Physical Exercise and Cognition: Mechanisms of Action and Evaluation of the Potential Therapeutic Value in Traumatic Brain Injury

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UNIVERSITAT AUTÒNOMA DE BARCELONA

DOCTORAL THESIS

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"Lack of activity destroys the good condition of every human being while movement and methodical physical exercise save and preserve it"
-Plato

Acknowledgments

First and foremost, I would like to dedicate this thesis to my late grandparents Ernest “Joe” Morris and Alan Turner, for without their generous help I would not have had the opportunity to begin, continue or complete my post-graduate or doctoral studies.

Speaking of opportunity, I must give thanks to both my parents. Their support has never wavered, even in the face of my oftentimes stuttered pursuit of my goals, and for that, I thank them with all of my heart.

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Abstract

Physical exercise, an economical and easily accessible lifestyle intervention can improve cognitive function in healthy adults and is a potential long-term treatment option for those who have sustained traumatic brain injury (TBI). Following TBI, the cognitive squeal of impairment can persist for years or even decades. As such, the use of physical exercise as a therapeutic intervention may have benefits both within the neurorehabilitation hospital as well as in community-dwelling individuals later in life. Many animal models of the effect of exercise on cognitive recovery following TBI have been reported but translation of these result into clinical practice is poor and numerous parameters of exercise appear to have differential effects. Our understanding of which is limited. Assessing the feasibility of exercise within the sub-acute phase of moderate-to-severe TBI, characterizing the mechanistic underpinnings of how exercise modulates cognitive function and evaluating the impact of exercise in community-dwelling individuals with TBI will improve our understanding of the potential impact this intervention may have for cognitive recovery post-TBI.

This thesis used multiple scientific study approaches (observational, systematic review, clinical and translational) to gain global insights into the potential use of physical exercise in cognitive recovery following TBI. Firstly, an extensive up-to-date systematic review of the extant literature on the role of exercise in cognitive recovery following TBI was performed (chapter 3). Secondly, the feasibility of adding an 8-week aerobic exercise program into the sub-acute phase of moderate-to-severe TBI, on top of standard multidisciplinary rehabilitation, including cognitive training, was assessed (chapter 4). Thirdly, a two by two within-subjects study design was performed to assess the effect of a single bout of light intensity aerobic exercise on multiple

constructs of executive function and a mechanistic understanding of this effect was sought using transcranial magnetic stimulation (TMS) measures of short-term neuroplasticity and serum levels of insulin-like growth factor-1 (IGF-1) and cortisol (chapter 5). Lastly, the association between self-reported physical activity and perceived cognitive health was studied in a nested case control study from a larger cohort of participants enrolled in the Barcelona Brain Health Initiative (chapter 6).

In chapter 3, results from the systematic review revealed that very few (6) studies had assessed the effect of aerobic exercise on cognitive recovery post-TBI and numerous issues with this type of research pose challenges to studying the effect of exercise on cognitive recovery in the sub-acute phase of moderate-to-severe TBI. Consequently, the study in chapter 4 was designed and performed. Results from this chapter reported the feasibility of including 8-weeks of 1-hour sessions of aerobic exercise into the sub-acute rehabilitation from moderate-to-severe TBI on top of standard rehabilitation that includes cognitive training. Poor correlations between heart rate reserve (HRR) and perceived exertion were seen however and only 2 individuals exercise within target heart rate zones of 50-70% HRR. The apparent inability of individuals with moderate-to-severe TBI to exercise at the higher intensities (50-70% heart rate reserve (HRR)) lead to the study design of chapter 5. This chapter found that whilst light aerobic exercise modulates intracortical facilitation and multi-tasking performance in healthy adults, exercise-mediated changes in spatial working memory and intracortical inhibition were seen in individuals with mild TBI. No changes in IGF-1 were seen at any time point in either group. Lastly, chapter 6 demonstrated that being physically active, compared to being insufficiently active, was associated with an increased odds of reporting good global health in those with and without a history of TBI. Additionally, in those with a history of TBI, this physical activity classification was associated with an increased odds of reporting good cognitive health also.

The study of the therapeutic benefit of aerobic exercise in the recovery of cognitive function post-TBI is in its infancy yet there is a growing body of evidence supporting its feasibility and potential efficacy. Whilst the optimal parameters of exercise are under debate, its use at different time points post-injury appear to be pragmatic and potentially beneficial. The efficacy of its therapeutic use in the sub-acute phase of injury should be studied yet methodological issues need to be overcome. The underlying biological mechanisms of its effect appear complex but highlight the window of opportunity for the optimization of different parameters. Finally, its efficacy across the lifespan following a TBI appears pragmatic yet how to improve adherence to a physically active lifestyle is an important issue in need of study.

List of Included publications

1. Morris, T., Gomes-Osman, J., Costa Miserachs, D., Tormos Muñoz, J.M., and Pascual-Leone, A. (2016). The Role of Physical Exercise for Cognitive Recovery After Traumatic Brain Injury: A Systematic Review. *Restorative neurology and neuroscience, 34 (2016) 977-988. DOI 10.3233.*

2. Morris, T., Costa Miserachs, D., Roriguez, P., Finestres, J., Bernabeu, M. Gomes-Osman, J., Pascual-Leone, A., and Tormos Muñoz, J.M. Physical Exercise and Cognitive Recovery After Moderate-to-Severe Traumatic Brain Injury: A Case Series Report. *Journal of neurologic physical therapy, accepted 08/04/2018.*

Abbreviations

Abbreviations are defined here and at first use within the thesis. The abbreviation is used on each occasion thereafter, unless defined again at first use within a published or submitted chapter. (chapters 3 or 4 or 5)

aMT: Active motor threshold
ATP: Adenosine triphosphate
BDNF: Brain derived neurotrophic factor
CMRglc: Cerebral metabolic rates for glucose
CREB: cAMP response element binding protein
DAI: Diffuse axonal injury
DAMP: Damage-associated molecular pattern molecules
EEG: Electroencephalography
EMG: Electromyography
HR: Heart rate
HRR: Heart rate reserve
ICF: Intracortical facilitation
IGF-1: Insulin-like growth factor-1
LTD: Long term depression
LTP: Long term potentiation
MAG: Myelin-associated glycoprotein
MEP: Motor evoked potential
NOGO-A: Neurite outgrowth inhibitor
ppTMS: paired pulse TMS
rMT: Resting motor threshold
rTMS: repetitive TMS
spTMS: single pulse TMS
SICI: Short interval intracortical inhibition
TBI: Traumatic brain injury
TMS: Transcranial magnetic stimulation

Contents

Chapter 1

Introduction

The benefits of physical activity for health have been considered since the time of Plato and Hippocrates who both believed that a bidirectional relationship between physical activity and health and physical inactivity and disease existed. After a brief period in the mid 20th century where physical activity was believed to be detrimental to health, seminal epidemiological studies in the 1960's showed that the incidence of coronary heart disease and sudden cardiac death was much lower in London's bus conductors (climbing roughly 500-750 steps per day) compared to their drivers (spent the day sedentary) (J. N. Morris, Kagan, Pattison, Gardner, & Raffle, 1966). Similarly, a reduced incidence of both cardiovascular conditions was shown in physically active postal workers a few years later (Fox & Haskell, 1968). Currently, the recommended dose of physical activity for general health benefits are at least 150-minutes of moderate-to-vigorous physical activity per week. Adhering to these guidelines is associated with a 20-30% lower risk of all-cause mortality and incidence of multiple chronic diseases (figure 1).

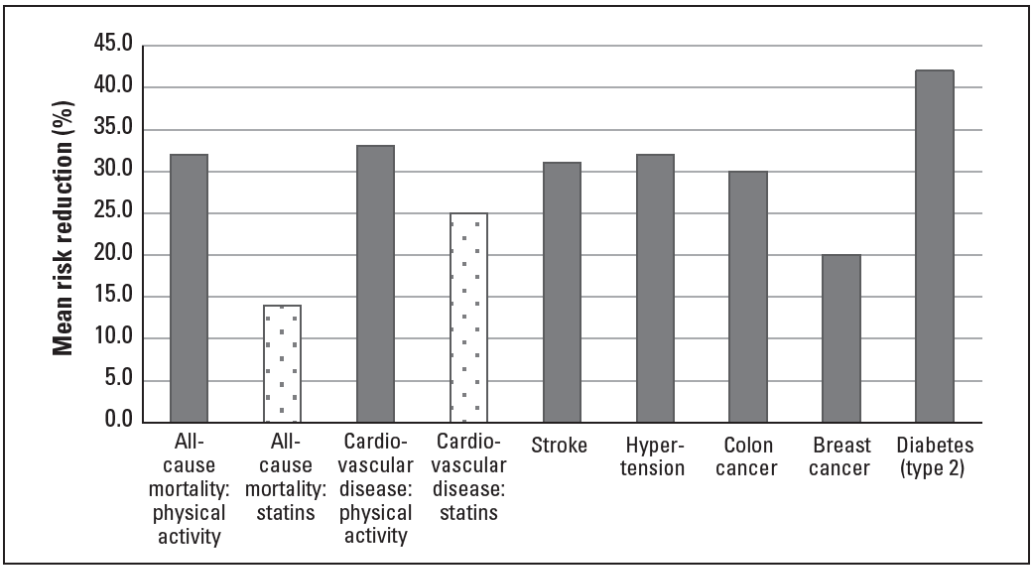

Figure 1. Mean risk reduction for all-cause mortality and other health conditions associated with physical activity. Taken from McKinney at al., 2016.

Beyond general health benefits, a link between physical activity brain health has also been drawn. In a seminal study in 1999, Blumenthal and colleagues reported that physical exercise was similarly efficacious as the leading pharmaceutical for the treatment of depression in older adults (Blumenthal et al., 1999). More importantly, the same group found, that at 10-weeks follow-up, those who continued to exercise regularly had significantly reduced probability of depression diagnosis, regardless of initial treatment group (Babyak et al., 2000). In the past two decades, much research has extended this study and has showed that regular participation in physical activity/exercise (see box 1 for definitions) has both neuro-restorative and neuroprotective effects on the brain.

Box 1. Definitions of various exercise related terminology

- **Physical activity:** Any bodily movements using large muscle groups that increases energy expenditure beyond resting levels.
- **Physical exercise:** Planned structured and goal-orientated physical activity designed to improve or maintain physical fitness**.** Often involves aerobic systems.
- **Cardiorespiratory fitness:** The body's ability to inhale, circulate and utilise oxygen during exercise. Gold standard measure is $V0_{2max,}$ expressed as the maximum amount of oxygen consumption in 1 minute per kilogram of body weight [mL • Kg • min^{-1}]. *Therein referred to as 'fitness'.*
- **Hear rate reserve**: Predicted maximum heart rate minus resting heart rate. Often used to calculate target heart rate zones to exercise at different intensities by using the Karvonen equation ((heart rate reserve * training%)+ resting heart rate)
- **Borg scale**: Rating scale with verbal and number anchors based on the physical sensations a person experiences during exercise, including increases in heart rate.
- **Light intensity exercise:** Equivalent to 40-60% of heart rate reserve maximum heart rate-resting heart rate) or 10-12 of Borg scale of ratings of perceived exertion. Has small effects on cardiorespiratory fitness
- **Moderate to vigorous intensity exercise:** Equivalent to 60-80% HRR or 14-16 on Borg scale.

The recent Lancet commission (Livingston et al., 2017) on dementia reported that mid-life physical activity represents a modifiable lifestyle factor capable of reducing the risk of neurodegeneration and the extant literature contains many systematic reviews and meta-analyses on the effect of physical exercise on cognitive function in older adults (Colcombe &

Kramer, 2003), adolescents (Hillman, Erickson, & Kramer, 2008) and those with neurodegenerative disease (Eggermont, Swaab, Hol, & Scherder, 2009; La Rue, Felten, & Turkstra, 2015). These reviews and analyses show consistent improvements in multiple cognitive function domains following physical exercise programs of varying durations and types. Colcombe and Kramer (Colcombe & Kramer, 2003) showed that the most consistent exercise-induced improvement in cognitive function falls in the executive function domain. More recently a comprehensive systematic review (Gomes-Osman, J et al., 2018) of the effect of physical exercise on cognitive function in older healthy adults and those with diagnoses of mild cognitive impairment or dementia aimed at understanding dose-dependent effects of exercise on cognitive function revealed two pertinent findings: (1) exercise is associated with consistent improvements in global cognition (Mini mental status exam and others), processing/speed, attention and executive functions and (2) that 52 total hours and 1 hour session durations are consistently associated with improvements in these cognitive domains (Gomes-Osman, J et al., 2018).

Advances in neuroimaging have allowed us to gain a greater understanding of the neurobiological substrates of exercise and changes in the brain. Positive associations have been seen between adults with high fitness levels, a biproduct of physical exercise, and greater fractional anisotropy in a multitude of white matter tracts, including the corpus callosum, cingulum, superior corona radiata and inferior longitudinal fasciculus (Hayes, Salat, Forman, Sperling, & Verfaellie, 2015; B L Marks, Katz, Styner, & Smith, 2011; Oberlin et al., 2016a; Sexton et al., 2016b), with the greatest changes seen in prefrontal regions (M. Voss et al., 2013). Furthermore, a longitudinal study found that lifelong exercise is positively associated with the preservation of white matter integrity (Tseng et al., 2013), together suggesting exercise is associated with and capable of maintaining white matter microstructure integrity, across a

lifespan. Further, positive associations between exercise and hippocampal volume have been shown, in both older and middle-aged adults (Erickson et al., 2009, 2011a; Thomas et al., 2016b). Physical exercise has also been shown to improve intraregional functional connectivity in various association networks, although, most notably in the default mode network (Johnson et al., 2016; M. W. Voss et al., 2016). Where, in adolescents, physical fitness may positively impact functional connectivity between the hippocampus and the DMN during memory coding (Herting & Nagel, 2013). Additionally, exercise has been shown to preserve neural tracts connecting the pre-frontal cortices with other cortical areas (Bonita L Marks et al., 2007).

The potential therapeutic value of physical exercise in the neurorehabilitation settings for recovery from acquired neurological injury and disease is currently being studied. Recent publications have shown the potential beneficial effects of exercise programs in diverse populations from multiple sclerosis (Sandroff, Motl, Scudder, & DeLuca, 2016) to stroke (Austin, Ploughman, Glynn, & Corbett, 2014; Marzolini, Oh, McIlroy, & Brooks, 2013) and traumatic brain injury (TBI) (Lisa M Chin, Keyser, Dsurney, & Chan, 2015). This thesis concerns the use of physical exercise in traumatic brain injury and its potential therapeutic value in cognitive recovery. As later chapters show, the use of physical exercise for cognitive recovery in traumatic brain injury is relatively novel and gaps in the literature regarding mechanisms of action, optimal parameters of exercise and feasibility of its use in sub-acute moderate-to-severe TBI exist. This thesis focuses on the preceding points.

1.1 Incidence and prevalence of traumatic brain injury (TBI)

Acquired brain injuries (ABI) are classified as injuries caused by or related to events at any time after birth. These include, amongst others, stroke and TBI. TBI is becoming a global health concern. Recent epidemiological studies in Europe show that TBI has an overall incidence of

approximately 262 cases per 100,000 every year and is most prevalent in those under 25 years of age and above 75 years of age, therefore impacting individuals at different times in a human lifespan (Peeters et al., 2015). The long-lasting consequences for survivors of TBI are devastating and constitute cognitive, behavioural and sensorimotor disabilities that can lead to many social, personal and economic burdens. In the US alone, an estimated 3.2 million Americans live with residual effects of TBI (Benedictus, Spikman, & van der Naalt, 2010a; Corrigan, Selassie, & Orman, 2010a). For example, studies reporting on return to work statistics in young individuals with TBI show poor outcomes. Following TBI, a mere 40% of individuals return to work within 1-year of their injury (van Velzen, van Bennekom, Edelaar, Sluiter, & Frings-Dresen, 2009a). One study found that in moderate to severe TBI patients, cognitive impairment was a major statistical predictor for return to work statistics (Benedictus et al., 2010a) and at 1-year post-injury, cognitive impairment was more common than physical limitations. Furthermore an increased risk of dementia has also been highlighted as a consequence of TBI (Kaup, Barnes, & Yaffe, 2015).

1.2 Cognitive impairment following TBI

Behavioural impairments such as an inability to initiate activity and deficits in self-awareness and self-monitoring pose serious challenges to the rehabilitation process and are common following TBI. Apathy is also prevalent (Starkstein & Pahissa, 2014) which not only can affect rehabilitation but can lead to social withdrawal and neglect of self-caring activities. Additionally, an inability to recognise the existence of injury can pose challenges to rehabilitation processes. Improvements in self-awareness are seen during recovery, such as the ability to recognise injury, but such improvements may still cause problems. For example

individuals may recover the ability to recognise their injury but may still fail to correctly estimate their ability to function (Sherer et al., 1998).

Beyond behavioural deficits, cognitive dysfunction is common post-TBI. A meta-analysis on the time course of these deficits suggest that in mild TBI, cognitive function can be restored to baseline levels some 1 to 3 months post-injury (Schretlen & Shapiro, 2003). Whereas in moderate-to-severe TBI, although in the first 2 years post-injury, significant improvements are seen, cognitive impairment can persist in individuals beyond the 2 year mark (Schretlen & Shapiro, 2003), and even up to as much as 10 years post injury (Draper & Ponsford, 2008). Albeit, improvements in cognitive function can be seen during 5 years post-injury in more severe TBI (Corrigan, Selassie, & Orman, 2010b).

The relationship between the cognitive squeal and the severity of the TBI appears to be linear and in one study the duration of loss of consciousness was predictive of the extent of cognitive dysfunction (S. Dikmen, Machamer, Richard Winn, & R. Temkin, 1995). The most common cognitive domains affected by TBI include memory, attention, processing speed and executive functioning (Rabinowitz & Levin, 2014). Executive dysfunction can be particularly disruptive as impairments in this domain can cause disruptions in other related domains, such as memory and top-down control of attention (Rabinowitz & Levin, 2014). Executive function is characterised by multiple distinct cognitive domains and executive dysfunction post-TBI may include impairments in communication, visuospatial processing, intellectual ability, awareness of deficit, decision making and reasoning (Ruff et al., 1993). Together, the cognitive dysfunction profile following TBI can have serious consequences regarding returning to work and health related quality of life (Benedictus, Spikman, & van der Naalt, 2010b).

Consequently, cognitive impairment following TBI is of great concern and novel strategies to improve and enhance recovery is fundamental in the rehabilitation process. The aetiology of cognitive dysfunction after TBI is not well understood but is likely related to the secondary injury mechanisms that are initiated in the seconds to minutes after the initial injury.

1.3 Pathophysiology of TBI

TBI can be classified by severity, usually measured by a scale (see box 2) such as the Glasgow Coma Scale (GCS) and/or post-traumatic amnesia (PTA) duration, by mechanism of injury, such as penetrating or closed-head injury or by region, such as the orbitofrontal, temporal polar or occipital regions.

Box 2. Definitions of TBI severity classification

- **Glasgow coma scale:** system used to assess coma and impaired consciousness, with components assessing eye opening, verbal responses and motor responses.
- **Post traumatic amnesia:** Interval from injury until the patient is oriented, often measured by the Galveston Orientation and Amnesia Test (Levin et al., 1979).
- **Mild TBI:** Traumatically induced physiological disruption of brain function manifested by one of more of the following: any loss of consciousness up to 30 minutes; any loss of memory for events immediately before or after event for up to 24h; any alteration in mental state at time of accident; GSC of 14/15 and PTA of <24 hours
- **Moderate TBI**: GCS of 9-13, PTA >24 hours
- **Severe TBI**: GCS of 3-8, PTA >24 hours

Focal and diffuse damage following TBI

The primary injury following TBI can produce both focal and diffuse damage and the severity of the injury can be the result of a complex mix of the two. Two main mechanisms are thought to be involved in TBI: direct contact and acceleration-deceleration. The former may result from

objects striking the external head or from the brain making forceful contact inside the skull. Such injuries can produce skull fractures as well as extradural and subdural hematomas and hematomas inside the parenchyma (Graham, McIntosh, Maxwell, & Nicoll, 2000). Diffuse multifocal injuries due to sudden acceleration-deceleration will impart shear tensile compressive strains and lead to diffuse axonal (DAI) injury and diffuse vascular injury (D. H. Smith, Meaney, & Shull; Werner & Engelhard, 2007a). DAI is universally common in TBI (J. H. Adams et al., 1989) and leads to disruption of both structural as well as functional connections, disconnecting large-scale brain networks leading to network dysfunction and cognitive impairment (Sharp, Scott, & Leech, 2014). The regional distribution of injury is important when profiling the associated cognitive impairment. Structural disconnection following injury will lead to functional network disruption. For example, reduced white matter integrity due to injury correlates with reduced information processing speed as well as executive function (Spitz, Maller, O'Sullivan, & Ponsford, 2013) and learning and memory (Strangman et al., 2012). At the same time injury leads to increased activity in the default mode network, who's failure to deactivate during tasks, is related to reduced inhibitory control (Bonnelle et al., 2012) and visual attention (Kim et al., 2009). The effects of DAI however are most likely much more complicated, as the brain functions as a constantly changing global unit, constrained by white matter connections, even damage to a single white matter tract can lead to diverse functional effects (Honey et al., 2009).

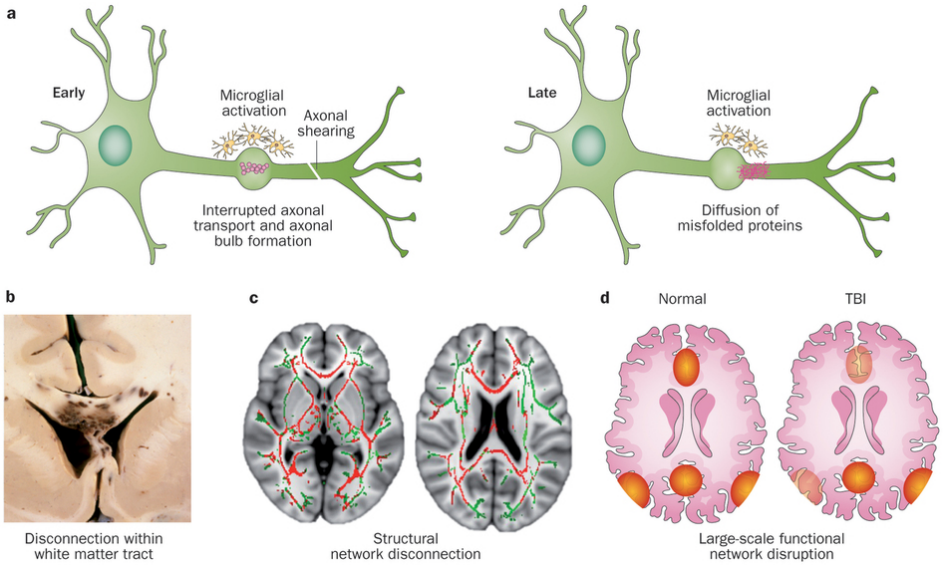

Figure 2. Structural and functional damage following TBI. Image from Sharp et al., 2014.

Cellular damage

In the seconds to minutes following the initial injury a complex interplay of mechanisms is initiated that can last for weeks to months and even years following the injury (figure 2). The degree to which each mechanism plays a part and the temporal sequence of such mechanisms play an important and complex role in determining the extent of injury and its impact on cognitive function and quality of life.

First, blood brain barrier permeability and direct membrane damage to cell bodies and blood vessels from cerebral haemorrhage causes excessive glutamate release and glutamate excitotoxicity (Bullock et al., 1998; Faden, Demediuk, Panter, & Vink, 1989). This leads to NMDA-dependent depolarizing post-synaptic potentials and neuronal and glial depolarisation. In parallel, cerebral ischemia due to a reduction in cerebral blood flow leads to oxygen deprivation and glucose delivery, causing an imbalance in cerebral oxygen delivery and consumption, indicative of metabolic stress. To maintain homeostasis there is an increase in energy demand, which depletes adenosine triphosphate (ATP) stores and leads to an

uncoupling of cerebral blood flow and glucose (Hovda, Yoshino, Kawamata, Katayama, & Becker, 1991). The subsequent inability to maintain basal ionic gradients leads to mitochondrial dysfunction and enhanced oxidative stress. The reduction in ATP stores contributes to the NMDA-dependant depolarising post-synaptic potentials and a massive influx of intracellular calcium as well as sodium and potassium fluxes. The intracellular calcium influx activates many downstream effectors such as cytokine release initiating inflammatory processes, calpain proteolysis and cellular collapse as well as caspase activation that leads to apoptosis and programmed cell death (Werner & Engelhard, 2007a). The sodium and potassium fluxes cause a compensatory ionic gradient increase in sodium and potassium ATPase activity which in turn increases metabolic demand and contributes to the enhanced oxidative stress. The enhanced oxidative stress leads to reactive oxygen species overproduction with increases in free radicals, hydrogen peroxide, nitrogen species (inducible and neuronal) as well as lipid peroxidation (H. Bramlett & Dietrich, 2014) . This, via peroxidation of cellular and vascular structures, protein oxidation, DNA cleavage and inhibition of the mitochondrial transport chain leads to both immediate cell death as well as apoptosis and inflammation (H. M. Bramlett & Dietrich, 2004).

In the later stages, prolonged reductions in cerebral blood flow occur which compromise the delivery of oxygen and glucose and allows the potential build-up of toxic substances (H. M. Bramlett & Dietrich, 2004). This, plus the increased NMDA-dependant excitotoxicity, increased calcium and potassium fluxes, related mitochondrial dysfunction and activation of intracellular proteases, result in reduced ATP production and increased cerebral metabolic rates for glucose (CMRglc). The increase in CMRglc most likely represents an increase in glycolysis in an attempt to restore energy balance as a result of metabolic and ionic changes (Hovda et al., 1991; Scafidi et al., 2009). Subsequently, cellular energy stores will deplete as cerebral

blood flow may not be capable of meeting the required energy demands and will result in an uncoupling between glucose and blood flow (Bergsneider et al., 2000).

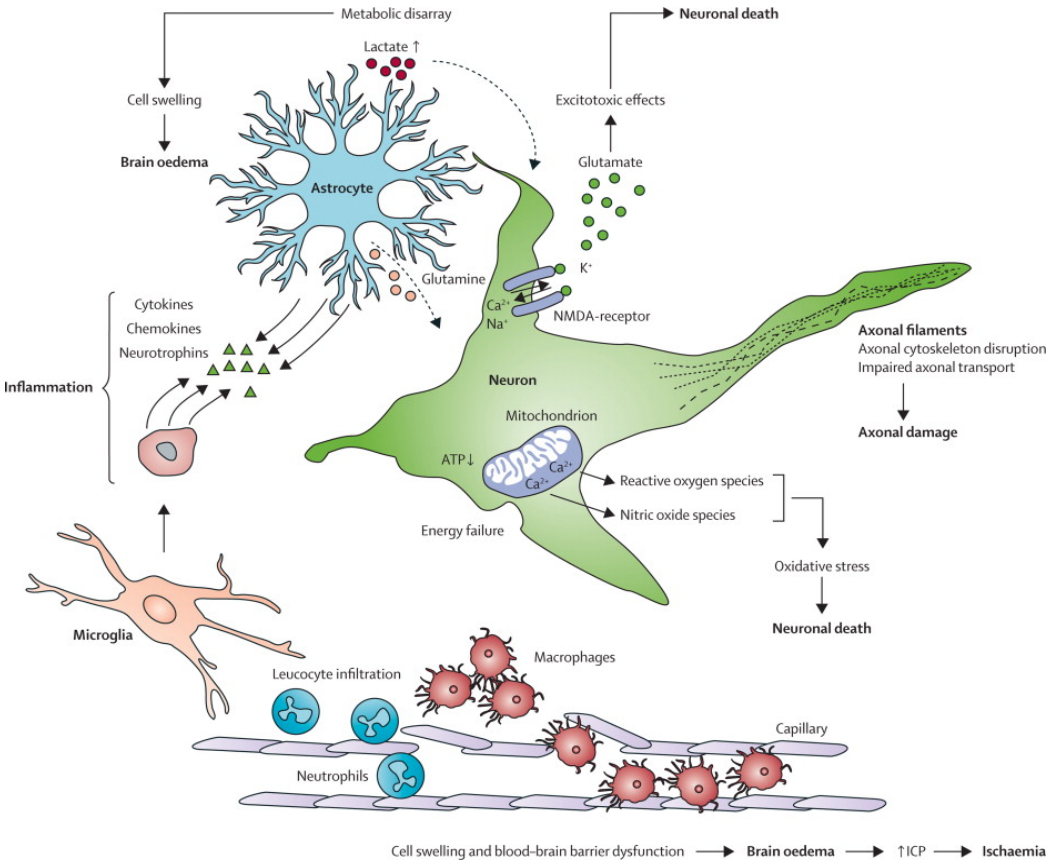

Figure 3. The pathophysiology of TBI. Image from (Rosenfeld et al., 2012)

Inflammation

Accompanying the secondary injury period is a coordinated immune response to trauma. Previously it was thought that the brain was an 'immune privileged' site with only resident microglia having access to the blood brain barrier-protected brain, however it is now recognised that activated immune cells can indeed access the intact brain (Hickey, Hsu, & Kimura, 1991) and after injury and blood brain barrier breakdown, a massive infiltration of immune cells into the brain parenchyma is seen (Walsh & Kipnis, 2011). Increases in intracellular calcium levels release pro-inflammatory cytokines, interleukin-1 alpha and beta

tumour necrosis factor and tnterleukins 6,8,11 (Werner & Engelhard, 2007a). Following TBI, these inflammatory cytokines produce alarmins (damage-associated molecular pattern molecules, or DAMP's) who are released by cells undergoing non-apoptopic cell death and who activate a sterile immune response designed to restore homeostasis (Manson, Thiemermann, & Brohi, 2012). A sterile immune response is a double-edged sword however, as, on one hand it plays a key role in host defence, thus a seemingly neuroprotective mechanism, but on the other, it is imprecise and, depending on severity and duration of injury, can become maladaptive causing collateral tissue damage (Rock, Latz, Ontiveros, & Kono, 2010). ATP release from damaged cells can act as a DAMP which, via purinergic receptor activation can elicit a sterile immune reaction augmenting neuroinflammation. However, this is usually dampened over time via a two-step process that turns the extracellular ATP into adenosine, via astrocyte and microglia activation (Corps, Roth, & McGavern, 2015).

Within minutes following tissue damage, purinergic receptor, astrocyte and ATP-dependant actions elicit an increase in microglia activation and movement of microglia to the glia limitans (Corps et al., 2015; Davalos et al., 2005). The glia limitans is composed of astrocytic foot processes and lies below the pia matter to form a barrier between the cerebro-spinal fluid and underlying parenchyma. In response to cell death some microglia transform into jellyfish-like phagocytic cells and insert themselves into the glia limitans in place of dead astrocytes to form a phagocytic protective barrier. Thus, microglia in the acute stage following injury not only clean-up debris from the injured brain but also help maintain glia limitans integrity (Corps et al., 2015). Furthermore, tissue damage within the parenchyma will induce a rapid increase of neutrophils at the damaged meninges via the choroid plexus. ATP release will activate the inflammasome via purinergic receptors to allow neutrophils to interact with dead cells, overall being neuroprotective (Corps et al., 2015). However, neutrophils have the capacity to break

down the blood-brain barrier via the release of metalloproteinases, proteases, tumor necrosis factor *a* and reactive oxygen species (Scholz, Cinatl, Schädel-Höpfner, & Windolf, 2007). Upon infiltration to the brain parenchyma, neutrophils have the capacity, through the same mechanisms that gained them entry, to induce neuronal cell death (Nguyen, O'Barr, & Anderson, 2007).

Synaptic plasticity and TBI

Hebb in 1949 proposed his theory of synaptic modification that suggested that information, the engram of memory, in response to internal and external stimulation is stored in the synapse. He proposed that synapses between cells were strengthened when those cells were active at the same time, coining the term, "cells that fire together wire together". In the 1970's researchers, including Bliss and Lomo, provided evidence for Hebb's theories in their descriptions of LTP and LTD, suggesting that they represent long-lasting synaptic plasticity related to memory consolidation (Bliss & Collingridge, 1993; Hölscher, 1999).

Animal models have characterised changes in LTP and LTD synaptic plasticity following TBI. *In vivo* electrophysiological recordings of CA1 hippocampal neurons have shown reduced excitatory post-synaptic potentials (EPSPs) in injured animals as well as reduced LTP in population spike responses to EPSPs (Miyazaki et al., 1992). In another *in vivo* study using electrophysiological recordings, Reeves and colleagues (Reeves, Lyeth, & Povlishock, 1995) found increased cellular excitability 2 days after injury and that LTP was significantly impaired in injured animals. In two *in vitro* studies LTP was impaired in hippocampal slices following lateral fluid percussion models of TBI (D'Ambrosio, Maris, Grady, Winn, & Janigro, 1998; Sick, Pérez-Pinzón, & Feng, 1998).

In human studies, non-invasive brain stimulation techniques, specifically transcranial magnetic stimulation (TMS) has been used to characterize cortical excitability and plasticity changes following TBI. Abnormal cortical excitability has been reported on with differences in short interval intracortical inhibition (Lapitskaya, Moerk, Gosseries, Nielsen, & de Noordhout, 2013) and central motor conduction time (Chistyakov et al., 2001) compared to non-injured adults. Bernabeau and colleagues (Bernabeu et al., 2009) reported that patterns of cortical inhibitory/excitatory impairment in the motor cortex of those with TBI are differential whereby alterations in excitability were greater in the presence of motor impairment and increased in severity with severity of DAI. Yet the coexistence of focal lesions was not associated with degree of impairment. In a case series study from Trembaly and colleagues (Tremblay, Vernet, Bashir, Pascual-Leone, & Theoret, 2015a) abnormal LTD-like synaptic plasticity as measured by continuous theta-burst stimulation was reported soon after mild TBI.

Compensatory mechanisms

Beyond the neurochemical processes, cortico-cortical and cortico-subcortico-cortical interactions compensate for lost networks due to both focal and diffuse axonal injury by structural reorganisation through mechanisms of plasticity. Dendritic absorption and synaptic plasticity possibly unearth previously dormant networks or parallel circuits originating from undamaged contralateral areas, allowing unaffected regions to perform the tasks of damaged areas (A Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Further compensatory mechanisms are also activated following the initial lesion. GABA, the central nervous systems primary inhibitory neurotransmitter is up-regulated in the acute phase of injury (Palmer, Marion, Botscheller, Bowen, & DeKosky, 1994), and either inter or intra-hemispherical inhibition of the peri-lesional site of injury occurs, limiting the hyper-excitability cascade. However, long term adaptation of these compensatory mechanisms may be maladaptive at the behavioural

level. For example, maintenance of GABA-mediated inhibition into the sub-acute phase has been linked with functional disability (Kobori & Dash, 2006).

1.4 New therapeutic approach

The multifaceted nature of TBI involves primary and secondary injury mechanisms combining both focal and diffuse injury patterns. This complex series of events, shows major heterogeneity, limiting the success of standard rehabilitation techniques (Saatman et al., 2008). Many treatments for TBI focus on reducing neuronal death with the acute administration of neuroprotective agents shortly after injury (Talley Watts et al., 2014). Nevertheless, to-date, 100% of new drug trials for TBI have failed. Given the chronic nature of TBI-related histological and functional alterations, it is necessary to search for additional therapeutic approaches that are capable of reducing the long-term sequalae of brain damage. Accordingly, physical exercise an inexpensive, easily administered and long-term treatment option has recently gained attention.

1.5 Exercise and Animal models of TBI

Physical exercise has the potential to modulate both the pathophysiological changes and cognitive recovery following TBI, and the vast majority of evidence for this has come from animal models (Chytrova, Ying, & Gomez-Pinilla, 2008; Grace S Griesbach, Gómez-Pinilla, & Hovda, 2007; Itoh et al., 2011; Jacotte-Simancas et al., 2015; Piao et al., 2013). The mechanisms by which exercise modulates recovery following TBI are likely multi-fold.

Exercise seems capable of up-regulating a variety of plasticity-related growth factors following

TBI such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1), as well as related proteins synapisin-1 and cyclic-AMP-response-element-binding protein (CAMP) (Grace S Griesbach et al., 2007; Grace Sophia Griesbach, Gomez-Pinilla, & Hovda, 2004; Grace Sophia Griesbach, Hovda, & Gomez-Pinilla, 2009; Piao et al., 2013). IGF-1 may play a crucial role in both the cognitive and physiological recovery from TBI as it has been implicated in exercise-induced angiogenesis (Ding, Vaynman, Akhavan, Ying, & Gomez-Pinilla, 2006a; Lopez-Lopez, LeRoith, & Torres-Aleman, 2004) and neurogenesis (Carro, Trejo, Busiguina, & Torres-Aleman, 2001; Trejo, Carro, & Torres-Aleman, 2001a) in heathy brains, as well as stimulating the up-regulation of BDNF (Carro et al., 2001; Ding et al., 2006a). Following injury significant influx of IGF-1 towards the lesion site is seen (Schober et al., 2010) and concomitantly a reduction in GH production, likely via damage to the pituitary gland resulting in hypopituitarism (Wagner et al., 2010; Zgaljardic et al., 2011). Studies have suggested that exercise can stimulate increases in IGF-1 (Cappon, Brasel, Mohan, & Cooper, 1994; Schwarz, Brasel, Hintz, Mohan, & Cooper, 1996) and that IGF-1 is a primary mediator of exercise effect on synaptic plasticity (Llorens-Martín, Torres-Alemán, & Trejo, 2009). BDNF has been widely implicated in a variety of exercise-induced benefits on the brain including the promotion of synaptic plasticity in the form of long-term potentiation (LTP) (Farmer et al., 2004). Given the reduced synaptic plasticity found in the acute phase of TBI (Tremblay, Vernet, Bashir, Pascual-Leone, & Theoret, 2015b) and the aberrant synaptic plasticity in the sub-acute to chronic phases of injury (De Beaumont, Tremblay, Poirier, Lassonde, & Théoret, 2012), this may be an important mechanism by which PE exerts its positive effects. Further, hippocampal neurogenesis, blockade of myelin inhibitors myelin associated glycoprotein (MAG) and neurite outgrowth inhibitor (NOGO-A), as well as the promotion of cognitive function have all been shown to be BDNF-dependent (Chytrova et al., 2008; Grace S Griesbach et al., 2007; Grace Sophia Griesbach et al., 2009; Kuipers et al.,

2016).

Additionally, exercise has been shown to increase neurogenesis in the dentate gyrus of the hippocampus and promote neuronal survival (Jacotte-Simancas et al., 2015; Piao et al., 2013; Van der Borght, Havekes, Bos, Eggen, & Van der Zee, 2007), with the number of new and mature neurons during exercise correlating with an improvement in memory acquisition and retention on an object recognition memory task (Jacotte-Simancas et al., 2015; Van der Borght et al., 2007).

Exercise has been shown to reduce neuronal degeneration and inhibit both neuronal apoptosis, resulting in improvements in spatial memory (Itoh et al., 2011) and the TBI-induced up-regulation of MAG and NOGO-A (Chytrova et al., 2008). Exercise also seems capable of reducing lesion volume size, both in the lateral ventricle and hippocampal formation (Jacotte-Simancas et al., 2015; Piao et al., 2013), as well as down-regulating microglia-associated pro-inflammatory processes and promoting an anti-inflammatory immune response, which correlate with improvements in both working memory and spatial memory performance (Piao et al., 2013).

Despite pragmatic results, differences in methodologies regarding type, intensity, duration and timing of initiation, have revealed conflicting results. Although both acute and chronic exercise have both shown positive results in reducing cognitive deficits following TBI some studies have reported that induction of exercise in the acute phase following TBI can have detrimental effects (Crane et al., 2012), with TBI animals performing worse on complex cognitive tasks when exercise was initiated shortly after the injury. However, when exercise is initiated a few days after TBI (3-4 days) benefits are generally seen. For example, Itoh and colleagues (Itoh

et al., 2011) found that early (for 7 consecutive days following the lesion) forced exercise (treadmill) had profound effects on increasing anti-apoptopic pathways, neurogenesis and survival and maturation of novel neurons (NeuN positive cells), as well as on BDNF and nerve growth factor levels. All these changes may have contributed to the increased spatial memory performance found in the exercise group. Furthermore, Jacotte-Simancas and colleagues (Jacotte-Simancas et al., 2015) found that voluntary physical exercise (running wheel), initiated 4 days post-injury, reverted the severe deficits in long-term (24 h) object recognition memory, induced by TBI. Exercise also had neuroprotective effects in the same study with a reduction in neuronal loss within the hilus of the dentate gyrus and in the perirhinal cortex and an increase in cell proliferation (BrdU+ cells) and neurogenesis (BrdU+-DCX+ cells). Moreover, there was a positive correlation between the number of BrdU+-DCX+ cells and performance in the memory task, indicating that the novel neurons born during physical exercise may have contributed to memory recovery. In contrast, Piao and colleagues (Piao et al., 2013) found that physical exercise initiated one week post-injury had detrimental effects. It has not been established whether the positive effects of exercise seen in some studies after early physical exercise are still effective if this treatment is administered with a long delay, akin to what some individuals with TBI would require. One study (Piao et al., 2013) found very promising effects of exercise initiated 5 weeks post injury. Effects included reductions in lesion size, up-regulation of alternative inflammatory mediators interleukin-6 and interleukin-10 (which can limit the neurotoxicity of the 'classic' inflammatory response), increases in BDNF and CREB, enhanced survival of new neurons and improved non-spatial hippocampal learning and memory, assessed by object recognition memory testing. This study was in concurrence with another study by Grieshbach and colleagues (Grace S Griesbach et al., 2007) who showed that BDNF and its downstream effectors were only up-regulated by exercise if it was initiated with a delay of 30 days. In contrast, Chen and colleagues (M.-F. Chen et al., 2013) found that

physical exercise was only effective to reduce memory deficits when the treatment was started soon after the lesion, but not when exercise initiation was delayed.

Consequently, the parameters of exercise regarding timing and intensity appear to be fundamental in the effect of exercise in the recovery from TBI. Yet in humans our understanding of these differential effects is limited. Indeed, the study of physical exercise for cognitive function post-TBI in humans is in its infancy.

Chapter 2

Objectives

The general objective of this thesis is to gain global insights into the potential use of physical exercise in cognitive recovery following TBI. With this general objective in mind, four specific objectives were set that have been worked on using different approaches.

Firstly, the animal literature shows that dedicated physical exercise programs may improve cognitive function in individuals with TBI. The ***first aim*** of this thesis was therefore to gain an up-to-date understanding of the extant literature on the topic of physical exercise and cognitive recovery in human individuals with TBI (chapter 3).

Chapter 3 highlighted that the sub-acute phase of moderate-to-severe TBI is characterised by concomitant extracranial physical injuries, apathy and behavioural issues that may hinder participation in and adherence to an aerobic exercise program when traditional cognitive and physical rehabilitation therapies are being performed. The ***second aim*** of this thesis was therefore to assess the feasibility of implementing an 8-week aerobic exercise program into sub-acute rehabilitation from moderate-to-severe TBI, within the neurorehabilitation setting (chapter 4).

Both the animal TBI and human literature show that exercise parameters, specifically intensity of exercise, are significant moderators of the effect of exercise on cognitive function. Chapter 4 raised the possibility that TBI populations may not be able to reach higher exercise intensities and little is known about the effects of light aerobic exercise on cognitive function, even in healthy adults. Additionally, how exercise impacts cognitive function is unclear, and an understanding of the underlying biological mechanisms of the effect will aid in the optimisation of these protocols. The ***third aim*** of this thesis was to assess the effects of a single bout of light

aerobic exercise on TMS measures of short-term neuroplasticity, blood biomarkers (IGF-1 and cortisol) and executive functions (chapter 5).

Aerobic exercise early after injury appears to be important but residual long-term deficits following a TBI can be prevalent. Consequently, aerobic exercise across the lifespan following a TBI may be fundamental in the long-term maintenance of global and cognitive brain health. The ***fourth and final aim*** of this thesis was to assess the association between self-reported physical activity levels and perceived cognitive health in community-dwelling adults aged 40-65 with a history of TBI with loss of consciousness (chapter 6).

Together, this thesis aimed to use different scientific study approaches (systematic review, translational and clinical and observational) to (1) assess the state of the literature regarding the effect of physical exercise on cognitive recovery in individuals with TBI (2) assess the feasibility of introducing physical exercise programs into sub-acute rehabilitation from moderate-to-severe TBI (3) assess the underlying mechanisms of physical exercise on cognitive function and (4) assess the relationship between physical activity and cognitive health in community dwelling individuals with a history of TBI.

Chapter 3

Experimental work

The role of physical exercise in cognitive recovery after traumatic brain injury: A systematic review

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The Role of Physical Exercise in Cognitive Recovery After Traumatic Brain Injury: A Systematic Review.

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Abstract

Background: There is a growing body of evidence revealing exercise-induced effects on brain structure and cognitive function across the lifespan. Animal models of traumatic brain injury also suggest exercise is capable of modulating not only the pathophysiological changes following trauma but also the associated cognitive deficits. **Objective:** To evaluate the effect of physical exercise on cognitive impairment following traumatic brain injury in humans. **Methods:** A systematic search of the PubMed database was performed using the search terms “cognition” and “executive function, memory or attention”, “traumatic brain injury” and “physical exercise”. Adult human traumatic brain injury studies that assessed cognitive function as an outcome measure (primary or secondary) and used physical exercise as a treatment (single or combined) were assessed by two independent reviewers. Data was

extracted under the guidance of the population intervention comparison outcome framework wherein, characteristics of included studies (exercise duration, intensity, combined or single intervention, control groups and cognitive measures) were collected, after which, methodological quality (Cochrane criteria) was assessed. **Results:** A total of 240 citations were identified, but only 6 met our inclusion criteria (3 from search records, 3 from reference lists**.** Only a small number of studies have evaluated the effect of exercise on cognition following traumatic brain injury in humans, and of those, assessment of efficacy is difficult due to low methodological strength and a high risk of different types of bias. **Conclusions:** Evidence of an effect of physical exercise on cognitive recovery suggests further studies should explore this treatment option with greater methodological approaches. Recommendations to reduce risk of bias and methodological shortfalls are discussed and include stricter inclusion criteria to create homogenous groups and larger patient pools, more rigorous cognitive assessments and the study and reporting of additional and combined rehabilitation techniques.

Key words: Traumatic brain injury, physical exercise, cognition, rehabilitation

Abbreviations: Brain-derived neurotrophic factor (BDNF), physical exercise (PE), traumatic brain injury (TBI).

1. Introduction

Traumatic brain injury (TBI) is a global health concern. Quality epidemiological data is scarce (Roozenbeek, Maas, & Menon, 2013), however recent studies in Europe show that TBI has an overall incidence of approximately 262 cases per 100,000 every year and is most prevalent in those under 25 and above 75 years of age thus impacting individuals at different times across the lifespan (Peeters et al., 2015). In the US alone, an estimated 3.2 million Americans live with residual effects of TBI (Benedictus, Spikman, & van der Naalt, 2010; Corrigan, Selassie,

& Orman, 2010). The long lasting consequences for survivors of TBI can be devastating and include cognitive, behavioural and sensorimotor disabilities that result in significant personal, social and economic burdens. An important metric for the impact of TBI on activities of daily living and quality of life concerns the effect of the lesion on one's ability to return to work. Studies reporting on return to work statistics in young TBI patients show poor outcomes. Following TBI, a mere 40% of patients return to work within one year of injury (van Velzen, van Bennekom, Edelaar, Sluiter, & Frings-Dresen, 2009). One study found that in patients with moderate to severe TBI, cognitive impairment was a major statistical predictor for return to work statistics (Benedictus et al., 2010), and at one-year post-injury, cognitive impairment was more common than physical limitations. Therefore, cognitive recovery is critical for functional recovery and quality of life.

TBI can be defined as brain pathology or alteration in brain function brought about by an external force (Menon, Schwab, Wright, & Maas, 2010). The multifaceted nature of TBI involves primary and secondary injury mechanisms combining both focal and diffuse injury patterns. Moreover, secondary injury processes and related damage can persist and progress for months to years after the initial injury (Hay, Johnson, Young, Smith, & Stewart, 2015; Loane, Kumar, Stoica, Cabatbat, & Faden, 2014), and in some cases diffuse damage is seen after initially focal damage (Saatman et al., 2008). This complex series of events shows significant heterogeneity, limiting the success of standard rehabilitation techniques. Many treatments for TBI focus on reducing neuronal death with the acute administration of neuroprotective agents shortly after injury (Talley Watts et al., 2014). However, given the chronic nature of TBI-related functional alterations (Stocchetti & Zanier, 2016) it is necessary to search for additional therapeutic approaches that are capable of both reducing the long-term sequels of brain damage and promoting optimal functional recovery.

Physical exercise (PE), an inexpensive, easily administered and long-term potential treatment option, has recently drawn attention. The major "physical health" benefits of PE are well established and include the reduction of cardiorespiratory-related complications associated with a sedentary lifestyle (hypertension, coronary heart disease and diabetes) (Warburton, Nicol, & Bredin, 2006). Additionally, it is also now believed that PE promotes "brain health" (Nagamatsu et al., 2014), and PE-induced effects on brain structure and cognitive function can be seen across the lifespan (M. W. Voss, Nagamatsu, Liu-ambrose, & Kramer, 2011). Furthermore, PE appears to be able to modulate both the pathophysiological changes and cognitive recovery following TBI (Chytrova, Ying, & Gomez-Pinilla, 2008; Grace S Griesbach, Gómez-Pinilla, & Hovda, 2007; Itoh et al., 2011; Jacotte-Simancas et al., 2015; Piao et al., 2013). However, a systematic and critical study of the available evidence supporting such statements in humans is lacking. The aims of this systematic review were to (1) determine whether increasing PE after TBI results in improvements in cognitive performance, (2) assess the quality of the studies to date, and (3) make recommendations for future studies and clinical PE programs after TBI.

2. **Methods**

On the 26th of April 2016 a search of the PubMed library database was performed using the terms "Traumatic brain injury", "Physical Exercise" and "Cognition". A filter was applied to limit the results to human only studies. The term "Cognition" was deemed to be too general, and subsequent searches were done using combinations of the first two search terms and the terms "attention", "memory" or "executive function". Further searches were done by replacing "Traumatic brain injury" with "concussion" to capture any citations using this terminology for mild traumatic brain injury. Duplicates were removed and titles and abstracts were screened

by two reviewers independently for eligibility. All relevant studies were reviewed in full. Manual searches of the reference lists of all identified articles were also performed to find potential articles not captured by the initial PubMed search. Inclusion criteria consisted of any adult human TBI study with or without an active control group, where cognitive function was assessed either as a primary or secondary measure after any aerobic or anaerobic physical exercise program was performed either alone or in combination with another treatment. Purely descriptive, observational studies and prior review articles were excuded.

The present systematic review was done under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement (PRISMA (Liberati et al., 2009)). Study characteristics (methods, interventions, participants, and outcomes) were collected using the Revman 5 software (version 5.1, Cochrane Collaboration, Canada) in adherence to the Population Intervention Comparison Outcome Framework (Liberati et al., 2009). Authors judgments of risk of bias and study appraisal were performed and reported under strict adherence to the Cochrane Handbook for Systematic Reviews and Interventions (Higgins et al., 2011) .The authors judgements of risk of bias (low risk, high risk, or unclear risk) were performed on the following potential sources: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other sources of bias.

3. **Results**

Our PubMed search revealed a total of 240 citations. Upon removal of duplicates and screening of titles and abstracts, 230 citations were deemed to be not relevant and were excluded. After examination of the remaining manuscripts a further 9 citations were removed as they did not meet the inclusion criteria. A total of three met the inclusion criteria and were included in this review. Within the process of the review a further three studies, deemed pertinent to the review, but not revealed in the PubMed search were identified and added to the study, resulting in the inclusion of 6 full-text studies. A flow chart showing the search strategy can been seen in figure 1 and details of the included studies can be found in table 1.

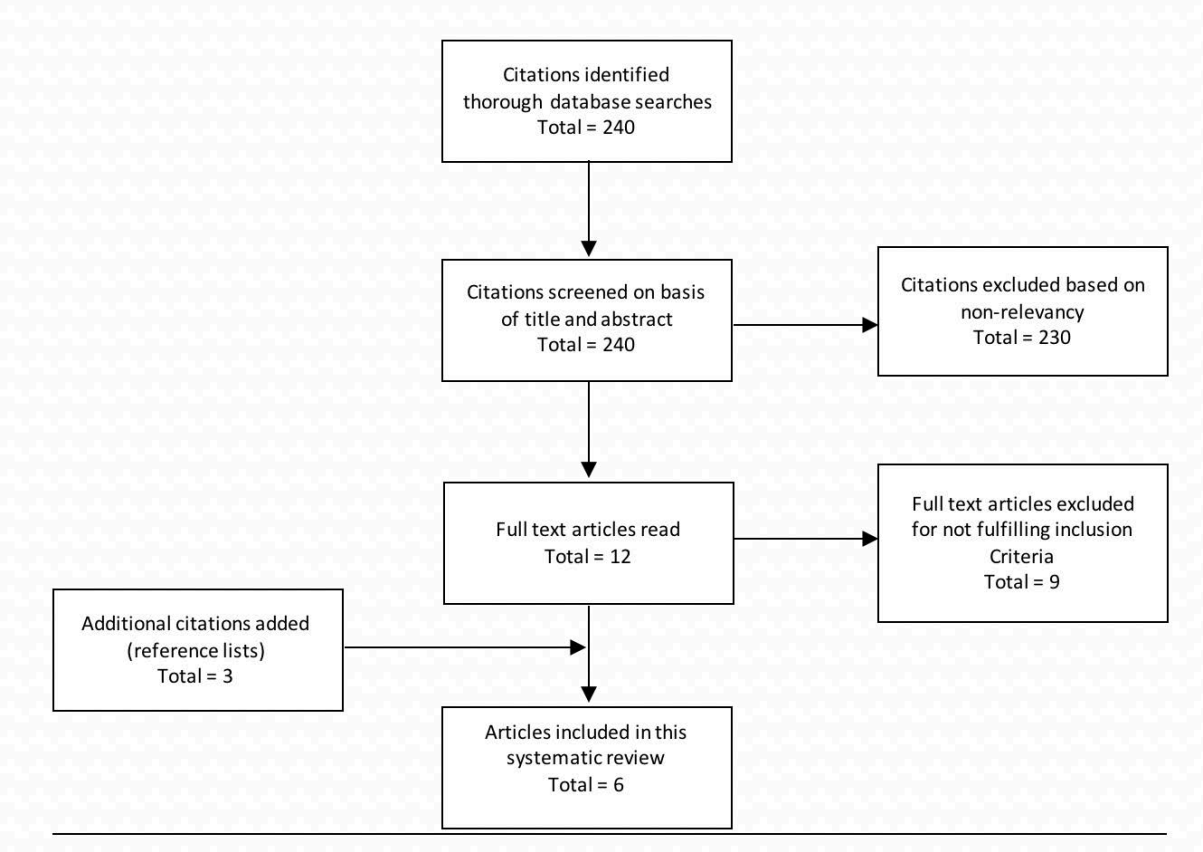

Fig 1. Flow chart displaying search strategy

Table 1. Study characteristics of the 6 PE, TBI and cognition studies

Author	Sample Size / Mean Age (years) / (control group? y/n)	TBI type and severity	Intervention (type, frequency, intensity)	Length of Intervention	Cognitive measure	Primary Result
Chin et al. (2015)	7 / 32.9 ± 6.5 / n	Chronic non-penetrating TBI. Mild= 4, Moderate= 3	Treadmill, 3*30mins/w at 70-80% HRR	12 weeks	TMT-A/B*, RBANS*	Significant improvements in TMT-A/B from baseline and in 3 out of 5 RBANS tests on visuospatial/constructional language and delayed memory
Lee at al. (2014)	12 / 48.22 ± 18.2 / y- waitlist AB cross over design	Chronic TBI	IntenSati, 2*60mins/w. Intensity n.s	8 weeks	TMT-A/B, Stroop colour and word, DSF and DSB (WAIS)	Non-significant small-to-medium effect size from baseline to post-treatment in all participants on the stroop test
McMillan et al. (2002)	35 / 31.4 ± 11 / y- non intervention control	Sub-acute to chronic TBI (3-12 months post-injury) Median GCS of 10	PE fitness training, 4* 45mins sessions. Intensity n.s	4 weeks	TMT-A/B, AMIPB, PASAT, SMQ	No significant between group or post-treatment results. Significant difference in self-reported cognitive failures questionnaire at 12-month follow-up
Bateman et al. (2001)	44 (TBI), 70 (stroke) 43 (other) / 41.7 ± 14.3 / y- relaxation exercises	Sub-acute to Chronic (median of 22 weeks post-injury)	Cycle ergometer, 3*30mins/w at 60-80% HRR	12 weeks	FIM-cog	No significant increase in between groups at 12 week follow-up
Grealy et al. (1999)	13 / 32.3 ± 13.1 / y- age, severity and time since lesion matched controls	Sub-acute to Chronic (1.7- 178.6 weeks post-injury) Severe TBI (GCS of 3-7)	Virtual reality cycle ergometer, 3*25mins/w at 10-12 on Borg rating scale	4 weeks	TMT/A/B, DSF, DSB, DS* (WAIS), AL*, Complex figure (Rey), VL*, LM (AMIPB)	Significant improvements in AL and VL as well as DS but no sig. in DSF/B o TMT/B
Gordon et al. (1998)†	64 / 37.8 ± 10.3 / y- TBIsed, non-TBIsed and non-TBIex	Chronic TBI	Self-reported exercise of at least 3*30mins/w	6 months	TIRR symptom checklist	Exercisers reported significantly less cognitive symptoms compared to non-exercisers

TMT-A/B= Trail making tests A and B; RBANS= Repeatable battery for the assessment of neurological symptoms; DSF, DSB= Digit span forward and backward; WAIS= Wechsler adult intelligence scale; DS= Digit symbol; AMIPB= The adult memory and information processing battery; PASAT= Paced auditory serial addition test; SMQ= Sunderland memory questionnaire; FIM-cog= Cognitive measures of the Functional independence measure; AL= Auditory learning; VL= Verbal learning; LM= logic memory; GCS= Glasgow Coma Scale, measure of lesion severity; HRR= heart rate reserve, IntenSati= physical exercise regime combined with self-affirmation verbal exercises n.s= not specified, *= significant change ($p<.05$)

†= Self-reported retrospective study; TBIsed= TBI patients who did not exercise; TBIex= TBI patients who undertook exercise.

Quality assessment

Quality assessment and individualised scored for each study (5 of the 6 studies) for the multiple sources of bias assessed is shown in figure 2. One study (Gordan et al., 1998) was not assessed for risk of bias because it is a retrospective analysis study. However, due to the small amount of published studies on this topic we made the decision to include this study in the present review. Only one study (Bateman et al., 2001) had low risk of bias, three (Lisa M Chin, Keyser, Dsurney, & Chan, 2015; Grealy, Johnson, & Rushton, 1999; McMillan, Robertson, Brock, & Chorlton, 2002) high risk and one (Lee, Ashman, Shang, & Suzuki, 2014) unclear risk for random sequence generation. All, except for one study (Bateman et al., 2001), were classified as having high risk of bias for allocation concealment. Whilst Bateman et al. (2001) attempted to address allocation concealment by using numbered and sealed envelopes opened by study physiotherapists at each centre, this procedure was not clearly reported. One study (Bateman et al., 2001) adopted and reported on blinding of participants and personnel, whereas four studies did not. Two studies (Bateman et al., 2001; McMillan et al., 2002) adopted methods of blinding of outcome assessment and three did not. Two studies (Bateman et al., 2001; Lisa M Chin et al., 2015) reported to have no attrition in their studies whereas three did not. For selective outcome reporting three studies (Bateman et al., 2001; Lisa M Chin et al., 2015; Lee et al., 2014) had low risk of bias and two high. No study was deemed to be at risk of other sources of bias.

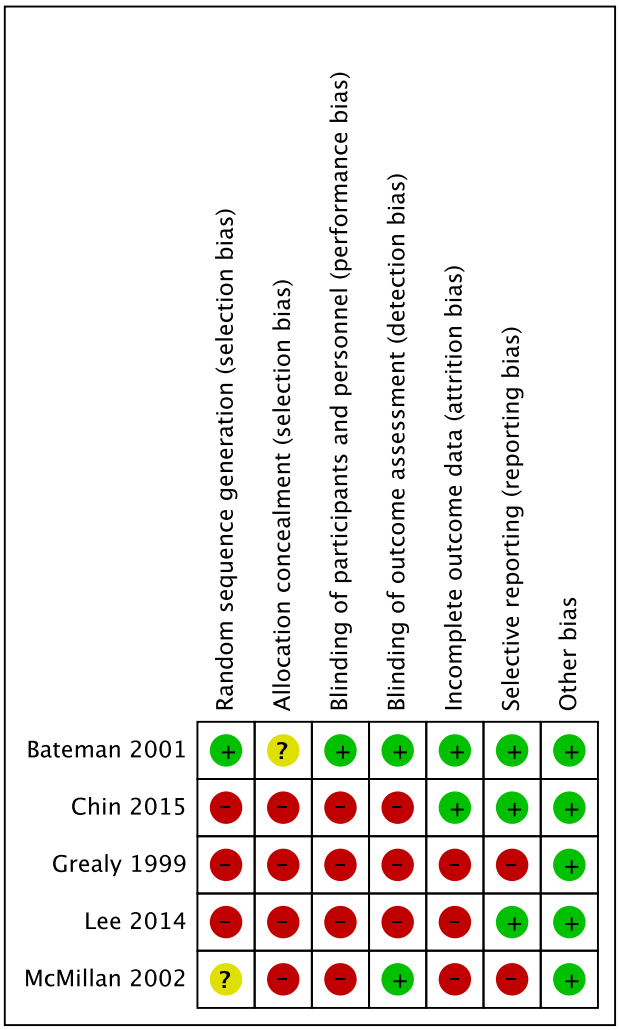

Fig 2. Risk of bias summary of the included articles

Interventions

All studies employed some type of aerobic PE which can be split into two groups (1) single intervention or (2) combined intervention. Two studies (Bateman et al., 2001; Lisa M Chin et al., 2015) used a single PE intervention, either using cycle ergometer or treadmill exercises three times a week for at least 30 minutes. Two studies used combined treatments (Grealy et al., 1999; Lee et al., 2014), with the use of exercise combined with either virtual reality or IntenSati (the use of verbal self-affirmation exercises). These session were done either three

(Grealy et al., 1999) or two (Lee et al., 2014) hours a week. One study, used retrospective analysis to assess self-reported levels of activity in TBI patients (Gordan et al., 1998) and the remaining studies used an unspecified "physical exercise" group, for which there was no information regarding actual exercise dose. Study durations lasted four weeks (Grealy et al., 1999; McMillan et al., 2002), 8 weeks (Lee et al., 2014) or 12 weeks (Bateman et al., 2001; Lisa M Chin et al., 2015), and the retrospective study (Gordan et al., 1998) assessed exercise levels over a 6 month period. Intensity of exercise was only reported in three of the 6 studies (Bateman et al., 2001; Lisa M Chin et al., 2015; Grealy et al., 1999). In two of these studies, participants undertook the exercise sessions at a percentage of heart rate reserve (HRR), between 60-80%, and in the other studies the exercise was performed at a rating of 10-12 of the Borg rating of perceived exertion scale (RPE scale).

Phase of injury, TBI severity and comparison groups

All studies included patients in the chronic phase of injury, in three studies (Bateman et al., 2001; Grealy et al., 1999; McMillan et al., 2002) some patients in the sub-acute phase of injury were also included. Across the studies, mild, moderate as well as severe TBI patients were included.

One study did not use a control group and undertook outcome assessments prior to and after the intervention period (Lisa M Chin et al., 2015). The remaining studies used either an A-B cross-over design (Lee et al., 2014), retrospective analysis of age, severity and time since injury-matched previous patient group (Grealy et al., 1999), no-intervention control group and mindfulness exercise group (McMillan et al., 2002), relaxation exercise group (Bateman et al., 2001) or no self-reported or low self-reported exercise groups (Gordan et al., 1998). \

Cognitive assessments and outcome measure results

Gordon and colleagues (1998) used the Institute of Rehabilitation and Research (TIRR) self-reported cognitive symptom checklist as the outcome assessment, in which, participants who reported greater levels of PE, reported significantly less cognitive symptoms, than those who reported lower levels of PE, or no PE. In the study by Bateman and colleagues' (2001), the cognitive section of the functional independence measure was used to measure cognitive performance. This measure did not reveal any significant between group differences compared with the group who performed relaxation exercises. The remaining three studies used more rigorous cognitive testing including the trail making test parts A and B (Lisa M Chin et al., 2015; Grealy et al., 1999; Lee et al., 2014; McMillan et al., 2002), the Repeatable battery for the assessment of neurological symptoms (RBANS) (Lisa M Chin et al., 2015), digit span forward and backward tests of the Wechsler adult intelligence scale (Grealy et al., 1999; Lee et al., 2014), the digit symbol test (Grealy et al., 1999), the word and colour section of the STROOP test (Lee et al., 2014) the adult memory and information processing battery, the paced auditory serial addition test and the Sunderland memory questionnaire (McMillan et al., 2002). Both Chin and colleagues (2015) and Grealy and colleagues (1998) found positive effects of PE on cognition. In Chin et al. (2015), improvements in the trail making tests part A and part B, as well as in three out of five tests of the RBANS questionnaire, in visuospatial memory, constructional language and delayed memory were seen, compared to baseline scores. Grealy et al. (1998) reported significant improvements in auditory and visual learning as well as in the digit span test in the PE group compared to their controls. However, no significant improvements were seen in the trail making tests, in contrast to Chin et al. (2015). In the remaining studies, no significant improvements in cognitive function were seen in the exercise

groups although, in Lee et al. (2014), a non-significant small-to-medium effect size was found in the word trial of the STROOP test in the exercise and IntenSati group.

Other assessments

Cognitive function as a primary outcome goal was assessed in two studies (Lisa M Chin et al., 2015; Grealy et al., 1999), whereas, in the other studies cognitive function was assessed along with other measures of rehabilitation outcomes. Anxiety and depression as measured by the Beck Depression Inventory (Gordan et al., 1998; Lee et al., 2014) and The Hospital Anxiety and Depression Scale (Bateman et al., 2001; McMillan et al., 2002), was used. Quality of life, using the Quality of Life interview and activities of daily living using the Nottingham Extended Activities of Daily Living were assessed in two studies (Bateman et al., 2001; Gordan et al., 1998). In addition, more physiological measures such as peak heart rate and work rate and balance (BERG balance scale) were assessed in one study (Bateman et al., 2001). Positive results in the Beck Depression Inventory were found in both studies that assessed this depression measure, whereas the Hospital Anxiety and Depression Scale showed no significant improvements in either of the studies in which it was employed. Peak heart rate showed no change over time in Bateman et al. (2001) although exercise patients significantly improved their peak work rate over time. Scores on the Berg scale were also non-significant over time and between groups in Bateman et al. (2001).

4. Discussion

A systematic assessment of the literature revealed few clinical studies evaluating PE as an intervention to improve cognitive impairment following TBI. Exercise was shown to improve select cognitive tests, including auditory and visual learning as well as visuospatial and delayed memory. Fluid intelligence and speed of processing were also shown to improve following PE. However, the findings are inconsistent across studies and some studies did not show any cognitive benefit of PE following TBI. Few studies used rigorous neuropsychological testing and thus meta-analysis was deemed unnecessary. In addition, quality appraisal of the included studies showed high levels of bias for nearly all items analysed, including, random sequence generation and allocation sequence concealment, as well as blinding of participants, personnel and outcome measures.

Therefore, positive results should be interpreted with caution and deriving concrete conclusions is difficult. The inclusion of patients with broad ranges of clinical characteristics (time since injury, severity, age) as well as injury sub-types (Stroke, TBI, subarachnoid haemorrhage) (Bateman et al., 2001), produces high heterogeneity when deriving conclusions regarding treatment effect based on group data. Spontaneous recovery of cognitive functions following severe TBI has been shown in one study to reach a plateau at approximately 8-months post-injury (León-carrión & Machuca-murga, 2001), with no major gains in recovery being seen after this point. Thus, the inclusion and analysis of patient pools containing both chronic and sub-acute patients as well as distinct injury types allow for high uncertainty. In addition, results from animal models of PE and TBI suggest that the timing of initiation of exercise is an important factor in its effect on TBI recovery (Grace S Griesbach et al., 2007). Therefore, future studies should restrict inclusion criteria to allow for homogeneous grouping regarding

type of injury and time since injury, include greater patient pools, and adopt more adaptable and individualised exercise protocols.

Rehabilitation following TBI is multi-disciplinary. Patients in the sub-acute phase of injury day-to-day may undergo sessions in physiotherapy and occupational therapy, balance, fitness and gait training as well as psychological treatment and cognitive rehabilitation. In the studies we identified including individuals with sub-acute TBI, detailed information regarding these interventions was not present. Thus, the study of the combined effects of PE with other rehabilitation techniques (cognitive training, virtual reality) in individuals with TBI opens up an interesting and unexplored area of research. Furthermore, some studies have found a negative interference of drug intake when combined with PE, compared to either one alone (Jacotte-Simancas et al., 2015). Thus reporting on other aspects of rehabilitation in PE studies (type, duration, frequency, drug intake) is important.

Of the identified studies, only two assessed cognitive function as a primary outcome objective, and few studies used rigorous cognitive assessments. To capture the real extent of exercise-induced benefits in TBI rehabilitation, rigorous cognitive testing using a battery of neuropsychological tests is necessary. We believe future studies should employ this type of testing as a primary outcome objective in order to gain a greater view of the role PE can play in TBI recovery.

Physical exercise after TBI; Challenges and opportunities

An interesting point to consider is that the first study of PE and cognitive recovery following TBI was performed in 1999 (Grealy et al., 1999). Since then, many animal models of PE,

cognition and TBI have been performed with very encouraging results. Unfortunately attempts at human translation to date are weak and strong conclusions cannot be drawn.

The lack of translation from experimental models to clinical trials may be due to problems with methodological constraints. Common problems facing TBI patients in the sub-acute and early chronic phases of injury include fatigue (Beaulieu-Bonneau & Ouellet, 2016), cardiorespiratory complications and diseases related to a sedentary lifestyle such as hypertension, diabetes and heart disease, as well as depression, sleep disturbances (Chen et al., 2015; Ouellet, Beaulieu-Bonneau, & Morin, 2015) and apathy (Starkstein & Pahissa, 2014). Furthermore, neurological problems causing sensorimotor deficits and spasticity also pose challenges for PE after TBI (Driver, Ede, Dodd, Stevens, & Warren, 2012; Pattuwage et al., 2016).

Interestingly however, PE may hold the key in the recovery from the very same symptoms that could initially hinder the adherence to and participation in a PE rehabilitation program. For example, PE programs have been shown, in selected studies to have a cardiorespiratory benefit in patients with TBI (Bhambhani, Rowland, & Farag, 2005; L M Chin et al., 2014; Hassett, Moseley, Whiteside, Barry, & Jones, 2012). Patients who underwent up to 30 minutes of exercise, at least 3 times a week working at an intensity of >50% of maximal heart rate improved their aerobic capacity (VO_2max) (Bhambhani et al., 2005; L M Chin et al., 2014) as well as decreased their fatigue status, as measured by the fatigue severity scale (L M Chin et al., 2014; Hoffman et al., 2010). PE in TBI patients has also shown benefits in mood and depression symptoms with similar exercise protocols (at least 30 minutes of exercise, 3 times a week at >50% of maximal heart rate), improving scores on the Beck depression index and quality of life questionnaires (Hoffman et al., 2010; Wise, Hoffman, Powell, Bombardier, &

Bell, 2012). This improvement was also seen in two of the studies included in this review (Gordan et al., 1998; Lee et al., 2014). Additionally, in non-injured adults, PE has been shown to increase sleep quality (Passos et al., 2011; Reid et al., 2010).

Potential exercise-induced mechanisms of action

Despite the small amount of studies employing PE as a treatment for cognitive impairment following TBI, in animal models of TBI, many positive results have been seen following a period of either forced or voluntary PE. In addition, the mechanisms by which PE exerts its neuroprotective/neuroreparative effects following TBI are most likely multifold. PE seems capable of up-regulating a variety of plasticity-related growth factors following TBI such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1), as well as related proteins synapsin-1 and cyclic-AMP-response-element-binding protein (CREB) (Grace S Griesbach et al., 2007; Grace Sophia Griesbach, Gomez-Pinilla, & Hovda, 2004; Grace Sophia Griesbach, Hovda, & Gomez-Pinilla, 2009; Piao et al., 2013). Insulin-like growth factor-1 may play a crucial role in both the cognitive and physiological recovery from TBI as it has been implicated in exercise-induced angiogenesis (Ding, Vaynman, Akhavan, Ying, & Gomez-Pinilla, 2006; Lopez-Lopez, LeRoith, & Torres-Aleman, 2004) and neurogenesis (Carro, Trejo, Busiguina, & Torres-Aleman, 2001; Trejo, Carro, & Torres-Aleman, 2001) in heathy brains, as well as stimulating the up-regulation of BDNF (Carro et al., 2001; Ding et al., 2006). BDNF in itself has been widely implicated in a variety of exercise-induced benefits on the brain including the promotion of synaptic plasticity in the form of long-term potentiation (LTP) (Farmer et al., 2004). Given the reduced synaptic plasticity found in the acute phase of TBI (Tremblay, Vernet, Bashir, Pascual-Leone, & Theoret, 2015) and the aberrant synaptic plasticity in the sub-acute to chronic phases of injury (De Beaumont, Tremblay, Poirier,

Lassonde, & Théoret, 2012), this may be an important mechanism by which PE exerts its positive effects. Further, hippocampal neurogenesis, blockade of myelin inhibitors NOGO-A and myelin associated glycoprotein (MAG) as well as the promotion of cognitive function have all been shown to be BDNF-dependent (Chytrova et al., 2008; Grace S Griesbach et al., 2007; Grace Sophia Griesbach et al., 2009; Kuipers et al., 2016). Additionally, PE has been shown to increase neurogenesis in the dendate gyrus of the hippocampus and promote neuronal survival (Jacotte-Simancas et al., 2015; Piao et al., 2013; Van der Borght, Havekes, Bos, Eggen, & Van der Zee, 2007), with the number of new neurons during PE correlating with the improvement in memory acquisition and retention found in these studies (Jacotte-Simancas et al., 2015; Van der Borght et al., 2007). Furthermore, PE has been shown to reduce neuronal degeneration and inhibit both neuronal apoptosis, resulting in improvements in spatial memory (Itoh et al., 2011) and the TBI-induced up-regulation of myelin inhibitors NOGO-A and myelin associated glycoprotein (MAG) (Chytrova et al., 2008). PE also seems capable of reducing lesion volume size, both in the lateral ventricle and hippocampal formation (Jacotte-Simancas et al., 2015; Piao et al., 2013), as well as down-regulating microglia-associated pro-inflammatory processes and promoting an anti-inflammatory immune response, which correlate with improvements in both working memory and spatial memory performance (Piao et al., 2013).

Physical exercise benefits in non-injured humans

Recent advances in neuroimaging have allowed researchers to gain a greater understanding of the neurobiological substrates of exercise-induced changes in the human brain and in non-injured humans positive associations have been seen between adults with either high cardiorespiratory fitness levels or high maximal oxygen uptake (Vo2max) levels and greater

fractional anisotropy in a multitude of white matter tracts, including the corpus callosum, cingulum, superior corona radiata and inferior longitudinal fasciculus (Hayes, Salat, Forman, Sperling, & Verfaellie, 2015; Marks, Katz, Styner, & Smith, 2011; Oberlin et al., 2016; Sexton et al., 2016), with the greatest changes seen in prefrontal regions (M. Voss et al., 2013). Further, positive associations between PE and hippocampal volume have been shown, in both older and middle-aged adults (Erickson et al., 2009, 2011; Thomas et al., 2016). Physical exercise has also been shown to improve intraregional functional connectivity in various association networks, although, most notably in the default mode network (Johnson et al., 2016; M. W. Voss et al., 2016). Where, in adolescents, physical fitness may positively impact functional connectivity between the hippocampus and the default mode network during memory coding (Herting & Nagel, 2013). In addition, exercise appears capable of promoting cognitive function (Hillman, Erickson, & Kramer, 2008). PE has been shown to improve hippocampus-dependent spatial and associate learning (Erickson et al., 2009, 2011; Herting & Nagel, 2013) as well as other hippocampus-dependent tasks, such as pattern separation (Dery et al., 2013). Information processing speed and attentional processes also seem to be enhanced by PE (Smith et al., 2011) as does memory coding and consolidation (Roig, Nordbrandt, Geertsen, & Nielsen, 2013). (Roig et al., 2013). PE seems to exert its greatest benefit on frontal lobe-dependent executive functions (Hillman et al., 2008) where studies have shown that regular physical exercise can positively impact selective attention, task switching, working memory, planning and scheduling and inhibition of prepotent responses (Colcombe & Kramer, 2003; Guiney & Machado, 2013; Oberlin et al., 2016; Ratey & Loehr, 2011).

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5. Conclusions

Given the results of animal models of TBI, PE and cognition as well as the highly promising results of PE in non-injured humans on both brain structure and cognitive function, we believe the use of PE as a treatment for cognitive impairment following TBI should be explored further. Future research will benefit from addressing the methodological shortfalls highlighted in this review. Rigorous cognitive testing is required to reveal the extent of recovery and in which domains and due to the heterogeneous nature of TBIs, stricter inclusion criteria and adaptable and individualised programs may reveal greater success in capturing the effect of PE on cognitive recovery. Combined treatments offer a more real-world approach to rehabilitation and the study of these as well as the reporting of other rehabilitation processes will allow practitioners to prescribe evidence-based exercise programs with greater individualism and specificity.

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Chapter 4

Experimental work

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Feasibility of Aerobic Exercise in the Subacute Phase of Recovery from Traumatic Brain Injury: A Case Series

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Abstract

Background and purpose: Injuries associated with traumatic brain injury (TBI) are common and can complicate rehabilitation. The objective of this study is to examine the feasibility of introducing aerobic physical exercise programs into the subacute phase of multidisciplinary rehabilitation from moderate-to-severe TBI, which includes computerized cognitive training.

Case description: Five individuals undergoing inpatient rehabilitation with moderate or severe TBIs who also have concomitant physical injuries. All of these individuals are in the subacute phase of recovery from their TBIs.

Intervention: An 8-week progressive aerobic physical exercise program. Participants were monitored to ensure that they could both adhere to and tolerate the exercise program. In

addition to the physical exercise, individuals were undergoing their standard rehabilitation procedures which included cognitive training. Neuropsychological testing was performed to gain an understanding of each individuals' cognitive function.

Outcomes: Two minor adverse events were reported. Participants adhered to both aerobic exercise and cognitive training. Poor correlations were noted between heart rate reserve and ratings of perceived effort.

Discussion: Despite concomitant injuries and cognitive impairments, progressive aerobic exercise programs seem feasible and well tolerated in subacute rehabilitation from moderate-to-severe TBI. Some findings highlight the difficulty in measuring exercise intensity in this population.

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1. Introduction

Traumatic brain injury (TBI) leads to many behavioural, sensorimotor and cognitive deficits, which result in significant social, personal and economic burdens. Cognitive impairment is an important statistical predictor of return to work (Benedictus et al., 2010b) and with a mere 40% of individuals with severe TBI returning to work within 1-year of injury (van Velzen, van Bennekom, Edelaar, Sluiter, & Frings-Dresen, 2009b), long-term treatments aimed at combating these deficits are critical for quality of life. Aerobic exercise, an inexpensive, easily administered and potentially long-term therapeutic intervention has been shown to have many physiological, structural and cognitive effects on the brain (Erickson et al., 2011b; Oberlin et al., 2016b; Sexton et al., 2016a; Thomas et al., 2016a; M. W. Voss et al., 2013). In non-injured adults, aerobic exercise appears capable of improving a variety of cognitive functions including attentional processes (P. J. Smith et al., 2011) and executive functions such as working memory

and task switching [9,10]. In clinical studies improved attention, delayed memory and executive functions (Lisa M Chin et al., 2015; Grealy, Johnson, & Rushton, 1999) have been observed in individuals with traumatic brain injury who participated in aerobic exercise. Additionally, a cardiorespiratory benefit of aerobic exercise in individuals with TBI has been shown (L M Chin et al., 2014; Hassett, Moseley, Whiteside, Barry, & Jones, 2012). However, these studies are few, with small sample sizes. A recent systematic review on aerobic exercise and cognitive recovery after TBI (T. Morris et al., 2016) highlighted some shortcomings inherent in these studies, including grouping together of individuals in different phases of recovery (subacute and chronic) and inadequate information on multidisciplinary rehabilitation procedures. Moreover, cognitive impairment and concomitant physical injuries may limit the participation in, and adherence to, an aerobic exercise program.

Common concomitant injuries associated with TBI include musculoskeletal injuries [16] and gait and balance impairments [17]. Apraxia and/or hypokinesia [18], pain [19] and spasticity [20] are also seen. These injuries may constitute barriers to aerobic exercise, especially in the subacute phase of injury. It is possible that the duration, intensity and frequency needed to induce an adaptive plastic response to enhance functional and cognitive recovery may not be achieved in individuals who present with serious concomitant injuries. It has been suggested that individuals with TBI have poor awareness of subjective fatigue however [21]. Assessing the feasibility of how to measure and control for these exercise parameters (frequency, duration and intensity), is therefore important

Inpatient, as well as early outpatient rehabilitation for TBI includes intensive sessions of physical therapy, occupational therapy, behavioural speech therapy and cognitive rehabilitation. This multidisciplinary approach means outcomes are unlikely to be influenced

greatly by any single therapeutic input [22]. Meta-analyses on cognitive rehabilitation outcomes suggest computerized cognitive training is beneficial for improving cognitive functions such as executive function and attention [23,24] and is a common therapeutic tool in neurorehabilitation clinics [25]. Research has postulated that the combination of aerobic exercise with cognitive training may be more effective than either one alone [26]. Since fatigue [27] and apathy [28] are common symptoms in subacute TBI, the addition of aerobic exercise to traditional rehabilitation may pose challenges regarding the adherence to both programs. Should both interventions prove efficacious, it is important that individuals can participate in both.

Therefore, the development of successful aerobic exercise programs early after TBI requires the assessment of their feasibility. The aim of this case series study is to assess the feasibility of the inclusion of an 8-week progressive aerobic exercise program in addition to standard multidisciplinary rehabilitation, which includes computerized cognitive training, for moderate-to-severe TBI in the subacute phase of recovery.

2. Case description

The demographics of five individuals with moderate or severe TBIs who were undertaking inpatient rehabilitation at the time of recruitment are seen in Table 1.

A.A – The participant was a 19-year-old male who collided at high velocity with a wooden shed whilst skiing. He was wearing a helmet at the time but the impact caused the helmet to split into two. He lost consciousness immediately and upon being admitted to the hospital was awake but minimally conscious. His injury resulted in gait impairments including ataxia and apraxia. He had been an active adult prior to the injury, participating in regular sport and

activity. He had undertaken the first year of undergraduate studies in computer engineering and spoke four languages.

B.B – The participant was a 56-year-old male who sustained a head injury in a motorcycle accident. He lost control of the motorcycle and was subsequently hit by a moving car. He presented with concomitant injuries of a cervical fracture at C4. He had been an active adult prior to injury participating in cycling multiple days per week. He had vocational education in mechanics.

C.C – The participant was a 34-year old male who sustained a head injury in a motor traffic accident. He fell from a motor cycle and hit the pavement with the front part of his head, breaking his helmet in two. He sustained a brachial plexus injury to the right arm, which caused severe pain as well as cervical compression myelopathy and a fractured right clavicle. He was an active adult prior to his injury participating in sport and resistance exercises multiple times per week. He worked as a computer engineer.

D.D – The participant was a 43-year-old male who sustained a head injury caused by a fall. He was found with anisocorous pupils with mydriasis of the right pupil. An urgent craniotomy on the right side was performed. He sustained no concomitant injuries as a result of his accident. He was active prior to his injury participating in sport and exercise multiple times per week.

E.E – The participant was a 32-year-old male who sustained a head injury after a collision with a motor vehicle while riding a bicycle. He presented with concomitant injuries consisting of atelectasis contusion in the left posterobasal pulmonary segments associated with mild

hemothorax and fractures of the posterior costal arches of ribs 10 and 11. He was physically active prior to the injury.

Table 1. Demographics

Participant	**A.A**	**B.B**	**C.C**	**D.D**	**E.E**
Age	19	56	34	43	32
Gender	M	M	M	M	M
Severity of Injury (GCS)	Severe (4)	Moderate (10)	Severe (3)	Moderate (11)	Severe (5)
Pre-intervention resting HR	58	79	67	58	58
Time since injury (days)	91	24	30	51	48
PTA time (days)	78	24	18	36	38
Cause of injury	Skiing accident	Traffic accident	Traffic accident	Traffic accident	Traffic accident
Concomitant injuries / barriers to exercise	Complete loss of independent ambulation, Apraxia / ataxia	C4 vertebral fracture	Brachial plexus injury / fractured clavicle / chronic pain	n/a	Rib fractures 10/11
Pre-injury activity level	Active	Active	Active	Active	Active

GCS, Glasgow coma score; PTA, post traumatic amnesia

3. Intervention

Recruitment

The education and ethics committee of the participating institution approved this study. All patients signed an informed consent prior to participating in the study. The informed consent documents were left with the participant and family members overnight and family members

were active in all consent processes. This manuscript has been prepared under the CARE guidelines: consensus-based clinical case reporting guideline development [29]. Participants were recruited from an acquired brain injury inpatient ward and were assessed by both a trained neuropsychologist and physiotherapist to assure they met the inclusion criteria for the study. Participants were considered eligible to participate in this study if they: i) had a diagnosis of moderate or severe TBI (3-8 or 9-13 on the Glasgow Coma Scale, respectively [30]) ii) had sufficient cognitive ability to understand written and verbal instructions (>6 on the Rancho Los Amigos Scale [31]); and iii) if they no longer displayed post-traumatic amnesia (measured by an average score of >75 on the Galveston Orientation Amnesia Scale over 3 consecutive days). Participants were excluded from the study if they had a history of a previous moderate or severe TBI, if they presented with any neurological or cardiorespiratory complications that were a contraindication to perform physical exercise, as described by the American College of Sports Medicine [32] or if they presented with aphasia, which would limit their ability to perform the cognitive assessments and study procedures. All participants began the study as inpatients and were discharged from the hospital during the 8-week intervention period. A.A, B.B and C.C returned as outpatients to continue their rehabilitation and the study whereas D.D and E.E did not live in the local area and did not come back for treatment in the outpatient clinic.

Description of rehabilitation procedures

All participants were undergoing standard and individualised multidisciplinary rehabilitation programs throughout the entire study period, which involved intensive 5 hours a day, 5-7 days a week of occupational therapy, physical therapy, and behavioural speech therapy. Cognitive training using a computerized cognitive training platform (Guttmann NeuroPersonal Trainer®, Barcelona, Spain) was performed by each participant at a similar frequency to the physical

exercise (three times per week for one hour during the 8-week study period). The cognitive training consists of a set of computerised cognitive tasks that cover different cognitive functions (attention, memory and executive functions) and sub-functions. For a full list of sub-functions see Solana et al., (2015) [25]. A baseline neuropsychological assessment determines the cognitive training program (which tasks, at what frequency and at what difficulty level to begin) and an automated algorithm, 'Intelligent therapy assist' [33] continuously monitors and updates an individual's progress.

Measures of neuropsychological function

Participants were administered a clinical battery of neuropsychological tests by a trained neuropsychologist prior to (<1-week) the 8-week intervention period. The trail making test A [34], where the participant is instructed to connect 25 numbered dots consecutively, as quickly and accurately as possible was used as a measure of processing speed and attention. The digit span forward, digit span backward and letter/numbers tests of the Wechsler adult intelligence scale part III (WAIS [35]), a series of tests during which the participant is read a series of numbers (or numbers and letters for letters/numbers) and asked to repeat them in the same order, or backwards were undertaken and which have been asserted to measure working memory. The Rey auditory verbal learning tests (RAVLT [36]) which measures episodic memory using a word-list learning task where 15 unrelated words are verbally presented and the participant is asked to recall as many as possible was performed. Five trials are presented which give measures of immediate word span (trial 1), total acquisition (all trials) and retention (after 20 to 45-minute delay). The block design task from the WAIS was also administered which measures visual abstract processing, spatial perception and problem solving. The participant is presented with red and white blocks (with two red sides and two white) and is asked to construct replicas of

designs previously presented by the examiner. Lastly, the verbal fluency task (FAS [37]) which consists of three word-naming trials where the participant has to say as many words beginning with a given letter of the alphabet (typically F A or S although in this study P M and R were used as part of the Spanish language version [38]) was administered.

Progressive aerobic exercise program

The aerobic exercise intervention took place 3 times per week for 8-weeks. An introductory session took place to introduce participants to the equipment and aerobic exercise program. Each participant's physical abilities dictated which exercise equipment was used. Two machines was available- an active/passive exercise trainer that delivered resistance for active exercising of the arm, leg or arms and legs (Motomed Muvi, RECK, Betzenweiler, Germany), and an upright cycle ergometer (Keiser M3 indoor, Fresno, CA). As an example, if the participant was non-ambulatory they initially began with the active/passive trainer, performing arm cycling only. Weekly assessments by the participant's physiotherapist assessed whether a move from active/passive arm cycling to both arm and leg cycling or to the cycle ergometer was appropriate. Decisions were based on functional capacity of the participant (e.g has the participant regained sufficient leg strength to perform active leg cycling? Or, has the participant regained ambulation and sufficient balance to ride the cycle ergometer?). The target exercise intensity zone was defined as 50-70% of heart rate reserve (HRR). The corresponding heart rate (HR) in beats per minute (BPM) was calculated using the Karvonen equation ([220-age]-resting heart rate * intended goal % of HRR + heart rate rest) and monitored continuously by a Polar A380 wrist-based photoplethysmographic heart rate monitor (Polar Electro, Kemple, Finland). Nursing staff recorded resting heart rate periodically during the early mornings, according to standard hospital protocol, and the average of the three lowest values in the three

days prior to enrolment in study was recorded as pre-intervention resting heart rate. Ratings of perceived exertion using the 6-20 Borg scale [39] were taken every 15-minutes. Borg's scale of perceived exertion is a widely used rating scale with both verbal anchors and corresponding numbers whereby 6 represents "no exertion at all" and 20 represents "maximal effort". The scale is based on the physical sensations a person experiences during exercise, including increases in HR. A high correlation between the numerical anchors (times by 10) and actual heart rate during exercise has been shown [40].The target HR zones of 50-70% of HRR are said to correspond to 12-14 ("somewhat hard") on this scale [32]. Each aerobic exercise session was designed to last between 45 minutes and one hour with a 10-minute warm-up and cool-down worked into each session. Warm-up sessions consisted of light resistance exercise. The exercise protocol aimed to allow each participant to become familiar with aerobic exercise, thus initially, participants were asked to undertake exercise at their own pace and were allowed to stop at any time. Upon having completed week one, the physical therapy staff asked participants to attempt to progressively increase their intensity (HR) and the duration of each session until they reached a consistent performance in each session that comprised 25 to 35 minutes of aerobic exercise within the target HRR zone. As patient engagement in health care may lead to greater outcomes [41] physical therapy staff attempted to engage participants to play a role in increasing the resistance of the exercise by using positive language as verbal motivation and feedback. The physical therapy staff monitored the participants HR and RPE to ensure intensity was increased in a progressive manner (i.e. not abruptly). Figure 1 shows a decision diagram of the aerobic exercise program.

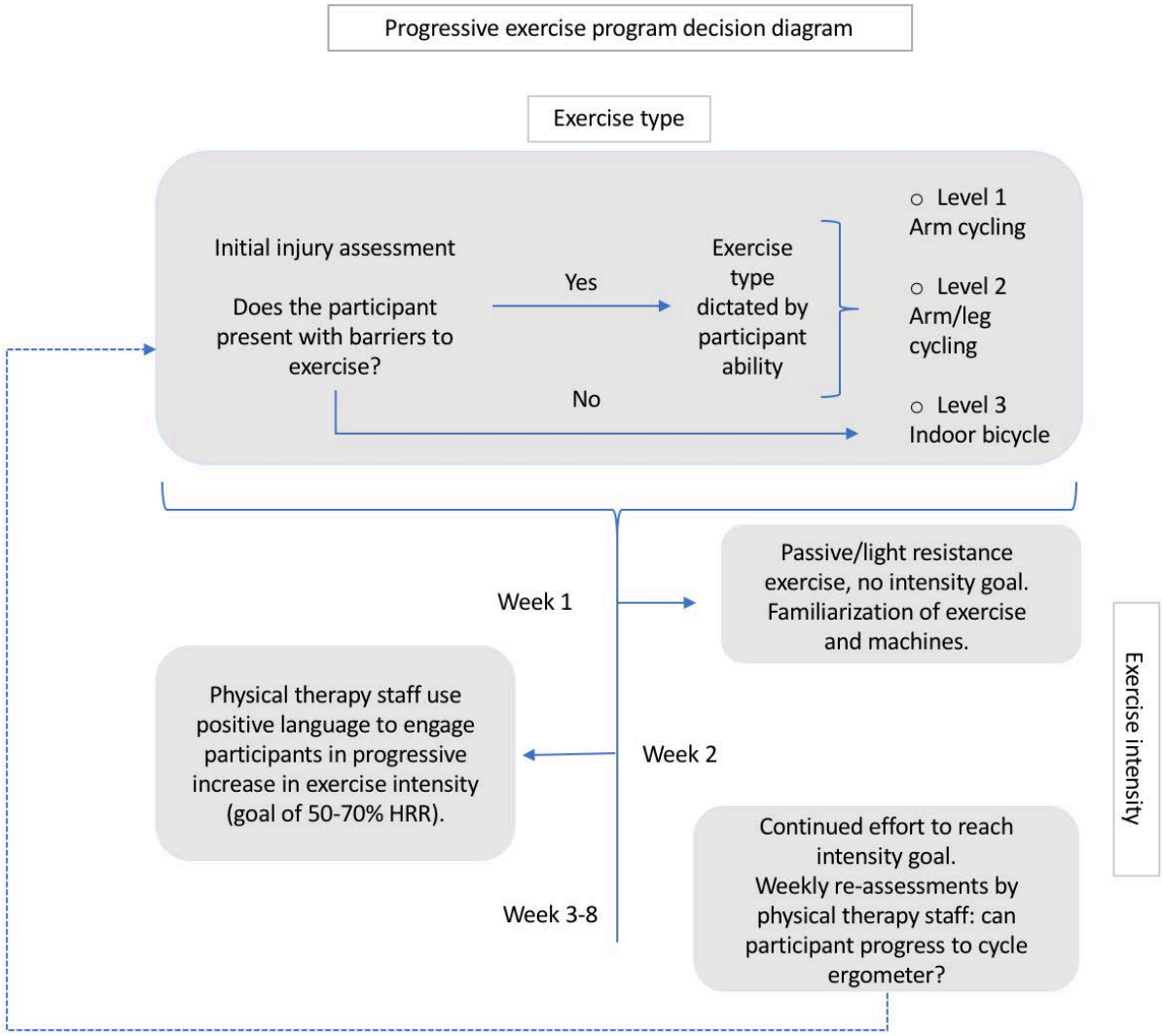

Figure 1. Flow diagram of the progressive aerobic exercise intervention

Outcome measures

Feasibility was measured using the following outcomes: number of adverse events reported, adherence to the aerobic exercise program (session durations and number of session attended), time spent in HRR training zones, the correlation between RPE and HRR and adherence to the cognitive rehabilitation training program (number of sessions attended and tasks performed).

Statistical analysis

Statistical analysis was performed using GraphPad Prism 7.00 for Macintosh, GraphPad software, La Jolla California, USA, www.graphpad.com. Pearson's correlation coefficients were calculated for the relationship between RPE and HRR. HRR was measured as the average HRR (calculated from bpm using the Karvonen equation) in the 30-seconds before and after the measurement of RPE at 15-minute intervals. Heart rate in beats per minute was recorded second-by-second and time spent in HRR training zones calculated by the amount of time (seconds) each participants' corresponding heart rate was at or above individual 50% HRR.

4. **Outcomes**

Table 2 shows the neuropsychological profile of each participant at the beginning of the intervention. Two adverse events were reported during the study. A.A complained of feelings of nausea during one session and B.B complained of feeling light-headed after one session within the first week. Throughout the study period no participant took beta-blockers or any other antiarrhythmic medications or medications that directly affect heart rate. Three participants (A.A, B.B, C.C) were being treated with benzodiazepines and antipsychotic medications, which could be associated with adverse effects on heart rate but all participants were prescribed the recommended dosages and no adverse events were reported. One participant (A.A) was taking clonidine but no side effects related to heart rate were reported.

Table 2. Neuropsychological test scores

Participant Test	**A.A**		**B.B**		**C.C**		**D.D**		**E.E**	
RAVLT Short term *(verbal memory)*	28	VS	33	M	34	VS	42	S	20	VS
RAVLT long term *(verbal memory)*	n/a*	VS	5	M	1	M	8	S	2	VS
RAVLT retention *(verbal memory)*	n/a*	VS	12	N	9	M	12	S	5	VS
WAIS digit span forward *(short term memory)*	6	N	4	S	6	N	6	N	5	S
WAIS digit span backwards *(working memory)*	7	N	4	N	4	N	5	N	3	S
WAIS letters/numbers *(working memory)*	5	S	10	N	11	N	8	S	n/a*	VS
WAIS block design *(visual construction)*	n/a^		26	N	46	N	27	M	15	S
TMT-A *(attention)*	77	VS	84	S	56	N	31	N	57	M
FAS *(executive function)*	20	VS	n/a*	VS	20	VS	19	VS	16	VS

Left column = test score, right column = level of deficit, based on age and level of education: VS = very severe, S = severe, M = moderate, N = normal. RAVLT, Rey auditory verbal learning test; WAIS, Wechsler adult intelligence scale; TMT-A, trail making test part A; FAS, phonemic verbal fluency test. n/a*, participant unable to complete test due to severe deficit; n/a^, participant unable to complete test due to motor impairment.

Table 3 presents feasibility data from the aerobic exercise program. Adherence percentages are presented as % of 15 sessions for D.D and E.E. All participants had adherence rates above 80% to the cognitive training program except D.D (73%). D.D and E.E spent 55% and 56%, respectively, of the aerobic exercise program within the target heart rate zone. B.B spent 4% of their time within the target zone, with a mean HRR of 40% over all sessions. A.A and C.C did not exercise within the target zone for any amount of time during the 8-week program. Individual mean %HRR every 15-minutes is shown in Figure 2A. RPE values for case E.E were not collected due to investigator error and therefore missing. Figure 2B-E displays mean individual plots of % HRR and RPE every 15-minutes. Pearson's correlation coefficients show low correlation between HRR and RPE in all participants (A.A $r = 0.33$; B.B $r = 0.5$; C.C $r = 0.28$; D.D $r = 0.17$).

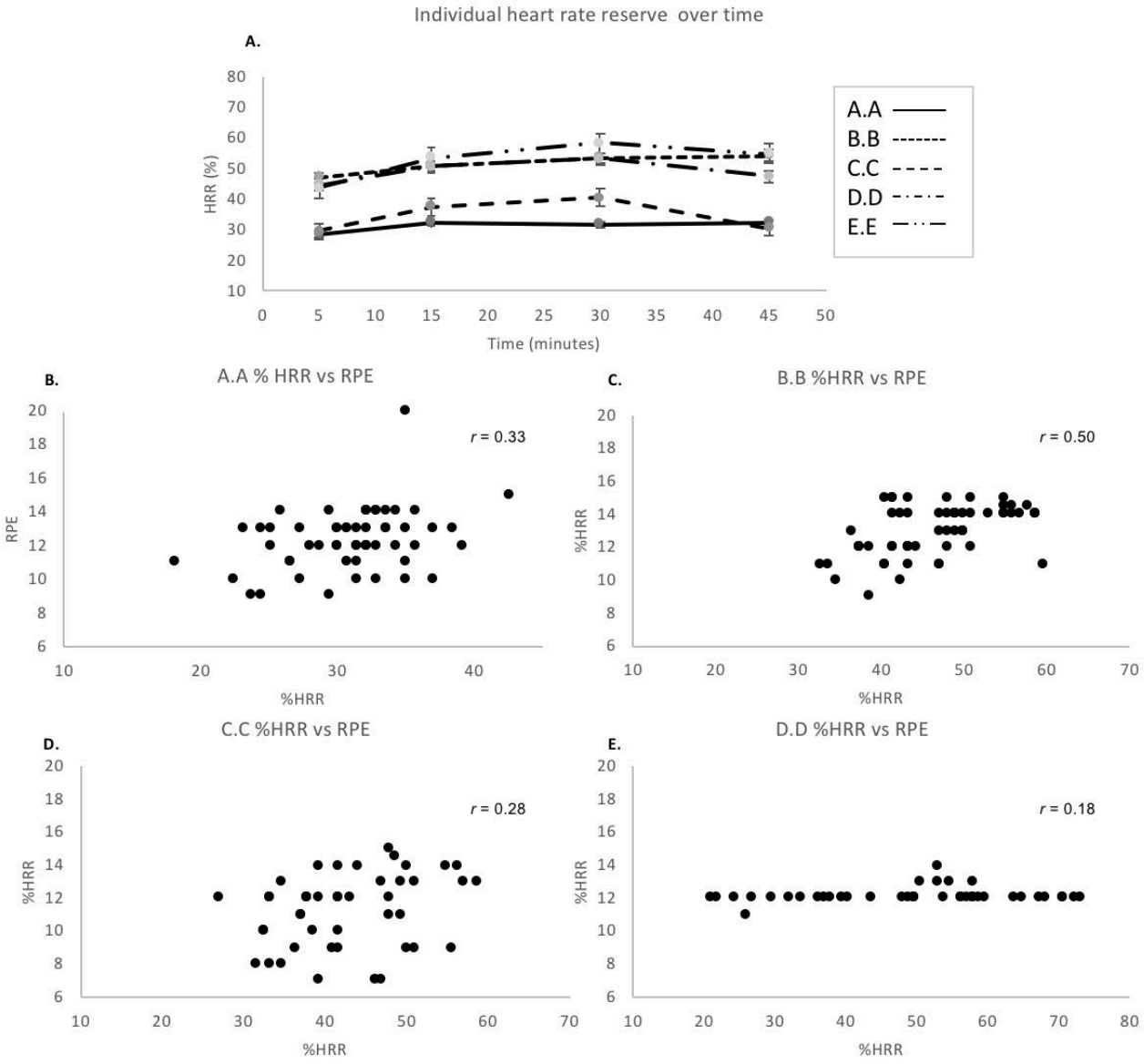

Figure 2. **A.** Individual mean %HRR at 15-minute intervals (1 minute average of HRR before and after each 15-minute mark) with standard error bars.**B-E.** Scatter plots for individual mean %HRR and mean RPE at 15-minutes intervals with Pearson's correlation coefficient values.

Table 3. Feasibility data from the aerobic exercise and cognitive training programs

Participant	**A.A**	**B.B**	**C.C**	**D.D**	**E.E**
Aerobic exercise					
Total number of sessions	24	23	23	12	13
% adherence	100%	95%	95%	80%	87%
Mean session duration (mins)	45	47	41	45	49
Mean % HRR	33%	40%	40%	55%	56%
Mean time spent in HRR training zone (%)	0	4%	0%	55%	62%
Mean BPM	102	109	108	116	128
Mean RPE	12	13	11	12	
Cognitive training					
Total number of sessions	24	24	24	11	12
% adherence	100%	100%	100%	73%	80%
# tasks performed	363	222	252	157	234

% adherence based on 24 sessions for A.A, B.B AND C.C and on 15 sessions for D.D and E.E. HRR, heart rate reserve; BPM, beats per minute; RPE, ratings of perceived exertion.

5. Discussion

This case series aimed to assess the feasibility of introducing progressive aerobic exercise programs into subacute rehabilitation of moderate-to-severe TBI. Despite cognitive impairments and concomitant physical injuries, participants adhered to the exercise program with minimal adverse events. Nevertheless, just two participants exercised for more than 50% of the time within the target heart rate zones and poor correlations between HRR and perception of effort were seen.

Inpatient as well as early outpatient rehabilitation from severe TBI involves intensive multidisciplinary treatments. However, damage to frontal lobes and networks integral to drive

and motivation can be problematic to the rehabilitation process [42]. Low motivation in individuals with TBI is often observed and commitment to, and perseverance in, rehabilitation can be negatively affected [43]. Fatigue [27] and apathy [28] are also common in this phase of recovery and so, aerobic exercise may be challenging to initiate and sustain. More recently, adherence to minimally supervised aerobic exercise programs within community-dwelling individuals with TBI was deemed feasible [44]. Importantly, such aerobic exercise programs may improve mood in chronic TBI [45,46]. Less is known about adherence to aerobic exercise in sub-acute rehabilitation however, and so the results from the present study suggest the addition of three, one-hour sessions of aerobic exercise per week for 8-weeks to the multidisciplinary rehabilitation schedule can be feasible.

Up to 78% of individuals with TBI may present with concomitant extracranial injuries, which have been significantly associated with long-term disability [47]. These physical barriers to aerobic exercise can also contribute to a sedentary lifestyle and result in long-term sedentary behaviour upon discharge from the hospital [48]. Therefore, the re-introduction of aerobic exercise soon after injury may be important. Indeed, aerobic exercise has been shown to improve clinical disability scores in other clinical populations [49] and so successful adherence to an early 8-week aerobic exercise program in individuals with concomitant injuries to TBI, such as loss of ambulation (A.A), cervical and clavicle and rib fractures (B.B and C.C and E.E) has the potential to improve long term disability. Nevertheless, despite adhering to both the exercise program and traditional rehabilitation, only two participants exercised for more than 50% of the time within the target intensity zones. A previous study showed that just 28% of individuals with severe TBI exercised above 50% of their heart rate reserve (HRR) during circuit class therapy [13]. The authors did not report on physical limitations of participants in that study. It is possible that the concomitant injuries sustained by the participants in this case series limited

their ability to exercise at higher HR intensities. However, contributions beyond physical limitations (which dictated exercise type) may also account for this. Participants A.A and B.B performed different exercises (arm/leg cycling and static upright cycling, respectively) and neither participant exercised within the target HR training zones. The Karvonen equation, used to calculate HR training zones, uses 220-age to predict HR maximum and may be a contributing factor. The peak aerobic capacity of individuals with TBI has been reported at 65-74% of non-injured adults [50-52] and so this widely used equation may underestimate intensity zones in this population.

The possible inability of the Karvonen equation to capture true HRR in individuals who have lower peak aerobic capacity could also explain the poor correlation between HRR and RPE seen. However, participant D.D reported the same RPE value at most time points regardless of HR and so it is more likely that this individual had difficulty in accurately communicating their true perception of effort. Indeed poor awareness of subjective fatigue in individuals with TBI compared to healthy controls has previously been reported [21]. Importantly, the Borg scale is not validated in individuals with TBI and discrepancies in the meaning of the verbal anchors may exist in this population [53]. Nevertheless, RPE is the preferred method to assess intensity in individuals who take medications that affect HR or pulse [54]. This is of particular importance as if the peak aerobic capacity of individuals with TBI is reduced [50–52] and/or medications that affect resting heart rate are taken, then heart rate measures to control for the intensity of exercise may be invalid. Yet the use of RPE may also prove inaccurate [53,55]. Larger studies to assess this phenomenon in individuals in this phase of recovery and a search for optimal methods to control for exercise intensity are required.

The results from this case series should be interpreted in light of their limitations. The recording of RPE at 15-minute intervals in a small sample is a limitation. Yet implementation of RPE recordings at greater frequencies within the clinic might be impractical. The use of wrist-based photoplethysmograpghy (PPG) technology to monitor HR is also a limitation with its susceptibility to motion artifact [56]. However, this may represent a best-case scenario as the use of the gold standard chest straps may be impractical in individuals with severe TBI who present with behavioral and cognitive impairments. Additionally, by not re-measuring resting heart rate prior to each exercise session changes in resting heart rate (which dictates heart rate training zones) over the 8-week intervention period an unaccounted for.

6. Summary

The inclusion of three, one-hour sessions of aerobic exercise for 8-weeks into intensive multidisciplinary rehabilitation for moderate-to-severe TBI was feasible. Individuals tolerated the aerobic exercise well and concomitant physical injuries did not hinder their participation. Despite this feasibility, future studies are required to better understand how the intensity of exercise can be controlled in this population.

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Chapter 5

Experimental work

The Influence of a Single Bout of Light Aerobic Exercise on Executive Function, Insulin-like Growth Factor-1 and Cortical Excitability

The following chapter was submitted to *Journal of Sport and Health Sciences* on the 28th of May 2018. Prior to the submitted manuscript is a preamble of the study techniques, specifically transcranial magnetic stimulation.

Preamble

This study was conducted using a non-invasive brain stimulation technique called transcranial magnetic stimulation (TMS) that warrants a dedicated introduction. TMS is based on Faraday's principles of electromagnetic conduction. A single pulse of TMS applied over the primary motor cortex (M1) produces a series of waves generated via large pyramidal tract neurons that travel down the cortico-spinal tract to peripheral muscles (Di Lazzaro & Rothwell, 2014). An object measure of the excitability of the corticospinal tract can be obtained via surface electromyography (EMG) electrodes placed typically on one or more intrinsic hand muscles. The TMS pulse will generate a compound muscle activation termed a motor evoked potential (MEP), the amplitude of which gives us an index of cortico-motor-spinal excitability. The threshold for induction of a MEP can be obtained both at rest (termed the resting motor threshold (rMT)) and during tonic muscle activation (termed the active motor threshold (aMT)). rMT is defined as the minimum amount of stimulation intensity (measured as a percentage of machine stimulator output), necessary to consistently evoke MEPs of at least 50μV 50 % of the time. aMT is defined as the lowest intensity necessary to evoke MEPs of $\geq$ 200 μV in five out of ten trials with the FDI muscle slightly contracted. In many cases, a percentage of the resting or active MTs are used to set the intensity of subsequent TMS parameters. rMT is related to corticospinal excitability, such that the lower the rMT, the higher the excitability of the corticospinal tract.

To gain measure of the baseline excitability of the corticospinal tract, a given amount of single pulses of TMS (typically between 60 and 120) are applied over the hand region of M1. spTMS is applied at 120% of rMT which will evoke consistent MEP responses in the corresponding hand muscle. Baseline MEP amplitude is the average MEP amplitude over all trials. This baseline measure of corticospinal tract excitability is then used as a reference amplitude for

subsequently TMS protocols such as paired pulse TMS (ppTMS). Certain TMS capacitors are capable of producing pairs of pulse in short succession, known as ppTMS. Here, a conditioning pulse (pulse A) is applied at a given intensity (as a percentage of rMT) and after a pre-determined inter stimulus interval (ISI), a second (pulse B) test pulse is applied. The resulting MEP amplitude is expressed as a percentage of the unconditioned pulse (baseline MEP amplitude). Different ppTMS parameters have been observed and pharmacological studies have given insight into the mechanisms behind the changes in MEPs observed from different ppTMS protocols.

Two ppTMS paradigms, namely short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) are observed with varying ISIs after conditioning and test pulses at 80 and 120% of rMT, respectively. That is, a conditioning pulse of 80% rMT is followed by an ISI of either 3-5ms (SICI) or 10-15ms (ICF) and the resulting MEP is either smaller (inhibition) or larger (facilitation) compared to an unconditioned MEP (baseline MEP amplitude). Given the conditioning and test pulses are of the same intensity, whether inhibition or facilitation is seen with these paradigms is dependent upon the ISI. Whereby shorter ISI result in SICI and longer ICF. SICI has been attributed to intracortical inhibitory processes. As the conditioning pulse is sub-threshold (80%) no MEP is elicited. Furthermore, studies have shown that H-reflexes, (peripheral simulation that gives a measure of spinal excitability) is un altered by SICI (Kujirai et al., 1993), suggesting that the effect is modulated within the motor cortex. Additionally, SICI has been attributed to GABA-a mediated intracortical circuits (Kujirai et al., 1993). That is, the duration of the inhibition is ~20ms, which is consistent with GABA-a mediated inhibitory post-synaptic potentials in animal studies (Krnjevic, Randic, & Straughan, 1964). Furthermore, benzodiazepines, a GABA-a agonist increases SICI (Ulf Ziemann, Lönnecker, Steinhoff, & Paulus, 1996). Similar to SICI, ICF is attributed to intracortical processes as no modulation of

the H-reflex is seen either (Ziemann U, Rothwell J C, & Ridding M C, 1996). However, ICF is attributed to the net facilitation (prevailing facilitation in face of weaker inhibition) of NMDA receptor mediated cortical circuits (R. Chen et al., 1998). That is, with NMDA receptor antagonists, a decrease in ICF is seen (U. Ziemann, Chen, Cohen, & Hallett, 1998). Together, an indication of the motor cortex inhibitory/excitatory balance is achieved.

The Influence of a Single Bout of Light Aerobic Exercise on Executive Function, Insulin-like Growth Factor-1 and Cortical Excitability.

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Author contributions

TM was involved in the study concept and design, carried out the data collection, performed the data analysis, interpreted the results and drafted the manuscript. PJF helped conceive the study, participated in data collection, data analysis and its interpretation and in the preparation of the manuscript. JM helped with the study set up, data collection, screening of participants and gave a critical review of the manuscript. AS was involved in the study design, participant recruitment and performed critical review of manuscript for intellectual content. JGO helped with the study concept, interpretation of data and gave a critical review of manuscript for intellectual content. DCM was involved in the study concept, interpretation of data and gave critical review of manuscript for intellectual content. JTM was involved in the study concept and gave a critical review of manuscript for intellectual content. ES conceived the study design, was involved in the data analysis and their interpretation and gave critical review of manuscript for intellectual content. APL conceived the study, was involved in its design, the interpretation of the data and gave a critical review of manuscript for intellectual content. All authors have read and approved the final version of the manuscript and agree to the order of their presentation in the aurthorship list.

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Conflict of Interest Disclosures

Dr. A. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Constant Therapy, Cognito, and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging. Dr. Santarnecchi serves on the scientific advisory boards for EBNeuro.

Abstract

Objectives: Increases in insulin-like growth factor-1 (IGF-1) and short-term changes in neuroplasticity are potential biological mechanisms of the effect of single bouts of aerobic exercise on executive function. Less is known about the effects of light aerobic exercise, an intensity of exercise more achievable for individuals with mild traumatic brain injury (mTBI). This study had two aims: Firstly, to assess the effect of a single bout of light aerobic exercise on multiple domains of executive function, on transcranial magnetic stimulation (TMS) measures of cortical excitability, and on peripheral levels of insulin-like growth factor-1 and cortisol. A secondary aim was to pilot this protocol in a group of individuals with mild TBI.

Methods: A randomized 2-by-2 within-subjects crossover study design was employed. On two separate days (≥7 days apart), fourteen healthy adults and four individuals with mTBI (≤3 months post injury) completed the following study procedures twice: Neurocognitive battery (multitasking performance, inhibitory control and spatial working memory), paired pulse TMS-measures of cortical excitability and serum levels of IGF-1 and cortisol. On each day these measures were taken before and after 30-minutes of either light aerobic exercise (cycling) or seated rest.

Results: Significant improvements in response times during multitasking performance and increases in intracortical facilitation (ICF) were seen following light aerobic exercise in healthy

adults. No change in IGF-1 was seen in either condition but cortisol levels were reduced following both rest and exercise in the healthy adults. In the mTBI group, large effect sizes were seen for spatial working memory in the exercise condition and cortical inhibition was increased following exercise compared to a reduction following rest.

Conclusions: Short bouts of light aerobic exercise can improve multitasking performance and modulate cortical excitability in healthy young adults. Individuals with mTBI may have a different response to light exercise as shown by modulation of spatial working memory and cortical inhibition.

Key Words: Transcranial magnetic stimulation; Plasticity; Light aerobic exercise: Insulin-like growth factor-1; Executive function; Multitasking; Traumatic brain injury

1. Introduction

Single bouts of aerobic exercise can improve cognitive performance in healthy adults. (Y. K. Chang, Labban, Gapin, & Etnier, 2012). Domain specific improvements have been reported and much focus has been placed on exercise-induced improvements in executive functions (Etnier & Chang, 2009). A variety of studies have examined the effects of short bouts of exercise on different executive functions, such as planning, task switching and working memory (Y.-K. Chang et al., 2011; Hung, Tsai, Chen, Wang, & Chang, 2013; Pontifex, Hillman, Fernhall, Thompson, & Valentini, 2009). Whilst these studies have shown facilitative effects of exercise, other studies have failed to show a benefit (Coles & Tomporowski, 2008; Tomporowski & Ganio, 2006). These inconsistent findings have generated debate surrounding the complexity of the executive function being assessed, the timing of assessment, and the population being tested (Etnier & Chang, 2009). Evidence from the exercise literature has

shown that beyond these variables, different exercise parameters, such as the intensity of exercise are significant moderators of this effect (Y. K. Chang et al., 2012; Coetsee & Terblanche, 2017; Davranche, Brisswalter, & Radel, 2015). In the rehabilitation setting, aerobic exercise is a commonly utilized therapeutic intervention that, beyond the benefits to physical function, has the potential to enhance deficits in executive function (Morris, Gomes Osman, Tormos Muñoz, Costa Miserachs, & Pascual Leone, 2016). For individuals with traumatic brain injury (TBI), who may present with concomitant extracranial physical injuries, higher exercise intensities may not be achievable (Mossberg, Ayala, Baker, Heard, & Masel, 2007). Therefore, investigating the cognitive effects and mechanistic underpinnings of light aerobic exercise is especially pertinent for this population. Similarly, the same may apply to previously sedentary older adults who may also stand to benefit from an exercise program (Colcombe & Kramer, 2003). However, not much is known regarding the cognitive effects of light aerobic exercise, even in healthy individuals.

Aerobic exercise can increase peripheral levels of growth factors such as brain-derived neurotrophic factor (BDNF) (Piepmeier & Etnier, 2015) and IGF-1 (Schwarz, Brasel, Hintz, Mohan, & Cooper, 1996) and in animal models, such increases have been associated with exercise-induced improvements in cognitive function (Cassilhas et al., 2012; Ding, Vaynman, Akhavan, Ying, & Gomez-Pinilla, 2006). These effects may represent an underlying biological mechanism of the effects of single bouts of aerobic exercise on executive functions in humans. While BDNF has been investigated for its role in the effect of exercise on cognition (Leckie et al., 2014; Piepmeier & Etnier, 2015), fewer studies have assessed the role of IGF-1. Like BDNF, IGF-1 can be measured in the periphery and is known to cross the blood brain barrier during both cognitive and physically-dependent actions (Trejo et al., 2007). Nevertheless, increases in IGF-1 have not been demonstrated after single bouts of light aerobic exercise

(Schwarz et al., 1996). Furthermore, it is also unclear whether light aerobic exercise modulates IGF-1 in TBI, where high cortical demand coupled with low serum levels is seen (Madathil & Saatman, 2015; Schober et al., 2010).

Exercise can also induce short term neuroplasticity within the motor cortex (Mooney et al., 2016; Singh, Duncan, Neva, & Staines, 2014; A. E. Smith, Goldsworthy, Garside, Wood, & Ridding, 2014) and the immediate effect of exercise on executive function tasks, specifically those measured via response times (multitasking, inhibitory control), may also be driven, in part, by neuroplastic changes related to neurotransmitter signaling (glutamate and gamma-aminobutyric (GABA)) (Kujirai et al., 1993; Maddock, Casazza, Fernandez, & Maddock, 2016). Transcranial magnetic stimulation paradigms provide a means to characterize cortical excitability balance in the motor cortex (Pascual-Leone et al., 2011). Paired-pulse TMS (ppTMS) can be applied with different inter-stimulus intervals to provide an understanding of excitatory and inhibitory GABAergic and glutamatergic systems (Kujirai et al., 1993; Valls-Solé, Pascual-Leone, Wassermann, & Hallett, 1992). Studies have shown that moderate intensity exercise can modulate TMS measures of intracortical facilitation (ICF) and inhibition, including short interval intracortical inhibition (SICI) and long interval intracortical inhibition (LICI) (Mooney et al., 2016; Singh et al., 2014; A. E. Smith et al., 2014), but it is not known if those intracortical circuits are also modulated by light aerobic exercise. Whilst studies have evaluated the effect of exercise on motor learning (Tunovic, Press, & Robertson, 2014) and procedural memory (Ostadan et al., 2016), and associated those improvements with cortical excitability and plasticity (Mang, Snow, Campbell, Ross, & Boyd, 2014), few studies have assessed the relationship between the effect of exercise on both executive function tasks and TMS measures of cortical excitability. Our previous work has shown the feasibility of using TMS measures of plasticity to assess the effect four weeks of light aerobic exercise on Stroop

and response inhibition improvements (Gomes-Osman et al., 2017). Yet the effect of a single bout of light aerobic exercise is unknown.

The present study was designed to assess the effect of a single bout of light aerobic exercise on several executive function tasks, peripheral levels of IGF-1 and cortisol and TMS measures of short-term neuroplasticity. A secondary aim was to pilot this protocol in a group of individuals with mild traumatic brain injury (mTBI). We hypothesized that a single bout of light aerobic exercise would improve multitask performance, inhibitory control and spatial working memory more so than a rest control intervention in both the healthy adults in in the TBI group. We further hypothesized that TMS and peripheral biomarker measures would be associated with such improvements.

2. Methods

2.1 Participants

The Institutional Review Board of the Beth Israel Deaconess Medical Center (BIDMC) approved this study and participants signed informed consent prior to participating in any research procedures. Participants were recruited via an internal repository of previous research participants from the Berenson-Allen Center for Non-Invasive Brain Stimulation (healthy adults) and via a concussion clinic (mTBI) at BIDMC. Interested participants were screened for eligibility using the following criteria: right-handed (confirmed by the modified version of the Edinburgh Handedness questionnaire (Milenkovic & Dragovic, 2013), between the ages of 18 and 60 years, without neurological or physical conditions that might affect performance on testing procedures or known contraindications to TMS (Rossi et al., 2009). Contraindications

to exercise testing were screened via the Physical Activity Readiness Questionnaire (PAR-Q) (Adams, 1999). Fourteen healthy adults (including 9 females) with a mean (±SD) age of 26 (±3) years completed all study procedures. As an exploratory arm of the study, the same experiments were performed on four individuals with mTBI (mean (±SD) age of 25 (±5)) who were a mean (±SD) of 53 (±40) days post-injury. The diagnosis of mTBI (traumatically induced physiological disruption to the brain with a Glasgow Coma Score of 13-15 and loss of consciousness <30 minutes) was confirmed by a board-certified neurologist and concussion specialist (AS). Criteria for diagnosis was defined as a traumatically induced physiologic disruption of brain function with manifestations such as loss of consciousness and memory as outlined in the clinical practice guidelines for mild traumatic brain injury (Marshall, Bayley, McCullagh, Velikonja, & Berrigan, 2012).

2.2 Protocol and study design

Participants completed two study visits in a randomized counterbalanced order design. Study visits consisted of the following procedures (Figure 1): cognitive testing, a TMS session, intravenous blood draw, either a 30-minute aerobic exercise (cycling) or control rest intervention followed by a repeat of the blood draw, cognitive tasks and finally the TMS session. Study visits were scheduled so that each procedure was undertaken at roughly the same time of day over both visits. A random number sequence generated by Microsoft Excel (Microsoft, USA) determined the order in which each participant completed the study to minimize practice effects of the cognitive tasks.

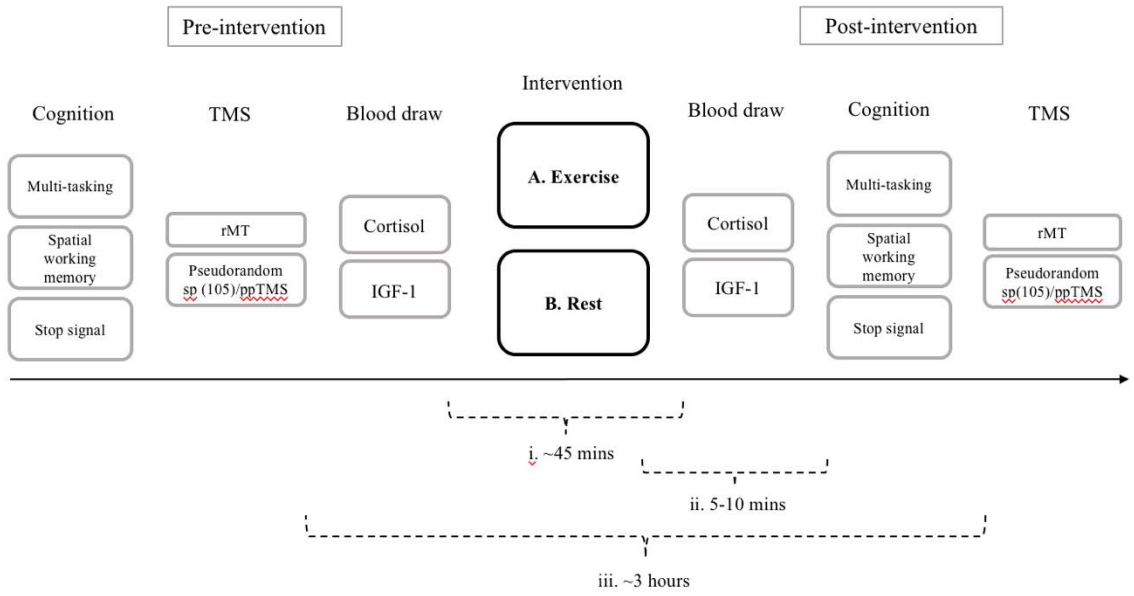

Figure 1. Figure 1. Timeline of study procedures. The study employed a 2*2 (intervention by block) within-subjects A-B randomized protocol whereby participants were randomized to either perform the exercise intervention or rest control first, followed by the remaining intervention ≥7days later. The post-intervention cognitive tasks, blood draw and TMS sessions were identical to the pre-intervention sessions. An IV was placed 15-minutes prior to the pre-intervention blood draw to minimize cortisol increases as a result of the IV insertion. The IV remained in place during the exercise or rest interventions. i: 45 minutes between the end of the pre-blood draw and the beginning of the post blood draw. ii: 5 to 10 minutes between the end of the exercise and the beginning of the post intervention cognitive tasks. iii: The time between the end of the pre-intervention TMS session the start of the post-intervention TMS session was 3 hours.

2.3 Intervention

The aerobic exercise intervention consisted of 30 minutes of light aerobic exercise on a Monarch 928 G3 static cycle electronic ergometer (Monarch exercise AB, Vansbro, Swenden). Prior to the intervention, a nurse recorded baseline vital signs (resting heart rate, blood

pressure, oxygen saturation, respiratory rate). A Polar H7 heart rate strap (Polar, Kemple, Finland) was worn measuring second-by-second heart rate (HR), recorded via the cycle ergometer with an ANT+ / 5KHz receiver. HR data was also collected using an iPad (Apple Inc, California) and commercial software (Polar Flow, Kemple, Finland). The ergometer was then fitted to each participant who subsequently undertook a 5-minute warm-up consisting of passive cycling with no resistance. After the warm-up, participants undertook 30-minutes of light intensity cycling. Intensity was calculated based on the Karvonen equation and the target HRR zone was 40 and 60% HRR:

(1) target HR = ((HRmax – resting HR) * intensity [0.4 - 0.6]) + resting HR.

This exercise intensity was chosen based on prior research with TMS and cortisol, which suggests higher intensity exercise interventions abolished the neuromodulatory effects of repetitive TMS, possibly related to exercise-induced increases in cortisol (McDonnell, Buckley, Opie, Ridding, & Semmler, 2013; A. E. Smith et al., 2018). Resistance of the cycle ergometer was adjusted by study researchers to ensure participants reached the exercise intensity zone. Upon completion of the intervention, participants cooled-down for 2-minutes (no resistance cycling), after which, post-intervention vital signs were recorded by the nurse. The control intervention consisted of seated rest for 30 minutes. During this time, participants could interact with study staff, use the mobile phones or read, but were seated and made no whole-body movements during the 30 minutes. HR was also recorded during the rest intervention using the same Polar strap.

2.4 Cognitive tasks.

A battery of three tablet-based executive function tasks was completed before and after each intervention using the Cantab cognitive testing software (Cambridge cognition, Cambridge, UK) on an iPad Pro (Apple Inc, California) (Luca et al., 2003). The Cantab battery has been

shown to be well correlations with traditional pen and paper neuropsychological tests (P. J. Smith, Need, Cirulli, Chiba-Falek, & Attix, 2013) and demonstrate moderate to high test-retest reliability (Gonçalves, Pinho, & Simões, 2016; Lowe & Rabbitt, 1998). Participants were given verbal instructions by the Cantab software as well as practice trials prior to each test. The tasks were identical at each time point. The following tasks were chosen to measure inhibitory control, processing of conflicting information (multitasking) and spatial working memory:

The *multitasking test* presented two virtual buttons on either side of the screen and a cue (side, direction) with an arrow above either button (left or right) indicating which button to select. Cues appeared (for the full duration of the trial) in consistent (single task) and in-consistent (multitask) trials and both congruent (arrow on right side pointing right) and incongruent trials (arrow on right side pointing left) were presented. The distribution of the trials was randomly ordered within the following constraints: if multiple trials are presented then 50% must be switch trials, 25% switch trials that are congruent and 25% which are switch trials that are incongruent. Outcome measures consisted of reaction times, errors and multitasking cost (mean latency of single blocks subtracted by mean latency on multitasking blocks).

The *inhibitory control task (stop signal task)* required participants to respond to an arrow stimulus pointing in a given direction. The first set consisted of 16 trials where the participant practiced the response. In the second set, the participant was told to inhibit their response if they heard an auditory signal (a beep). An adaptive *staircase* was employed for the stop signal delay allowing the task to adapt to the performance of the participant to narrow in on a 50% success rate. An inter-stimulus interval of 1000ms was applied. The outcome measure was stop signal reaction time, the estimate of when an individual can

successfully inhibit their response 50% of the time. This is inferred as the time before all actions become ballistic and the person is no longer able to stop the action.

A *spatial working memory task* required participants to find tokens hidden behind covered boxes and transfer them to empty boxes on the right-hand side of the screen without re-opening a box that has previously been selected. This task displayed four, six or eight boxes and outcome measures consisted of errors (trials when a participant revisits a box in which a token has been previously found) and strategy. It has been suggested that an efficient strategy to complete this task is to follow a predetermined sequence beginning with a given box and once a token has been found return to the same box to begin the next search (Owen, Sahakian, Semple, Polkey, & Robbins, 1995). Participants were not informed of this strategy. To estimate how well this strategy was utilized, the number of times a subject begins a new search with the same box was calculated. A high score represents poor use of this strategy and a low score, effective use.

2.6 Transcranial magnetic stimulation (TMS) and Electromyography (EMG)

To measure the amplitude of TMS-induced motor evoked potentials (MEPs), surface electrodes were placed in a belly-tendon montage on the right first dorsal interosseus (FDI; target muscle) and the abductor pollicis brevis (APB; reference muscle) with a ground on the ulnar styloid process. Electrodes were connected to a PowerLab 4/25T data acquisition device (ADInstruments, Colorado Springs, CO, USA). EMG data epochs (100 ms pre-trigger to 500 ms post-trigger) were digitized at 1 kHz and amplified with a range of ±10 mV (band-pass filter 0.3–1000 Hz) and peak-to-peak MEP amplitude of the non-rectified signal was calculated on individual waveforms using LabChart 8 software (ADInstruments).

All TMS parameters used in this study conform to the guidelines of the International Federation of Clinical Neurophysiology (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009). In accordance with these guidelines the following TMS procedures were applied before and after each intervention: The optimal spot for the maximal responses of the right FDI muscle was localized and deemed the "motor hotspot." Resting motor threshold (rMT) was obtained and used to set the intensity of subsequent TMS. rMT was defined as the lowest stimulation intensity required to evoke MEPs ≥ 50 μV in the relaxed right FDI muscle, in five out of ten trials. TMS was applied to the left primary motor cortex using a passive-cooled handheld MagPro MC-B70 Butterfly Coil (outer diameter: 97 mm) connected to a MagPro X100 stimulator (MagVenture A/S, Farum, Denmark). The coil was placed tangential to each participant's head with the handle oriented approximately 45° relative to the mid-sagittal axis. A monophasic current flowing anterior-posterior (AP) through the coil center was used to induce a posterior-anterior (PA) current approximately orthogonal to the central sulcus. Consistent targeting of the motor hotspot throughout the experiment was achieved by means of a Polaris infrared optical tracking system (Northern Digital Inc., Waterloo, ON, Canada) and a Brainsight TMS neuronavigation system (Rogue Research Inc., Montreal, QC, Canada) using the Montreal Neurological Institute structural MRI template brain. The head-tracker (headband) was removed between each TMS session and at the beginning of each subsequent session, the motor hotspot and rMT were re-checked.

After determining the motor hotspot and rMT, interleaved single pulse TMS (spTMS) and ppTMS were applied over the course of three separate blocks. Each block consisted of spTMS (5 trials each at 80% rMT and 120%rMT), 10 trials of SICI (80%-rMT conditioning stimulus, 120%-rMT test stimulus, 3ms interval), 10 trials of ICF (80%-rMT conditioning stimulus,

120% test stimulus, 12ms interval), and 10 trials of LICI (120%-rMT conditioning stimulus, 120%-rMT test stimulus, 100ms interval). The trial order and the inter-trial interval were pseudorandomized to avoid any block effects or train effects, respectively. Unconditioned cortico-motor reactivity was determined by combining trails of spTMS at 120% with the conditioning stimulus of LICI. Conditioned MEPs were averaged across each ppTMS protocols. Like protocols were averaged across the three blocks.

2.7 Blood sample

Blood samples were obtained by peripheral intravenous draw by a research nurse approximately 5-10 minutes following the end of the pre-intervention TMS session. A 15-minute period prior to the blood draw was adhered to minimize any effects of the IV insertion on cortisol levels. 2 mL of blood was drawn and collected in a BD vacutainer tube. The samples were spun at room temperature at 16 *g* for 10 minutes in a Horizon 642E centrifuge (LabCorp, Burlington, NC, USA) to separate serum. Serum samples were refrigerated for up to 24 hours before being collected by a LabCorp technician. Samples were processed by LabCorp for levels of IGF-1 (Test 010363, CPT 84305) using an immunochemiluminometric assay (ICMA) and cortisol (Test 004051, CPT 82533) using an electrochemiluminescence immunoassay (ELICA).

2.8 Statistical analysis

All statistical analyses were performed using JMP Pro (v 13.0, The SAS Institute Inc., Cary, North Carolina, USA) assuming a normal distribution and a two-tailed 95% confidence interval (α=.05). Following a within-subjects design, data corresponding to cognitive function scores,

TMS measures, and serum IGF-1 and cortisol levels were each entered into separate 2*2 random-effects linear models, with *intervention* (exercise, rest) and *block* (pre-intervention, post-intervention) as main factors. TMS measures consisted of rMT (% of maximum stimulator output; %MSO), unconditioned cortical reactivity (spTMS at 120% and the LICI conditioning pulse), and ppTMS measures of SICI, LICI and ICF (% change of conditioned MEP from unconditioned cortical reactivity). As practice effects have been evidenced for the cognitive tasks (Cacciamani et al., 2018), our main hypothesis was that exercise would improve cognitive test scores more so than rest. Accordingly, post hoc comparisons using Tukey's honestly significant difference (HSD) tests were performed when a significant main effect of block was found for the cognitive task data, or when an intervention by block interaction was found for the TMS, IGF-1 or cortisol analyses. The effect size was presented as partial eta squared (η_ρ^2) for significant effects. Simple bivariate correlations (Pearson's R coefficient) were performed on variables highlighted by the linear models to show significant changes across and within interventions. Data for the mTBI group is presented in table 2 as mean ± SD of all outcome variables with Cohen's D effect sizes for the pre/post effect of each intervention separately.

3. Results

3.1 Healthy adults

Mean exercise HRR for the exercise condition was 48 ± 5% HRR and was significantly different compared to the rest condition (5 ± 4% HRR).

3.1.1 Executive functions

Table 1 presents mean ± SD scores for the executive function tasks at each time point. Random-effects linear models showed significant main effects of *block* for mean latency reaction times

on the multitasking test for all congruent trials ($F_{1,17} = 25.27$, $p = <.001$, $\eta_\rho^2 = .60$), incongruent trials ($F_{1,13} = 23.04$, $p = <.001$, $\eta_\rho^2 = .64$), multitasking trials where both rules (side and direction) were used ($F_{1,13} = 23.73$, $p = <.001$, $\eta_\rho^2 = .68$) as well as the multitasking cost ($F_{1,13} = 9.39$, $p = .009$, $\eta_\rho^2 = .42$). A *block*intervention* interaction was observed in the multitasking trials (Figure 2), though it did not reach significance ($F_{1,13} = 2.35$, $p = .095$). Post hoc comparisons showed significant improvements in the exercise condition ($p = .003$) but not in the rest condition ($p = .338$). Further comparisons of the significant effects of *block* in these outcomes revealed significant pre/post differences in the exercise condition for the congruent ($p = .007$) and incongruent ($p = .003$) trials but not in the rest condition (congruent: $p = .101$; incongruent: $p = .338$). No change in either condition was seen for the multitasking cost.

Table 1. Mean and SD scores for executive function tasks

Task	**Pre-exercise**	**Post-exercise**	Δ	***P***	**Pre-rest**	**Post-rest**	Δ	***P***
Multitasking test								
Congruent	555.6 ± 112.7	499.3 ± 78	-47.9 ± 52.9	.001	554.5 ± 102.8	518.6 ± 78.8	-35.9 ± 53.2	.083
Incongruent	622.8 ± 119.9	553.1 ±125.2	-69.4 ± 49.7	<.001	611.2 ± 122.4	584.6 ± 92.7	-27.2 ± 65.3	.324
Multitasking	690.3 ± 184.4	597.2 ±125.2	-93.1 ± 88.3	.007	682.5 ± 178.2	630.2 ± 116.4	-52.3 ± 98.3	.204
Cost	201.7 ± 150.4	141.9 ±100.1	-59.8 ± 97	.178	198.7 ± 139.9	157.9 ± 74.5	-40.8 ± 97.8	.437
SST								
Stop signal RT	206.7 ± 29.7	221.6 ± 40	14.4 ± 43.4		211.2 ± 42.5	219.7 ± 34.8	8.5 ± 32.9	
SWM								
BE	4.4 ± 5.2	5.7 ± 6.3	0.4 ± 1.6		5.1 ± 5.3	6.2 ± 8.1	0.5 ± 9.2	
Strategy	5.3 ± 2.7	5.4 ± 3.1	0.1 ± 1.6		5.5 ± 2.8	5.6 ± 3.2	0.1 ± 3.4	

P statistic from Tukey HSD post hoc comparisons of the 2*2 linear models which showed a main effect of block.

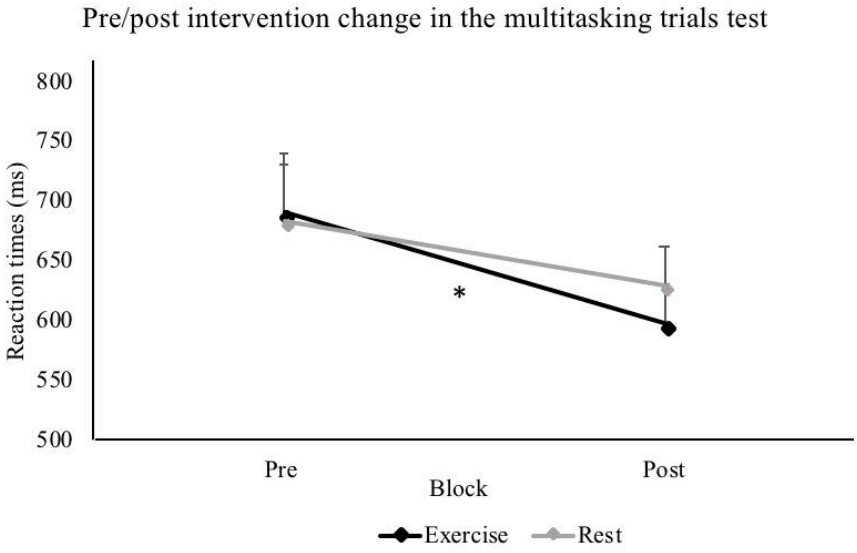

Figure 2. Evidence of an improvement in the multitasking trials (where both congruent and incongruent rules are used) of the multitasking test. A non-significant block *intervention interaction was observed (p = .095) and post hoc comparisons showed a significant pre/post change in the exercise condition (p = .003) but not in the rest condition (p = .338). * indicates significant post hoc change in the exercise condition.

No significant effects of *block* or *block*intervention* interaction were seen in stop signal reaction time (*block*: $F_{1,13}$ = 4.01, p = .066; *block*intervention*: $F_{1,13}$ = 0.12, p = .734), spatial working memory between errors (*block*: $F_{1,13}$ = 0.24, p = .632; *block*intervention*: $F_{1,13}$ = 0.02, p = .965) or strategy (block: $F_{1,13}$ = 0.08, p = .787; *block*intervention*: $F_{1,13}$ = 0.01, p = .953).

3.1.2 TMS measures

The random-effects linear model revealed a significant main effect of *block* ($F_{1,13}$ = 7.29, p = .018 η_p^2 = .36) for rMT. Specifically, there was a change pre-to-post intervention of -1.12 ± .40 %MSO (95% CI's .22, 1.99) (Table 2). A significant main effect of *block* ($F_{1,12}$ = 5.38, p = .040 η_p^2 = .31) and an *intervention*block* interaction for ICF was found ($F_{1,11}$ = 7.51, p = .018

η_p^2 = .41) (Figure 3). Post hoc comparisons showed a significant increase in ICF pre-to-post exercise (p = .021). No main effects of *block* were seen for SICI ($F_{1,13}$ = 2.44, p = .626), LICI ($F_{1,11}$ = 1.56, p = .189) or MEP amplitude ($F_{1,13}$ = 1.18, p = .885).

Table 2. Mean and SD scores for peripheral and TMS biomarkers

Task	Pre- exercise	Post exercise	Δ	*P*	Pre-rest	Post rest	Δ	*P*
Peripheral biomarkers								
IGF-1	196 ± 51.6	201.1 ± 51.8	5.1 ± 9.1		202.6 ± 53.3	202.5 ± 51.7	-0.1 ± 7.7	
Cortisol	11.7 ± 4.5	10.2 ± 2.7	-1.6 ± 4.4		9.6 ± 4	7.8 ± 3.7	-1.9 ± 0.9	
TMS measures								
rMT			-1 ± 2.3				1.2 ± 1.9	
MEP amplitude (uV)	856.7 ± 570.3	1097.1 ± 630.7	191.4 ± 598.4		1216.4 ± 710.7	1191.5 ± 629.6	-24.9 ± 438.9	
ICF	75.5 ± 82.1	114.5 ± 89.2	40 ± 63.2	.021	85.3 ± 94.2	74.87 ± 68.2	-10 ± 53.5	
SICI	-34.7 ± 36.6	-43.9 ± 48.4	-9.2 ± 60.9		-38 ± 46.5	-40.1 ± 31.5	-2 ± 52.4	
LICI	-65.1 ± 33.9	-84.5 ± 28.1	-19.4 ± 36.5		-74.8 ± 47.3	-77.9 ± 19.6	-2.1 ± 51.5	

P statistic from Tukey HSD post hoc comparisons of 2*2 linear models with main effect of block.

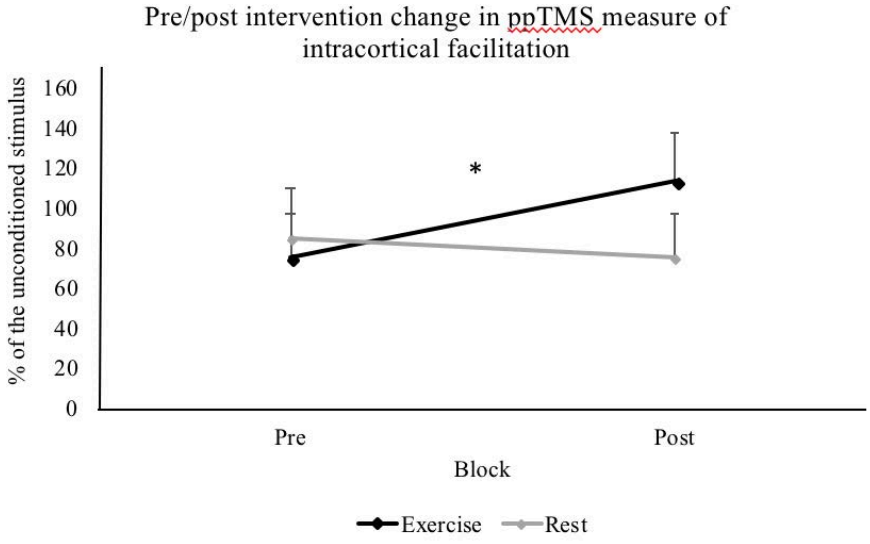

Figure 3. A significant block by intervention interaction (p = .018) in ICF was seen. A significant increase in ICF following exercise (p = .021) was observed. * indicates significant post hoc change in the exercise condition.

3.1.3 Cortisol and IGF-1

Significant main effects of *block* ($F_{1,12}$ = 7.59, p = .017 η_p^2 = .39) and *intervention* ($F_{1,12}$ = 4.83, p = .048 η_p^2 = .29) were seen for serum levels of cortisol, but no *block*intervention* interaction ($F_{1,12}$ = 0.06, p = .818). Cortisol levels were higher prior to the exercise intervention (12 ± 5 μg/dL) compared to before rest (10 ± 4 μg/dL), however a reduction in cortisol was seen in both conditions (Table 2). No significant effects of *block* ($F_{1,12}$ = 2.01, p = .180), *intervention* ($F_{1,11}$ = 0.44, p = .520) or *block*intervention* ($F_{1,12}$ = 2.97, p = .110) were seen for IGF-1, suggesting levels did not change in either the exercise intervention (Table 2).

3.1.4 Correlational analyses between significant outcomes and cognitive improvements

Simple linear regression yielded no significant correlations between %Δ in ICF and %Δ in multitask performance for any multitask outcome (congruent trials: R_{12} = -.16, p =.591; incongruent trials: R_{12} = -.32, p = .264; multitask trials: R_{12} = .06, p = .839; multitask cost: R_{12} = -.12, p = .687).

3.2 Results from the mTBI group

The HRR values for this group in the exercise condition were 44 ± 3% HRR and 6 ± 3% for the rest condition. Table 3 presents mean ± SD and Cohen's D effect sizes for all outcome variables in the mTBI group

Table 3. Results from the mTBI group

	Pre-exercise	Post-exercise	Δ	EF	Pre-rest	Post-rest	Δ	EF
Cognition								
Multitasking test								
Congruent	556.3 ± 208.6	492.1 ± 161.4	-64.2 ± 52.7	-0.34	583.3 ± 140.9	540.8 ± 75	-42.5 ± 85.7	-0.38
Incongruent	604.8 ± 215.3	541 ± 193	-62.8 ± 22.5	-0.31	661.1 ± 157.5	596.8 ±116.8	-64.3 ± 67.1	-0.46
Multitasking	684.6 ± 291.4	571.4 ±258.5	-113.2 ± 36.6	-0.41	763.9 ± 220.9	655.6 ± 139.7	-108.2 ± 108.4	-0.59
Cost	206.7 ± 156.7	108 ± 163.9	-98.8 ± 27.9	-0.62	283.4 ± 147.8	173.3 ± 93.7	-110.1 ± 75	-0.89
Stop signal task								
Stop signal RT	197.1 ± 21.4	194.2 ± 34.7	-2.9 ± 42.9	-0.1	218.5 ± 11.7	199.6 ± 32.2	-19 ± 31.2	-0.78
Spatial working memory								
Between errors	8.75 ± 7.7	1 ± 1.4	-7.8 ± 7.4	-1.4	3.5 ± 4	5.8 ± 9	2.25 ± 5.9	0.32
Strategy	6.5 ± 3.3	3.3 ± 2.5	-3.25 ± 3	-1.11	5.5 ± 3.5	4.8 ± 3.4	-0.8 ± 1	-0.22
Peripheral biomarkers								
IGF-1	244 ± 90. 5	237.3 ± 78.6	-5.0	-0.07	231.3 ± 65.3	235 ± 60	3.8 ± 10	-0.59
Cortisol	7.4 ± 2.4	7.7 ± 2.2	2.2	0.15	7.7 ± 2.2	7.5 ± 2.1	-0.2	-0.09
TMS measures								
rMT	41.3 ± 8	41.3 ± 8	0.0	0.0	41.3 ± 8	41.3 ± 8	0.0	0.0
MEP amplitude (uV)	737.5 ± 58.4	587.5 ± 188.4	-150 ± 664.9	-0.35	977.5 ± 244.1	597.5 ± 94.3	-380 ± 229.1	-2.05
ICF	38.4 ± 89.3	38.1 ± 74.2	-0.3 ± 20	0	43.7 ± 49.6	50 ± 44.9	6.3 ± 25.9	0.13
SICI	-65.75 ± 15.3	-74.6 ±35.7	-8.8	-0.32	-70.6 ± 30.4	-61.05 ± 12.7	9.5	0.41
LICI	-72.7 ± 9.1	-94.2 ± 28.4	-16.3 ± 24	-1.02	-103.4 ± 29	-85.7 ± 24.2	17.7 ± 37.1	0.66

Mean ± standard deviation of cognitive test scores, peripheral biomarker levels and TMS measures at each time point plus change scores and Cohen's D effect sizes.

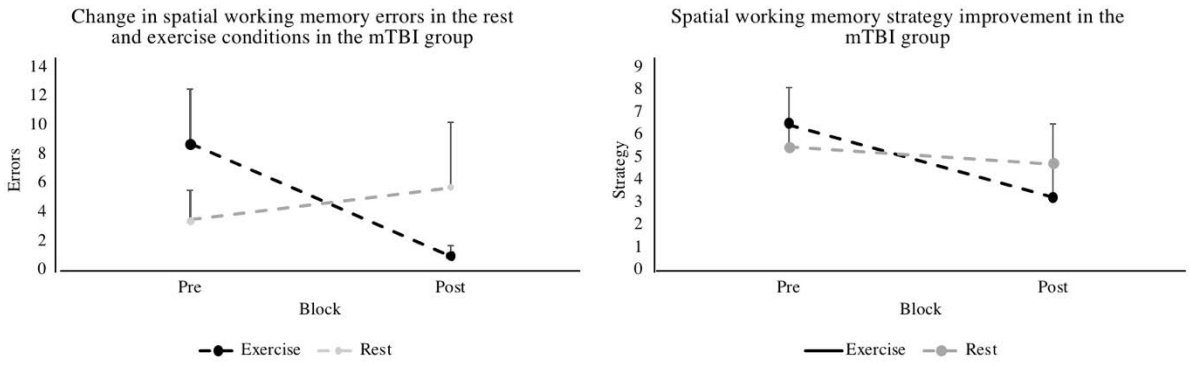

Figure 4. Large effect sizes (pre to post) in the exercise condition for spatial working memory errors (**A**; -1.4) and strategy (**B**; -1.1) are seen.

4. Discussion

Few studies have assessed how light aerobic exercise impacts executive function, IGF-1 and TMS measures of short-term neuroplasticity. The present study found that 30-minutes of light aerobic exercise improved response times on multiple outcomes of a multitasking task but did not improve inhibitory control or spatial working memory. Exercise-mediated increases in cortical excitability (ICF) were also observed. The intensity of our exercise intervention reduced cortisol levels at a similar rate to the rest condition however increases in IGF-1 were not seen. Large effect sizes for spatial working memory improvements were seen post-exercise in the mTBI group but similar to the healthy adults, no exercise-induced changes in IGF-1 or TMS measures were seen.

Meta-analyses on the effect of single bouts of exercise on cognitive function show a small but consistent improvement (Y. K. Chang et al., 2012). Nevertheless, some studies have failed to show an effect (Wang et al., 2015), suggesting exercise may not have broad widespread effects on all executive function domains. Indeed, our results show exercise enhanced several

measures of the multitasking test, but not for the inhibitory control and spatial working memory tasks. The present results add to the debate regarding the interactions of intensity of exercise and cognitive improvements. Moderate intensity aerobic exercise shows more consistent improvements in executive functions (Y.-K. Chang et al., 2011; Hung et al., 2013; Pontifex et al., 2009). It is conceivable that light aerobic exercise may not be intense enough to induce an adaptive plastic response necessary to improve more widespread executive functions.

Exercise-mediated gains in executive functions have been attributed to the increase in peripheral levels of BDNF in studies using longer-term exercise programs (Leckie et al., 2014), but some studies on acute effects of exercise on BDNF and cognitive function have failed to show any relationship (Ferris, Williams, & Shen, 2007). We chose to measure IGF-1 as this is an important neuroprotective mechanism following traumatic brain injury (Madathil & Saatman, 2015) and has been highlighted as a main signaling factor in exercise-effect on neuroplasticity (Llorens-Martín, Torres-Alemán, & Trejo, 2009). Nevertheless, our light aerobic exercise intervention did not increase IGF-1 levels, which is consistent with previous reports (Schwarz et al., 1996). Schwarz and colleagues (1996) reported that higher intensity exercise did lead to increases in peripheral IGF-1 levels, suggesting this effect may also be intensity-dependent. We chose light aerobic exercise for two reasons: (1) as it is an attractive priming intervention for individuals with TBI who may not be capable of exercising at higher intensities and (2), as higher intensity exercise can lead to a stress response characterized by increases in cortisol (Hill et al., 2008), which can have detrimental effects on cognitive performance (Vedhara, Hyde, Gilchrist, Tytherleigh, & Plummer, 2000). IGF-1 levels have been shown to be reduced following TBI (Wagner et al., 2010; Zgaljardic et al., 2011), but in our small sample, baseline levels were within normal age-dependent ranges and no participant

showed exercise-mediated increases. Further suggesting light aerobic exercise may not be intense enough to increase serum levels of IGF-1.

In a prior study by Ostadan and colleagues (2016), a correlation between exercise-increased cortico-spinal excitability (as measured by MEP amplitude) and procedural memory consolidation was shown, highlighting how TMS measures may be related to the effect of exercise on cognitive functions. In the present study, ppTMS measures of ICF were significantly increased after light exercise, consistent with previous reports (McDonnell et al., 2013; Singh et al., 2014), suggesting low intensity exercise may enhance NDMA receptor-mediated glutamatergic excitability in the motor cortex. However, the change in ICF was not correlated with the improvements in multitask performance, suggesting the effects of exercise on response times during processing of conflicting information and motor cortex excitability were independent. Although the motor cortex is involved in motor planning and execution (Cheney, 1985) and motor cortex excitability (as measured by ICF and SICI) is associated with voluntary movement (Christova et al., 2006; Nikolova, Pondev, Christova, Wolf, & Kossev, 2006), the ability to process conflicting information (incongruent trials and multitask cost) is dependent on higher-order cognitive regions outside of the primary motor area (Banich et al., 2000). Whereby the total response times of such tasks are a function of the sum of the encoding, decision and response output processes of task execution (Ratcliff & McKoon, 2008). Neuroimaging studies show associations between multitask performance and fronto-parietal networks, including regions such as the anterior cingulate cortex, lateral prefrontal cortices, parietal lobule and the anterior insula (Roberts & Hall, 2008). As such, the direct effect of exercise on ICF within the motor cortex may not reflect the more global effect exercise exerts on the brain (Weng et al., 2017). Advances in technology that allow real-time integration of TMS with electroencephalography (Farzan et al., 2016; Pascual-Leone et al., 2011) may

provide a means to better assess exercise-improved cognitive performance in regions outside of the motor area. Future research characterizing the cognitive and neurophysiological effects of exercise beyond the motor cortex may benefit from this technique.

Individuals with TBI show aberrant cortical excitability as measured by TMS compared to healthy adults (Bernabeu et al., 2009; Chistyakov et al., 2001; Lapitskaya, Moerk, Gosseries, Nielsen, & de Noordhout, 2013). It is possible that exercise may impact these variables differently in individuals who have brain injury compared to healthy adults. Few studies have used TMS to assess the effect of exercise on cortical excitability and plasticity in brain injured populations however. A recent study in individuals with stroke reported that light aerobic exercise did not evoke any changes in TMS measures of plasticity (Murdoch, Buckley, & McDonnell, 2016). Whilst our sample of mTBI individuals is too small to perform reliable means testing and correlations, some inferences can be made by looking at the direction and magnitude of the change induced by exercise compared to rest. Whilst ICF did not appear to change, the two measures of cortical inhibition (SICI and LICI) were increased by exercise and reduced following rest. In one previous study, SICI was reduced compared to healthy controls (Lapitskaya et al., 2013), suggesting the presence of abnormal inhibitory cortical circuits in these individuals. Whilst we cannot compare groups due to sample size differences, our results suggest that a single bout of light aerobic exercise may be capable of modulating inhibitory cortical circuits in individuals with mTBI. TMS therefore presents a pragmatic tool to assess cortical changes as well as exercise-mediated changes following TBI (Demirtas-Tatlided, Vahabzadeh-Hagh, Bernabeu, Tormos, & Pascual-Leone, 2013) and future studies should address the debate regarding intensity-dependent effects in larger populations of individuals with TBI.

Our results should be interpreted in light of the following limitations. Our sample of participants was relatively small with a narrow age range, and so our results may not be generalizable to older populations. Recruitment of brain injured populations, specifically those soon after injury for clinical research is inherently challenging (Bayley et al., 2014) as reflected by our small sample of individuals with mTBI. We do not attempt to delineate conclusions from our mTBI sample rather present them as preliminary evidence of our protocol and to show that this type of priming intervention can be assessed in this population. Aerobic exercise is a potential therapeutic treatment for both changes in neuroplasticity and executive function following TBI and so this type of research may enhance the knowledge regarding the mechanisms of the effect of exercise in this population.

5. Conclusions

A greater understanding of the mechanistic underpinnings of exercise's effect on cognitive performance will lead to the development of optimal exercise interventions for individuals affected by neurological disorders, such as TBI. Light aerobic exercise can modulate cortical excitation in healthy adults and cortical inhibition appears to be modulated in those with mTBI. Also, multitasking performance is improved following light aerobic exercise. Consequently, patients with deficits in this domain may benefit from bouts of light aerobic exercise, especially those who may not be able to reach higher exercise intensities due to illness severity.

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Chapter 6

Experimental research

Self-Reported Physical Activity Levels Predict Perceived Cognitive Health in Individuals with History of Traumatic Brain Injury

Physical Activity is Associated with Global and Cognitive Health in Individuals With and Without a History of Traumatic Brain Injury.

Abstract

Introduction: Physical exercise has many global health benefits and is a potential long-term therapeutic intervention for individuals living with residual effects of traumatic brain injury (TBI). Whilst the association between physical exercise and health-related quality of life in the general population is better established, such an association in individuals with a history of TBI is not. **Methods:** A nested case control study was performed on survey data collected as part of a larger study (The Barcelona Brain Health Initiative). 81 individuals reported a history of TBI with loss of consciousness (1.8%) and age and gender matched healthy controls were randomly selected from the wider cohort. The associations between self-reported physical activity and the PROMIS global health and NeuroQoL cognitive function questionnaires were performed using logistic regression with odds ratios (OR) and 95% confidence intervals. **Results:** Healthy adults were almost twice times as likely to report good global (OR=1.88, 95% CIs: 1.15, 3.08) and good NeuroQoL cognitive function (OR=1.90, 95% CIs: 1.16, 3.11) compared to those with a history of TBI. Being *active* significantly increased the odds of good global health in those with (OR=4.31 95% CIs: 1.21, 15.32) and without a history of TBI (OR=1.63, 85% CIs: 1.04, 2.53). The same physical activity classification was associated with increased odds of good NeuroQoL cognitive function in those with a history of TBI (OR=5.89, 95% CIs: 1.04, 31.38). **Conclusions:** Those with a history of TBI report lower perceptions of global and cognitive brain health compared to healthy adults. Being physically active is associated with better global and cognitive health in those with a history of TBI. Consequently, efforts to increase or maintain exercise following TBI across the lifespan are important.

Introduction

The long-term health consequences of traumatic brain injury (TBI) include cognitive, sensorimotor, behavioural and social problems that can negatively affect quality of life (Stocchetti & Zanier, 2016), and in the US alone, an estimated 3.2 million individuals live with residual effects of TBI (Benedictus, Spikman, & van der Naalt, 2010).

Physical exercise is associated with a 20-30% lower risk in all-cause mortality and incidence of multiple chronic conditions (James McKinney et al., 2016), and is a potential therapeutic treatment for recovery from TBI (Morris, Gomes Osman, Tormos Muñoz, Costa Miserachs, & Pascual Leone, 2016). Animal models of exercise and TBI have shed light on the mechanistic pathways by which aerobic exercise modulates cognitive recovery post-injury (Archer, 2011). Exercise appears to inhibit neuronal degeneration (Itoh et al., 2011), stimulate neurogenesis (Jacotte-Simancas et al., 2015) and upregulate a variety of plasticity-related growth factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1) (G S Griesbach, Hovda, Molteni, Wu, & Gomez-Pinilla, 2004; Grace S Griesbach, Gómez-Pinilla, & Hovda, 2007), associated with improvements in cognitive function (Loprinzi & Frith, n.d.). In human studies, improvements in executive functions, attention and working memory have been demonstrated after aerobic exercise interventions in individuals with TBI (For a review see; Morris et al., 2016).

The feasibility of exercising within the community following moderate-to-severe TBI has been demonstrated (Devine, Wong, Gervino, Pascual-Leone, & Alexander, 2016), but the association between physical exercise and global and cognitive brain health has not been assessed. Whilst in healthy adults a link between physical exercise and brain health is clearer (Gomes-Osman et a., 2018, ahead of print), certain barriers to performing physical exercise (Rimmer, Riley, Wang, Rauworth, & Jurkowski, 2004) and underlying pathophysiology of TBI

(Werner & Engelhard, 2007) may mean that this relationship differs in individuals with a history of TBI.

We aimed to assess the associations between physical exercise and perceived global and cognitive health in individuals who reported a history of TBI with loss of consciousness, and in a random selection of aged and gender matched neurologically healthy adults. We hypothesized that physical exercise would be predictive of good global and cognitive health in both those with and without a history of TBI.

Methods

2.1 Study design

Starting in 2017, a cohort of community-dwelling adults, mainly in the Catalonia region of Spain, began to be established as part of the Barcelona Brain Health Initiative. Adults aged 40-65 were invited to participate in an online questionnaire-based survey via television and local advertisements. At the time of analysis, a total of 4,624 individuals had completed our survey. Of those, 81 individuals (1.8%) answered positively to the question: *Have you ever had a traumatic brain injury with loss of consciousness?*

A control group was randomly selected from the total cohort using a random-number sequence and age (blocks of 5 years) and gender matched to the participants with a history of TBI. Five adults free from any neurological or psychological disorders were selected for every participant with TBI.

2.2 Outcomes and covariates

Our main outcome variables were perceived global health and perceived cognitive function. To measure these constructs, the PROMIS global health questionnaire (Cella et al.,

2010) and the NeuroQoL cognitive function questionnaire were used (Gershon et al., 2012). PROMIS global health is a 10-item 5-point Likert scale (1-poor, 5-excellent) that probes respondents physical, mental and social health. Higher scores mean more of the construct is being measured (i.e better global health). NeuroQoL cognitive function is 5-point Likert scale (1-very often, 5-never) with 12 items that probes respondents thinking, attention, planning, new task learning and comprehension. Higher scores mean more of the construct is being measured (i.e better perceived cognitive function). For both questionnaires, a standardized Z-score was calculated, and responses were dichotomised (either 'good' (above cut off score), or 'less good' (below cut off score)) using a median split (good- top 50% percentile for whole population, less good- bottom 50% percentile for whole population).

Our main predictor variable was physical exercise levels. We chose to implement the Godin-Shepard leisure time physical activity questionnaire (GSLTPAQ; Godin & Shephard, 1985) to measure this. The GSLTPAQ, can classify individuals into *active* and *insufficiently active* by probing the number of times are spent performing moderate (not exhausting) or strenuous (heart beats rapidly) physical activity of at least 15-minutes during a typical 7-day period (Godin, G, 2011). The frequency score is multiplied by a corresponding metabolic equivalent for task (MET) value (moderate = * 5; strenuous = * 9) and summed to obtain an arbitrary leisure score index (LSI). An LSI of ≥24 is *active* where as those ≤23 are *insufficiently active.* The rational for these cut off points originate from the World Organisation (WHO, 2018) and American College of Sports Medicine (Ferguson, 2014) guidelines for weekly physical activity associated with significant health benefits (combination of moderate and strenuous exercise 3-5 times per week). Consequently, those culminating in a score of ≥24 using questions that pertain to moderate and strenuous physical activity and LSI calculations based on both frequency and energy expenditure will likely meet the physical activity guidelines. The utility and accuracy of these cut off scores have been validated in healthy adults

(Amireault & Godin, 2015). Raw scores above 7 for each question were excluded from analysis as these were believed to be derived from a misinterpretation of the question.

Co-variates included age and was asked in years and three categories were created; 40-49, 50-59 and 60 and above. Level of education was asked, and response options included primary only (up to 8 years, equivalent to primary education), secondary (up to 12 years, equivalent of secondary school or high school) or higher education (more than 12 years, equivalent of university degree/diploma). Self-perceived negative affect in depression, anxiety and stress was assessed using the 21-item sub scale version of the Depression Anxiety Stress Scale (T. A. Brown, Chorpita, Korotitsch, & Barlow, 1997). This is a 4-point Likert scale (1-never, 4-always) where higher scores represent higher negative affective state.

2.3 Statistical analysis

All statistical analyses were performed in JMP Pro version 13. We screened age, gender, education level, body mass index and negative affective status as potential confounding variables in our analysis. Confounding variables were defined as those which predicted good global or cognitive health with a $p < .20$ when adjusted for age. Potential confounding variables were placed into a logistic regression model with our main predictor variable (GSLTPAQ) in order to assess the independent associations between physical exercise and perceived health outcome measures, which are reported as adjusted odds ratios (aOR). We considered statistical significance at the 95% level of confidence.

Results

Our age and gender matched control group consisted of 405 healthy adults (49% female). Mean age ± SD of the TBI cohort was 51 ± 7 and for the healthy cohort, 52 ± 7 (t(116)

= -0.3, p = >.740). The majority of adults, both with and without a history of TBI were classed as insufficiently active (table 1).

Table 1. Distribution of physical activity status according to the GSLTPAQ

	Healthy	**History of TBI**
Active	34%	38%
Insufficiently active	66%	62%

After adjusting for age, healthy adults were significantly more likely to report good global health and NeuroQoL cognitive function compared to those with a history of TBI (table 2). Gender and education did not significantly predict good global health or NeuroQoL cognitive function. However, for every one-unit increase in DASS21 negative affect, a 4% reduction in the likelihood of reporting good global health and good NeuroQoL cognitive function was seen. Meaning that the higher the negative affective status the lower the odds of reporting good global health and NeuroQoL cognitive function were (table 2).

Table 2: Age-adjusted odds ratios of individual covariates for those who reported good global and cognitive health compared to those who did not.

	Global health	**NeuroQoL**
	^Odds ratios (95% CIs)	
Age (years)		
≥60	– –	– –
50-59	1.07 (0.77 – 1.75)	1.05 (0.65 – 1.71)
40-49	0.91 (0.56 – 1.47)	1.20 (0.74 – 1.95)
Gender		
Female	– –	– –
Male	1.06 (0.74 – 1.55)	1.37 (0.95 – 1.99)
Education		
Primary	– –	– –
Secondary	1.51 (0.52 – 4.35)	1.40 (0.51 – 3.83)
Higher	2.58 (0.94 – 7.04)	1.49 (0.57 – 3.87)
DASS21	0.96 (0.94 – 0.98)	0.96 (0.94 – 0.97)
Diagnosis		
TBI	– –	– –
Healthy	1.88 (1.15 – 3.08)	1.90 (1.16 – 3.11)

^ Age adjusted odds ratio; 95% CI's are significant in those which do not include 1.0.

After adjusting for age, education and negative affective status, which met our definition for potential confounding variable in the global health model, both individuals with and without a history of TBI with loss of consciousness, who were classed as active were almost twice as likely to report good global health compared to those who were insufficiently active (table 3). After adjusting for age, gender and negative affective status (potential confounding variables in the NeuroQoL model), those with a history of TBI with loss of

consciousness were almost 6 times as likely to report good NeuroQoL cognitive function than those who were insufficiently active (table 3), however this was not the case for those without a history of TBI.

Table 3: Odds ratios of reporting good global health and NeuroQoL cognitive function in those who were active compared to those who were insufficiently active, classified by the GSLTPAQ

	Global health		**NeuroQoL**	
	aOR (95% CIs)			
	Healthy	*TBI*	*Healthy*	*TBI*
GSLTPAQ				
Insufficiently active	– –	– –	– –	– –
Active	1.63 (1.04 – 2.53)	4.31 (1.21 – 15.32)	1.21 (0.78 – 1.89)	5.89 (1.11 – 31.38)

95% CI's are significant in those which do not include 1.0.

Discussion

In this study we aimed to assess the relationship between self-reported physical activity levels and global and cognitive brain health in neurologically healthy adults and community-dwelling adults with a history of TBI with loss of consciousness. We found that healthy adults were more likely to report good global and cognitive brain health compared to those with a history of TBI. Being classed as active compared to insufficiently active, in relation to weekly physical activity guidelines (Ferguson, 2014; WHO, 2018), was a significant predictor of good global health in both groups. The same activity classification was predicative of good perceived cognitive function in those with a history of TBI, but not in healthy adults.

Physical activity has been associated with a 20-30% reduction in all-cause mortality and self-reported levels of physical activity have been associated with numerous protective health benefits such as reduced risk of cognitive impairment (Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001) and cognitive decline (Sofi et al., 2011), mortality due to cardiovascular disease (Nocon et al., 2008) and reduced incident rates of dementia (Larson et al., 2006). Self-report physical activity has also been associated with better health-related quality of life (HRQOL) (D. W. Brown et al., 2003). These findings from the 2001 behavioural risk factor surveillance system survey found that adhering to recommended levels of physical activity was significantly associated with less days of poor perceived mental and physical health. Similarly, our results suggest being physically active, consisting of performing a combination of moderate and strenuous exercise at least 3-5 times per week, is associated with better global health perceptions (mental, physical and social) in individuals with a history of TBI with loss of consciousness and those without this history.

Whereas in the general population, a relationship between physical activity and health appears more established, such a relationship in TBI is not. Although some concepts of HRQOL in TBI overlap with those of the general population, research suggests that HRQOL following TBI may be more complex (Carlozzi, Tulsky, & Kisala, 2011). We saw that individuals with a history of TBI had significantly lower self-reported global and cognitive brain health compared to neurologically healthy adults. Whilst we cannot be certain that this lower perception of global and cognitive brain health is derived from the injury, previous reports have shown many individuals with a history of TBI live with residual negative effects of the injury (Benedictus et al., 2010). Cognitive dysfunction is prevalent post-injury and deficits can be seen at 6 months (Dikmen et al., 2009) and for as long as 10 years after injury (Draper & Ponsford, 2008). Long-term lifestyle interventions aimed at reducing these deficits are therefore of great importance to those living with residual effects of TBI.

Physical exercise is emerging as a potential treatment for cognitive impairments following TBI (Morris et al., 2016). If our results hold true they are of great importance to community-dwelling individuals with a history of TBI. Our results suggest that being physically active is associated with better global and cognitive health. As such, recommendations to increase physical exercise in these individuals can be made. The feasibility of dedicated exercise intervention within the rehabilitation setting soon after moderate-to-severe TBI has been demonstrated (Morris, et al., 2018) yet whether this translates into long-term adherence to exercise across the lifespan is unknown. Promising results from a feasibility study of aerobic exercise programs in community-dwelling individuals with a history of moderate-to-severe TBI showed good adherence and feasibility when free access to local gymnasiums was given (Devine et al., 2016). This is of great importance given a large percentage of the general population do not meet the recommended weekly physical activity guidelines and in individuals with disability, economical, physical, environmental and other barriers may prevent long-term adherence to exercise (Rimmer et al., 2004). Indeed, the majority of participants from our cohort met the criteria for insufficiently active also. Together, our results suggest that efforts to increase (or maintain) adherence to recommended weekly physical activity guidelines in individuals with a history of TBI will impact global and cognitive health in these individuals.

Our study has certain limitations that may limit their interpretations. Our cohort of persons with a history of TBI is moderately sized which may have reduced our power to detect true effect. Our healthy cohort was randomly selected from stratified quantiles based on the age and gender of the TBI cohort and therefore may not be fully representative or generalizable to the Catalan or Spanish general population. We did not assess the severity of an individual's TBI nor the time since injury in our cohort of TBI. Whilst this should not affect the exposure/outcome relationship, it means that we cannot be certain whether different injury

severities are more or less associated with the results found. This might be of interest to future studies. Whilst recovery from less severe TBIs such as concussion appear to be relatively quick with few long-term deficits (Schretlen & Shapiro, 2003), more severe TBIs may have greater effects. We did not see any relationship between physical activity and cognitive health in the group without a history of TBI. Many previous studies have shown that dedicated aerobic exercise programs are associated with improvements in cognitive function (Gomes-Osman, J et al., 2018). However, it is likely that given the NeuroQoL scale was developed to assess the cognitive health of individuals with neurological impairments, a ceiling effect saturated any potential relationship between exercise and this scale in healthy adults.

Conclusions

Individuals with a history of TBI have poorer perceptions of global and cognitive brain health compared to healthy adults. Adhering to physical activity guidelines of performing moderate to strenuous exercise at least 3-5 times per week was associated with better global health in individuals with and without a history of TBI and loss of consciousness. In those with a history of TBI with loss of consciousness being active increased the odds of better cognitive health also. Consequently, efforts to increase or maintain exercise participation across the lifespan will improve both global and cognitive health following TBI.

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Chapter 7

General Discussion

When discussing the therapeutic value of physical exercise in TBI one can distinguish between planned exercise programs (with a given intensity, frequency, and duration) prescribed as part of the rehabilitation program and the global long-term physical activity performed by an individual with a history of TBI across the lifespan. Through chapters 4, 5 and 6, this thesis has empirically studied aspects of both of these in the context of recovery from TBI. The thesis has utilized numerous research approaches (observational, clinical and translational and systematic review) in its study of the application of physical exercise for cognitive function after TBI. The following paragraphs contain a discussion of the combined results from the experimental chapters, how they have informed our knowledge of this topic and the questions raised by the results for future studies to tackle. The limitations to the research included in this thesis are discussed within each paragraph.

Aerobic exercise programs in sub-acute moderate-to-severe TBI are feasible

Chapter 3 led to the study presented in chapter 4. The systematic review showed that despite promising evidence from animal models, physical exercise as a therapeutic intervention for cognitive recovery has not been extensively studied in TBI populations. More so, the review showed that very few studies included individuals with moderate-to-severe TBI, and even fewer in the sub-acute phase of recovery.

In the sub-acute phase of moderate-to-severe TBI, behavioural, physical and cognitive impairments pose significant challenges to the participation in and adherence to aerobic exercise programs. The results from chapter 4 showed that, despite significant physical injuries and cognitive dysfunction, the participants with moderate-to-severe TBIs adhered well to the 8-week program. Despite this feasibility, the study results regarding how to control for the intensity of exercise raised some issues. Only 2 of the participants exercised within the target

heart rate zones (50-70%HRR) and all participant's perceived ratings of exertion were poorly correlated with their heart rate response to exercise. These target heart rate zones were based on previous research (from the studies included in the systematic review from chapter 3 and others in individuals with stroke (Marzolini et al., 2013; Quaney, He, Mayo, & Macko, 2011). Consequently, the finding that those individuals in the sub-acute phase were unable to exercise within these zones was unexpected. Given these results, the study in chapter 5 was planned with the objective of assessing the effect, and the underlying mechanisms of an effect, of exercise performed at an intensity more achievable for individuals who cannot exercise at higher intensities. This is of great importance as some previous research has suggested an intensity-threshold exists for exercise to exert an adaptive plastic response (Chmura, Nazar, & Kaciuba-Uścilko, 1994) and subsequently, improvements in cognitive function. Furthermore, less is known about the effect of light aerobic exercise on cognitive function, even in healthy adults. If light aerobic exercise is not sufficiently intense to evoke an adaptive plastic response however, yet individuals with more severe TBIs cannot exercise at higher intensities, then the use of aerobic exercise becomes less pragmatic. In chapter 5, light aerobic exercise modulated differential cognitive domains across the two groups (healthy and TBI) yet neither group saw a widespread effect of this exercise intervention on multiple executive function domains. Further dose-response studies are necessary to delineate the optimal exercise intensity for sub-acute TBI.

Furthermore, as discussed in chapter 4, individuals with severe TBI have a reduced heart rate response to exercise and so it is possible that this phenomenon is responsible for the inability to exercise within the target heart rate zones. However, the question therefore remains as to what importance HR plays in the intensity of exercise in individuals with impaired parasympathetic control due to injury. Should it be the case that despite lower HR response to

exercise a positive effect of exercise on cognitive recovery is demonstrated, then other ways to control for the intensity of exercise in this population should be sought. Along those lines, RPE were poorly correlated with HR in this study. The use of such ratings scales for perception of effort in TBI may also be problematic (Dawes et al., 2005) pertaining to the understanding of the constructs of each level of effort, yet whether individual differences in the extent to which HR response to exercise is affected by TBI are responsible for the poor correlations found is unclear.

The take home message from chapter 4 is that rehabilitation hospitals can feasibly introduce dedicated physical exercise regimes into sub-acute rehabilitation from moderate-to-severe TBI without interfering in current standard practice rehabilitation. However certain limitations to the study of the effect of such interventions on cognitive recovery might hinder the inclusion of dedicated aerobic exercise programs being considered standard interventions for cognitive rehabilitation. The use of a pragmatic control group poses significant challenges for future studies of the efficacy of aerobic exercise in TBI. Given sport and physical education are practised as standard as part of the physical rehabilitation from TBI, an ethical conundrum arises when attempting to assess the effect of exercise in sub-acute rehabilitation. Research cannot remove the sport and physical activity from standard rehabilitation, limiting the ability to compare the effect of dedicated exercise programs. The use of a clinical sub-group of patients who have suffered both a paralysing spinal cord injury and TBI have been discussed and may present as an intriguing control group, however various challenges in recruitment of such patients must be considered first. Namely, their low prevalence. Additionally, in this phase of injury, as discussed in both chapters 4 and 5, spontaneous recovery is inherent. Consequently, it would be difficult to truly establish whether a single intervention such as

exercise has a significant effect on cognitive recovery. Nevertheless, future studies with significantly larger patient samples may overcome such challenges.

Mechanisms of exercise in TBI

Results from chapter 5 found differential effects of light aerobic exercise in the healthy and mild TBI group. Where light aerobic exercise improved multitasking in the healthy group, exercise had an effect of spatial working memory in the mild TBI group. Regarding TMS measures of cortical excitability, in the healthy group, light exercise enhanced intracortical facilitation whereas cortical inhibitory processes were modulated in the mild TBI group. Neither group saw exercise-mediated changes in IGF-1 and the light intensity of the exercise did not provoke a cortisol response.

As the sample sizes in each group differ significantly, the chapter does not discuss differences between groups rather it uses a within-subjects design for each group separately. The narrative of the discussion however focuses on the intensity-dependent relationship of single bouts of aerobic exercise on cognitive function and the potential mechanisms studied. The majority of previous research detailing the effects of single bouts of aerobic exercise have done so using moderate or higher intensity exercise. This study chose light aerobic exercise as the intervention for numerous reasons. Firstly, less is known about the effect of light aerobic exercise, even in healthy adults. Additionally, those individuals with concomitant physical injuries may not be capable of reaching higher exercise intensities, a point demonstrated in chapter 4. Consequently, this intensity is desirable in the sub-acute rehabilitation setting. Lastly, exercise-mediated increases in the stress hormone cortisol have been evidenced (Hill et al., 2008) and that such a stress response can be detrimental to cognitive performance (Hsu, Garside, Massey, & McAllister-Williams, 2003) and inhibit exercised-mediated induction of

plasticity (Sale, Ridding, & Nordstrom, 2008). In the cognitive enhancement literature, studies have suggested that various aspects of the cognitive tasks being used, such as the timing of the tasks in relation to the exercise and the cognitive domain being tested, are all moderators of exercise's effect (Etnier & Chang, 2009). However, evidence from the exercise literature also points to the parameters of exercise, such as intensity of exercise, as moderators of the effect. Whilst studies with using more moderate intensity show a small but largely consistent improvement in executive function (Y. K. Chang et al., 2012), it is conceivable that the results found are better explained by an intensity-dependent relationship. The intervention from chapter 5 improved multi-tasking performance in healthy adults suggesting that individual or populations with deficits in this executive function domain may benefit from this type of intervention. However, higher intensity exercise may be required to see more widespread improvements in other executive function domains. In the TBI group, results suggest that single bouts of light aerobic exercise may modulate spatial working memory. This domain is often disrupted following TBI and so these results are promising.

The study in chapter 5 also aimed to gain insights into how light aerobic exercise may impact executive function. The study chose to assess how this intensity of exercise may impact IGF-1, a growth factor implicated in neuroprotection post-injury (Llorens-Martín et al., 2009) and also in exercise's effect on synaptic plasticity (Trejo, Carro, & Torres-Aleman, 2001b). The results in both groups however seem indicative of light intensity exercise not being sufficiently intense to evoke a widespread adaptive plastic response. Serum levels of IGF-1 were stable across interventions. In healthy adults this result has previously been demonstrated (Schwarz, Brasel, Hintz, Mohan, & Cooper, 1996) whereby high intensity exercise did evoke an increase in IGF-1 but light intensity did not. Suggesting the results from chapter 5 add to the intensity-dependent debate. Unfortunately, in the mild TBI group, the sample size did not permit strong

conclusions to be made. Consequently, some questions remain to be answered: If TBI decreases circulating IGF-1 levels what is the intensity-threshold required for exercise to increase them? Direct comparison studies are required to answer this question, which would also benefit research in healthy adults. These studies might directly compare bouts of exercise performed at different intensities and their result on stimulating IGF-1 levels. This approach was theorized by Chmura and colleagues (Chmura, Nazar, & Kaciuba-Uścilko, 1994) who examined the possibility that the point at which adrenaline and noradrenaline exponentially increase in response to exercise would correlate with increase in speed of cognition. Similarly, future hypotheses regarding IGF-1 would regard IGF-1's role as a primary mediator of exercise's effect of synaptic plasticity. The hypothesis being that the threshold at which exercise increases peripheral levels would be correlated with increases in synaptic plasticity.

Regarding the TMS results, this chapter raises some interesting points regarding the feasibility and utility of TMS in TBI. Following TBI, abnormal cortical excitability has been demonstrated (Bernabeu et al., 2009) and no study to date has used TMS measures to assess the effect of exercise on cortical circuitry in TBI. Whilst the group is small, an effect of exercise was noted on cortical inhibitory processes, but not excitatory. Cortical excitatory/inhibition balance is an important process in learning and memory and in animal models of TBI, various temporally-dependent changes in inhibitory and excitatory neurotransmitter concentrations (glutamate and GABA) and receptor populations are seen (Guerriero, Giza, & Rotenberg, 2015). Given the differences in the time since injury in the mild TBI individuals in chapter 5, it is unclear to what extent such changes contribute to the TMS measures found, but the results suggest that exercise may influence cortical inhibition following injury.

The inclusion of TMS measures was conceived to study the underlying effects of exercise on executive function gains and as such, in the healthy group, correlations between TMS measures of intracortical facilitation and improvements in multitasking performance were performed. No such correlations were seen but the chapter discusses the pragmatic use of real-time integration of TMS-EEG to study the effects of exercise on executive function in cortical areas outside of the motor cortex. Cortical areas that may play larger roles in execution of the cognitive tasks performed, compared to the primary motor cortex. This tool may be better suited to studying such effects and consequently future studies should employ this technique. Should a TMS-EEG biomarker of exercise-mediated improvements in executive function following TBI be found, it can subsequently be used to study the intensity-dependent effects of exercise. Similar to the theory discussed in relation to IGF-1, a TMS-EEG biomarker would allow one to study the threshold at which exercise modulates such a biomarker in relation to improvements in cognitive function. Beyond that however, using this type of tool, a move towards individualised interventions can be made. By developing a TMS-EEG biomarker that is sensitive to inter-individual changes and modulated by exercise, one can design interventions that are more personalised in nature for a given group of individuals with certain characteristics. This point is further discussed in future paragraphs.

Physical exercise beyond the rehabilitation hospital

Chapter 6 discusses previous research that demonstrates cognitive dysfunction some 10 years post-injury (Draper & Ponsford, 2008) and the results from this chapter showed that healthy adults were twice as likely to report good global and cognitive health compared to those with a history of TBI. The result showed that adhering to weekly guidelines (as set by the American college of Sports Medicine and The World Health Organization) is associated with an increase in the odds of reporting good global and cognitive health in community-dwelling adults with a

history of TBI with loss of consciousness. The results point to the importance of continuing aerobic exercise beyond the rehabilitation hospital. A recommendation equating to a change in lifestyle habits. A concern however is that upon being discharged from the rehabilitation hospital, adherence to exercise may decrease. The feasibility of adhering to exercise programs in the community when individuals with TBI are presented with free access to local gymnasiums has been demonstrated (Devine, Wong, Gervino, Pascual-Leone, & Alexander, 2016). And chapter 4 demonstrates the feasibility of begging dedicated exercise programs soon after injury. However. whether beginning dedicated exercise programs for cognition rehabilitation within the rehabilitation hospital increases later life-adherence to exercise is unknown, yet future studies on this topic may have a large impact. Especially given that more adults with a history of TBI did not adhere to the weekly guidelines compared to those who did.

Whilst there is still more to study regarding long-term exercise after TBI, the results from chapter 6 do allow for some specific recommendations, should they hold true. The classification of active and insufficiently active individuals based on frequency (times per week) and energy expenditure (metabolic equivalents for task, or moderate/strenuous exercise) allows clinicians to recommend that individuals with a history of TBI increase or maintain their physical activity to reach levels of at least 3-5 times per week at moderate to strenuous intensities. However, when we take the results from chapter 5 into account, one might discuss the intensity-dependent relationship in long-term exercise. The current weekly guidelines suggest 3 times per week of strenuous exercise, 5 times per week of moderate exercise of 3-5 times per week of a combination of both. For increased general health benefits, the WHO suggests increases in these guidelines can be performed. Whether this is the case for individuals living with residual effects of TBI is unclear. Indeed, whether differences in the intensity of

exercise across the temporal time frame from the date of injury are necessary is also unclear. It might be hypothesised that during the early phases of recovery lighter intensity exercise has a greater benefit whereby chronic phases may be best modulated by more intense exercise.

Future directions: Towards an individualised approach

Studies presented in this thesis have added to the literature regarding exercise and cognition in individuals with TBI, but significant work is still to be done in order to consolidate the therapeutic value of aerobic exercise for various applications regarding cognitive recovery. Chapter 5 aimed to gain insights into the underlying mechanisms of aerobic exercise on cognitive function with an end goal of manipulating such biomarkers of the effect to find the optimal parameters of exercise. However more recently, approaches to understand the individualised nature of exercise-mediated gains in cognitive function have been reported on (Baniqued et al., 2018). This approach allows for two advantages over traditional research that utilises mean averages to find an effect. Firstly, it allows one to highlight, based on certain characteristics (in the case of Baniqued and colleagues (2018), network modularity), who will most likely gain from a given exercise intervention. Subsequently, this approach can then allow one to take those who do not benefit from the initial intervention and prescribe them a different, more individualised intervention. Or alternativity, study why certain people gain from a given intervention and why others do not. Given the heterogeneity in TBI, this approach may have significant impact. Similarly, this technique has been employed to predict adherence to exercise. Whereby Gujral and colleagues (Gujral, McAuley, Oberlin, Kramer, & Erickson, 2018), reported that both grey matter volume and white matter microstructure predicted adherence to an exercise program. This again allows for certain advantages. Should clinicians/researchers or community workers know who is less likely to adhere to an exercise

program before its commencement, more individualised/innovate interventions to help those groups of persons maintain exercise levels can be developed.

Limitations

Certain limitations to individual studies in each chapter have been discussed in previous paragraphs but some general limitations still remain that should be taken into account when interpreting the experimental research in this thesis. Across all 4 experimental chapters, results rely on very few individuals with TBI. In chapter 6, just 81 (1.8%) out of the total cohort of the Barcelona Brain Health Initiative (4624) reported a history of TBI with loss of consciousness. In chapter 3, just 6 previous studies had explored the use of aerobic exercise for cognitive function in the recovery from TBI. Chapter 5 included 4 individuals with mild traumatic brain injury and chapter 4, 5 individuals with moderate-to-severe TBI. Whilst this may limit strong conclusions being made regarding the interpretation of the results it serves to highlight the need for more research into this important and potentially impactful topic.

Chapter 8

Conclusions

1. Dedicated aerobic exercise programs for cognitive recovery within sub-acute rehabilitation from moderate-to-severe TBI can feasibly be introduced.
2. Controlling for exercise intensity in the sub-acute phase of moderate-to-severe TBI is challenging and in need of further study.
3. Light aerobic exercise may be more achievable for individuals with moderate-to-severe TBI.
4. Light aerobic exercise appears to modulate spatial working memory in those with a mild TBI and multi-tasking performance in healthy young adults.
5. Light aerobic exercise appears to modulate cortical excitability differentially between those with a mild TBI and those without. Cortical inhibition is modulated by light aerobic exercise in mild TBI whereas cortical facilitation is increased in those without a mild TBI.
6. Long-term exercise across the lifespan following TBI is important for global and cognitive health.
7. The study of aerobic exercise for cognitive recovery following TBI is in its infancy but preliminary evidence to support its benefit is promising and future studies will have a large impact on its development as a standard therapeutic intervention.

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Annex 1

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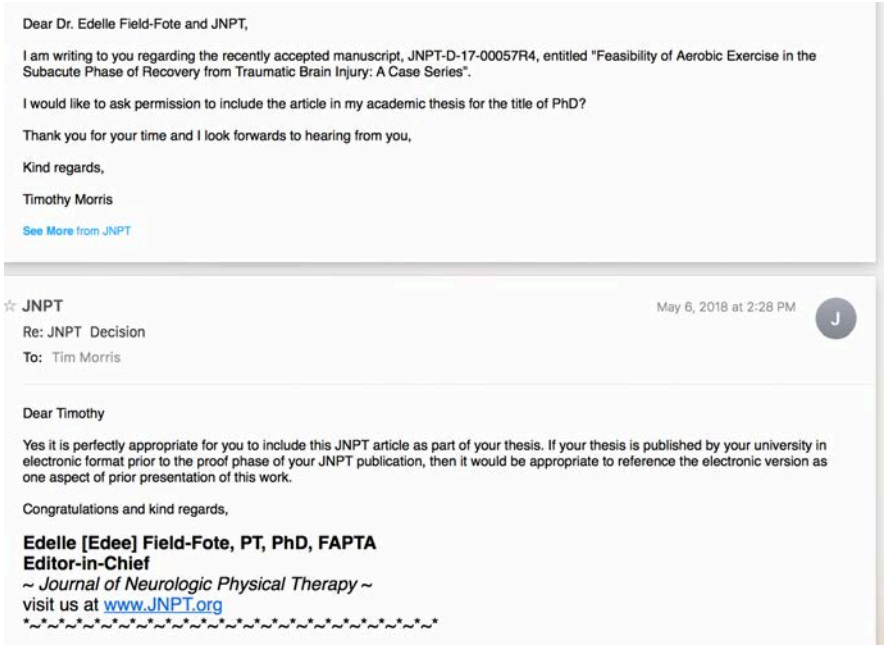

Dear Dr. Edelle Field-Fote and JNPT,

I am writing to you regarding the recently accepted manuscript, JNPT-D-17-00057R4, entitled "Feasibility of Aerobic Exercise in the Subacute Phase of Recovery from Traumatic Brain Injury: A Case Series".

I would like to ask permission to include the article in my academic thesis for the title of PhD?

Thank you for your time and I look forwards to hearing from you,

Kind regards,

Timothy Morris

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☆ JNPT May 6, 2018 at 2:28 PM

Re: JNPT Decision

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Dear Timothy

Yes it is perfectly appropriate for you to include this JNPT article as part of your thesis. If your thesis is published by your university in electronic format prior to the proof phase of your JNPT publication, then it would be appropriate to reference the electronic version as one aspect of prior presentation of this work.

Congratulations and kind regards,

Edelle [Edee] Field-Fote, PT, PhD, FAPTA
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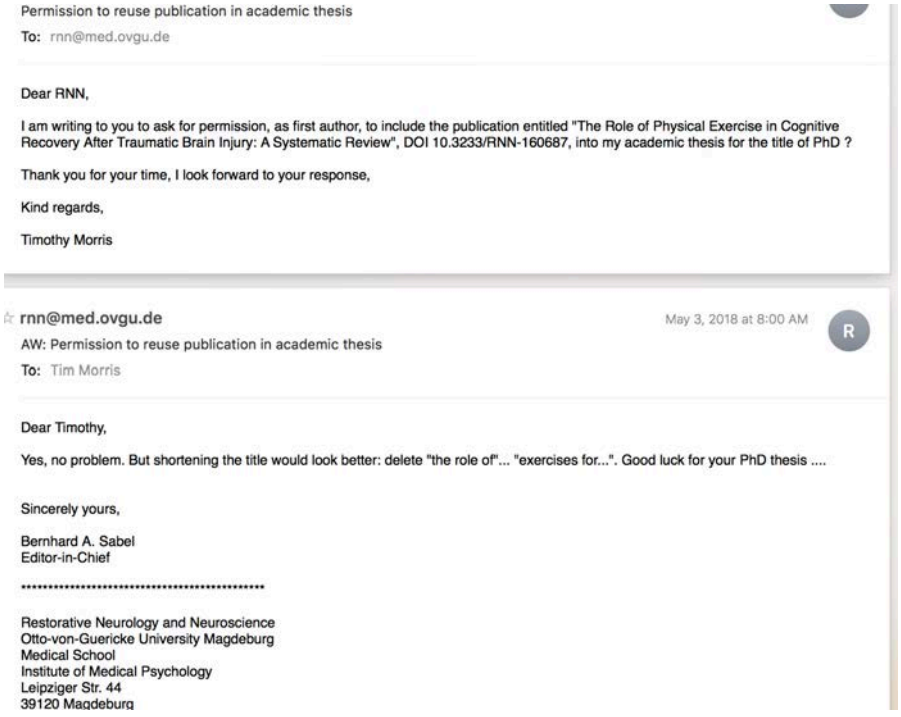

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Dear Timothy,

Yes, no problem. But shortening the title would look better: delete "the role of"... "exercises for...". Good luck for your PhD thesis ....

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****

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