Assessment of Communication Skills (FACS)
			Hopkins Verbal Learning test (HVLT)
			Mini-Mental State Exam (MMSE)
			Rapid Evaluation of Cognitive Functions test (ERFC)
	Suspected CTE	Global cognitive function	Saint Louis University Mental Status (SLUMS)
			PROMIS short form v2.0 – cognitive function 8a
		Executive function	Executive Skills Questionnaire (ESQ)
		Attention	Mindful Attention Awareness Scale (MAAS)
Mood/behaviour	Suspected CTE	Mental health	Global Mental Health Assessment Tool (GMHAT)
		Anxiety	PROMIS short form v1.0 – Anxiety 8a
		Depression	PROMIS short form v1.0 – Depression 8b

		Loneliness	UCLA Loneliness Scale
		Irritability	Brief Irritability Test (BITe)
		Sleep	Pittsburgh Sleep Quality Index (PSQI)
Motor function	Tauopathy	Global motor function	Unified Parkinson's Disease Rating Score (UPDRS)
		Functional mobility	Functional Gate Assessment (FGA)
			Freezing of gait (FoG)
			Sit to stand time
			Short Physical Performance Battery (SPPB)
			Timed up and go test (TUG)
			Turning time
			Step length
			Cadence
		Gait speed/velocity	Gait time
			Gait velocity
			6-minute walk test (6mWT)
		Balance	Berg Balance Scale (BBS), or single components
	Suspected CTE	General motor function	PROMIS bank v2.0 - Physical function 24a

There is no established collection of outcome measures for those with suspected CTE, largely due to a lack of CTE clinical research in general (see subsection 4.5.2). Various cognitive function assessments were included in this thesis. Although a recommendation for a specific assessment cannot be made, this thesis does provide evidence that future research and clinical practice should consider measuring executive function. This is supported by the observation that executive function was the only symptom identified across all participants in the case series. This also supported by the update in TES criterion which now requires the presence of memory impairment or executive dysfunction (Katz et al., 2021). Anxiety and depression were the other outcomes identified across a majority of the sample. All but one participant (Niall) had at least one of the symptoms, with three participants experiencing both symptoms (Luigi, Kristen, Abel). Again, no specific recommendation for assessment measures can be made, but future research and clinical practice should consider measuring these symptoms.

UPDRS, an assessment used to measure general motor function, was the most used assessment in the umbrella review; however, only PD populations were included in this analysis. When considering specific components of motor function, this study identified two outcome measures to be considered for future use. The umbrella review identified TUG and BBS as two measures that were widely used and showed consistent results. Further, BBS was also identified as a component of mTBI testing. The umbrella review observed a stronger and more consistent effect when using the entire scale as opposed to individual components. Future research should seek to validate BBS and TUG for the use in populations with suspected CTE.

6.2.3 Considering contextual factors

There were several contextual factors that appeared to influence the success of the active rehabilitation programme, some of which were evident across multiple cases. The most obvious influence which impacted every participant was the presence of the COVID-19 pandemic and subsequent lockdown restrictions. This seemed to influence Niall and Luigi the most. These two participants began the study at the very start of the pandemic where restrictions were the harshest and the levels of uncertainty were

the highest. It seemed to effect Kristen the least, who lives in a quite secluded part of New York (state). The presence of the pandemic had both a direct and indirect effect on the success of the intervention. Directly, the pandemic influenced some of the outcomes of interest. This is especially true for symptoms of anxiety and depression, but lockdown restrictions could also influence executive function as illustrated with Niall whose reported things like motivation, attention, and concentration were disrupted. It should be noted that two participants contracted COVID-19 during the study (Kristen, Abel), resulting in further direct effects of the global pandemic. In addition to the respiratory and inflammatory symptoms associated with COVID-19 such as fever, cough, and shortness of breath, contracting COVID-19 has also been associated with the development of fatigue, anxiety, depression, and cognitive disturbances (Nalbandian et al., 2021). Indirectly, the success of the programme was negatively influenced by the disruption in preferred activities. Niall was not able to go to the gym or consistently take part in field hockey which was a source of frustration. Luigi noted that he struggled to find ‘me time’ as he never felt comfortable returning to the gym even when it was open despite this being his preferred setting. Simon struggled with the inconsistency which resulted in constant changes to his programmes. Sometimes he was able to attend the gym, sometimes he wasn’t. He expressed his dislike for inconsistency, which likely contributed to the lack of intervention effectiveness.

The political discourse present in the United States affected all the American participants to some degree; however, this effect varied. Abel considers himself passionate about, and therefore hyper-involved in, the political culture of the US. Therefore, the BLM protests, the Capitol attack, and the Presidential election caused a great deal of stress for him. This effect was vastly reduced in the second half of the study following the end of the election cycle. While still effected by the same factors, Gemma was less involved and therefore found that the political discourse had more of an exhausting effect and produced feelings of irritability. Finally, Kristen reported some levels of stress concerning the present circumstances; however, she was better able to compartmentalise. Again, being in a more secluded living area also helped as she was not as directly exposed to some of the unrest compared to Abel and Gemma who were more city-based.

Work was another factor that was mentioned by several participants (Luigi, Abel, Gemma). As someone working in the healthcare industry, who also received a promotion during the study, Luigi felt direct pressure from the COVID-19 pandemic. This was expressed through his levels of PSS scores. Abel and Gemma both suffered from job instability. Abel changed jobs at least three times during the study, as each position was more seasonal in nature. As a free-lance writer, he expressed frustration and anxiety as he lacked the energy or motivation to pursue this path as adamantly as he would have liked. Further, each job had different demands that impacted Abel differently. The camp positions were physically demanding, where nannying was intensive and caused some mental fatigue. His final job before he returned to camp was especially frustrating for Abel as he felt unfulfilled. It was monotonous with long hours, which left him apathetic. Finally, Gemma's was work was directly impacted by the COVID-19 pandemic. She was working as paediatric physical therapist prior to the pandemic. After the onset of the pandemic, her job position became less stable. She tried taking on per diem work or working as a virtual personal trainer, but regardless her work situation was unstable largely throughout the study.

Exercise intolerance was another contextual factor to be considered. This was present in two participants (Kristen, Simon) who both reported a history of moderate-to-severe TBI. Kristen struggled with fully participating in the study as a direct result of her exercise intolerance. While she was willing to 'push through' some short-term adverse reactions as a result of the study, she expressed that any time she overcome her exercise intolerance the phase would change to a non-intervention phase and she had to start all over with the next intervention phase. Simon's exercise intolerance was less severe, but it did have an impact on what activities could be completed. He did not report any adverse events as a result of the programme, aside from his difficulty with constant disruption and lack of control over his programmes.

What should be noted here is despite the various contextual factors that have been discussed, some of which were unprecedented and, at times, had a substantial influence on participant symptoms, this thesis was still able to provide positive results. If repeated under more stable conditions than those observed in 2020 (the year that data collection took place in), there is a potential for a greater number of observed

positive effects. In contrast, some of the participants may not have met the eligibility criteria had these unprecedented factors been present. For example, Niall's levels of loneliness were only above population during the baseline phase and proceeded to drop throughout the first half of the study independent of the active rehabilitation programme. Narrowing the sample to those with true impairments will increase the reliability of the results in future research.

6.2.4 Programme prescription

This thesis has provided several potential modes of active rehabilitation to be considered in future research and clinical practice. The literature review (see subsection 2.4), provided the following potential modes of active rehabilitation:

- Sub-symptom threshold aerobic activity
- Aerobic activity
- Multimodal programme with aerobic activity as primary mode
- Sport specific activity (return to play protocols)

Sub-symptom threshold aerobic activity was the most reported intervention mode for managing mTBI (see subsection 2.4). Further, it observed the most consistent positive effect. Utilising sub-symptom threshold aerobic activity allows for close monitoring of activity intensities, ensuring that it is not so high as to elicit a negative symptom response. Further, sub-symptom threshold aerobic activity aligns with PCC as intensity prescriptions are directly determined by specific participant abilities.
The umbrella review (see Chapter 3), provided the following potential modes of active rehabilitation:

- General exercise or physiotherapy
- Cardiovascular exercise (e.g., treadmill running)
- Resistance training
- Multimodal programme (combination of cardiovascular and resistance training)
- Mind & body (including tai chi, yoga, martial arts)
- Dance

The only notable difference across the various modes of active rehabilitation was the effect of mind and body exercises (tai chi, yoga, martial arts) on levels of general motor function and balance. All other symptoms observed similar effects across all intervention modes. That is, all modes reported largely positive effects with no particular differences in the size of expected effect.

As supported by the effects reported in Chapter 2 and Chapter 3, the MMSCR series (see Chapter 5), concerned with the effect that active rehabilitation has on symptoms of suspected CTE, utilised a multimodal approach. Every participant completed a cardiovascular component and a resistance training component. The modes of each component varied across participants and was determined by the participant's preference. Table 34 illustrates the effect that the intervention had on the participant (desired, undesired, trivial/inconclusive) alongside the various modes of activity observed across both the prescribed intervention programme as well as the additional activities which were reported.

Table 34. Summary of case series modes of activity

Participant	Prescribed activities	Additional activities
Niall	• Resistance training mixed between gym and at-home • At-home circuit training • Steady state/interval jogging • Sprints	• Calisthenics • Recreational sport (field hockey, five-a-side football) • Gym based resistance training • Various cardiovascular activities (walks, basketball, punching bag)
Luigi	• At-home resistance training • Steady-state treadmill jogging	• Treadmill jogging • Rollerblading • Therapeutic exercises • Playing with kids • Outdoor manual labour
Kristen	• At-home resistance training • Outdoor walks	• Housework • Therapeutic exercises
Abel	• At-home resistance training • Steady-state treadmill jogging • At-home circuit training	• Camp activities • Outdoor manual labour • Walks • Recreational sport (flag American football, basketball) • Yoga
Gemma	• Circuit resistance training • Steady state/interval jogging • Sprints	• Hiking • Yoga • HIIT training • Circuit resistance training • Gym class workouts • Therapeutic exercises • Calisthenics
Simon	• Single-limb resistance training mixed between gym and at-home • Interval running	• Steady state jogging • Resistance training mixed between gym and at-home • Cycling • Touch rugby

Desired effect. Undesired effect. Trivial effect/inconclusive.

Considering the various modes which were utilised across cases, there did not appear to be a clear indication of any modes which were more or less effective. Consideration of additional activities did not offer any clear conclusions either. From what was reported in follow-up interviews, adherence did not differ across participants. No participant reported a notable issue with programme adherence. Therefore, no conclusions could be drawn on what might increase participant adherence. The inability to infer what modes future research and clinical practice should consider was further confounded by the impact that the COVID-19 pandemic had on participation experiences (see subsection 6.2.2).

6.3 Implications for future research and clinical practice

6.3.1 Symptoms and outcome measures

This thesis has provided preliminary evidence for the use of active rehabilitation as an intervention tool for the management of symptoms associated with suspected CTE, a concept suggested by previous narrative reviews and expert opinions (Cantu and Budson, 2019; Pierre et al., 2021). This is supported by the positive effect of active rehabilitation effects observed in mTBI (see subsection 2.4) and tauopathies (see Chapter 3), as well as the largely positive or inconclusive effects observed across a series of cases with suspected CTE (see Chapter 5, subsection 6.2.1; Table 35). Only one case demonstrated a negative effect (Kristen) for which contextual information should be considered when interpreting this result.

Currently, there are no outcome measures specific to populations of CTE. As supported by the updated TES criteria (Katz et al., 2021) and the outcome measures included in the case series, future research and clinical practice should consider executive function as a primary outcome of interest. Executive function was the only outcome measure included across all participants, and it was also the outcome measure that demonstrated the most consistent positive effect following a period of active rehabilitation. Anxiety and depression are symptoms which should also be considered; however, further research is needed to better establish a link with suspected CTE. While anxiety or depression was identified in every participant of the case series (Chapter 5), these symptoms are currently considered as supplementary

features for a TES diagnosis due to high population base rates and an increased potential for false-positive diagnosis (Kratz et al., 2021).

This thesis has provided one specific suggestion to be considered for use in future research and clinical practice. BBS is an outcome measure widely used for the identification and management of mTBI (see subsection 6.2.2). This outcome measure was also used most often in the measurement of balance in tauopathies, as demonstrated in the umbrella review (Chapter 3). The umbrella review also demonstrated that the use of the entire BBS, as opposed to singular components such as the single leg stance or tandem stance, demonstrated a larger and more consistent positive effect. Therefore, future research should seek to validate the use of BBS for participants and patients with suspected CTE, using the entire assessment rather than singular components.

Future research may also consider a holistic approach which incorporates multiple examinations within a single assessment, such as those assessments used for identifying mTBI and PCS. These assessments provide separate sections to identify cognitive, mood/behaviour, and motor symptoms with the use of one tool. Due to the causal relationship between mTBI and CTE, and the similarities in symptoms, these assessments may be of potential use; however, the difference in the acute nature of mTBI symptoms versus the delayed onset of symptoms noted in CTE populations should be considered.

6.3.2 Considering contextual factors

This thesis has illustrated the benefit of a PCC approach to both clinical research and practice. Including a qualitative component to the SCED allowed for an understanding of the complex lives of the participants and what influences may have impacted their feelings and behaviours during the study. Considering contextual factors such as personal circumstances (e.g., increased work-related stress, illness), cultural climate (e.g., global pandemic, civil unrest), and detailed perceptions of the programme generally allowed for a better understanding of the intervention effect within the context of the single case. This can provide detailed information that should be

considered in future research, including eligibility criteria, exercise prescription, and size of intervention effect. Further still, this informs clinicians who should consider contextual factors relevant to the patient when determining the most effective and efficient treatment plan.

Due to the scope of the study, this thesis only analysed select interviews (see subsection 4.5.2). Analysing interviews that match every data point and every programme prescription, as opposed to the more general approach of including interviews from the end of each matched phase done in this thesis, may better explain some of the variability of the phases and offer deeper understanding of context. For example, in phase B3 Abel reported levels of anxiety much higher than those predicted by the previous phase (A3). The levels were also much higher than the subsequent levels reported for the remainder of the double phase (B3 + B4). This was right after the US Capitol attack, during a time where Abel was moving from one job to another, and around the time that Abel contracted COVID-19. Analysing the interviews during B3 may have offered more context than what this thesis was able to provide. While not a primary aim of this thesis, future qualitative analysis which includes all available interviews may provide useful information about the reported symptom levels, exercise prescription, and size of intervention effect.

6.3.3 Intervention prescription

This thesis offered multiple interventions to be considered in future research and clinical practice. While the case series did not offer any evidence to suggest which mode(s) may be more effective than others, the umbrella review offered evidence to suggest future research may consider whether target symptoms should dictate the intervention mode. Individuals with cognitive impairment may benefit from the use of aerobic training or a multi-modal approach, while individuals with motor function impairment may benefit from modes such as tai chi, yoga, martial arts, or dance.

In subsection 4.2.1, it was emphasised the importance of providing both EBM and PCC in clinical care. In subsection 4.2.3.1, a 5-3-20 criteria was presented which would allow the use of multiple n-of-1 studies to provide Level 1 evidence for a

particular intervention. While not within the scope of this thesis, future RCT studies utilising a PCC approach can still be considered in future research as well. Specific parameters for intervention prescription have yet to be identified; however, this thesis has provided evidence to suggest future research and clinical practice may consider using sub-symptom threshold aerobic activity as one mode of rehabilitation prescription. The intervention prescription of this mode of active rehabilitation is determined by the provocation of symptoms, where a sub-maximal symptom exacerbation threshold is established using a treadmill test and then a therapy 'dose' is prescribed at 80-90% of this symptom threshold (Leddy et al., 2018a; Leddy et al., 2018b). This would meet the requirements of a PCC management protocol and has been successfully used in multiple RCT designs where the control group consisted of current standard care (I.e., rest) (Leddy et al., 2018a; Leddy et al., 2018b). The use of a usual care control group would meet the recommendations laid out in subsection 3.5.3, where future research should consider using control groups with no additional intervention provided.

Finally, this study has provided evidence for the use of multi-modal intervention, or at the very least a PCC approach to prescription, where an individual's concerns are used to determine an appropriate intervention mode. Further, this study has provided evidence to suggest that attention to specific components such as goal-setting or group-based activity specific to the individual should be considered. Luigi may have experienced greater effect from the study had the intervention programme begun with a goal-setting activity, as indicated by some of his follow-up interviews. Niall may have experienced greater benefit had he been involved in a more social setting, as indicated by increased improvements during the phases where he was more involved in hockey training or was able to go the gym with friends. And finally, Simon may have benefit more from a structured, long-term, stable plan, as indicated by some of his follow-up interviews (B1, final interview).

6.3.4 Dissemination of key findings

At the time of writing, the umbrella review (Chapter 3) has been preliminarily accepted for publication with PLOS One and is awaiting formal acceptance. Publication of the MMSCR will also be pursued following submission of the thesis. A manuscript

detailing the highlights of each case, including the qualitative components, will be prepared. The American Journal of Sports Medicine and NeuroRehabilitation are journals being considered at present. Following publication preparation, an abstract will be prepared for submission to conferences for presentation. The International Conference on Concussion and Sports Neurology, the IOC Prevention of Injury and Illness in Sport conference, and the British Association of Sport and Exercise Medicine conference are such examples being considered at present.

Throughout the PhD process, various presentations of current work were given. This included a guest lecture, as well as presentations for the psychology department's journal club where discussion of relevant journal articles were presented alongside updates on the thesis research. In addition to presentations, consulting advice was given to offer help with columns about CTE and American football written for the Guardian. Currently, a magazine article for Gridiron, a column for the ReadOptional, a potential podcast mini-series, and a potential Guardian column are being prepared offering expert opinion on discussions surrounding CTE and concussion protocols across sport leagues.

6.4 Strengths and limitations

6.4.1 Traumatic Encephalopathy Syndrome criteria

A lack of diagnostic tools continues to be a challenge for CTE research. In line with a pragmatic paradigm, the criterion used for this study was very broad with the only major overlap observed across cases being executive function, anxiety, and depression. The updated TES criteria requiring dysregulation of emotions or behaviour as seen with symptoms such as (but not limited to) explosiveness, impulsivity, rage, violent outbursts, short fuse, emotional lability, or mood swings, in addition to anxiety only serving as supportive features (of which two are still required) had a significant effect on those individuals that would have been eligible for inclusion. Only Luigi provided evidence of meeting such criterion. It is likely that Simon would also have met such criteria had emotional liability been investigated further. Simon never expressed in his initial meetings feeling as though he struggled

with emotional dysregulation, but it became apparent particularly with his inability to tolerate changes to his normal routine. While this calls for caution when interpreting the case results and may reduce the likelihood for inclusion of all results into future meta-analyses seeking to meet the 5-3-20 criteria (see subsection 4.2.3.1) it is important to remember that this updated TES criterion has not been validated and is intended to help clinicians and researchers identify suspected, possible, or probable CTE (Katz et al., 2021).

6.4.2 Methodology

The use of an umbrella review as well as an n-of-1 methodology were both strong designs for the exploration of a new intervention within an emerging field (see subsections 3.2 and 4.2.31). An umbrella review allowed for the broad exploration of an intervention (active rehabilitation) across a wide range of similar conditions (tauopathies). Further, using an n-of-1 design allowed for the exploration of a new intervention within a newly understood condition using the participant as their own control. This supports the utilisation of both TES criteria as well as self-report measures (see subsections 6.4.1 and 6.4.3). Further, such methodology removes the emphasis on P values for determining the success of an intervention, considering 95%CI, 95%PI, and detailed changes in data points instead. This requires an increased consideration of context and clinical applicability, further promoting a pragmatic ideology.

The addition of mixed methods by implementing a QCS component further strengthened the results of this study. Not only did the semi-structured interviews offer a better understanding of the results, but it may also have influenced the effectiveness of the intervention itself. Introducing a semi-structured follow-up interview at every collection point allowed for the implementation of PCC within a research-context. This allowed for a personalised active rehabilitation programme that met the needs and preferences of the participant. This can lead to increased adherence but may also be manipulated in clinical practice and future research to address the specific concerns of the participant. Further still, offering biweekly interviews served as a sort of therapy for some of the participants. This was

especially true when considering the effects of the COVID-19 global pandemic and the US civil unrest that was occurring during this study. This was a sentiment stated by various participants, particularly in the final interviews.

Future research and clinical applicability should consider the differences in how these follow-up interviews may be conducted in the future. It may be difficult to closely replicate or synthesize the findings of this study. Not all clinicians, nor patients, are comfortable with the vulnerability and sociability which was demonstrated in most of the n-of-1 cases. Further still, the necessary resources may not have the ability to implement such services. This is especially true when considering the health care systems present in, for example, Canada and the UK versus that of the US. A 12-month rehabilitation programme with therapist contact every two weeks may not be financially viable or practical for all patients.

6.4.3 Outcome measures

The outcome measures utilised were a weakness in this study. Not to say that the selected outcome measures were inherently weak, but rather the validity of using these outcome measures within this population is unestablished. Currently, there are no outcome measures specific to CTE populations (see subsection 4.5.2). Further, only self-report measures were used, meaning that an objective effect of the intervention on symptoms of CTE cannot yet be established. It is not possible, at present, to investigate pathology-modifying interventions; therefore, the focus should be on enabling individuals to adequately manage their symptoms. Research utilising self-report measures can still provide useful information for clinical management as well as future research. When considering that the eligibility was based on TES criterion rather than a CTE diagnosis, along with an increased focused on PCC, self-report measures remained a preferrable choice. CTE cannot be diagnosed in the living, therefore, the focus of intervention research in the field of CTE should be person-centred. Current research is presently seeking to establish imaging (diffuser tensor imaging, functional MRI, PET) or biomarkers (t-tau. sTREM2, CCL11 (chemokine), neurofilament light chain, and glial fibrillary acidic protein) as a way of identifying CTE (Pierre et al., 2021). This would not only make identification in

research and clinical practice more precise, but such findings would enable future outcome measures to be validated with TES/CTE populations.

6.4.4 Study context

While conducting a study entirely online restricted close monitoring of both the intervention programmes and the completion of the outcome assessments, there were strengths that came with this setting as well. The ability for the study participation to easily fit the programme into their daily life despite the burden of responsibilities should not be understated. Participants were able to manage the load of tasks in a way that worked best for them. This led to only two dropouts, of which neither made it through the first pair of phases so this had no impact on analysis. Another strength of the study setting was an ability to access the study globally. This allowed for quite a diverse population, and it was a significant contributor to the large sample size that was recruited (six out of the 20 required for a review of SCED research – see subsection 4.2.3.1). Participants across various sports were included and from various backgrounds. This can also help clinicians better apply the results to clinical practice.

6.4.5 Reflexivity

Researcher involvement is something that should be considered when interpreting the results of the MMSCR. One the one hand, many of the contextual factors which applied to the participants also applied to me. The presence of the COVID-19 pandemic and the civil unrest in the United States were two factors that were especially influential, and this may have influenced some of the follow-up interview discussions. This is especially true for one of the participants which lived in an area close to me, as well as those participants living in the US. Further still, my position as an American football athletic trainer, passionate sports person, and advocate for CTE indicates a potential for confirmation bias when interpreting and analysing the results of this study. The role of the supervisory team was especially important here. In the umbrella review, the supervisory team checked data extraction and the interpretation

of the results to ensure unbiased results. In the MMSCR, the supervisory team checked both quantitative results and transcripts prior to the integration of the results.

The relationship that ultimately developed between myself and many of the participants should also be considered. As a practicing clinician, and one that strongly emphasizes practicing within a framework of PCC, developing close professional relationships with the participants that I worked with for over a year was almost inevitable. A clinician who chooses to practice PCC must take on roles which go beyond the traditional job roles and wear multiple 'hats', such as friend, mentor, and counsellor. This type of relationship is necessary to cultivate an environment filled with trust and vulnerability, things that are needed to encourage participants and patients to feel comfortable speaking and making shared decisions. This resulted in follow-up interviews often consisting of not just discussion about study specific topics, but also personal topics and lots of unrelated dialogue. Further still, conducting (and participating in) a study during the COVID-19 global pandemic was a unique experience for all of us, something which was expressed by multiple participants. On multiple occasions, participants expressed that participating in this study acted as a sort of 'lifeline' as they lived through such 'unprecedented times'. This may be difficult to control for in future studies, as more traditional means for controlling social desirability bias would have been difficult to fit into the present protocols. Blinding responses was not possible; however, future research may consider utilising neutral questions once CTE/TES assessments are developed. Including assessments and tests to measure social desirability bias would have increased the burden of participation in this study; however, as future research develops (meaning the list of outcome measures is more considered and therefore may reduce), this may be less of an issue and could be included. One characteristic of this study which may have decreased, or at least made any social desirability bias more apparent, was the repetition of the questionnaires and interviews across such a long period of time (51 weeks). Participants would have had to maintain these responses across 24 data points spanning the length of a year.

6.5 Conclusion

This study has provided evidence to establish the potential use of active rehabilitation for the management of suspected CTE. The size of this effect has yet to be determined; however, this thesis has offered preliminary evidence which suggests active rehabilitation is not harmful and may offer some benefit to individuals with symptoms of suspected CTE. This thesis did not identify any specific mode of exercise which appeared most beneficial; however, multiple interventions were found to be successful and should be considered in future rehabilitation and research programmes for CTE. This thesis also provides strong evidence for future research and clinical practice to consider measuring executive function in patients with suspected CTE. Finally, this thesis has illustrated the benefit of PCC approach to both clinical research and practice. Considering contextual factors such as personal circumstances, cultural climate, and detailed intervention response allows for a better understanding of an intervention effect within the context of the study. This not only better informs future research by identifying criteria to be considered, but it can also aid clinicians with having a better understanding of the applicability of the findings to their patients. Further, it may lead to better treatment adherence and increased intervention effect.

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Appendices

Appendix 1 Database Search Syntax

Appendix 1.1 Cochrane

Title Abstract Keyword: (disease OR disorder OR symptom* OR dementia OR *degenerat*)

AND Title Abstract Keyword: (Alzheimer OR Parkinson OR “Lewy body” OR frontotemporal OR corticobasal)

AND Title Abstract Keyword: (therapy OR intervention OR treatment OR rehabilitation)

AND Title Abstract Keyword: (exercise OR "physical activity" OR "resistance training" OR "aerobic exercise" OR "balance training" OR walking OR sport OR yoga OR pilates)

AND Title Abstract Keyword: ("systematic review")

Appendix 1.2 Web of Science

All fields: (disease OR disorder OR symptom* OR dementia OR *degenerat*)

AND All fields: (Alzheimer OR Parkinson OR “Lewy body” OR frontotemporal OR corticobasal)

AND All fields: (therapy OR intervention OR treatment OR rehabilitation)

AND All fields: (exercise OR "physical activity" OR "resistance training" OR "aerobic exercise" OR "balance training" OR walking OR sport OR yoga OR pilates)

AND All fields: ("systematic review")

Appendix 2 Project poster

Manchester Metropolitan University

Participants Needed

Have you participated in sports considered high risk for concussions?

Such as: boxing, American football, wrestling, rugby, football (soccer), hockey, lacrosse, skiing, karate, horseback riding, parachuting

What will I be asked to do?

- Complete an initial interview & symptom screening assessments.
- Partake in a 12 month study, alternating in six-week blocks between active participation (working under an exercise protocol) and six weeks of inactive participation.
- Keep a record of daily physical activity.
- Attend biweekly video meetings with a researcher & complete short symptom assessments.

Who can partake & when?

The study will begin January 2020 and will have a rolling admission. It will be conducted entirely online and can be undertaken from anywhere in the world. Ability to speak English is mandatory. The exercise program can be completed at a gym or at home.

Contact

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Information sheet with further details immediately available upon request

Appendix 3 Participant information sheet

Participant Information Sheet

Determining efficacy of active rehabilitation in the management of Chronic Traumatic Encephalopathy symptoms.

1. Invitation to research

My name is Rachael Hearn, I am a PhD candidate in the Department of Health Professions at Manchester Metropolitan University, and I would like to invite you to take part in my research study. This study is looking at whether active rehabilitation techniques such as strength training, aerobic training, and balance and gait training have a positive impact on symptoms associated with Chronic Traumatic Encephalopathy (CTE).

2. Why have I been invited?

You are being invited to participate because you have a history of participating in sports with a high risk of concussion and sub-concussive forces. Participation in such sports has been linked to an increased risk of developing symptoms associated with CTE.

3. Do I have to take part?

It is up to you to decide. I will describe the study and go through the information sheet, which I will give to you. I will then ask you to sign a consent form to show you agreed to take part. You are free to withdraw at any time without reason. It should be understood that all data collected up until the point of a completed cycle (a paired A and a B phase) will be kept for analysis. Further, once data is anonymized it will no longer be possible to withdraw your data from the study.

4. What will I be asked to do?

You will first be asked to take part in an interview. This will allow the researcher to gain an understanding of your needs and concerns. At this time, three screening assessments will be used in order to record any subtle signs and symptoms you may not be aware of. If any scores become a concern to the health, safety, and well-being of you or others around you, then your General Practitioner will be informed so that appropriate care can be given in a timely manner. This initial meeting, including the interview and assessments, should last approximately one hour. Following the initial interview, three baseline measures will be taken, once weekly for three weeks. This should take approximately 20 minutes each time, depending on the number of assessments that are needed.

Once the study has begun, it will last 12 months. This timeline will be broken up into eight phases, each lasting six weeks. Four of these phases will be inactive (phase A) and four of these phases will be active (phase B). This means six months out of the year long study will be

inactive. The study timeline will follow a pattern of either ABBABAAB or BAABABBA, depending on the random selection made at the start of the study.

During the inactive phase, you will be asked to complete three tasks. The first is to keep a log of any significant day to day activity (i.e. went for a 20-minute walk with the dogs, played a recreational game of football, etc). This can be kept in any format you prefer (pen & paper, online, notes app). The second task is to complete some assessments used to measure your symptoms (between 1 and 5 tests, depending on the symptoms present). These can be found and reported in a OneDrive file that will be created for each participant. This will be done every other week in accordance with task three. The third task is to attend a video chat meeting with the researcher every other week. These meetings will last approximately 20 minutes. Throughout the study, you will complete 26 of these meetings in total. During these meetings, you will share your activity journal and answer questions about your experience thus far in the study. All meetings that take place will be audio recorded and later transcribed. The details of these interviews will be anonymous and will be used only as a data point. They will not be published or shared in their entirety.

During the active phases of the study, you are asked to continue keeping an activity journal, taking and reporting symptom assessments, and to attend the biweekly video chat meetings. You will also be asked to partake in two training days a week using either a gym- or home-based programme. Either option will be made available based on your preference. One will be a cardio day, lasting 30 minutes. Any mode may be used (cycling, jogging, incline walking, rowing, etc). The second will be a strength training day, lasting approximately 45 minutes.

5. Are there any risks if I participate?

The risks of participating in this study are minimal. There will be a disruption in your normal routine with the addition of video chat meetings and exercise days. With any physical activity, there exists a minimal risk of minor injury. If injury does occur, you should inform the primary researcher who will offer advice on injury management. It is possible that symptoms may become more prevalent; however, this will likely be due to the passing of time and not participation in the study. If your symptoms do begin to progress and reach a concerning level as indicated by the assessment tools used in this study, we will advise you to contact your GP or if you prefer the researcher will contact the GP directly (we will ask you for your details in the consent form). Only in extreme (and highly unlikely) circumstances that you are not able or capable to contact your GP, and/or you are at risk of harm to yourself or anyone else, the GP listed in the consent form will be contacted to ensure that you can receive appropriate care.

6. Are there any advantages if I participate?

There is no known direct benefit to participating in the study; however, I hope to find this study offers a potential intervention strategy to improve symptoms related to CTE.

7. What will happen with the data I provide?

When you agree to participate in this research, we will collect from you personally-identifiable information.

The Manchester Metropolitan University ('the University') is the Data Controller in respect of this research and any personal data that you provide as a research participant.

The University is registered with the Information Commissioner's Office (ICO), and manages personal data in accordance with the General Data Protection Regulation (GDPR) and the University's Data Protection Policy.

We collect personal data as part of this research (such as name, telephone numbers or age). As a public authority acting in the public interest we rely upon the 'public task' lawful basis. When we collect special category data (such as medical information or ethnicity) we rely upon the research and archiving purposes in the public interest lawful basis.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained.

We will not share your personal data collected in this form with any third parties.

If your data is shared this will be under the terms of a Research Collaboration Agreement which defines use, and agrees confidentiality and information security provisions. It is the University's policy to only publish anonymised data unless you have given your explicit written consent to be identified in the research. **The University never sells personal data to third parties.**

We will only retain your personal data for twelve months as this is the length of the study and the period in which the researcher may need to contact your GP. After this period of time, personal data will be destroyed via appropriate university protocols. All data from this point forward will be anonymized. Electronic files of all data will be stored for 10 years on a password protected file on a password protected computer with access restricted only to the researcher and supervisory team. The final data set will be uploaded to the university repository system in accordance with potential publication requirements. Any necessary paperwork will be scanned, filed electronically, and physical documents then shredded. Participants will be assigned a random number to which all paperwork will be associated with so confidentiality will be maintained throughout.

For further information about use of your personal data and your data protection rights please see the University's Data Protection Pages.

What will happen to the results of the research study?

Findings of this study will be reported in a thesis for the attainment of a PhD and potentially submitted to a peer-review journal or presented at a conference. All data and results reported will be anonymous.

You may contact the primary researcher following 1st November 2021, date analysis is expected to be completed, to ask for a summary of the findings if you wish.

Who has reviewed this research project?

This study has been reviewed by a supervisor team consisting of members from the Faculty of Health, Psychology, and Social Care (HPSC). It has also been approved by a panel of scrutineers from the faculty of HPSC and a Manchester Metropolitan University ethics committee.

Who do I contact if I have concerns about this study or I wish to complain?

If you have any questions about the study, please contact the researcher Rachael Hearn via email at Rachael.Hearn@stu.mmu.ac.uk , by phone at +44 (0) 161 247 6837, or in writing to Manchester Movement Unit, Brooks Building, 53 Bonsall Street, Manchester, M15 6GX.

You may also contact James Selfe via email using j.selfe@mmu.ac.uk, by phone at +44 (0)161 247 2965, or in writing to: Faculty of Health, Psychology, and Social Care, Brooks Building, Bonsall Street, Manchester, M15 6GX.

If at any time concerns or complaints about the study arise, please contact Professor Juliet Goldbart by email using J.Goldbart@mmu.ac.uk, by phone at +44 (0)161 247 2020, or in writing to: Faculty of Health, Psychology, and Social Care, Brooks Building, Bonsall Street, Manchester, M15 6GX.

If you have any concerns regarding the personal data collected from you, our Data Protection Officer can be contacted using the legal@mmu.ac.uk e-mail address, by calling 0161 247 3331 or in writing to: Data Protection Officer, Legal Services, All Saints Building, Manchester Metropolitan University, Manchester, M15 6BH. You also have a right to lodge a complaint in respect of the processing of your personal data with the Information Commissioner's Office as the supervisory authority. Please see: https://ico.org.uk/global/contact-us/

THANK YOU FOR CONSIDERING PARTICIPATING IN THIS PROJECT

Appendix 4 Participant Consent Form

Participant Identification Number:

CONSENT FORM

Title of Project: *Determining efficacy of active rehabilitation in the management of Chronic Traumatic Encephalopathy symptoms.*

Name of Researcher: *Rachael Hearn*

Please initial box

1. I confirm that I have read the information sheet dated 13 September 2019 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without reason and without my legal rights being affected. I understand that data collected for any completed cycles (a paired A and B phase) will still be used for analysis. I understand that once personal information is destroyed and data is anonymized, it will not be possible to withdraw my data from the study. ☐
3. I understand that a breach of confidentiality may be necessary in case of health and safety concerns. The primary researcher has permission to contact my GP at: ☐

GP Name: _____

GP Address: _____

_____

GP Phone: _____

4. I understand that all interviews that take place will be recorded. I have been told that all recordings are for transcription and accurate data collection purposes only. They will not be released or identified in any way. Excerpts in the form of quotes may be used for data reporting only but will remain anonymous. ☐
5. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other ☐

researchers. This includes the need to upload final data collections to the university repository.

6. I agree to take part in the above study. ☐

Name of Participant: _____

Date: _____

Signature: _____

Name of Person taking consent: _____

Date: _____

Signature: _____

Appendix 5 Ethos Approval Letter – Ref 11822

Manchester Metropolitan University

16/10/2019
Project Title: Determining efficacy of active rehabilitation in the management of Chronic Traumatic Encephalopathy symptoms.

EthOS Reference Number: 11822

Ethical Opinion

Dear Rachael Lynn Hearn,

The above application was reviewed by the Health, Psychology and Social Care Research Ethics and Governance Committee and, on the 16/10/2019, was given a favourable ethical opinion. The approval is in place until 07/01/2022 .

Conditions of favourable ethical opinion
** Please amend the PIS statement referring to withdrawal from the first person "I recognise..." to the second person.

**Please add your supervisor/DoS's details between your own and Professor Goldbart's for queries or concerns. PhD students need three points of contact.

Application Documents

Document Type	File Name	Date	Version
Additional Documentation	MMU Insurance Checklist (1)	27/09/2019	1
Additional Documentation	MMSE-printable-mini-mental-state-examination	27/09/2019	1
Additional Documentation	Apapthy evaluation scle	27/09/2019	1
Additional Documentation	PROMIS SF v1.0 - ED-Anxiety 8a 6-2-2016 (2)	27/09/2019	1
Additional Documentation	PROMIS SF v1.0 - ED-Depression 8a 6-26-2016 (1)	27/09/2019	1
Additional Documentation	PROMIS SF v1.1 - ED-Anger 5a 4-27-2016 (2)	27/09/2019	1
Additional Documentation	PROMIS SF v2.0 - Physical Function 24a PROMIS HAQ 04-16-2019	27/09/2019	1
Additional Documentation	MOCA-Test-English	27/09/2019	1
Additional Documentation	IowaTrailMaking	27/09/2019	1
Consent Form	Consent Form (5)	06/10/2019	1
Information Sheet	Brochure (2)	06/10/2019	1
Information Sheet	Participant Information Final (5)	06/10/2019	1
Project Protocol	Project Protocol Final (5)	06/10/2019	1

The Health, Psychology and Social Care Research Ethics and Governance Committee favourable ethical opinion is granted with the following conditions

Adherence to Manchester Metropolitan University's Policies and procedures

This ethical approval is conditional on adherence to Manchester Metropolitan University's Policies, Procedures, guidance and Standard Operating procedures. These can be found on the Manchester Metropolitan University Research Ethics and Governance webpages.

Amendments

If you wish to make a change to this approved application, you will be required to submit an amendment. Please visit the Manchester Metropolitan University Research Ethics and Governance webpages or contact your Faculty research officer for advice around how to do this.

We wish you every success with your project.

HPSC Research Ethics and Governance Committee

Appendix 6 Determining if symptoms can be explained by conditions other than CTE

To exclude possible AD:

- Under the age of 60
    - Mean age of clinical onset: 76 in APOE carriers & 84 in non carriers
    - First clinical signs occur after the age of 65
- Family history of AD
    - Genetic risk factor

To exclude possible HD:

- Family history
    - Highest risk factor, especially paternal
- Onset of motor disturbances initially
    - Used along with family history and/or genetics test to diagnose
- Under the age of 40
    - Average onset is 45 years and disease is fatal 15-20 years later

To exclude possible FTLD:

- Family history
    - Observed in 40-50% of patients
- Under age 40
    - 10% of all FTD patients are under the age of 45 & 30% are over the age of 65
    - Therefore, highest population (60%) is between 45-65
- *Primary* symptoms are disinhibition and inappropriate social behaviors
    - Less common in CTE while they are cardinal symptoms in a FTLD diagnosis

To exclude possible PD:

- First symptoms that are those of Parkinsonism (rest tremor, rigidity, both)
    - This must first be diagnosed for an accurate PD diagnosis

Appendix 7 Consolidated Standards of Reporting Trials (CONSORT) extension for N-of-1 trials (CENT) 2015 statement

Section/Topic	CONSORT 2010			CENT 2015	
	No	Item		No	Item
Title and abstract					
	1a	Identification as a randomised trial in the title		1a	Identify as an "N-of-1 trial" in the title *For series:* Identify as "a series of N-of-1 trials" in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)		1b	For specific guidance, see CENT guidance for abstracts (table 2)
Introduction					
Background and objectives	2a	Scientific background and explanation of rationale		2a.1	
				2a.2	Rationale for using N-of-1 approach
	2b	Specific objectives or hypotheses		2b	
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio		3a	Describe trial design, planned number of periods, and duration of each period (including run-in and wash out, if applicable) *In addition for series:* Whether and how the design was individualized to each participant, and explain the series design

Section/Topic	CONSORT 2010			CENT 2015	
	No	Item		No	Item
	3b	Important changes to methods after trial start (such as eligibility criteria), with reasons		3b	
Participant(s)	4a	Eligibility criteria for participants		4a†	Diagnosis or disorder, diagnostic criteria, comorbid conditions, and concurrent therapies. *For series:* Same as CONSORT item 4a
	4b	Settings and locations where the data were collected		4b†	
				4c	Whether the trial(s) represents a research study and if so, whether institutional ethics approval was obtained
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered		5	The interventions for each period with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed		6a.1	
				6a.2	Description and measurement properties (validity and reliability) of outcome assessment tools

Section/Topic	CONSORT 2010			CENT 2015	
	No	Item		No	Item
	6b	Any changes to trial outcomes after the trial commenced, with reasons		6b	
Sample size	7a	How sample size was determined		7a	
	7b	When applicable, explanation of any interim analyses and stopping guidelines		7b	
Randomisation:					
Sequence generation	8a	Method used to generate the random allocation sequence		8a	Whether the order of treatment periods was randomised, with rationale, and method used to generate allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)		8b	When applicable, type of randomisation; details of any restrictions (such as pairs, blocking)
				8c	Full, intended sequence of periods
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned		9	
Implementation	10	Who generated the random allocation sequence, who enrolled		10	

Section/Topic	CONSORT 2010			CENT 2015	
	No	Item		No	Item
		participants, and who assigned participants to interventions			
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		11a	
	11b	If relevant, description of the similarity of interventions		11b	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes		12a	Methods used to summarize data and compare interventions for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		12b	*For series:* If done, methods of quantitative synthesis of individual trial data, including subgroup analyses, adjusted analyses, and how heterogeneity between participants was assessed *(for specific guidance on reporting syntheses of multiple trials, please consult the PRISMA Statement)*
				12c	Statistical methods used to account for carryover effect, period effects, and intra-subject correlation
Results					

Section/Topic	CONSORT 2010		CENT 2015	
	No	Item	No	Item
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13a.1	Number and sequence of periods completed, and any changes from original plan with reasons
			13a.2	*For series:* The number of participants who were enrolled, assigned to interventions, and analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons	13c	*For series:* Losses or exclusions of participants after treatment assignment, with reasons, and period in which this occurred, if applicable
Recruitment	14a	Dates defining the periods of recruitment and follow-up	14a†	
	14b	Why the trial ended or was stopped	14b	Whether any periods were stopped early and/or whether trial was stopped early, with reason(s).
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15†	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	16	For each intervention, number of periods analysed. *In addition for series:* If quantitative synthesis was performed, number of trials for which data were synthesized

Section/Topic	CONSORT 2010		CENT 2015	
	No	Item	No	Item
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	17a.1	For each primary and secondary outcome, results for each period; an accompanying figure displaying the trial data is recommended.
			17a.2	For each primary and secondary outcome, the estimated effect size and its precision (such as 95% confidence interval) *In addition for series:* If quantitative synthesis was performed, group estimates of effect and precision for each primary and secondary outcome
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	17b	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	18	Results of any other analyses performed, including assessment of carryover effects, period effects, intra-subject correlation *In addition for series:* If done, results of subgroup or sensitivity analyses
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	19	All harms or unintended effects for each intervention. *(for specific guidance see CONSORT for harms)*
Discussion				

Section/Topic	CONSORT 2010			CENT 2015	
	No	Item		No	Item
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		20	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings		21	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		22	
Other information					
Registration	23	Registration number and name of trial registry		23	
Protocol	24	Where the full trial protocol can be accessed, if available		24	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		25	

*It is strongly recommended that this checklist be read in conjunction with the CENT 2015 Explanation and Elaboration[24] for important clarification on the items. The copyright for CENT (including checklist) is held by the CENT Group and is distributed under a Creative Commons Attribution (CC-BY 4.0) license.
†Caution should be taken when reporting potentially identifying information pertaining to CENT items 4a, 4b, 14a, and 15.

(Shamseer et al., 2015; Vohra et al., 2015)

Appendix 8 Intervention delivery

Appendix 8.1 Example programme PDF

CTE Rehabilitation Study

Active phase exercise programme

Manchester Metropolitan University

28 May, 2020 – 10 June, 2020

Week 3:

Session 1 = Resistance Training
Session 2 = Cardio Training

Week 4:

Session 3 = Resistance Training
Session 4 = Cardio Training

Please log the weight you've lifted (if any)/if you modified the exercise to make it more/less intense in your daily activity log and rate how hard the sets were to allow for progression in the following weeks.

 Please contact Rachael Hearn (rachael.hearn@stu.mmu.ac.uk) if you need any assistance with this programme.

CTE Rehabilitation Study

Active phase exercise programme

Session 1 Warm up -

Participant may choose between a 10-minute walk outside or the raise exercises prescribed below, followed by the Activate/Mobilise/Potentiate components.

Raise (10 m distance, if able)	**Activate**	**Mobilise**	**Potentiate**
Butt kicks (Link)	Cat-cow (Link)	Wall slides (Link)	Wall angels (Link)
Forward jog, back peddle (Link)	Bird-dog (Link)	Thoracic spine needle thread (Link)	Wall press-up (Link)

Session 2-4 Warm up -

Participant may choose between a 10-minute walk outside or the raise exercises prescribed below, followed by the Activate/Mobilise/Potentiate components.

Raise (10 m distance, if able)	**Activate**	**Mobilise**	**Potentiate**
Butt kicks (Link)	Walking lunge with side bend, 10x (Link)	Sprinter stretch with side bend, 10x each side (Link)	High knees, 20x (Link)
Forward jog, back peddle (Link)	Dynamic lateral lunge, 10x (Link)	Knee cradle to single leg deadlift, 10x (Link)	Cherry pickers, 10x (Link)

 Please contact Rachael Hearn (rachael.hearn@stu.mmu.ac.uk) if you need any assistance with this programme.

CTE Rehabilitation Study

Active phase exercise programme

Manchester Metropolitan University

Session 1 – Resistance Training

Warm up

	Exercise (Links) *(Intensity prescribed using RPE - reference chart below)*	**Sets x Reps** *(Rest between Sets)*	*Comments/Coaching Cues*
1	***Decline press-up (Link)*** *Intensity: 6*	***3 x 15*** *(30sec)*	*To increase intensity, increase the level of the decline. The higher the decline, the harder.*
2	***Press-up (Link)*** *Intensity: 10*	***3 x to failure*** *(30sec)*	*To increase intensity, you can press against a band wrapped across your back. Or, wear a backpack filled with weighted objects such as books.Please record reps achieved.*
3	***Incline press-ups (Link)*** *Intensity: 4*	***3 x 15*** *(45sec - 60sec)*	*To increase intensity, lower the level of the incline. The higher the incline, the easier.*
4	***Plank up-downs (Link)*** *Intensity: 6*	***3 x 24 (12 each side)*** *(45sec - 60sec)*	*To increase intensity,alternate lifting legs. Or, wear a backpack filled with weighted objects such as books.*
5	***Plank hold w/ alternating leg lift (Link)*** *Intensity: 5*	***3 x 30 sec Leg hold for 5-10 sec at a time*** *(45sec - 60sec)*	*To increase intensity, hold the leg up for longer periods of time. Or, wear a backpack filled with weighted objects such as books.*
6	***Plank to alternate pike (Link)*** *Intensity: 5*	***3 x 24 (12 each side)*** *(45sec - 60sec)*	*To increase intensity, wear a backpack filled with weighted objects such as books.*

Session 2 – Cardio Training

Warm up

Jog for 20 minutes. Intensity 13/14 on Borg 6-20 scale (see below).

 Please contact Rachael Hearn (rachael.hearn@stu.mmu.ac.uk) if you need any assistance with this programme.

Appendix 8.2 Examples of written exercise descriptions

1. *Butt kicks*

With knees staying in line with the body, the feet alternate kicking back as far as flexibility will allow before returning to the ground. You should feel a stretch in the front of the thigh (the quads).

2. *Forward jog, back peddle*

Jog forward at a comfortable warm-up pace before stopping in place. Now crouch into a slight squat position, making sure to keep a flat back and chest is up. Move backwards, peddling the arms and moving the feet quickly.

3. *Walking lunge with side bend*

Start in an upright position. Place the left foot forward (about 2-3 feet away from the right foot) and then bend the left knee. The right knee should be bent, hovering just above the floor. Keep the rest of the body upright, chest up and back flat. The back foot will provide stability as you hold this position. Now, lift the left arm forward until it is straight above. Slightly bend to the right, feeling a stretch along the left side of the torso. After holding for 1-2 seconds, bring the torso back to neutral and then use the right foot to push off the ground bringing it to meet the left foot. Repeat, moving with the right foot now.

4. *Dynamic lateral lunge*

Start in an upright position. Place the left foot sideways (about 2-3 away from the right foot). As the knee bends forward, the torso will move to the left until it is inline with the foot. The torso should remain upright, with the chest up and back flat. While remaining in this position, bring the right foot to meet the left. Repeat one more time before turning 180 degrees and leading with the right foot for two reps.

5. *Sprinter stretch with side bend*

Place the right foot on an elevated surface, such as a chair or table. While keeping the torso upright, move the pelvis forward. You should feel a stretch in the left hip flexors (upper thigh). Now, bring the right arm up above your head and then lean slightly to the left. You should now feel a stretch along the right side of the torso as well as the outer glute (right outer hip).

6. *Knee cradle to single leg deadlift*

Bring the right foot up and place it on the inner thigh, as far up as flexibility will allow. Now, grab the shin with both hands and slightly pull the lower leg up higher. This should cause a stretching sensation in the glute. Hold for 2-3 seconds before letting go of the shin. In a slow and controlled fashion, extend the leg out behind you. As the leg extends behind, you should tilt from the hips, bending over while still maintaining a flat back (chest up). Bend down as far as you can without compromising this flat back. You should now feel a stretch in your hamstrings (back of the thigh).

Appendix 8.3 Still shots of video demonstration example

Appendix 9 Interview Questions

Appendix 9.1 Initial interview questions

Initial interview		
No.	Question	Investigating/Follow-ups
1	What is your sporting history?	
2	What is your injury history?	a. Establish history of injury b. Meet TES criteria of injury history c. Assess activity level now & ensure they are not involved in organized sport
3	Do you have a history (diagnosed or not) of concussions?	a. How did you feel? b. What was the management protocol that was followed?
4	What concerns and struggles have you been managing that brought you to this study?	a. Establish the primary concerns of the participant and what symptoms are present b. Begin to delve into TES clinical features with probing questions
5	When did you first start noticing these things?	a. Establish timeline and disease progression b. Meet TES criteria of 12 months
6	Is there any history of mental or physical health problems in your family?	a. Looking for exclusion criteria or other explanations for symptomatology
7	Do you have any questions for me?	

Appendix 9.2 Follow-up interview questions

Follow-up interviews		
No.	Question	Investigating/Follow-ups
1	Self-report what's going on outside of the study scope	a. Any extracurricular physical activities (i.e walk the dog, went to the gym for 30 minutes, went for a hike on Saturday, etc) b. Any new supplements, medications, dietary changes, etc
2	How are you feeling during this stage in the study?	a. Ask specific questions about individuals symptoms b. Have you noticed a change with (specific symptom)?
3	Are you feeling this stage in the study has had any effect?	a. Positive or negative?
4	What things would you want to change if you could?	a. Allow them to have a say in treatment choices which is both important to a clinical study but also vital in my approach to treating any patient
5	Are you having any concerns thus far?	a. Discuss ways to address any concerns
6	How are things going in regards to Covid-19?	a. Has it had a significant impact on your life (in regards to work, social life, sports)?
7	Have you noticed any new or abnormal changes in behavior?	

Appendix 10 RPE charts

RPE	Classification*
1	Could do 12 more reps
2	Could do 10 more reps
3	Could do 9 more reps
4	Could do 7 more reps
5	Could do 5 more reps
6	Could do 4 more reps
7	Could do 3 more reps
8	Could do 2 more reps
9	Could do 1 more rep
10	Couldn't do another rep

Borg RPE Chart for prescribing resistance exercise. Classification refers to the number of repetitions a participant feels they could complete after a set is complete.

RPE	Classification
6	No exertion
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal Exertion

Borg 6-20 for prescribing aerobic exercise.

Appendix 11 Visual analysis

Appendix 11.1 Niall Visual Analysis

Question	Response		
	CF	EF	LSO
TIER 1 CONTRAST: Project trend line of A1 into B1+B2. Is the level (L), trend (T) or variability (V) in B1+B2 different than what you would predict based on A1?	L: Y	L: N	L: Y
	T: N	T: N	T: N
(1.0 point)	V: N	V: N	V: Y
IMMEDIACY: Is there an immediate change from the last 3 data points in the A1 to the first 3-5 data points in B1?	Y		Y
(0.25 points)			
OVERLAP: Do less than 30% of the data points in B1+B2 overlap with the data points in A1?	Y		Y
(0.25 points)			
TIER 2 CONTRAST: Project trend line of B1+B2 into A2. Is the level (L), trend (T) or variability (V) in A2 different than what you would predict based on B1+B2?	L: N	L: N	L: N
	T: N	T: Y	T: Y
(1.0 point)	V: N	V: N	V: Y
IMMEDIACY: Is there an immediate change from the last 3 data points in B2 to the first 3 data points in A2?		N	Y
(0.25 points)			
OVERLAP: Do less than 30% of the data points in A2 overlap with the data points in B1+B2?		N	Y
(0.25 points)			
	L: Y	L: N	L: Y

TIER 3 CONTRAST: Project trend line of A2 into B3. Is the level (L), trend (T) or variability (V) in B3 different than what you would predict based on A2? (1.0 point)	T: N V: N	T: Y V: N	T: Y V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in A2 to the first 3 data points in B3? (0.25 points)	N	N	Y
OVERLAP: Do less than 30% of the data points in B3 overlap with the data points in A2? (0.25 points)	N	N	N
TIER 4 CONTRAST: Project trend line of B3 into A3+A4. Is the level (L), trend (T) or variability (V) in A3+A4 different than what you would predict based on B3? (1.0 point)	L: Y T: Y V: Y	L: N T: N V: N	L: Y T: Y V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in B3 to the first 3 data points in A3? (0.25 points)	N		N
OVERLAP: Do less than 30% of the data points in A3+A4 overlap with the data points in B3? (0.25 points)	N		N
TIER 5 CONTRAST: Project trend line of A3+A4 into B4. Is the level (L), trend (T) or variability (V) in B4 different than what you would predict based on A3+A4? (1.0 point)	L: Y T: N V: Y	L: Y T: N V: N	L: N T: Y V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in A4 to the first 3 data points in B4?	Y	Y	N

(0.25 points) OVERLAP: Do less than 30% of the data points in B4 overlap with the data points in A3+A4? (0.25 points)	N	Y	N
CONSISTENCY: Are the data patterns of the intervention phases similar in trend, level and variability? (0.25 points)	L: N T: N V: N	L: N T: N V: Y	L: N T: N V: N
CONSISTENCY: Are the data patterns of the non-intervention phases similar in trend, level and variability? (0.25 points)	L: N T: N V: N	L: N T: N V: Y	L: N T: N V: Y
Total Points:	4.75	4.00	6.50

CF: cognitive function; EF: executive function; L: level; LSO: loneliness; T: trend; V: variability. Source: Wolfe et al., 2019. Questions of immediacy or overlap do not apply if no basic effect was observed.

Appendix 11.2 Luigi Visual Analysis

Question	Response			
	EF	ANXTY	DPN	IRR
TIER 1 CONTRAST: Project trend line of A1 into B1+B2. Is the level (L), trend (T) or variability (V) in B1+B2 different than what you would predict based on A1? (1.0 point)	L: N T: N V: Y	L: Y T: Y V: Y	L: Y T: Y V: N	L: Y T: Y V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in the A1 to the first 3-5 data points in B1? (0.25 points)	Y	Y	N	N

OVERLAP: Do less than 30% of the data points in B1+B2 overlap with the data points in A1? (0.25 points)	N	N	N	N
TIER 2 CONTRAST: Project trend line of B1+B2 into A2. Is the level (L), trend (T) or variability (V) in A2 different than what you would predict based on B1+B2? (1.0 point)	L: Y T: Y V: N	L: N T: N V: N	L: N T: N V: N	L: Y T: N V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in B2 to the first 3 data points in A2? (0.25 points)	Y			Y
OVERLAP: Do less than 30% of the data points in A2 overlap with the data points in B1+B2? (0.25 points)	N			Y
TIER 3 CONTRAST: Project trend line of A2 into B3. Is the level (L), trend (T) or variability (V) in B3 different than what you would predict based on A2? (1.0 point)	L: Y T: Y V: Y	L: Y T: Y V: N	L: Y T: Y V: Y	L: N T: Y V: Y
IMMEDIACY: Is there an immediate change from the last 3 data points in A2 to the first 3 data points in B3? (0.25 points)	Y	Y	N	Y
OVERLAP: Do less than 30% of the data points in B3 overlap with the data points in A2? (0.25 points)	Y	N	N	N
	L: Y T: Y	L: Y T: Y	L: Y T: Y	L: Y T: Y

TIER 4 CONTRAST: Project trend line of B3 into A3+A4. Is the level (L), trend (T) or variability (V) in A3+A4 different than what you would predict based on B3? (1.0 point)	V: Y	V: Y	V: N	V: Y
IMMEDIACY: Is there an immediate change from the last 3 data points in B3 to the first 3 data points in A3? (0.25 points)	N	Y	Y	Y
OVERLAP: Do less than 30% of the data points in A3+A4 overlap with the data points in B3? (0.25 points)	N	N	N	Y
TIER 5 CONTRAST: Project trend line of A3+A4 into B4. Is the level (L), trend (T) or variability (V) in B4 different than what you would predict based on A3+A4? (1.0 point)	L: Y T: Y V: Y	L: Y T: Y V: Y	L: Y T: N V: N	L: Y T: Y V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in A4 to the first 3 data points in B4? (0.25 points)	Y	N	Y	Y
OVERLAP: Do less than 30% of the data points in B4 overlap with the data points in A3+A4? (0.25 points)	Y	Y	Y	Y
CONSISTENCY: Are the data patterns of the intervention phases similar in trend, level and variability? (0.25 points)	L: Y T: Y V: N L: N	L: N T: N V: N L: N	L: N T: N V: N L: N	L: N T: N V: N L: N

CONSISTENCY: Are the data patterns of the non-intervention phases similar in trend, level and variability? (0.25 points)	T: N V: N	T: N V: N	T: N V: N	T: N V: Y
Total Points:	7.00	5.00	4.75	7.00

ANXTY: anxiety; DPN: depression; EF: executive function; IRR: irritability; L: level; T: trend; V: variability. Source: Wolfe et al., 2019. Questions of immediacy or overlap do not apply if no basic effect was observed.

Appendix 11.3 Kristen Visual Analysis

Question	Response				
	CF	EF	ANXTY	DPN	SP
TIER 1 CONTRAST: Project trend line of B1 into A1+A2. Is the level (L), trend (T) or variability (V) in B1+B2 different than what you would predict based on B1? (1.0 point)	L: N T: N V: N	L: Y T: N V: N	L: Y T: Y V: N	L: Y T: Y V: Y	L: N T: N V: Y
IMMEDIACY: Is there an immediate change from the last 3 data points in the B1 to the first 3-5 data points in A1? (0.25 points)		Y	Y	Y	Y
OVERLAP: Do less than 30% of the data points in A1+A2 overlap with the data points in A1? (0.25 points)		N	N	Y	Y
TIER 2 CONTRAST: Project trend line of A1+A2 into B2. Is the level (L), trend (T) or variability (V) in A2 different than what you would predict based on A1+A2? (1.0 point)	L: Y T: N V: N	L: N T: N V: Y	L: Y T: Y V: Y	L: Y T: Y V: N	L: N T: N V: N

IMMEDIACY: Is there an immediate change from the last 3 data points in A2 to the first 3 data points in B2? (0.25 points)	Y	N	Y	N	
OVERLAP: Do less than 30% of the data points in B2 overlap with the data points in A1+A2? (0.25 points)	N	N	N	N	
TIER 3 CONTRAST: Project trend line of B2 into A3. Is the level (L), trend (T) or variability (V) in A3 different than what you would predict based on B2? (1.0 point)	L: Y T: Y V: N	L: Y T: Y V: Y	L: Y T: Y V: Y	L: Y T: Y V: Y	L: N T: N V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in B2 to the first 3 data points in A3? (0.25 points)	Y	N	N	N	
OVERLAP: Do less than 30% of the data points in A3 overlap with the data points in B2? (0.25 points)	Y	N	N	N	
TIER 4 CONTRAST: Project trend line of A3 into B3+B4. Is the level (L), trend (T) or variability (V) in B3+B4 different than what you would predict based on A3? (1.0 point)	L: Y T: N V: Y	L: N T: N V: Y	L: Y T: Y V: N	L: N T: Y V: Y	L: N T: N V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in A3 to the first 3 data points in B3? (0.25 points)	N	N	N	Y	

OVERLAP: Do less than 30% of the data points in B3+B4 overlap with the data points in A3? (0.25 points)	N	N	N	N	
TIER 5 CONTRAST: Project trend line of B3 + B4 into A4. Is the level (L), trend (T) or variability (V) in A4 different than what you would predict based on B3+B4? (1.0 point)	L: Y T: Y V: N	L: Y T: N V: Y	L: Y T: Y V: N	L: N T: N V: N	L: Y T: N V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in B4 to the first 3 data points in A4? (0.25 points)	N	N	Y		Y
OVERLAP: Do less than 30% of the data points in A4 overlap with the data points in B3+B4? (0.25 points)	N	N	N		N
CONSISTENCY: Are the data patterns of the intervention phases similar in trend, level and variability? (0.25 points)	L: N T: N V: N	L: N T: N V: N	L: N T: N V: N	L: N T: N V: N	
CONSISTENCY: Are the data patterns of the non-intervention phases similar in trend, level and variability? (0.25 points)	L: N T: N V: N	L: N T: N V: Y	L: N T: N V: N	L: N T: N V: N	
Total Points:	4.5	5.5	6.0	4.75	

ANXTY: anxiety; DPN: depression; CF: cognitive function; EF: executive function; IRR: irritability; L: level; SP: sleep; T: trend; V: variability. Source: Wolfe et al., 2019. Questions of immediacy or overlap do not apply if no basic effect was observed.

Appendix 11.4 Abel Visual Analysis

Question	Response			
	EF	MA	ANXTY	DPN
TIER 1 CONTRAST: Project trend line of B1 into A1+A2. Is the level (L), trend (T) or variability (V) in B1+B2 different than what you would predict based on B1? (1.0 point)	L: Y T: N V: N	L: Y T: N V: N	L: Y T: Y V: Y	L: Y T: Y V: Y
IMMEDIACY: Is there an immediate change from the last 3 data points in the B1 to the first 3-5 data points in A1? (0.25 points)	Y	Y	Y	N
OVERLAP: Do less than 30% of the data points in A1+A2 overlap with the data points in B1? (0.25 points)	N	N	N	N
TIER 2 CONTRAST: Project trend line of A1+A2 into B2. Is the level (L), trend (T) or variability (V) in A2 different than what you would predict based on A1+A2? (1.0 point)	L: N T: Y V: N	L: Y T: N V: N	L: Y T: N V: N	L: Y T: Y V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in A2 to the first 3 data points in B2? (0.25 points)	Y	Y	Y	N
OVERLAP: Do less than 30% of the data points in B2 overlap with the data points in A1+A2? (0.25 points)	N	N	N	N
TIER 3 CONTRAST: Project trend line of B2 into A3. Is the level (L), trend (T) or variability (V) in B3 different than what you would predict based on B2? (1.0 point)	L: N T: Y V: N	L: Y T: Y V: Y	L: N T: Y V: Y	L: Y T: Y V: Y

IMMEDIACY: Is there an immediate change from the last 3 data points in B2 to the first 3 data points in A3? (0.25 points)	N	N	Y	N
OVERLAP: Do less than 30% of the data points in A3 overlap with the data points in B2? (0.25 points)	N	N	N	N
TIER 4 CONTRAST: Project trend line of A3 into B3+B4. Is the level (L), trend (T) or variability (V) in A3+A4 different than what you would predict based on A3? (1.0 point)	L: Y T: N V: Y	L: Y T: Y V: Y	L: Y T: N V: Y	L: N T: N V: Y
IMMEDIACY: Is there an immediate change from the last 3 data points in A3 to the first 3 data points in B3? (0.25 points)	Y	Y	Y	Y
OVERLAP: Do less than 30% of the data points in B3+B4 overlap with the data points in A3? (0.25 points)	N	N	N	N
TIER 5 CONTRAST: Project trend line of B3+B4 into A4. Is the level (L), trend (T) or variability (V) in B4 different than what you would predict based on B3+B4? (1.0 point)				
IMMEDIACY: Is there an immediate change from the last 3 data points in B4 to the first 3 data points in A4? (0.25 points)				
OVERLAP: Do less than 30% of the data points in A4 overlap with the data points in B3+B4? (0.25 points)				

CONSISTENCY: Are the data patterns of the intervention phases similar in trend, level and variability? (0.25 points)	L: N T: N V: N	L: N T: N V: N	L: N T: N V: N	L: N T: N V: N
CONSISTENCY: Are the data patterns of the non-intervention phases similar in trend, level and variability? (0.25 points)	L: N T: N V: N	L: N T: N V: N	L: N T: N V: N	L: N T: N V: N
Total Points:	4.75	4.75	5.00	4.25

ANXTY: anxiety; DPN: depression; EF: executive function; MA: mindful attention; L: level; T: trend; V: variability. Source: Wolfe et al., 2019. Questions of immediacy or overlap do not apply if no basic effect was observed.

Appendix 11.5 Gemma Visual Analysis

Question	Response	
	EF	ANXTY
TIER 1 CONTRAST: Project trend line of B1 into A1+A2. Is the level (L), trend (T) or variability (V) in A1+A2 different than what you would predict based on B1? (1.0 point)	L: N T: N V: N	L: N T: N V: Y
IMMEDIACY: Is there an immediate change from the last 3 data points in the B1 to the first 3-5 data points in A1? (0.25 points)		Y
OVERLAP: Do less than 30% of the data points in A1+A2 overlap with the data points in B1? (0.25 points)		Y
	L: N	L: Y

TIER 2 CONTRAST: Project trend line of A1+A2 into B2. Is the level (L), trend (T) or variability (V) in A2 different than what you would predict based on B1+B2? (1.0 point)	T: Y V: N	T: N V: Y
IMMEDIACY: Is there an immediate change from the last 3 data points in A2 to the first 3 data points in B2? (0.25 points)	N	Y
OVERLAP: Do less than 30% of the data points in B2 overlap with the data points in A1+A2? (0.25 points)	N	N
TIER 3 CONTRAST: Project trend line of B2 into A3. Is the level (L), trend (T) or variability (V) in A3 different than what you would predict based on B2? (1.0 point)	L: T: Y V:	L: Y T: N V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in B2 to the first 3 data points in A3? (0.25 points)	N	Y
OVERLAP: Do less than 30% of the data points in A3 overlap with the data points in B2? (0.25 points)	N	N
TIER 4 CONTRAST: Project trend line of A3 into B3+B4. Is the level (L), trend (T) or variability (V) in B3+B4 different than what you would predict based on A3? (1.0 point)	L: N T: N V: N	L: N T: N V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in A3 to the first 3 data points in B3? (0.25 points)		

OVERLAP: Do less than 30% of the data points in B3+B4 overlap with the data points in A3? (0.25 points)		
TIER 5 CONTRAST: Project trend line of B3+B4 into A4. Is the level (L), trend (T) or variability (V) in A4 different than what you would predict based on B3+B4? (1.0 point)	L: N T: N V: N	L: Y T: Y V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in B4 to the first 3 data points in A4? (0.25 points)		N
OVERLAP: Do less than 30% of the data points in A4 overlap with the data points in B3+B4? (0.25 points)		N
CONSISTENCY: Are the data patterns of the intervention phases similar in trend, level and variability? (0.25 points)		L: N T: Y V: N
CONSISTENCY: Are the data patterns of the non-intervention phases similar in trend, level and variability? (0.25 points)		L: N T: N V: N
Total Points:		5.25

ANXTY: anxiety; EF: executive function; L: level; T: trend; V: variability. Source: Wolfe et al., 2019. Questions of immediacy or overlap do not apply if no basic effect was observed.

Appendix 11.6 Simon Visual Analysis

Question	Response			
	CF	EF	MA	DPN
	L: Y	L: Y	L: Y	L: Y

TIER 1 CONTRAST: Project trend line of A1 into B1+B2. Is the level (L), trend (T) or variability (V) in B1+B2 different than what you would predict based on A1?	T: N V: Y	T: Y V: Y	T: N V: N	T: Y V: Y
(1.0 point) IMMEDIACY: Is there an immediate change from the last 3 data points in the A1 to the first 3-5 data points in B1?	Y	Y	N	Y
(0.25 points) OVERLAP: Do less than 30% of the data points in B1+B2 overlap with the data points in A1?	N	N	N	N
(0.25 points) TIER 2 CONTRAST: Project trend line of B1+B2 into A2. Is the level (L), trend (T) or variability (V) in A2 different than what you would predict based on B1+B2?	L: Y T: N V: N	L: N T: N V: N	L: Y T: Y V: N	L: N T: N V: N
(1.0 point) IMMEDIACY: Is there an immediate change from the last 3 data points in B2 to the first 3 data points in A2?	Y		Y	
(0.25 points) OVERLAP: Do less than 30% of the data points in A2 overlap with the data points in B1+B2?	N		N	
(0.25 points) TIER 3 CONTRAST: Project trend line of A2 into B3. Is the level (L), trend (T) or variability (V) in B3 different than what you would predict based on A2?	L: Y T: N V: Y	L: N T: Y V: N	L: Y T: N V: Y	L: Y T: Y V: Y
(1.0 point) IMMEDIACY: Is there an immediate change from the last 3 data points in A2 to the first 3 data points in B3?	N	N	Y	Y

(0.25 points) OVERLAP: Do less than 30% of the data points in B3 overlap with the data points in A2?	N	N	N	N
(0.25 points) TIER 4 CONTRAST: Project trend line of B3 into A3+A4. Is the level (L), trend (T) or variability (V) in A3+A4 different than what you would predict based on B3? (1.0 point)	L: Y T: N V: N	L: Y T: N V: N	L: Y T: Y V: Y	L: Y T: N V: Y
IMMEDIACY: Is there an immediate change from the last 3 data points in B3 to the first 3 data points in A3?	N		Y	N
(0.25 points) OVERLAP: Do less than 30% of the data points in A3+A4 overlap with the data points in B3?	N		Y	N
(0.25 points) TIER 5 CONTRAST: Project trend line of A3+A4 into B4. Is the level (L), trend (T) or variability (V) in B4 different than what you would predict based on A3+A4? (1.0 point)	L: N T: N V: Y	L: Y T: N V: Y	L: N T: N V: Y	L: N T: N V: N
IMMEDIACY: Is there an immediate change from the last 3 data points in A4 to the first 3 data points in B4?	N	Y	N	
(0.25 points) OVERLAP: Do less than 30% of the data points in B4 overlap with the data points in A3+A4?	N	N	N	
(0.25 points) CONSISTENCY: Are the data patterns of the intervention phases similar in trend, level and variability?	L: N T: Y V: N	L: N T: N V: N	L: N T: N V: N	L: N T: N V: N

(0.25 points) CONSISTENCY: Are the data patterns of the non-intervention phases similar in trend, level and variability? (0.25 points)	L: N T: Y V: N	L: N T: N V: N	L: N T: N V: N	L: N T: N V: N
Total Points:	5.75	4.5	6.00	3.5

CF: cognitive function; DPN: depression; EF: executive function; MA: mindful attention; L: level; T: trend; V: variability. Source: Wolfe et al., 2019. Questions of immediacy or overlap do not apply if no basic effect was observed.