

Effects of a Multi-modal Exercise Program on Cognitive and Physical Functions and Brain- Derived Neurotrophic Factor in Older Women

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Abstract

Background

Age-related cognitive decline (ARCD) is a pattern of deterioration in cognitive functions that gradually impairs the ability to think, reason, concentrate and remember. It has been identified as a major health threat for older adults because of the potential deleterious effects on independence, social engagement and quality of life. The trend in the experimental literature suggests that cardiovascular exercise training may have the capacity to counter ARCD. However, the efficacy of single modality interventions is inconclusive and there is currently a move towards investigating the effects of combination exercise interventions. The assumption is that optimisation of the intervention stimulus, in this way, might induce more pronounced cognitive outcomes than the modest levels of enhancement elicited by cardiovascular training alone. There are theoretical indications that these effects may be more likely to be achieved by the inclusion of motor skills training; as this modality involves complexity and novelty that requires sustained mental effort or cognitive load. The suggestion is that sustained mental effort is likely to both induce (positive) brain changes and stimulate higher-order cognitive processes (executive functions). In theory, the inclusion of these design elements may benefit executive function (higher order cognitive processes most susceptible to ARCD) and induce positive neuroplasticity (the life-long neuronal capacity of the brain to preserve or optimise function, in response to experiential stimuli).

Three additional aspects of research into the relationship between exercise training and the ageing brain represent gaps in the literature that are attracting current interest. The underlying mechanisms that may give rise to exercise-induced cognitive changes remain unclear. However, neurotrophins such as brain derived neurotrophic factor (BDNF) have been implicated in human and non-human studies. Moreover, little is known about the clinical significance of benefits that may arise from exercise training generally and multi-modal exercise programs in particular. Lastly, the ecological validity of a number of the commonly employed neurocognitive instruments used in this type of research is far from being established.

Aims

There were two main aims of this study. First, to test the effect of a complex, multi-modal exercise program on neurocognitive functions, exercise capacity, physical functioning and a

biomarker of brain plasticity; and second, to investigate the benefits and acceptability of a multi-modal exercise program as expressed by the participants.

Design

This study was designed as a single-blinded, parallel group randomised controlled trial (RCT) of a multi-modal exercise intervention, with an embedded qualitative component.

Settings

Griffith University campus and community based halls.

Subjects

Forty-nine non-depressed women, aged between 65 and 75 years, with no cognitive impairment and not undertaking more than one hour of formal exercise training per week, were recruited into the RCT. These volunteers were then randomly allocated, by a blinded research assistant using the Griffith University Health Practice Innovation Centre internet-based randomisation service, to either the intervention or wait-list control groups. Fifteen of the 25 participants in the intervention group also participated in the interviews and focus group undertaken for the qualitative component.

Methods

In the RCT component of the study the intervention group attended a 60-minute multi-modal class twice each week, for 16 weeks, which included cardiovascular, strength, and motor fitness training. The program was conducted by two qualified and accredited fitness instructors. The primary outcome measures were performance scores in a range of neurocognitive tests: the California Older Adult Stroop Test (COAST); the Controlled Oral Word Association Test (COWAT); the Letter-Number Sequencing (LNS) Test and the Trail Making Test (TMT) (A and B). Secondary outcome measures included the Deary-Liewald Reaction Time Task (simple and complex), the Six Minute Walk Test (6MWT); the Timed Up-and-Go Test (TUGT) and the One-legged Stance Test (OLST). In addition, whole blood samples were collected and processed to obtain plasma which was then analysed for BDNF concentrations.

Participants in the control group were placed on a waiting list to attend the 16-week program which commenced at the end of the study and immediately after follow-up data collection. The control group participants were asked to maintain their usual life style during the 16 week wait period. Baseline data collection was conducted one week prior to the commencement of the intervention, and follow-up testing occurred within two weeks of the intervention delivery completion. Rigorous data collection procedures were followed and participants were

randomised after baseline data collection. Data were analysed by analysis of covariance (ANCOVA) using baseline measurements as covariates.

In the qualitative arm of the study, the participants engaged in semi-structured, digitally recorded, face-to-face interviews. These interviews were transcribed verbatim and were then read and re-read by the PhD candidate. Codes were highlighted in the text and categorised. These categories were further interrogated to elicit the major themes contained within the data. This study was approved by Griffith University Human Research Ethics Committee.

Results

Twenty-five participants were randomised to the intervention group and 24 to the control group. One control participant withdrew before follow-up data collection. The intervention group performed better than the control group at follow-up (when controlled for baseline) in the TMT A (Estimated Marginal Mean difference (EMM) = -4.2; $p=0.024$), the TMT B (EMM = -9.3; $p=0.037$), the COAST Word (EMM = -2.1; $p = 0.013$), COAST Interference (EMM = -8.5; $p = 0.002$), COAST Total (EMM = -14.3; $p < 0.001$), COWAT (EMM = 5.2; $p = 0.024$), TUGT (EMM = -1.7; $p < 0.001$), 6MWT (EMM = 113.1; $p < 0.001$), OLST (EMM = 52; $p , 0.001$) and BDNF (EMM = 1.0; $p = 0.023$). The cognitive and physical improvements were congruent with the qualitative data.

The qualitative data revealed that enjoyment of the program maximised engagement in the intervention, engagement maximised adherence and adherence to the program resulted in change. All of the participants who were interviewed reported physical or mental (including cognitive) gains which they attributed to participation in the exercise program.

Conclusion

This multi-modal exercise program resulted in neurocognitive and physical performance improvements and increased levels of plasma BDNF, in older women, when compared to controls. This research provides evidence that a multi-modal exercise intervention can achieve larger effect sizes than those generally resulting from single-modality interventions. Increases in BDNF levels imply neurogenesis may be a component of the mechanisms underpinning the cognitive improvements associated with multi-modal exercise. It is also apparent that, contrary to previous findings, good levels of retention can be achieved given the right constellation of ingredients serving to promote motivation, enjoyment and engagement. Future research is required to establish whether these results can be replicated in men, in other age groups and to establish the dose required, to elicit and maintain cognitive benefits.

Statement of originality

This work has not been submitted for a degree or a diploma in any other university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

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Sue Vaughan

Statement of contribution

This is a doctoral thesis and the candidate was supervised by academic supervisors. In addition, a number of people provided statistical and methodological advice.

The conceptualisation of the study, the research design, organisation and management of data collection, collection of baseline cognitive function data, data analysis and interpretation of study results, along with the preparation of the thesis document and manuscripts for publication was the work of the candidate.

The candidate acknowledges the contribution of research assistants who collected data under the direction of the candidate. In addition, the contribution of all authors included in the jointly published manuscripts is acknowledged.

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Sue Vaughan

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Publications related to the study

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Vaughan, S., Wallis, M., Polit, D. F., Steele, M., Shum, D., & Morris, N. R. (In press 2013 - accepted 22 November 2013). The effects of multi-modal exercise on cognitive and physical functioning and brain-derived neurotrophic factor in older women: a randomised controlled trial. *Age and Ageing*.

Glossary of terms

These definitions are provided for terms used in this thesis that may be either unfamiliar to readers or contested in the literature but which need a clear definition in this thesis.

Aerobic exercise (training): may also be referred to as endurance, cardiorespiratory or cardiovascular exercise and involves large muscle groups in dynamic activities that result in increases in heart rate and energy expenditure.

Angiogenesis: is the physiological process through which new blood vessels form from pre-existing vessels. This is distinct from vasculogenesis, which is the formation of new endothelial cells from mesoderm cell precursors.

Ante-cubital fossa: The triangular area on the anterior of the elbow. Veins in this area are frequently accessed for the drawing of blood

Brain-derived neurotrophic factor (BDNF): Brain-derived neurotrophic factor, also known as BDNF, is a secreted protein. It is a member of the "neurotrophin" family of growth factors, and is the most abundant neurotrophin in the brain, with an important role in brain neurogenesis, synaptic plasticity, learning and memory (Knaepen, Goekint, Heyman & Meeusen, 2010; Ratey & Loehr, 2011). The brain has been found to be the main source of BDNF concentrations in venous blood (circulating BDNF) (Rasmussen et al., 2009). BDNF may play a key role in brain plasticity by regulating the growth, maintenance and survival of neurons in the adult brain.

Cardiorespiratory fitness: the ability of the cardiovascular and respiratory systems to supply oxygen to the working muscles during heavy dynamic exercise.

Clinical significance: Is the practical 'real world' value of a treatment effect and whether it is perceived by the individual to constitute beneficial change.

Cognition: Refers to the actions of thinking and knowing and the processing of information. It includes abilities such as learning, memory, reasoning and attention and incorporates the abilities to think, reason, concentrate and remember.

Cognitive load: A multidimensional concept representing the load that performing a particular task imposes on an individual's cognitive system (Lavie, Hirst, de Fockert & Viding, 2004). Cognitive load is a characteristic of tasks that involve novelty and complexity as these factors

generally necessitate mental effort which is more likely to engage higher order cognitive processes.

Ecological validity: The ecological validity of a test refers to the extent to which test performance corresponds to performance in 'real life' (Conn, Hafdahl & Mehr, 2011).

Executive function: Various defined but generally refers to high level cognitive capabilities related to goal-directed behaviour, that control and integrate other cognitive processes (Pichierri, Wolf, Murer & de Bruin, 2011). These abilities include the capacity to plan and implement strategies and tasks, and inhibit task-irrelevant information (inhibition).

Exercise: The "planned, structured, repetitive bodily movement," (National Institutes for Health, 1995, p. 1), generally undertaken with the objective of improving or maintaining fitness. Exercise can be undertaken informally as part of the broad spectrum of physical and recreational activities or more formally in the form of organised sport. Exercise can also be administered in a controlled environment for the purposes of eliciting a predicted outcome, as part of an experiment.

Inhibition (or cognitive inhibition/response inhibition): The ability to tune out stimuli that are distracting or irrelevant to a task, process or emotional state. Response inhibition can refer more specifically to the suppression of actions that are inappropriate in a given context or interfere with goal-driven behavior.

Neurogenesis: The process by which neurons are generated from neural stem and progenitor cells.

Neuroplasticity/neuronal plasticity: changes at the neuronal level such as neurogenesis, synaptogenesis and network re-organisation stimulated by experience.

Neurotrophins: are proteins that induce the survival, development, and function of neurons.

Physical activity: has been formally defined as "any bodily movement produced by skeletal muscles that result in energy expenditure" (Caspersen, Powell & Christenson, 1985, p. 126). As an umbrella term, physical activity denotes involvement in activities that require movement that varies according to levels of exertion (light, moderate, strenuous/vigorous) and the summative amount of time spent engaging in particular pursuits such as walking or the physical demands of domestic, recreational or occupational life (hours per week). In a more technical (and objective) sense, amounts of energy expended can be measured in kilojoules

(kJ) and the rate of expenditure can be expressed as a continuous variable from low to high. Physical activity, engaged in as part of everyday life, including any type of task that is not categorised as formal exercise, has also been referred to as “weekly” (Yaffe, Barnes, Nevitt, Lui & Covinsky, 2001, p. 1704) or ‘incidental’ (Glass, de Leon, Marottoli & Berkman, 1999) activity.

Physical fitness/Fitness: The product of exercise and physical activity, defined by (Caspersen et al., 1985, p. 128) as “a set of attributes that people have or achieve (...) that relates to the ability to perform physical activity.” Alternative definitions subdivide physical fitness into components related to health (e.g., cardiorespiratory endurance, muscular strength, flexibility) and components related to the skill sets involved in athletic performance or sporting ability such as agility, power and speed (American Physical Therapy Association, 2009; Corbin, Pangrazi & Frank, 2000). A more general proposition is that physical fitness is “a dynamic physical state – comprising cardiovascular/pulmonary endurance, muscle strength, power, endurance and flexibility; relaxation and body composition – that allows optimal and efficient performance of daily and leisure activities”, (American Physical Therapy Association, 2009, p. 1).

Plasticity: The capacity of an organism to change and adapt in its environment. Positive neuroplasticity refers to the brain's ability to make more and stronger connections between neurons in response to exposure to novel stimulation. This process supports better cognitive functioning in general. Likewise, negative neuroplasticity refers to the atrophy of such connections between neurons in response to low stimulation or physiological insults.

Proprioception: The perception of limb position and movement relative to the rest of the body (Jones & Rose, 2005).

Mental fitness: The product of the effective functioning of mental processes.

Multi-modal exercise: There is no formal definition in the literature that qualifies the parameters of what is loosely and variously referred to as multi-modal, combination, multidimensional or combined exercise. In general, the terms refer to supervised exercise classes conducted for a specified period of time (usually one hour); where different elements of physical and motor fitness are formally instructed, delivered sequentially or concurrently, and are aimed at improving or preserving fitness and physical functioning or functionality. The physical fitness component usually entails cardiovascular/aerobic and/or resistance training; while motor fitness training focusses on dimensions such as balance, coordination, proprioception, agility, flexibility and reaction-time. The most commonly combined modalities

are balance, strength and aerobic exercises although current guidelines for older adults also recommend the inclusion of flexibility training (Cress, Buchner & Prohaska, 2004; Sims, Hill, Hunt & Haralambous, 2010).

Resistance exercise (training): exercise designed specifically to increase muscular strength, power, and endurance by varying the resistance, the number of times the resistance is moved in a single group (set) of exercise, the number of sets done, and the rest interval provided between sets.

Synaptogenesis: A synapse is a structure that permits a neuron to pass an electrical or chemical signal to another cell (neural or otherwise). Synapses, therefore, are essential to neuronal function. Synaptogenesis is the formation of synapses between neurons in the nervous system.

List of abbreviations

ADL	Activities of daily living
ARCD	Age-related cognitive decline
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ACSM	American College of Sports Medicine
ATS	American thoracic society
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BP	Blood pressure
CI	Cognitive impairment
CNS	Central nervous system
COAST	California Older Adult Stroop Test
COPD	Chronic obstructive pulmonary disease
COWAT	Controlled Oral Word Association Test
CPR	Cardio-pulmonary resuscitation
CRT	Choice reaction time
CVA	Cerebrovascular accident
DASS	Depression and Anxiety Stress Scale
DLW	Doubly labelled water
DSST	Digit Symbol Substitution Test
EET	Endurance exercise training
ELISA	Enzyme-linked immunoabsorbent assay
EPIC	European prospective investigation into cancer
FCSRT	Free and Cued Selective Reminding Test
fMRI	Functional magnetic resonance imaging
GP	General practitioner
GPS	Global positioning system
HREC	Human research ethics committee
HR	Heart rate
IFG-1	Insulin-like growth factor
ITT	Intention-to-treat
IQ	Intelligence quotient
kJ	Kilojoules
LNS	Letter-Number Sequencing
LNST	Letter-Number Sequencing Test
MANCOVA	Multivariate analysis of covariance
MB	Mind-body
MCI	Mild cognitive impairment
MMSE	Mini mental state examination
mMMSE	Modified MMSE
OUES	Oxygen Uptake Efficiency Slope
PASE	Physical activity scale for the elderly
RAVLT	Rey Auditory Verbal Learning Test
RBMT	Rivermead Behavioural Memory Test
RCT	Randomised controlled trial
ROM	Range of motion
RT	Reaction time
SD(s)	Standard deviation(s)
SES	Socio-economic statuses

6MWT	Six Minute Walk Test
TICS	Telephone Interview for Cognitive Status
TMT	Trail Making Test
TUGT	Timed Up and Go Test
T2DM	Type II Diabetes Mellitus
VEGF	Vascular endothelial growth factor
WE	Western exercise
YPAS	Yale Physical Activity Survey

Chapter 1: Introduction

1.1 Background

Age-related cognitive decline (ARCD) is a pattern of deterioration in cognitive functions that gradually impairs the ability to think, reason, concentrate and remember (Drag & Bieliauskas, 2010). This process of deterioration is related to a number of structural, metabolic and physiological changes in the brain (Grady, 2008). Cognitive decline has been identified as a major health threat for older adults because of the profound adverse implications for the critical capacities of independence, social engagement and quality of life (Bishop, Lu & Yankner, 2010).

The potential scale of ARCD as a public health problem has been magnified by the onset of the predicted global trend towards ageing populations. This demographic shift represents a larger and growing pool of people over the age of 60 years, with an estimated 40% expected to experience some degree of ARCD (Caracciolo et al., 2008). Significantly, the prevalence and severity of impairment increases in the presence of co-morbidities such as cardiovascular disease (Shadish, Cook & Campbell, 2002). There are also indications that gradual and unchecked deterioration can advance to clinical cognitive impairment, which in turn carries a higher risk for progression to dementia (Caracciolo et al., 2008; Carlson, Xue, Zhou, & Fried, 2009; Gauthier et al., 2006). Cumulatively, the nature, effects and potential magnitude of the problem are expected to have enormous social, economic and service delivery repercussions, both nationally and internationally (Australian Institute of Health and Welfare, 2008; Deary et al., 2007). Consequently, there is enormous current public and research interest in finding an affordable, effective strategy to stem the “avalanche” of cognitive decline that is expected to occur by 2050 (Brookmeyer, Johnson, Ziegler-Graham & Arrighi, 2007, p. 186).

Exercise training may have the capacity to mitigate cognitive decline. The cognitive benefits of physical activity and cardiovascular fitness have been extensively investigated and the evidence is generally regarded as equivocal, but promising (Smith et al., 2010). Observational studies conducted over several decades have repeatedly indicated that better fitness is associated with better cognition (e.g., Chang et al., 2010; Etgen et al., 2010). However, methodological and technological limitations have obscured the true significance of most findings. Intervention studies, also beset by ambiguity, have to some extent provided more robust evidence. Systematic reviews and meta-analyses suggest that formal exercise training,

which results in increased cardiorespiratory fitness, can also produce small to moderate improvements in cognitive performance in older adults (Angevaren, Aufdemkampe, Verhaar, Aleman & Vanhees, 2008; Colcombe & Kramer, 2003; Etnier, Nowell, Landers & Sibley, 2006; van Uffelen, Chin A Paw, Hopman-Rock & van Mechelen, 2008). Importantly, there is insufficient evidence that cognitive improvements are attributable to improved cardiovascular fitness. The implication is that other factors may be involved. A number of potential and emerging research directions could prove instrumental in identifying these factors, the degree of benefit that exercise training actually represents and the related underlying mechanisms that may give rise to exercise-induced cognitive benefits, in later life. These include: evidence for lifelong positive neuroplasticity; burgeoning interest in the effects of motor fitness training; a departure from single and dual-modality exercise interventions; and investigation into the mechanisms that underpin exercise-induced brain changes.

1.2 Emerging and potential research directions

1.2.1 The science of neuroplasticity

The ground-breaking discovery that the brain retains a life-long capacity to change and adapt in response to environmental and experiential stimuli, has propelled efforts to develop strategies that ameliorate ARCD. This capacity, referred to as brain plasticity or neuroplasticity is thought to entail neurobiological processes resulting in the attenuation of age, disease or injury related decline in brain function (Knaepen et al., 2010). Moreover, these changes have been found to correspond with better cognitive performance (cognitive plasticity) (Ratey & Loehr, 2011). Neuroplasticity in ageing animals subjected to exercise training is thought to be particularly associated with exercise that is diverse, complex and novel (Kempermann, et al., 2010). The prospect of a similar possibility in older humans has attracted significant interest. There are theoretical indications that neuroplastic changes are more likely to occur as a result of novel exercise interventions that require focussed attention and concentration (cognitive load) (Adkins, Boychuk, Remple & Kleim, 2006; Kempermann, van Praag & Gage, 2000; Voelcker-Rehage, Godde & Staudinger, 2010). The motor aspect of fitness incorporates balance, coordination, agility, proprioception, flexibility and reaction times (Baker, Atlantis & Fiatarone Singh, 2007; Voelcker-Rehage et al., 2010). It involves movement-based complexity requiring new learning, cognitive and physical coordination demands and sustained mental effort. Hence, from a theoretical perspective there is an inherent logic supporting research into the capacity of motor fitness to promote neuroplasticity.

1.2.2 Motor fitness training

Although fitness is a multifaceted concept consisting of cardiovascular (aerobic), resistance (strength) and motor dimensions; aerobic activity has overwhelmingly been the most studied component of exercise in relation to cognition, in later life (Angevaren et al., 2008; Smith et al., 2010). To a lesser extent resistance training and combined aerobic and resistance training have also been investigated (Snowden et al., 2011; van Uffelen et al., 2008). Recent developments have inspired a growing interest in the contribution of the motor component of exercise (Adkins et al., 2006; Schaefer, Huxhold & Lindenberger, 2006). For example, Voelcker-Rehage et al. (2010), used functional magnetic resonance imaging (fMRI) to demonstrate that different areas of the brain are used to complete complex psychomotor tasks in individuals with high levels of motor fitness compared to individuals with high levels of physical fitness (Voelcker-Rehage et al., 2010). This finding of differential brain activation patterns (physically fit versus motor fit), lends further support to the theoretical proposition that better motor fitness may be linked to brain activation in a way that could potentially elicit cognitive benefits in later life. This finding is also consistent with the results of pioneering animal studies conducted by Black, Issacs, Anderson, Alcantara and Greenough (1990), which indicated that different exercise modalities might influence the neurobiological substrates of the brain in different ways. In this research with rodents, cardiovascular training was associated with an increase in the density of capillaries (angiogenesis) and the proliferation of brain cells (neurogenesis). In contrast, coordination activities were associated with changes in inter-neuron communication (synaptogenesis).

1.2.3 Multi-modal or combination exercise interventions

A notion that arises from the amalgam of findings of Voelcker-Rehage et al. (2010) and Black et al. (1990), is the question of whether the sum total of brain activity could be amplified by combining physical (cardiovascular and resistance) training with motor training. The suggestion here is that optimisation of the intervention stimulus in this way might induce more pronounced cognitive outcomes than the modest levels of enhancement potentially elicited by cardiovascular training alone. Little is known about the potency and the effects of fitness training that is based on the more comprehensive parameters of a broad definition of exercise. Previous research investigating the effects of exercise on the ageing brain has largely been based on single-modality interventions. Recently, multi-modal exercise interventions have begun to be applied (Forte et al., 2013; Voelcker-Rehage, Godde & Staudinger, 2011) to address the limitations of repeatedly evaluating a single component of exercise training in

relation to cognition. The question of whether this particular multi-modal combination (cardiovascular, resistance and motor exercise training) is capable of achieving more cognitive benefits than a single or dual-component intervention is yet to be ascertained.

1.2.4 Mechanisms that underpin exercise induced cognitive change

Research efforts are also increasingly focussing on the mechanisms that give rise to exercise-induced cognitive gains (Ratey & Loehr, 2011). The assumption is that a better understanding of these neurobiological mechanisms and processes may result in innovative neuro-protective interventions (van Praag, 2008). This research has historically been based on animal studies (e.g., Kempermann et al., 2000; Klempin & Kempermann, 2007; van Praag, Christie, Sejnowski & Gage, 1999; van Praag, Shubert, Zhao & Gage, 2005). However, human studies are increasing being undertaken, largely due to the development of sophisticated neuroimaging and electrophysiological methodologies that permit the detailed visualisation of the morphology and inner workings of the brain (Erickson et al., 2010; Li et al., 2009a; Voelcker-Rehage et al., 2010). A particularly fledgling, but novel avenue of investigation is 'in vivo' fMRI, which is conducted as the participant completes a neurocognitive test of some aspect of cognitive function. These types of investigations represent early but decisive inroads into a comprehensive understanding of the links between performance-based manifestations of cognitive abilities (elicited by physical activity and exercise training); and the neuro-electrical, cellular and molecular activities that underpin them. At this stage the downstream and upstream sequences, 'set in train' from agents of improvement (e.g., physical activity) or impairment (e.g., ageing), to the cognitive change or functional end-point (e.g., better memory or conversely, cognitive decline), is not well understood. Nevertheless, the likely neurobiochemical and morphological componentry is progressively being identified.

Animal studies indicate that cardiovascular exercise (running) in rodents precipitates a complex interactive signalling cascade whereby growth factors (protein molecules that act as chemical messengers) (van Praag et al., 1999; van Praag et al., 2005) work in concert to instruct a number of downstream responses that regulate cell division and survival, promoting positive neuroplasticity (the brain's ability to make more and stronger connections between neurons in response to exposure to novel stimulation). Synaptic proteins (Farmer et al., 2004; Vaynman & Gomez-Pinilla, 2006), glutamate receptors (Farmer et al., 2004; Vaynman, Ying, Yin & Gomez-Pinilla, 2006) and growth-factors, such as BDNF (Tang, Chu, Hui, Helme & Law, 2008; Vaynman et al., 2006), vascular endothelial growth factor (VEGF) (Fabel et al., 2003) and insulin-like growth factor (IGF-1) (Llorens-Martín, Torres-Alemán & Trejo, 2009) are some of

the biochemical ingredients that elicit the brain changes that underpin improved neuroplasticity. At the level of functional organisation (physiology), these brain changes include: cerebral capillary proliferation (angiogenesis) particularly in the motor cortex (Swain et al., 2003); increased cell production (neurogenesis) in the hippocampus (van Praag, 2008) (specifically in the dentate gyrus); and conductivity enhancement (synaptogenesis) (Vaynman et al., 2006). Although the mechanism that gives rise to increased capillary density is less delineated, it is hypothesised that increasing the size of vessels and the attendant blood supply assists in circulating growth factors throughout the dentate gyrus (van Praag et al., 2005).

To date there have been few studies, related to the mechanisms underpinning exercise-induced cognitive change, in humans. However, changes associated with exercise have been demonstrated; in gene expression (Cotman & Berchtold, 2002), cerebral blood volume (Pereira et al., 2007), P300 amplitude and latency (Kamijo & Takeda, 2010; Pontifex, Hillman, Fernhall, Thompson & Valentini, 2009), BDNF (Li et al., 2009a) and brain volume (Colcombe et al., 2003; Gordon et al., 2008). In a recent randomised controlled trial (RCT) of older adults, moderate intensity walking that resulted in improved fitness, increased the size of the anterior hippocampus and improved spatial memory. These effects were possibly mediated by increases in BDNF that were also associated with increased exercise (Erickson et al., 2011).

BDNF is a protein and the most abundant neurotrophin in the brain, with an important role in brain neurogenesis, synaptic plasticity, learning and memory (Knaepen et al., 2010; Ratey & Loehr, 2011). The brain has been found to be the main source of BDNF concentrations in venous blood (circulating BDNF) (Rasmussen et al., 2009). The suggestion of a potential BDNF mechanism contributing to cognitive function is also supported in a study that found that reduced cerebrospinal fluid BDNF concentration was associated with ARCD (Li et al., 2009a). BDNF may play a key role in brain plasticity by regulating the growth, maintenance and survival of neurons in the adult brain. Plasma BDNF has been found to be a biomarker of cognitive function in women (Komulainen et al., 2008). Thus, on the basis of human and non-human studies, the prospect that variation in BDNF (as a biomarker of brain changes) might be associated with exercise induced changes in cognitive function, is worthy of further exploration.

1.3 Purpose of the study

The main purpose of this study was to test whether a multi-modal exercise intervention could improve cognitive and physical performance, in older women. Conducted as a RCT this study

fulfils a methodological recommendation that has consistently been made in systematic reviews of the extant literature (e.g., Angevaren et al., 2008; Smith et al., 2010). There are currently no controlled experimental studies where this particular design has been used to test whether the combination of cardiovascular, strength and motor fitness training can elicit cognitive effects in later life. In addition, this randomised controlled trial sought to ascertain the physical effects of a multi-modal exercise program, as they relate to physical functioning, mobility, balance ability and exercise capacity.

A second purpose was to evaluate the acceptability of a multi-modal exercise format for women aged between 65 and 75 years and to determine the elements of the program that most contributed to enjoyment and participation. A third purpose was to appraise the everyday relevance of any cognitive or physical changes that were perceived to be attributable to participation in the intervention. Finally, there is still a gap in the literature regarding the mechanisms that might underpin the cognitive effects of exercise. By exploring cognitive performance and the possibility of changes in plasma BDNF, following the exercise intervention, this study was expected to make a contribution to the current body of knowledge.

1.4 Aims of the study

This study focussed on healthy, community dwelling, women aged 65 to 75 years of age without clinical cognitive impairment or uncontrolled major medical conditions. It aimed to:

1. test the effect of a complex, multi-modal exercise program on cognitive functions, physical functioning and a biomarker of brain plasticity; and
2. investigate the benefits and acceptability of a multi-modal exercise program as expressed by the participants.

1.5 Overview of the study

To address the aims, as stated above, this two-phased study was designed as a RCT with an embedded qualitative arm. First, a RCT of a multi-modal exercise intervention was conducted. Forty-nine women aged between 65 and 75 years, with no cognitive impairment and not undertaking more than one hour of formal exercise training per week, were recruited and randomised into two groups. The intervention group attended a 60-minute multi-modal class twice a week for 16 weeks. The exercise intervention included cardiovascular, strength, and

motor fitness training. The control group was asked to retain their usual lifestyle. The primary outcome was neurocognitive functioning; secondary outcomes were physical functioning, reaction times and plasma levels of BDNF.

In the second phase of the study a sub-group from the intervention group was invited to participate in semi-structured, face-to-face interviews and a focus group. In these interviews the participants were asked about the aspects of the program they had found to be helpful and/or enjoyable; their experience of the content and structure of the program; and their perception of any changes they attributed to participation in the program.

1.6 Structure of the thesis

Chapter One introduced the study and provided an overview of the research and the background on which it is based. It describes the significance and identifies the purpose, of the study. Terms used throughout the thesis are also clarified.

Chapter Two presents a review of the observational and experimental research studies conducted to date, that examine the effects of exercise on neurocognitive functioning in older adults.

Chapter Three focusses on a critical review of the methodological issues in previous research. This critique explores the state of current knowledge and provides a background to the rationale and decision-making that underpinned the methodological design outlined in the following chapter.

Chapter Four then details the design of the RCT and the supplementary qualitative component that formed the basis of this study. Specifically, the rationale behind the setting, methods of recruitment, sampling, randomisation, data collection and data analysis, are provided for the RCT. In addition, detail about the methods employed in the qualitative component of the study is also provided.

Chapter Five presents the results of the RCT and Chapter Six details the results of the qualitative component.

Finally, Chapter Seven provides a discussion of the results of this study including, the contribution of the study to future multi-modal exercise intervention designs; and the 'everyday' relevance of changes induced by the exercise program.

Chapter 2: Literature Review/Introduction

2.1 Introduction

Research into the influence of exercise and physical activity on the ageing brain has been conducted over several decades. Interestingly, the belief that exercise has the capacity to preserve and improve brain functions that subserve cognitive abilities in older adults is widely held. However, in reality, the evidence is mixed. Although promising, it remains equivocal (e.g., Etnier et al., 2006). The following is a critical review of the literature examining the effects of physical activity on cognitive performance in later life.

A hallmark of this research is a tendency towards ambiguity. This emanates from a number of factors. Firstly, although the terms 'physical activity', 'exercise' and 'fitness' are not synonymous, they are often used interchangeably. In this review, the taxonomies will be specifically defined. Secondly, the veracity of both study and review findings have, in many instances, been difficult to ascertain because conclusions have been drawn from: non-equivalent study design comparisons; indeterminate results derived from disparate or crude instrumentation; inadequate provisions for the control of bias; or because inferences of causality have been asserted on the basis of longitudinal and cross-sectional association. The present exposition will present and analyse the evidence in the light of the requisite predictive ability of both the stated study design and the attendant instrumentation. Thirdly, an additional source of obscurity is that research has often been based on highly heterogeneous clinical populations with chronic conditions, cognitive impairment or an established diagnosis of dementia. To address the potential confounding effect of these inconsistencies and further clarify the status of evidence for a causal relationship, the current appraisal of evidence is confined to non-clinical populations; that is, to healthy community dwelling older adults, without clinical cognitive impairment or uncontrolled major medical conditions.

Finally, examinations of the relationship between neurocognitive functioning and physical activity for older cohorts have largely been conducted along two trajectories. Each of these approaches will be considered with reference to the respective incumbent and prescribed parameters that constitute necessary criteria for the establishment of definitive findings. Non-intervention observational studies, which by definition do not assume a cause-effect relationship, have focussed on the question of whether there is an association between levels of physical activity and levels of cognitive performance. Intervention studies have addressed the question of whether structured, definable exercise can induce the maintenance or

improvement of cognitive capacity in older adults. Figure 2.1 is a diagrammatic overview of the study designs and categories used to investigate physical activity and exercise in relation to cognition in later life. Figure 2.1 also indicates what elements of this body of knowledge have been included in the present literature review, and to which areas the tables included in this review refer.

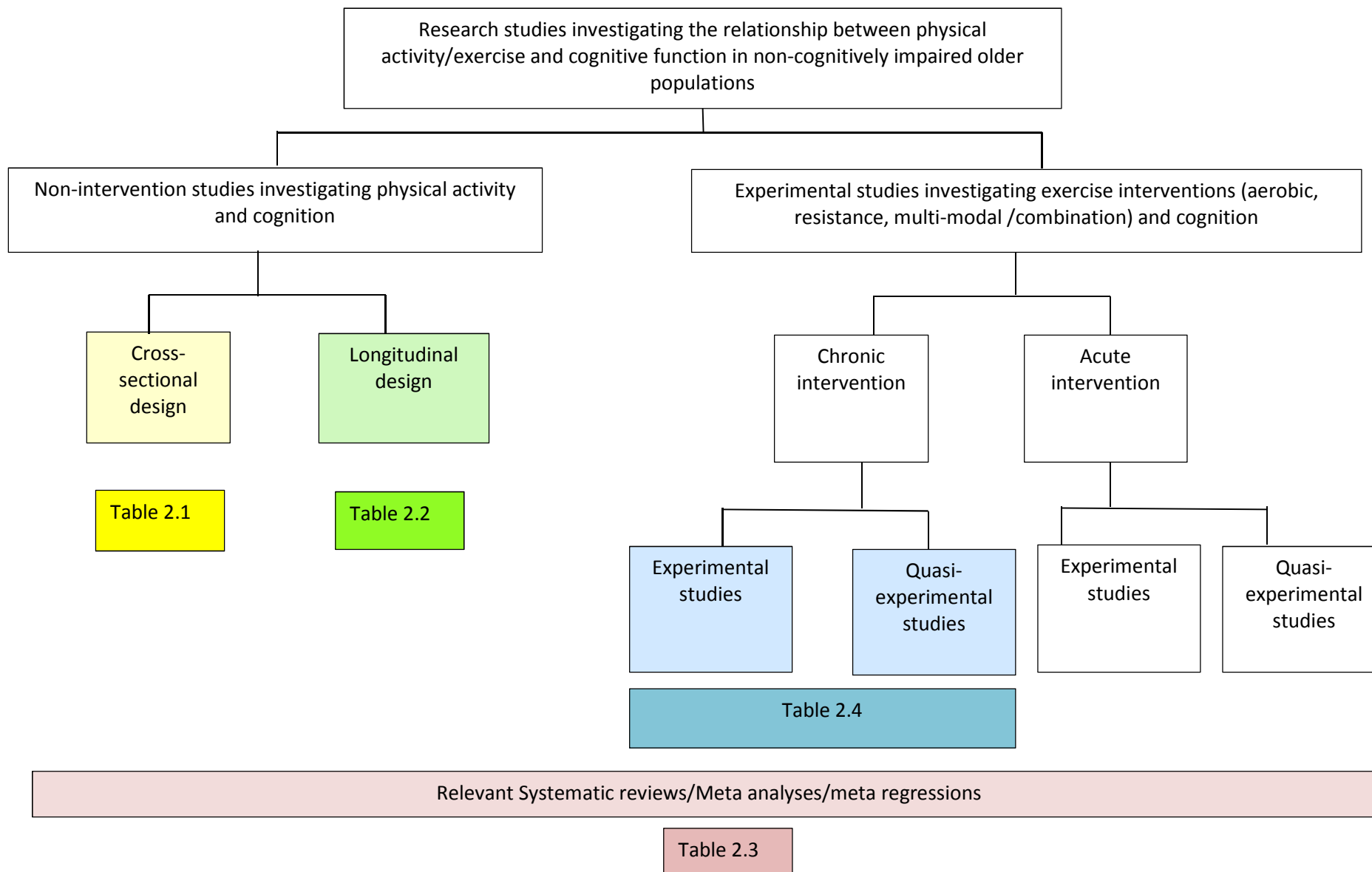


Figure 2.1: Categories of empirical studies investigating relationships between some form of physical activity and cognitive function, among older adults

2.2 Definitions

Relevant investigations have largely focussed on the measurement of cognition in relation to physical activity, exercise and/or physical fitness. Physical activity has been formally defined as “... any bodily movement produced by skeletal muscles that result in energy expenditure” (Caspersen et al., 1985, p. 126). As an umbrella term, physical activity denotes involvement in activities that require movement that varies according to levels of exertion (light, moderate, strenuous/vigorous) and the summative amount of time spent engaging in particular pursuits such as walking or the physical demands of domestic, recreational or occupational life (hours per week). In a more technical (and objective) sense, amounts of energy expended can be measured in kilojoules (kJ) and the rate of expenditure can be expressed as a continuous variable from low to high. Physical activity, engaged in as part of everyday life, including any type of task that is not categorised as formal exercise, has also been referred to as ‘weekly’ (Yaffe et al., 2001, p. 1704) or ‘incidental’ (Glass et al., 1999) activity.

Exercise is considered to be a sub-set of physical activity and is generally undertaken with the objective of improving or maintaining fitness. Defined as “...planned, structured, repetitive bodily movement” (National Institutes for Health, 1995, p. 1), exercise can be undertaken informally as part of a broad spectrum of physical and recreational activities, or more formally in the form of organised sport. Exercise can also be administered in a controlled environment for the purposes of eliciting a predicted outcome, as part of an experiment.

Exercise interventions in the literature have generally been delivered as an acute bout (once) or at regular defined intervals (chronic). Aerobic exercise, otherwise known as endurance, cardiorespiratory or cardiovascular exercise, has attracted the greatest number of investigative efforts. Other intervention studies have examined resistance exercise protocols, specific modalities such as Tai Chi and yoga and multi-modal or combination formats, which may include aerobic, and/or resistance and/or flexibility and/or balance training. Although it is beyond the scope of this review, it is worth noting the small number of studies where exercise has been combined with cognitive or mental training targeting domains such as memory, perception, attention and language (e.g., Fabre, Chamari, Mucci, Massé-Biron & Préfaut, 2002; O'Dwyer, Burton, Pachana & Brown, 2007).

Physical fitness is the product of exercise and physical activity, and was defined by (Caspersen et al., 1985, p. 128) as “...a set of attributes that people have or achieve (...) that relates to the ability to perform physical activity.” Alternative definitions subdivide physical fitness into

components related to health (e.g., cardiorespiratory endurance, muscular strength & flexibility) and components related to the skill sets involved in athletic performance or sporting ability such as agility, power and speed (American Physical Therapy Association, 2009; Corbin et al., 2000). A more general proposition is that physical fitness is "...a dynamic physical state - comprising cardiovascular/pulmonary endurance, muscle strength, power, endurance and flexibility; relaxation and body composition – that allows optimal and efficient performance of daily and leisure activities" (American Physical Therapy Association, 2009, p. 1). 'Fitness' has also been conceptualised as an overarching concept incorporating not only physical (i.e. cardiovascular fitness and muscular strength), but also motor fitness "...indexed by components such as flexibility, speed, balance and fine coordination" (Voelcker-Rehage et al., 2010, p. 167).

In the current literature, the vast majority of observational studies have centred on physical activity. Intervention studies have largely focussed on single-modality exercise interventions and the cardiovascular component of exercise. Two recent developments include the emerging concept of multi-modal exercise interventions (Kraft, 2012) and beginning interest in the specific contributions that the motor component of exercise may have, in relation to cognitive capacity in later adult life (Voelcker-Rehage et al., 2010). There is no formal definition in the literature that qualifies the parameters of what is loosely and variously referred to as multi-modal, combination, multidimensional or combined exercise. However, in general the terms refer to: supervised exercise classes conducted for a specified period of time (usually one hour); where different elements of physical and motor fitness are formally instructed, delivered sequentially or concurrently; and are aimed at improving or preserving fitness and physical functioning or functionality. The physical fitness component usually entails cardiovascular/aerobic and/or resistance training; while motor fitness training focusses on dimensions such as balance, coordination, proprioception, agility, flexibility and reaction-time. The most commonly combined modalities are balance, strength and aerobic exercises although current guidelines for older adults also recommend the inclusion of flexibility training (Cress et al., 2004; Sims et al., 2010).

The key outcome of interest in this review is cognition or cognitive abilities, as a function of exercise. The term 'cognition' is derived from the Latin word 'cognoscere' meaning 'to know' and refers to the actions of thinking and knowing and the processing of information. This includes abilities such as learning, memory and attention (Pietropaolo & Crusio, 2011).

The concept known as 'executive functions', although variously defined, generally refers to high level cognitive capabilities related to goal-directed behaviour, that control and integrate other cognitive processes (Pichierri et al., 2011). These abilities include the capacity to plan and implement strategies and tasks, and inhibit task-irrelevant information (inhibition). Age-related deterioration of executive functions is thought to correspond with structural changes in the prefrontal lobe of the brain (Jurado & Rosselli, 2007). As an umbrella term 'executive function' is frequently referred to in the current literature because the associated constructs have been found to be vulnerable to ARCD, with inhibition being one of the earliest capacities to manifest impairment (Deary et al., 2009; Park & Lorenz, 2009). There is significant interest in whether exercise training can attenuate and target age related cognitive decrements associated with executive functions. Finally, 'cognitive load' has been defined as a multidimensional concept representing the load that performing a particular task imposes on an individual's cognitive system (Lavie et al., 2004). Cognitive load is a characteristic of tasks that involve novelty and complexity, as these factors generally necessitate mental effort that is more likely to engage higher order cognitive processes. Experiential stimuli, including exercise training, which require sustained mental effort, may promote the prospect of eliciting cognitive enhancement in older adults (Kempermann et al. 2000; Kempermann et al., 2010).

2.3 Literature search strategy

The following databases were searched from January 2000 to November 2013: Cochrane Collaboration library (including database of systematic reviews and clinical trials register); Medline; CINAHL; Informit; Journals@Ovid; PEDro; Google Scholar and Web of Science. The keywords used were adjusted for the specific databases, and included various combinations of the following:

Cochrane – physical fitness, exercise, motor activity, ageing, aged, mental processes, cognition.

Medline – Leisure activities, physical activity, exercise, lifestyle, healthy people programs, ageing, older people, older adults, aged+, seniors, mature age, executive function, brain health, neurocognitive functioning, mental processes, musculoskeletal and neural physiological phenomena. Also to limit the search the following terms were used: review, clinical trial+, controlled clinical trial, case-control studies.

CINAHL – Adults, aged, ageing, exercise, physical fitness, physical activity, exercise physiology, mental processes, executive function, brain health, lifestyle, neurocognitive functioning and cognitive processes.

Informit – Aged, ageing, older adults, adult, aged 80 and over fitness, physical fitness, exercise, mental processes, cognition, efficacy and effects.

Journals@Ovid – exercise, cognition and age*.

PEDro – Exercise, cognition, ageing, fitness training, reduced exercise tolerance and gerontology.

Google Scholar – exercise, cognition and ageing.

Web of Science – exercise, exer*, cognition, cognitive function, executive function.

In addition the terms multi-modal, combination exercise and multi-component were added as keywords to refine searches later in the search strategy.

Numerous combinations were entered into the databases and a record kept of all search results. The reference lists of all articles found in this search were reviewed and further articles were identified from this search of citations. Exclusion criteria were: publication in a language other than English; not available by inter-library loan service in Australia; and publication dates before 2000 as this represents the current status of research in the area.

2.4 Appraisal of observational studies related to ‘physical activity’ and cognition

A cursory examination of the relevant literature creates the impression that there is general acceptance of the principle that higher physical activity levels are associated with less cognitive decline and greater preservation of cognitive function in later life. Indeed, the majority of cross sectional (Chan et al., 2005; Hillman, Kramer, Belopolsky & Smith, 2006; Middleton, Barnes, Lui & Yaffe, 2010) and longitudinal studies (Chang et al., 2010; Etgen et al., 2010; Lytle, Vander Bilt, Pandav, Dodge & Ganguli, 2004), indicate a lower incidence of cognitive impairment among those who report active lifestyles, compared with sedentary lifestyles. Despite the prevailing trend of positive findings and the intuitive appeal of such a proposition, a more critical analysis reveals that the conclusiveness of this finding is yet to be fully established. To date, few studies have been able to comprehensively surmount the challenges posed by the

‘threats to validity’ (West & Thoemmes, 2010) that are rife in the observational literature examining the influence of physical activity on the ageing brain.

2.4.1 Cross-sectional studies

In Table 2.1, the key findings and design parameters of seven cross-sectional studies examining cognition, physical activity and ageing are outlined. These studies cover a broad band of age groups (55-96 years), with one study comparing the performance of a sample of 241 participants in the 15 to 71 age range (Hillman et al., 2006). At either end of the continuum, sample sizes range from 72 (Voelcker-Rehage et al., 2010) to 9,344 (Middleton et al., 2010), with the remainder of the samples varying between 120 and 1,927 (Bixby et al., 2007; Lindwall, Rennemark & Berggren, 2008). Whereas some studies are based solely on samples of women (Middleton et al., 2010), others have included men and women, although adjustment for gender has not always been undertaken.

In general, and in conjunction with a number of caveats, the cross sectional findings (see Table 2.1) indicate that physical activity may be beneficial to both general and selective aspects of age-related cognitive and brain function. For example, Middleton and her colleagues (2010), asked participants to recall their physical activity levels at four age points in their lives (adolescence, 30 years, 50 years and current mean age of 71.6 years). These researchers found less likelihood of cognitive impairment in late life among older women who reported being physically active over their life course, especially in adolescence. However, this study exemplifies one of the major limitations inherent in the cross sectional and longitudinal literature alike. Significant equivocality has arisen from the fact that subjective measures (self-report), mostly in the form of recall interviews, have traditionally been the most used means of quantifying physical activity. Although a truer index would be expected from cross sectional studies employing formal questionnaires with recognised properties of validity and reliability (e.g., Angevaren et al., 2007; Bixby et al., 2007; Eggermont, Milberg, Lipsitz, Scherder & Leveille, 2009), the measurement flaws inherent in all forms of self-report, are well recognised (Prince et al., 2008). In addition to the prospect of bias arising from issues related to memory and social desirability, inaccurate data may also stem from the tendency for fitter or well-trained individuals to under report activity levels and for less fit individuals to over-report (Prince et al., 2008).

Table 2.1: Cross sectional studies investigating relationships between physical activity and cognitive functioning

Reference	Sample	Design	Measurement of physical activity /fitness	Cognitive function tests and screening tools	Major findings
(Angevaeren et al., 2007)	N=1927 healthy men and women Aged 45-70 yrs. (mean = 56.4, SD = 7.1)	Cross sectional study. Data collection by interview.	European Prospective Investigation into Cancer (EPIC) and nutrition physical activity questionnaire. Has questions on hours per week spent on leisure activities in summer and winter and sports all year round. Activity then transformed into METS	Battery of cognitive function tests including Dutch versions of: <ul style="list-style-type: none"> • (Visual) Verbal learning (WAIS) • Concept shifting test • Stroop Colour Word test • Word fluency test 	MV linear regression showed that intensity of physical activity and variation in physical activity was associated with processing speed, memory, mental flexibility and overall cognitive function. There were no associations between time spent on weekly physical activity and any of the cognitive domains.
(Bixby et al., 2007)	n=120 healthy men and women Aged 65–92 yrs. (mean = 78.9, SD = 5.8 Had stable patterns of physical activity during a 3- to 5-yr period before the study.	Cross sectional study. Data collection by interview.	Yale Physical Activity Survey (YPAS) for older adults. Includes activities involved in Household chores, recreation, and structured exercise.	Mini mental state examination (MMSE) to screen for dementia Executive function: <ol style="list-style-type: none"> 1. Stroop Colour Test 2. Stroop Word Test 	YPAS summary index scores explained a small, but significant amount of variance in Stroop colour–word and interference scores ($\Delta R^2 = 2$ and 4%, respectively) after accounting for intelligence and age. The YPAS index was unrelated to non-executive performance. Conclusions: The results support specificity of the physical activity/cognition relationship in older individuals.

Reference	Sample	Design	Measurement of physical activity /fitness	Cognitive function tests and screening tools	Major findings
(Chan et al., 2005)	n=140 Age > 55yrs HK Chinese community dwelling men and women.	Cross sectional study in 2002-3. Comparing memory function in those who practiced mind-body (MB) or cardiovascular (CV) exercises with those who did not exercise.	Self-report of frequency of exercise. Type of exercise (MB or CV) was defined by motion speed, emphasis on relaxing the mind and conscious control of movement. Four groups were defined: MB, CV, MB+CV, NO. Medical condition, BP, HR and peak flow.	1. Chinese version of the Mattis Dementia Rating Scale (CDRS) 2. The Hong Kong List Learning Test 3. Chinese version of the Boston Naming Test (CBNT)	MB and CV exercises appear to have a combined effect that might help to preserve memory in older adults. In addition, MB exercises may be considered as an alternative training for older adults who cannot practice strenuous physical exercise.
(Eggermont et al., 2009)	n= 544; mean age 78, 62% female Older community-dwelling adults Boston area	Cross-sectional correlational/predictor study	Medical history (self-reported), musculo-skeletal pain, and Hopkins Revision of the Center for Epidemiologic Studies Depression Scale. - Demographic info. interviewer-administered questions. BMI, BP. Engagement in physical activity Physical Activity Scale for the Elderly (PASE).	Cognitive function was measured using a battery of neuropsychological tests: 1. MMSE 2. Clock Drawing 3. Category Fluency 4. Animal Naming 5. Trail Making Test	Subjects who engaged in more physical activity had significantly better performance on all cognitive tests, except for Letter Fluency and the memory test of delayed recall, after adjusting for age, sex, education, and total number of medications. -With further adjustment for CVD and CVD risk factors (heart disease, diabetes mellitus, stroke, and hypertension), pain, and depressive symptoms, PASE score remained significantly associated with executive function tests.

Reference	Sample	Design	Measurement of Physical Activity/Fitness	Cognitive function tests and screening tools	Major findings
(Hillman et al., 2006)	n=241 Age range = 15-71 yrs. Community dwelling men and women. Twins and their non-twin siblings. (Only one twin included in this study)	Cross sectional cohort study – from a larger twin study.	Self-report of the number of times per week the subjects exercised sufficiently to sweat.	Eriksen flanker task WAIS-III	Reaction time decreased with age. Physical activity was associated with faster RT during these conditions, regardless of age. Response accuracy findings indicated that increased physical activity was associated with better performance only during the incongruent condition for the older cohort. Physical activity may be beneficial to both general and selective aspects of cognition, particularly among older adults.
(Lindwall et al., 2008)	n=813 Men and women from Sweden. Age-cohorts from 60–96 years	Cross-sectional cohort study – part of larger longitudinal study.	Self-report in response to questions about light and moderate exercise – then subjects were placed into one of four groups for each of the two types of exercise, comparing activity now and one year before.	MMSE Free recall Recognition of positions Vocabulary test Digit cancellation test Digit span Comparing figures	ANCOVA, controlling for age, education, depression, functional status and co-morbidity, demonstrated a main effect for light exercise, but not for strenuous exercise, on five of the six cognitive tests and the MMSE, for men but not for women. A negative change in exercise status was associated with lower MMSE scores for men but not for women.

Reference	Sample	Design	Measurement of Physical Activity/Fitness	Cognitive function tests and screening tools	Major findings
(Middleton et al., 2010)	n= 9344 American women Mean age 71.6 years	Cross sectional cohort study	Self-report in old age of physical activity frequency of different intensity at four age points (teen, 30yrs, 50yrs and current)	Modified MMSE (mMMSE)	Women who reported being physically active had a lower prevalence of cognitive impairment in later life than women who were inactive at each time (teenage, 30yrs, 50yrs, old age). Women who reported being physically active at any point over the life course, especially as teenagers, had a lower likelihood of cognitive impairment in later life.
(Voelcker-Rehage et al., 2010)	n= 72; mean age 69, 72% female. Healthy non-demented older community-dwelling adults in Germany	Cross sectional predictor study	Physical and motor fitness. Motor fitness: 1.Shoulder flexibility 2.Hand tapping 3.Feet tapping 4.Agility test 5.Backwards beam walk 6.One-leg-stand with eyes open and closed 7.Purdue peg board test Physical fitness 1.Grip force 2.Spiroergometry – VO2 peak	Screening = MMSE Perceptual speed: 1. Identical Picture Test 2. Visual Search task Executive Control: 1. Flanker Task 2. Letter n-Back Task Also fMRI neuroimaging For analysis divided groups into low fit and high fit.	Physical fitness, indexed by cardiovascular fitness and muscular strength, and also motor fitness including movement speed, balance, motor coordination and flexibility, showed a strong association with cognitive functioning. Functional brain imaging data revealed that physical and motor fitness were differentially related to cognitive processes.

Selective cognitive effects (e.g., memory, executive function) related to physical activity participation have been reported in a number of cross sectional studies. Chan et al. (2005), compared inactive older individuals with more active counterparts, and found better learning and memory function in those who engaged in a combination of cardiovascular activities and mind-body activity requiring concentration (i.e. Tai Chi). However, the meaning of this finding is somewhat dubious, due to the arbitrary manner in which the summative amount of exercise (reported by participants) was categorised. More activity is also purported to be related to better reaction times (Hillman et al., 2006) and better executive function (Bixby et al., 2007; Eggermont et al., 2009). The finding in relation to executive function is noteworthy since both of the cited studies are among the better designed cross sectional investigations. Both employed validated questionnaires (Yale Physical Activity Scale (YPAS) & Physical Activity Scale for the Elderly (PASE), respectively), in conjunction with statistical adjustment for confounding variables. However, the finding of a contemporaneous relationship between physical activity and specific domains of cognitive performance is not clear-cut. For example, distinct moderating effects appear to emerge in those studies where more rigorous statistical scrutiny is applied to the influence of relevant extraneous variables.

The application of statistical strategies to attenuate the effects of covariance is an important index of the robustness of the present research because variables such as normal age changes, age, sex, race, education, depression, participation in cognitive activities, vascular disease, intelligence quotient (IQ) and socio-economic status (SES), have all been demonstrated to differentially affect cognitive performance (Deary et al., 2009). In a study where covariates were included in the analysis Bixby et al. (2007), tested for the absence of depression and adjusted for age, education and IQ. They found that while physical activity was associated with executive function, it accounted for only two to four per cent of the variance. Age accounted for 13%; and IQ was positively associated with all categories of cognitive performance, specifically accounting for 17% of task performance representing executive function. Similarly, Eggermont et al. (2009), found an association between physical activity and executive function (but not episodic memory) after adjusting for an array of likely confounders including race, age, sex, education, pain, depression, cardiovascular related co-morbidity (heart disease, hypertension, stroke, diabetes) and total number of medications. However, the significance of this particular study is not solely in the finding of a positive association between physical activity and executive function, but also in the trend that emerged in relation to the degree of precision employed in the statistical analysis. Eggermont et al., (2009) employed a three phase statistical design wherein associations were analysed in the absence of adjustment for

covariance (Model 1); after adjustment for socio-demographic variables (race, age, sex, race and education) (Model 2); and in relation to further adjustment for co-morbidity, chronic pain and the total number of medications (Model 3). Interestingly, the unadjusted model found that more active participants demonstrated better scores across the whole spectrum of neurocognitive tests (Clock-in-a-Box Test, Animal Naming, Trail Making Test [parts A, B & Delta], Letter Fluency, Hopkins Verbal Learning Test) compared with less active counterparts. However, the Trail Making Delta, Letter Fluency Test and Hopkins Verbal Learning Test were no longer significantly associated with physical activity after the fully adjusted analysis. This trend is consistent with meta-analyses that report an inverse relationship between the effect size of physical activity and exercise on the ageing brain; and the quality of the study design (Etnier & Salazar, 1997; Smith et al., 2010).

Other moderator variables germane to understanding the specific nature of the posited nexus between physical activity and cognition include gender and the level of physical activity. Although the concept of dose-response is highly relevant to ascertaining the amount and intensity of physical activity (or structured exercise) that might optimally benefit older adults, neither of these factors have been given particular primacy in cross sectional investigations. In research where these factors have been considered, Angevaren et al. (2007) found better memory, processing speed, mental flexibility and overall cognitive function in those participating in physical activities deemed to involve greater variation and greater average intensity. This study reported no significant association between the relevant cognitive domains and the time spent each week on physical activity. Conversely, Lindwall et al. (2008) found that significant cognitive benefits (on measures of free recall, vocabulary and digit span), were manifested by respondents (mean age =75.1 years; n=813; 58% of total sample) reporting light but not strenuous exercise. In the gender-specific analysis, light exercise was associated with better cognitive performance, in five out of six neurocognitive tests for men, but not for women. The limitations of retrospective self-report data and non-validated instruments obscure the interpretation of these findings; although, ordinarily, a large sample size might be regarded as a mitigating factor, this study is inconsistent regarding the sample's stated representativeness. The meaningfulness of the finding that inactive women outscored inactive men, in terms of the Mini Mental State Examination (MMSE of 26.6 and 24, respectively) and a battery of neurocognitive tests, is also unclear. Since a MMSE score of 24 is commonly applied as a cut-off to distinguish subjects with cognitive decline (Folstein, Folstein & McHugh, 1975), the confounding effect of differential cognitive status and the issue of

reverse causation (pre-existing cognitive impairment in men) assume relevance. (Note: MMSE scores range from 0-30 with scores of 25 or more traditionally being considered normal).

Research by Voelcker-Rehage et al. (2010) represents a departure from the inherent bias in subjective measurement in cross sectional research. This study is also unique in the adoption of a broader definition of fitness differentiating between physical fitness (cardiovascular fitness expressed as peak oxygen uptake (VO_{2peak}), muscular strength (indexed as grip force) and motor fitness encompassing flexibility, speed, fine coordination and balance. Seventy-two participants (mean age=68.99 years; SD=3.66; 52 females) were assessed and analysed in terms of four fitness groups (low motor/low physical; low motor/high physical; high motor/low physical; high motor/high physical) to investigate the likelihood of differential associations with cognitive processes. Psychometric testing reflected perceptual speed (Identical Picture Test; Visual Search Task) and executive control (modified Flanker Task and a letter n-Back Task to address working memory). The Flanker Task (a test of attention in the presence of distracting information) was conducted within a fMRI scanner.

Both the imaging and behavioural data indicate that physical fitness is mainly related to executive control processes, whereas motor fitness is additionally significantly related to perceptual speed tasks. More specifically, the imaging data reveals that in both fitness dimensions fitter participants exhibit less activation in the superior and middle frontal gyrus, the occipital cortex and the superior temporal gyrus (Voelcker-Rehage et al., 2010). This configuration is postulated to represent less effort in relation to visual perception and cognitive control. Separate effects derived from neuroimaging included a positive relationship between high physical fitness and greater activation in the left temporal gyrus and left parahippocampal gyrus; while high motor fitness groups are characterised by stronger activation in the parietal cortex (bilaterally). This specificity is postulated to support the view that for older adults, different brain processes are facilitated by different dimensions of fitness or exercise capacity. Moreover, the authors hypothesise that improved recruitment of task-specific areas of brain activation may represent less compensatory 'over activation' in other areas of the brain. This proposition represents an attempt by the authors to interpret findings in the light of a possible underlying mechanism. The 'compensation hypothesis' (e.g., Reuter-Lorenz & Cappell, 2008) is based on research demonstrating stronger and more extensive frontal lobe activation in older, compared to younger subjects, suggestive of compensatory cerebral processes with ageing. Commentators such as Anderson, Greenwood and McCloskey (2010) have highlighted the need to elucidate the mechanisms likely to underpin the evidence

for exercise attenuated ARCD; as this frontier may finally reveal the true nature of the association. To date, few studies have attempted to do this, largely due to the technological constraints characterising previous generations of research.

In sum, cross sectional research suggests there is an association between more physical activity and better cognitive performance in later life, in relation to global functioning; specific processes such as learning, memory function and reaction times and, according to more robust studies, in relation to facets of executive functions. There is also the possibility that for older adults, certain levels, modalities and volumes of physical activity may yield different neurocognitive responses; from different areas of the brain and to different degrees. However, there is much less evidence supporting the notions of dose-response and differential cognitive outcomes. Nevertheless, the cross sectional research remains contentious because of a gamut of recurring methodological shortcomings such as subjective measurement; the heterogeneity of cognitive testing protocols; post-hoc categorisation of self-reported activity levels (that are then compared as if the study were an experiment); unabated covariance; and the relative absence of a theoretical paradigm to guide the direction and interpretation of research efforts.

The consistent trends in the cross sectional literature, however, provide significant impetus for further, more robust investigation. Recent methodological advances, such as fMRI and rapidly advancing activity monitoring technology (Casaburi, 2007) may represent substantial possibilities for more stringent indexing of neurocognitive functioning and the objective measurement of physical activity. At this early stage, these developments are not yet significantly reflected in the cross sectional literature.

2.4.2 Longitudinal studies

Table 2.2 represents an overview of the key design elements and findings of some of the most recent and more frequently cited longitudinal studies investigating relationships between ageing, physical activity and cognition. A strength of the longitudinal research is the disposition towards large sample sizes. The findings of the 11 selected articles are based on a total of 51,155 individuals with sample numbers ranging from 299 to 18,766. Within this range, the remaining nine studies average 3,565 participants.

Table 2.2: Longitudinal studies investigating relationships between physical activity and cognitive functioning

Reference	Sample	Design	Measurement of physical activity/fitness	Cognitive function tests and screening tools	Major findings
(Angevaeren, Vanhees, Nooyens, Wendel-Vos & Verschuren, 2010)	n=1904 Aged 45-75 yrs. Healthy, community dwelling men and women	Prospective longitudinal cohort study. Subjects enrolled 1995-2000 – followed up for 5 years	European Prospective Investigation into Cancer and Nutrition – short physical activity questionnaire (EPIC – Dutch version)	Cognitive Function: 1. Processing speed 2. Memory function 3. Mental flexibility 4. Overall cognitive function Cognitive Testing: 1. 15 Words Verbal Learning Test 2. Stroop Colour Word Test 3. Letter Digit Substitution Test 4. Word Fluency Test	Changes in time spent on physical activity were not associated with changes in cognitive function. Increased intensity of weekly activities was associated with better processing speed.
(Barnes, Yaffe, Satariano & Tager, 2003)	n = 349 Healthy community dwelling men and women Mean age at baseline = 69 (range = 59-88).	Prospective longitudinal cohort study. Testing completed at baseline and 6 years later.	Treadmill exercise testing of peak VO_2 ($\text{mL/kg}\cdot\text{min}^{-1}$). Duration of treadmill exercise. Oxygen Uptake Efficiency Slope (OUES).	<ul style="list-style-type: none"> • mMMSE • Attention/executive function: Trail-Making, Stroop Interference, Digit Symbol Test • Verbal memory: California Verbal learning Test (CVLT) • Verbal Fluency 	Participants with worse cardiorespiratory fitness at baseline experienced greater decline on the mMMSE over 6 yrs and had poorer test results on cognitive tests performed at follow-up

Reference	Sample	Design	Measurement of physical activity/fitness	Cognitive function tests and screening tools	Major findings
(Chang et al., 2010)	n=4945 Mean age at enrolment = 51yrs Community dwelling men and women (4% (n=184) had dementia at follow-up)	Prospective longitudinal cohort study. Subjects enrolled 1967 followed up for an average of 26 years	Self-report of type and number of hours a week. Divided into 3 categories of none, ≤5 hrs/week, >5 hrs/week.	Speed of processing: 1. Digit symbol substitution test 2. Figure Composition 3. Modified Stroop Test Memory: 1. Calif. Verbal Learning Test – immediate and delayed Exec Function: 1. Digits backwards 2. Short CANTAB Spatial Working Memory 3. Stroop Part III	No midlife physical activity was reported by 68.8%, ≤5hours physical activity by 26.5%, and >5 hours physical activity by 4.5%. Both physical activity groups had significantly faster speed of processing, better memory, and executive function, after controlling for demographic and cardiovascular factors. The ≤5 hours of physical activity group was significantly less likely to have dementia in later life, compared with no midlife physical activity. The effect of physical activity was restricted to non-carriers of the APOE ε4 allele.
(Dik, Deeg, Visser & Jonker, 2003)	n=1241. Mean age =74.9. Men = 49%	Longitudinal cohort study. Subjects enrolled 1992-1993.	Retrospective questioning re participation in sport or recreation that induced sweating when they were 15-25 years old = categorised into four groups by no. of hours per week of strenuous exercise.	MMSE – to determine eligibility for study (no dementia). Alphabet Coding Task -15	There was a positive association between regular physical activity early in life and level of information processing speed in older men but not in women. There was no association between current physical activity or other lifestyle factors and cognitive function.

Reference	Sample	Design	Measurement of physical activity/fitness	Cognitive function tests and screening tools	Major findings
(Erickson et al., 2010)	n= 299; US men and women. Aged ≥65 years. Mean age = 78 at this study	Longitudinal cohort study. Baseline = 1989-90, follow-up at 8 then 13 years	At baseline by Minnesota Leisure-Time Activities Questionnaire – however only the total number of blocks walked over one week was used.	1. mMMSE 2. Digit Substitution Test 3. Low resolution MRI 2-3 yrs. after baseline (too poor for vol. assessment) 4. Nine year follow-up = voxel-based morphometry (VBM) = brain volume (gray matter, white matter and CSF)	Greater physical activity predicted greater volumes of frontal, occipital, entorhinal, and hippocampal regions 9 years later. Walking 72 blocks was necessary to increase gray matter volume. Greater gray matter volume with physical activity reduced the risk for cognitive impairment 2-fold.
(Etgen et al., 2010)	n=3903 Aged ≥55 Community dwelling men and women	Prospective longitudinal cohort study. 2001-2003 and follow-up for 2 years	Self-report of activity levels (classified as low, moderate or high activity)	1. 6CIT	Physical activity is associated with lowered incidence of cognitive impairment after 2 years in older adults
(Geda et al., 2010)	n=1324 (MCI = 198, no CI = 1126) Median age of each group = MCI = 83yrs No CI = 80yrs Community dwelling men and women.	Population case control study comparing subjects having mild cognitive impairment (MCI) with subjects having no cognitive impairment (CI).	Self-report of frequency and intensity of exercise – used questions from 1985 National Health Interview Survey and Minnesota Heart Survey. Within one year of recruitment and memory of midlife exercise.	Screening: 1. Neurological exam by Dr 2. Risk factor evaluation 3. Neurological evaluation – CDRS, Short Test of Mental Status, Wechsler Memory Scale –R, Trail Making, WAIS-R, Boston Naming Test Lead to classification of subjects into two groups MCI and No CI.	Any frequency of moderate exercise performed in midlife or late life was associated with a reduced odds of having MCI.

Reference	Sample	Design	Measurement of physical activity/fitness	Cognitive function tests and screening tools	Major findings
(Gillum & Obisesan, 2010)	n= 2431 (from original sample of n=5903) American men and women Aged ≥60 years	Longitudinal cohort study. Subjects enrolled in 1988-1994 and were followed an average of 8.5 years.	Self-reported Leisure-Time Physical Activity (LTPA) (some Qs from 1985 National Health Interview Survey) also socio-demographic data, health status, and physical and biochemical measurements	Short form Index of Cognitive Function (SICF)	Bivariate and multivariate analyses indicated a lower risk of death independent of confounders among those with frequent LTPA. Much of the effect of low cognitive function could be explained by other risk factors at ages 60 to 74 but not 75 years and older.
(Lytle et al., 2004)	n= 1146; US rural men and women. Aged ≥65 years. Mean age 76.8 (± 5.3) years.	Longitudinal cohort study Two years to follow-up	Self-report exercise habits. Subjects categorised into three groups of high(aerobic exercise of ≥ 30 minute duration ≥ 3 times a week), low (all other exercise) and no exercise	MMSE	Using MLR high exercise level at the baseline was negatively associated with, i.e., was protective against, being in the group with the greatest amount of decline two years later. When high exercise was redefined using frequency as ≥ 5 days per week, both low exercise and high exercise were negatively associated with cognitive decline.
(Middleton, Mitnitski, Fallah, Kirkland & Rockwood, 2008)	n= 5376 Canadian men and women. Aged ≥65 years. Mean age 76.1 years.	Secondary analysis of longitudinal cohort study data. Markov chain model analysis. Five year follow-up.	Self-rated health, chronic conditions, functional ability. Physical activity = 2 self-rated questions re frequency and intensity. Subjects divided into two groups 'high' and 'low or no' exercise.	MMSE	Exercise is strongly associated with improving cognition. As the majority of mortality benefit of exercise is at the highest level of cognition, and declines as cognition declines, the net effect of exercise should be to improve cognition at the population level, even with more people living longer.

Reference	Sample	Design	Measurement of physical activity/fitness	Cognitive function tests and screening tools	Major findings
(Sturman et al., 2005)	n=4055 Aged≥65 years Community dwelling men and women	Prospective longitudinal cohort study. Subjects enrolled 1993-1996 – followed up for an average of 6.4 years	Self-report using the US Health Interview Survey = number of hours of physical activity per week	1. East Boston Test of Immediate 2. Memory East Boston Test of Recall 3. MMSE 4. Symbol Digit Modalities Test	Models adjusted for normal age changes, age, sex, race and education = each additional hour of physical activity is associated with a slower rate of cognitive decline. If adjust further for participation in cognitive activities, depression, vascular disease cognitive score at baseline – no relationship between physical activity and rate of cognitive decline.
(Verghese et al., 2006)	N=488 Aged≥75 years Community dwelling men and women	Longitudinal cohort study. Followed up for 21 years (median = 5.6yrs)	Scale constructed by researchers based on frequency of participation in 10 specified activities (problematic)	Development of amnesic MCI (aMCI) or dementia (assessed by medics)	An increase on the Cognitive but not Physical Activities Scale was associated with lower risk of aMCI.

Reference	Sample	Design	Measurement of physical activity/fitness	Cognitive function tests and screening tools	Major findings
(Weuve et al., 2004)	Nurses' Health Study. n= 18766 US women aged 70 to 81 years.	Longitudinal survey – predictor study	<p>Women were asked to estimate the average amount of time per week during the past year spent on the following activities: running; jogging; walking or hiking outdoors; racquet sports; lap swimming; bicycling; aerobic dance or use of exercise machines; other vigorous activities; and low-intensity exercise. Participants also indicated their usual outdoor walking pace: easy, normal, brisk, or very brisk, and the number of flights of stairs climbed daily. Each activity was assigned a metabolic equivalent value (MET).</p> <p>Validation studies among women in the Nurses' Health Study II (a similar cohort of nurses), participants' responses, 1 year apart, to these questions on activity were reasonably correlated ($r = 0.59$).</p>	Validated telephone assessments of cognition administered twice approximately 2 years apart (1995-2001 and 1997-2003), including tests of general cognition, verbal memory, category fluency, and attention.	<p>Higher levels of activity were associated with better cognitive performance.</p> <p>On a global score combining results of all 6 tests, women in the second through fifth quintiles of energy expenditure scored an average of 0.06, 0.06, 0.09, and 0.10 standard units higher than women in the lowest quintile (p for trend $<.001$). Compared with women in the lowest physical activity quintile, there was a 20% lower risk of cognitive impairment for women in the highest quintile of activity.</p>

Reference	Sample	Design	Measurement of physical activity/fitness	Cognitive function tests and screening tools	Major findings
(Yaffe et al., 2001)	n= 5,925 mainly white community dwelling women, aged ≥65	Prospective longitudinal survey	Number of city blocks walked each day and number of flights of stairs climbed each day. Plus modified Paffenberger scale – interview re – frequency and duration of participation in 33 activities in a week for the past year. Activities classified as low, medium and high and converted to kCal expended.	Completed at baseline and 6 and 8 years later. mMMSE Cognitive decline is a decline of three or more point on the 26 point scale.	Women with higher levels of baseline physical activity were less likely to develop cognitive decline. This association was not explained by differences in baseline function or health status. This finding supports the hypothesis that physical activity prevents cognitive decline in older community-dwelling women.
(Yaffe et al., 2009)	n= 2,509 community dwelling men and women, aged 70-79 at enrolment	Prospective longitudinal study over 8 years.	Engagement in moderate to vigorous exercise and activity (e.g., aerobics, weight training or brisk walking) at least once a week.	mMMSE	Variables significantly associated with being a maintainer vs. a minor decliner (in mMMSE score) were age, white race, high school education level or greater, ninth grade literacy level or greater, weekly moderate/vigorous exercise and not smoking.

With the exception of the study by Sturman et al. (2005), all longitudinal studies report positive associations between physical activity and some aspect of cognitive function. Chang et al., (2010), for example, found that midlife physical activity was related to better cognitive performance, and less incidence of dementia among individuals tracked across a 26 year period. Angevaren et al., (2010) found that whereas changes in time spent being physically active were not associated with cognitive function, increased intensity of weekly activities was associated with some improvement in the domain of better processing speed. More physical activity has also been correlated with greater volumes of gray matter (Erickson et al., 2010); in turn, greater gray matter volume was associated with a two-fold reduced risk of cognitive impairment. Barnes et al., (2003) examined the preservation of cognitive function across a six-year period in relation to baseline measures of cardiorespiratory fitness (VO_{2peak}); they found a modest positive relationship with global cognitive function and attention/executive function, after adjustment for covariates. Counterpoised with the quality afforded to this study by the implementation of 'best practice' measurement of fitness (VO_{2peak}) as an objective marker of physical activity, is the weakness constituted by the absence of cognitive testing, other than the modified MMSE (as an index of global functioning), at baseline. In what was, in many ways, one of the better designed studies, the testing of the specific domains of cognition at follow-up only, is unfortunate. Consequently, the possibility that some of the association at follow-up was a function of a conjoined pathological process between poorer fitness and poorer cognitive ability at baseline; cannot be excluded.

Other concomitant findings, in the literature include a positive association between: physical activity and a lowered incidence of cognitive impairment after two years (Etgen et al., 2010) and after eight years (Yaffe et al., 2001); for low or high physical activity levels (Lytle et al., 2004); with higher levels of physical activity being more likely to result in cognitive enhancement (Middleton et al., 2008; Weuve et al., 2004). In contrast, Sturman et al., (2005) followed up a sample of 4,055 men and women (aged ≥ 65 years) using an approach that adjusted for normal age changes, age, sex, race, education, depression, participation in cognitive activities and vascular disease (but not IQ or socio-economic status). Unlike the majority of other longitudinal studies, this research (Sturman et al., 2005) employed a random effects model fully adjusted for the contribution of possible confounding variables. Interestingly, these researchers found no relationship between physical activity and the rate of cognitive decline.

Consonant with the cross sectional literature, data in longitudinal examinations of physical activity in relation to ageing, has typically been collected either by asking simple, non-validated questions designed by the investigators or by using validated questionnaires (sometimes in conjunction with additional questions designed by the investigators). A third method employs validated questionnaires that have been modified for a particular population or circumstance. At the less probing end of the data collection spectrum, participants have been asked one or two general questions conducted in the context of a telephone (e.g., Weuve et al., 2004) or face-to-face interview or by completing a written survey. In a study by Etgen et al. (2010), for example, general practitioners (n=65) asked participants (n=3903) how many days per week they performed strenuous activities. Responses were then classified as no activity, moderate activity (< 3 x per week) or high activity (≥ 3 x per week). This type of approach is potentially fraught with recall and response bias and relies on assumed consistency of interpretation, between respondents, between raters and between respondents and their respective rater (Prince et al., 2008).

Similarly, Chang et al., (2010) based the measurement of physical activity on two questions asked at 'midlife' (mean age of 51 years) but not repeated at follow-up (26 years later). Those assenting to the question of whether they had 'regularly participated in sports or exercised at any time during their adult life' were then asked to calculate the numbers of hours of exercise they had participated in each week. In essence, participants were being asked to estimate their recollection of physical activity, at an ill-defined time, which was not delineated by criteria that might engender confidence in the assumption of response consistency. In addition, there is no way of ascertaining whether a particular 'snapshot' of physical activity levels derived from designated timeframes such as 'anytime during adulthood' reliably capture the absolute parameters of physical activity had been undertaken or whether the index of measurement is representative of a true average over time. An additional aspect of ambiguity is the fact that in several studies, the timeframe represented is either unclear or unreported (e.g., Lytle et al., 2004; Middleton et al., 2008). Despite these flaws there is a tendency in the literature to infer causality and/or to assert the validity of findings without due regard to methodological limitations.

These methods of assessment feature prominently in earlier research because have the advantages of low cost, practicality and minimal demands on the time and resources of respondents. In conjunction with large samples, the 'simple question' method has been instrumental in the accumulation of valuable heuristic information that has ultimately formed

the platform for more robust interventional endeavours. Nevertheless, subjective measurement techniques are fundamentally characterised by an inherent potential for bias. This limitation compromises the strength of any associations or inferences that may emerge from longitudinal data, thereby weakening the predictive value that might otherwise have been gained from large sample sizes.

2.4.3 Summary of observational studies addressing physical activity and cognition

Taken together, there is no doubt that the observational literature consistently suggests that physical activity and exercise participation are associated with better cognitive functioning. With few exceptions, a procession of investigations report that compared with inactivity, physical activity in generally healthy older people, is associated with better neurocognitive functions and better preservation of neurocognitive function. A paradox exists, despite the swathe of literature. The validity of the observational research remains questionable and will continue to be so for as long as doubt is cast by the prevalence and corollaries, of unadjusted covariance and subjective, heterogeneous instrumentation, non-equivalence of data, reporting bias and the absence of a theoretical framework to inform choices about what aspects of cognitive function might be connected to successful ageing. Observational research appears to have reached the limits of its methodological capacity to elucidate the relationship between exercise and cognitive function, while ever it continues to be conducted within the inherent limits of subjective measurement. However, the faithful adoption of standardised, valid and reliable study designs, coupled with the objectivity and precision of more recent technological advances in measurement, provide the very real prospect of future studies confirming or challenging the associations suggested by these observational studies.

2.5 Appraisal of intervention studies related to exercise and cognition

The influence of physical activity on the ageing brain has also been investigated more formally using experimental and quasi-experimental designs where structured exercise is administered as the independent variable. This section presents a review of extant interventional studies related to the influence of exercise on cognition in later life.

Acute exercise as a brief individual bout has, to a lesser extent, been employed to evaluate the short-term after-effects of exercise on the brain function of older adults. However, the more usual paradigm has been based on chronic exercise delivered as regular occasions of supervised, prescribed exercise, for a designated period of time (e.g., 30 mins, 3 times each

week, for a period of six months). The significant advantage of experimental over observational approaches is the potential capacity to describe outcomes attributable to deliberately manipulated treatments, to elucidate causal relationships. Nevertheless, this body of evidence has also generated mixed results and continues to be hampered by the fact that understandings of the mechanisms that may underpin altered neurocognitive functioning as a function of physical activity and exercise, remain in their infancy.

2.5.1 Systematic reviews of the effects of exercise on cognition

RCTs investigating the effects of chronic cardiorespiratory exercise interventions on the neurocognitive performance of non-cognitively impaired older people have been comprehensively appraised by a Cochrane review (Angevaren et al., 2008) and subsequent systematic reviews (e.g., Smith et al., 2010; Snowden et al., 2011; van Uffelen et al., 2008) (see Table 2.3) . Since these evaluations there have been a small number of additional RCTs pertinent to the current review (Klusmann et al., 2010; Masley, Roetzheim & Gualtieri, 2009; Muscari et al., 2010; Taylor-Piliae et al., 2010; Williamson et al., 2009) (see section 2.5.3 and Table 2.4 below).

As can be seen in Table 2.3, Angevaren et al. (2008), conducted an exhaustive examination of peer-reviewed experimental literature and based their statistical analysis on 11 studies of adults aged 55 years and over (average study duration of 14 weeks). These interventions were deemed to possess the design properties and methodological quality necessary to establish efficacy in the case of induced treatment effects. A total of 33 neurocognitive tests were employed within the included RCTs; those considered to approximately measure the same construct, were categorised accordingly, into 11 domain classifications (cognitive speed, verbal and visual memory function (immediate), working memory, memory function (delayed), executive function, perception, cognitive inhibition, visual and auditory attention and motor function) as derived from the work of Lezak and colleagues (Lezak, Howieson & Loring, 2004).

In Angevaren et al.'s (2008) review, eight of the 11 studies found that cardiorespiratory (aerobic) interventions resulted in increased cardiorespiratory fitness (increased VO_{2max} by approximately 14%); and improvement in at least one subcategory of cognitive function. Significant positive effects of aerobic exercise compared with 'any other intervention' were identified in relation to cognitive speed (speed at which information is processed) and visual

Table 2.3: Comparison of systematic reviews of effects of exercise interventions on cognitive functions

Studies	Angevaren et al. (2008)	Smith et al. (2010)	Snowden et al. (2011)	van Uffelen et al. (2008)
Type of review	Systematic review with meta-analysis	Systematic review with meta-analysis	Systematic review with narrative analysis	Systematic review with meta-analysis
Focus of systematic review	To assess the effectiveness of physical activity, aimed at improving cardiorespiratory fitness, on cognitive function in older people without known cognitive impairment	To assess the effects of aerobic exercise training, in adults, on neurocognitive performance	To assess the effect of physical activity and exercise intervention trials on cognition in older adults	To assess the effect of physical exercise on cognition in older adults with and without cognitive decline
Inclusion criteria				
Study designs	Published RCTs	Randomized treatment allocation	Randomised trial, quasi-experiment, or single-group intervention	Published RCTs
Sample minimum age	Older than 55 years of age	18 years of age	Aged 50 and older	Aged 55 and older
Sample health	Healthy and age related illnesses and specific disorders (e.g., COPD and heart failure). Depression CVA excluded.	No cognitive impairment and MCI but dementia excluded.	Community dwelling older adults with or without dementia.	Cognitively healthy older adults or adults with cognitive decline or dementia but no mental disorders other than dementia, such as depression.
Interventions	Aerobic physical activity programmes, aimed at improving cardiorespiratory fitness (VO _{2max})	Incorporated aerobic exercise components - duration of treatment 1 month; supervised exercise training.	Defined exercise intervention – cardiorespiratory, strength or multicomponent.	Physical exercise program

Studies	Angevaren et al. (2008)	Smith et al. (2010)	Snowden et al. (2011)	van Uffelen et al. (2008)
Comparisons	Any other intervention or no intervention	Non-aerobic exercise control group	Unclear	Aerobic v no exercise; Strength v no exercise; combination of aerobic and strength v no exercise; aerobic v strength. Without cognitive decline or with cognitive impairment.
Numbers of studies	11	29	30	23 (15 = cognitively healthy; 8= cognitive decline)
Quality assessment	Criteria list for quality assessment of nonpharmaceutical trials (CLEAR NPT) process. Two reviewers assessed sampling method, randomisation, measurement, intervention and reporting of biases and limitations. Inter-rater reliability was assessed (Cohen's kappa). Discordance was resolved by discussion and arbitration with a third reviewer.	Two raters: assessed: Duration of treatment, intensity of exercise, modality of exercise, blinding of assessment personnel to treatment status during assessments, intention-to-treat (ITT) analyses, and time of follow-up assessment. Interrater reliability was assessed (Cohen's kappa).	The expert panel (n = 8) used "Community Guide" procedures. Quality indicators = sampling, inclusion and exclusion criteria, data analysis, interpretation of results, and level of description of the study population and the intervention. Ratings identified good, fair, or limited quality.	Verhagen process. Two reviewers assessed randomisation, sampling method, measurement, intervention and reporting of biases and limitations.

Studies	Angevaren et al. (2008)	Smith et al. (2010)	Snowden et al. (2011)	van Uffelen et al. (2008)
Results	In the majority of domains exercise yielded no significant cognitive effects. Where significant effects occurred the largest were found on motor function and auditory attention (effect sizes of 1.17 and 0.50 respectively). Moderate effects were observed for cognitive speed (effect size 0.26) and visual attention (effect size 0.26).	Individuals randomly assigned to receive aerobic exercise training demonstrated small improvements in attention and processing speed (effect size 0.158), executive function (effect size 0.123), and memory (effect size 0.128).	Of the 30 studies reviewed, some had positive outcomes for certain exercise types and cognitive domains, but many found no significant benefits.	In cognitively healthy subjects, significant beneficial intervention effects were observed in 5/15 studies on information processing, executive function, or memory. In subjects with cognitive decline, 5/8 studies observed beneficial effects on general cognition, executive functions, and memory.
Conclusions	The data are insufficient to show that the improvements in cognitive function which can be attributed to physical exercise are due to improvements in cardiovascular fitness.	Aerobic exercise training is associated with modest improvements in attention and processing speed, executive function, and memory, although the effects of exercise on working memory are less consistent. Rigorous RCTs are needed with larger samples, appropriate controls, and longer follow-up periods.	There is insufficient evidence that physical activity or exercise improved cognition in older adults. Future research should report exercise adherence, use longer study durations, and determine the clinical relevance of measures used.	The majority of the studies did not find any effect. The small number of included studies; lack of high-quality studies; and the large variability in study populations, exercise protocols, and outcome measures complicate interpretation of the results. More high-quality trials are needed.

attention (effect sizes of 0.24 and 0.26, respectively). However, the other nine of the 11 cognitive subcategories returned no significant effects. When compared with the 'non-intervention groups', aerobic exercise demonstrated a significant effect in relation to motor function and auditory attention (effect sizes of 1.17, 0.52).

Again, the majority of comparisons (nine of the 11 subsets of cognition), manifested no significant statistical relationship with aerobic exercise interventions. Angevaren et al., (2008) concluded that there was insufficient data to substantiate the view that cardiovascular fitness mediates the improvements in cognition accredited to exercise interventions. The Cochrane review, in all probability, represents the most stringent, rigorous and objective evaluation of the interventional literature and was last assessed as being current in April of 2008. Since then, a systematic review by van Uffelen (2008), a meta-analytic review by Smith et al., (2010) and a systematic review by narrative analysis (Snowden et al., 2011) have each evaluated subsequent RCTs and reprised some of the studies evaluated by the Cochrane review. While Angevaren et al. (2008) explicitly examined only RCTs involving older people without known cognitive impairment; these three expositions also included the literature pertaining to older subjects with cognitive impairment (Smith et al., 2010), dementia (Snowden et al., 2011) and cognitive decline and dementia (van Uffelen et al., 2008) (see Table 2.3).

Smith et al., (2010) found some improvement in the domains of attention and processing speed (effect size 0.16), executive function (effect size 0.12), and memory (effect size 0.13), but not working memory. Effect sizes for attention and processing speed showed greater improvement when aerobic training was delivered in conjunction with strength training; as distinct from aerobic treatments alone. This conclusion was derived from the application of a moderator analysis which also indicated that working memory benefits from a combination exercise modality approach. Van Uffelen et al. (2008) identified 23 RCTs that included 15 studies conducted among 'cognitively healthy subjects'. Using a quality assessment procedure based on the Delphi criteria list (Verhagen, de Vet, de Bie & et al., 1998), each of the studies was rated from zero to nine. High quality was defined as a score of five or more. One of the 15 studies, where aerobic treatments were applied to ostensibly non-cognitively impaired populations, was rated as 'high quality' (Oken et al., 2006); however, no significant effects were found. Of the three pertinent studies returning a significant result, two reported better memory performance (Hassmén & Koivula, 1997; Williams & Lord, 1997); and one found improvements in information processing (organisation and auditory processing) as indexed by the Ross Information Processing Assessment (Moul, Goldman & Warren, 1995). However,

these studies were rated as two and three out of nine, respectively. Furthermore, since only one of the relevant 15 studies screened subjects for global cognitive function (Okumiya et al., 1996), it is unclear whether comparisons are based on equivalent sample populations with reference to cognitive status; the van Uffelen (2008) review simply made the assumption of non-impairment where screening was not undertaken.

As well as the themes of small, negligible or absent effect sizes manifested by the RCTs included in these systematic reviews, there is also significant inconsistency in the conduct and conclusions of the systematic reviews. The reviews vary in their findings according to the inclusion criteria and classifications used for study selection, study quality assessment and the classification of neurocognitive outcomes. For example, Smith et al., (2010) attempted to gauge study quality by statistically testing whether treatment effects varied according to the presence or absence of blinding assessment or the use of intention-to-treat analysis. They concluded that neurocognitive effects did not differ on the basis of the use or omission of these procedures. In contrast, van Uffelen et al., (2008) downgraded the quality of studies where these two variables were absent. An additional and noteworthy theme of variability in the reviews (with the exception of Angevaren et al., 2008) is the differential manner in which cognitive status is considered. The concepts of normative ARCD, MCI and dementia remain controversial with considerable debate in the literature in terms of diagnostic criteria and cut-off points for pathological versus non-pathological conditions (Petersen et al., 2009). This ambiguity is likewise reflected in the inconsistency manifested in the present literature.

2.5.2 Randomised controlled trials of the effect of exercise on cognition

The literature search conducted as a part of this study also found four relevant RCTs not evaluated by the aforementioned systematic reviews. These studies were RCTs by Klusmann et al. (2010), Masley et al. (2009), Muscari et al. (2010) and Williamson et al. (2009). Most of these RCTs focussed on healthy adults, including both genders, but the Klusmann et al. (2010) study only included women. The general age range was over 65 years, with one study including participants in the 18 to 70 years age bracket (Masley et al., 2009). There were a variety of interventions and comparison interventions used in the studies and all, except Williamson, et al., (2009), included a no exercise training control group. Most studies used a battery of different cognitive function tests. However, the Muscari et al. (2010) study used only the MMSE at baseline and follow-up (see Table 2.4).

Table 2.4: Experimental and quasi-experimental studies of an exercise interventions

Reference	Design	Intervention	Sample	Data collection and analysis	Main results
Coubard 2011	Non randomised trial	Three groups – approx. 6 months of <ul style="list-style-type: none"> falls prevention, contemporary dance Tai Chi Chuan 	N=110 – mainly women aged 65-83 16 = Contemp Dance 64 = Falls prevention classes 24 = Tai Chi Chuan Groups matched for past physical activity.	<ul style="list-style-type: none"> Attentional control <ol style="list-style-type: none"> setting attention, - Arithmetic Word Problems suppressing attention, - Stroop test switching attention - Rule Shift Cards Sorting Test 	No differences between groups: CD v falls or CD v TCC – except for rule shift test between CD and Fall
Forte et al. 2013	Quasi-experiment – time series. (T1) = baseline, (T2) = following a 4-week control period and (T3) = post-intervention	Twice weekly for 3 months in either: (1) multicomponent training, - neuromuscular coordination (balance, agility, and exec control); or (2) progressive resistance training for strength conditioning.	N = 42 healthy community dwelling adults aged 65 to 75 years	<ol style="list-style-type: none"> Executive function: inhibition = random number generation. Trailmaking Test (TMT) (B-A = ΔTMT) VO2 max Knee extension and flexion torques Max walking speed – talk and box carrying 	Indices of inhibition and measures of functional mobility improved after the intervention, independent of training type. Mediation analysis suggested that different mechanisms underlie the effects of multicomponent and progressive resistance training. Multicomponent training seemed to directly affect inhibitory capacity, resistance training seemed to affect it indirectly through gains in muscular strength.

Reference	Design	Intervention	Sample	Data collection and analysis	Main results
Klusman et al. (2010)	RCT of a cognitive and a physical standardized 6-month activity intervention (3 × 1.5 hrs/wk) Measurements at baseline and 6 months.	Three groups: 1) a computer course (n = 92) 2) an exercise course (n = 91) 3) a control group (n = 76)	n= 259 healthy women 70–93 years of whom 230 completed the 6-month assessment	Baseline and post-intervention assessments of MMSE, sub-maximal cycle ergometer test, selected anthropometric measurements and bloods. Primary outcomes: Episodic memory = verbal fluency; working memory = Rivermead Behavioural Memory Test (RBMT) and the Free and Cued Selective Reminding Test (FCSRT); executive attention = Trail Making Tests (TMT B/A), and the Stroop Test. Secondary outcomes: 6MWT	Both the exercise and control groups had improved story recall compared to control. Also both exercise and computer groups maintained performance in delayed word recall and working memory while the control group declined.
(Lui-Ambrose et al., 2010)	Single-blinded randomized trial	Three groups: 1. x1 per week resistance training (n=54) 2. x2 per week resistance training(n=52) 3. X 2 per week balance and tone classes (n=49).	n=155 community-dwelling women aged 65 to 75 years	Primary outcome = Stroop test (executive cognitive test of selective attention and conflict resolution) Secondary outcomes = Executive cognitive functions - set shifting (TMT A&B) and working memory - verbal digit span forward and	Both resistance training groups significantly improved their performance on the Stroop test compared with those in the balance and tone group ($P=0.03$). Task performance improved by 12.6% and 10.9% in the once-weekly and twice-weekly resistance training groups, respectively; it deteriorated by 0.5% in the balance and tone group.

Reference	Design	Intervention	Sample	Data collection and analysis	Main results
				backward tests. Gait speed, muscular function, and whole-brain volume were also secondary outcome measures.	Enhanced selective attention and conflict resolution was significantly associated with increased gait speed. Both resistance training groups demonstrated reductions in whole-brain volume compared with the balance and tone group at the end of the study (p=0.03).
(Masley et al., 2009)	Two stages to the study: 1) Stratified RCT (pilot study) 2) Non-randomised comparative group study = pilot + extra people recruited to the intervention arm	10 week exercise program led by American College of Sports Medicine (ACSM) certified instructors (assessment and once a week 1 hr session) Treadmill at 70-85% of VO_{2max} x 5-6 days per week for 30-45 minutes. (Additional intervention for pilot study period was dietary changes as well - \uparrow fibre + \downarrow fat + \downarrow stress). Control group did usual exercise = some did as much as the intervention group	Men and women aged 18-70. Study 1: N=56 – randomly assigned to x2 groups (n= 28) – (i) exercise program and (ii) usual exercise Follow-up – intervention group = 27/28; control group = 20/28. Study 2: Added 44 people to the intervention arm – classified all the data into high medium and low exercisers and re-analysed the data.	Baseline assessment of demographics, BMI and VO_{2max} and 10 week VO_{2max} . Outcome measures: Baseline and 10 week assessment of CNS Vital Signs battery – includes memory and executive function tests – self-admin in 30 minutes. Within group change = paired samples t-tests. Between group change in outcomes = independent t-test + ANOVA (when divided into three groups). MANCOVA – repeated measures.	No between group differences for RCT groups. After recruiting additional people to the intervention and dividing all subjects into three groups and controlling for age, gender and education – small effect for cognitive flexibility alone.

Reference	Design	Intervention	Sample	Data collection and analysis	Main results
(Muscari et al., 2010)	RCT of endurance exercise training (EET) on the cognitive status of healthy, community-dwelling older adults.	Two groups: 1) supervised EET in a community gym, 3 hours a week (n=60) 2) control – (n=60) lifestyle education, including individualized self-administered programs to increase physical activity	120 healthy subjects aged 65–74 years, both Genders. 120 consecutively identified healthy adults who were part of an epidemiological study	Baseline and post-intervention assessments of MMSE, sub-maximal cycle ergometer test, selected anthropometric measurements and blood drawing for laboratory determinations.	MMSE in the control group decreased more than that of the intervention group. The odds ratio for the treated older adults to have a stable cognitive status after 1 year, as compared to the control group, was 2.74 (95% CI 1.16/6.48) after adjustment for age, gender, educational level and several other possible confounders.
(Taylor-Piliae et al., 2010)	Two phases to a randomized trial. Phase 1 = First six months. Adoption phase – compared three groups (including control) Phase 2 = Second six months – no control group	Three groups: 1) Tai Chi (TC, n = 37) 2) Western exercise (WE, n = 39) 3) Attention-control group (C, n = 56) TC and WE involved combined class and home-based protocols	132 healthy adults age 69 ± 5.8 years.	Physical functioning included balance, strength, flexibility, and cardiorespiratory endurance. Cognitive functioning included semantic fluency and digit-span tests. Data were analysed using intention-to-treat analysis.	At 6 months WE had greater improvements in upper body flexibility than TC and control. TC had greater improvements in balance and a cognitive-function than WE and control. The differential cognitive-function improvements observed in TC were maintained through 12 months.

Reference	Design	Intervention	Sample	Data collection and analysis	Main results
(Williamson et al., 2009)	A pilot RCT of the relative impact of physical activity on 1-year changes in cognitive outcomes	Two groups: 1) moderate-intensity Physical Activity 2) health education.	n=102 sedentary men and women aged 70-89 years.	Digit Symbol Substitution Test (DSST), Rey Auditory Verbal Learning Test (RAVLT), modified Stroop test, and MMSE at baseline and 1 year	Group differences were not significant but improvements in cognitive scores were associated with improvements in physical function. The DSST significantly correlated with change in the Short Physical Performance Battery score, in chair stand score, in balance score, and in 400-m gait speed. Change recall on the RAVLT and in the Stroop test was also positively correlated with changes in chair stand and balance, respectively.

These RCTs represent a shift from the traditional emphasis on testing single-modality cardiovascular interventions, to a combined exercise approach that integrates a broad array of the components of exercise training. In addition, and beyond the focus of this exposition, some studies have compared non-exercise based predictor variables (e.g., computer classes) with combination exercise, based on the assumption that both approaches are cognitively stimulating or engaging and therefore potentially capable of evoking cognitive gains. Klusmann et al., (2010) compared a complex physical treatment (combined exercise including aerobic, resistance, flexibility, balance and coordination training) with a complex mental treatment (computer classes); Williamson et al., (2009) conducted a pilot study looking at the effect of a combined physical activity intervention, compared to a health education intervention on cognitive performance; and Taylor-Piliae et al., (2010) tried to establish whether Tai Chi could evince cognitive benefits in healthy older adults compared with the effects of a combined exercise format (incorporating endurance, resistance and flexibility training).

In the Klusmann et al. (2010) study both the exercise intervention and computer classes resulted in similar improvements in immediate and delayed story recall (26% and 40% respectively for exercise; and approximately 30 and 35% for computer classes). There were no other statistically significant improvements in relation to the nine other tests included in the neurocognitive assessment battery. However, performance in delayed word recall and working memory was maintained across the six months of the study for both treatment groups, whereas the control group experienced a decline. The Williamson et al. (2009) study was designed as a pilot study and was not powered “to detect meaningful differences between groups for the cognition measures” (p. 690). Post hoc correlational analysis of the data indicated a small association between improvements in physical function and improvements in cognitive test scores. In another study Tai Chi was associated with better performance (compared with the combination exercise and control groups) on the backwards digit span test as an index of cognitive function (attention, concentration and mental tracking) (Taylor-Piliae et al., 2010). Aside from the two significant findings by Klusmann et al. (2010) these studies demonstrate either relatively small or no cognitive effects; they were therefore unable to show clear and robust treatment effects. However, they do represent some evidence for the likely contribution of other modalities of exercise or activity to the maintenance or promotion of cognitive function.

Of the RCTs that focussed on endurance training Muscari et al. (2010) showed maintenance of cognitive status (as measured by the MMSE) over a 12-month period (compared with a decline

in the control group). These results were interpreted as evidence for the capacity of aerobic exercise to slow age-related decline in cognitive functioning. Interestingly, this study was unable to show that changes in fitness were associated with changes in cognitive function. Masley et al., (2009) conducted a two stage study that included a stratified RCT (pilot study), followed by a non-randomised comparative group study (pilot with extra people recruited to the intervention arm). Both studies had an exercise intervention group and a usual exercise control group. No between group differences were found in the RCT. An association between exercise and cognitive function, in the comparative study, was limited to a small effect for cognitive flexibility only.

The results of these more recent RCTs imply concordance with the results of the previously conducted systematic reviews of RCTs. These RCTs demonstrate a continuation of the methodological limitations of past efforts. What is different is that these studies mark a transition towards the exploration of modalities beyond aerobic exercise. To this end, these studies represent some promise in seeking to elucidate what is likely to be the multifaceted nature of the contributions that exercise can make to cognitive performance (Kraft, 2012). Most of all these studies further reinforce the need to operationalise recommendations for improvement in study design, as outlined above and strongly proposed by Angevaren et al. (2008).

2.5.3 Non-RCT experimental studies of the effects of exercise on cognition

Forte et al., (2013) conducted a randomised trial, stratified for age and gender (no control group), to examine the effects of 12 weeks of either multicomponent exercise training (n=22) or resistance training (n=20), on measures of executive function and physical mobility (see Table 2.4). The sample consisted of forty-two healthy community dwelling adults aged between 65 and 75 years. The multicomponent exercise intervention (coordination, balance, agility, strength, flexibility and relaxation) was imbedded with additional task elements in the form of cognitive, locomotive and dynamic balance challenges. The authors did not report between group differences, but rather, changes in outcome measures between T1 (baseline), T2 (4 week non-intervention control period commencing from T1, where participants act as their own controls) and T3 (after the 12 week intervention interval). Significantly, the statistical analysis was based on data collapsed across the two groups (n=42); presumably because a between-group analysis did not yield significant results. An explanation of this is that participants showed functional improvements between T1 and T2 (i.e. in a period of no intervention). In addition the Trail Making Test improved between T1 and T2 only. This study is

significant because it is one of the first instances of experimental research entailing both a multi-modal exercise format and the motor component of exercise training, in conjunction with elements of cognitive load. However, the absence of an independent control group was unfortunate, inherently diluting the power of the study to detect treatment effects.

Another quasi-experiment examined contemporary dance as compared to Tai Chi and a falls prevention program (Coubard, Duretz, Lefebvre, Lapalus & Ferrufino, 2011). Contemporary dance improved switching (Rule Shift Cards Test) compared to falls prevention training ($p=0.042$); but not compared to Tai Chi. There were no other significant results in relation to cognitive flexibility (Arithmetic Word Problems) or inhibition (Stroop test).

2.5.4 Summary of evidence from intervention studies

Taken together, there are several key points of concordance between the recommendations and findings of the experimental research. All temper their findings by emphasising the need for more high quality research. There is a general entreaty for greater rigour in the form of larger samples, longer follow-up and the need for consensus regarding which neurocognitive assessment tools might be most appropriate to the measurement of neurocognition, in relation to aerobic exercise and older people. Fledgling research into combined exercise formats appears to trend towards potential treatment effects. While there is a broad view that aerobic exercise confers modest to moderate cognitive benefits in cognitively healthy older people, it is also true the majority of RCTs have not found any effect.

Chapter 3: Critical review of methodological issues in previous research

3.1 Introduction

Despite the caveats identified in the last chapter, two consistent themes in the present literature appear to compel and inspire ongoing investigation. There is certainly a strong trend in the literature suggesting that exercise beneficially effects cognition. However there is also a distinct pattern in the findings and commentary regarding the nature of research limitations and failings. It is clear that there are methodological design parameters, which are inherently insufficient to the task of determining the effect of exercise on cognition and the ageing brain. Taken together, these recurring themes represent a rich store of data with considerable heuristic latency. Knowing what approaches are unlikely to produce dividends sheds light on what elements of research design might possess the necessary properties for evidentiary advancement. This chapter provides an examination of the methodological themes derived from the present literature, that potentially inform better designed and higher quality research with the capacity to garner more valid and reliable results. Robust studies, capable of providing more definitive research findings may be promoted by: the development of theoretical frameworks to guide research design; the use of methodologies that can appropriately test cause and effect; the objective measurement of physical activity; the selection of appropriate tests of cognitive function; the inclusion of tests for possible underlying mechanisms; design strategies calibrated to manage covariance; and a directional change in the format of exercise interventions.

3.2 Utilisation of a theoretical framework

One innovation that could catalyse substantial methodological advancement, in the area of exercise and cognition in later life, is applying theory to guide decision-making in the research design process. To date, much research in this area has been discovery based and atheoretical. A theory-led approach could inform the logic of a methodical and strategic examination that could then be scientifically examined and refined. Moreover, a sound conceptual framework possesses the capacity to organise complex, multifaceted interrelationships through the systematic ordering of ideas (Bordage, 2009). For example, in the present literature, the accruing volume of current knowledge; the likelihood of a multidimensional explanation for what elicits and what mediates exercise-induced changes; and the sophistication of data emanating from technological advances, are some of the factors that increasingly necessitate

the use of a theoretical structure to organise and provide testable meaning, to an ensemble of intricate data.

A number of bodies of knowledge potentially inform theory formulation relevant to exercise and the ageing brain. These include, but are not limited to the disciplines of neuroscience, neurocognitive psychology and the physiology of ageing. The application of these discrete domains of research, in combination, could hold the key to a new frontier (Biswal et al., 2010). For example, investigations into the nature and trajectory of the ageing process have benefited from imaging and software applications; much is now known about the sequence, timing and nature of lifetime morphological and substrate changes in the brain (Bishop et al., 2010; Greenwood & Parasuraman, 2010; Ratey & Loehr, 2011). Logic would suggest that the mechanisms that underpin the brain changes (and associated cognitive processes), associated with advancing age, should correspond to the mechanisms (induced by interventions such as physical activity) that reverse or constrain such changes. In other words, these respective processes may constitute the efferent and afferent pathways of the same mechanism. The task of understanding the means by which physical activity produces cognitive effects in older adults is surely inseparable from an understanding of the ageing brain itself. Taken together, the cumulative and interrelated tenets and propositions of these parallel lines of scientific inquiry may have many benefits. This integrated approach could provide insights from different but inextricably related vantage points which could then reveal common pathways or identify bi-directional corroborative evidence. In addition, taking this approach would guide decisions about the timing of interventions (based on knowledge about the temporal sequence of normal brain deterioration) and the targeting of interventions (based on knowledge about which part of the brain and what aspects of brain function are most susceptible to ageing and are therefore most pertinent to the preservation of brain function in later life). Finally, a more comprehensive approach to the topic could provide the ingredients to develop a cogent conceptual framework, formulated on the basis of aggregated data-sets, capable of directing a comprehensive program of discovery research.

3.3 Improvements in study design

Scrutiny of the variability in the findings from experimental studies into exercise and cognitive ageing reveals a broad spectrum of additional opportunities for methodological advancement. These essentially cluster around: (i) the need for designs that test cause and effect; (ii) larger and more representative samples; (iii) longer intervention and follow-up phases to establish

the true efficacy and likely duration of effects; (iv) progress towards neurocognitive testing consistency; (v) the testing of combination exercise modalities (that may or may not include a cardiorespiratory component) to examine the possibility of differential brain (and cognitive) effects; and (vi) a directional shift placing greater emphasis on the unearthing of underlying mechanisms that mediate exercise (and physical activity) related cognitive benefits.

Much of the relevant data accumulated over the past three decades has been derived from cross-sectional, longitudinal or quasi-experimental studies. As previously outlined, although this body of knowledge has been instrumental in signposting the possible cognitive benefits of exercise, conclusions from this research are limited by an inherent inability to validly address the issue of causality. To achieve the level of rigour required to truly establish a cause and effect relationship between exercise and cognition among older adults, a future design would need to comprise sedentary adults, who underwent a chronic (as distinct from acute) exercise intervention, where participants are randomly assigned to the intervention group (Friedman, Furberg & DeMets, 1998; Shadish et al., 2002). Random assignment facilitates causal inference by equating groups, eliminating investigator bias and reducing threats to validity by distributing risks factors randomly across groups (Friedman et al., 1998). The inclusion of a randomised non-exercising control group is important as this counters the possibility of a threat to internal validity posed by a maturation effect (changes that can occur within a participant, during the time period of the study, which are unrelated to the treatment or independent variable) (Shadish et al., 2002). Accordingly, RCTs are considered by many to present the best prospect of demonstrating causality (Hulley, Cummings, Browner, Grady & Newman, 2013). A final element of precision lacking in this area of research is the detailing of the intervention exercise program. This has rarely been done and where descriptions have been provided, they have usually been expressed in general rather than specific terms. Without this information, a study cannot be faithfully replicated.

The problem with small sample sizes is the inherent potential for bias and the fact that genuine effects may not be detected (Leon, 2008). The meaning of the trend towards smaller than expected effect sizes in the present literature (e.g., Angevaren et al., 2008; Etnier et al., 2006) continues to be difficult to interpret. However, the accrual of data based on adequate samples would at least eliminate this suspect. The question is whether the recurring finding of modest statistical associations reflects the 'true' nature of the relationship between physical activity (or exercise training) and cognition in later life, or whether it represents spurious findings emanating from the imprecision of underpowered sample sizes and less than representative

samples (Leon, 2008). An explicit process of sample size estimation performed *a priori* provides the bedrock for eliminating vagaries generated by sample size insufficiency. This method of formal sample planning necessitates the availability of effect size values derived from prior studies in possession of adequate study design equivalence. In the absence of these data, pilot studies can provide values that are vital to the accurate estimation of sample size. Appended to the issue of power-related shortcomings is the tendency of previous research to 'over-fit' the relevant statistical model by including a large number of variables (predictor variables, outcome variables or both); which are then considered simultaneously (Friedman et al., 1998; Leon, 2008). As the number of factors simultaneously examined increases, so does the probability of erroneous conclusions and the incumbent risk of 'under' or 'over' reporting. Greater clarity might be gained from a smaller array of comparisons initially; the conundrum of what predictor and outcome variables to include could be addressed by a process of selection based on rationales derived from theory, in combination with cumulative evidence from prior research (Leon, 2008).

The suggestion that future experimental studies would benefit from longer intervention and follow-up periods arises out of a context in which the ideal duration remains uncharted, and where previous RCTs have averaged 14 weeks with post-intervention follow-up intervals ranging from 10 weeks to one year (Masley et al., 2009; Williamson et al., 2009). Obviously the realities of attrition and funding constraints have a significant bearing on the feasibility of implementing more protracted exercise interventions and the prospect of monitoring and measuring longer term effects. Ultimately, questions about the duration of exercise effects on the ageing brain and the optimal intervention period required to induce such effects will necessitate the resources of sufficiently funded, collaborative, multi-site initiatives. This domain of knowledge remains critical to determining and defining the long term cognitive benefits of exercise training as well as the parameters of volume, intensity and frequency ('dose') required for the attainment of enhancement effects ('response') for older people (Stiggebout, Popkema, Hopman-Rock, de Greef & van Mechelen, 2004). As well as providing important information for relevant public health and policy decisions, this particular research focus holds the key to effective exercise prescription. It could provide insight into whether the mixed nature of previous study results are, to any extent, artefacts of the exercise intervention being too brief to elicit a latent 'therapeutic threshold' capability.

3.4 Objective measurement of physical activity

A primary theme relevant to observational research in this area of study is the need for objective measurement of physical activity. The accuracy of the regular finding of an association between more physical activity and better neurocognitive performance in the ageing brain will remain uncertain while ever it is based on the recognised imprecision of subjective report measures. The objective measurement of physical activity usually entails the monitoring of physiological markers related to energy expenditure such as heart rate (HR), body oxygen consumption (direct and indirect calorimetry) or movement (motion sensors). For older populations and depending on the level of funding and the sample size, the method of choice would be likely to: incorporate precision and objectivity; be time and cost effective; enable continuous, comfortable, long term and detailed physical activity monitoring (Murphy, 2009); and remain unobtrusive (LaPorte, Montoye & Caspersen, 1985) and logistically feasibility.

An array of objective measures capable is of indexing energy expenditure and fitness. Calorimetry, although accurate, is usually laboratory based, costly, requires medical supervision in the case of older adults and sequesters the subject, inhibiting normal physical activity (Wells & Fuller, 1998). Heart rate monitors are practical, low cost and yield information about total energy expenditure as well as duration, frequency and intensity of activity. However, used alone they do not provide accurate energy expenditure estimates and are therefore usually recommended for use in combination with motion sensors (pedometers, accelerometers) (Andre et al., 2006). Motion sensors, such as pedometers (step counters), have been largely superseded by new generation accelerometers (acceleration detectors) with software linked, algorithm-derived capabilities, which convert movement into values representing a range of variables (e.g., total energy expenditure, body position, step rate, metabolic rate). Accelerometers can also provide information about the frequency, quantity, intensity and duration of physical activity in day-to-day life. This technology is rapidly advancing and depending on the particular device varies in terms of measurement properties (reliability and validity) (Andre et al., 2006).

The 'doubly labelled water' (DLW) technique is considered to be the gold standard for measuring energy expenditure under free living conditions (Valanou, Bamia & Trichopoulou, 2006). The main advantage of DLW is that it accurately measures energy expenditure (as a proxy for physical activity) in daily life over extended periods (1-3 weeks). The disadvantages

are that it can be costly and cannot discern the patterns, types or intensity of day-to-day activity; it lacks temporal resolution. Nevertheless this technique is accepted as the benchmark for establishing the validity of other techniques. To that end the recommended method for the objective assessment of physical activity is often DLW validated accelerometers (Westerterp, 2009) or a combination of instruments such as motion sensors, self-report measures (to capture contextual information) and HR monitors (Valanou et al., 2006). Future refinements of wearable accelerometers may include multi-sensor devices that detect posture and activity type and models that allow the simultaneous and accurate measurement of heart rate, enabling the indexing of physical fitness (Plasqui & Westerterp, 2005). Advances based on global positioning system (GPS) and 'Bluetooth' technology; and accelerometers integrated into mobile phones are emerging as the next progression, in the objective measurement of physical activity (Stanley & Osgood, 2011).

3.5 Selection of appropriate outcome measures

The issue surrounding the call for consensus regarding neurocognitive testing (Angevaren et al., 2008) does not merely reflect reservations about the psychometric properties (validity and reliability) of traditionally used instruments, but also about the number used and the attendant diminishment of meaningful comparisons that could have otherwise been made. In addition, the ability of the instruments to reflect 'real' experience or 'real' change may not have been established. With reference to the detection of induced cognitive enhancements in older people (without cognitive decline), there is also the issue of the applicability of most commonly used neurocognitive tools, since most have been developed to detect deficits in clinical populations. These instruments may lack sensitivity to detect subtle changes, especially when a ceiling effect implicit in the measurement of 'normal' age-indexed, cognitive function probably exists. Resolution of this complex issue would likely require the resources of a well-funded, concerted, international collaboration. In the interim, the application of theory might provide some redress. For example, the cognitive constructs targeted by neurocognitive testing could be based on logic derived from research indicating what cognitive processes are most crucial to independence and quality of life, or what processes decay earliest and in what sequence.

An even more amorphous, but equally salient issue, is related to the question of the 'everyday life' relevance of the tasks embodied in (and the outcomes derived from) traditional neurocognitive tests. Two concepts are relevant to this issue. The ecological validity of a test

refers to the extent to which test performance corresponds to performance in 'real life' (Conn et al., 2011). Here, validity pertains to the inferences derived from the test, rather than the test itself. Hence, the diagnostic validity of an instrument does not necessarily equate to ecological validity. Conversely, clinical significance is the practical 'real world' value of a treatment effect and whether it is perceived by the participant to constitute beneficial change (Conn, Valentine & Cooper, 2002). It is unclear how well performance in various neurocognitive tests (e.g., digit span) translates into the functional abilities required for competency in the instrumental activities of daily living. Measurement of the 'real life' behavioural and functional manifestations of exercise-enhanced cognitive function necessitates agreement on what behavioural and functional indices (e.g. independence and social engagement) best reflect optimal cognitive functioning in later adulthood; and a determination of what neurocognitive and functional scales might best measure these particular indicators. In the absence of standardised measures, qualitative methodologies may provide the tools to both gain insight into the experiences of participants, and also enrich the meaning derived from quantitative data. The concept of a mixed method study, where RCTs are combined with a qualitative arm, are increasingly being applied. This measure facilitates the prospect of both gathering information from participants about the acceptability of a particular intervention; and importantly, gaining insight into changes or effects perceived by the participant to be both a function of the intervention and to translate into day-to-day abilities.

3.6 The inclusion of sub-studies of underlying mechanisms

Arguably, the most crucial recalibration of research focus towards furthering knowledge in this area is the extrication of the underlying mechanisms that mediate physical activity and exercise-elicited cognitive enhancement (Biswal et al., 2010; Ratey & Loehr, 2011). Contemporary and emerging research technology, and evidence derived from animal studies, has a great prospect of discerning the nature of the cascade of genetic and neurobiochemical inter-relations that may underpin the link between physical activity, ageing and cognitive ability (Anderson et al., 2010; Bishop et al., 2010). At this stage the downstream and upstream sequence 'set in train' from stimulus (physical activity or conversely, ageing) to the cognitive change or functional end-point (e.g., better memory or conversely, cognitive decline) is not well understood; although the likely neurobiochemical and morphological componentry is progressively being identified.

Animal studies indicate that cardiovascular exercise (running) in rodents precipitates a complex interactive signalling cascade whereby growth factors (protein molecules that act as chemical messengers) (Kempermann et al., 2010) work in concert to instruct a number of downstream responses that regulate cell division and survival and promote positive neuroplasticity (Kempermann et al., 2010). Positive neuroplasticity in this context refers to the life-long neuronal capacity of the brain to preserve or optimise function, in response to environmental and experiential stimuli, including exercise training (Greenwood & Parasuraman, 2010). Synaptic proteins (Farmer et al., 2004; Vaynman & Gomez-Pinilla, 2006), glutamate receptors (Farmer et al., 2004; Vaynman et al., 2006) and growth-factors such as BDNF (Tang et al., 2008; Vaynman et al., 2006), VEGF (Fabel et al., 2003) and IGF-1 (Llorens-Martín et al., 2009) are some of the biochemical ingredients believed to promote brain changes that underpin improved neuroplasticity. At the level of functional organisation (physiology) these brain changes include: cerebral capillary proliferation (angiogenesis) particularly in the motor cortex (Swain et al., 2003); increased cell production (neurogenesis) in the hippocampus (van Praag, 2008) (specifically in the dentate gyrus); and conductivity enhancement (synaptogenesis) also in the hippocampus (Cotman, Berchtold & Christie, 2007). Although the mechanism that stimulates increased capillary density is less delineated, it is hypothesised that increasing vessel size and the attendant blood supply assists in circulating growth factors throughout the dentate gyrus (van Praag et al., 2005).

To date there have been fewer studies of neurotrophins in humans. However, studies conducted with older subjects have demonstrated changes associated with exercise in: gene expression (Cotman & Berchtold, 2002); cerebral blood volume (Pereira et al., 2007); P300 amplitude and latency (Kamijo & Takeda, 2010; Pontifex et al., 2009); BDNF (Li et al., 2009a); and brain volume (Colcombe et al., 2003; Gordon et al., 2008). BDNF may be an important target in human research. BDNF is the most abundant neurotrophin in the brain, with an important role in brain neurogenesis, synaptic plasticity, learning and memory (Knaepen et al., 2010; Ratey & Loehr, 2011). The brain has been found to be the main source of BDNF concentrations in venous blood (circulating BDNF) (Rasmussen et al., 2009). The suggestion of a potential BDNF mechanism contributing to cognitive function has been supported in a study that found reduced cerebrospinal fluid BDNF concentration was associated with ARCD (Li et al., 2009a). Further, plasma BDNF has been found to be a biomarker of cognitive function in women (Komulainen et al., 2008).

There is a lack of knowledge about the underlying factors that mediate exercise elicited cognitive enhancement. Until this deficit is addressed there will be two major difficulties: (i) it will continue to be impossible to untangle the issue of causal direction and (ii) the notion of whether exercise training and physical activity or other factors (related to such things as social participation, genetic predisposition or an overall healthy lifestyle) might protect against cognitive decline.

3.7 Controlling for extraneous variables

Another opportunity for improving the quality of evidence is the application of strategies to measure and control for extraneous variables. In the context of the present literature factors that can independently exert an effect on cognitive functioning could potentially confound the nature of statistical relationships leading to spurious results. For example, there is evidence that depression and anxiety (Bierman, Comijs, Jonker & Beekman, 2005), a number of chronic conditions including truncal obesity, diabetes mellitus and insulin resistance (Beydoun, Beydoun & Wang, 2008) and cardiovascular conditions including hyperlipidaemia, cerebrovascular accident and hypertension can adversely affect cognitive performance (Fox et al., 2011; Killgore, 2010). Intelligence quotient and education level can be related to cognitive function in older people (Leibovici, Ritchie, Ledésert & Touchon, 1996). Several studies have reported differential associations between physical activity and cognition as a function of gender and age (Hertzog, Kramer, Wilson & Lindenberger, 2008).

In particular, the undetected presence of clinical or non-clinical cognitive impairment represents a significant risk for bias in this research, as the prevalence of cognitive compromise increases significantly with age; cognitive status weighs heavily on neurocognitive testing outcomes (Lezak et al., 2004). Minimising the prospect of measurement error mandates appropriate statistical adjustment or control measures (e.g., analysis of covariance, randomisation, the inclusion of a control or comparison group and design elements for holding extraneous variables constant) and the routine screening of cognitive status. There is no doubt that the thorough mitigation of known covariates represents a relatively onerous screening and measurement process. Nevertheless, the accumulation of a 'critical mass' of equivocal findings has demonstrated that ambiguity is the wholly predictable consequence of not adjusting or controlling for covariance, including cognitive status. It would appear there are no discernible benefits or advancements to be derived from repeating study designs that do not take account of these safeguards.

3.8 Improvements in design of interventions

In relation to the exercise typologies applied in past research, interest has overwhelmingly centred on the beneficial effects of aerobic interventions on cognitive functions. Yet there is insufficient evidence that exercise induced cognitive improvements are attributable to enhanced cardiovascular fitness itself (Angevaren et al., 2008). This lack of clarity may be a function of limitations in the quality of the research. Nevertheless, the overall cognitive benefits of exercise in later life cannot be thoroughly ascertained until the full gamut of elements related to exercise training has been examined. There are suggestions that the multifaceted stimuli inherent in a combined modality approach (i.e., a combination of resistance, flexibility, balance and coordination training) may be more likely to produce a significant treatment effect (Kraft, 2012). There are also indications that motor fitness, indexed by movement speed, balance, motor coordination and flexibility may demonstrate differential training effects on cognitive performance, as compared to physical fitness (cardiovascular and muscular strength) (Voelcker-Rehage et al., 2010). This proposition is consistent with the idea that cognitive changes are to some degree related to the stimulus inputs and neurobiological processes activated by the adjunct sensorimotor or loco-motor activity that accompanies aerobic training (Kempermann et al., 2010). It is yet to be established whether multi-modal exercise has the capacity to provide cognitive dividends in later life.

3.9 Summary

There are currently unique opportunities for furthering our understanding of the relationship between ageing, cognition and the spectrum of physical activities that includes fitness training. Evidence from earlier observational studies inspired and sustained ongoing efforts that are now being exponentially augmented by a new generation of objective measurement technologies. The complexity that characterises the evidence gathered by contemporary instrumentation has created the need for mechanisms by which the volume, detail and intricacy of emerging information can be meaningfully interpreted. The aggregation of data concerning the mechanisms of both cognitive decline (normal brain ageing) and exercise induced cognitive enhancement, represents a rich repository of 'raw ingredients'. The addition of a sound theoretical framework guiding study and intervention designs, modified by knowledge acquired through previous investigative enterprises, might afford future studies the opportunity to catapult the relevant literature into new frontiers of understanding.

Chapter 4: Research Methods

4.1 Introduction

As discussed in the literature review, there is currently a need for more rigorous research to test the efficacy of exercise training, as a possible countermeasure to cognitive decline. Previous research has largely been based on observational and quasi-experimental data. Although this tradition has yielded an important platform of evidence, with considerable heuristic value, a randomised controlled trial (RCT) design was chosen for this study, to address a current theme in the literature recommending experimental studies (Angevaren et al., 2008; Smith et al., 2010; Snowden et al., 2011; van Uffelen et al., 2008). While no single study is definitive, Friedman et al. (1998, p. 7) have suggested that clinical trials... "can provide a sounder rationale for intervention than is obtainable by other methods of investigation". An overarching goal of this study was to extend previous work in a number of significant ways. These include: the application of a multi-modal exercise intervention to address the fact that previous research has primarily focussed on single or sometimes bi-modality interventions; the adoption of a theoretical and thereby more strategic approach to study and program designs to redress a traditional tendency towards atheoretical examinations; and the exploration of the underlying mechanisms that may prompt cognitive effects induced by exercise.

Recent developments suggest a multi-modal exercise intervention that includes motor as well as physical training may better elicit the actual potency of exercise to enhance cognitive performance (Forte et al., 2013; Voelcker-Rehage et al., 2010). Hence, this study employs a multi-modal intervention based on a broad definition of exercise training that includes motor, as well as physical (cardiovascular and resistance) training, to test the effects on cognitive and physical functioning, and plasma BDNF levels in older women. The intervention was designed in line with theoretical indications that changes in cognitive performance are more likely to occur as a result of interventions involving novelty, learning and complexity, necessitating sustained mental effort or cognitive load (Kempermann et al., 2000; Voelcker-Rehage et al., 2010). The biomarker BDNF as a proxy for brain-based neurogenesis is included as an outcome measure to investigate the possible link between exercise training and cognitive changes, which has been suggested by research conducted with ageing animals.

In addition, this RCT is embedded with a qualitative component. Audiotaped interviews were conducted with a sub-set of the intervention group (n=15) at the completion of the 16 week

exercise program. The results of the experimental arm of the study were triangulated with the qualitative data. The qualitative component of the study aims to obtain information from participants about the acceptability of the programme, as well as any effects perceived as attributable to participation in the intervention. A further goal is to gain greater insight into the every day relevance of any perceived changes. The quantitative data were secondarily analysed, in combination with the qualitative findings, in an effort to shed light on the clinical significance and ecological validity of the study.

This chapter will first present details of the methods of data collection and analysis employed in the RCT and then follow with the same information related to the qualitative component.

4.2 Randomised controlled trial

4.2.1 Research design

This single-blinded RCT design consisted of two parallel groups (intervention group versus control group), with a participant ratio of 1:1. Participants were randomly allocated to the intervention group or to a no formal exercise wait-list control group. Figure 4.1 below outlines the main elements of the study design and the sequence in which these elements were enacted. The subsequent sections of this part of the thesis outline the theoretical approaches to various elements in the study design and describe what was undertaken.

4.2.2 Setting

Exercise classes were conducted in a community hall on the Gold Coast which is located in South Eastern Queensland, Australia. Data collection took place either in this community hall or at Griffith University, Gold Coast Campus, Queensland, Australia.

4.2.3 Sample

The population targeted for this RCT was generally healthy, community dwelling women, aged between 65 and 75 years, currently residing on the Gold Coast. There are a number of reasons why the sample was confined to women. First, by limiting the study to one gender we sought to eliminate this variable as a potential confounding factor (Friedman et al., 1998). Second, as the life expectancy of women exceeds that of men (Australian Institute of Health and Welfare, 2008) and prevalence of cognitive decline increases with age the burden of disease for this condition is greater in women than in men (Deary, 2009). Third, mixed results from the few

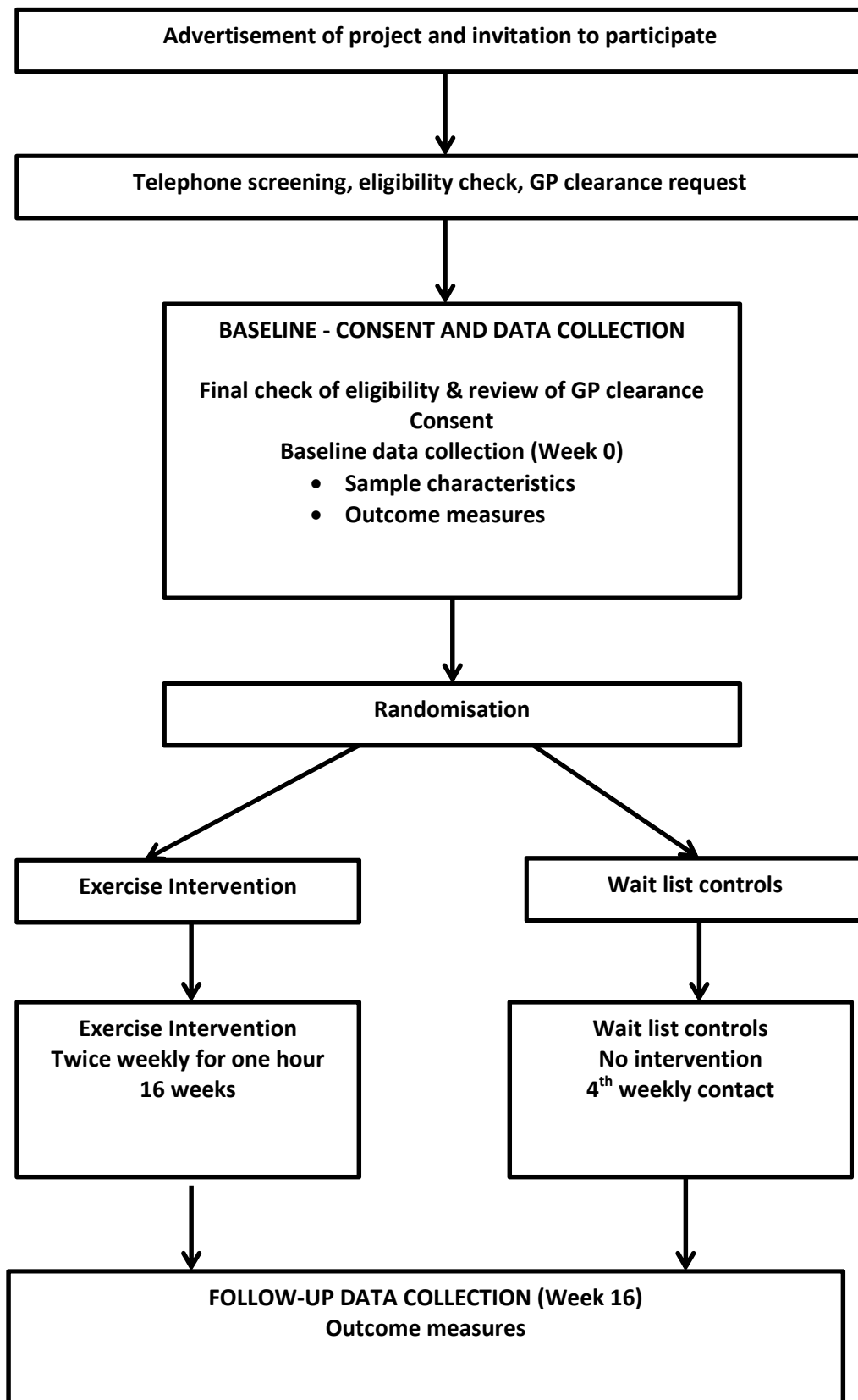


Figure 4.1: The design of the study

human studies indicate that poorly understood gender effects may obscure the interpretation of biomarkers of cognitive function such as Brain Derived Neurotrophic Factor (BDNF) (Bus et al., 2012). Finally, one study found BDNF was not associated with cognition in men but is a biomarker of general cognitive function in older women (Komulainen et al., 2008). Accordingly this study focused on older women. In addition, the age range (65-75 years) was limited to this particular bracket to enhance the homogeneity of the sample and because the literature suggests that detectable ARCD is largely manifested beyond the age of 65 years (Deary et al., 2009).

All potential participants were screened for cognitive and physical status. Given the high prevalence of chronic conditions (such as, coronary artery disease and diabetes) which could affect cognitive function in this age-group, an effective intervention must be able to produce improvement in people living independent lives in the community with these conditions. Consequently, while co-morbidities were assessed they were not included as exclusion criteria. To exclude the possibility of cognitive impairment volunteers were required to undertake the Telephone Interview for Cognitive Status (TICS) (Appendix 1). Potential participants were also assessed for their ability to walk 20 metres unaided as an index of their ability to participate in the intervention.

Eligibility criteria

The inclusion and exclusion criteria were as follows:

Inclusion criteria

Potential participants were included in the study if they were:

- Female
- Aged 65-75 years

Exclusion criteria

Potential participants were excluded from the study if they were:

- Currently engaged in supervised exercise training of more than 60 minutes per week.
- Unable to walk 20 metres independently (independent of assistance from other people)

- Unable to understand and speak English sufficiently to understand instruction
- Diagnosed with dementia, cerebrovascular accident, Parkinson's disease or cognitive impairment (Telephone Interview of Cognitive Status score ≥ 31), or had suffered a head injury within the past 12 months.

4.2.4 Sample size calculation

It was estimated that a sample of 54 participants (27 in each group) would provide an 80% power (with an $\alpha = 0.05$) of detecting differences between group means for an effect size of 0.6 in the Trail Making B test of neurocognitive function (G*Power 3.1) (Faul, Erdfelder, Buchner & Lang, 2009; Faul, Erdfelder, Lang & Buchner, 2007). Previous RCTs of exercise interventions have shown effect sizes between 0.24 and 1.17, in similar populations, for cognitive performance outcome measures, as a result of aerobic interventions (Angevaren et al., 2008). An effect size of 0.6 was chosen for the sample size calculation as it was a conservative estimate given the range of effect sizes seen in previous studies.

4.2.5 Recruitment

Recruitment was conducted during July and August 2012 (see Figure 4.1). Participants were enlisted primarily in response to an advertisement placed in a free community newspaper known to be popular with the target age group. In addition, a commercial television station ran a prime time news segment about the study in response to a general press release issued by the external relations department at the university.

Respondents initially made telephone contact with a research assistant. The study purpose, requirements and potential benefits and risks to participants, were fully explained. Those who met the initial eligibility requirements related to age, gender, amount of weekly exercise, self-report of ability to walk 20 metres and availability (able to attend classes at the allotted times and location, for the duration of 16 weeks), were then invited to undertake the next stage of screening.

4.2.6 Screening

Telephone screening was conducted by the PhD candidate (a Clinical Psychologist); those who met the full screening criteria were enrolled in the study (see Figure 4.1). Formal telephone screening included the TICS (Welsh, Breitner & Magruder-Habib, 1993)(see Appendix 1) and the Pre-Activity Readiness Questionnaire (PAR-Q) (American College of Sports Medicine, 2010)

(see Appendix 1). The TICS is a brief, standardised dementia screening measure that is said to test global cognitive functioning (Welsh, et al., 1993). Scores of 30 or less indicate cognitive impairment. This instrument is reported to possess the properties of high test-retest reliability, sensitivity and specificity (Barber & Stott, 2004); and to not manifest susceptibility to ceiling effects like other measures such as the MMSE (de Jager, Budge & Clarke, 2008). The PAR-Q is a standardised questionnaire designed to identify medical conditions that may require medical advice before exercise can be safely undertaken. Individuals reporting serious medical conditions were sent medical clearance forms in the post, and were asked to bring written permission from their GPs, to participate in the study, to the baseline data collection session. All participants provided signed informed consent prior to baseline testing and randomisation (see Figure 4.1).

4.2.7 Baseline measurement

Sample population characteristics

Anthropometric measures

Once individuals had been assessed as being eligible to participate in the study they were invited to attend a data collection session where demographic and health information was collected along with baseline outcome measures (see Appendix 2 for the data recording sheet employed at data collection). For the convenience of participants, data collection took place at two locations (on the university campus and at a community hall).

Information was gathered about age, education level, language spoken at home and marital status. Anthropometric measurement was conducted by registered nurses and included height, weight, waist and hip circumference, blood pressure using a sphygmomanometer (Welch Allyn 767, Skaneateles Falls, USA) and resting heart rate derived from palpation of the radial pulse for one minute. Participants completed the 21 item Depression, Anxiety and Stress Scale (DASS-21) (Gloster et al., 2008) which is reported to demonstrate good internal consistency and validity. The Geriatric Index of Co-morbidity also demonstrates good validity (Rozzini et al., 2002) and this instrument was used to gather information about the numbers and severity of medical conditions for each participant (see Appendix 2). In an effort to obtain an objective index of activity levels at baseline, participants were fitted with an Omron (Walking Style Pro, Kyoto, Japan) step counter by a physiotherapist and asked to wear the device for five days.

4.2.8 Outcome measurement

Rationale for primary outcome measures

Outcomes were measured at baseline and repeated within two weeks of the end of the 16 week intervention delivery period (between November and December 2012). The primary outcome measures were performance scores in a range of neurocognitive tests regarded as being indicators of cognitive processes such as inhibition, working memory, shifting, and verbal fluency. These abilities have been found to be highly associated with ARCD, mobility and the ability to perform activities of daily living (Deary et al., 2009).

Working memory, verbal fluency, cognitive inhibition and shifting, are commonly regarded as being components of executive function. Executive function is an umbrella term for a variety of cognitive processes that subserve goal-directed behaviour (Miller & Cohen, 2001). They are mainly associated with the prefrontal cortex of the brain and are especially important in novel, complex or demanding situations. Hence, these capacities have direct relevance to the intervention design and focus of the current study. The primary outcome measures in this study were chosen because a) age-related decline has been demonstrated in these domains (Carlson, Xue, Zhou & Fried, 2009); b) these components have relevance to the competent performance of day-to-day instrumental activities (Vaughan & Giovanello, 2010) and c) although invariably there is some degree of co-activation of executive function components (as well as involvement from non-executive function processes) (Miyake et al., 2000), there is evidence from neuroimaging studies that these processes involve different regions within the prefrontal cortex (Aron, Robbins & Poldrack, 2004; Crone, Wendelken, Donohue & Bunge, 2006; Narayanan et al., 2005).

Primary outcome measures

On the basis of previous research including animal and human studies the following neurocognitive tests would be expected to change in response to a complex exercise intervention and were consequently chosen as primary outcome measures. The California Older Adult Stroop Test (COAST) was developed specifically for use with older populations and assesses the ability to suppress a habitual response in favour of an unusual response (inhibition) (Pachana, Thompson, Marcopulous & Yoash-Gantz, 2004). The Controlled Oral Word Association Test (COWAT) measures verbal fluency and also draws on memory (Strauss, Sherman, & Spreen, 2006). The Letter-Number Sequencing Test (LNS) test (Strauss et al., 2006)

measures working memory as well as sequencing, attention and concentration abilities. The two-part Trail Making Test (TMT) (A and B) assesses attention, motor function, flexibility of thinking and visual search ability. Part B centres on shifting ability or the capacity for environmental adaptation by quickly switching from one mental set to another (Strauss et al., 2006). In particular the TMT B, COAST Interference and COWAT (FAS) are considered to be tests of executive function (Kang et al., 2013). See Appendices 3 to 6 for detail of the primary outcome measures used in this study.

California Older Adult Stroop Test (COAST) (inhibition) (Appendix 3)

Stroop tests assess the ability to suppress a habitual response in favour of an unusual response (Aron, 2007). They generally demonstrate good test-retest reliability (0.90, 0.83 and 0.91 for the three parts of the test) (Spreen & Strauss, 1998) and minimal susceptibility to practice effects (Lezak et al., 2004). The COAST is a Stroop test developed specifically for use with older populations (Pachana et al., 2004). Participants are required to first name colours (Colour), then read colour name words (Word); and then name ink colours when the names of colours are printed in a different (non-corresponding/incongruent) colour ink. During the incongruent condition, the two conflicting sources of colour information cause a competing effect (Interference) which is most typically observed as a prolonged reaction time compared to the neutral or congruent conditions (Laird et al., 2005). Three scores are obtained on each of the three COAST tests (Colour, Word, Interference). These are total time to complete the 50 items, number of self-corrected errors and total number of errors.

Controlled Oral Word Association Test (COWAT) (verbal fluency) (Appendix 4)

Different forms of the COWAT test measure verbal fluency and also draw on executive function and memory. Participants are given one minute to generate as many words as possible that begin with a specific letter. This task is repeated three times with three different letters (e.g., F, A, S). The measure obtained for this test was the total number of legitimate words generated for the three letters. These tests generally demonstrate inter-scorer reliability of 0.70, retest reliability of 0.88 and concurrent validity (Strauss et al., 2006).

Letter-Number Sequencing Test (LNS) (working memory) (Appendix 5)

The LNS test (Wechsler, 1997) measures working memory as well as sequencing, attention and concentration abilities. The participant is read a combination of numbers and letters and is asked to recall the numbers first in ascending order and then the letters in alphabetical order.

Each item consists of two trials, and each trial is a different combination of numbers and letters. There are seven items ranging from 2-letter/number sequences (e.g., B-7) to 8-letter/number sequences (e.g., S-2-L-8-B-1-G-7). The maximum score possible is 24 points. The validity and reliability of this test is well established in older adults with test-retest reliability in the range of 0.70 to 0.80 and a factor loading of 0.62 with the Working Memory Index (Groth-Marnat, 2003).

Trail Making Test (TMT) (Part A & B) (shifting) (Appendix 6)

The TMT is considered a test of visual search, attention, flexibility of thinking, motor function, and executive function (Lezak et al., 2004; Shum, O'Gorman & Myors, 2006; Strauss et al., 2006). Part B of the TMT requires the individual to mentally shift between two well-rehearsed sequences (numbers and letters) as quickly and as accurately as possible. Shifting ability represents the capacity to adapt to changes in the environment by switching from one mental set to another.

In Part A, the task is to connect the numbers in ascending order (i.e. 1-2-3-4...). Part B involves alternately connecting numbers and letters in ascending order (for the numbers) and sequential order for the alphabet letters (i.e. 1-A-2-B...). The score derived for each trail is the total time (in seconds) required to complete the task (Strauss et al., 2006). Test-retest reliability indices for the TMT range from 0.60 to 0.90 (Groth-Marnat, 2003) and the test is particularly useful for detecting early stages of dementia (Groth-Marnat, 2003).

Secondary outcome measures

Rationale for secondary outcome measures

Psychomotor and processing speed was measured using a computer-based program (Deary-Liewald Reaction Time Task) (Deary, Liewald & Nissan, 2011) designed to detect reaction time, defined as the time between stimulus presentation and response initiation. In addition, on the basis of previous research including animal and human studies the following biomarker and indices of physical functioning would be expected to change in response to a complex exercise intervention. BDNF plasma levels were measured. BDNF is a protein and the most abundant neurotrophin in the brain, with an important role in brain neurogenesis, synaptic plasticity, learning and memory (Knaepen et al., 2010; Ratey & Loehr, 2011). The brain has been found to be the main source of BDNF concentrations in venous blood (circulating BDNF) (Rasmussen et al., 2009). Exercise capacity, as a proxy for physical fitness and functioning, was included as a secondary outcome measure to determine whether a combination exercise approach also had

the ability to improve physical fitness. Specifically, the Six Minute Walk Test, Timed Up and Go Test and One-Legged Stance Test were included. See Appendices 7 to 10 for detail of the secondary outcome measures used in this study.

Psychomotor Speed (Simple Reaction Time and Complex Reaction Time) (Appendix 7)

Reaction Time, the time between presentation of a stimulus and initiation of a response, is said to reflect psychomotor and processing speed. This was measured using a computer-based program (Deary-Liewald Reaction Time Task) (Deary et al., 2011) designed to assess 1-choice and 4-choice stimulus conditions. In these tests, a subject presses designated keys on a computer keyboard when an 'X' appears on the screen. The aim is to press the appropriate key in response to the stimulus as quickly as possible. In the first stimulus condition the subject identifies a single object ('X'); in the second stimulus condition, the subject identifies which of four boxes the 'X' appears in from among 4 object choices. Simple reaction time (RT-1) and 4-choice reaction time (RT-4) are calculated as the time (milliseconds) from appearance of the stimulus to key activation. Split half reliability of up to 0.90 has been reported for this task (Spreen & Strauss, 1998).

Plasma Brain Derived Neurotrophic Factor (BDNF)

Participants were asked to have their usual breakfast (1-2 hours before venipuncture) and were asked to refrain from exercise for 36 hours prior to the blood draw. Eight milliliters of venous blood was taken from the ante-cubital fossa area, specifically in the morning, to control for diurnal range variation in BDNF levels (Trajkovska et al., 2007). Lysed blood samples were assessed for BDNF concentrations using a commonly used (Trajkovska et al., 2007) commercially available two-site sandwich enzyme-linked immunoabsorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA). The samples were processed according to the manufacturer's specifications. Plasma was obtained by centrifugation of additive-free containers for 15 minutes at 2000×g and 24 °C. Plasma was aliquoted and stored at -80 °C until measured. The frozen samples were transported to an accredited private laboratory for analysis.

Physical functioning: Six Minute Walk Test (6MWT) (Appendix 8)

The Six-Minute Walk Test (6MWT) is a functional validated measure of aerobic fitness (exercise capacity); and is based on the number of meters walked in six minutes (American Thoracic Society, 2002). The 6MWT was performed indoors, along a 30 meter walking course that was

flat and straight with a starting line and turnaround point clearly marked. The total distance walked was tallied using pre-marked intervals as a guide. The 6MWT is reported to have strong test-retest reliability when used before and after cardiac rehabilitation programs (Bellet et al., 2011). A recent study has confirmed that while there is a learning effect that can increase the distance walked; when used as an outcome measure, one measurement is sufficient to show change in performance over time (Bellet et al., 2011).

Physical functioning: Timed Up-and-Go Test (TUGT) (Appendix 9)

This is a clinical performance based measure of mobility, lower extremities function and fall risk. It is normally distributed, related to executive function and suitable for the assessment of healthy older adults (Herman, Giladi & Hausdorff, 2011). The TUGT was conducted using a chair placed upon a flat surface with cones marking the 3 metre turning point (Shumway-Cook, Brauer & Woollacott, 2000). Subjects were instructed: “On the word ‘go’, get up and walk as quickly and as safely as possible to cross the line marked on the path, turn around, walk back and sit down” (Shumway-Cook et al., 2000). The activity was timed from the subject’s back leaving the back of the chair to the return of the subject to this same position. Using a standardised protocol, each subject was required to perform one untimed, practice TUGT followed by two timed TUGTs (i.e. TUGT1 and TUGT2).

Physical functioning: Balance Test (The One-Legged Stance Test) (Appendix 10)

The one-leg stance test (Fregly & Graybiel, 1968) requires participants to stand unassisted on one leg with hands on hips. Participants were asked to stand on one preferred leg, flex the opposite knee allowing the foot to clear the floor, then balance on the one leg for as long as possible. Timing began when the leg was lifted and was timed in seconds until the participant returned the non-weight bearing foot to the ground. The test has good reliability in older adults (ICC =0.92) (Mancini & Horak, 2010).

4.2.9 Randomisation, concealment and blinding

Following baseline data collection participants were randomly assigned to either intervention or control groups (randomisation with 1:1 ratio) (see Figure 4.1). Random allocations were computer-generated via the Griffith University, Research Centre for Health Practice Innovation, Randomisation and Recruitment Service, following baseline data collection entry. A research assistant, not involved in other aspects of the study, contacted each participant by telephone and informed them of their group allocation and provided details of the processes

and requirements pertinent to their group. Participants and instructors could not be blinded due to the nature of the intervention. The follow-up data collectors were blinded to group allocation as were the laboratory staff involved in BDNF analysis. Data analysis was conducted by the PhD candidate on a de-identified database.

4.2.10 Exercise training intervention

Intervention group

Participants in this group received a multi-modal exercise class, twice weekly, for a period of 16-weeks. Classes were conducted for 60 minutes and the overall program was designed to include progressions and variations (see Table 4.1). Each session included aerobic (cardiovascular), strength (resistance) and motor fitness (balance, coordination, flexibility and agility) training in accordance with the ACSM Guidelines for Exercise Testing and Prescription (American College of Sports Medicine, 2010) (see Table 4.2 for details). The cardiovascular component was set to music and choreographed movements were cued in random rather than serial order to impose the need for focussed attention. Strength training incorporated progressive weight training and weight bearing exercises involving the major muscle groups. Motor training involved both static and dynamic balance, coordination and agility requiring manoeuvring around and stepping over objects and fitness boxing. Reaction time training included ball activities and flexibility training involved dynamic and static stretches for all major muscle groups (see Table 4.2). Sessions were conducted by fitness instructors accredited by *Fitness Australia*. Two instructors were present in all sessions.

Table 4.1 Overview of three phases of exercise intervention program

Component	Phase 1	Phase 2	Phase 3
	Time	Time	Time
Group freestyle			
Aerobics	10 mins	15 mins	15 mins
Agility	-	5 mins	5 mins
Group and/or circuit			
Strength	15 mins	10 mins	10 mins
Balance	10 mins	10 mins	7 mins
Coordination/ Agility/ Reaction time	15 mins	10 mins	7 mins
Cardio	-	-	6 mins
Group			
Flexibility and warm down	10 mins	10 mins	10 mins

Table 4.2 Detailed description of exercise intervention

Modality (Type)	Format	Exercises	Examples of exercises	Intensity	Progressions	Variations
Phase 1 – Weeks 1-4 – neural adaptation and coordination						
Cardio (aerobic)	Freestyle aerobics set to music	Antero-postero movements Lateral movements Minimal arm movement Isodirectional upper and lower limb movements	Marching on the spot Three steps forward and back Side step Side tap	3-4/10 RPE Music at 124-126 bpm	Increasing number of simultaneous limb movements	Remove lateral movements and shoulder ROM as necessary
Strength	Group	All major upper, lower body and core muscle groups	Half squats Arm and leg curls Seated theraband rows	x2 sets 6-8 reps with light dumbbell (d/b) weights	Commence with no weight progress to light weights (1kg)	Remove weights Substitute wrist or ankle weights as necessary.
Balance	Group	Static balance with decreasing support as able	Supported standing on one leg	N/A	Increased time + Challenges to concentration	One-to-one supervision and support as necessary
Coordination Agility Reaction time	Some elements included in free style aerobics	Manoeuvring around and stepping over objects Flat foot heel drumming	Weaving in and out of chairs Fast, fixed-pattern, foot tapping Wall ball throws	N/A	Chairs closer	One-to-one supervision and support as necessary
Flexibility + warm down	Group	Static stretches on floor	Cat and camel stretches Lying hamstring stretches Back extensions	3-4/10 RPE Minimum 20 secs.	Vary with musculo-skeletal status	Substitute as necessary

Modality (Type)	Format	Exercises	Examples of exercises	Intensity	Progressions	Variations
Phase 2 – Weeks 5-11 – conditioning						
Cardio (aerobic)	Freestyle aerobics set to music	Antero-postero movements Lateral movements Multiple direction changes Increased strength component Arm movement Non-isodirectional upper and lower limb movements	As for Phase 1 plus Zig-zag movements Knee lifts Lateral lower body with antero-postero upper body movements	4-5/10 RPE and 126-128 bpm music	Increase complexity of movements & pace of directional changes	Participant sets own pace as able
Strength	Circuit	All major muscle groups Compounded exercise	Different stations including: Continuous rolling movement on mat Fitball squats Weighted bag drags Ball bouncing	Recommended RPE = 4-5/10 2x 30 second intervals per station	Increase weights as able	Remove/reduce weights Substitute wrist or ankle weights as necessary.
Balance	Circuit	Static and dynamic balance	Heel-toe (walk the line) One-leg pose with ball throws	2x 30 second intervals per station	Challenges to concentration	One-to-one supervision or remove element (e.g., ball throws)
Coordination Agility Reaction time	Free style aerobics + Circuit + Group	Circuit: Dynamic combination/compounded exercises Group: Dynamic knee lifts alternating with rapid foot movements	Circuit: Flat foot heel drumming Walking ball bounces Group: Various moving foot sequences Catch dropping objects (noodle drops) Fitness boxing	Circuit: 2x 30 second intervals per station	Faster movements as able Substitute smaller balls Alternate between dominate & non-dominate hands	One-to-one supervision and reduce speed of movement
Flexibility + warm down	Circuit + Group	Circuit: Spinal rotation Group: Static stretches on floor	Circuit: Alternating wall taps Group: Cat and camel stretches Lying hamstring stretches Back extensions	Circuit: 2x 30 second intervals Group: 4-5/10 RPE Minimum 20 s	Increase according to tolerance & musculo-skeletal status	Decrease with musculo-skeletal status

Modality (Type)	Format	Exercises	Examples of exercises	Intensity	Progressions	Variations
Phase 3 – Weeks 12-16 – conditioning						
Cardio (aerobic)	Freestyle aerobics set to music	Antero-postero movements Lateral movements Multiple direction changes Increased demands on postural control Higher arm movement Non-isodirectional upper and lower limb movements	As for phases 1 and 2 plus: 'Pride of Erin' dance steps Marching with alternating parallel and 45 degree angle arm movements	5-6/10 RPE and 128-132 bpm music	Participant sets own pace as able (increases as able)	Participant sets own pace (decreases intensity or complexity of movement as required)
Strength	Circuit	All major muscle groups Compounded exercise	Lunges D/b flies supine on roller Modified (wall) push ups	Recommended RPE = 5-6/10 2x 40 second intervals per station	Increase weight as able	Remove/reduce weight or substitute exercises targeting same muscle group as tolerated
Balance	Circuit	Static and dynamic balance	Stand on foam Step onto foam and assume one leg pose One-legged stand and reach	2x 40 second intervals per station	Introduce perturbation/reduce base of support	One-to-one supervision or remove element (e.g., ball throws)
Coordination Agility Reaction time	Free style aerobics + Circuit + Group	Circuit: Dynamic combination exercises Group: Dynamic knee lifts in combination with rapid foot movements	Circuit: Noodle drops Group: Freestyle aerobic routine + noodle Fitness boxing – random alternating sequences	Circuit: 2x 40 second intervals per station	Faster movements as able	One-to-one supervision and reduce speed of movement
Flexibility + warm down	Circuit + Group	Circuit: Spinal rotation Group: Static stretches on floor	Circuit: Alternating wall taps Group: Cat and camel stretches Lying hamstring stretches Back extensions Quadruplex	Circuit: 2x 40 second intervals per station	Increase with musculo-skeletal status	Decrease with musculo-skeletal status

Control group

Participants in the control group were on a waiting list to attend the 16-week program which commenced at the end of the study and immediately after follow-up data collection. This group was asked to continue with usual activities during the wait period, including refraining from participating in more than 60 minutes of formal exercise each week. To enhance the prospect of retention, participants in the control group were contacted by telephone at four week intervals by a research assistant.

Intervention fidelity

To maximise intervention fidelity, two instructors were present in each class and followed a pre-determined intervention protocol. Only these two instructors administered the intervention. At random intervals an independent assessor observed the classes and monitored for content consistency using a checklist based on the explicit components of the exercise intervention protocol. In addition, instructors maintained a log of activities in each class and these logs were reviewed by the independent assessor to check for intervention fidelity. See Appendix 11 for the completed checklists and Appendix 12 for an example of attendance sheets.

Adherence to intervention protocol

Trained fitness instructors documented attendance at each class. Participants in the intervention group were asked to attend at least 85% of classes and were followed up by telephone if they were absent for two consecutive classes. To maximise participant contact and follow-up, participants in both groups were asked to provide at least two sets of contact details: direct and via a friend or family member. In total, four participants were followed up by telephone on at least one occasion.

4.2.11 Research questions

There were two main questions answered in this study. These are presented below along with the null hypotheses which were tested statistically.

1. What is the effect of participation in a 16-week, multimodal exercise program, as compared to non-exercising controls, on specific measures of cognitive performance (working memory, inhibition, verbal fluency and shifting), controlling for baseline performance, in healthy community dwelling older women?

Null Hypothesis 1: For variables that are normally distributed at baseline, there will be no difference in mean follow-up scores in cognitive performance between the intervention and control groups, controlling for baseline.

Null Hypothesis 2: For variables that are not normally distributed at baseline, there will be no difference in mean log transformed follow-up scores in cognitive performance between the intervention and control groups, controlling for baseline.

2. What is the effect of attending the intervention exercise program, compared to no-exercise, on psychomotor speed (simple and choice reaction times), exercise capacity (six minute walk distance), physical functioning (TUGT and One-Legged Stance Test), and plasma levels of BDNF, controlling for baseline performance, in healthy community dwelling older women?

Null Hypothesis 3: For variables that are normally distributed at baseline, there will be no difference in mean follow-up scores for reaction time, exercise capacity and physical functioning, between the two groups controlling for baseline.

Null Hypothesis 4: For variables that are not normally distributed at baseline, there will be no difference in mean log transformed follow-up scores for physical functioning and BDNF, between the intervention and control groups, controlling for baseline.

4.2.12 Data analysis

Data analysis for the randomised controlled trial

To characterise the sample in this study, means or proportions and standard deviations (SD s) were calculated by randomisation group for multiple baseline demographic, cognitive functioning and anthropometric variables. T-tests or Mann-Whitney U tests, as appropriate, were conducted to assess the similarity of the groups at baseline. Unadjusted means and SD s for each cognitive performance measure obtained at the baseline and follow-up visits, were calculated. All data were double entered by two different research assistants and all analyses were by intention-to-treat (Friedman et al., 1998; Polit & Gillespie, 2010). To test the effects of multi-modal exercise, between group differences were examined using analysis of covariance with baseline scores as covariates. Data were checked for normalcy of distribution by performing a Q-Q plot, as well as assessing the calculations for kurtosis and skewness. Where

data were not normally distributed, log transformed data were used to calculate p-values in the ANCOVA. Cohen's d effect size was calculated from the SPSS output of partial Eta squared (Cohen, 1988).

Theoretically, there are three possible ways in which the data analysis for this study could have been undertaken. These include: a t-test of follow-up data only; the computation of a change variable whereby the baseline score is subtracted from the follow-up score and an independent samples t-test then calculated using these change scores; or finally, an ANCOVA undertaken with baseline values as the covariate. All of these analyses were considered, however, the ANCOVA with baseline as covariate was deemed the most appropriate test. This approach was based on the rationale that student t-tests of outcome variables do not take account of baseline variation. T-tests of change variables are problematic as analysing change does not control for baseline imbalance because of the inherent tendency towards regression to the mean. As Vickers and Altman (2001, p. 1123) indicate, "...baseline values are negatively correlated with change because patients with low scores at baseline generally improve more than those with high scores". Use of ANCOVA incorporating the baseline score as a covariate allows for regression but takes account of baseline (Vickers & Altman, 2001). Finally, for variables that were not normally distributed at baseline these data were log transformed again as suggested by Vickers and Altman (2001).

4.3 Qualitative study

4.3.1 Introduction

A qualitative component was embedded within the RCT design to elicit information from participants about: the acceptability of the study; their experience of the intervention; their subjective observations of any changes perceived to have arisen from the intervention; and the impact of any treatment effects on day-to-day life. Qualitative methods were once regarded by purists as being incongruent with experimental designs (Fielding, 2012). However, the contemporary pragmatist viewpoint is that qualitative data adds dimensions to intervention findings that cannot be extrapolated from variables alone (Hesse-Biber, 2012).

An embedded design is a research strategy in which the study is framed by a primary methodology with a secondary method incorporated into the research design (Caracelli & Greene, 1997); quantitative and qualitative methods are combined giving priority to one of the approaches. Using this Priority-Sequence modelling (Morgan, 1998) approach means that the

sequencing of the complementary method is determined by research project's goals and may be operationalised prior to the principal method's commencement or at follow-up. In the disciplines of health and social science there is growing interest in embedding qualitative methods within quantitative experimental frameworks, including RCTs (Plano Clark et al., 2013). The key advantage of using an embedded design is that it combines the relative strengths of quantitative and qualitative methodologies, theoretically maximising the capacity of a study to address complexity and to add greater depth to the interpretation of results. According to Daigneault and Jacob (2013 in press, p. 2) this type of integration is "...much more than the mere collection of quantitative and qualitative data within the same study". The supplementary contribution of the secondary method effectively enhances the findings derived from the primary framework. In this study the qualitative component was expected to enrich the experimental data; by having both forms of data the results could be compared for convergence or divergence. Additionally, the inclusion of a qualitative component was intended to garner illustration, elaboration and clarification (Greene, Caracelli & Graham, 1989) as interpretive resources that could be applied to the analysis of the quantitative results.

The qualitative component of this study was intended to provide a distinguishable yet defined ancillary role. Therefore, it was deemed necessary to employ a distinctive and credible qualitative methodology that was least likely to result in descriptions of the qualitative data being overly imbued with conceptual, theoretical, philosophical or abstract overtones. The approach employed in this study, known as 'qualitative description', has been described as the qualitative methodological approach of choice where plain (least interpretive) descriptions of phenomena are required (Sandelowski, 2000). This approach emphasises descriptive validity which refers to the centrality of accurate accounting of the meanings intended by the participants (Sandelowski, 2010). The theoretical location of this methodology (Naturalistic Inquiry) (Lincoln & Guba, 1985) is within the interpretive paradigm, but it does not prescribe a theoretical view of the phenomena of interest. The focus and purpose of this framework is to sample the content of interest as it presents itself (Lincoln & Guba, 1985; Thomas, 2006).

The rationale for augmenting the quantitative data with findings from a qualitative component encompassed a number of factors. First, the results of the RCT alone address efficacy but do not explicate the likely effectiveness of the intervention from the perspective of those making exercise choices. It would also reveal whether the experience of the exercise program was acceptable and therefore likely to attract ongoing interest and engagement. Second, the triangulation or comparison of different types of data (quantitative and qualitative) enables

cross-validation of the results. Convergence between the data-sets reinforces the credibility of the experimental outcome data, while divergence implies the likelihood of spurious results. Moreover, the incorporation of information derived from the qualitative arm may further assist in explaining any disparity in the experimental study findings. Third, the extant literature lacks clarity about how well performance in various neurocognitive tests translates into the functional abilities required for competency in the instrumental activities of daily living (ecological validity) (Conn et al., 2011). It is postulated that the embedded approach might provide insight into the extent to which performance in the neurocognitive instruments employed in this study correspond to performance in 'real life'. Fourth, it was anticipated that the inclusion of a qualitative component might elicit information about the practical 'everyday' value of any treatment effects, as an index of the clinical significance of the intervention (Conn et al., 2002). Finally, it was envisaged that the possibility of variability and paradoxes emerging from the two data sources (Johnson, Onwuegbuzie & Turner, 2007) might represent the opportunity to stimulate new ways of thinking about the links between the neuroprotective properties of exercise, in relation to cognition and the ageing brain, as well as data pertaining to the optimal means of delivering interventions that are both effective and likely to engender retention.

4.3.2 Selection of participants and sampling technique

Interviews and confirmatory focus groups were undertaken with a sub-set of the study population allocated to the intervention group. According to Morse (1991) research that combines methodologies must satisfy the methodological standards of each paradigm being undertaken. Accordingly, each method must adhere to the principles and assumptions of their respective approaches, regardless of which method is being prioritised. A distinguishing feature of qualitative approaches is that they do not seek generalisability but rather trustworthiness, where the analysis represents a credible representation of participant perspectives. The sampling goal is to attain an amalgam of data to the point of data saturation (where subjective viewpoints are being repeated to the extent that, effectively, nothing is being added to the findings); in conjunction with the concerted sampling of extreme and maximum variation of viewpoints (Sandelowski, 2000). This process potentially yields both common and unique themes from the subjective content.

In concordance with the principles of qualitative research, the participants were recruited to the qualitative arm with a strategy designed to precipitate both homogeneity and heterogeneity in terms of representativeness and subjective opinion. Participants continued to

be enlisted in the interview process, until data saturation was apparent. High attendance RCT participants as well as those who struggled to attend 85% of sessions were invited to be interviewed. To ensure maximum variation sampling, the demographic and physical profile of participants was checked and a range of participants was interviewed including those who were married and widowed or single; those who had BMIs under 25 and over 30; as well as participants who had different levels of education and co-morbidities. Thematic analysis was undertaken simultaneously with sample recruitment, so that emergent themes could be identified. When the analysis revealed repetitive themes, data saturation was considered to have occurred and sampling ceased.

4.3.3 Data collection by individual interview

Face-to-face, digitally audiotaped, individual interviews were conducted with 15 of the 25 intervention participants who gave written informed consent. Each volunteer was interviewed once within two weeks of the completion of the intervention either at follow-up data collection or in their own homes. Each interview lasted on average 20 minutes with a range of 10-45 minutes. All the participants were informed, at the time of providing written consent to participate in the quantitative component, that interviews would be audiotaped and that these recordings would later be transcribed (see Appendix 14). The aim was to record good quality material using unobtrusive equipment. Interview participants were informed of their right to have the recording device stopped at any time, but the role of the recorder was not emphasised. The interviews were conducted by two experienced research assistants who were trained by the PhD candidate, using role-play (Minichiello, Aroni, Timewell & Alexander, 1999). Examples of the interview question are included in the Qualitative Interview Schedule (Appendix 13). Before each interview started the interviewers re-iterated the purpose of the interviews and asked the participants to give an additional verbal assent to the interview process and the audiotaping of the interviews.

4.3.4 Transcribing of audiotapes

As agreed to by all participants the audiotapes were transcribed verbatim. Once transcribed and checked, the digital audio files were deleted as mandated by the Ethics Committee. The only computer copy of the transcripts is stored in a password protected file in a computer in a locked research facility. Transcripts were identified by a number and pseudonyms have been used for all the participants in this thesis.

4.3.5 Focus groups to confirm interpretation of the data

Following the initial identification of categories and themes from the qualitative data, a focus group was conducted with participants from the intervention group. The aim was to corroborate the initial interpretative analysis with additional feedback from the group. Overall, the information gleaned from the focus group verified the themes derived from the original interviews. In particular, the information obtained through the focus group discussion shed light on the relative informational significance of some of the themes identified in the initial qualitative interviews.

4.3.6 Qualitative data analysis

In keeping with the qualitative description research methodology employed in this arm of the study, a general inductive approach to analysing qualitative data was adopted (Thomas, 2006). The general inductive approach allows “research findings to emerge from the frequent, dominant, or significant themes inherent in raw data, without the restraints imposed by structured methodologies” (Thomas, 2006, p. 238). While this approach is consistent with the general patterns of qualitative data analysis described by numerous other authors (e.g., Miles & Huberman, 1994; Pope, Ziebland & Mays, 2000; Punch, 1998; Strauss & Corbin, 1998), it differs in that it provides a more detailed set of procedures for analysing and reporting qualitative data (data reduction and display) (Thomas, 2006).

A general inductive approach is particularly appropriate for this study as it was developed specifically to be used in evaluation studies (Thomas, 2006). The qualitative component of this research project sought, among other things, to evaluate the appropriateness and the effectiveness of the exercise intervention from the perspective of participants. In a general inductive analysis the process is guided by the research questions, which identify domains and topics to be investigated. The inductive component of the analysis is carried out through multiple readings and interpretations of the raw data. Although the findings are influenced by the research questions, the findings arise directly from the analysis of the raw data, not from a *priori* frameworks or models (Thomas, 2006).

The primary mode of analysis is the development of categories from the raw data into a framework. This framework contains key themes, categories and processes identified by the researcher during the coding process. The findings result from multiple interpretations made from the raw data by the researcher (or researchers) who code the data. For example, categories may be created from actual phrases derived from specific segments of the text

(Thomas, 2006). Consistent with a basic underlying tenet of all research in the interpretive paradigm, the findings are influenced by the assumptions and experiences of the researcher conducting the study and carrying out the data analysis. This is due to the researcher needing to be engaged and reflexive throughout the research.

Initially, immediately following the interviews, the researcher listened to them and began to record first impressions of the categories and themes emerging from the data. This was necessary to determine when no new data were being uncovered in the interviews. This process, called concurrent analysis, allows the researcher to judge when data saturation has been reached. The initial analysis was not very detailed but helped to determine when a sufficient number of interviews had been undertaken.

Once all interviews had been completed direct verbatim transcripts of the interviews were searched to (a) make comparisons between events, interactions and actions; and (b) ask questions that allowed the conceptualisation of the themes within the data. In this study *independent parallel coding* (Thomas, 2006) was undertaken by the PhD candidate and an experienced qualitative researcher. Initially the PhD candidate undertook a line-by-line approach to coding the data and then developed a set of categories. The process entailed continuing revision and refinement including the extrapolation of contradictory or unique perspectives or insights. Quotations that appeared to capture key themes were also catalogued. These categories constituted the preliminary findings. Then a research assistant, who was an experienced qualitative researcher, was given the evaluation objectives (the research questions) and the transcripts of the interviews from which the initial categories were developed. The research assistant was then asked to create a second set of categories from the raw text. The researcher and the research assistant then compared the two sets of categories to establish the extent of overlap, disparity and unique findings. Following further analysis and discussion a set of categories and some overarching themes were identified that mapped the acceptability of the program and the effects of the intervention as experienced by participants and those around them.

A triangulation approach to the incorporation of qualitative and quantitative data was applied at the stage of results' interpretation (O'Cathain, Murphy & Nicholl, 2010). At this stage of the comparative analysis the triangulated data were further scrutinised to extrapolate any inferences that could be distinguished in relation to the cross-validity between the quantitative and qualitative data, the issues of ecological validity, issues of clinical significance and any

insights that might be apparent about the suitability of the instruments employed in this study. These interpretations are presented in the discussion chapter of this thesis.

4.3.7 Rigour

In quantitative research the rigour of a study is determined by adopting methods to ensure the validity and reliability of data collection and data analysis. In qualitative research the concepts of validity and reliability are replaced with the concept of trustworthiness (Lincoln & Guba, 1985; Shenton, 2004). The trustworthiness of findings derived from qualitative descriptive methods "...can be assessed using similar techniques to those that are used with other types of qualitative analysis (e.g., Lincoln & Guba, 1985)" (Thomas 2006, p.240). Lincoln and Guba (1985) described four general types of trustworthiness in qualitative research: credibility, transferability, dependability, and confirmability.

Credibility refers to confidence in the truth of the data and the interpretation of the data. It involves two steps: namely, carrying out and reporting the study in a way that enables appraisal of the believability of the findings; and taking steps to demonstrate credibility to consumers (Lincoln & Guba, 1985; Sandelowski, 1986). As instanced in the reporting of this study, it may involve the use of verbatim quotes in the findings section to allow readers to audit the researcher's interpretation of the data. It can also take the form of debriefings with participants to ensure that data were collected in ways that promoted and facilitated the prospect of interviewees expressing their views with detail and clarity.

Transferability relates to how well the results can be transferred to other groups or settings. This study was limited to community dwelling older women, so it is important that the interpretation of the results is limited to this population (Shenton, 2004). Dependability refers to the process involved in writing the discussion chapter of this thesis where findings from this study will be confirmed with other theoretical and empirical work in the area (Lincoln & Guba, 1985). It is important that the other literature selected for comparison or exemplification is appropriate in its focus and scope.

Confirmability is enhanced through the use of stakeholder or member checks. People with a specific interest in the evaluation, such as participants, comment on the categories, themes and/or interpretations formulated by the data analysis (Guba & Lincoln, 1989). In this study confirmability was addressed by conducting focus groups with participants after the preliminary data analysis had been undertaken.

4.4 Ethical considerations

The ethical framework underpinning this research project was derived from the Australian National Statement on Ethical Conduct in Human Research. These guidelines espouse the values of research merit and integrity, justice, beneficence and respect for human beings (The National Health and Medical Research Council, 2007 (updated May 2013)).

Research that has merit and integrity is said to be justifiable because of the potential benefits that arise from increased knowledge, both theoretical and practical, about the chosen topic. A key goal of this study was to advance the current state of knowledge in the area of exercise and the ageing brain by employing a research method with the capacity to provide definitive evidence. A RCT design with an embedded qualitative component was chosen in preference to an observational study because this method represents the best prospect of demonstrating causality (Friedman et al., 1998). The study was based on a thorough review of broad ranging literature and the proposal was peer reviewed at confirmation and with the publication of Article 1 (Vaughan, Morris, Shum, O'Dwyer & Polit, 2012). All aspects of the research were conducted based on the national guidelines for the conduct of ethical research in humans and supervised by appropriately qualified personnel. The protocol for this study was approved by Griffith University Human Research Ethics Committee (GU Ref No: PES/05/12HREC) (see Appendix 15).

The notion of justice addresses the principle of fairness. It implies that all participants should be provided with equal opportunity in terms of recruitment, inclusion, exclusion and benefit. In the present study this was achieved, in part, through the processes of recruitment and randomisation. Moreover, all participants were offered the opportunity to receive the exercise intervention (the control group was provided the intervention after follow-up data collection was complete) to ensure fair distribution of potential benefits. The exercise program was also provided free of charge to all participants. The results were disseminated to participants' verbally through formal presentation and in written form with the provision of individual results.

Beneficence is an aspect of ethical research practice that underpins efforts to maximise the possible benefits of an intervention while simultaneously ensuring that participants are protected from harm. Physical and social risks to individuals in this study were managed through a number of processes that included: cognitive and physical screening; the requirement of a GP's clearance in the case of diagnosed medical conditions; the provision of

privacy in environments where personal data were collected and security of all forms of data storage. All participants were required to provide written informed consent following full disclosure of the risks and benefits of study participation (see Appendix 14 - Participant Information and Consent Form). Written information was provided regarding the participant's right to withdraw from the project at any time. All exercise sessions and data collection were overseen by qualified personnel certified in First Aid and cardiopulmonary resuscitation (CPR). There were no adverse events; however, provision was made for that possibility by pre-convening a data safety monitoring board.

Respect for human beings is an overarching tenet of ethical conduct. It requires researchers to abide by the values of merit and integrity, justice and beneficence, as a manifestation of due regard for the value and welfare of all individuals involved in the research enterprise. Respect includes the notions of privacy and confidentiality and the safeguarding of participants' capacity to make independent decisions. In this study inclusion criteria were as broad as possible within the limits of the research design and questions of interest. Participation was voluntary. The central aim of the intervention was to achieve health and welfare benefits for the participants. Informed written consent was obtained to include the collection of verbatim transcripts of interviews and the use of quotations in the final report. Pseudonyms were used to protect the identity of individuals and quantitative data were only reported in aggregated form. All data were de-identified, using participant identity codes, prior to data analysis and archiving. However, in case of an unforeseen long-term adverse outcome the data are able to be re-identified. Data were stored on a password-protected computer and in a locked filing cabinet to ensure participant anonymity. Data will be destroyed five years from the completion of the study.

4.5 Summary

The extant literature is replete with commentary recommending more rigorous research to establish the true efficacy of exercise training as a countermeasure to ARCD (Angevaren et al., 2008; Smith et al., 2010; Snowden et al., 2011; van Uffelen et al., 2008). A RCT was employed in this study, because this design represents the gold standard for assessing the efficacy of an intervention (Friedman et al., 1998). The RCT was embedded with a qualitative component to gauge participants' overall subjective experience of the intervention, the acceptability of the exercise program and participant observations about any changes perceived to have arisen from the intervention. The qualitative component was also intended to assess the impact of

any treatment effects on day-to-day life. It was envisaged that the supplementary qualitative evidence would both enrich the interpretation of the quantitative experimental data and shed light on the ecological validity and clinical significance of these findings.

Both methodologies were designed to incorporate the principles of rigour. The RCT included a number of measures to reduce the likelihood of bias, including randomisation to groups and the blinding of assessors. The qualitative component employed 'qualitative description' which is an approach that emphasises descriptive validity and has been described as the qualitative methodological approach of choice where least interpretive descriptions of phenomena are required (Sandelowski, 2000). The concept of rigour in the qualitative analysis was further addressed by the inclusion of measures designed to incorporate the four general types of trustworthiness in qualitative research: credibility, transferability, dependability, and confirmability. Finally, ethical considerations were fundamental guiding principles in the undertaking of this study. The design and implementation of this research was underpinned by the values of research merit and integrity, justice, beneficence and respect for human beings as advocated by the Australian National Statement on Ethical Conduct in Human Research (The National Health and Medical Research Council, 2007 (updated May 2013)). The following chapter (Chapter 5) sets out the results of the RCT and the quantitative analysis as derived from the methodological processes and procedures detailed above.

Chapter 5: Results - Randomised controlled trial

5.1 Introduction

The capacity of multi-modal exercise programs to elicit cognitive benefits in older adults is uncertain. There are theoretical indications that induced gains may be possible by combining a broad array of exercise modalities that include motor fitness training. This proposition is yet to be tested using a randomised, controlled intervention design. The principal aim of the present study is to test the efficacy of a 16-week multi-modal exercise program on neurocognitive and physical functioning and brain-derived neurotrophic factor (BDNF), in older women. The program included complex motor skills training implemented in a manner requiring sustained attention and concentration. This chapter details the results of this single-blinded, parallel-group RCT. A secondary objective of this study was to gather qualitative data from participants in the intervention group to enhance the interpretation of the quantitative data. Evidence from the qualitative arm of this study is presented in Chapter Six.

5.2 Study recruitment

One hundred and sixty (n=160) volunteers were assessed for eligibility. One hundred and eleven (n=111) individuals did not fulfil the necessary criteria for a variety of reasons. The main grounds for ineligibility were geographical distance from the study location (n=80) and unavailability during the designated study period (n=12). Forty nine (n=49) eligible participants were enrolled, with 25 randomly allocated to the intervention group and 24 to the control group. Seventeen were required to provide clearance by their general medical practitioner prior to randomisation. All of the 25 participants allocated to the intervention group completed at least 85 % of the 32 classes conducted over the 16-week delivery period (mean = 30.0; sd = 1.7). There were no adverse events or injuries reported as a result of this intervention.

Follow-up data were collected from the entire intervention group; one of the 24 participants randomised to the control group was lost to follow-up. Feedback from this participant indicated that she found the baseline cognitive testing onerous and was disappointed at being allocated to the control group. The research assistant re-iterated that all participants would be given the opportunity to receive the intervention program (control group after follow-up data collection). However, the participant declined to be tested at follow-up. Figure 5.1 describes the participant flow through the trial.

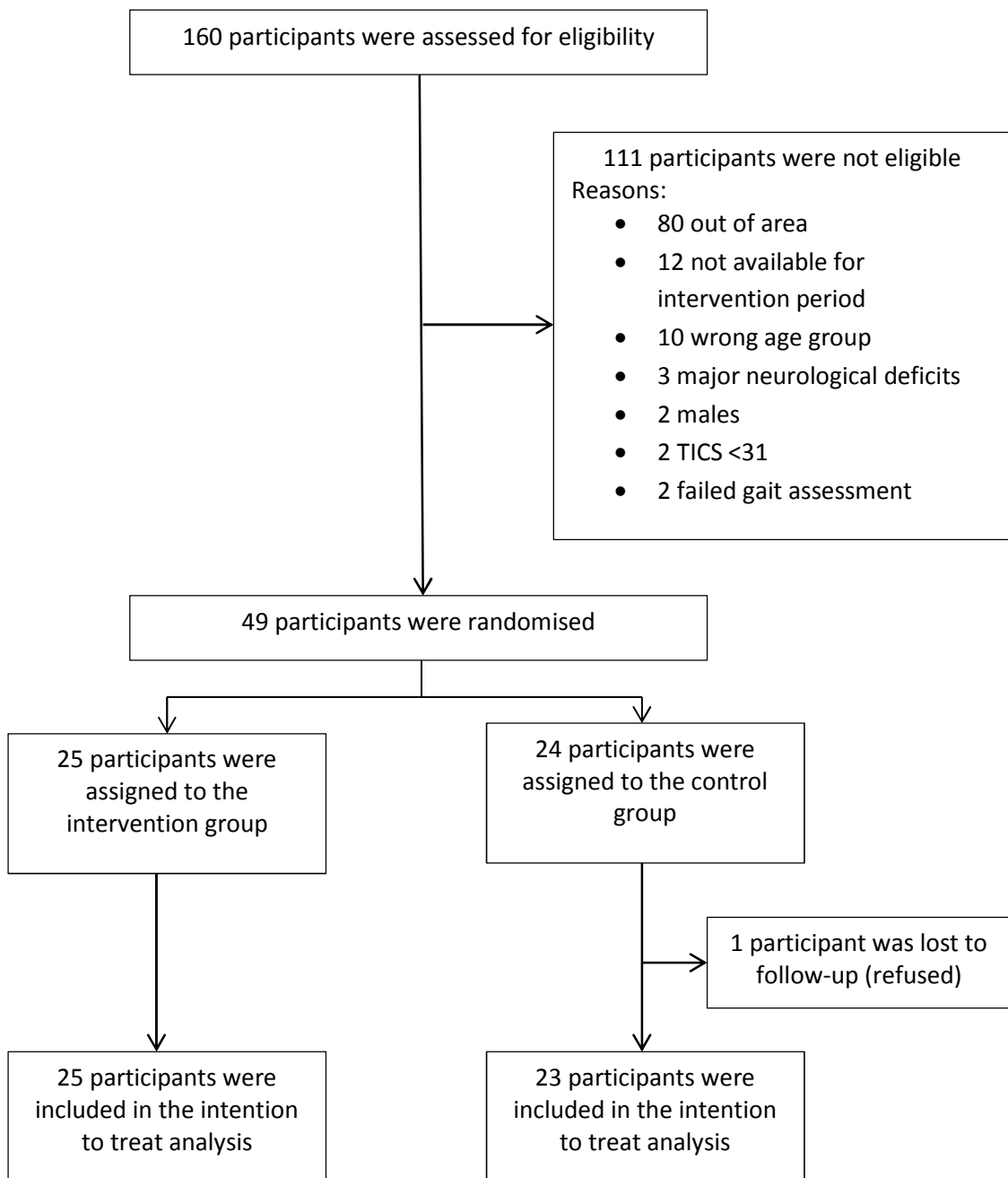


Figure 5.1: Flow diagram of the numbers of people recruited, assessed for eligibility, randomised and completed the study

5.3 Sample characteristics

Table 5.1 displays participant characteristics at baseline. The participant characteristics were similar between the groups on trial entry. Above and beyond the descriptor variables, there were no differences in the group means in terms of the TICS (cognitive status), the number of pedometer-assessed steps taken per day (activity levels) or the depression sub-scale of the DASS (participants non- depressed).

Table 5.1: Mean values (SD) and t-tests of participant characteristics for intervention and control groups

Variable	Intervention Group Mean (SD) (n=25)	Control Group Mean (SD) (n=24)	t(df)	p value
Baseline sample descriptor variables				
Age (years)	69.0 (3.1)	68.8 (3.5)	0.14 (47)	0.89
Education in years	12.3 (2.9)	12.7 (3.5)	-0.47 (47)	0.64
Body Mass Index (Kg/m ²)	25.8 (4.6)	28.4 (6.1)	-1.64 (47)	0.11
Waist-to-Hip Ratio	0.8 (0.1)	0.9 (0.1)	-1.28 (47)	0.21
Resting Heart Rate (beats/min)	73.9 (12.8)	73.5 (8.9)	0.12 (47)	0.90
Resting Mean Blood Pressure (mmHg)	97.8 (7.0)	101.1 (10.7)	-1.28 (47)	0.21
Mean daily steps (pedometer)	5193 (2306)	5029 (2890)	0.20 (39)	0.84
TICS (≤31 implies impairment)	38.3 (4.1)	36.9 (3.0)	1.34 (47)	0.19
Depression (DASS -21)(0- 9 =non-depressed)	6.8 (7.3)	7.8 (6.8)	-0.47 (47)	0.64
Anxiety (DASS -21)	4.3 (3.9)	4.3 (3.9)	-0.01 (47)	0.99
Stress (DASS -21)	9.5 (6.8)	10.1 (6.7)	-0.29 (47)	0.77
DASS-21 Total	20.6 (15.6)	22.2 (14.0)	-0.36 (47)	0.72
Geriatric Index of Co- morbidity Score	4.2 (3.2)	4.5 (2.7)	-0.50 (47)	0.62

Legend: TICS = Telephone interview of Cognitive Status; DASS = Depression, anxiety and stress scale

Since the mean scores for the DASS did not reach the cut-off for depression (>9), this variable did not need to be considered as a covariate in the ANCOVA. The mean daily steps as recorded by the pedometers served to confirm that both groups were not engaging in frequent physical exercise or formal exercise for more than 60 minutes per week.

5.4 Between group comparisons of outcome measures at baseline

Table 5.2 depicts the mean values and standard deviations (SDs) of the baseline outcome measures data for the intervention and control groups. In addition, this table reports the independent t-test results comparing mean baseline outcome measure scores between the groups.

Table 5.2: Mean values (SD) and t-tests of baseline data collection for intervention and control groups

Variable	Intervention Group Mean (SD) (n=25)	Control Group Mean (SD) (n=24)	t(df)	p value
Primary outcome measures				
Trail Making Test A (s)	33.7 (11.8)	30.3 (7.9)	1.22 (47)	0.23
Trail Making Test B (s)	65.8 (21.0)	69.6 (23.0)	-0.60 (47)	0.55
Letter Number Sequences	14.9 (3.0)	13.7 (3.1)	1.44 (47)	0.16
COAST_Colour (s)	33.0 (6.4)	31.9 (5.6)	0.67 (47)	0.51
COAST_Word (s)	26.8 (6.4)	24.5 (4.2)	1.47 (47)	0.15
COAST_Interference (s)	61.3 (13.0)	65.1 (24.1)	-0.69 (47)	0.50
COAST_Total_Time (s)	121.1 (21.9)	121.5 (30.2)	-0.05 (47)	0.96
COWAT_FAS_Total (s)	42.0 (12.6)	42.9 (14.2)	-0.25 (47)	0.81
Secondary outcome measures				
6 minute walk test (m)	503.9 (93.7)	507.3 (73.6)	-0.14 (47)	0.89
Timed Up & Go (s)	6.6 (1.4)	6.7 (1.3)	-0.26 (47)	0.80
One-legged stance test	54.9 (50.7)	22.3 (19.2)	2.99 (47)	0.004*
Simple Reaction Time (Mean - ms)	308.1 (36.3)	306.1 (33.4)	0.21 (47)	0.84
Choice Reaction Time (Mean - ms)	583.0 (86.0)	565.1 (75.3)	0.77 (47)	0.44
BDNF (ng/ml)	4.5 (2.2)	5.6 (1.8)	-2.05 (46)	0.047*

Legend: COAST = California Older Adult Stroop Test; COWAT = Controlled Word Association Test; s= seconds; ms = milliseconds; m = metres.

* = $P \leq 0.05$

All baseline outcome variables were normally distributed and showed no statistically significant differences between the groups, with the exception of the one-legged stance test and BDNF levels.

As the one-legged stance test and BDNF results were skewed to the right the data were logarithmically transformed prior to analysis (as explained in section 4.2.12). Following log transformation these data were re-assessed for normality of distribution by checking kurtosis and skew and plotting Q-Q curves. Log transformation resulted in normally distributed data which could then be used to assess the effect of the intervention on these outcome measures.

5.5 Effect of a multimodal exercise program on primary outcomes

Table 5.3 shows the differences in the primary outcomes between the intervention and control groups, at follow-up, using ANCOVA adjusted for baseline. The primary outcome neurocognitive performance scores showed significant between group differences for Trail Making A and B tests, the COAST (Word, Interference and Total) and the COWAT. In each of these cases the intervention group performed better than the controls. Performance in the COAST colour test showed a difference between the two groups that almost reached statistical significance ($p=0.056$). Cohen's d effect sizes (derived from the Eta squares provided by the SPSS output – see Section 4.2.12) were moderate to large (Cohen, 1988) for the cognitive outcomes that reached statistical significance.

Table 5.3: ANCOVAs of primary outcome measures

Variable	Mean (sd) Intervention group (n=25)		Mean (sd) Control group (n=23)		EMM difference between groups (I - C)	p value	95% confidence interval of the mean difference		Effect size (d)
	Baseline	Follow-up	Baseline	Follow-up			Lower	Upper	
ANCOVA Tests									
Trail Making Test A (s)	33.7 (11.8)	25.5 (6.3)	30.3 (7.9)	28.2 (8.2)	-4.2	0.024	-7.8	-0.6	0.70
Trail Making Test B (s)	65.8 (21.0)	53.0 (20.3)	69.6 (23.0)	64.6 (17.3)	-9.3	0.037	-17.9	-0.6	0.63
Letter Number Sequences	14.9 (3.0)	16.3 (3.8)	13.7 (3.1)	15.2 (3.0)	0.1	0.908	-1.4	1.6	N/A
COAST_Colour (s)	33.0 (6.4)	29.5 (3.5)	31.9 (5.6)	31.0 (5.4)	-2.2	0.056	-4.4	0.1	N/A
COAST_Word (s)	26.8 (6.4)	23.3 (3.6)	24.5 (4.2)	24.4 (4.0)	-2.1	0.013	-3.8	-0.4	0.77
COAST_Interference (s)	61.3 (13.0)	49.0 (9.5)	65.1 (24.1)	60.5 (25.2)	-8.5	0.002	-13.7	-3.3	0.97
COAST_Total_Time (s)	121.1 (21.9)	101.8 (14.1)	121.5 (30.2)	115.9 (31.4)	-14.3	<0.001	-21.0	-7.6	1.28
COWAT_FAS_Total (s)	42.0 (12.6)	50.0 (16.0)	42.9 (14.2)	45.4 (15.1)	5.2	0.024	0.7	9.7	0.70

Legend: EMM = Estimated marginal mean; COAST = California Older Adult Stroop Test; COWAT = Controlled Word Association Test; s = seconds.

5.6 Effect of a multimodal exercise program on secondary outcomes

Table 5.4 shows the differences in secondary outcome measure scores, between the intervention and control groups, at follow-up, after adjustment for baseline. There were no between group differences for reaction times (simple and choice). The 6MWT and the TUGT show statistically significant differences between the groups. The adjusted data indicates that the intervention group performed better than the controls. Cohen's d effect sizes would be indexed as large for these physical outcome measures (Cohen, 1988).

Table 5.4: ANCOVAs of secondary outcome measures

Variable	Mean (SD) Intervention group (n=25)		Mean (SD) Control group (n=23)		EMM difference between groups (I - C)	p value	95% confidence interval of the mean difference		Effect size (d)
	Baseline	Follow-up	Baseline	Follow-up			Lower	Upper	
ANCOVA Tests									
6 minute walk test (m)	503.9 (93.7)	602.0(67.5)	507.3 (73.6)	488.7 (101.8)	113.1	<0.001	73.2	153.1	1.70
Timed Up & Go (s)	6.6 (1.4)	4.9 (0.7)	6.7 (1.3)	6.7 (1.4)	-1.7	<0.001	-2.3	-1.2	2.04
Simple Reaction Time (Mean - ms)	308.1 (36.3)	297.2 (34.0)	306.1 (33.4)	301.7 (18.6)	-5.1	0.449	-18.6	8.4	N/A
Choice Reaction Time (Mean - ms)	583.0 (86.0)	566.8 (80.0)	565.1 (75.3)	540.2 (61.2)	16.3	0.257	-12.3	45.0	N/A

Legend: EMM = Estimated marginal mean; s= seconds; ms = milliseconds; m = metres.

As stated earlier, the data related to the One-Legged Stance Test and the BDNF levels were not normally distributed, at baseline, and were therefore log transformed prior to analysis. Table 5.5 shows the results of the ANCOVA performed on the log transformed data for the One-Legged Stance Test and the BDNF levels using the log transformed baseline scores as covariates. The log transformed values for both of these secondary outcomes demonstrated a statistically significant difference between the groups. The intervention group performed better than the controls in the test of balance ability (One-Legged Stance Test). BDNF levels show an increase for the intervention group and a decrease for the control group and this difference reached statistical significance.

Table 5.5: ANCOVA with baseline as covariate of log transformed variables

Variable	Mean (SD) Intervention group (n=25)		Mean (SD) Control group (n=23)		p value
	Baseline	Follow-up	Baseline	Follow-up	
ANCOVA Tests					
One-Legged Stance Test (s)	54.9 (50.7)	99.1 (60.8)	22.3 (19.2)	21.9 (21.3)	<0.001*
BDNF (ng/ml)	4.5 (2.2)	5.2 (1.8)	5.6 (1.8)	4.7 (2.4)	0.023*

Legend: *Log transformed data were used in this ANCOVA as the data were not normally distributed; s = seconds.

5.7 Summary

Overall, the results of the present study show that this 16-week multi-modal exercise program had a statistically significant beneficial effect on a number of measures of neurocognitive and physical functioning; as well as circulating blood levels of plasma BDNF. After adjustment for baseline in the ANCOVA, the primary outcome neurocognitive performance scores showed statistically significant between group differences for the following tests of executive function: Trail Making A and B tests (that assess attention, motor function, flexibility of thinking and visual search ability); the COAST (Word, Interference and Total) (tests of inhibition); and the COWAT (a test of verbal fluency). Performance in the COAST colour test showed a difference between the two groups that almost reached statistical significance ($p=0.056$). Cohen's d effect sizes would be indexed as moderate to large for the cognitive outcomes that reached statistical significance (Cohen, 1988). In relation to the secondary outcomes, the adjusted data

show statistically significant differences between the groups in the 6MWT and the TUGT, with the intervention group performing better than the controls. Cohen's *d* effect sizes would be indexed as large for these physical outcomes (Cohen, 1988). The results of the ANCOVA performed on the log transformed data for the One-Legged Stance Test and BDNF levels demonstrated a statistically significant difference between the groups. The intervention group achieved better results for the One-Legged Stance Test and increased BDNF levels, while the control group had decreased BDNF levels.

These effects were elicited in a sample of non-depressed older women (65-75 yrs.) where the intervention and control groups were found to be equivalent in terms of cognitive status (non-impaired), years of education, body mass index, waist-to-hip ratio, heart rate, mean blood pressure and physical activity levels (pedometer-assessed mean daily steps). All of the 25 participants allocated to the intervention group completed at least 85 % of the 32 classes conducted over the 16-week delivery period; follow-up data were collected from the entire intervention group. One of the 24 participants randomised to the control group was lost to follow-up. The following chapter (Chapter 6) details the results of the qualitative component of this study.

Chapter 6: Results – Qualitative study

6.1 Introduction

This chapter details the qualitative results emanating from participant interviews (n=15) that were conducted within two weeks of the completion of the exercise intervention. Data derived from the follow-up focus group are also integrated into this chapter. In general, participants were prompted to describe their subjective experience of the program. Respondents were asked about what aspects they liked or disliked; what changes (if any) they had noticed; whether any changes had been noticed by people around them; and what aspects of the program might have contributed to any changes (see interview questions, Appendix 13). In the focus group some of the key themes extracted from the interviews were presented to the group for verification and elaboration.

Undertaking concurrent data collection and analysis, it was possible to determine when similar codes and categories began to emerge from the interviews. After 12 to 14 interviews it became apparent that no new categories of data were emerging. A final interview was undertaken to confirm this trend. The data were analysed with a view to ascertaining the acceptability and feasibility of the intervention and changes perceived by participants to have arisen as a consequence of the program.

6.2 Acceptability and feasibility of the program

Two major themes emerged from the qualitative data pertaining to the acceptability and feasibility of the program; namely *enjoyment of the program maximised engagement* in the program and *engagement with the program maximised adherence*. Table 6.1 outlines the categories and codes that emerged, related to these first two themes. The next section of this thesis will present the categories and codes that underpin these themes and the direct verbatim quotes from interviews and the focus group to support this analytical structure.

Table 6.1 Themes, categories and codes related to the intervention programme acceptability and feasibility

Theme	Category	Code
Enjoyment of the program maximises engagement	Fun	<ul style="list-style-type: none"> • Use of humour • Age appropriate music- lively/resonant/familiar & evocative of movement • The variety of the exercise format- comprehensive/ not boring • Interactive group environment
	Presence and extent of challenge	<ul style="list-style-type: none"> • Challenging exercises - novelty • Challenging format - complexity • Sufficient but not excessive challenge
	Social safety and cohesion	<ul style="list-style-type: none"> • Lack of judgement • Goodwill
Engagement with the program maximises adherence	Feasibility	<ul style="list-style-type: none"> • Convenience: travel, location, timing • Commitment: overcoming illness, misadventure, variation in motivation; work and family obligations. • Manageability of the exercise: appropriate level and progressions; individualised variations
	Feeling valued	<ul style="list-style-type: none"> • Individual attention/attunement of instructors • Dedication of instructors • Instructors belief in participant's ability • Sense of purpose
	Physical safety	<ul style="list-style-type: none"> • Safe with pre-existing medical conditions • Minimal risk of injury

6.2.1 Enjoyment of the program maximises engagement

Without exception participants expressed highly favourable views of the program as a whole. Two views that capture the general sentiment of the group were, “...I don't honestly believe that you can get...any better program...” (Interviewee 02) and “...I look forward to it [classes], the release, and I never miss one...” (Interviewee 36).

Overall, participants liked the format, content and intensity of the classes and found all aspects manageable. More specifically, a number of key categories emerged from the data that appear to have been pivotal in the likelihood of individuals engaging in the exercise intervention. First

and foremost, the classes were viewed as being enjoyable. The enjoyment factor was largely attributed to the categories of fun, the sense of challenge provided by particular exercises and routines and the cohesive, harmonious and good-natured spirit of the social interactions within the group (see Table 6.1).

Category - Fun

The experience of fun was attributed to components such as the *use of humour* by the instructors; the inclusion of cohort appropriate music; variety in the exercise format; the group format and the interactive nature of the exercise classes. The difference made by the use of humour is represented by the following quotations. Both participants emphasise the fact that light-heartedness generated fun, but not to the detriment of the formal purpose of the exercises. They articulate an awareness that tangible training is embedded within the atmosphere of levity. For example, one participant said, “... *great fun. Two words... just magic. From the minute you get there you’re relaxed...you know it’s going to be fun...they (instructors) just keep that level of its ‘fun to do’ sort of thing, but in the background they’re really training my body and my brain*” (Interviewee 31). Another agreed, “...*they (instructors) keep it fun. It’s serious in that we know we’re doing good stuff for ourselves. But it’s not so serious it becomes a chore. It’s fun (...)*” (Interviewee 27).

Humour it seems, can transform the experience of exercise, so that is not a chore. Furthermore, for some, the fun generated by a humorous approach can make it feel like not really being engaged in exercise. For example, “...*they’re so witty. They’re so funny, they make you laugh and that just makes (...) it so enjoyable, light-hearted and you don’t feel as though you are doing exercise because they make it that it’s just so much fun*” (Interviewee 36).

In relation to the *music*, participants reported that they found the music to be appropriate and familiar, “...*it’s the right sort of music for our age...*” (Interviewee 20) and “...*very good pop music very much from our younger years*” (Interviewee 25). For others it was also evocative, because it was uplifting and engendered feelings of joy, pleasure and enthusiasm. “*I just loved the music and the exercises*” (Interviewee 33); “*I’ve always loved dancing, I love music and dancing and of course we get both at the exercise program, which is just wonderful*” (Interviewee 36). In addition, some noted that the appeal of this cohort-referenced music predisposed them to movement, “...*I think because you feel it, you want to dance. So it makes it easier to move (...)*” (Interviewee 25). It was also distracting in a way that facilitated additional effort. As observed by one participant “*(...) every class the whole time was fun and*

... the music (...) was good. I'd be able to push myself with it because the music was distracting" (Interviewee 31). The notion of distraction here appears to pertain to mental or emotional engagement with the music. The implication is that the right music – lively, enjoyable, resonant music - can engender the impetus to strive or persist because it evokes a more appealing experience (for some), than engagement with the feelings evoked by effortful exercise.

The qualitative data suggest that enjoyment was also promoted by the *variety in the exercise program*. The broad array of exercises and exercise modalities meant that there was something in the program content for everyone. Each of the exercise categories were nominated, by more than one individual, as their favourite aspect of the exercise format. Some participants enjoyed the comprehensive nature of the program.

I think they're all important aspects. I think... like getting the heart rate up each week ... [it] is very important. I think the other exercises that we do including the floor exercises, the wall exercises, the ball, the coordination, hand, eye coordination, the whole lot, it's a whole package. So it's not just one thing that I enjoy. I enjoy the whole lot (Interviewee 32).

A comprehensive 'broad spectrum' approach, reflected in the provision of variety, was also viewed as an important principle in how exercise should be undertaken.

... they engage in a variety of exercises, it's just not cardiovascular and it's a mixture, so you've got your cardiovascular, which is great to get the heart going, but there's also the strength training, like the weights and the balance training and then of course, the stretching. So it encompasses a broad spectrum and I feel that all of those things are important, I don't think you can concentrate on any one really (Interviewee 43).

The inclusion of variety was also engaging and enjoyable seemingly because it was perceived as being time efficient, convenient and value added.

This is what I think Sue has done with her program; she's looked at it as a holistic type of exercise, whereas if you go to a yoga class then you've got to go to a cardiovascular class and then you've got to go to strength training or a weight training class, usually you find those as separate entities. Whereas with Sue, I feel that she's tried in a limited amount of time to incorporate all of those things into the one class, which means we're getting four classes in one (Interviewee 43).

An additional and less emphasised code associated with the experience of fun, was the fact that exercise was conducted in the form of a *group format* which enabled social interaction while exercise was being undertaken. Fun was derived from “... *being surrounded by other people*” (Interviewee 31) and the sense of “... *good company*” (Interviewee 02). Above and beyond the fun of exercising in an interactive group (as distinct from exercising alone or in parallel with others with no emphasis on, or facilitation of, interaction); there was another dimension of group participation that promoted enjoyment. This facet pertained more to the nature of group dynamics and group culture; this aspect of the data will be examined and elaborated under the category of social safety and cohesion.

Category – Challenge

The codes that emerged in relation to enjoyment generated by the presence and extent of challenge in the exercise program included: a sense of challenge provided by the exercises themselves, the exercise format; and the degree of challenge imposed by either the exercise intervention or the expectations of the instructors. The experience of challenge in the exercise program was largely stimulated by the instructors applying variation of pace and intensity, multi-tasking or distraction to particular exercises (e.g., fitness boxing) and drills (e.g., ball routines). This design was intended to produce challenge through the experience of movement-based complexity and novelty. The experience of novelty (newness) for some was inherent in the exercise itself and the enjoyment factor is quite evident. For example, “(...) *I'm 65 and I've never done boxing in my life and I didn't think I'd like it. Well, I love it*” (Interviewee 20). In relation to pace and intensity, “... *[boxing] gives you a real workout and you can really get going;*” (Interviewee 25) and, “...*the ball work. [Bouncing balls] against the walls, the quickness of it. I loved the quickness of it*” (Interviewee 47).

The exercise format sometimes required extra resources from participants (i.e. challenge through complexity) as reflected in the following quotations: “*No, we don't do the same thing every week, no. She changes it all the time. Then you've got to concentrate on what you're doing or you get left behind*” (Interviewee 13); and “... *we don't just box. She calls numbers and then we have to count how many - or stop and then do five and stop and do one* (Interviewee 27). Also, “... *with the cardio we do, you don't know what she's going to do. You don't know what she's going to say next. So you can't learn it. You can learn the individual steps, (...) you can learn the arm movements, but you don't know what combination she's going to tell you to do*” (Interviewee 27).

Overall the presence of challenge seemed to create enjoyment because it evoked a feeling of energy, the experience of vigour and skills acquisition or improvement that promoted a feeling of attainment and mastery. Importantly, the level of challenge was regarded as sufficient to stimulate these attributes and not so onerous as to be confronting or de-motivating. As one respondent remarked, *"I never felt pushed. Sue always said look, if you don't feel comfortable with something just don't do it"* (Interviewee 10). The level of challenge was introduced in successive approximations and this facilitated the acquisition of skills that were either new or represented a level somewhat beyond the participant's perceived ability. One of the participants said, *"Initially when I first went I thought, oh I was feeling really tired after the first one, but the way that Sue has got it structured, she only taught us a little bit at a time and we only did what we felt we could do"* (Interviewee 32). Another significant factor, in challenge not being experienced as excessive, was that the level was not substantially externally imposed by the instructors. Rather, participants were encouraged to set their own level of exertion or engagement: *"You increase at your level"* (Interviewee 32). Furthermore, differences in ability were actively normalised by the instructors, *"So everybody has a different level in the class and everybody works to their own level"* (Interviewee 32). This strategy was intended to reduce the prospect of participants inadvertently imposing excessive demands on themselves, by comparing their performance to that of more proficient others. Overall, the inclusion of appropriately calibrated and individualised elements of challenge in the intervention was not only enjoyable, but essentially motivating and invigorating.

Category – Social safety and cohesion

Within the category of social safety and cohesion a number of codes appeared to contribute to individuals engaging in the program, as a function of enjoyment. These categories appear to pertain to notions of an atmosphere of low interpersonal risk or threat (e.g., of embarrassment, alienation or criticism); and strong, harmonious ties, within the group (cohesiveness). The data imply that the attitude of the instructors and the group as a whole was supportive and inclusive, and importantly, non-judgemental. The perceived lack of judgement appeared to encourage a willingness to attempt new tasks and movements. Participants reported a feeling of interpersonal safety which enabled them to engage actively in the classes rather than being immobilised by the fear of failure or criticism. One participant, reflecting on the attitude of the instructors said, *"I think it's the atmosphere, because it doesn't matter if we do something wrong. No one's going to growl at us... So we feel safe (...). They make it - they're not - how can I explain it? They're not judgemental, right? They don't - you don't feel as if you do something wrong, you're in trouble"* (Interviewee 27). Another

individual spoke about her pre-existing worry about the possibility of public humiliation in classes. This participant directly linked her enjoyment of and engagement with the intervention, to the lack of judgement. *"You know you're not going to be embarrassed (...) you know it's going to be fun. Your mind just doesn't go to [worrying about] making a fool of yourself which is absolutely excellent. It's something I was really nervous to do, I thought oh I'll make a fool of myself in front [of the other people in the class] - but no"* (Interviewee 31).

The lack of judgement seemed to coalesce with a second code, the overarching attitude of goodwill within the group. Participants described this benevolence in various ways, *"...the ladies are really lovely and everybody supports one another. They are all very caring"* (Interviewee 32); *"... it was a lovely mix of people"* (Interviewee 28); and, in particular, *"...I just wasn't afraid of being laughed at"* (Interviewee 31). The goodwill also extended, it seems, to openness towards playfulness which is echoed in the following statement. *"We might throw in a bit of Nutbush (a dance performed to Tina Turner's song "Nutmash City Limits"). Oh you should see us doing that. Geez, we're good (laughs)"* (Interviewee 27). This category of social safety and cohesion, in combination with the aforementioned categories of fun and challenge contributed to the maximisation of the exercise intervention's enjoyment. Cleary (as highlighted by the comments of Interviewee 31 above) some codes, such as the lack of judgement, overlap with both themes of enjoyment and engagement. With this in mind, the next section of this document considers categories and the related factors that more particularly appear to contribute to engagement in the program, and adherence.

6.2.2 Engagement with the program maximises adherence

Category - Feasibility

The feasibility of the program was considered along three lines: (i) could the participants get to classes; (ii) could they maintain their commitment in the face of competing claims and variation in levels of motivation; and (iii) could they manage the exercise program. The code of *convenience* refers to aspects such as the convenience of the time of day that classes were held and the convenience of travel requirements. For a minority of participants this was an issue. For example, a couple of the participants noted, *"I enjoyed it all, apart from the driving down there and driving back because I live up this end of town. So it takes a big chunk out of your day, but that's okay"* (Interviewee 28) and, *"[The least enjoyable element was] the travelling, I have to go to Robina"* (Interviewee 31). Nevertheless, these two participants still fulfilled the requested 85% attendance rate. They, like several of the women in the study,

demonstrated unerring commitment to the program, despite encountering contrary circumstances.

The code of *commitment* refers to maintenance of commitment in the face of a variety of circumstances including, unexpected illness, family and work commitments, misadventure and/or waning motivation. As would be expected some of these circumstances arose. For example,

Through those 16 weeks, I've had a lot of setbacks which I didn't think I would have had at the beginning. This is just with... [my husband]. He's been in hospital seven times since September and has a lot of problems". (...) Also I work and they don't call me for ages and then as soon as I start the class, work, work, work, work (Interviewee 33).

However, participants in some instances went to great lengths to organise contingencies to ensure attendance. As one participant said, *"I have a busy lifestyle (...) but [the exercise class] is one of my priorities - well it is my priority"* (Interviewee 10).

A number of the participants reflected on how a commitment to the exercise program strengthened other commitments:

You can't just let yourself get lazier and lazier and lazier. It's too easy to just fall into a habit of doing nothing or doing as little as possible (...) ... but I know now that [because of the program] I will get back into my routine and get back to work (...) and I will be motivated again to get on with my work (Interviewee 28).

Another participant implied that a largely externally driven sense of commitment (a sense of loyalty to the researcher) was ultimately transformed into an internal source of motivation and commitment. As she perceived positive change from engagement in the program, there was a 'snowball' effect. Engagement began to be propelled more by commitment to herself and to furthering or maintaining improvements. In turn, this seemed to have a direct effect on sustaining ongoing engagement with the exercise program itself,

I enjoy the commitment in a way because I tend to be a bit lazy. I might start something and I think oh, if I don't have to go today I won't; but, you see, I wouldn't let her [researcher] down. So it makes me keep coming [laughs]. So that's been a good thing in a way. Once you have done that many weeks then you're into the routine of it anyway, so it's not a problem to keep it going; or you want to because you've reached a point where the difference is there, and that makes you want to keep going (Interviewee 10).

The final aspect of feasibility relevant to this study was whether the participants were able to contend with all of the elements of the program (the manageability of the exercise program). The key concepts here were that participants found that the exercises and routines did not unduly exceed their abilities. Further, they were aware of pace and intensity levels gradually increasing, but felt that they could accommodate these progressions. In the words of two of the participants, (...) *as we're getting towards the end, the music goes faster. She doesn't think we notice but we notice*" (Interviewee 20) and "(...) *they were really (...) good exercises but not too difficult*" (Interviewee 43).

In particular, participants mentioned feeling they were not under pressure to perform anything they were uncomfortable with, and that the provision of individual variations was instrumental to the experience of manageability. *"Sue and Fran both emphasised it didn't matter if you couldn't do it (...) it was having that laid back attitude ..."* (Interviewee 31) and *"(...) there was nothing that really I thought could be doing me more harm than good. If there was something I was a little bit doubtful of (...) Sue understood that, (...) - and that was good, that made me more confident too that I could do all of this, it wasn't going to cause anything that wasn't quite right, to be worse"* (Interviewee 43). Moreover, *"(...) they [the instructors] really do help you. They will stop and they will help you and that's wonderful and you feel good then because you know you are keeping up with the others"* (Interviewee 45).

Category – Feeling valued

The sentiment of feeling valued in the group was one of the strongest categories to emerge in relation to the manifestations of engagement and adherence in this study. Participants highlighted the importance and significance of receiving *individual attention* and the attunement of the instructors to their needs. *"They supported us all the way ... if we couldn't do something they gave us individual encouragement and programs"* (Interviewee 02). Two additional codes related to engagement and adherence were the perceived dedication of the instructors and the instructor's apparent belief in the participants' abilities. One respondent summarised the spirit of the relevant feedback when she said *"(...) it's just the fact that their dedication and their beliefs and the fact that it's real, they are doing this because it's meaningful to them and you can feel that. It's not just like it's a job, they believe that this is something that's going to benefit all of us greatly."* (Interviewee 43) Another participant said, *"(...) you look at them and you know that they're doing that for us..."* (Interviewee 47).

A poignant view related to feeling valued, was particularly articulated and emphasised in the course of the focus group. This code is best described as a *sense of purpose*. At the individual level and as expressed in the interviews, some felt that the exercise classes were enjoyable because they gave purpose to their week, “... *just to get out twice a week is wonderful for me*” (Interviewee 47). Others placed value on the fact that attending the classes contributed something specific to their personal needs and reserves. One woman said that [the classes were] “(...) *something for me. Something I'm doing for me*” (Interviewee 27). In the focus group several participants spoke about their experience of feeling that with age they had lost a role and significance in their broader families resulting in a diminishment of their overall sense of having a contribution to make in life. Involvement in this research project for many of the women engendered a feeling they still had something valuable to contribute to science, others and life. One focus group member summarised her view in this way, “(...) *our children are busy with their own families and you kind of feel like you have nothing to contribute. We don't really have a role...but this has helped us feel like we are capable and that we are helping people by being in this study...so we do have something important to contribute...*” (Focus group - interviewee 25).

Category – Safety

A final category that emerged in relation to engagement and the maximisation of adherence was that of physical safety. Participants articulated that they felt safe undertaking the exercise content in the program even with pre-existing medical conditions. Several respondents also commented on the experience of feeling that the program was designed and conducted in a way that minimised the risk of injury. These codes are reflected in the following quotations:

Well walking anywhere has previously been a problem because of my feet and the pain, (...) but with the aerobics [part of the] class I was able to discover a far greater depth of things that I could do with my feet and therefore with the rest of me (...) I found that very helpful and my feet don't hurt near as much (Interviewee 02).

and; “*Sue's always been very careful and mindful of our safety (...) it's better to have it slower and get there, than to do some damage faster.*” (Interviewee 43) Finally;

They both - they remembered the problem I had. I said I can't get up [and down onto mats] and (...) the minute it was time to get up, I wouldn't have to look around, they'd both be there. Just watching, just in case I needed help, they would help me up the first couple of weeks and that. But then when I have the chair and start doing it with the chair, they'd still know that I'd be - they'd be

*there or they were looking after other people and they'd be there.
That was just magic* (Interviewee 31).

Lastly, as an adjunct to indexing the acceptability and feasibility of the intervention, interviewees were asked to nominate aspects of the program that they least enjoyed. In the main, respondents could not identify aspects of the program they had not enjoyed. However, when pressed participants were able to nominate balance training and 'getting up and down from the floor' as aspects they considered to be ultimately manageable and worthwhile, but also, less enjoyable. In addition, "*...balancing is a bit hard, so you're not quite as happy to do it, but you do. Eventually it just becomes – you don't think about it anymore...*" (Interviewee 10) and "*...the getting up and getting down [off floor mats]...it's good. It's a bit like medicine; you know it's good for you but you don't want to take it...*" (Interviewee 27).

As a reflection of the degree of satisfaction with the program, a number of respondents expressed their desire to see the classes continue beyond the intervention period. As three participants indicated, "*...it's been very, very, beneficial. In fact, I don't know anybody [participants] who doesn't want to continue doing it...*" (Interviewee 10); (...) *[I] would be devastated if it [the classes] stopped, [I] really would be...*" (Interviewee 36); and "*...we'll pay to come because I'm just not going to go back to the way I was...*" (Interviewee 20).

In summary, enjoyment of the program (as a result of having fun, being challenged but in a safe manner and being in a cohesive social setting) led to engagement. While for some people the engagement took a while to materialise, once they engaged they became very motivated, in turn, this maximised adherence to the program. Given that all the participants completed the program the next aspect of the qualitative interviews explored the participants' perceptions of the ways in which their physical and cognitive functioning changed over the 16 weeks. The participants' perceptions about how they were physically and cognitively at the beginning of the study, and the differences at the end or along the way, are examined in the next section of this document. Section 6.3 presents the qualitative data related to change as a consequence of the study intervention.

6.3 Change as a consequence of the program

Only one theme emerged from the data related to *changes perceived to be a consequence of the program*. This was '*improved mental and physical functions*'. Data related to changes in cognitive functions are the first of six categories presented. Table 6.2 presents the codes and categories for this theme.

Table 6.2: Themes, categories and codes related to change as a consequence of the program

Theme	Category	Code
Improved mental and physical functions	Improved cognitive functions	<ul style="list-style-type: none"> • Memory • Focus (of attention)/concentration
	Improved mental outlook	<ul style="list-style-type: none"> • Confidence • Optimism • Mood • Motivation
	Increased energy and vitality	<ul style="list-style-type: none"> • Cardiovascular fitness and stamina
	Improved mobility and strength	<ul style="list-style-type: none"> • Strength • Agility/nimbleness • Falls reduction
	Reduction of symptoms related to pre-existing conditions	<ul style="list-style-type: none"> • Pain • Sleep • Symptoms particular to specific diagnoses- e.g. Diabetes Mellitus, Meniere's disease, fibromyalgia • Being overweight
	Elusive concept – something is different	<ul style="list-style-type: none"> • “Can’t put a finger on it...” ? aliveness

Category - Improved cognitive functions

Two codes emerged from the category of changes pertaining to cognitive functions; namely, *memory* and *focus* (of attention) or *concentration*. To some degree there were mixed reports about memory ability. Some said they could retain more in memory; (...) *if I read something I can retain it* (Interviewee 45) and “(...) *I seem to be able to retain memory*” (Interviewee 20). Some gave specific instances of better memory in day-to-day life such as, “*I used to have to have a shopping list (...) now; I don't need a shopping list*. Interviewer: *That's a big change*. Interviewee: *Yeah, I think it is. I just feel I've got confidence back in my ability to think whereas before I didn't trust myself, so I'd write myself notes*” (Interviewee 20).

One particular participant elaborated further and seemed to be reporting improvements in her ability to encode, retain in and retrieve from memory:

I noticed it about a month ago that I was retaining and I could remember things. Normally, when I was younger I had a very good memory and I could remember numbers and phone numbers (...) and I was losing that, but now it's come back. [So] I'm more sociable. It makes you... you don't feel a fool, like [you do when] your mind goes blank (Interviewee 45)

Another respondent, in detailing her experience of memory changes, also made reference to a perceived improvement in problem solving. In her words:

Even the mental part - now I do (...) puzzles, crosswords, (...) and problems and I can solve them. (...) Now I can think of a word, and I can get it 'there and then', whereas before I'd have to think about, now, what was I going to say then? It really has helped me that way. I'd go into a room and think, what have I come in here for? Now I don't do that (Interviewee 47).

In contrast, another participant had not noticed any particular change related to memory. Her comment was “(...) I don't know whether I could say that it gets any better [memory]. I still have those gaps when I should know that person's name and I can't remember. So I don't know, I mean I think that probably takes a little bit longer” (Interviewee 43).

A second code that was frequently mentioned was better *focus* (of attention) and *concentration*. The manifestation of this improvement included the ability to “(...) really hone in on one thing and focus better” (Interviewee 27); to ignore distraction, “(...) I can really focus on what I'm doing. I can actually hear all these conversations going on around me, but they're not distracting me (...)” (Interviewee 27); and to exercise impulse control, “(...) now I'll focus and make sure that I don't get distracted by other things. To me that's my type of focus (...). I'll say no, I've got to do this and I'll stop myself thinking (...), just go and do something that's fun” (Interviewee 31). For others, changes in the ability to concentrate took the form of being able to concentrate for longer. One participant first noticed this change in the context of the exercise class;

One big thing that I've found is concentration, I can more stare at a spot on the floor and do what I'm asked to do [e.g. balancing] and do right to the full, whereas before, I couldn't; the concentration would be there [only] for a while (Interviewee 47).

Better focus and concentration was also credited with improvements in coordination by this participant, who said “(...) my coordination I found, I'm not too good. Then I found I do have that; like, after the four months (...) at first I was dropping the balls, but then I found by

focusing (...) it was bringing back all of that" (Interviewee 31). A number of participants also outlined their impressions of what parts of the intervention may have contributed to the acquisition of better focus of attention. Factors mentioned included the multifaceted nature of the exercise routines and the pace of switching between movements:

(...) you really have to focus [in the exercise classes], because some of the things she does; it's a little bit like patting your head and rubbing your belly at the same time (...) we do cardio (...) [and] she keeps the mind going at the same time, because she changes things all the time. So we've really got to focus, because she could go from one thing to another very quickly (Interviewee 27).

This included the sustained attention required to follow routines that were randomly cued, *"(...) we don't do the same thing every week (...). She changes it all the time. (...) you've got to concentrate on what you're doing or you get left behind;* (Interviewee 13) or delivered in the presence of deliberate distraction, as articulated in the following quotation,

When we were doing the boxing, Sue was calling out numbers. We had to do four or five or whatever. Then Fran came over, and she's shouting out a different lot of numbers. I had to really focus on what Sue was saying. Yeah, I got through it, but Fran's shouting out all these other numbers. It's like all these things going on at once (...) it's got to help with driving and all that sort of thing, because you've got to be able to focus (Interviewee 27).

In addition to the changes reported in relation to cognitive or mental processes, there was also a significant amount of qualitative data indicating noticeable change related to mental outlook.

Category - Improved mental outlook

A second category related to the theme of enhanced mental function is the notion of an *improved mental outlook*. The codes incorporated in this category include changes in *confidence, optimism, mood* and *motivation*. There were quite emphatic accounts of shifts in personal confidence. Enhanced confidence seemed to underpin some women's burgeoning ability to variously advocate for themselves; assert boundaries and limits; and to feel more self-assured about their own capabilities; *"(...) [To] sum it up I suppose [increased] confidence (...) confidence is a big thing - confidence in my own ability. I've always been a very confident person, but I think since I've retired, I've kind of lost that. I feel as if I'm now back to where I was, before I left work. It's that confidence is back again"* (Interviewee 27). Another participant said, *"...now I feel that nothing, and I really mean this, nothing can stop me from doing*

anything I want to do. Nothing can put a barrier up any longer to not being able to do it, whether it's physical [or] mental” (Interviewee 47).

In quite a poignant articulation of the perception of enhanced confidence enabling self-advocacy and limit-setting, this participant said,

Well, I was always letting other people use me, I never said no. I always did for others, I really did (...) I've stopped and I've said to myself, it's my time, I'm 70 now, I need to have a life, because I got married when I was 17, so I didn't have a life. Now I've got a life and now I'm starting to say, no I'm sorry I can't do that, whereas before I would have made myself ill keeping up with looking after and worrying for other people. I don't do that now (Interviewee 47).

A feeling of greater *optimism* arising from the experience of the intervention is implied in a number of comments. This participant touched on a number of changes including a more positive outlook; *“(...) my reaction time is definitely faster and funny enough I don't seem to worry about things quite so much. I seem to be prioritising and focusing differently on the more positive aspect of things” (Interviewee 02).* Other participants variously described the perception of enhanced optimism (...) in the following terms; *“(...) I feel like I am a more positive person because of it, I feel very empowered because I have been given abilities that I didn't realise I had before and I have been encouraged to be positive as well” (Interviewee 02);* and, *“(...) [I'm] feeling fitter, stronger, [and] more positive in life [and] attitude (...) (Interviewee 47).*

A third code pertinent to the category of improved mental outlook was an elevation in *mood*. Some participants said they were; *“(...) maybe a bit more alert, (...) [and] I just feel brighter and maybe happier, maybe a little bit happier” (Interviewee 36).* Others attributed improvements in the manageability of their depression to their experience of the intervention; *“(...) I suffer from depression. I'm on medication. I was taking 60 milligram, and I made the decision with my doctor to cut down to 30 (...) [now] I'm just steady on the 30” (Interviewee 27).*

The fourth and final code relevant to improvements in the mental outlook of participants was the perception of change in levels of *motivation*. Improved motivation was observed in relation to work and involvement in life generally. For one particular interviewee greater motivation was attributed to the energy and invigoration derived from participation in the exercise program; *“(...) I work from home, I write and I've always been very self-motivated.*

Over this last 12 months, up until I started the exercise, all that just slipped away. I've done very little work and now I feel... well now I'm motivated to get back, not only into exercising but into working again" (Interviewee 28). Another participant reflected on what she believed to be a decline in motivation that, in her view, might accompany the ageing process; *"(...) I didn't expect, with ageing, ...that you would lose some of your motivation, you've got to really hang on to it and I found that I'm not having to concentrate so much at hanging on to that now. I think exercise helps your motivation to do things"* (Interviewee 43). The link with better energy levels was expressed in the following way; *"(...) now I can enjoy shopping again, because it's just that when you feel that the energy's flowing through your body better, you just feel more energised, more invigorated. That of course helps the motivation"* (Interviewee 43).

The previous quotation is an example of the overlap apparent in some of the codes, categories and themes that characterise the qualitative data. This participant not only explicated her experience of changes in motivation levels, but also highlighted the nexus between this code and the experience of greater energy and invigoration. Increases in energy and vitality emerged as a third category tendered by participants to explain the improvements they observed in their mental and physical function.

Category - Increased energy and vitality

Increases in *energy* and *vitality* emerged as a distinct category of changes reported in relation to improvements in mental and physical functioning. There was only one code deemed relevant to this category and that was *cardiovascular fitness and stamina*. Participants generally described a better ability to walk further or faster and to run up stairs in a way that either wasn't possible previously. They may have been previously encumbered by breathlessness (lack of cardiovascular/ aerobic capacity). The changes described in the following quotation were apparent to both the participant and to a member of her family. The example identifies a clear contrast between prior and subsequent cardiovascular fitness. *"Well my son took me for the walk on the beach on Monday and he couldn't believe that I hadn't really gone on the beach for, like a year. He noticed [because] normally (...) I can't keep up to him [this week] he noticed the difference in my pace"* (Interviewee 31).

For others reporting more energy and vitality, better fitness meant that *"(...) now I can run up the stairs. It's very good. I can get up and down and I can move"* (Interviewee 45) and *"I used to walk maybe, what, three days a week, now I will walk five days a week, early in the morning and I can walk faster and fitter and you don't get puffed out"* (Interviewee 45). Another

respondent said, *“Walking and shopping and things like that, I am walking in the park more for instance, down the road. Walking around the house and standing for long periods of time, I couldn’t do that at all before”* (Interviewee 02). This example exemplifies a number of interwoven improvements that were echoed in the qualitative data. For this participant and others, improved physical and mental functioning was associated with enhanced levels of vitality and energy underpinned by better cardiovascular fitness, a capacity for sustained periods of movement and physical exertion (stamina) and in some cases, new abilities that enabled a greater capacity to successfully engage in activities of daily living. A fourth category of change reported by study participants in relation to physical and mental functioning was improved mobility.

Category - Improved mobility and strength

Three specific codes provided detail to the category of improved mobility as a function of the exercise program. Firstly, a number of participants expressed improvements in *strength*, *“(…) well I know I can get up out of a chair a lot more easily”* (Interviewee 33) and,

(…) today my husband was putting a new tap on and he couldn't get the screw underneath. I just got in there and I tugged away at those screws and like he said, I'm stronger than even he is. He's always said that he's strong, but it's given me enough strength to do things. Yeah, I can lift and I've done everything around the home. Where my husband couldn't do it now, I can do that. I feel so proud of myself (Interviewee 47).

Improved strength was also highlighted in this participant’s comments,

(…) my husband was cleaning up the garage and he's (...) up the ladder, and there was big box of really heavy stuff from the caravan - jacks and things like that. I said I'll pass it up to you. He said don't, you can't lift that. It's too heavy. So I said hang on, let me have a feel. I went yeah okay, there you go. I just seem to have more strength. I pulled [in] the tummy, engaged the abs (Interviewee 27).

Generally, participants observed improved upper leg strength, which was reflected in the ability to either get down and up from the floor more proficiently (or for the first time in years) and to get up and down from a chair using leg strength alone, without upper body leverage.

Secondly, the study participants also reported greater *agility* or *nimbleness*,

I used to just sit down and forget it and say I can't do this, this is too much for me, but now I 'do'. Now I'm - well my husband says,

you're forever moving, love. (...) I have the music on, I'm always moving around, I'm always dancing; I'm always wriggling my body at home. Yeah, I do it all the time and my husband just sits there in amazement, he can't believe that I'm so agile (Interviewee 47).

and *"I just seem to be more nimble on my feet"* (Interviewee 27). This code of *agility* was quite pronounced in the interview data and was mentioned in conjunction with a number of other changes such as, *"I'm more confident, more agile, and more focussed towards where my life is going"* (Interviewee 47) and *"I can walk more [and] faster. I can get down on the floor, which I couldn't do before... then easily get up, that was the hard part. [I'm] more agile, up and down the stairs"* (Int. 13). The same code was also referred to with reference to changes in the speed of movement generally, (...) *"They [my movements] are a lot quicker and I can move around a lot better"*. (Interviewee 13) and *"(...) it's a control of movement (...) I can move - I can kind of move my feet quicker"* (Interviewee 27).

The third mobility related code, *falls reduction*, was also highlighted by a number of participants. For instance, *"(...) now I have learnt to pick up my feet (...) my feet are more accurate now where I am going. (...) Last year I was tripping over things, this year even if (...) I do trip over them [things housemates leave lying around] I have immediate recovery and immediate re-balancing and no problems; I'm not hitting the ground anymore"* (Interviewee 02); and *"(...)we were doing the garage and I'm trying to tiptoe through all the stuff all over the floor. I did do a little bit of a trip, but I didn't fall. So yes, I'm sure it's helped* (Interviewee 27). Improvements in mobility appeared to have direct effects on people's ability to avoid tripping and falling. In turn, this engendered a renewed confidence and willingness to engage in previously relinquished activities. For instance:

(...) I had to stop in the last year going on the beach [because of fear of falling after a number of falls]. I hadn't been in swimming and I love to swim and surf and that. (...)Last Monday, I went on the beach and I went for a three-quarter of an hour walk and then I went in for a swim. That was something! (Interviewee 31).

The last comment captures the value placed on this aspect of mobility enhancement, particularly for those with a history of falling; *"... after the fall I always had this fear of falling, so I didn't wear high heel shoes and I was just always very cautious. That fear has completely gone. I wondered whether it would ever go (...) I feel quite stable, and that's huge. It really is."* (Interviewee 10) As an interesting anecdote, one of the participants talked about when she first noticed mobility changes related to this particular code:

(...) it must have been about six weeks into the exercise [program] and I had my whole family over for dinner. (...) the new little dog (...) shot across in front of my feet. I put my foot out, landed safely, did little running steps and came up with my glass of wine still in my hand. Everybody cheered. I think it was the glass of wine that impressed them (...) I hadn't spilt it (Interviewee 28).

Finally, a quote that perhaps goes to the heart of the whole category of mobility enhancement was contributed by a participant with, among other things, significant proprioception (the perception of limb position and movement relative to the rest of the body (Jones & Rose, 2005) problems and foot numbness.

(...) I had a severe car accident back in 1993 and I was told by all the specialists (...) that I would end up in a wheel chair. (...) Basically working with Sue and Fran I think well... I seriously doubt it now because they have given me the skills to do things I that I couldn't do before. There are still things that I can't do but I feel I can fight back now and overcome it. I have overcome a lot of those [mobility] problems I had (Interviewee 02).

The beneficial outcomes attributed to participation in the exercise program by this individual, make a distinct reference to better mobility. The spirit of this quotation also alludes to the next category derived from the qualitative data pertaining to mental and physical functioning. That is, the reduction of symptoms from pre-existing conditions.

Category - Reduction of symptoms from pre-existing conditions

As would be expected in people aged between 65 and 75 years, many of the participants entered the study with pre-existing conditions. None of the conditions precluded them from eligibility. However, in many instances the associated symptoms had a considerable deleterious effect on aspects of daily living and an overall sense of wellbeing and ability. The codes relevant to this category involve the experience of *pain, sleep, specific diagnoses* and *being overweight*.

Within the code distinguished as *pain*, two notions emerged as changes considered elicited by the exercise program. On the one hand participants with diagnosed conditions reported the absence of pain after exercise:

Interviewee: I find that a lot of my aches and pains have disappeared. I had a bad hip. I can get up and down the stairs easy.

Interviewer: A lot of people would think that if you had a sore hip you shouldn't exercise, but yours has got better with it?

Interviewee: *Oh yes. I haven't had a lot of pain. I haven't had pain,*
(Interviewee 13).

Conversely, a number of individuals reported diminishment in the severity of their pre-existing symptoms. One of the participants expressed it this way; *"(...) I never ever came away (...) feeling worse than when I came [and] (...) if I had a pain in the hip or something it never got worse, it was better, so it was good"* (Interviewee 43) and for some, this was attributed to increases in strength, *"(...) I don't get pain in my neck as much as I used to. It [the resistance training] has really strengthened my neck. Yeah, I don't get all that"* (Interviewee 47).

Changes in *sleep* patterns were also noticed by the participants and for this code the key issue was the spontaneous manifestation of more sleep. One participant simply said, *"(...) before [the exercise program] I would be awake at 4:00 pacing the house. I don't do that anymore,"* (Interviewee 20) and another elaborated more specifically on her experience; *"(...) before [the exercise program] I would get four hours sleep and that would be it, no more. But now I do (...) I get probably about six or seven hours sleep a night and I put that down to the exercises because you want to do more, so you are doing more things. Instead of sitting down, you are getting up and doing things"* (Interviewee 45).

Within the code of *pre-existing conditions* a number of beneficial changes were reported by the participants and these improvements were attributed, by them, to the effects of the exercise program. For example, there appeared to be quite pronounced effects on the status of the diagnosis of Type II Diabetes Mellitus (T2DM) as instanced by the following two descriptions. *"(...) [I was having] diabetes complications where your mouth dries out, you get giddy and you have all these complications. Since about after the first six weeks of the cardio aerobics classes this has eased right back, I haven't had that since then"* (Interviewee 02). In fact, this participant's blood sugar indices improved to the point where, during the course of the intervention study, she no longer met the criteria for T2DM. At interview she said *"(...) 'I'm starting to feel like what it's like again to have muscles and to have balance and to feel positive and it has just totally changed it and then losing the diabetes pretty much 'like that', it has been a miracle for me, the whole thing actually"* (Interviewee 02).

At the beginning of the exercise program this participant consulted a diabetes educator for the first time;

Interviewee: *(...) the diabetic educator (...) saw me when I was not well and I was really not well - very lethargic, very tired because that's how diabetics feel if they're not*

managing and my diabetes was spiking (...) I had to go back to her (...) and she said, you look so well (...) what are you doing? Someone else noticed. Now I haven't had a spike for about a month (...).

Interviewer: *Are you on medication?*

Interviewee: *Yes, but that didn't seem to matter. I was still spiking.*

Interviewer: *Yeah, but not anymore?*

Interviewee: *No. (Interviewee 20)*

Other medical conditions that were mentioned in the context of symptom reduction included hypertension, Meniere's Disease, forms of peripheral neuropathy associated with impaired proprioception, arthritis, bursitis and fibromyalgia. In the case of Meniere's Disease, balance training that includes walking in a straight line, 'heel to toe' (a component of the study exercise program), can represent a particular challenge, as echoed in the following account "(...) *Walking the straight line... At the beginning I couldn't do that because I have Meniere's and you can lose your balance (...).*" (Interviewee 45) After 16 weeks the same participant said "*I can do that [balance exercise] now, very well.*" (Interviewee 45) For those with pre-existing proprioception deficits, there were noticeable gains in terms of balance, agility and coordination. Individuals with arthritis observed they were experiencing less joint stiffness and pain, "(...) *I don't get pain in my neck as much as I used to*" (Interviewee 47).

As an additional index of perceived exercise-induced symptom reduction, this same participant spoke about previously feeling immobilised by the symptoms of fibromyalgia. She ultimately learnt (during the course of the program) that initial discomfort with movement 'faded away' with low intensity persistence. Applying that learning, she was able to complete the classes without ill effects and to incorporate that principle into daily life:

(...) because I've got fibromyalgia, whereas before I would sit down, because I was hurting so much, I'd sit down and put my legs up and feel sorry for myself and I really do stress, feel sorry for myself. Now I don't. Now I get up and I say, move it [Name], move it. I've got a new way. I've got a wonderful life ahead of me because I can see things different (Interviewee 47).

Finally, beneficial *weight changes* were not mentioned with the same frequency as the other codes in this category. However, of those who did report weight reduction (considered to be associated with participation in the program) the following two examples typify this aspect of

the qualitative data; “(...) I've actually lost 16 kilos altogether through the time [of the study] - from May,” (Interviewee 27) and,

I visited a friend after 14 months just a couple of weekends ago and I walked in the door and the husband and wife just looked at me and said, ‘Oh my goodness what have you done? You have lost weight, you look years younger, you look so fit, oh this is wonderful, I can’t believe the changes in you’. (...) I’m not sure how much weight I have actually lost (...) the good thing is that it is turning from fat to muscle and I can feel the difference and I have gone down two dress sizes so far and that’s not bad for just over four months. (Interviewee 02)

This quote also reflects the changes in participants that were noticed by others. This ‘third party’ perspective provided important corroborative evidence supporting the subjective experience of the participants.

Category - Elusive concept – ‘something is different’

A final less tangible category of change underpinning improvements in mental and physical functioning was the conviction that something overall in the participant’s constitution and demeanour had changed. This aspect was apparent enough to be experienced subjectively, “(...)well (...) I don't know, I just feel fitter or something, something's different” (Interviewee 36); and to be noticed and commented upon by others, “(...)“my husband (...) says I get up with more energy, I have more (...) life radiating or something like that, if that makes sense” (Interviewee 25). In struggling to find the words to express this dimension of change, the key words articulated by the focus group were terms such as aliveness, liveliness, vitality, youthfulness and feeling more alert. One participant said she felt that years had been “stripped off” (Interviewee 02) and she felt like she did in younger years. Several participants made reference to a sense of decline they had felt since retirement and that the experience of the exercise classes had “reversed” what they considered to be a trajectory of progressive disengagement and de-motivation. One interviewee said that she felt, “(...) less aged” (Interviewee 43); another described this aspect of change as being “(...) like rejuvenation” (Interviewee 47); and still another said “(...) every exercise and everything we were doing [in the classes] was making my brain [say] wake up, come on, start going” (Interviewee 31).

An interesting observation also emerged from a woman who was previously unknown to the group. As articulated by one of the participants “(...) we had a lady; I think she came [to our class] by mistake or something. Anyway she had coffee with us after. We were chatting to her.

She said what struck me when I walked in the room, [was] you all looked so alive” (Interviewee 27). ‘Third party’ observations such as this provided a supplementary seam of qualitative data that in many cases provided important evidence for the utility of improved mental and physical functions in the everyday life of participants.

6.4 Summary

Analysis of the qualitative data garnered from participant interviews and a follow-up focus group identified three prominent themes. In this study enjoyment of the program maximised engagement in the intervention, engagement maximised adherence and adherence to the program resulted in change. The format, content and overall pace, intensity and atmosphere of the exercise classes engendered enthusiastic and dedicated participation to the extent that all of the participants remained in the study and attained an attendance rate of at least 85%. Although a number of participants encountered unforeseen adverse circumstances during the study period, all initiated contingencies so they could maintain attendance levels.

Overall, the program was acceptable to the participants largely because it was fun and challenging in good measure. The lack of judgement and prevailing atmosphere of goodwill was particularly influential in promoting willingness to engage in challenging activities that represented degrees of social risk. The program was also feasible. The extent of pace, intensity and complexity was generally manageable and could be readily varied to accommodate the requirements posed by pre-existing conditions.

All of the participants who were interviewed reported physical or mental (including cognitive) gains which they attributed to participation in the exercise program. Many also reported that these changes had been noticed and commented upon by people around them. The amalgamated qualitative and quantitative results of this study will be discussed in the following chapter (Chapter 7). This synthesis will also address the implications of the design, methodology and outcomes of this study in relation to clinical significance, ecological validity and future research.

Chapter 7: Discussion

7.1 Introduction

There is a pressing need to establish the true capacity of exercise training to induce cognitive benefits in the ageing brain. The current precipitous and expanding global increase in the proportion of older adults, in the age bracket most at risk of developing ARCD, is one imperative. The scale of the associated economic, public health and global social burden is another. A swathe of cross-sectional and longitudinal studies indicates that physically active older adults tend to have better neurocognitive function than their sedentary counterparts (see Chapter 2 Section 4). Moreover, the trend in the intervention literature suggests that exercise training may have the capacity to ameliorate the effects of ARCD (see Chapter 2, Section 5). However, the findings of the experimental studies conducted so far have been inconsistent and causal inferences are yet to be comprehensively demonstrated or defined.

More definitive evidence, about the degree to which exercise training can attenuate the effects of brain ageing, informs whether precious research dollars should continue to be spent on this enterprise or whether the yield is so negligible that others solutions should be sought. In particular, in response to the imperative of expediency as outlined above and in keeping with the principle of responsible allocation of research funds, it is important that research efforts are progressively refined to avoid repeating methodological and intervention designs that are no longer likely to harvest new knowledge (Friedman et al., 1998; Polit & Beck, 2012; Shadish et al., 2002). The extant literature suggests a number of research directions and methodologies that might be likely to achieve evidence beyond that previously garnered. Accordingly, this study employed a RCT as the methodology of choice in an attempt to test efficacy. In addition, a multi-modal exercise intervention was implemented. The goal was to test the power of exercise as a broadly defined multifaceted and more complete concept, as distinct from investigating a partial aspect of exercise in the form of a singular component or sub-set.

To address the preponderance of largely atheoretical intervention designs, the intervention design in this study drew upon theoretical assumptions derived from findings in a number of disciplines including neuropsychology, exercise physiology and the neurobiology of ageing. Ultimately this knowledge informed the inclusion of two particular features of the intervention

design: motor skills training and the imposition of cognitive load. Motor skills training inherently entails sustained mental focus and attention and the classes were delivered in a style that necessitated mental effort and concentration (cognitive load). The theoretical implication is that sustained mental effort is likely to both stimulate higher-order cognitive processes (executive functions) associated with the frontal lobe (prefrontal cortex) of the brain (Kempermann et al., 2000), and induce (positive) brain changes (Voelcker-Rehage et al., 2010). These design aspects represent a deliberate attempt to target executive function (higher order cognitive processes most susceptible to ARCD) (Jurado & Rosselli, 2007) and positive neuroplasticity (the neuronal capacity of the brain to preserve or optimise function, in response to experiential stimuli) (Greenwood & Parasuraman, 2010).

Three other aspects of research into the relationship between exercise training and the ageing brain were addressed. These aspects all represent what would be regarded as gaps in the current literature. First, peripheral blood concentrations of plasma BDNF were analysed to gain greater insight into whether neurogenesis might have a role among the underlying mechanisms giving rise to exercise-induced cognitive changes. Second, qualitative data were gathered to shed light on the clinical significance of benefits that may arise from a multi-modal exercise program. Lastly, the qualitative data were further analysed to gauge the ecological validity of a number of commonly employed neurocognitive instruments used in this study.

7.2 Representativeness and data saturation in the samples

The literature relevant to exercise and the ageing brain broadly divides into research targeting older adults with degrees of cognitive impairment, including categories of dementia (e.g., Heyn, Abreu & Ottenbacher, 2004), those with co-morbidities such as diabetes and depression (e.g., Nylen, Kokkinos, Myers & Faselis, 2010; Williams & Tappen, 2008), those living in residential care (Resnick, 2000) and also the profile of older adults represented in the present study: healthy, community-dwelling older adults without cognitive impairment (e.g., Angevaren et al., 2008). The intervention effects in this study were elicited in a sample of non-depressed older women, aged 65 to 75 years. As would be expected in this age group most participants had at least one medical condition (Uijen & van de Lisdonk, 2008). With the exception of a few individuals, these were not severe (Geriatric Co-morbidities Index Score = 4.2 and 4.5 for intervention and control groups respectively). In all cases any medical conditions were considered to be stable as assessed by the treating medical practitioner.

The recruitment and randomisation techniques implemented in the RCT, appear to have been appropriate. The lack of equivalent experimental studies somewhat hampered the pre-study sample size calculations as there were no effect sizes that could be derived from similar multi-modal intervention studies. However, using effect sizes from single-modality exercise intervention trials, it was estimated that a sample of 54 individuals (27 in each group) would be required. While five fewer participants were recruited to the study, moderate to large effects for most of the primary and secondary outcome measures were recorded, indicating that the study was adequately powered (Friedman et al., 1998).

Recruiting and retaining older participants in exercise trials is associated with unique challenges (Chao, Foy & Farmer, 2000) and typically high levels of attrition are reported, particularly within the initial period of the exercise intervention (Schutzer & Graves, 2004). Consequently, a number of strategies were designed in the planning process and were implemented at different stages of the recruitment and intervention phases, in an effort to neutralise the expected and significant potential for loss to follow-up. These strategies will be detailed later in the discussion. However, as an indication of the effectiveness of this regime and in contrast to the difficulties reported in a number of other studies (Carter, Elward, Malmgren, Martin & Larson, 1991; Knechel, 2013; Saag et al., 2012), 49 eligible women were recruited across a period of four to five weeks. The entire intervention group completed the 16 week program, with an attendance rate of at least 85 percent. One member of the control group was lost to follow-up. The intervention group requested that the exercise classes continue beyond the completion of the study and expressed their willingness to pay to ensure that possibility.

Randomisation procedures appear to have been successful, as the intervention and control groups were equivalent in terms of cognitive status (non-impaired), years of education, body mass index, waist-to-hip ratio, heart rate, mean blood pressure and physical activity levels (pedometer-assessed mean daily steps). The use of an internet-based randomisation service and a research assistant who had no other part in the study ensured the concealment of group allocation (Zlowodzki, Jonsson & Bhandari, 2006).

At baseline there were significant differences between the intervention and control groups in relation to balance ability (One-Legged Stance Test) and BDNF levels, with the intervention group exceeding the control group on both measures. These differences were controlled for in the statistical analysis of outcome measures; however, the reasons for these differences are not immediately apparent. Certainly, although the BDNF levels reported in this study are

consistent with a study by Komulainen et al. (2008), there is clear evidence in the literature of significant variability in BDNF readings (Seifert et al., 2010). The reasons for the baseline between-group differences in balance ability are less easily understood. For example, there were no significant differences between the groups at baseline in terms of co-morbidities or cognitive status as key factors known to influence balance ability (Hsu, Nagamatsu, Davis & Liu-Ambrose, 2012; Vu, Finch & Day, 2011).

7.3 Effects of the multi-modal exercise program

The 16-week multi-modal exercise program implemented in this study resulted in improvements in six out of the eight primary outcome measures associated with neurocognitive function and all of the secondary outcomes associated with physical functioning, in women aged between 65 and 75 years. In addition, at the end of the intervention, BDNF levels were significantly higher for the intervention group as compared to the control group, after adjusting for baseline. These quantitative outcomes were generally corroborated by the qualitative data, as they were reflected in the changes observed by both participants and third parties. Improvements in the primary outcome measures (neurocognitive performance) represent enhanced executive functions in relation to verbal fluency and information processing speed, and a better ability to attend, concentrate, think flexibly and resist distraction. This constellation of improvements is significant because these particular cognitive functions are among those most associated with age-associated decline (Drag & Bieliauskas, 2010). They are also among the first cognitive functions to deteriorate with age (Drag & Bieliauskas, 2010).

An extensive review of the literature, including the grey literature, has failed to reveal other experimental studies, focussing on non-cognitively impaired older adults, with the same combination of design, content, population, delivery and measurement parameters as the present study. Therefore, a direct comparison with previous experimental studies is hampered by distinct differences in methodologies, participant characteristics and intervention typologies. In many instances the details of previous interventions are either unclear or absent. In particular, there is pronounced variability in the neurocognitive instruments employed and the classification of various neurocognitive measures. With these caveats in mind there are noteworthy similarities and differences between previous (albeit disparate) research, and the current study.

In this study, the primary outcome of neurocognitive performance scores, related to executive function, showed statistically significant between group differences for the Trail Making A ($d=0.7$) and B ($d=0.63$) tests (attention, motor function, flexibility of thinking and visual search ability); the COAST (Word, Interference and Total) ($d=0.77$; $d=0.97$; and $d=1.28$, respectively) (inhibition); and the COWAT ($d=0.70$) (verbal fluency). Performance in the COAST colour test showed a difference between the two groups that almost reached statistical significance ($p=0.056$). Cohen's d effect sizes would be indexed as moderate to large for the statistically significant cognitive outcomes (Cohen, 1988).

By comparison, systematic reviews of predominantly single modality cardiovascular/aerobic exercise interventions indicate that many (and perhaps the majority) of studies did not evince a treatment effect in relation to neurocognitive functions (Angevaren et al., 2008; Etnier et al., 2006; Snowden et al., 2011; van Uffelen et al., 2008). Where statistically significant results have been demonstrated the effect sizes have generally been in the small to moderate range (Angevaren et al., 2008; Smith et al., 2010). The systematic review with meta-analysis conducted by Smith et al., (2010) found modest improvements in the domains of attention and processing speed (effect size 0.158) and executive function (effect size 0.123). Similarly, Angevaren et al., (2008) found small improvements in visual attention (effect size 0.26) and cognitive speed (0.26), and a moderate overall effect for auditory attention (effect size=0.50), in an analysis of 11 peer reviewed experimental studies.

Recent research based on combination exercise interventions has generally taken the form of quasi-experimental studies (Coubard et al., 2011; Forte et al., 2013; Taylor-Piliae et al., 2010). None have included the same configuration of intervention elements tested in this study. However, Forte et al., (2013) conducted a randomised trial (using subjects as their own control) comparing multicomponent exercise with progressive resistance training. The multicomponent exercise combination does appear to be similar to that of the present study (coordination, balance, agility, strength and flexibility). The results showed no between group differences, however, the lack of an independent, randomly assigned, control group may have obscured the effect of the intervention.

In two other studies, another form of multicomponent exercise, Tai Chi, was compared to contemporary dance and a falls prevention program (Coubard et al., 2011) and western exercise and an attention-control group (Taylor-Piliae et al., 2010). The Tai Chi intervention conducted by Taylor-Pillae et al. (2010) demonstrated some effect on working memory (digits backwards) ($p=0.014$) (Taylor-Piliae et al., 2010), however, this was not found in the Coubard

et al. (2011) study in relation to Tai Chi. In the Coubard et al. (2011) study, contemporary dance improved switching (Rule Shift Cards Test) compared to falls prevention training ($p=0.042$). There were no other significant results in relation to cognitive flexibility (Arithmetic Word Problems) or inhibition (Stroop test) (Coubard et al., 2011). In the current study cognitive flexibility and inhibition (as measured by TMT B and the COAST) showed moderate to large effects (see Table 5.3).

RCTs of multi-modal exercise programs with different combinations to the present study, have been conducted by Liu-Ambrose et al. (2010) and Klusmann et al. (2010). Liu-Ambrose et al. (2010) conducted a 12-month RCT with older women comparing the effect of once weekly and twice-weekly resistance training with that of twice-weekly balance and tone exercise training (control group). The study found significant between group differences for resistance training compared with balance and tone (no aerobics) ($p \leq 0.03$) for the Stroop test, after 12 months. There were no significant between group differences for set shifting (TMT A & B) or digit span (working memory). Klusmann et al. (2010) compared multicomponent exercise with a computer based cognitive enhancement program and a control group. The exercise program had some similarities to the present study in that it consisted of aerobic endurance, strength, flexibility balance and coordination training. However, the program did not appear to manipulate cognitive load, the cardiovascular component consisted of 30 minutes of endurance training on bicycle ergometers or treadmills; and the program entailed one and a half hours of exercise, three times per week. Both intervention groups showed statistically significant improvements in performance on tests of working memory (Rivermead Behavioural Memory Test) and memory (Free and Cued Selective Reminding Test) compared to controls. These differences manifested very small effect sizes ($\eta^2 = 0.03$ to 0.04). There were no between group differences for the Stroop test or verbal fluency (Animals, Food).

In contrast to the absent, small or moderate effects on neurocognitive performance reported in previous studies of single modality and combination exercise training in healthy older adults, this study has demonstrated moderate to large effects with the application of a multi-modal exercise format. These effect sizes translate into a 19% mean improvement in performance for the TMT B; a 20% improvement for the COAST interference test; a 43% mean improvement for the COWAT. These quantitative results are congruent with the qualitative data with participants, and relevant third parties, reporting perceptions of better concentration and attention, clearer thinking and faster mental processing; as well as better balance, agility and postural control.

Working memory as a primary outcome measure and simple and choice reaction time as a secondary outcome measure of cognitive performance, did not demonstrate significant improvements as measured by the instruments employed in this study. Findings related to exercise and working memory in other studies have been mixed and inconclusive. Only two of the studies included in the Smith et al. (2010) review and none of the additional studies in other reviews or more recent RCTs (Angevaren et al., 2008; Snowden et al., 2011; van Uffelen et al., 2008) employed the Letter Number Sequencing (LNS) test used in this project. The studies that did use LNS did not find any effect on performance scores. On the basis of other tests of working memory (e.g. Digit Span, N-Back) the Smith et al. (2010) review found that combined aerobic and resistance training improved working memory ($g = 0.288$) to a greater extent than aerobic exercise alone ($g = -0.042$). The pattern of absent-to-small-to-moderate improvements found for other aspects of executive functions as a result of singular or combination modality exercise training (e.g. attention, processing speed) does not seem to be the same for working memory. While the Smith et al. (2010) and Colcombe and Kramer (2003) reviews imply that combination exercise has the potential to improve working memory, the lack of benefit in this multi-modal format (even when other executive functions improved significantly), may be a function of the LNS Test. For example, education and self-regulation of emotional responses may confound performance in this test (Buelow & Frakey, 2013). Alternatively, exercise-related changes in working memory may be contingent upon a dose-response requiring longer intervention periods to attain performance enhancement. As an interesting aside, the domain of memory was not measured in this study. Working memory was chosen because the key primary outcome of interest was the neurocognitive domain of executive function. However, better memory retention was specifically reported in the qualitative data (e.g. "I used to have to have a shopping list (...) now; I don't need a shopping list ...").

Although participants reported noticeable improvements in the speed of their reactions this was not borne out by the specific reaction time testing device used in this study. Participants reported definite improvements in reaction times in the form of better agility and nimbleness and improved ability to process information more quickly, such as responding to cueing and instructions in the context of the classes. This improvement was generally attributed to an improvement in their ability to focus mentally. This outcome was also at odds with the increase in TUGT time, since this test has also been found to reflect reaction times, to some extent (Kwan, Lin, Chen, Close & Lord, 2011). It is unclear how well the instrument used to gauge reaction time (Deary-Liewald Reaction Time Task), which requires upper body dexterity

(fine motor skills), actually reflects lower body agility (gross motor skills). Also, research suggests that this particular demographic may be adversely affected by not being familiar or comfortable with computer based testing technology (Browndyke et al., 2002).

This controlled intervention study also demonstrated the positive effects of a multimodal exercise program on a number of aspects of physical functioning. Changes in the secondary outcome measures related to physical functions represent marked improvements in mobility and lower extremity function (Herman et al., 2011) and exercise capacity (American Thoracic Society, 2002). Cohen's *d* effect sizes would be indexed as large for these physical outcomes (Cohen, 1988). Improvements in physical performance measures represent a 20%, 26% and 80% mean performance improvement on the 6MWT, TUGT and One-Legged Stance Test respectively. The TUGT assesses multiple components of balance and mobility and requires cognitive resources, particularly executive functions (Donoghue et al., 2012). Poorer results on the TUGT are associated with poorer performance in tests of executive function in older individuals; and deficits in executive function are associated with greater falls risk (Herman, Mirelman, Giladi, Schweiger & Hausdorff, 2010). Hence, the importance of these results is not only relevant to the benefits of improved physical functioning; there are also implications for the domain of executive function and falls prevention (Beling & Roller, 2009).

As would be predicted by previous research, better performance in the TUGT in this study is consistent with improvements demonstrated in the primary outcome measures related to executive functions (Donoghue et al., 2012). Moreover, these physical improvements were clearly congruent with the qualitative data with participants reporting a multitude of everyday examples of enhanced or new abilities related to strength, stamina, agility and postural control. In many cases these changes were sufficiently apparent to be noticed and commented upon by those around them. These findings are consistent although perhaps more pronounced, than those generally reported in the single and combination exercise literature (Liu & Latham, 2009).

The results of the ANCOVA performed on the log transformed data for the one-legged stance test and BDNF levels in this study demonstrate a statistically significant difference between the groups. The intervention group achieved better results for One-Legged Stance Test compared to controls (mean difference of +44.2 seconds versus -0.4 seconds). Improvements in balance were clearly articulated in the qualitative data. In addition, the intervention group increased BDNF levels (from 4.5ng/ml to 5.2ng/ml), while the control group had decreased BDNF levels (5.6ng/ml to 4.7ng/ml). A study by Komulainen et al. (2008), indicated that BDNF was a

biomarker for general cognitive function in older women; the BDNF levels reported in this study were consistent with the present research.

Exercise-induced increases in circulating BDNF have certainly been reflected in animal studies that employed exercise modalities deemed to be equivalent to motor training (Black et al., 1990; Klintsova, Dickson, Yoshida & Greenough, 2004). There have also been a few human studies based on cardiovascular exercise indicating that BDNF may play a role in exercise-induced changes in cognitive performance (e.g., Erickson et al., 2011). It may be that this is the first time that changes in plasma BDNF levels have been demonstrated, in women, as a result of a multi-modal exercise intervention configured to impose cognitive load. This finding is also largely convergent with the rest of the experimental data in this study. BDNF expression plays a major role in the control of synaptic plasticity and neurogenesis within the prefrontal cortex and hippocampus (Knaepen et al., 2010); these regions are vital for memory formation and executive functions (Barnes, Dean, Nandam, O'Connell & Bellgrove, 2011). Logically, an increase in BDNF (as a proxy for increased neurogenesis) should be reflected in improvements in neurocognitive performance measures of executive functions, as was the case in this experimental study. This outcome also corresponds with the findings of the thematic analysis of the qualitative data where participants and third parties reported changes consistent with better cognitive (executive) functions. This finding suggests that, as in animal studies (Coelho et al., 2012; Cotman & Berchtold, 2002; Kempermann et al., 2010), neurogenesis or the growth, maintenance and survival of neurons may be part of the mechanism that mediates exercise induced improvement in cognitive functioning in older women.

7.4 Acceptability and feasibility of the intervention

The qualitative data, derived from interviews with 15 participants and a follow-up focus group, were thematically analysed and provided data related to the acceptability and feasibility of the exercise program. The aim, in part, was to understand the participants' experiences of the intervention. The intention was to discover what elements may have influenced engagement, adherence and the overall manageability of the program; and what aspects of the program may have been unhelpful.

Retention of the entire intervention group for the duration of the program is indicative of the level of engagement in the program. The aspect of the program that most appears to account for this degree and extent of involvement, is the fact that so many participants enjoyed the exercise program and the overall experience of the intervention. The factors that generated

most enjoyment appear to include fun generated by elements of humour, music, variety and a group format. Enjoyment was also derived from the inclusion of appropriate levels of challenge and the atmosphere being characterised by goodwill and an absence of judgement.

The role of humour in human interactions does not seem to have been extensively investigated in the literature (Li et al., 2009b). In general, there are suggestions that humour may build rapport; foster, facilitate, and maintain relationships (MacDonald, 2004; Treger, Sprecher & Erber, 2013); and facilitate group cohesiveness by creating a sense of 'us' or 'we' when humour takes the form of 'laughing with' as distinct from 'laughing at' (Li et al., 2009b). There is evidence that humour can make interactions enjoyable and that humour and laughter may have a positive effect on emotional states (Treger et al., 2013). Consistent with this finding the qualitative data indicate that the atmosphere of levity, among other things, relieved the apprehension that some of the participants experienced both at the beginning of the program and in attempting novel and challenging activities. The key message that was intended in the use of humour was that exercise does not need to be arduous and sombre to be effective. The qualitative data confirmed that many of the participants made that realisation. The data also show that the use of humour was influential and instrumental, in how that message was conveyed.

In keeping with the literature, participants identified the use of music as a feature of the program that evoked heightened arousal, motivation, positive emotions and memories, and rhythmic movement (Karageorghis & Priest, 2012). The 'era' and tempo of the music were two properties most enjoyed by the participants. The music was purposely selected to represent songs that had been most popular in this cohort's adolescence and early adulthood. The sociobiological significance of music peaks in this period of life (Bailey & Cohen, 2002) and music preferences usually form in these years. The aim was not only to provide music that was most likely to be rated as enjoyable by the group, but also to exploit personal associations likely to induce motivational and stimulatory benefits (Karageorghis & Priest, 2012). Songs were further chosen on the basis of being 'up tempo', characterised by 4/4 metred time, with an evident beat or background auditory pulse. The goal was to solicit attention and engagement and to provide a structure likely to induce locomotion and movement at the set pace (124-132 beats per minute). Participants identified that the music motivated them to move. This predisposition has been referred to in the literature as the 'rhythm response', which is an innate tendency to synchronise movement to preferred musical rhythms (Karageorghis & Priest, 2012). Participants also noted a willingness to exert themselves and

persist, in response to the music. Music can increase tolerance of the amount of time engaged in exercise and the level of exertion, because the positive distraction decreases the level of perception of negative states that can accompany greater intensities and longer periods of effort (Madison, Paulin & Aasa, 2013).

Enjoyment was also associated with the variety in the program. There has been scant research into the influence of exercise variety among older adults. However, a recent study found that the provision of 'high variety' increased exercise participation, enjoyment and adherence as compared to 'low variety' formats (Juvancic-Heltzel, Glickman & Barkley, 2013). The qualitative data in this study suggests that the provision of variety may positively alter perceptions about exercise. The perception that exercise can be enjoyable is said to diminish with age partly because it is viewed as monotonous and uninteresting (Dacey, Baltzell & Zaichkowsky, 2008). Conversely, variety in this study appears to have contributed to the perception that exercise can be enjoyable when it is diverse, interesting and stimulating.

The finding that enjoyment was derived from the exercise taking place in the company of other people (group environment) is very much in keeping with a large body of research (McAuley, Jerome, Elavsky, Marquez & Ramsey, 2003; Stathi, Mckenna & Fox, 2010). However, there were two other categories in the qualitative data that do not appear to have been strongly identified in the extant literature on exercise and ageing: namely, the importance of the experience of challenge for these older women; and the degree of value ascribed to an atmosphere deemed to be characterised by goodwill and the absence of a judgemental attitude.

The presence, configuration and extent of challenge in this exercise intervention were particularly salient in the qualitative data. First, the participants clearly articulated their desire and preference for exercise to be challenging. The novelty, complexity, pace and intensity that underpinned the challenge element of the exercise program appear to have expressly stimulated the experience of liveliness, vigour and dynamism; this combination was particularly appealing and therefore enjoyable and engaging for the participants. Second, it would appear that the perceived degree of challenge was critical to this outcome. It was important that the level and experience of challenge did not unduly exceed people's perception of their own capabilities. More specifically and in particular, it was important that the challenge being presented did not represent the risk or prospect of injury or humiliation. Where participants exhibited any sign of reticence, the relevant challenge was modified so that it was individually tailored to achieve the same results (e.g. divided into smaller

increments). The provision of individualised variations was important because it appears to have signalled that there was a pathway to success for everyone. Further, the need for modification was conveyed and received as being normal (and for some special), rather than representing failure or an imposition on the instructors.

Finally, the valuing and significance of a non-judgement attitude and evident goodwill, evinced by the group, appears to have particular pertinence. There are strong indications from this study that the risk of embarrassment and humiliation, or the perception of criticism, may be a significant consideration for adults in this cohort in relation to a willingness (or otherwise) to engage in group exercise. This may be particularly so when the exercise typologies are unfamiliar and /or entail non-latent skills and abilities that require movement-based learning. Taken together, all of the aforementioned categories appear to have individually (and in combination) resulted in an overarching experience of enjoyment which translated into a high degree of engagement in this exercise intervention. Engagement with the program, in turn, maximised adherence. Additional factors that appeared to strengthen adherence levels above and beyond the influence of enjoyment were related to the feasibility of the program, the perception of being valued and a feeling of physical safety.

The current findings are consistent with previous research suggesting factors affecting feasibility such as logistical inconvenience, health problems and lack of time arising from family or work commitments potentially adversely affect exercise adherence in this age group (Hughes, Seymour, Campbell, Whitelaw & Bazzarre, 2009; Stathi et al., 2010). Nevertheless all of these considerations were circumvented by participant initiatives in this study. The impetus for this effort seems to have been a mixture of a sense of commitment to the project; recognition of the benefits of participation in the program; a sense of purpose in being part of the research enterprise; and perhaps most of all, a tangible sense of being valued. These latter two factors are not well-documented in the literature; however, a recent study found that the influence of exercise instructors can significantly affect adherence (Hawley-Hague et al., 2013). The qualitative data in the present study implies that instructor attunement and attention to the individual needs of participants had a role in inspiring a sense of purpose and being valued. In line with previous findings (e.g., Lucidi, Grano, Barbaranelli & Violani, 2006; Yardley et al., 2006; Yardley, Donovan-Hall, Francis & Todd, 2007) adherence also seems to have been bolstered by the instructor's belief in participants' capacities to achieve positive outcomes. Finally, there was no potential impediment or disincentive in this program in the form of concerns about the safety or manageability of the exercises. This aspect may have enhanced a

sense of self-efficacy which is the belief and conviction in one's own ability to perform a given activity (Bandura, 1977). Self-efficacy has been well documented as a significant factor that can affect exercise adherence in older adults (McAuley et al., 2003).

7.5 Recruitment and retention of older adult participants in exercise trials

The recruitment process was based on a number of pre-determined principles including accessibility, convenience, credibility, affordability and desirability. The program was conducted in a community hall assessed as being accessible, safe and well located in relation to all forms of transport, within the geographical region of interest. Newspaper advertisements and prime time media coverage clearly conveyed the fact that the program was being conducted as a university project. The program was free of charge. The message conveyed in the recruitment process deliberately outlined the comprehensive nature of the exercise program, in lay language, with the intention of depicting the uniqueness and potential additive value of the intervention.

Testing was conducted at various locations to accommodate the preferences of volunteers and to attenuate the likely prospect of apprehension. Driving to unfamiliar locations, for example, can be anxiety provoking for older adults (Blanchard & Myers, 2010). From the point of initial contact volunteers were comprehensively briefed about the requirements of the study, the nature of the commitment that was being requested and the complete objectivity of the randomisation process resulting in assignment to the control condition. The intention was to recruit on the basis of realistic expectations and to highlight the pivotal contribution made by the control group.

The control group was offered the same 16-week program, free of charge, to ensure equity and as an incentive to assuage the disappointment of being randomised to the control group (Friedman et al., 1998). At the commencement of the study, the control group was invited to a morning tea. The aims were to be introduced to the research assistant, who would ultimately conduct monthly telephone contact and to reinforce the importance of maintaining their usual lifestyle. Programmed telephone contact was intended to assist in maintaining a sense of being part of the study, as distinct from being redundant or irrelevant to the enterprise. The control group was retained for the duration of the study with the exception of one participant who refused follow-up testing. The cited reason was that she had felt inadequate, ostensibly in response to the experience of baseline cognitive testing. Interestingly, independent scrutiny of

this individual's cognitive assessment revealed an overall above average performance at baseline. A similar response has been reported in a study by Williamson et al. (2009).

The qualitative data in particular, enabled the identification of a number of salient principles pertinent to participant retention. First, the provision of variety, challenge, intensity and pace was influential in engaging and maintaining older women in the exercise program. Second, this level of energy, dynamism and attentional demand appears more likely to maintain ongoing engagement if it is perceived to be manageable. The perception of manageability in this study was facilitated by the incremental introduction of activities that were then progressed in response to the manifestation of success or mastery. Third, the strategy of normalising the need for exercise variations, to accommodate limitations related to pre-existing conditions and/or fitness and skill deficits, appears to have been especially important. In this study, the ready availability of individually tailored exercise options seems to have been instrumental in averting disengagement. This tailoring, prevented participants experiencing the aversiveness associated with exceeding appropriate levels of effort and exertion. In addition, individualisation of the program reduced reticence to participate related to concerns about safety or embarrassment.

The inclusion of measures likely to promote enjoyment may also have promoted retention (e.g., Karageorghis & Priest, 2012). Sources of extrinsic motivation such as music, opportunities for social interaction and activities that engender fun may promote attendance until such time as the intrinsic motivation provided by subjectively perceived improvements 'kick in'. Finally, the time commitment required to participate fully in a twice -weekly, 16-week program is considerable. Motivating individuals to commit in the face of medical, logistical and lifestyle demands means that the overall allure of the program needs to have the power to counter the force of competing demands.

7.6 The clinical significance of interventions and the ecological validity of measures – the relevance of the intervention in day to day life

The qualitative data provided valuable insights into the practical 'real world' value of the cognitive and physical effects of the exercise program (the clinical significance). Overall, the statistically significant differences between the groups appear to have translated into functional differences for the intervention group. These changes were perceived to be both significant and beneficial by the participants. The qualitative data suggest that participants noticed better functioning in key aspects of daily life such as shopping, decision making,

driving, social interaction and effectively attending to tasks, in the presence of distraction. Better performance in daily living activities was attributed to improvements in mental processes (such as concentration, memory and processing speed) as a function of participation in the exercise intervention. The implication is that the neurocognitive benefits induced by this multi-modal intervention may translate into functional gains relevant to independence and competence in the instrumental activities of older adults (clinical significance). In keeping with previous research (Jurado & Rosselli, 2007), the convergence of the qualitative and experimental findings related to neurocognition in this study also implies that executive functions may have an essential role in the execution of activities of daily living (ADL) in later life.

The qualitative data also shed light on the clinical significance of the physical changes elicited by this multi-modal intervention. Changes in physical function were mainly related to improved stamina, balance, co-ordination, strength and postural control, which contributed to feelings of mastery and competence. Greater physical competency was manifest, for example, in a number of accounts of trips or falls that were averted due to greater vigilance, better reaction times and better agility. In combination, the perception of enhanced physical and cognitive functioning appears to have engendered improvements in mental outlook characterised by improved mood, greater confidence, optimism, and motivation; and a sense of agency. As a reflection of the clinical significance of these changes, participants embarked on new endeavours and re-established aspects of their previous lifestyle that had been abandoned due to fear, anxiety, concerns about diminished cognitive function, a lack of fitness, loss of motivation or the impost of limitations associated with chronic conditions

The perception of 'something being different' as a result of participation in the exercise program also appears to have had an influence on the experience of everyday life. The 'something' of difference was variously articulated by participants as noticed and noticeable change, connected in some way to the concepts and 'lived experience' of vitality, aliveness and alertness, reminiscent of a bygone feeling of youthfulness. In a practical sense this translated into more active play with grandchildren, an ability to keep pace with the activities of adult children and a predisposition towards motivation and activity, as opposed to the inertia and de-motivation experienced by some, post retirement. Cumulatively and singularly, the cognitive and physical changes induced by this exercise intervention appear to be clinically significant, as they represent performance gains in a number of important and relevant activities of everyday life. Moreover, the practical 'real world' value of the treatment effects

were overwhelmingly perceived by the participants to constitute beneficial change. In turn, these improvements appear to have translated into more activity and greater engagement in life.

Triangulation of the quantitative and qualitative data also provided a degree of insight into the relative correspondence between neurocognitive test performance (experimental data) and post-intervention performance in activities of everyday life (qualitative data) (i.e. the ecological validity of the instruments). Overall, the induced positive neuroplasticity implied in the moderate to large effect sizes demonstrated in all of the neurocognitive measures of executive functions (except working memory and the COAST colour test) were consistent with the functional cognitive gains reported by the participants. Specifically, observed improvements in attention and flexibility of thinking are concordant with the domains purportedly measured by the Trail Making A and B tests. Statistically significant improvements in the COAST (Word, Interference and Total) outcome scores ostensibly reflect a better ability to inhibit habitual responses. Improved performance in this domain was clearly articulated by a number of participants. The qualitative data indicate an enhanced ability to retrieve words from memory in the context of social interactions and this outcome converges with better verbal fluency and memory performance, as indexed by the COWAT.

Certainly the TMT A & B, the COWAT and various forms of the Stroop test have commonly been used in the detection of cognitive change in previous research centred on exercise and the ageing brain (Smith et al., 2010). However, previous research has not typically included measures to ascertain the functional significance of any elicited cognitive changes. In this study, the statistically significant improvements in cognitive performance indexed by these particular tools appear to correspond well with the 'real life' functional performance gains induced by the intervention. The extent to which congruity between the quantitative and qualitative findings reflects the ecological validity of these respective instruments is difficult to ascertain. However, the trend of consistency is promising and points to the likelihood that these tools possess ecological validity in the measurement of exercise elicited executive functions in older adults.

The large effect sizes obtained in the 6MWT, the TUGT and the one-legged stance test were congruent with the improvements in physical functioning reported by the participants. The exercise-induced physical benefits instanced in the qualitative data included greater tolerance of cardiovascular activity and greater proficiency in day-to-day activities requiring balance, postural control and coordination, such as manoeuvring safely in cluttered environments and

trip recovery. The correspondence between test performance and physical performance in daily living activities suggests that these instruments do possess ecological validity in relation to the measurement of multi-modal exercise-induced enhancement of physical capacities, among older women. Conversely, whereas improvements in reaction times and psychomotor speed were clearly articulated in the qualitative data and somewhat implied in the results of the TUGT (that also, in part, reflects reaction times), this was not demonstrated in the experimental findings. The implication is that the computer based Deary-Liewald Reaction Time Task may lack ecological validity in relation to this kind of research with older adults.

Improvements in working memory were not manifest in the results of the LNS test and though memory improvements were reported in the qualitative data the examples did not appear to pertain to working memory specifically. On the basis of this study the ecological validity of this tool cannot be ascertained. Nor is the explanation for the absence of treatment effects for working memory apparent. It is not clear whether the treatment stimuli in the intervention were sufficient or appropriate to the task of eliciting change in this domain. Alternatively, treatment effects may be contingent upon dose effects related to intensity and duration that were not achieved. It may be that improvements in working memory were achieved to some degree but were not detected at a psychometric level (as an artefact of the instrument) or at a subjective level. Changes in working memory may be more subtle (and less easily subjectively identified) than other cognitive abilities. Working memory may not be as significant as other aspects of executive function in the daily activities of older adults. The suitability of the LNS test for older adults appears to require more evaluation. It may be noteworthy that the clinicians who conducted the neurocognitive testing observed a noticeable emotional response in participants, to the task demands of the LNS test.

7.7 Strengths and limitations of the research

The strengths of this study include the high levels of retention and adherence, objective measurement of activity levels at baseline (previous work generally relies on subjective measures) and the application of a RCT as a robust methodology, capable of establishing causality. The study was controlled for variables that may affect cognitive performance, such as cognitive status, depression, gender and physical activity levels. It was also adequately powered to demonstrate the effect of the intervention on cognitive and physical functions and plasma levels of BDNF. Uniquely, this study garnered cross-validated evidence through the triangulation of quantitative and qualitative data that included evidence detected at a

cognitive, functional/psychomotor and biochemical level. This study also sheds light on the clinical significance for older women of outcomes derived from a multi-modal intervention, as well as the ecological validity of a number of measurement tools commonly employed in this type of research. The publication of peer reviewed papers (Vaughan et al., 2012; Vaughan et al., 2013 in press) that specify the details of the intervention means that, unlike many previous studies, there is the possibility of replication. Finally, this research makes some contribution to the state of knowledge regarding the mechanisms that may underpin exercise- induced cognitive enhancement in older women.

The limitations of this study include the fact that it is difficult to calculate the extent to which the program's success is reliant upon the effect of the particular fitness instructors involved. The degree to which social interaction contributed to the outcomes is also unclear. There was also no monitoring of physical activity in the control group and the results of this study can only be generalised to older women in the 65 to 75 years age group.

7.8 Recommendations for exercise intervention design

A number of principles derived from the implementation process and the qualitative data appear to be pertinent to future exercise intervention designs. First, the particular multi-modal combination that achieved results in this study included cardiovascular and resistance training; and motor fitness training that incorporated, balance (dynamic and static), flexibility, coordination reaction time and agility exercises. Apart from the cardiovascular component the majority of the program was delivered in a circuit. Second, the inclusion of variety and novelty within the different exercise modalities appears to be an important design aspect as it both stimulates interest and occasions higher levels of attentional focus. For example, fitness boxing and ball and agility drills were particularly popular with this group of older women. Third, music appeared to make a significant contribution to the energy, atmosphere and overall tempo of the classes. However, it would seem that music choices should ideally be based on the preference of the cohort, to be more likely to elicit this response. Fourth, the programming of exercise variations is important for this age group to accommodate the likelihood of a variety of medical and musculoskeletal considerations. In this intervention variations were based on a thorough assessment of the individual needs of each participant. In keeping with the principles of effective programming and to promote ongoing neural adaptations (American College of Sports Medicine, 2010) the systematic implementation of progressions is also recommended. Finally, the attitude of the instructors can be influential in the success of group

exercise programs (Hawley-Hague et al., 2013 in press). The attitudinal stance and ethos conveyed by the instructors in this study was underpinned firstly, by the principle of respect and secondly, by the principle that the primary goal of the program, was to benefit participants. Further, individual needs were actively normalised to avoid the possibility of participants feeling embarrassed, judged or that the need for individual assistance was an imposition on the instructors.

7.9 Recommendations for future research

Analysis of the extant literature suggests there may be little to be gained by continuing to focus on single modality cardiovascular exercise interventions. The knowledge gained from previous research appears to have reached a point of saturation. Further, the current study indicates that multi-modal programs may have the capacity to achieve more in terms of cognitive and physical performance, at least among older women. Therefore, the first recommendation is that future research focus more on experimental studies of multi-modal intervention designs, including investigations into the relative merits of different kinds of modality combinations. The effects of combination exercise are also yet to be tested in relation to gender effects, dose-effects, different age groups and older populations manifesting degrees of cognitive impairment. Second, it would appear to be a matter of some urgency that consensus be achieved in relation to the neurocognitive instruments and batteries that are most suitable for evaluating exercise- induced cognitive change in older adults. A second tier of research related to this priority might be the establishment of concerted collaborative efforts to identify a beginning suite of measurement tools, which possess ecological validity, as well as the psychometric properties of reliability and validity.

Third, there is no doubt that the inclusion of a qualitative component in this study afforded many advantages. These include the opportunity for cross-validation of data; a means to understand the effect and acceptability of the program from the perspective of the participants; the prospect of gauging the clinical significance of the treatment effects; and some preliminary understanding of the ecological validity of the measurement instruments employed in this study. Future research may benefit from mixed method research. Additional recommendations include investigations into the suitability and efficacy of this type of intervention for older men, and assessment of the parameters of the dose-response relationship required to effect cognitive enhancement in older adults.

Finally, even though this study demonstrated the likelihood that BDNF plays a role in the cognitive gains elicited by multi-modal exercise, the biochemical and metabolic pathways underpinning exercise-induced cognitive change are likely to be multifaceted (Lista & Sorrentino, 2010). Investigations into biomarkers such as IGF-1 and VEGF may help to identify the relative contributions of angiogenesis, neurogenesis and synaptogenesis, and the exercise activities and modalities most likely to stimulate these processes to promote positive neuroplasticity in older adults.

7.10 Conclusion

This study represents a breakthrough in the strategies available to confer cognitive benefits to older women. It demonstrates, perhaps for the first time that multi-modal exercise conducted in a controlled environment, including motor training and imposing a high cognitive load, can induce better cognitive performance in the form of executive functions than single-modality cardiovascular interventions. It is also apparent that, contrary to previous findings, good levels of retention can be achieved given the right constellation of ingredients serving to promote motivation, enjoyment and engagement. An important finding is that multi-modal exercise can also result in increased levels of plasma BDNF. This implies that, as in animal studies, neurogenesis is a likely component of the mechanism whereby exercise training induces improvement in cognitive functioning in older humans. Future research is required to establish whether these results can be replicated in men, in other age groups and to establish the dose required, to elicit and maintain cognitive benefits.

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Appendices

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Appendix 1: Telephone Screening Interview Tool

The interviewer will introduce themselves and remind the potential participant of their interest in the research study.

The interviewer will then say:

If this is a convenient time for you I would like to ask you some questions about your health. The process will take about 15 minutes.

The idea is for me to be able to work out whether this study is appropriate for you. At the end of the questions I will be able to let you know if it is OK for you to go to the next stage of the research.

Before we begin do you have any other questions?

Ok so now I will ask you about a series of medical conditions and I would like you to tell me if you have ever had or you take medications for any of the following:

Part A: Physical Activity Readiness Questionnaire (PAR-Q)

Yes	No	Heart problems	Diabetes	Yes	No
Yes	No	Discomfort or pain in chest	High Cholesterol	Yes	No
Yes	No	Rheumatic fever	High blood pressure	Yes	No
Yes	No	Lung problems	Stroke	Yes	No
Yes	No	Arthritis or major joint injury	Hernia	Yes	No
Yes	No	Thyroid condition	Osteoporosis	Yes	No
Yes	No	Liver condition	Swollen feet or ankles	Yes	No
Yes	No	Kidney condition	Glandular fever	Yes	No
Yes	No	Epilepsy	Dizziness/fainting	Yes	No
Yes	No	Severe varicose veins	Cancer	Yes	No
Yes	No	Other (please describe)			

Medical Conditions Total _____

GP Clearance Required? Yes / No

Part B: Telephone Interview of Cognitive Status

Now I'd like you to do some little mental exercises for me. These exercises don't involve a pencil or paper. You just have to do them in your head. Are you ready?

Please tell me your full name?

- | | | |
|-------------------------------------|-----------|----------------------|
| <input type="checkbox"/> First name | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Last name | = 1 point | <input type="text"/> |

What day of the week is it today?

- | | | |
|--------------------------------|-----------|----------------------|
| <input type="checkbox"/> _____ | = 1 point | <input type="text"/> |
|--------------------------------|-----------|----------------------|

Can you tell me today's date?

- | | | |
|--------------------------------|-----------|----------------------|
| <input type="checkbox"/> Date | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Month | = 1 point | |
| <input type="checkbox"/> Year | = 1 point | |

What season is it?

- | | | |
|--------------------------------|-----------|----------------------|
| <input type="checkbox"/> _____ | = 1 point | <input type="text"/> |
|--------------------------------|-----------|----------------------|

What is your phone number, including the area code?

- | | | |
|---------------------------------------|-----------|----------------------|
| <input type="checkbox"/> STD code | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Phone number | = 1 point | <input type="text"/> |

Count backwards from 20 to 1 (*allow two trials*)

- | | | |
|---|------------|----------------------|
| <input type="checkbox"/> Correct 1 st time | = 2 points | <input type="text"/> |
| <input type="checkbox"/> Correct 2 nd time | = 1 point | <input type="text"/> |

I'm going to read you a list of ten words. Please listen carefully and try to remember them. When I am finished, tell me as many of the words as you can. Ready?

The words are (*read list*)

Now tell me all the words you can remember.

- | | | |
|-----------------------------------|-----------|----------------------|
| <input type="checkbox"/> Cabin | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Pipe | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Elephant | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Chest | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Silk | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Theatre | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Watch | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Whip | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Pillow | = 1 point | <input type="text"/> |
| <input type="checkbox"/> Giant | = 1 point | <input type="text"/> |

One hundred minus 7 equals what?

(stop at 5 serial subtractions, do not inform of incorrect responses, but allow subtractions to be made from last response)

- | | | | | |
|----------------|--------------------------|----|-----------|----------------------|
| | <input type="checkbox"/> | 93 | = 1 point | <input type="text"/> |
| and from that? | <input type="checkbox"/> | 86 | = 1 point | <input type="text"/> |
| and from that? | <input type="checkbox"/> | 79 | = 1 point | <input type="text"/> |
| and from that? | <input type="checkbox"/> | 72 | = 1 point | <input type="text"/> |
| and from that? | <input type="checkbox"/> | 65 | = 1 point | <input type="text"/> |

What do people normally use to cut paper?

- | | | | |
|--------------------------|-------------------|-----------|----------------------|
| <input type="checkbox"/> | Scissors / shears | = 1 point | <input type="text"/> |
|--------------------------|-------------------|-----------|----------------------|

How many things are in a dozen?

- | | | | |
|--------------------------|----|-----------|----------------------|
| <input type="checkbox"/> | 12 | = 1 point | <input type="text"/> |
|--------------------------|----|-----------|----------------------|

What do you call the prickly green plant that lives in the desert?

- | | | | |
|--------------------------|--------|-----------|----------------------|
| <input type="checkbox"/> | Cactus | = 1 point | <input type="text"/> |
|--------------------------|--------|-----------|----------------------|

What animal does wool come from?

- | | | | |
|--------------------------|--------------|-----------|----------------------|
| <input type="checkbox"/> | Sheep / lamb | = 1 point | <input type="text"/> |
|--------------------------|--------------|-----------|----------------------|

Say this

(repeat only if poorly presented)

- | | | | |
|--------------------------|-----------------------|-----------|----------------------|
| <input type="checkbox"/> | No ifs, ands, or buts | = 1 point | <input type="text"/> |
| <input type="checkbox"/> | Methodist Episcopal | = 1 point | <input type="text"/> |

Who is the Prime Minister of Australia right now?

- | | | | |
|--------------------------|---------|-----------|----------------------|
| <input type="checkbox"/> | Julia | = 1 point | <input type="text"/> |
| <input type="checkbox"/> | Gillard | = 1 point | <input type="text"/> |

Who is the Premier of Queensland right now?

- | | | | |
|--------------------------|-------|-----------|----------------------|
| <input type="checkbox"/> | Anna | = 1 point | <input type="text"/> |
| <input type="checkbox"/> | Bligh | = 1 point | <input type="text"/> |

With your finger, tap 5 times on the part of the phone you speak into.

- | | | | |
|--------------------------|---------------------|------------|----------------------|
| <input type="checkbox"/> | 5 taps | = 2 points | <input type="text"/> |
| <input type="checkbox"/> | More or less than 5 | = 1 point | <input type="text"/> |

I'm going to give you a word and I want you to give me its opposite. For example, the opposite of hot is cold.

What is the opposite of "west"? ☐ East = 1 point

What is the opposite of "generous"? ☐ Selfish / stingy etc = 1 point

Can you tell me as many words as can from the original list that I read to you earlier?

<input type="checkbox"/> Cabin	= 1 point	<input type="text"/>
<input type="checkbox"/> Pipe	= 1 point	<input type="text"/>
<input type="checkbox"/> Elephant	= 1 point	<input type="text"/>
<input type="checkbox"/> Chest	= 1 point	<input type="text"/>
<input type="checkbox"/> Silk	= 1 point	<input type="text"/>
<input type="checkbox"/> Theatre	= 1 point	<input type="text"/>
<input type="checkbox"/> Watch	= 1 point	<input type="text"/>
<input type="checkbox"/> Whip	= 1 point	<input type="text"/>
<input type="checkbox"/> Pillow	= 1 point	<input type="text"/>
<input type="checkbox"/> Giant	= 1 point	<input type="text"/>

TICS Total

Appendix 2: Data Collection Tool**The Effects of a Multi-Modal Exercise Program on Cognition in Older Women:
A Randomised Controlled Trial****Participant's Name:** _____**Please take these sheets with you for all your tests.****Then please leave these sheets with the research assistant or some member of
the research team before you go home.****If found please return these sheets to:****Sue Vaughan**

C/- School of Rehabilitation Sciences

Building G02

Griffith University

Gold Coast Campus

QLD 4222

.....

Office use only:Front 2 pages removed ☐CID on all subsequent pages ☐Checklist completed ☐ By: _____

**The Effects of a Multi-Modal Exercise Program on Cognition in Older Women:
A Randomised Controlled Trial**

Baseline Data Collection Tool

Contact details

Participant Name	Contact Phone No:	
Address		
DOB	GP Name & Surgery:	
Emergency contact: Name: Relationship:		Phone No.s
Contact if having difficulty with participant contact Name: Relationship:		Phone No.s

The Effects of a Multi-Modal Exercise Program on Cognition in Older Women

Data Collection Tool: Anthropometric, Demographic and Health History

Anthropometric variables

Measure	Value
Height (m)	
Weight (kgs)	
Waist Circumference (cms)	
Hip Circumference (cms)	
Heart rate (bpm)	
Blood pressure (mmHg) – Sys/Dias	

Demographic/medical history variables

Measure	Value
Age	
Years of education	

Health History – Geriatric Index of Comorbidities: Score: _____

	No (0)	Asympt (1)	Sympt + Rx = Control (2)	Sympt + Rx = Uncont (3)	Life threat (4)
Heart problems (ischaemic, organic, arrhythmia)	0	1	2	3	4
Other heart disease (failure, cardiomyopathy)	0	1	2	3	4
Hypertension	0	1	2	3	4
Stroke	0	1	2	3	4
Peripheral Vascular Disease	0	1	2	3	4
Diabetes	0	1	2	3	4
Anaemia	0	1	2	3	4
GIT disease	0	1	2	3	4
Liver/biliary disease	0	1	2	3	4
Renal disease	0	1	2	3	4
Respiratory disease	0	1	2	3	4
Parkinson's disease	0	1	2	3	4
Non-vascular neuro disease	0	1	2	3	4
Musculo-skeletal	0	1	2	3	4
Cancer	0	1	2	3	4

The Effects of a Multi-Modal Exercise Program on Cognition in Older Women
Data Collection Record
Cognitive Tests – Scoring Record

<i>Test</i>	<i>Test completed (X + Initials)</i>	<i>Result</i>
Letter number sequencing		
Total correct (x/24)	<input type="checkbox"/>	
Longest span correct		

COWAT		
Numbers of words - F	<input type="checkbox"/>	
Numbers of words - A		
Numbers of words - S		

California Older Adult Stroop Test		Time	Self-corrected errors	Uncorrected errors
Colours	<input type="checkbox"/>			
Word				
Interference				
Total				

Trail Making Test		
Part A – total time (secs)	<input type="checkbox"/>	
Part B – total time (secs)		

Reaction time		
Simple reaction time (secs)	<input type="checkbox"/>	
Complex reaction time (secs)		

Older Women, Exercise and Cognition Study: Protocol Version 2 Date 24-7-12

The Effects of a Multi-Modal Exercise Program on Cognition in Older Women

Data Collection Record

Physical functioning scoring record

Test	Results	Notes
Timed up and go		
Time (secs)	T1	
Time (secs)	T2	Unstable on turning Yes No
Time (secs)	T3	Walking aide used? Yes – type of aid No
6 minute walk test		
Laps		
Distance		
Balance test (one-legged)		
Time (mins:secs)	T1	
Time (mins:secs)	T2	
Time (mins:secs)	T3	

Comments

--

The Effects of a Multi-Modal Exercise Program on Cognition in Older Women**Data Collection Record****Blood Test Record**

Test
Collected By: Place: Date: Transported by: Aliquots Number stored: Stored Date: Place: Analysed By: Date:

DASS 21

Please read each statement and circle a number 0, 1, 2, 3 which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all

1 Applied to me to some degree, or some of the time

2 Applied to me to a considerable degree, or a good part of the time

3 Applied to me very much, or most of the time

		Not at all /Never	Some	A lot	Very much
1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (i.e. in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (e.g., racing heart or missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt life was meaningless	0	1	2	3

Appendix 3: California Older Adult Stroop Test (COAST)

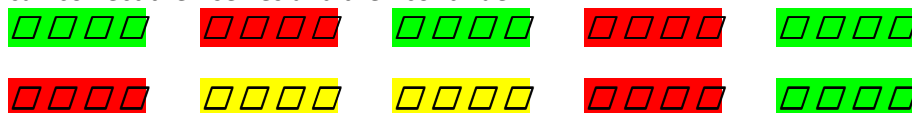
California Older Adult Stroop Test

Participants are required to first name colours (Colour), then read colour name words (Word); and then name ink colours when the names of colours are printed in a different (non-corresponding/incongruent) colour ink (Interference). COAST has been developed for use with older populations (Pachana et al., 2004).

Example:

There are three cards given to participants in order.

Card 1 = Has patches of the colours green, red and yellow (see below) covering the A4 page and participants are asked to read out the colours of the 50 patches from left to right, from the top of the page to the bottom, as quickly as possible. They are informed that if they make a mistake they can correct themselves and then continue.



Etc, etc x 10 lines

Card 2 = Has the words GREEN, RED and YELLOW (see below) covering the A4 page and participants are asked to read out the words from left to right, from the top of the page to the bottom, as quickly as possible. They are informed that if they make a mistake they can correct themselves and then continue.

RED	GREEN	YELLOW	RED	YELLOW
GREEN	YELLOW	RED	YELLOW	GREEN

Etc, etc x 10 lines

Card 3 = Has the words GREEN, RED and YELLOW (see below) written in non-concordant colours covering the A4 page and participants are asked to read out the colour of the ink the words are written in (not what the word spells) from left to right, from the top of the page to the bottom, as quickly as possible. They are informed that if they make a mistake they can correct themselves and then continue.

RED	GREEN	YELLOW	RED	YELLOW
GREEN	YELLOW	RED	YELLOW	GREEN

Etc, etc x 10 lines

Scoring = Three scores: 1) time taken to read out each card

2) the number of self-corrected errors for each card.

3) the number of uncorrected errors for each card

Appendix 4: Controlled Word Association Test (COWAT)

Controlled Oral Word Association Test (COWAT)

Participants are given one minute to generate as many words as possible that begin with a specific letter. This task is repeated three times with three different letters (e.g., F, A, S).

I will say a letter of the alphabet. Then I want you to give me as many words that begin with that letter as quickly as you can. For instance, if I say “B” you might give me “bad”, “bottle”, “bed”. I do not want you to use words that are proper names such as “Brisbane”, “Bob” or “Bunnings”. Also do not use the same word again with a different ending such as “Beat” and “Beating”. Any questions? (pause)

Begin when I say the letter. The first letter is “F”. Go ahead.

Write down all the words said.

If the person becomes silent, encourage them to think of additional words and/or repeat some of the instructions.

After 60 seconds say – **Good. Now I’m going to give you the second letter. It is “A” – go ahead.**

Write down all the words said.

If the person becomes silent, encourage them to think of additional words and/or repeat some of the instructions.

After that 60 seconds say – **Good. Now I’m going to give you the third letter. It is “S” – go ahead.**

Write down all the words said.

If the person becomes silent, encourage them to think of additional words and/or repeat some of the instructions.

After 60 seconds say – **Good. That’s the end of that test.**

To calculate the final score count all the correct words (i.e. not proper nouns, repetitions or additional words with different endings).

Appendix 5: Letter-Number Sequencing Test (LNST)

The Letter-Number Sequencing test measures executive function, specifically working memory. The participant is read a combination of numbers and letters and is asked to recall the numbers first in ascending order and then the letters in alphabetical order. There are six trials and each consists of four items with different combinations of numbers and letters. The six trials range from 2-letter/number sequences (e.g., B-7) to 8-letter/number sequences (e.g., S-2-L-8-B-1-G-7). Prior to the test trials, one practice trial is given. The tester says each combination at a rate of one number or letter per second, and allows the participant sufficient time to respond. Testing is discontinued after scores of zero for four items in the same row. For each item, the participant is given a score of 1 for a correct response and a score of 0 for an incorrect response. A response is incorrect if a number or letter is omitted or not given in the specified sequence within the block (i.e., letter block or number block). The maximum score possible is 24 points, four items in each of the six trials.

Letter Number Sequencing Test

ADMINISTRATION

1. FOLLOW THE INSTRUCTIONS BELOW FOR PRACTICE ITEMS AND EXPERIMENTAL CONDITIONS:

- This test is not timed.
- Read each item sequence at the rate of one character per second. You may use your stopwatch to ensure a steady pace.
- Be sure to clearly enunciate each letter and number so that the participant hears you correctly. Items may not be repeated.
- The correct answers are in parentheses below each item. Write the participant's response on the line below each item.
- If the participant gives the wrong sequence, circle the item.
- A participant may correct herself if the administrator has not yet moved on to the next sequence. If this happens, write "self-correct" next to the item.

2. GIVE INSTRUCTIONS FOR ADMINISTRATION OF PRACTICE ITEMS:

"I am going to say a list of numbers and letters. When I am through, I want you to first tell me the numbers in order from smallest to biggest. Then, I want you to tell me the letters in alphabetical order. So, for example, if I say A4, the answer is 4A. The number goes first, then the letter. If I say 8B2, you answer 28B, numbers first in order, then letters. Try these."

PRACTICE ITEMS

7C	B9	2P9	Z9A	8MB
(7C)	(9B)	(29P)	(9AZ)	(8BM)
_____	_____	_____	_____	_____

IF:	THEN:
The participant gets any practice item wrong.	Correct her and say, <i>“Remember to first tell me the numbers in order from smallest to biggest and then the letters in alphabetical order.”</i> Continue to the next practice item.
The participant gets two of the three-symbol sequences wrong (2P9, Z9A, 8MB).	Repeat the full instructions and administer all practice items again. The practice trial may be administered no more than five times before moving on to the Experimental Condition.

3. ADMINISTER THE TEST:

“Good! Let’s try some more. Again, remember to say the numbers first and then the letters.”

IF:	THEN:
The participant asks you to repeat a sequence.	Say, <i>“I’m sorry, I cannot repeat it. Just do the best you can with what you thought you heard.”</i>
The participant gets any item wrong on the first line	Repeat the instructions.
The participant fails all four items on one line.	Stop testing and draw a line through the remaining items that were not attempted.

1. D6 (6D) _____	4L (4L) _____	M2 (2M) _____	3B (3B) _____
2. A1C (1AC) _____	W7T (7TW) _____	5R8 (58R) _____	9X3 (39X) _____
3. Y8G2 (28GY) _____	J3N1 (13JN) _____	2Z5H (25HZ) _____	4F5S (45FS) _____
4. 4L5C8 (458CL) _____	B1J7W (17BJW) _____	9K3E2 (239EK) _____	N6R2U (26NRU) _____
5. D7G4S2 (247DGS) _____	P6L3C1 (136CLP) _____	2W8K9A (289AKW) _____	4J5T7X (457JTX) _____
6. C7G4Q1S (147CGQS) _____	8R6M3F2 (2368FMR) _____	A2E6J9T (269AEJT) _____	3T4P7M9 (3479MPT) _____

Appendix 6: The Trail Making test (TMT) (Parts A & B)

Parts A & B of the TMT require the individual to mentally shift between two well-rehearsed sequences (numbers and letters). Shifting ability represents the capacity to adapt to changes in the environment by switching from one mental set to another.

Trail Making Test (TMT) Parts A & B

Instructions:

Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed.

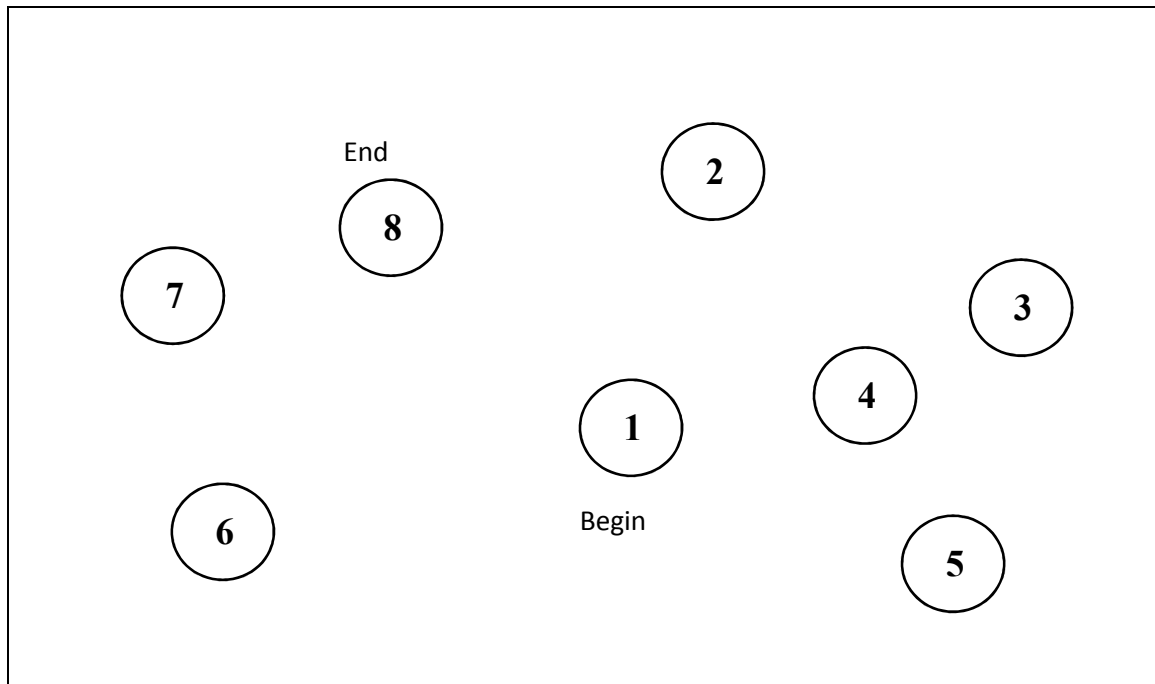
- Step 1: Give the patient a copy of the Trail Making Test Part A worksheet and a pen or pencil.
- Step 2: Demonstrate the test to the patient using the sample sheet (Trail Making Part A – *SAMPLE*).
- Step 3: Time the patient as he or she follows the "trail" made by the numbers on the test.
- Step 4: Record the time.
- Step 5: Repeat the procedure for Trail Making Test Part B.

Scoring:

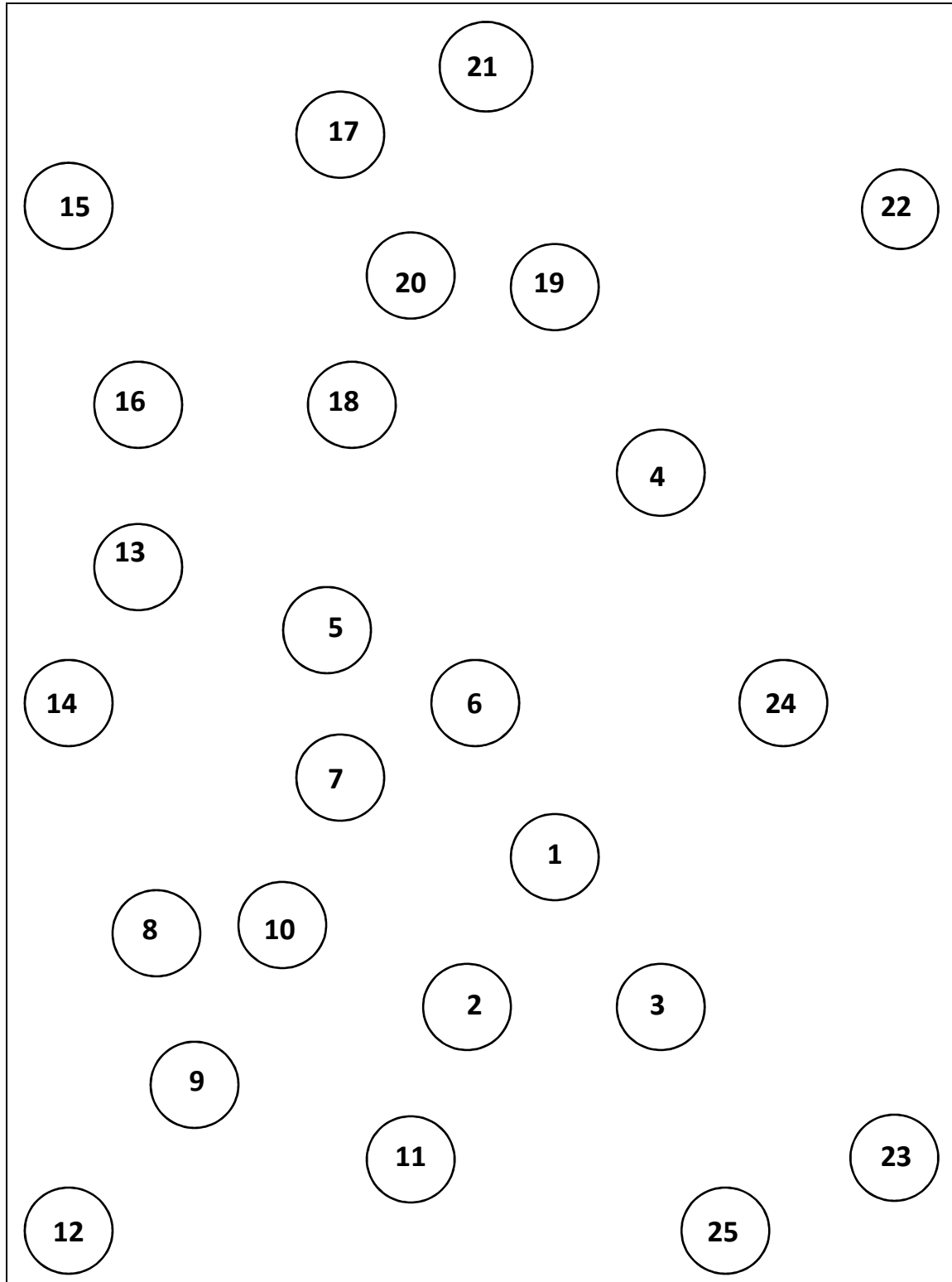
Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment.

	Average	Deficient	Rule of Thumb
Trail A	29 seconds	> 78 seconds	Most in 90 seconds
Trail B	75 seconds	> 273 seconds	Most in 3 minutes

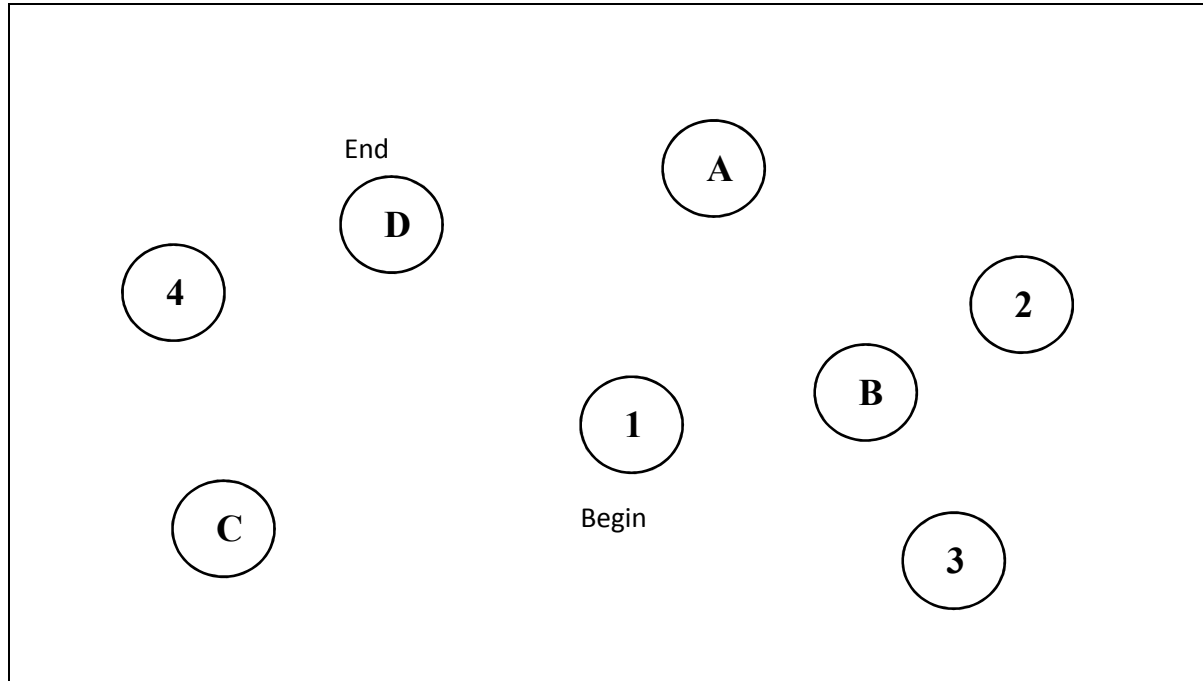
Trail Making Test Part A - Sample



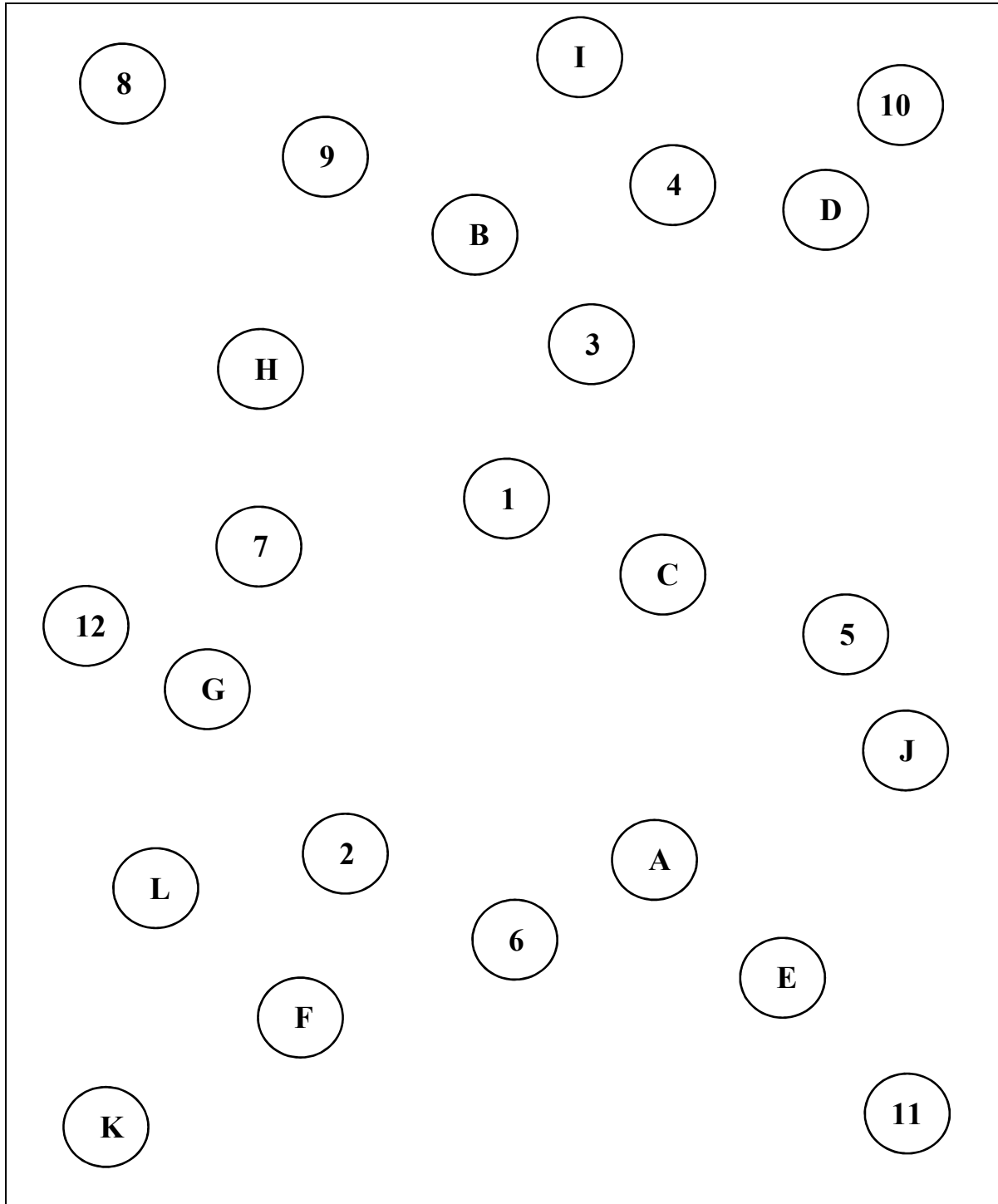
Trail Making Test Part A



Trail Making Test Part B - sample



Trail Making Test Part B



Appendix 7: Instructions for Reaction Time testing

Deary-Liewald Reaction Time Task – Standard Operating Procedure

Downloading the Programme:

Click on the download link on the website. Download the zip file and extract the files to the appropriate directory.

Compatibility:

You will need a computer which runs Windows XP, Vista or Windows 7 and a standard keyboard. We recommend using a screen with a vertical refresh rate of 60Hz or better.

Test Setup:

To open the programme, double click the “DLRT” application file. A window will appear, titled “Deary-Liewald Reaction Time Tester”. It displays a space for the Subject ID at the top, and three sections below with the titles “Simple Reaction Time”, “Choice Reaction Time” and “System Settings”, each containing various options and settings. These settings, and how to adjust and save them, are described in the “Adjustments to the Test” section below.

Deary-Liewald Reaction Time Tester

Active Dataset

Subject ID : 12345

Simple Reaction Time

Number of Practice Trials : 8 Number of Experiment Trials : 20

Response Range (ms) From 150 To 1500

Inter Stimulus Interval (ms) From 1000 To 3000

Run SRT Practice Run SRT Test

Choice Reaction Time

Number of Practice Trials : 8 Number of Experiment Trials : 40

Response Range (ms) From 200 To 1500

Inter Stimulus Interval (ms) From 1000 To 3000

CRT Key Box 1 Z CRT Key Box 2 X CRT Key Box 3 . CRT Key Box 4 .

Run CRT Practice Run CRT Test

System Settings

Create Study Save Settings Load Study

Creating a Study:

First you need to create a study: click “Create Study” under the “System Settings” section. This creates four CSV databases where the results are saved. To select where you want to save the results, either type or paste the directory into the space provided, or click on the icon to the right to browse folders. *We recommend that you create a new folder to save the results in.* Once you have selected an appropriate directory, click OK. A pop up window should appear saying “New Dataset Created and Activated!”.

Next you must save the settings you wish to use: See ‘Adjustments to Test’ section below for what the settings are and how to adjust them. (The default settings may be used and have been validated and used in previous studies, see [Deary, Liewald and Nissan, 2011](#).) Once you have chosen the settings (even if these are the default settings), click “Save Settings” under the “System Settings” section, and save to the appropriate directory. This creates a file which links the settings to the results databases you have just created for the study. You can reload this file at a later date and continue collecting results to the same databases. If you do not save settings you will have to create a new study each time you open the programme. To reload the study at a later date, click “Load Study” and open the appropriate settings file.

Running the Test:

First, make sure you have created a study and saved the settings.

Next, enter the Subject ID in the space provided. Make sure the participant is sitting comfortably with the computer and keyboard on a table in front of them.

(a) Simple Reaction Time

Click “Run SRT practice”. Confirm “Test Start” in the following dialogue box. Say:

First of all you will have a practice session. A cross will appear in the box on the screen (x) times and each time it appears you should press any key as quickly as you can. Don’t hold the key down, but press and release it when the cross appears. Use the index finger of your preferred hand to press the key throughout the test. When you are ready, press any key to start.

At the end of the practice a message will read “Test Completed Thank You!”. Wait a few moments for the screen to disappear.

Check the participant understands what to do. Click “Run SRT Test”. Confirm “Test Start” in the following dialogue box. Say:

Now a cross will appear another (x) times and you should press any key as quickly as you can, as in the practice. When you are ready, press any key to start.

At the end of the test a message will read “Test Completed Thank You!”. Wait a few moments for the screen to disappear.

You can abort the experiment at any time by hitting the “Escape” key on the keyboard.

N.B. If a participant holds a key down instead of releasing it, the cross will remain on the screen and the next trial will not begin until the key is released. Also, if a response falls out of the response range, it will not be recorded and will be replaced by another trial.

(b) Four Choice Reaction Time

Say:

In this test there will be four boxes on the screen. A cross will appear in one of them and you have to press the correct key for that box as quickly as you can.

Click “Run CRT practice”. Confirm “Test Start” in the following dialogue box. Say:

When the cross appears in the box on the far left press the “z” key (point to each), when it appears in the box one from the left press the “x” key (point to each); when the cross appears in the box on the far right press the “full stop” key (point to each) and when it appears in the box one from the right press the “comma” key (point to each).

Place the middle and index fingers of your left hand over the “z” and “x” keys like this (indicate which keys) and the index and middle fingers of your right hand over the “comma” and “full stop” keys like this (indicate which keys).

As before you will have a practice of (x) crosses first. Remember, a cross can appear in any of the four boxes. When you are ready, press any key to start.

At the end of the practice a message will read “Test Completed Thank You!”. Wait a few moments for the screen to disappear.

Check the participant understands what to do. Click “Run CRT Test”. Confirm “Test Start” in the following dialogue box. Say:

You will now see another (x) crosses appear one after another and you should respond as quickly as you can by pressing the correct key, as in the practice. When you are ready, press any key to start.

At the end of the test a message will read “Test Completed Thank You!”. Wait a few moments for the screen to disappear.

You can abort the experiment at any time by hitting the “Escape” key on the keyboard.

N.B. If a participant holds a key down instead of releasing it, the cross will remain on the screen and the next trial will not begin until the key is released. Also, if a response falls out of the response range, it will not be recorded and will be replaced by another trial.

Adjustments to the Test

Number of Trials: You can adjust the number of practice trials and experiment trials in both the Simple Reaction Time and Choice Reaction Time tasks. To do this, simply type in the number of trials you want to use.

Response Range and Inter Stimulus Interval: You can adjust the “Response Range” and “Inter Stimulus Interval” for both the Simple Reaction Time and Choice Reaction Time tasks. To do this you simply type in the times you want to use.

- *Response Range* is measured in milliseconds and is the range of reaction times for which the response is recorded. If a person’s response is outside of this range, it will not be recorded. For example, if the Response Range is from 150ms to 1500ms, a response of 100ms will not be recorded.

- *Inter Stimulus Interval* is measured in milliseconds and refers to the gap between each response and when the next cross is displayed. The Inter Stimulus Interval specifies the longest and shortest gap permitted, and the crosses appear randomly within these boundaries.

Response Keys: You can adjust the keys used in the Choice Reaction Time task. To do this you simply type in the keys you want to use. “CRT key box 1” corresponds to the box on the far left of the screen, “CRT key box 2” corresponds to the box second from the left, “CRT key box 3” to the box third from the left, and “CRT key box 4” to the box on the far right.

Saving Settings: You can save any adjustments by clicking the “Save Settings” button in the “System Settings” section, and then load them up later by clicking the “Load Study” button.

(*Note:* when you save settings, this saves a file which links the settings to the results databases you are currently working on. So when you load a settings file it will continue to collect results to the same databases that were in use when that settings files was saved. If you wish to save results to a new database, you will need to create a new study.)

The original default settings for the task have been validated and used in previous studies, see [Deary, Liewald and Nissan, 2011](#). These were the settings used in the Griffith University Effects of a Multi-Modal Exercise Program on Cognition in Older Women Study. They are as follows:

Simple Reaction Time:

Number of Practice Trials = 8
 Number of Experiment Trials = 20
 Response Range = 150-1500ms
 Inter Stimulus Interval = 1000-3000ms

Choice Reaction Time:

Number of Practice Trials = 8
 Number of Experiment Trials = 40
 Response Range = 200-1500ms
 Inter Stimulus Interval = 1000-3000ms
 CRT Key Box 1 = z
 CRT Key Box 2 = x
 CRT Key Box 3 = ‘comma’
 CRT Key Box 4 = ‘full-stop’

Viewing the Results:

The results of the Simple Reaction Time task and the Choice Reaction Time tasks are saved to the directory chosen when the study was created (see above). Results are saved to four different CSV files (these files can be opened and edited with Microsoft Excel and other applications). Data from the Simple Reaction Time task are stored in the SRT_Detail and SRT_Header files. Data from the Choice Reaction Time task are stored in the CRT_Detail and CRT_Header files. The “Detail” files show the individual item data for each trial, and the “Header” files show summary statistics for each participant.

The data from the SRT Header and CRT Header files were copied and pasted into SPSS for data analysis.

Appendix 8: Instructions for Six Minute Walk Test (6MWT)

Instructions

Six minute walk test

The Six-minute walk test is a functional measure of aerobic fitness and is based on the number of meters walked in six minutes (American Thoracic Society, 2002).

Six Minute Walk Test (6MWT) - Instructions

General Description

Purpose

The original purpose of the six minute walk was to test exercise tolerance in chronic respiratory disease and heart failure. The test has since been used as a performance-based measure of functional exercise capacity in other populations including healthy older adults, people undergoing knee or hip arthroplasty, fibromyalgia, and scleroderma. It has also been used with children.

Content

The six-minute walk test (6MWT) measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway.

Administration

Method This is ideally conducted in an enclosed, quiet hallway by a single administrator. However, it is important to note that there are variations among studies in how the test is conducted which affects performance. These variations include the instructions provided to the participant, the number of turns in the course, the frequency and type of encouragement given, and the number of trials performed. Each of these variations will be outlined briefly.

- **Test instructions:** Participants walk at their usual pace or a comfortable pace and to walk as far as possible. Participants are instructed prior to the test to wear comfortable clothing and shoes and to use their typical walking aid during the test.
- **Walkway length and number of turns in the course:** The American Thoracic Society (ATS) recommends an indoor, 30 meter corridor or walkway with cones placed at the beginning and end of the 30 meter boundary to indicate turns. In the literature, the corridor distance across studies varies which is likely due to the need to use what is readily available.
- **Use of Encouragement:** Encouragement is given in a standardized manner, starting at the halfway point and then every 30 seconds.
- **Number of Trials Performed:** Number of trials has been known to increase 6 minute walk distance. Thus in this study the walk will be performed twice on each occasion.
- **Safety Issues and Contraindications:** As with any physical performance test, technicians should have certification in Basic Life Support. Contraindications for this test as recommended by the ATS include unstable angina in the previous month, myocardial

infarction in the previous month, and high blood pressure (resting heart rate of > 120, systolic blood pressure of 180 mm Hg, or diastolic blood pressure > 100 mm Hg). The test should be stopped if a person reports chest pain, intolerable shortness of breath, leg cramps, staggering, diaphoresis, or pale/ashen appearance¹⁵.

- **Training:** A standard protocol should be followed and each new technician should be trained in test administration and observed several times.

Time to administer/complete

20 minutes or less.

Equipment needed

- A 30 meter, pre-measured flat walking area with interval markings every three meters.
- Cones or brightly colored tape to mark boundaries of the course
- Watch or timer to time 6 minutes
- Chair available if patients need to rest during testing

Scoring

Outcomes measured

The primary outcome is the distance covered in meters or converted measure (such as meters) over 6 minutes.

Interpretation of scores

A lower score (reflecting less distance covered in 6 minutes) indicates worse function.

Method of scoring

Administrator tallies the total distance walked using the pre-marked intervals as a guide.

Appendix 9: Instructions for the Timed Up and Go Test (TUGT)

Instructions

Physical functioning: Timed Up-and-Go

This is a clinical performance based measure of mobility, lower extremities function and fall risk. It is normally distributed, related to executive function and suitable for the assessment of healthy older adults (Herman et al., 2011).

Timed “Up and Go”*

Directions

The timed “Up and Go” test measures, in seconds, the time taken by an individual to stand up from a standard arm chair (approximate seat height of 46 cm [18in], arm height 65 cm [25.6 in]), walk a distance of 3 meters (118 inches, approximately 10 feet), turn, walk back to the chair, and sit down. The subject wears their regular footwear and uses their customary walking aid (none, cane, walker). No physical assistance is given. They start with their back against the chair, their arms resting on the armrests, and their walking aid at hand. They are instructed that, on the word “go” they are to get up and walk at a comfortable and safe pace to a line on the floor 3 meters away, turn, return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a stopwatch or a wristwatch with a second hand can be used to time the trial.

Instructions to the patient

“When I say ‘go’ I want you to stand up and walk to the line, turn and then walk back to the chair and sit down again. Walk at your normal pace.”

Variations

You may have the patient walk at a fast pace to see how quickly they can ambulate. Also you could have them turn to the left and to the right to test any differences.

*Podsiadlo D, Richardson S. The timed “up and go”: a test of basic functional mobility for frail elderly persons. *JAGS* 1991; 39: 142-148.

Scoring

Time for ‘Up and Go’ test _____ sec.

Unstable on turning?

Walking aid used? Type of aid: _____

Appendix 10: Instructions for the One Legged Stance Test (OLST)

One Legged Stance Test

Instructions

The one-leg stance test requires participants to stand unassisted on one leg with hands on hips.

Participants are asked to stand on one preferred leg, flex the opposite knee allowing the foot to clear the floor; then balance on the one leg for as long as possible.

Timing begins when the leg is lifted and is timed in seconds until the person returns the non-weight bearing foot to the ground.

SCORE: Time in seconds: tenths of a second

Appendix 11: Completed intervention fidelity checklists

Phase 1 checklist – Weeks 1-5

Component	Allocated Time	Actual time Week 2	Actual time Week 5
Group freestyle			
Aerobics	10 mins	10 mins	9.5 mins
Agility	-		
Group and/or circuit			
Strength	15 mins	14.5 mins	15 mins
Balance	10 mins	11 mins	10 mins
Co-ordination/ Agility/ Reaction time	15 mins	15.5 mins	15 mins
Cardio	-		
Group			
Flexibility and warm down	10 mins	10 mins	10 mins

Phase 2 checklist – Weeks 6-9

Component	Allocated Time	Actual time Week 7	Actual time Week 9
Group freestyle			
Aerobics	15 mins	15 mins	15 mins
Agility	5 mins	5 mins	5 mins
Group and/or circuit			
Strength	10 mins	10 mins	10 mins
Balance	10 mins	10 mins	10 mins
Co-ordination/ Agility/ Reaction time	10 mins	10 mins	10 mins
Cardio	-	-	-
Group			
Flexibility and warm down	10 mins	10 mins	10 mins

Phase 3 checklist – Weeks 10-16

Component	Allocated Time	Actual time Week 11	Actual time Week 15
Group freestyle			
Aerobics	15 mins	16 mins	15 mins
Agility	5 mins	7 mins	5 mins
Group and/or circuit			
Strength	10 mins	10 mins	10 mins
Balance	7 mins	7 mins	7 mins
Co-ordination/ Agility/ Reaction time	7 mins	5 mins	7 mins
Cardio	6 mins	5 mins	6 mins
Group			
Flexibility and warm down	10 mins	10 mins	10 mins

Appendix 12: Exercise intervention participant attendance sheet

Names (In alphabetical order)	Week:		Week:		Week:		Week:		Week:		Week:		Week:		Total attendances
	Tues	Fri	Tues	Fri	Tues	Fri	Tues	Fri	Tues	Fri	Tues	Fri	Tues	Fri	
A															
B															
C															
D															
E															
F															
G															
H															
I															
J															
K															
L															
M															
N															
O															
P															
Q															
R															
S															
T															
U															
V															
W															
X															

Appendix 13 = Qualitative interview schedule

Conversational interview style

Introduce yourself to participant

Explain that they have already signed a consent form but you want to check it is OK to:

1. Talk to them about the classes and any changes they have experienced in the past 16 weeks
2. Digitally record the interviews so that they can be written down accurately

Then commence recording.

Sequence of interview:

1. State: date, time and venue
2. State: Name of participant and name of interviewer
3. Questions about the classes (if getting the same data repeatedly drop this question)
 - Please describe a typical exercise class.
 - What aspects of the class did you find most/least enjoyable?
4. Questions about changes to the participant
 - What aspects of the class did you find least/most beneficial?
 - Why?
 - What changes if any, have you noticed about yourself that you think may relate to class attendance? Can you give me an example?
5. Questions about anecdotal changes reported by others
 - Has anyone else (family or friends) noticed a difference in you? What did they say?

Appendix 14: Participant information and consent form**Participant Information and Consent Form**

Full Project Title: Effects of a multi-modal exercise program on cognitive functions in older women

Primary Supervisor: Professor Norm Morris

School of Physiotherapy and Exercise Science, Gold Coast Campus, Griffith University: (07) 5552 8921. Email: n.morris@griffith.edu.au

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Associate Supervisor: Dr Siobhan O'Dwyer

Research Centre for Clinical Practice Innovation, Nathan Campus, Griffith University: (07) 3735 6619 Email: s.o'dwyer@griffith.edu.au

1. Your Consent

You are invited to take part in a research project being conducted by Sue Vaughan who is a student researcher currently enrolled as a PhD candidate in the School of Physiotherapy and Exercise Science at Griffith University

This Participant Information form contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures and activities involved in this project before you decide whether or not to take part in it.

Please read this Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of the Participant Information and Consent Form to keep as a record.

2. Purpose and Background

The purpose of this project is to determine how effective a 16-week program of combination exercise classes is in increasing the cognitive function (mental processes), and physical function in women between the ages of 65 and 75 years. Specifically the primary aim of this research is to contribute to knowledge about how exercise affects memory, concentration, distractibility and reaction times in older women.

It is known that exercise has beneficial effects on physical functioning including balance, strength and stamina. Some studies have also indicated that there might be a link between exercise and the ability of the brain to work well, in later life. What is not clear is whether exercise that specifically targets the workings of the brain can result in better memory, concentration, reaction times and less distractibility. It is also not completely clear how specific exercise programs might improve physical functioning.

Previous studies have suggested that a good combination of exercises might include not just activities that raise the heart rate and increase strength but also exercises that deliberately target balance, flexibility and things like co-ordination, concentration and agility. In this study a specifically designed program which includes all these elements will be tested.

3. What you will be asked to do

Participation in this project will involve:

- Completion of one questionnaire and six tests of your mental abilities at the beginning of the study and again after the completion of the study (16 weeks later). This should take less than one hour to complete.
- Completion of three tests of your physical functioning performed at the commencement of the study and 16 weeks later. These tests assess your capacity to walk, rise from a seated position and maintain your balance and will take less than 15 minutes to complete.
- Collection of information about your health status including measurement of blood pressure, height, weight, waist:hip ratio and co-morbidities.
- The collection of a sample of your blood (approximately 8mls) at the commencement of the study and 16 weeks later. The blood will be collected by an appropriately qualified health professional and will not involve any cost to you.
- Being allocated to either a control or intervention group. Half the participants will be randomly assigned to an intervention group and will participate in the 16-week exercise program being tested and the other half will maintain their usual lifestyle and activities for the duration of the study. Participants not in the initial exercise program will be offered the 16-week exercise program free of charge. This second 16-week program will commence when testing has been completed at the end of the initial 16-week study.
- The intervention is a one-hour, twice a week program that will be conducted on Tuesday and Friday mornings for 16-weeks. Participants are asked to plan on attending at least 85% of the 32 sessions (27 sessions).

- The classes will be offered in nearby, local community halls and you will be responsible for your own transport to the classes.
- If you are randomly allocated to the intervention (exercise group) you may be invited to participate in a tape-recorded interview about your experiences in the exercise program. The interviews will be transcribed and the original audio files deleted.

Continual review and monitoring will take place, regarding the efficiency and safety of the research project, and this will enable early detection of any problems, in the unlikely event that they arise.

4. Why you have been invited to participate

You have been invited to participate in this important study because you are a relatively healthy woman between the ages of 65-75 years, who is not currently engaged in more than one hour per week of formal exercise and you have been assessed as being able to participate safely in the exercise program.

5. Possible Benefits

Exercise has been demonstrated to result in physical improvements related to balance, stamina, strength and flexibility. This program may also result in improved brain functioning in areas such as memory and concentration. While we cannot guarantee or promise that you will receive any benefits from this study it will help us establish whether this exercise program is effective and could thus benefit many older women in the future. If the research indicates that this program is not effective the results may save people time and money in the future by identifying an ineffective program.

6. Possible Risks

The physical risks associated with this study are those associated with any exercise program. There is always the risk that some form of injury could occur during exercise; however, specific steps have been taken to increase the safety of this particular program including the presence of two instructors at each class.

The main risk involved in the testing of physical functioning is that of physical injury. However, all testing will be undertaken by appropriately trained members of the research team and according to strict safety protocols.

The main risks of blood tests are discomfort and bruising at the site where the needle is inserted. These issues usually are minor and go away shortly after the tests are done.

The psychological risks associated with the study are also slight and include the possibility of encouraging a sense of anticipation of improved brain function when this kind of outcome is not realised.

There may be additional unforeseen or unknown risks. Consequently we will ask you to report any concerns or observations to the research team, the exercise instructors or the research assistants who will be in regular contact with you.

7. Lifestyle While Involved in This Study

During the 16 weeks of the study, whether you are in the exercise group or the waiting list group, you will be asked to continue with your usual lifestyle.

8. Privacy, Confidentiality and Disclosure of Information

Griffith University conducts research in accordance with the National Statement on Ethical Conduct in Human Research. The conduct of this research involves the collection, access and / or use of your identified personal information. The information collected is confidential and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. A de-identified copy of this data may be used for other research purposes. However, your anonymity will at all times be safeguarded. If you participate in the tape-recorded interview about your experiences in the exercise program the audio recordings will be erased/ destroyed by the student investigator, once transcribed and after being checked by the student investigator. Again your anonymity will be safeguarded at all times. If you give us your permission by signing the Consent Form, we plan to report on the findings of the study in such a way that no individuals will be identifiable. We plan to complete a report for Griffith University, other funding bodies, the ethics committee involved and to publish papers in research and health professional journals.

For further information you can consult the University's Privacy Plan at <http://www.griffith.edu.au/privacy-plan> or telephone (07) 3735 5585

9. Participation is Voluntary and Free of Charge

Participation in this research project is voluntary and completely free of charge. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, in this project, or to take part and then withdraw, will not affect your relationship with Griffith University or with the exercise professionals conducting this program.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers. If you decide to withdraw from this project, please notify a member of the research team before you withdraw.

10. If you have any questions

If you have any questions we hope and expect that you will ask us. If you have any additional questions later, Sue Vaughan or any of the Research Assistants involved in the project will be happy to answer them. They can be contacted on either 0405 536 994 or (07) 5527 7240.

This study has been reviewed and approved by the Human Research Ethics Committee of Griffith University. Should you wish to discuss the study with someone not directly involved, in particular in relation to matters concerning policies, information about the conduct of the study or your rights as a participant, or should you wish to make an independent complaint, you can contact the Senior Manager, Research Ethics and Integrity on 3735 5585 or research-ethics@griffith.edu.au.

11. Feedback to you

If you wish to have individual feedback on the results of the tests and questionnaires you completed during the study you will be asked to provide contact details at the last data collection session. If any of your testing indicates an unexpected abnormal result, this will be communicated to you so that you can consult your general practitioner.

This information has been provided to allow you to give informed consent.

Consent Form**Version 3 Dated 21st June 2012****Site: Griffith University****Full Project Title: Effects of a multi-modal exercise program on cognitive functions in older women**

Thank-you for agreeing to participate in this important research study. Although you may not benefit personally, you will have helped provide valuable information that will help us to deliver safe and cost effective care.

I have had the contents of this information sheet explained to me and I have been provided with a copy. I agree to be enrolled in the project and understand that this will involve either participation in a 16 week exercise program or in being on a waiting list for the 16-week exercise program.

Please read the following carefully, and sign below if you agree with these statements and are happy to participate in the study

1. I have read and understood the information sheet and this consent form.
2. I have had the opportunity to ask questions about the study and these have been answered to my satisfaction.
3. I understand that this project is for research and that I may not benefit directly.
4. I have been informed that the information collected about me in this study will remain confidential and will be adequately safeguarded, and that when results are published, they will be presented in such a way that I cannot be identified.
5. I understand that if I do participate, I am free to withdraw my consent and to discontinue participation at any time without comment, and with no effect on my treatment or my relations with Griffith University in any way.
6. If I have any questions or comments about the study at any time I am free to contact, Sue Vaughan, at Griffith University on (07) 5527 7240 or 0405 536 994.
7. If I have any complaints about the ethical conduct of the study, I may direct these to the Senior Manager, Research Ethics and Integrity, Griffith University, on (07) 3735 5585

I agree to participate in the study.

Name:.....Signature:.....Date: __/__/__

Appendix 15: Griffith University Human Ethics Committee (HREC) approvals and correspondence

GRIFFITH UNIVERSITY HUMAN RESEARCH ETHICS COMMITTEE

17-Mar-2012

Dear Ms Vaughan

I write further to your application for ethical clearance for your project "Full Review: The Effects of a Multi-Modal Exercise Program on Cognition in Older Women: A Randomised Controlled Trial" (GU Ref No: PES/05/12/HREC). This project has been considered by Human full review.

The Committee resolved to grant this project provisional ethical clearance, subject to your response to the following matters:

Please note that not all members of the HREC were present at this meeting and therefore the information may be subject to amendment. We have allowed 14 days for our consultation with the absent members. We will contact you again if any further comments or conditions arise from that consultation.

Please clarify as to why men are not included in the study as the GUHREC could not find any justification provided within the application other than Women only will be recruited to the study, as women live longer than men and are more at risk of cognitive impairment. There also seems to be a gender effect for aerobic exercise on cognitive function, thus limiting the groups to women removes this confounding variable.

The control group is described in the Proposal Description as being "asked to refrain from formal exercise for the 16-weeks of the study". In the Participant Information and Consent Form, point 7 asks that this group does not engage in "formal exercise activities that exceed one hour per week". Which is the correct requirement?

Following on from the above the GUHREC is of the view that it would be against the participants interest to ask them to refrain from exercise, it is assumed that normal practice should be maintained.

Clarification as to when the exercise classes will be held and how participants will be accommodated with respect to transport arrangements. It is noted that participants will be taken to venues for data collection, will this also happen for the exercise classes. This information should be provided in the informed consent materials.

Clarification as to whether any public liability insurance is required for the duration of the activities to be undertaken in community halls. If so how will this be funded. The applicant is asked to consult Mr Trevor Case the University Risk Insurance Manager.

Please note (s7.15) clinical trial data is required to be kept for 15 years from completion of trial and 10 years after last patient service provision or medico-legal action. (see <http://www62.gu.edu.au/policylibrary.nsf/binders/d5a1e9c2c478bafb4a25753d0062edf6?opendocument>)

Clarification as to whether the student researcher will be undertaking all the testing as described (for example: questionnaires, physical testing, DXA scans,). Please include a list of personnel involved in each of the testing procedures with their relevant qualifications and expertise.

Following on from the above, how will confidentiality be maintained if there are a number of people involved in data-sharing.

Given the age group involved, what experiences do members of the Research Team (including supervisors) have in gerontological studies?

Clarification as to whether the student researcher has previous experience running fitness classes for women aged 65 – 75.

Provision of the personal details (Name, qualifications) of the person who will Chair the Data and Safety Monitoring Board once s/he becomes known to the research team.

Throughout the application the risks are described as minor or low, yet in s5.4.1 there is discussion of 'incidents that may result in death or hospitalisation' please comment on this discrepancy.

Amendment of the informed consent package to include a legal privacy statement. Please note that the Commonwealth Privacy Commissioner has classified opinions as personal information. Sample wording for such statements can be found in Booklet 22 of the Manual for example; where no ordinary disclosure is anticipated: The conduct of this research involves the collection, access and / or use of your identified personal information. The information collected is confidential and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. A de-identified copy of this data may be used for other research purposes. However, your anonymity will at all times be safeguarded. For further information consult the University's Privacy Plan at <http://www.griffith.edu.au/privacy-plan>. or telephone (07) 3735 5585.

Amendment to the information material to indicate that Griffith University conducts research in accordance with the National Statement on Ethical Conduct in Human Research. If potential participants have any concerns or complaints about the ethical conduct of the research project they should contact the Senior Manager, Research Ethics and Integrity on 3735 5585 or research-ethics@griffith.edu.au.

Provision of further information on the informed consent material as to the 3 tests to determine 'physical functioning'.

Clarification as to the costs involved in blood testing, and how they will be borne by the research team. Participants should be informed that they will have no costs and this should be made clear on the informed consent materials.

The informed consent material indicates that participants might be invited to a tape recorded interview – there was no mention of this in the NEAF.

Provision of some sample questions to be asked to participant groups which gives a sense of the most intrusive or ethically sensitive line of questioning.

Clarification of whether digital [video/audio] recordings are to be erased/deleted following transcription / analysis. This should be discussed in the informed consent materials and specific consent sought for any proposed retention and use beyond transcription / analysis.

Clarification as to when the participants in the control group receive their treatment; this must be explained to participants.

Correction on the informed consent materials: Section 4 - third line: please correct "or" to "of", as this typographical error affects the sense of what is being said.=Clarification as to whether there will be any conflict of interest if the student researcher asks clients from her business interestes to participate in the research.

Provision of an amended copy of the Informed Consent materials containing a statement that the research is being conducted as part of the student's course of study (and specifying the course of study).

Clarification as to whether phone interviews are the best way to screen participants, Some interviewees may have a degree of mental incapacity which is expressed sporadically i.e. it might

not affect them during the telephone interview. How effective is such an interview when dealing with possible responses to “Other”, in the list of Co-morbidities?

Please indicate protocols should there be coincidental recruitment of women of Aboriginal or Torres Strait Islander descent; women with mental impairment or women engaged in illegal activity. It is believed that the s6.1.1 was misunderstood.

Clarification as to whether the student will only have de-identified data on her home computer, or will there be suitable security be to counter against theft or loss.

This decision was made on 17-Mar-12. Your response to these matters will be considered by Office for Research.

The ethical clearance for this protocol runs from 17-Mar-12 to 30-Dec-13.

Please forward your response to Dr Gary Allen, Manager, Research Ethics, Office for Research as per the details below.

Please refer to the attached sheet for the standard conditions of ethical clearance at Griffith University, as well as responses to questions commonly posed by researchers.

It would be appreciated if you could give your urgent attention to the issues raised by the Committee so that we can finalise the ethical clearance for your protocol promptly.

Regards

Dr Gary Allen
Manager, Research Ethics
Office for Research
G39 room 3.55 Gold Coast Campus
Griffith University
ph: 3735 5585
fax: 07 5552 9058
email: g.allen@griffith.edu.au

GRIFFITH UNIVERSITY HUMAN RESEARCH ETHICS COMMITTEE

27-Mar-2012

Dear Ms Vaughan

I write further to the additional information provided in relation to the provisional approval granted to your application for ethical clearance for your project "Full Review: The Effects of a Multi-Modal Exercise Program on Cognition in Older Women: A Randomised Controlled Trial" (GU Ref No: PES/05/12/HREC).

The additional information was considered by Office for Research.

This is to confirm that this response has addressed the comments and concerns of the HREC.

Consequently, you are authorised to immediately commence this research on this basis.

The standard conditions of approval attached to our previous correspondence about this protocol continue to apply.

Regards

Dr Gary Allen
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Griffith University
ph: 3735 5585
fax: 07 5552 9058
email: g.allen@griffith.edu.au

GRIFFITH UNIVERSITY HUMAN RESEARCH ETHICS COMMITTEE

20-Jun-2012

Dear Ms Vaughan

I write further to your application for a variation to your approved protocol "Full Review: The Effects of a Multi-Modal Exercise Program on Cognition in Older Women: A Randomised Controlled Trial" (GU Ref No: PES/05/12/HREC). This request has been considered by the Chair.

The Chair resolved to approve the requested variation:

Data collection for study to be expanded to include:

- 1) Completion of the Depression, Anxiety and Stress Scale (a 21 item questionnaire) in the baseline data collection. The results of this scale will then be used as a covariate in the data analysis.
- 2) Participants recording the number of steps completed daily in the week following initial data collection, using a pedometer. This will provide a measure of physical activity at baseline and again this will be included as a covariate in the between group data analysis.
- 3) Completion of the Controlled Oral Word Association Test (COWAT) at baseline and at study completion as a measure of verbal fluency. The COWAT draws on executive function and memory. Participants are given one minute to generate as many words as possible that begin with a specific letter.

While these additional methods of data collection will increase the burden on the research participants full informed consent will be required and no potential participant will be compelled to complete these additional data collection measures. The additional pencil and paper tests are anticipated to add approximately 7-10 minutes to initial data collection and 3 minutes to final data collection. The wearing of the pedometer is simple to perform and feedback on numbers of steps will be offered to all participants.

Please provide an assurance that the informed consent materials will be updated to include the 3 additional tasks and to advise the potential participants that they are optional.

This decision is subject to ratification at the next meeting of the HREC. However, you are authorised to immediately commence the revised project on this basis. I will only contact you again about this matter if the HREC raises any additional questions or comments about this variation.

Regards

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