

The Effect of an Aerobic Exercise Intervention on Episodic Memory in Individuals With and
Without Subjective Cognitive Decline

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I declare that this thesis is my own account of IPAC study research and the main content of the work has not previously been submitted for a degree at any other tertiary education institution.

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Abstract

The benefit exercise has on cognition in older adults has been evidenced in many studies, however the impact exercise has on specific cognitive domains, and in individuals at greatest risk of cognitive decline, requires clarification. Individuals with early cognitive decline, identified as having subjective cognitive decline (SCD), may be most receptive to cognitive benefits provided by exercise interventions. Therefore, this study aimed to investigate whether a six month aerobic exercise intervention could improve episodic memory in healthy individuals with and without subjective cognitive decline (SCD). Ninety community-dwelling healthy older adults, aged 69.19 ± 5.21 years (53% female), were randomised into either high intensity exercise, moderate intensity exercise, or a control group. Intervention groups cycled twice a week for 50 minutes, and outcome measures included the California Verbal Learning Test (CVLT-II), the Brief Visuospatial Learning Task (BVMT) and the Groton maze recall to measure episodic memory; as well as right and left hippocampal volume. Individuals in the intervention groups did not significantly differ in their performance from pre- to post-intervention on any episodic memory measure or hippocampal volume, compared to the control. There were no significant differences from pre- to post-intervention between those with and without SCD on any episodic memory measure, or for hippocampal volume. However, SCD moderated the relationship between cardiorespiratory fitness and BVMT performance, indicating that at low levels of SCD, as cardiorespiratory fitness increases, so does episodic memory. This provides partial support for the use of exercise as a prevention tool for cognitive decline; however further research is required to

clarify the mechanisms of these benefits and determine the crucial window of opportunity to implement exercise interventions.

Keywords: aerobic, physical activity, exercise, episodic memory, cognition, subjective cognitive decline, subjective cognitive complaints, subjective memory complaints

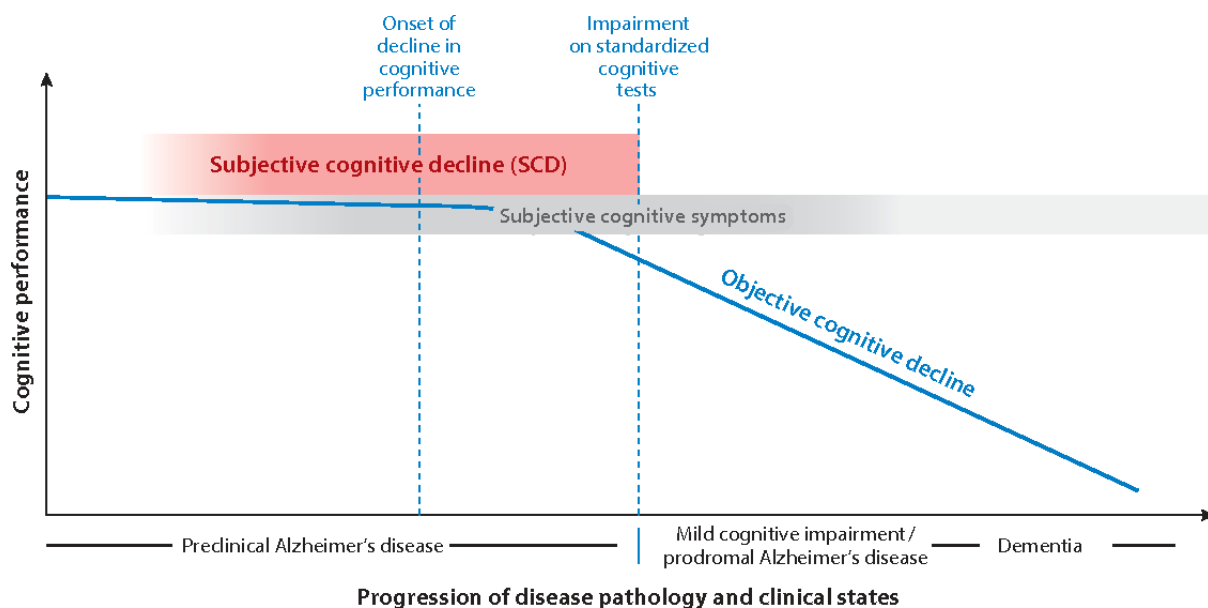
The Effect of an Aerobic Exercise Intervention on Episodic Memory in Individuals With and Without Subjective Cognitive Decline

The world is experiencing a ‘greying population’, with the number of individuals aged 65 and over increasing more rapidly than any other age group (United Nations Populations Division, 2010). A major concern in older adulthood is the decline of cognitive and physical abilities (Reese, Cherry, & Norris, 1999). Among these concerns is the increasing prevalence of dementia, which has been declared a public health priority (World Health Organisation, 2012). Dementia is a neurocognitive disorder characterised by a significant decline in one or more areas of cognition, which interferes with everyday tasks (Sachdev et al., 2014). Worldwide, someone is diagnosed with dementia every four seconds (World Health Organisation, 2012), and there are currently over 46.8 million people living with dementia, set to increase to 131.5 million in 2050 (Prince et al., 2015). Not only does the increasing prevalence of dementia have a detrimental impact on families and loved ones, in 2015, dementia had an estimated global cost of US\$818 billion per year (Wimo et al., 2017).

There is currently no effective cure for dementia, and researching and implementing prevention strategies is crucial (Livingston et al., 2017). By delaying Alzheimer’s disease (AD) (the most common form of dementia) onset by just 12 months, there would be 9.2 million fewer cases by 2050 (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). Therefore, current research is focussed on identifying preventative or early intervention strategies to reduce the prevalence of dementia.

Subjective Cognitive Decline

Studies have shown that the accumulation of amyloid beta ($A\beta$), which is a neuropathological hallmark of AD (Brown, Peiffer, & Rainey-Smith, 2019; Sperling et al., 2013), may begin as early as two decades before the onset of clinical symptoms (i.e. clinically detectable cognitive change). $A\beta$ accumulation is indicative of preclinical AD (Figure 1); and evidences the need for prevention strategies to be implemented as early as possible (Villemagne et al., 2013). The first identifiable stage of cognitive decline is subjective cognitive decline (SCD), which is a general term describing an individual's perception of subtle deterioration in their cognitive abilities, without the presence of objective evidence on standardized cognitive tests (Figure 1), (Jessen, Amariglio, et al., 2014). Throughout the literature, multiple terms are used interchangeably for SCD, including



subjective cognitive complaints (SCC), subjective memory complaints (SMC), and subjective memory impairment (SMI) (Abdulrab & Heun, 2008; Jessen, Amariglio, et al., 2014).

Recently, researchers have posited the ongoing use of the term SCD, and for the purposes of the current paper, this construct (regardless of what term was used in the paper cited) will be referred to as subjective cognitive decline (SCD).

Figure 1. Progression From Healthy Aging to Cognitive Decline. From “Subjective Cognitive Decline in Preclinical Alzheimer's Disease,” By L. A. Rabin, C. M. Smart, and R. E. Amariglio, 2017, *Annual Review of Clinical Psychology*, 13(1), 369-396.

Not all individuals with SCD progress to dementia; however they are at an increased risk of future cognitive impairment. For example, estimates suggest that those with SCD are at up to a three-fold higher risk of progressing to mild cognitive impairment (MCI), compared to those without SCD (Mendonça, Alves, & Bugalho, 2016). Individuals with mild cognitive impairment show deficits of one to one and a half standard deviations below the age- and education-adjusted mean on objective neuropsychological tests (Gauthier et al., 2006; Petersen et al., 1999). Mild cognitive impairment differs from SCD, in that those with SCD do not show objective decline, whereas those with MCI do (Jessen, Amariglio, et al., 2014). Individuals with SCD or MCI may eventually progress to dementia. Understanding the possible outcomes of SCD is crucial to recognise the clinical utility of this research.

In previous research, SCD has primarily been indicated through perception of episodic memory decline, rather than perceptions of global cognitive function (Brini et al., 2018; Jessen, Amariglio, et al., 2014). Episodic memory is the memory system responsible for receiving and storing information about personal events; and their relation to other events in space and time (Tulving, 1972). In early stages of cognitive decline, episodic memory is one of the domains most greatly impacted (Langbaum et al., 2014); and may be an indicator of decline related to A β , the hallmark of AD.

Currently, neuroimaging techniques are used to identify early dementia pathologies (ie. A β); which may or may not be accompanied by cognitive decline (Villemagne et al., 2013). These techniques are expensive and are not viable for large-scale screening of the population. Therefore, it is crucial to explore other ways to identify those showing early

pathology, and SCD has been proposed as a cost-effective and widely applicable method to do so.

Subjective cognitive decline may be influenced by many factors, for example depression and anxiety (Balash et al., 2013). Higher levels of depressive symptoms have been observed in those with SCD (Balash et al., 2013). However, the relationship between SCD, depression and cognitive decline is complex, as those with higher depression levels perform worse on cognitive testing in general (Yaffe et al., 1999), therefore their cognitive complaints may be reflecting realistic observations (Schmand, Jonker, Geerlings, & Lindeboom, 1997). It is important to take these extraneous factors into account when studying individuals with SCD.

Identifying those with SCD is a low-cost and widely applicable way to detect the earliest stages of cognitive decline. Individuals with SCD are at higher risk of progression to MCI and dementia, and it is vital they are specifically targeted with prevention strategies. Delaying the onset of cognitive decline is a priority in order to reduce the high social and financial costs of dementia, which place a significant burden on Australian society; forecast to worsen in the coming decades. One prevention strategy is exercise, which has been linked to reduced cognitive decline, increased brain volume, enhanced cognition, and decreased risk of dementia (Brown et al., 2012; Brown et al., 2013; Callisaya et al., 2017; Erickson et al., 2011; Lautenschlager et al., 2008; Schuit, Feskens, Launer, & Kromhout, 2001), and is therefore a very promising prevention strategy for maintaining cognition in older age. Targeting exercise interventions to those at a higher risk of developing MCI or dementia (those with SCD) may be an effective way to use this strategy.

Exercise and Cognition

It is important to note the difference between exercise and physical activity (PA). Both PA and exercise use skeletal muscle to produce movement, resulting in energy

expenditure; however exercise is any structured or planned physical activity, usually aiming to increase or maintain fitness, and is a form of PA (Caspersen, Powell, & Christenson, 1985). Throughout this paper, where relevant, PA has been distinguished from planned exercise interventions.

Physical inactivity is one of the greatest modifiable risk factors for cognitive decline (Stillman, Cohen, Lehman, & Erickson, 2016). Exercise may be used as a behavioural intervention to preserve cognitive function at very early stages (Brini et al., 2018; Haan & Wallace, 2004), when dementia pathology is accumulating, before cognitive decline can be detected (Brown et al., 2019; Sperling et al., 2013). However, exercise has also been employed as an intervention strategy for individuals already experiencing decline, namely those with MCI. Exercise has positive impacts on global cognition, attention and executive function within those with MCI (Öhman, Savikko, Strandberg, & Pitkälä, 2014). Further, a meta-analysis of randomised controlled trials (RCTs) in individuals with dementia showed that exercise increased overall cognitive function (Farina, Rusted, & Tabet, 2014). However, other meta-analyses of RCTs concluded there was no sufficient evidence that exercise significantly impacts cognitive function in individuals with dementia (Forbes, Forbes, Blake, Thiessen, & Forbes, 2015). Although these studies show minor improvements in cognition from exercise interventions in declining individuals, findings on the effectiveness and clinical relevance of this intervention remain inconclusive (Livingston et al., 2017). Therefore, exercise may be most useful as a prevention strategy, before decline becomes irreversible (Haan & Wallace, 2004; Jessen, Wolfsgruber, et al., 2014).

In cognitively normal individuals, habitual activity levels are linked to cognition (Chang et al., 2010). Longitudinal studies consistently show that those with higher baseline PA levels are protected against cognitive decline decades later (Blondell, Hammersley-Mather, & Veerman, 2014; Sofi et al., 2011). However, evidence from RCTs is less

consistent. Young, Angevaren, Rusted, and Tabet (2015), conducted a Cochrane meta-analysis of RCTs employing aerobic exercise interventions to improve cognition, and showed that cognition did not improve in intervention groups, compared to controls. Conversely, Northey, Cherbuin, Pumpa, Smee, and Rattray (2018) conducted a meta-analysis of RCTs employing various exercise interventions to improve cognition, and showed that exercise improved cognition in all domains, except global cognition. A key difference between these studies is that Young et al. (2015) included studies employing aerobic interventions only, whereas Northey et al. (2018) included various types of exercise interventions (resistance, aerobic, and multicomponent training). This may explain the differences in results, in that Northey et al. (2018) included a more representative sample of the literature. Further, Northey et al. (2018) only included exercise interventions that were supervised, whereas Young et al. (2015) included any aerobic intervention. Finally, Northey et al. (2018) conducted this meta-analysis three years after Young et al. (2015), and there may have been additional studies published during this time. These differences indicate that Northey et al. (2018) results may be more representative of the literature, indeed this is consistent with previous meta-analyses showing that exercise has a positive impact on cognition in cognitively normal individuals (Colcombe & Kramer, 2003; Smith et al., 2010).

There are some differences in the methodologies of RCTs examining the impact of exercise on cognition that may explain the aforementioned conflicting results. Cognitive outcomes are influenced by the frequency, duration, intensity and type of exercise implemented in the prescribed intervention, and these factors often vary between studies. Exercise intensity is positively associated with cognitive function; whereas exercise duration does not significantly impact cognitive function (Angevaren et al., 2007; Brown et al., 2012). This indicates that high intensity exercise may be more beneficial in cognitively normal individuals, whilst also being more time-efficient, providing similar benefits to moderate

intensity exercise. Additionally, exercise type is important, and the literature indicates that aerobic training, as opposed to resistance training, has more consistent positive impacts on cognition (Nagamatsu et al., 2013; Pontifex, Hillman, Fernhall, Thompson, & Valentini, 2009). A RCT examining the effects of varying aerobic exercise intensities on cognitive function is vital, in order to understand the importance of exercise intensity in cognitively normal individuals.

One mechanism through which exercise exerts its positive influence on cognition is the hippocampus. The hippocampus is involved in many brain processes including memory encoding and retrieval (Bartsch, 2012; Bartsch & Wulff, 2015). It is widely accepted that the hippocampus is involved in episodic memory in particular (Burgess, Maguire, & O'Keefe, 2002); and is one of the brain areas most vulnerable to volume loss with age (Raz et al., 2005). The hippocampus is believed to be the brain region with the highest capability for neuroplasticity, meaning it can adapt to its internal and external environment (Cramer et al., 2011): it is theorised that this feature also creates a high vulnerability to neurodegeneration (Bartsch & Wulff, 2015). However, this neuroplasticity also allows the hippocampus to be targeted for exercise interventions. For example, Erickson et al. (2011) conducted a RCT with cognitively normal participants to examine the impact of aerobic exercise on hippocampal volume and memory. Participants completed a one year intervention, and results showed that hippocampal volume increased by 2% in the intervention group, as opposed to a 1% decline in the control group. This landmark study was the first to demonstrate that exercise can alter hippocampal volume; nevertheless, contributing questions regarding the optimal parameters of exercise, and whether certain individuals are most likely to respond to intervention, remain unanswered, and further research is required.

When implemented as a prevention strategy, exercise may delay the onset of cognitive decline by preserving functioning at a higher level, before damage becomes

irreversible. The evidence presented above details that cognitively normal individuals most consistently show a cognitive benefit from exercise. Cognitive decline occurs over a long period, and the time from which an individual converts from being cognitively normal, to developing cognitive impairment, represents a crucial window of opportunity for intervention. Those experiencing small, sometimes even undetectable, cognitive decline may benefit most from exercise interventions (De Souto Barreto, Andrieu, Rolland, & Vellas, 2018). Indeed, this notion is supported by Sabia et al. (2017) who found that PA was significantly lower in the 10 years preceding dementia diagnosis, compared to those who never developed dementia. This presents a crucial time for intervention, and SCD may be an effective way to identify this period.

Subjective Cognitive Decline, Exercise and Cognition

Based on the accepted definition of SCD, studies reviewed below are considered to have measured SCD if they measured any form of subjective cognitive complaints (SCC) or subjective memory complaints (SMC). As discussed earlier, these terms are often used interchangeably within the literature, and this concept will be referred to as SCD; regardless of the terminology used in the relevant paper.

The link between exercise and SCD has been well-established in cross-sectional studies, with those individuals with high PA levels reporting less SCD (Lee, Hsiao, & Wang, 2013; McAuley et al., 2011; Nemoto et al., 2018). However, research investigating the impact of exercise on cognition in individuals with SCD is relatively limited, compared to research in those with MCI or dementia. Further research on individuals with SCD is crucial, as these individuals are at a higher risk for developing MCI and dementia, and SCD presents a crucial window of opportunity for implementing prevention strategies. There are currently

no meta-analyses examining individuals with SCD, likely due to inconsistencies in the definition of SCD and lack of randomized controlled trials. Due to the limited literature, studies evaluated here are not restricted to studies measuring only episodic memory outcomes, and include any cognitive domain.

It has been shown that a six month moderate intensity exercise intervention can improve overall cognition in older adults with either MCI or SCD ($n = 170$) (Lautenschlager et al., 2008). In this study, the intervention group showed improved scores on the Alzheimer Disease Assessment Scale (ADAS-Cog) from baseline to follow-up, whereas the control group declined in their scores on the ADAS-Cog from baseline to follow-up (1.3 point difference between groups at follow-up, $p = .04$). The study identified those with SCD using a singular question (answering yes to: “do you have any difficulty with your memory?”), and found that there were no differences in cognitive improvement between those with SCD and those with MCI. The exercise intervention in this study was not supervised, hence the measurement of duration and intensity of performed exercise may not be reliable. Further, the clinical relevance of a 1.3 point improvement on the ADAS-Cog should be considered. This improvement may only be relevant if individuals see benefits in their day-to-day cognition, especially in those MCI. However, this small benefit may be crucial for those with SCD, as the aim for this population is primarily to maintain their current level of functioning. Further, it should be noted that the ADAS-Cog was originally developed to measure dysfunction in AD (Kueper, Speechley, & Montero-Odasso, 2018). Thus, this measure may not be sensitive enough to detect important minor changes in cognitively normal individuals (Kueper et al., 2018), and may be underestimating the impact exercise can have on specific cognitive domains. These weaknesses emphasise the importance of studying individuals with SCD using sensitive outcome measures; to capitalise on this crucial window of opportunity for intervention.

Studies have also shown that low- and moderate-intensity exercise interventions can improve outcomes on executive function measures in individuals with SCD (Kamegaya et al., 2012; Maki et al., 2012). Specifically, Kamegaya et al. (2012) employed a 12-week exercise intervention consisting of stretching and aerobic exercise, and found that during the intervention period, compared to the control period, the group showed greater improvements in the Weschler Digit Symbol substitution test ($n = 30$). Similarly, Maki et al. (2012) found that a 12-week walking intervention improved scores on a verbal fluency task in the intervention group, compared to the control (total $n = 150$). Both studies identified SCD using two or three self-report questions regarding mental functioning (eg. “Do you often have to ask the same questions repeatedly?”), and participants were required to answer ‘yes’ to one of these questions to be eligible for study participation. Importantly, Kamegaya et al. (2012) also included those with MCI in their sample, and found that there were no differences on cognitive outcomes between those with MCI and those with SCD. Both of these studies measured SCD using a minimal amount of self-report questions, as opposed to the recommended use of a validated questionnaire (Mendonça et al., 2016). Therefore, these studies may not be accurately identifying those with SCD, and future research should focus on employing validated measurement tools to accurately assess those with SCD. It should be noted that Maki et al. (2012) and Kamegaya et al. (2012) employed exercise interventions consisting primarily of walking at low frequencies (ie. once per week). The volume and intensity of this intervention may not have been sufficient to significantly contribute to changes in cognition, particularly memory. The cognitive benefits seen on measures of executive function may indicate that this cognitive domain is particularly sensitive to exercise interventions, even at a low intensity, which is consistent with previous literature (Northey et al., 2018). Therefore, it appears that in populations with SCD, more intense exercise interventions may be required to have significant impacts on memory. Future studies should

focus on employing exercise interventions at higher intensities in order to determine particular aspects of cognition that can be maintained or improved through exercise interventions.

Although the studies reviewed above have primarily implemented aerobic exercise interventions, resistance training may also benefit cognition in individuals with SCD. Busse et al. (2008) employed a nine month resistance training intervention twice per week, and found that those in the intervention group demonstrated improved scores on the Rivermead Behavioural Memory test following the intervention, compared to the control group ($p = .02$; total $n = 31$). Individuals were required to have SCD to be eligible for the study; SCD was identified through memory complaints from the individual or an informant, as well as using the memory complaints scale derived from the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX): with greater scores indicating greater memory complaints. This study provides promising results, as SCD was identified using sound methodology, exercise was fully supervised, and there were positive impacts of exercise on memory outcomes. It is crucial that these results are replicated in a study with a larger sample, and replicating these results with an aerobic exercise intervention, as opposed to resistance, is vital in order to determine the specific impacts of various forms of exercise on cognition.

The impact of exercise interventions on memory and hippocampal volume has been investigated by Nagamatsu et al. (2013) and Ten Brinke et al. (2015). Multiple manuscripts, each employing different analyses, arose from this RCT. The RCT investigated the effects of a six month exercise intervention on memory and hippocampal volume in older women ($n = 86$) (Nagamatsu et al., 2013; Ten Brinke et al., 2015). There were two intervention groups and one control group for this study: a resistance training group, aerobic training group, and a balance and tone control. Subjective cognitive decline was measured using a single question, (“Do you have difficulty with your memory?”), participants were required to answer yes to

this question, as well as score $<26/30$ on the Montreal Cognitive Assessment (MoCA), in order to participate in the study. In terms of structural brain changes, the aerobic training group showed increased total hippocampal volume following the intervention, compared to the control group ($p = .01$) (Ten Brinke et al., 2015). In regards to functional changes, the aerobic training group showed improvements in memory retention on the Rey auditory verbal learning task (RAVLT), compared to the control group ($p = .04$), whereas the resistance group did not show a significant difference compared to the control (Nagamatsu et al., 2013). The study was not powered to directly compare the resistance and aerobic training groups. One limitation of this trial is that the sample was female, and women may show more favourable results in response to exercise interventions compared to men (Colcombe & Kramer, 2003); skewing the interpretation of the results. This limitation can be overcome by employing various sampling techniques to ensure future samples have equal sexes. A further limitation of Ten Brinke et al. (2015) and Nagamatsu et al. (2013) study is that inclusion criteria required scoring $<26/30$ on the MoCA, showing an objective deficit, which is inconsistent with the working definition of SCD (Jessen, Amariglio, et al., 2014). Despite this, the study has been included for review as the sample had not been not diagnosed with MCI or dementia. Future studies should overcome this limitation by following Jessen, Amariglio, et al. (2014) clear SCD theoretical framework, recommendations and definitions.

The studies reviewed above provide crucial insights into the impact of exercise on cognition in older adults with SCD. Indeed, Nagamatsu et al. (2013); Ten Brinke et al. (2015) and Busse et al. (2008) showed that exercise interventions improved outcomes on memory measures. These studies are the most methodologically sound of the studies reviewed, as they employ fully supervised, higher intensity exercise interventions, compared to Kamegaya et al. (2012) and Maki et al. (2012). Thus, Nagamatsu et al. (2013), Ten Brinke et al. (2015) and Busse et al. (2008) provide the most reliable results, indicating that future studies should

focus on examining the specific impact higher intensity exercise interventions have on memory outcomes.

As previously discussed, SCD has primarily been indicated throughout the literature by using measures of episodic memory (Brini et al., 2018; Jessen, Amariglio, et al., 2014). Indeed, episodic memory is one cognitive domain most greatly affected in early stages of cognitive decline (Langbaum et al., 2014). Further, the hippocampus is directly related to episodic memory function (Burgess et al., 2002) and the hippocampus is very susceptible to volume loss in aging (Raz et al., 2005). Episodic memory is arguably one of the most crucial cognitive domains to research, as it is the memory store for autobiographical memories (Tulving, 1972); and thus may have the most clinical relevance for individuals experiencing slight cognitive declines (those with SCD). Conducting future studies in this area is crucial in order to determine the most effective exercise prescription for preserving cognitive function.

The results presented above provide promise for a window of opportunity for preventing cognitive decline, where individuals are still cognitively normal, and damage is not yet irreversible. Exercise is a low cost intervention that is easy to implement, with potential to provide the widest benefit to the greatest amount of people. The above studies demonstrate that exercise interventions have a positive impact on memory, executive function and overall cognition. However, most studies only demonstrate an effect on one or two cognitive tasks (from large cognitive batteries), and it is clear that intensity of exercise was relatively low. In addition, unsupervised exercise interventions make it difficult to discern exactly how much exercise is being delivered to participants. Thus, future research should be conducted utilizing supervised interventions that deliver various exercise intensities.

The Current Study

The current study is a randomised controlled trial (RCT) examining the impact of a six month aerobic exercise intervention, including high-intensity and moderate-intensity exercise, on episodic memory in individuals with and without SCD. This study will add to the body of literature by overcoming some of the aforementioned limitations, for example employing a sample with equal sexes, using a comprehensive measure of SCD, and examining specific mechanisms of exercise. In addition, this study will provide novel evidence to the field by delivering exercise at different intensities, namely by a high intensity exercise group (HI), moderate intensity exercise group (MI) and control group, to clarify the relationship between exercise intensity and cognitive health. By using MRI techniques, this study will expand the body of literature by examining structural changes within individuals with SCD, as this has only been investigated by one previous study (Ten Brinke et al., 2015). Further, the current study will add to the literature by comparing the benefits of exercise in those with SCD to those without SCD, something which has yet to be explored.

Based on previous literature regarding the positive impact of exercise on cognition, it was hypothesised that there would be a dose-response of the exercise intervention on episodic memory and hippocampal volume, between the three groups. Namely, the HI group would show the greatest improvement in episodic memory and hippocampal volume; compared to the MI and control groups, and the MI group would show greater improvement than the control group. It was also hypothesised that those with SCD would show greater improvements (due to the exercise intervention) on episodic memory measures and hippocampal volume, compared to those without SCD. This is because, as previously described, these individuals are at a greater risk of future cognitive decline and present a crucial window of opportunity for implementing prevention strategies. Preventative strategies such as exercise may be most effective in those already experiencing a slight decline; but have not declined so much that the damage is irreversible. Therefore, individuals with SCD

may be most sensitive to exercise interventions. As a secondary outcome, it was hypothesised that within the HI and MI groups, there would be a positive relationship between changes in cardiorespiratory fitness from pre- to post-intervention, and changes episodic memory from pre- to post-intervention, which would be moderated by a quantitative SCD score.

Method

Participants and Design

Participants for this study were part of the Intense Physical Activity and Cognition (IPAC) study, which was a six month, single-blind, single-centre RCT (Registered with the Australian New Zealand Clinical Trials Registry, number: ACTRN12617000643370). Participants were cognitively normal (>26 on the Mini Mental State Examination, MMSE, at screening), community dwelling men and women aged 60-80, recruited via newspaper advertisements and word of mouth. Participants spoke adequate English, had adequate auditory and visual acuity and provided informed consent, as well as a letter from their general practitioner endorsing participation in the exercise intervention (regardless of group allocation). Participants were excluded if they met any of the following criteria: a dementia diagnosis, scored <26 on MMSE, scored >6 on the geriatric depression scale, inability to undertake cycling exercise, inability to obtain medical clearance, history of schizophrenia, schizoaffective or bipolar disorder, untreated sleep apnoea, history of electroconvulsive therapy or serious head injury resulting in prolonged unconsciousness, alcohol abuse or dependence within two years of screening, history of cancer within the last five years, systemic illness or unstable medical condition, insulin-requiring diabetes or uncontrolled diabetes mellitus, uncontrolled hypertension (systolic blood pressure >170 or diastolic blood pressure >100 mmHg), or if MRI was contraindicated. Participants did not currently engage in high intensity physical exercise (determined by an exercise physiologist) (Brown et al., 2017).

The IPAC study was funded by National Health and Medical Research Council National Institute of Dementia, and was approved by Murdoch University and Edith Cowan University human research ethics committees.

Materials

Memory Assessment Clinical-Questionnaire. Subjective memory complaints, which are indicative of general SCD, were measured using the memory assessment clinical-questionnaire (MAC-Q) at baseline only (Crook, Feher, & Larrabee, 1992). The measure includes six items, five of which describe specific situations in which memory is required (eg. remembering the name of a person just introduced to you), and one item comparing current memory function to high school. Participants rate items on a five point Likert scale ranging from 1 (*much better now*) to 5 (*much poorer now*), with a minimum score of seven and a maximum score of 35. Participants were classified as having SCD if they scored 25 or above on the MAC-Q (Crook et al., 1992). The Depression Anxiety and Stress scale (DASS-21) was used to measure depressive symptoms at baseline (Lovibond & Lovibond, 1995).

Cardiorespiratory Fitness Assessment. At pre- and post-intervention physical fitness was assessed using cycling-based graded exercise test (consistent increases in resistance every 2 minutes until volitional fatigue) to calculate peak aerobic capacity (VO_{2peak}). To do this, ventilation was averaged in 15 second intervals during each test and the rate of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) was measured using a Parvo TrueOne (ParvoMedics USA) metabolic cart. VO_{2peak} was determined by using the highest 15 second average interval obtained within the last 2 minutes of testing. Heart rate was continuously recorded during testing, and maximum heart rate was determined as the highest recorded heart rate value. Additionally, for VO_{2peak} assessment, participants must reach a maximum heart rate greater than 85% of their predicted maximum for their age, $(220 - \text{age}) * 0.85$, as well as a respiratory exchange ratio (VCO_2/VO_2) of above 1.15.

Neuropsychological Measures. Cognitive function was assessed using a comprehensive neuropsychological battery which included tests with demonstrated sensitivity, reliability and validity in similar groups (Salmon & Bondi, 2009). These assessments were conducted at baseline and at six month follow-up and measured general and domain-specific cognitive function. The current study examined measures of episodic memory only (for a description of the comprehensive battery see Brown et al., 2017). Based on the work of others in the field (Lim et al., 2016), episodic memory was measured using the long delay free recall (LDFR) score from the California Verbal Learning Test (CVLT-II), delayed recall (DR) score on the Brief Visual Memory Test (BVMT), and Groton Maze recall (in which higher scores indicate worse performance) from the Cogstate battery.

Hippocampal Volume Measure. Hippocampal volume was assessed at baseline and six months by obtaining a brief scout T1-weighted (T1W) image using a standard head coil. This was followed by a magnetization-prepared rapid gradient-echo sequence (MPRAGE) and a T2 sequence. Cerebrospinal fluid was computed and these images were segmented into white matter and grey matter. Hippocampal volume was obtained by propagating an atlas to the T1W images. Hippocampal volume was adjusted for total brain volume using the following formula: Adjusted hippocampal volume = raw hippocampal volume – b (global brain volume – mean global brain volume), where b = the slope for a linear regression of hippocampal volume on global volume.

Intervention Procedure

Participants were randomly assigned to one of three groups: high intensity (HI), moderate intensity (MI) or control, using a randomisation protocol with a block size of three. Age and gender are related to cognitive function, so participants were stratified by these factors before randomisation.

Both the HI and MI groups completed a six month cycling program intervention, supervised by an exercise physiologist. Sessions were 50 minutes in duration twice weekly. Target exercise intensity was set using the Borg scale of perceived exertion (Borg, 1998), and was measured using heart rate monitors and power output (wattage) from the cycle ergometer. All interventions were work matched, in that both intervention groups exerted a similar amount of total work per session, within $\pm 0.4\%$ over their respective timeframes, so that only intensity varied between groups.

In the MI group, participants cycled at a constant intensity (50-60% of aerobic capacity; 13 Borg scale) for 50 minutes. In the HI group, participants completed a 10 minute warm up (30-40% aerobic capacity; 11 Borg scale). This was followed by 11 intervals of 1 minute of hard exertion cycling (>80% aerobic capacity; 18 Borg scale), interspersed by 2 minutes of active recovery (30-40% aerobic capacity; 12 Borg scale), and lastly a 9 minute cool down (11 Borg Scale). Participants in the control group attended one information session regarding benefit of diet and exercise with respect to cognition, dementia and brain aging. All participants required a clearance from their general practitioner, and completed the Exercise and Sports Science Australia pre-screening questionnaire prior to commencing any portion of the study.

Data Analysis and Statistical Procedure

Firstly, four univariate analyses of variance (ANOVA) were conducted to determine whether control, MI and HI groups significantly differed on baseline characteristics. This procedure was repeated to determine any differences between individuals with and without SCD. For dichotomous variables (gender and Apolipoprotein E status), a chi-square analysis was conducted. For main analyses, data were analysed using a Mixed Model Analysis of Covariance (ANCOVA). Specifically, two separate models were used to analyse the first and second hypotheses. A 2 x 3 mixed model repeated measures ANCOVA was conducted to

analyse the impact of the exercise intervention on episodic memory scores, using gender, age and education level as covariates, pertaining to the first hypothesis. Main effects for time and group are not reported for this model, as only the interaction term (time*group) is of interest. Pertaining to the second hypothesis, a 2 x 2 x 2 mixed model ANCOVA was conducted to analyse whether the effects of the exercise intervention differed for individuals with SCD, compared to those without SCD. In this model, the control group was excluded, as this is investigating the hypothesis of differences in exercise-induced cognitive change between SCD and non-SCD groups. Education level and DASS-21 scores were included as covariates for this model; age was excluded due to concerns regarding power with the reduction in sample size, and also because mean age did not significantly differ between any groups. The main effect of SCD status is reported, as differences in cognition between SCDs and non-SCDs is an outcome of interest, as well as the interaction term (SCD*time*group). Finally, a moderation analysis was conducted to examine the secondary outcome of whether memory complaints (SCD) moderate the relationship between cardiorespiratory fitness and episodic memory. The moderation analysis was conducted using change scores of VO_{2peak} (i.e. post intervention score minus pre intervention score), as well as change scores for the respective episodic memory measure (Figure 2). For all post-hoc analyses, the Bonferroni correction for multiple tests was applied within SPSS. Further, for each model a p -value threshold of $p = .01$ ($5/0.05$, where 5 is the number of DVs) was employed to protect against type 1 error.

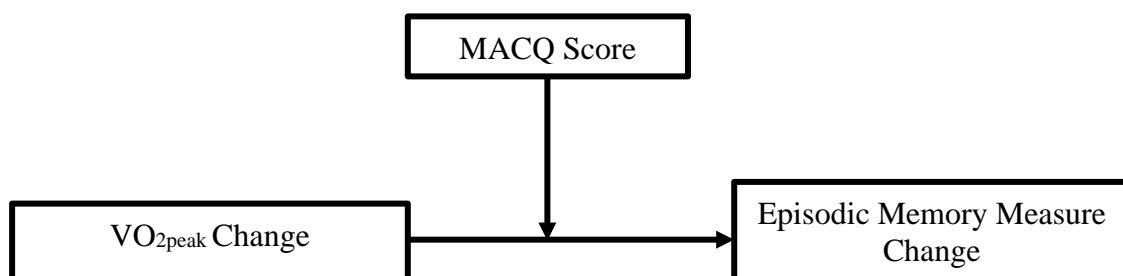


Figure 2. Moderation Analysis Model.

The assumptions of each model were considered and investigated. Briefly, the Shapiro-Wilk test, skewness and kurtosis were used to assess normality. A minority of variables showed departures from normality for both ANCOVA models, with significant *p*-values in the Shapiro-Wilk test. However, inspection of the skewness and kurtosis indicated that these were relatively small departures. Therefore, mixed model ANCOVA's were still conducted, as small to moderate departures from normality do not meaningfully impact results for this test (Allen, Bennet, & Heritage, 2014). The assumption of homogeneity of covariance matrices was upheld (assessed by Box's M). For the moderation analysis, a linear relationship was confirmed between predictor and outcome variables, and homoscedasticity of residuals was adjusted for using Hayes Process (version 3; Hayes, 2017), to uphold this assumption.

A power analysis was conducted using G*Power software (Faul, Erdfelder, Lang, & Buchner, 2007) to determine the required sample size for the current study. This analysis was based on the primary outcome measure of cognitive function, with an effect size of 0.35 as this is average effect size observed in prior studies of exercise and cognition (Smith et al., 2010). The sample size required to detect a group difference at 80% power and 5% level of significance with three covariates was a total sample of 82, or 27 participants per group. The IPAC study recruited a total of 99 participants at baseline, randomised into high intensity, moderate intensity and control groups (Figure 3). Finally, the complete analysis for the current study included 90 participants (note: excluding control $n = 60$), and was adequately powered for the main analyses.

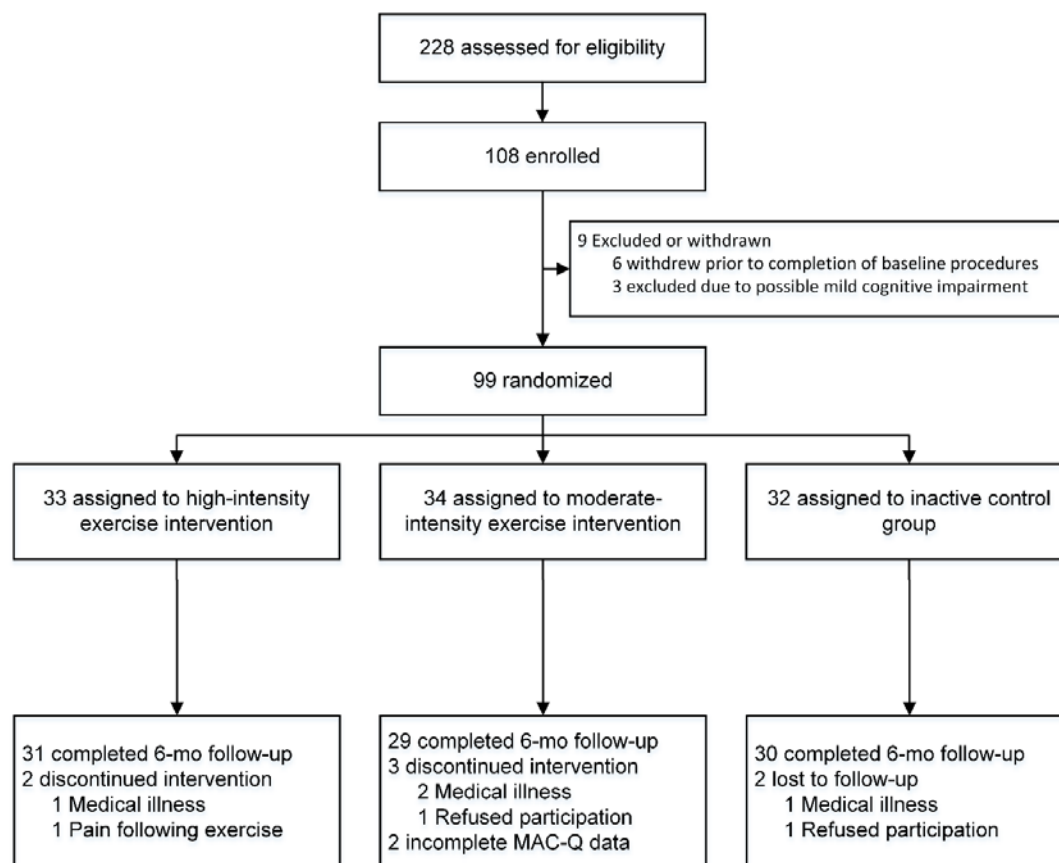


Figure 3. CONSORT Diagram of Participant Flow

There were some missing values within the dataset, ($n = 4$ for CVLT; $n = 4$ for BVMT; $n = 8$ for Groton Maze; $n = 5$ for hippocampal volume). Using Little's missing completely at random test, these were confirmed to be randomly distributed ($\chi^2 = 228.10$, $df = 226$, $p = .45$). Therefore, missing values were estimated through expectation maximization missing value analysis.

All data were analysed using SPSS (version 26), along with Hayes Process plug-in (version 3; Hayes, 2017) for the moderation analysis.

Results

Descriptive statistics are presented in Table 1, and show no significant differences between any group (HI, MI and control) for baseline characteristics. For those with and

without SCD, there was only a significant difference in DASS-21 scores, with those with SCD reporting more depressive symptoms.

The intervention was delivered as intended, with a 86% adherence rate. Participants were only included in the current dataset if they successfully completed the intervention and six month follow-up measures. There were no adverse events or side effects recorded for any group.

A 3 x 2 mixed model ANCOVA, investigating differences in exercise-induced cognitive change between control, MI and HI groups, showed that there were no significant differences between study groups over time for any episodic memory measure, or for hippocampal volume (See Table 2).

Table 1

Baseline descriptive statistics of study participants, broken down by High intensity, Moderate intensity and Control group, and SCD status.

Variable	HI (<i>n</i> = 31)	MI (<i>n</i> = 29)	Control (<i>n</i> = 30)	<i>p</i> -value	SCD (<i>n</i> = 52)	No SCD (<i>n</i> = 38)	<i>p</i> - value
Age, years	70.13 ± 5.17	68.41 ± 4.33	68.97 ± 5.99	.43	69.69 ± 5.22	68.5 ± 5.18	.29
Gender, %female (<i>n</i>)	48.39 (15)	48.28 (14)	63.33 (19)	.41	50 (26)	58.89 (22)	.46
APOE 4 allele carriage (% carriers (<i>n</i>))	25% (8)	31% (9)	23% (7)	.80	23% (12)	32% (12)	.37
Years of Education	13.58 ± 2.28	14.14 ± 2.55	14.3 ± 2.07	.45	14.29 ± 2.25	13.61 ± 2.34	.17
Global Cognition: MoCA	26.06 ± 2.08	26.52 ± 2.92	26.7 ± 2.10	.57	26.10 ± 2.70	26.87 ± 1.79	.13
DASS-21 Score	7.22 ± 4.02	6.62 ± 5.48	6.77 ± 4.45	.88	7.78 ± 4.66	5.63 ± 4.34	.02

Note. APOE = Apolipoprotein E; MoCA = Montreal Cognitive Assessment; DASS-21 = Depression, Anxiety, Stress Scale; HI = High Intensity; MI = Moderate intensity; SCD = Subjective Cognitive Decline. *p*-values were calculated using analysis of variance for continuous variables and chi-square for categorical variables.

Table 2

Effects of time and the exercise intervention on episodic memory outcomes (Results from analysis of covariance)

Dependent variable	Raw Score Mean Difference From Baseline [95% CI]			Predictor	df	F	p	Partial η^2
	Control	Moderate Intensity	High Intensity					
CVLT LDFR	.96 [-.08, 2.00]	.91 [-.11, 1.92]	.47 [-.52, 1.46]	Time x Group	2, 82	.28	.76	.00
BVMT DR	.66 [-.14, 1.47]	.36 [-.42, 1.15]	.60 [-.17, 1.36]	Time x Group	2, 82	.16	.85	.00
Groton Maze	.51 [-1.24, 2.27]	1.17 [-.55, 2.89]	-1.49 [-3.17, .18]	Time x Group	2, 82	1.35	.27	.03
Right Hippocampal Volume	102.00 [-110.81, 314.80]	-185.22 [-393.88, 23.43]	-87.33 [-290.22, 115.56]	Time x Group	2, 82	1.90	.16	.04
Left Hippocampal Volume	90.64 [-89.28, 270.57]	-146.21 [-322.63, 30.21]	64.19 [-235.73, 107.36]	Time x Group	2, 82	1.80	.17	.04

Note. For the Groton Maze task a reduction in scores indicates better performance. Covariates included in this model were age, education level and gender.

The second analysis, a 2 x 2 x 2 mixed model ANCOVA, showed that there were no significant differences between those with and without SCD for any episodic memory measure or for hippocampal volume. Further, there were no significant interactions between time, group and SCD status for any outcome (See Table 3).

A moderation analysis was conducted to assess the relationship between memory complaint score and changes in VO_{2peak} , episodic memory and hippocampal volume (Table 4). The analysis showed that MAC-Q scores did not moderate the relationship between VO_{2peak} change and CVLT LDFR score change, Groton maze recall score change, or right and left hippocampal volume change ($F(6, 53) = 1.63, p = .16, R^2 = .16$; $F(6, 53) = 1.43, p = .22, R^2 = .14$; $F(6, 53) = 1.45, p = .22, R^2 = .14$; $F(6, 53) = .97, p = .45, R^2 = .10$, respectively), (for information on individual predictors, see Table 4).

Table 3

Effects of time, exercise intervention and subjective cognitive decline status on episodic memory outcomes (Results from analysis of covariance)

Dependent variable	Raw Score Mean Difference From Baseline [95% CI]				Predictor	df	F	p	Partial η^2
	SCD + Moderate Intensity	SCD + High Intensity	Non-SCD + Moderate Intensity	Non-SCD + High Intensity					
CVLT LDFR	1.15 [-.04, 2.33]	-.18 [-.09, .74]	.44 [-1.52, 2.41]	1.30 [-.44, 3.02]	SCD	1, 54	.89	.35	.02
					SCD x time x group	1, 54	2.63	.11	.05
BVMT DR	.40 [-.54, 1.34]	.82 [-.07, 1.72]	.33 [-1.15, 1.82]	.19 [-1.12, 1.51]	SCD	1, 54	1.35	.25	.02
					SCD x time x group	1, 54	.11	.74	.002
Groton Maze	.77 [-2.25, 3.78]	-1.06 [-3.70, 1.58]	1.89 [-2.73, 6.51]	-2.06 [-3.61, -.52]	SCD	1, 54	.02	.90	.00
					SCD x time x group	1, 54	1.28	.26	.02
Right Hippocampal Volume	-122.88 [-367.59, 121.82]	-142.95 [-429.82, 143.92]	-85.65 [-1136.27, 498.03]	-7.69 [-63.65, 48.27]	SCD	1, 54	3.22	.08	.06
					SCD x time x group	1, 54	.99	.33	.02
Left Hippocampal Volume	-81.53 [-271.68, 108.62]	-118.24 [-362.47, 126.00]	-284.00 [-1018.64, 450.16]	13.17 [-28.98, 55.31]	SCD	1, 54	2.12	.15	.04
					SCD x time x group	1, 54	1.35	.25	.02

Note. CVLT LDFR = California Verbal Learning Test Long Delay Free Recall; BVMT DR = Brief Visuospatial Memory Task Delayed Recall; SCD = Subjective Cognitive Decline.

Covariates included in this model were education level and Depression, Anxiety, Stress Scale (DASS-21) score.

Table 4

Linear Models examining the relationship between memory complaint score and changes in VO_{2peak}, Episodic Memory and Hippocampal Volume from pre- to post-intervention

	<i>b</i> [95% CI]	<i>SE b</i>	<i>t</i>	<i>p</i>
Predictors of CVLT Change				
MAC-Q Score	-.08 [-.25, .09]	.08	-.96	.34
VO _{2peak} Change	.21 [-.63, 1.05]	.42	.50	.62
MAC-Q score x VO _{2peak} Change	-.01 [-.04, .03]	.02	-.54	.59
Predictors of BVMT Change				
MAC-Q Score	.17 [.05, .29]	.06	2.76	.008
VO _{2peak} Change	1.10 [.50, 1.70]	.29	3.70	.001
MAC-Q score x VO _{2peak} Change	-.04 [-.07, -.02]	.01	-3.63	.001
Predictors of Groton Maze Recall Change				
MAC-Q Score	-.06 [-.43, .31]	.19	-.32	.75
VO _{2peak} Change	-.88 [-2.73, .98]	.93	-.95	.35
MAC-Q score x VO _{2peak} Change	.02 [-.05, .10]	.04	.62	.54
Predictors of Right Hippocampal Volume Change				
MAC-Q Score	-14.56 [-54.44, 25.33]	19.89	-.73	.47
VO _{2peak} Change	-57.48 [-254.04, 139.09]	103.99	-.59	.56
MAC-Q score x VO _{2peak} Change	2.29 [-5.80, 10.38]	4.03	.57	.57
Predictors of Left Hippocampal Volume Change				
MAC-Q Score	-12.72 [-47.75, 22.30]	17.46	-.73	.47
VO _{2peak} Change	-49.04 [-221.63, 123.55]	86.05	-.57	.57
MAC-Q score x VO _{2peak} Change	2.09 [-5.01, 9.18]	3.54	.59	.56

Note. $N = 60$. CI = Confidence interval; SE = Standard Error; CVLT = California Verbal Learning Task; MAC-Q = memory assessment clinical-questionnaire; BVMT = Brief Visuospatial Memory Task; VO_{2peak} = Peak of Aerobic Capacity

MAC-Q scores moderated the relationship between VO_{2peak} change and BVMT change, $F(6, 53) = 5.29, p = .0002, R^2 = .37$. As shown in Table 4, both VO_{2peak} increase and MAC-Q score increase were predictive of BVMT increase. The interaction term was significant for this model, evidencing a relationship between VO_{2peak} change and BVMT score change, moderated by MAC-Q. Inspection of the simple slopes analysis and Johnson-Neyman output indicated that when MAC-Q scores were low (21 or below: indicated by significance regions in the Johnson-Neyman output), there was a significant positive relationship between VO_{2peak} change and BVMT change, ($b = .16, 95\% \text{ CI } [.03, .30], t(53) = 2.51, p = .02$). However, this relationship was not observed for higher MAC-Q scores (above 21), where the relationship was not significant (See Figure 4). This indicates that at low levels of SCD, as VO_{2peak} increases, so does BVMT performance.

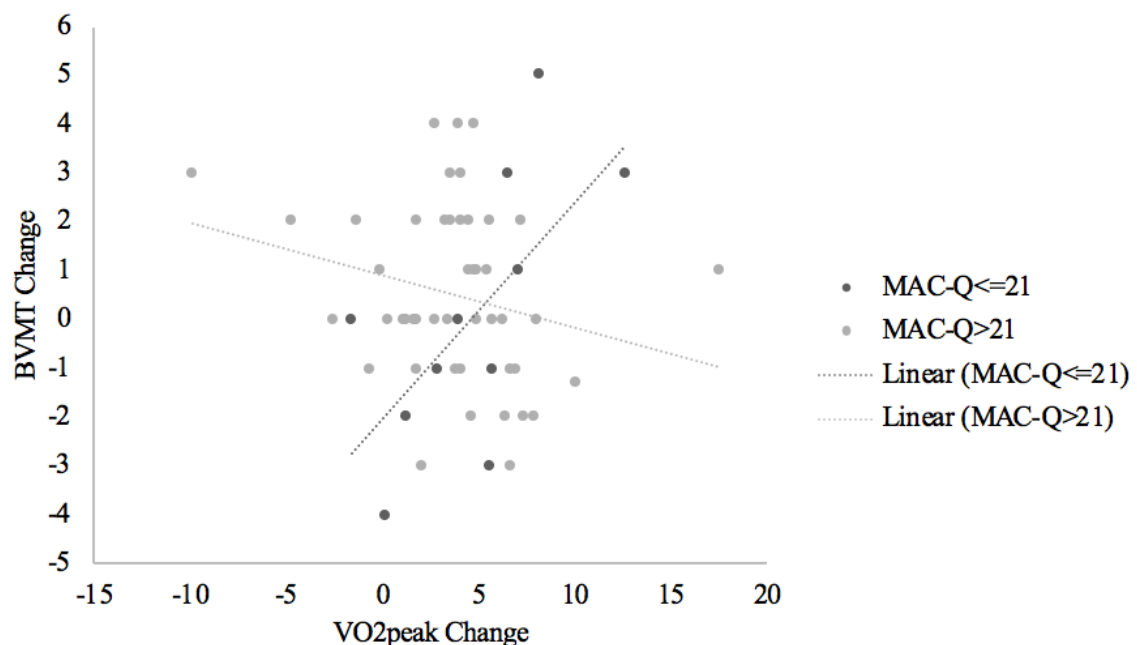


Figure 4. Relationship Between VO_{2peak} change and BVMT change at high and low MAC-Q

Scores. MAC-Q \leq 21 $n = 11$; MAC-Q $>$ 21 $n = 45$; BVMT = Brief Visiospatial Memory task; MAC-Q = Memory assessment clinical-questionnaire; VO_{2peak} = Peak of Aerobic Capacity

Discussion

The current study aimed to examine whether a six month aerobic exercise intervention improved episodic memory and hippocampal volume in older adults, and whether this differentially impacted those with and without subjective cognitive decline (SCD). The results showed that there were no significant differences between the control, MI and HI groups on any episodic memory measure, or hippocampal volume, from pre- to post-intervention. Further, there were no significant differences between those with SCD and those without SCD from pre- to post-intervention on episodic memory outcomes, or hippocampal volume. These results do not support the first two hypotheses, and are contrary to the current literature. Subjective cognitive decline (measured by MAC-Q scores) did moderate the relationship between change in cardiorespiratory fitness and change in BVMT scores from pre- to post-intervention, however this moderation was not observed for any other episodic memory outcome. These results partially support the third hypothesis; as at low levels of SCD, increases in cardiorespiratory fitness were related to increases in BVMT performance, but this relationship is not observed at high levels of SCD.

The current study did not detect an effect of aerobic exercise on episodic memory, contrary to the prior literature. We conceive the results were not as expected due to the highly educated sample (M years of education = 14), compared to the general Australian population (M years of education = 12.9), (United Nations Development Program, 2017). Although we used multiple, sensitive episodic memory measures, these measures may still be susceptible to ceiling effects in highly educated participants. For example, 12% of the current sample

performed at the ceiling level on the BVMT at baseline (i.e. reached maximum score of 12 on delayed recall), with an additional 12% performing just below ceiling level (score of 11); there is little to no ability to detect improvement in these individuals. This evidences the need to examine individuals more likely to be declining to detect any benefit from exercise interventions. Further, awareness of health risks of physical inactivity is a significant predictor of PA adherence throughout life (Martin, Morrow, Jackson, & Dunn, 2000). Those highly educated may be more aware of the risks of being physically inactive, thus more likely to engage in PA throughout life. However, it should be noted that participants in the current study were not engaged in high levels of PA at baseline. Nevertheless, previous PA behaviours may have significantly impacted the detection of cognitive change in our study; as active individuals are significantly protected against cognitive decline in the long term (Sofi et al., 2011), and those who are more active in midlife have better cognitive function later in life (Chang et al., 2010). Lastly, highly educated individuals may have an ability to deal with cognitive decline or pathology more effectively; namely they have greater cognitive reserve (Scarmeas & Stern, 2003). Cognitive reserve may make it difficult to detect any subtle changes in cognition that occur. Therefore, due to the combination of extensive education, midlife PA and cognitive reserve, any benefits of the exercise intervention may have been very difficult to detect. Indeed, the current results are in contrast to majority of the wider literature, and some additional methodological differences between studies, including sample size and intervention protocol and duration, may further explain the conflicting results.

Exercise and Episodic Memory

Although the current study did not show improvement on memory measures between pre- and post-exercise intervention, previous studies have shown that exercise interventions can improve memory recall scores after a 12-week intervention (Chapman et al., 2013).

These contrasting results may be due to differences in sample size (37 vs. 90 in the current

study), as well as differences in intervention length (12 weeks vs. 24 weeks in the current study). The larger sample size and longer intervention time of the current study increase its reliability; and lower quality studies in this field often produce larger effect sizes (Smart et al., 2017). These conflicting results may also be due to differences in exercise intervention protocols. The current study employed a cycling program only, whereas Chapman et al. (2013) used both treadmill and cycling protocols. Chapman et al. also delivered supervised training three times per week, whereas in the current study participants exercised twice a week. Future studies should increase exercise frequency; however, the impact of decreased adherence should be considered and tested within pilot trials of high-intensity exercise, before increasing intervention frequencies.

The current results are also in contrast to studies showing that aerobic exercise interventions can increase hippocampal volume in cognitively normal older adults (Erickson et al., 2011). In the current study, there were no significant differences between the control, MI and HI groups in hippocampal volume from pre- to post-intervention. These conflicting results may be due to the shorter intervention length of our study (six months vs. one year in Erickson et al., 2011). It is theorised that exercise exerts its influence on hippocampal volume through increasing levels of BDNF, which may mediate hippocampal neurogenesis and dendritic growth (Pencea, Bingaman, Wiegand, & Luskin, 2001). Exercise can increase BDNF levels in as short as sixteen weeks (Vaughan et al., 2014), and high-intensity exercise may induce BDNF production at a faster rate (Marquez, Vanaudenaerde, Troosters, & Wenderoth, 2015). Therefore, in the current study it was expected that changes in hippocampal volume would be detectable at six month follow-up. However, the impact of BDNF on neurogenesis and dendritic expansion which explains hippocampal volume increase may take longer to exert its influence, thus explaining the conflicting results. Future

studies should employ longer follow-up periods to ensure they capture any benefits of the intervention which may take longer to arise.

In the current study, there were no differences between groups on improvement in episodic memory tasks. In contrast, Nagamatsu et al. (2013) showed that an aerobic exercise intervention improved performance on the Rey auditory verbal learning task, which is comparable to the CVLT used in our study (Stallings, Boake, & Sherer, 1995). A possible explanation for these conflicting results is that Nagamatsu et al. (2013) used a sample of individuals with probable MCI (MoCA <26), whereas the current study employed cognitively normal participants with and without SCD (no objective deficit). The sample in Nagamatsu et al. may have been at a later stage of decline, where exercise interventions may have greater impacts. Indeed, this is supported by the aforementioned influence of ceiling effects which make cognitive change difficult to detect. Future studies should focus on implementing exercise interventions for individuals with identified SCD who are currently declining; which may be identified through recruiting from memory clinics or longitudinal studies that have been tested over multiple timepoints. This will aid in pinpointing the window of opportunity for implementing preventative strategies, before decline becomes irreversible.

Although our findings of no effect of exercise on episodic memory and hippocampal volume is contrary to much of the previous literature, these results are consistent with a small portion of studies. For example, studies have shown that exercise interventions do not significantly impact memory outcomes in cognitively normal individuals (Kramer et al., 2001; Sink, 2015). Crucially, participants in Sink (2015) study were also highly educated, and this may explain why both that study and the current study produced null results, contrary to the wider literature. It appears that education may moderate the relationship between exercise and cognition, and this should be investigated in future studies. Future studies should also employ a variety of sampling techniques, ideally in multiple locations to

obtain a representative community sample, enhancing the generalisability of the results; decreasing the likelihood of a highly educated sample.

Results from the moderation analysis in the current study showed that improvements in VO_{2peak} predicted improvements in BVMT performance. Interestingly, Kramer et al. (2001) also conducted a regression analysis additional to group comparisons, and showed a relationship between improvement in VO_{2max} , and improved memory; consistent with the current results. This is important as there are individual differences in benefits gained from exercise; and changes in cardiorespiratory fitness may not be seen for all participants in intervention groups, which explains why these results are not evidenced in group comparisons. These results indicate that actual improvements in cardiorespiratory fitness are related to improvements in episodic memory.

An alternative explanation for the current findings is that exercise does not significantly impact cognitive function. For example, studies show a statistically significant positive impact of exercise on cognition for only 8% of cognitive outcome measures (Gates, Fiatarone Singh, Sachdev, & Valenzuela, 2013). However, it is important to note that Gates et al. (2013) meta-analysis was conducted using studies employing participants with MCI, as opposed to cognitively normal individuals. Further, the study concluded that 42% of cognitive outcomes may be clinically relevant, and due to the current lack of interventions; any clinically relevant cognitive benefit is important. Publication bias, the phenomenon that studies with significant results are more likely to be published (Easterbrook, Gopalan, Berlin, & Matthews, 1991), may also influence results in this field. However, publication bias may be remedied by continuing to register clinical trials, increasing the likelihood of publication, regardless of results. Lastly, lower quality studies in this field produce larger effect sizes, potentially over-estimating the impact exercise has on cognition (Smart et al., 2017). However, Smart et al. (2017) and multiple others (Colcombe & Kramer, 2003; Smith et al.,

2010), have concluded that exercise does have a positive impact on cognition, and there is a large wealth of evidence supporting this. Further, even if exercise does only have a small impact on cognition, any benefit is crucial considering the lack of effective interventions for cognitive decline (Livingston et al., 2017). Considering this evidence, it is much more likely that the current results are due to the aforementioned study limitations, rather than an overall lack of effect of exercise on the brain.

Subjective Cognitive Decline, Exercise and Cognitive outcomes

The current results showed that an aerobic exercise intervention did not differentially impact episodic memory in those with SCD compared to those without SCD, contrary to our hypothesis. Although no prior study has directly compared the cognitive benefits of exercise for those with SCD to those without, it is well established that exercise interventions positively impact cognition in individuals with SCD (Busse et al., 2008; Kamegaya et al., 2012; Lautenschlager et al., 2008; Maki et al., 2012). Therefore, it would be expected that the exercise intervention would more greatly benefit those with SCD.

An explanation for these conflicting results may be the operationalisation and measurement of SCD. For example, some studies have included those with objective deficits in their SCD sample (Ten Brinke et al., 2015), contradicting of the definition of SCD. Further, most studies measure SCD using two or three questions regarding memory function (Busse et al., 2008; Kamegaya et al., 2012; Lautenschlager et al., 2008; Maki et al., 2012); not by using a validated measurement tool. In contrast, in the current study, participants showed no objective deficits, and a validated tool was used to measure memory complaints (MAC-Q). One RCT also used the MAC-Q to identify SCD, employing a 12-week exercise intervention in 80 healthy older adults (Iuliano et al., 2017). Iuliano et al. (2017) measured objective memory performance and administered the MAC-Q at pre- and post-intervention. They showed that from pre- to post-intervention MAC-Q scores significantly improved in the

exercise group compared to the control; however there were no differences between groups for objective memory scores. Similar results are reflected in the current study, in that a six month aerobic intervention did not improve objective memory performance in individuals with SCD. However, the current study administered the MAC-Q pre-intervention only, and was unable to analyse whether MAC-Q scores improved. This is because the current analysis was not planned *a-priori*, and the MAC-Q was originally employed as a stratification tool; not an outcome measure. Although Iuliano et al. (2017) showed no improvement in objective measures, improvement in MAC-Q scores is important as SCD may predict future cognitive decline (Mendonça et al., 2016); and subjectively reported improvement shows the clinical relevance of exercise interventions. Therefore, future studies should employ validated measures of SCD at both pre- and post-intervention to gain a greater understanding of the impact of exercise on SCD.

In the current study, a moderation analysis showed that at low levels of SCD, as cardiorespiratory fitness increased, BVMT performance also increased. This partially supports the hypothesis, in that MAC-Q scores did moderate a positive relationship between cardiorespiratory fitness and BVMT performance. However, this relationship was only observed at low levels of SCD, not at higher levels. As previously established, studies have shown the cognitive benefits from exercise in those with both SCD and MCI (Öhman et al., 2014). Therefore, it was expected that the current intervention would provide more benefit to those with greater complaints, however the opposite effect was shown. It appears that increases in cardiorespiratory fitness more greatly benefit cognition in individuals without SCD, compared to those with SCD. This is contrary to previous literature which found that those already showing cognitive decline get the most cognitive benefit from PA (De Souto Barreto et al., 2018). However, it should be noted that De Souto Barreto et al. (2018) study was observational and did not include an intervention, which may explain the conflicting

results. Nevertheless, multiple studies have shown benefits to cognition following an exercise intervention in those with SCD and MCI (Farina et al., 2014; Öhman et al., 2014). It should be acknowledged that the current results are based on a sample of 11 individuals (ie. those that scored less than 21 on the MAC-Q); however, statistical procedures were used to correct for multiple comparisons and the study was adequately powered for these analyses. This was the first study directly comparing those with SCD to those without SCD, and these novel results present a new area for investigation in the literature. However, replication studies are required to clarify these results. Specifically, a RCT with a large sample, whose primary outcome is to investigate the differential benefits from aerobic exercise in those with SCD, compared to those without SCD, should be conducted. A study such as this would help clarify the relationship between exercise, SCD and cognition, and help determine the window of opportunity for implementing preventative strategies.

Overall, from the current study it is difficult to extrapolate whether an exercise intervention would differentially impact those with SCD, compared to those without. This is because, contrary to the wider literature, the initial intervention did not produce the expected benefits to cognition, likely due to the highly educated sample and exercise frequency. Therefore, it is unreliable to say that an effective intervention would not greatly benefit those with SCD, compared to those without. To the authors' knowledge, this is the first study comparing SCD to non-SCD, and a replication study is required.

Limitations

Firstly, the current sample was highly educated and was from an area with a relatively high socioeconomic status; therefore, the null results may be due to ceiling effects. However, a comprehensive, sensitive neuropsychological battery was used with in an attempt to differentiate this population. Secondly, the frequency of the exercise intervention was relatively low, with participants exercising twice a week, for a total of 120 minutes per week.

Nevertheless, the HI group in our study was meeting the PA guidelines for 75 minutes of intense exercise per week, however the MI group was not meeting PA guidelines (World Health Organisation, 2004). Previous studies have shown no significant differences in cognitive benefit between high and low frequency interventions (Groot et al., 2016); however, this meta-analysis was conducted using studies in dementia populations. Therefore, it remains that in cognitively normal individuals, exercise frequency may be an important factor impacting cognition. Null differences between high and low frequency interventions may also be due to higher adherence levels at lower exercise frequencies. Future studies should consider maintaining a balance between high frequency interventions and high adherence rates. In terms of SCD, one limitation of the current study is that memory complaints were not measured at the completion of the exercise intervention. An exercise intervention may reduce memory complaints, without changing performance on objective measures (Iuliano et al., 2017); and reduction of memory complaints is crucial, as they may predict future decline, especially in highly educated individuals (Mendonça et al., 2016). Finally, the current study did not include any long term follow-up data. This is important as longer follow-up periods may show sustained benefits of exercise interventions. This was not included in the current study due to practical time constraints, and should be considered for future studies.

Future Directions

Although our study did not show improvements in episodic memory from an aerobic exercise intervention, the mechanisms of this potential influence are crucial to identify. These mechanisms occur acutely following exercise, and contribute to longer term cognitive changes; possibly contributing to the lack of detectable change on cognitive assessments in this study. Therefore, it is crucial for future studies to employ longer follow-up periods to assess the mechanisms and sustainability of the cognitive benefits of exercise interventions.

Currently, research into the mechanisms of the impact of exercise on cognitive function has focussed at the molecular level; where exercise may increase levels of BDNF, facilitating neurogenesis. The influence of exercise on cognition may also be mediated by Insulin-like growth factor 1 (IGF-1), which may protect against AD (Steen et al., 2005). Exercise also has indirect impacts on dementia risk, for example, by decreasing the risk of cardiovascular diseases and metabolic syndromes (such as diabetes mellitus), which have been associated with increased risk of AD (Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003; Mayer-Davis & Costacou, 2001). However, there has been considerably less literature focussing on behavioural level mechanisms, for example the possible mediating role of sleep (Stillman et al., 2016). Future research should focus on these behavioural factors, in order to gain a deeper understanding of the mechanisms that underlie the impact exercise has on cognition; allowing us to directly target these mechanisms when designing interventions.

A weakness throughout the literature is the inconsistent operationalisation of SCD. Future studies should follow Jessen, Amariglio, et al. (2014) recommendations and definitions, namely ensuring individuals identified as having SCD do not show objective cognitive deficits. Further, SCD should be measured using a validated measurement tool, not merely by asking a single question. To the author's knowledge, this is the first study comparing changes in cognitive outcomes from an exercise intervention in individuals with SCD, to individuals without SCD. It is crucial that replication studies are conducted, to allow a greater understanding of whether individuals with SCD are more receptive to exercise interventions; to determine the crucial window of opportunity to prevent future cognitive decline. Finally, supervised, high frequency exercise interventions should be implemented in representative samples with varying education levels.

Conclusion

The current study aimed to investigate the impact of a six month aerobic exercise intervention on episodic memory, in individuals with and without SCD. Contrary to the hypotheses, the results showed that the exercise intervention did not significantly impact episodic memory. This is the first study to directly compare the impact of an exercise intervention on cognitive outcomes in individuals with SCD, to individuals without SCD. In the current study, increases in cardiorespiratory fitness were associated with increases in episodic memory performance at low levels of SCD, but not at high levels of SCD. These results suggest that individuals without SCD may have greater cognitive benefits from increases in cardiorespiratory fitness, compared to those with SCD; however further research is required to confirm this. Future studies should focus on overcoming methodological flaws and clarifying mechanisms and mediating factors associated with the relationship between exercise and cognition, in those with and without SCD. These results present novel findings regarding the window of opportunity for implementing prevention strategies to delay cognitive decline. Further clarification of the best time to intervene is crucial in order to maximise the potential benefits of exercise and potentially delay the onset of dementia and Alzheimer's disease.

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