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The Effect of a Combined Multiple-Modality Exercise Intervention on Sensorimotor Function in Community Dwelling Older Adults, with A Subjective Cognitive Complaint: The M4 Study (Multi-Modal; Mind Motor)

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Graduate Program in Kinesiology
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science
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THE EFFECT OF A COMBINED MULTIPLE-MODALITY EXERCISE
INTERVENTION ON SENSORIMOTOR FUNCTION IN COMMUNITY DWELLING
OLDER ADULTS, WITH A SUBJECTIVE COGNITIVE COMPLAINT:
THE M4 STUDY (MULTI-MODAL; MIND MOTOR)

By

Sam Titheridge

A thesis submitted in partial fulfillment
of the requirements for the degree of
MSc. Kinesiology

The School of Graduate and Postdoctoral Studies
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Sam Titheridge 2015

ABSTRACT

Aging is associated with the increased onset of diseases such as cognitive impairment, and ultimately dementia. Participants, 55+ years, with a self-reported cognitive complaint completed a 6-month exercise intervention. They were randomized to either a multiple modality exercise program (M2), consisting of aerobic, stretching and balancing exercises or a multiple modality plus mind motor program (M4), whereby a square stepping exercise was incorporated. Participants were assessed for reaction time (RT), movement time (MT) and % errors at baseline and at 6-months using an eye tracking 1000 system. Participants performed prosaccades and antisaccades (AS). AS RT was significantly quicker from baseline – 6-months when M2 and M4 were collated $p = 0.037$. AS MT showed no significant difference from baseline – 6-months, $p > 0.05$. % Errors displayed no significant changes from baseline – 6-months, $p > 0.05$. No differences were seen between M2 and M4 groups for any of the sensorimotor outcomes examined. This study elucidates the impact of an exercise intervention on sensorimotor functioning through improvements in AS RT, however no differences were seen between groups. A multiple-modality exercise intervention can be seen to attenuate cognitive decline in older adults with a self-reported cognitive complaint.

Keywords:

Cognition; exercise; multiple-modality; mind motor; aging; older adults; sensorimotor control; saccade; antisaccade; reaction time.

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List of Terms and Abbreviations

1RM – 1 repetition maximum

AD – Alzheimer’s disease

AS – Antisaccade

BDNF – Brain derived neurotrophic factor

BMI – Body mass index

CIND – Cognitive impairment not dementia

DLPFC – Dorsal lateral prefrontal cortex

EF – Executive Function

FEF – Frontal eye fields

fMRI – Functional magnetic resonance imaging

IADL – Instrumental activities of daily living

PS – Prosaccade

M2 – Multiple modality exercise group

M4 – Multiple modality plus mind-motor exercise group

MCI – Mild cognitive impairment

MMSE – Mini Mental State Examination

MRI – Magnetic resonance imaging

MT – Movement time

SC – Superior Colliculus

SSE – Square stepping exercise

VO₂max – Maximal oxygen uptake by an individual during exercise

Chapter 1

1.1 Literature Review

1.2 Aging and Cognitive Impairment

Chronological aging, or senescence, is associated with increased onset of various diseases such as strokes, cardiac infarctions and hypertension (Rowe & Kahn, 1997). Researchers and health professionals alike aim to alleviate the prevalence of diseases in order to increase longevity. In a sense, successful or healthy aging can refer to the reduction in diseases as well as the ability for an individual to interact with their environment. One particular prevalent, and new area of concern for health is cognitive decline. In Canada, it was estimated in 2011 that nearly 15% (747,000) older adults were diagnosed with dementia or Alzheimer's disease (AD). In addition, it is predicted, that by 2031 this figure will rise to 1.4 million, unless treatments are implemented. (Alzheimer Society, 2012). These debilitating diseases are correlated with increased age and attribute themselves with loss of mobility, functionality and well-being. Indicators of these diseases have been identified in mild cognitive impairment (MCI) and/or cognitive impairment not dementia (CIND) as well as subjective cognitive complaints. MCI and CIND both refer to an intermediate stage between normal cognitive aging and dementias, usually regarded a precursor for developing AD it entails cognitive related declines in memory (Peterson et al, 1999; Jacova et al, 2008). Subjective cognitive complaints, refer to an older adult who believes that their thinking or memory skills have become worse recently (Jessen et al, 2007). These so called precursors towards the onset of cognitive decline have been identified as indicators of not only cognitive health but also mild losses in functionality (Gregory et al, 2013). One way the assessment of cognition can be performed is through a Mini Mental State Exam (MMSE), a basic array of cognitively based questions to highlight possible declines in cognition. Mild reductions in cognitive functions have been shown to be a normal part of aging; however, it is the rapid deterioration that leads to debilitating functionality in individuals (Hertzog et al, 2008). With normal aging there are deteriorations in a multitude of cognitive tasks. Penke et al

(2010) highlight diminishes in processing speed come as an early result of aging, which has been attributed to loss in white matter. Working memory, the ability to consciously maintain and manipulate information has also been shown to be highly age sensitive. These deficits in tasks have been attributed to lessened activation in the frontal regions of the cerebral cortex compared to younger adults.

More recently the utilization of structural and functional brain imaging studies highlight possible brain mechanisms associated with cognitive aging. A review from Dennis et al, (2008) suggests that reductions in brain volume occur faster in adults over the age of fifty with an annual decline of 0.35% compared to 0.12% in young adults. Additionally, similar accelerated changes were observed for ventricle dilation and cerebral structures. Furthermore, cerebral metabolism is influenced by age, with a reduction in regional cerebral metabolic rates for oxygen, glucose and blood flow. Taken together, reduced ability in these tasks and physiological markers, outline reductions in functionality and autonomy.

One particular function that has been identified with cognitive health is executive function (EF). Executive function refers to an umbrella term related to the regulation and control of cognitive processes, including memory, reasoning, problem solving and inhibitory control (Boucard et al, 2012). The focus has remained on executive processes as a determining factor for assessing cognitive decline as it encompasses tasks that are associated with deteriorations or lesions to regions such as the prefrontal cortex, the region of the brain not only utilized for such tasks as memory, reasoning and inhibitory control, but the region found to initially atrophy with aging (Dennis et al, 2008).

Executive function processes have also been related to performing everyday tasks efficiently. Vaughan & Giovanello (2010) argue that executive processes play a role in instrumental activities of daily living (IADL); additionally they saw correlations in executive function and the predictive power in determining IADL performance. Taken together, the correlations indicate the importance of identifying the precursors that highlight early stages of cognitive decline in older adults.

1.3 Exercise on Brain Health

Many authors stress that cognitive decline must be addressed in order to alleviate the individuals diagnosed with dementia and AD. It has been suggested from multiple authors (Colcombe et al, 2003; Colcombe et al 2004; & Baker et al, 2010) that exercise can have mitigating impacts on cognitive decline, Bherer and colleagues (2013) argue introducing physical activity, as a lifestyle change, can be the most protective against the deleterious effects of aging on health and cognition. Physical exercise is a form of physical activity and relates to a structured and planned form of physical activity (Caspersen, 1985). Physical activity throughout life has been related to lower incidences of certain chronic diseases such as cancer, diabetes and cardiovascular and coronary heart diseases (Booth et al, 2000). Recent studies even posit that exercise can have positive outcomes on dementia (Larson et al, 2006; Baker et al, 2010). Specifically, exercise based interventions in older adults have many encouraging outcomes on cerebral and cognitive health (Colcombe et al, 2003; Foster et al, 2011; Gregory et al, 2013). Furthermore exercise interventions have been seen to have a protective effect on cognition later on in life (Colcombe et al, 2003; Erickson et al, 2013). Radak and colleagues (2001) even suggest that physical exercise is one of “the best non-pharmacological strategies that can be used to antagonize brain dysfunction associated with age- related neurodegenerative diseases”.

Previous studies (Baker et al, 2010; & Foster et al, 2011; Liu-Ambrose et al, 2012) highlight certain beneficial impacts of exercise interventions on cognitive performance and executive functioning tasks. The findings in the aforementioned studies collectively outline the potential for exercise to be used as a treatment. Furthermore, these studies demonstrate the necessity of understanding the physiological adaptations that develop, and that cause increased cognitive performance and mitigation of cognitive decline. Adding on to this, Speisman et al (2013) contend that with exercise there is a decrease in brain tissue loss in aging rats. In similar human studies, Colcombe et al (2003) compared unfit and fit individuals utilizing magnetic resonance imaging (MRI) and showed that the fit individuals displayed less age related brain atrophy in frontal and temporal regions. Voelcker et al. (2013) research suggests that with exercise the brain attains physiological

alterations allowing for better functionality and ability to adapt to stimuli. An interesting finding to note is that rodent models genetically predisposed to AD, through the detection of the APOE gene, were seen to have protection against the disease as a result of improved hippocampal plasticity, after regular exercise (Nichol et al, 2009). This indicates the possibility that genetic predisposition to cognitive decline can be altered through exercise. Taken together, the improvements in these markers and neurological alterations can be attributed to healthy cognitive aging and improved brain functionality and have the possibility of emerging as protective adaptations against dementia and AD.

The extent of the relationship between physiological effects of various interventions on cognitive outcomes and cerebral markers has yet to be thoroughly studied and analyzed. Moreover, the limited research performed in areas, as highlighted by Bherer et al (2013) necessitate further research, such as the dose-response relationship, the level of change or protection provided by physical activity and the biological and/or psychological mechanisms that these outcomes engender. A recent systematic review from Van Uffelen et al (2008) highlights the scarcity of knowledge on the effects of different types of exercise on cognitive function in older adults with and without cognitive decline. There can be seen to be two main factors in assessing cognitive decline; the first is that of neuroplasticity and the physiological impact exercise plays in attenuating cognitive decline. Secondly, some researchers have identified task related performances as an indicator for cognitive adeptness.

1.4 Exercise and Neuroplasticity

Physical exercise aimed at modifiable risk factors and neuroprotective mechanisms may reduce declines in cognitive performance associated with senescence, resulting in a reduced prevalence of Alzheimer's disease and other dementias.

A desired neurological adaptation from frequent exercising is improved, or at least, maintained cognitive function and an increase in neurocognitive plasticity. Brain shrinkage occurs in later life and is the primary factor associated with cognitive decline (Raz et al., 2005; Driscoll et al., 2009); thus, understanding mechanisms that mitigate brain atrophy are critical. Plasticity can be broadly defined as the ability of the nervous system to adapt to the external environment as well as its integrity (i.e. lesions), in order

to maintain, recover and enhance cognitive functionality (Ashford & Jarvik, 1985). Recent research has suggested that the brain is also capable of achieving plasticity, even in later life (Erickson et al, 2013). With regards to ameliorating cognitive decline, both exercise and neuroplasticity are strongly related. Additionally, Hayes et al (2013) highlight a strong correlation between fitness levels and brain plasticity in older adults. At a basic level researchers have identified task orientated or functional adaptations in the brain both in humans and rats (Baker et al, 2010; Colcombe et al, 2003; & Foster et al, 2011), highlighting brain plasticity to some extent. Colcombe et al (2003), showed that level of fitness is related to maintained brain matter in older adults. Specifically, brain atrophy seems to be mitigated in frontal, parietal and temporal cortices with relation to improved aerobic fitness. However, more physiological related research (Cole et al, 2007; Erickson et al 2010; Marques-Alexio et al, 2012) has revealed factors that could potentially explain these functional changes, whilst further developing knowledge on the adequacy of preventing cognitive decline.

Brain Derived Neurotrophic Factor (BDNF)

A basic protein found in high concentrations in the hippocampus is BDNF (Phillips et al., 1990; Wetmore et al., 1990; Murer et al, 2001), and is responsible for neurobiology and neurogenesis, since it positively interferes in the structural and functional plasticity in the central nervous system (Mattson et al, 2004). BDNF plays a pivotal role in neuroplasticity (McAllister & Katz, 1999). Foster and colleagues (2011) suggest that decreased peripheral levels of BDNF are associated to age-related neuronal loss. It has been seen that with aging there are reductions in BDNF. Erickson and colleagues (2011) identified BDNF serum levels as a significant factor related to hippocampal atrophy and memory decline in older adults. Erickson et al found reduced serum BDNF levels related to brain atrophy, specifically the hippocampal region, and memory deficits in older adults. Given the documented tendency, whereby smaller hippocampal volumes predict more rapid conversion to dementia (Grundman et al., 2002), BDNF can be seen to be a prominent factor related to cognitive decline. Holsinger et al, (2000) found that these reductions in peripheral BDNF levels have also been attributed to neurodegenerative diseases including AD and related dementias. There are positive indications of BDNF

levels with regard to exercise in humans and rodent models (Gustafsson et al 2009; Knaepen et al, 2010; Erickson et al, 2011; Coelho et al, 2011; Coelho et al, 2013). Knaepen et al 2010 found increases in serum BDNF levels following eight weeks of aerobic training in individuals with multiple sclerosis. Furthermore, additional findings from Gustafsson et al, (2009) involving acute aerobic sessions, found increases in serum BDNF levels in adult individuals with depression. Erickson et al (2011) found significant increases in the serum levels of BDNF, which was associated with increases in the hippocampus volume and better spatial memory, following a one-year aerobically based intervention. Taken together these findings highlight physical exercise, through the increased synthesis of BDNF, as neuroprotective with additional roles of mitigating cognitive decline and thus with it neurodegenerative diseases.

Brain plasticity as aforementioned is the ability for the brain to adapt to external environment in order to maintain, recover and enhance cognitive functionality. Through exercise-induced adaptations to processes such as increased BDNF levels, alterations and neuroplasticity adaptations mitigation of cognitive decline can be attained and thus with it the decreased risk of AD and related dementias.

1.5 Exercise and Cognitive Functions

As previously highlighted, exercise can be seen to elicit a positive response on neuroplasticity. In order to understand the extent to which cognitive decline is precluded through exercise, cognitive ability should also be ascertained. Cross sectional studies such as, indicate that fit older adults show a smaller difference in cognitive ability than older sedentary individuals when compared to younger healthy individuals (Renaud et al, 2010). Moreover, observational studies indicate that staying physically active throughout life will decrease your chances of developing cognitive decline and dementia. Different exercise modalities have been shown to influence areas of the brain and thus with it attain different alterations its cognitive ability. Cognitive benefits in EF and memory have been shown following aerobic exercise (Colcombe & Kramer, 2003). Resistance based exercises seem to have an influence on executive functions and verbal fluency in healthy older adults (Cassilhas et al, 2007) whilst improvements in episodic memory seems to be a result of cognitive training (Engvig et al, 2010). In addition to these findings, recent reviews indicate that a combined multiple modality exercise intervention can attenuate

cognitive decline greater than aerobic, resistance or cognitive training alone (Bherer et al, 2013; Gregory et al, 2013; & Law et al, 2014).

1.5.1 Aerobic Training

Aerobic training has been utilized to prevent many chronic diseases. Recently the role for aerobic exercise in reducing and mitigating cognitive decline is becoming apparent.

Guiney and colleagues (2013), and other contemporaries, agree that aerobic exercise is the most readily available form of exercise that requires no specialist knowledge and has been seen to have a direct link to cardiovascular fitness, which in turn has been linked with cognitive benefits.

A review from Colcombe and Kramer (2003) show that aerobic exercise interventions can have promising impacts on cognition, specifically executive function. Hawkins et al (1992) showed improvements in alternation speed and time-sharing efficiency in healthy older adults versus controls, following a 10-week aquatic aerobic exercise intervention. Kramer et al (1999) observed significant improvements in task switching in previously sedentary older adults following an intervention involving brisk walking for 6 months, 3 times a week, unlike those in the stretching and breathing group. The improvements were also correlated to VO₂max scores. Williamson et al (2009) took previously sedentary individuals at increased risk for disability and cognitive decline and exercised them for 12-months in an aerobically based intervention. The intervention consisted of an individualized program with the end goal to reach 150 minutes weekly of walking exercise. They observed improvements in Digital Symbol Substitution Test (DSST) scores that were associated with improvements in physical function. More recently, Baker and colleagues (2010) observed improvements on executive function following 6-months of high intensity (75%-85% of heart rate reserve) aerobic exercise for 45 – 60 mins a day, 4 days a week, in amnesic mild cognitively impaired older adults. For women improvements in multiple cognitive tasks were found. For men, aerobic exercise effected Trail B performance task only. Taken together these findings show the influence aerobic exercise can play on cognition both in individuals with and without cognitive impairment. The main reason believed to be behind the link of aerobic exercise and cognition is improved cardiovascular health. The improvement could result in up regulation of neuroprotective hormones (Foster et al, 2011; Cole et al 2007; & Erickson

et al, 2010), as well as maintenance of vital brain cortices such as the prefrontal cortex (Foster et al 2011; Colcombe et al, 2004). It should be noted that not all literature is in accordance with these findings. A recent Cochrane review from Young et al, 2014) found no desirable effect of aerobic exercise on cognition in healthy adults. These findings although contradictory, do bring attention to other exercise modalities and their potential effects on cognitive functions, moreover, it provides reasoning behind targeting individuals who are at an increased risk, such as those with subjective cognitive complaints.

1.5.2 Resistance Training

The studies reported above support how aerobic exercise enhances brain functionality. Recent evidence involving resistance-training interventions also show positive effects on cognition. Perrig et al (1998) saw modest effects on cognitive functioning following 2-months of resistance-based exercises, once a week, among 46 older adults. An interesting finding to note was the observed long-term effects of the intervention. After a 1-year follow up assessment significant improvements were seen in strength and memory performance in the training group, highlighting the possible chronic mitigating characteristics of resistance training in older adults. Cassilhas and colleagues (2007) found that a 6-month resistance based exercise intervention 3 times a week at either moderate (50% 1RM) or high (80% 1RM) intensities for 60 minutes a day improved memory performance and concept formation in 62-community dwelling men aged 65 - 75. More recently, Nagamatsu et al (2012) showed that a 12-week resistance-based exercise program (2 times a week; 60 minutes a day) can have positive impacts on cognitive performance among community dwelling older women aged 70-80 years of age, with probable cognitive impairment (<26 MoCA score/ subjective cognitive complaint). The effects of resistance-based interventions are seen to be promising in nature with regards to attenuating cognitive decline; furthermore, it seems that there are modest improvements following even short-term resistance interventions. The literature pertaining to this research area is limited, thus further research outlining and identifying resistance-based interventions must be performed.

1.5.3 Cognitive Training

Cognitive training, also known as cognitive exercise, refers to a standardized set of mental exercises that are repeated and progress in difficulty, focusing in on specific cognitive functions (Gates & Valenzuela, 2010). The role for cognitive training and attenuating cognitive decline has been studied recently and thus, scientific evidence in this direction has grown over the past few years. The protective effects of cognitive training have been noted in older adults (Bamidis et al, 2014). The understanding is that cognitive training requires an underlying ability of higher cognitive function. Simply put, engaging in cognitive training not only improves the trained task but also has subsidized effects on everyday tasks and functions. This has been demonstrated through improvements in intelligence tests (Jaeggi et al., 2008), episodic memory tasks (Buschkuhl et al., 2008) as well as instrumental activities of daily living (Ball et al., 2007). Moreover, it is seen that staying cognitively stimulated throughout adulthood and into late-life can have mitigating impacts on cognitive decline (Lachman et al, 2010). Finally, beneficial impacts on structural and functional areas of the brain can occur following cognitive training (Lustig et al, 2009). Taken together, these findings highlight cognitive training and its utilization as a preventative measure, including interventions, with regards to cognitive decline.

Engvig et al, (2010) performed an intervention designed to impact visuo-motor skills and abstract learning, in an 8-week intensive memory training program. They employed a visualization mnemonic technique among elderly subjects and reported improvements in serial verbal recollection memory. Complementary to these findings, Kirchoff and peers (2012) observed improvements in ease of memory recognition performance following self-initiated encoding strategies (i.e. personal relevance, pleasantness and sentence generation strategies) in older adults. Additionally, through utilizing fMRI, the training group demonstrated increased brain activity in certain regions of the brain (medial superior frontal gyrus, right precentral gyrus, and left caudate), indicating functional adaptations through cognitive training. Lastly, Klusmann et al (2010) found that 6-months of cognitive brain training had similar effects to that of an aerobic based intervention on episodic memory in older women with mild cognitive impairment. The study highlighted the potential for cognitive training to mitigate cognitive decline and

maintain cognitive function. Moreover, this demonstrates the importance of researching further interventions that combine exercise and cognitive training.

1.5.4 Combined Training

The combination of diverse exercise modalities in interventions that train and combine aerobic, strength, balance/coordination, flexibility and cognitive training might demonstrate and unlock a promising approach to improving various cognitive functions in healthy and declining older adults. Recently, the general understanding that a combination of exercise and cognitive interventions either sequentially or simultaneously (dual-tasking) appears to have the potential to maintain or improve cognitive functions and has attracted increasing interest (Law et al, 2014).

Van het Rev & de Bruin (2014) found significant improvements in divided attention (Computerized Vienna Test) following a 3-month, 2 times a week, 30 minutes a day of progressive resistance training, balance and cognitive training based exercise intervention, versus just strength and balance alone. Adding to this, a recent randomized controlled trial intervention study by Linde & Alfermann (2014) found beneficial effects for concentration and cognitive speed following a 4 month intervention, 2 times per week, comprising of either a physical intervention (aerobic and strength exercises) alone, a cognitive intervention alone or a combined physical plus cognitive intervention, versus a waiting control group, among healthy older adults (aged 60-75). In detail, combined physical plus cognitive training displayed immediate improvements in concentration and cognitive speed, as well as prolonged effects (3 month follow up) for cognitive speed. Moreover, these findings show the extent to which the various exercise modalities impacted cognitive health. More recently, Rahe et al (2015) observed the potential differences in cognitive training alone versus its protective factors with the addition of physical activity in healthy older adults (aged 50-85 years). Participants were trained twice weekly in 90 minutes sessions for 6.5 weeks in either cognitive training group (memory, attention and executive functions) or cognitive training plus physical activity (aerobic, strength, flexibility, and coordination/ balance). Improvements in attention were seen for both groups; however, significant longer terms effects (1-year follow-up) were seen in the cognitive plus physical training group only. These findings demonstrate a possible chronic effect of combined training even after a short intervention. Interestingly,

Barnes et al (2013) observed significant changes in overall cognitive functions following 3 months of home-based mental activity plus a class based physical intervention (1 hour a day, 3 times a week) in sedentary, community dwelling older adults with cognitive complaints. An interesting finding to note was the absence of significant differences between the intervention and active control groups. These findings may suggest that the amount of physical activity is more important than the type (Barnes et al, 2013); furthermore, it could suggest the type of cognitive training administered is vital to maximizing interventions designed to attenuate cognitive decline.

1.5.5 Dual-Tasking and Cognition

One component of combining exercise and cognitive modalities is dual-tasking. Dual-tasking refers to the ability to perform two tasks at once (i.e. exercising whilst performing a cognitive task). In everyday life such examples can be seen as key components for functionality; walking whilst talking efficiently is one such example. Due to its nature, completing two tasks simultaneously, it is understood that it requires a higher level of cognitive functioning to adequately accomplish a dual-task. Dual tasking in life is seen to become an increased cognitive stressor for older adults and older adults with onset of dementias (Hawkins et al, 1992).

You et al (2009) showed improved memory performance following 6-weeks (5 times a day) of walking for 30 minutes whilst performing cognitive tasks (memorizing and computing tasks) among healthy older adults with a history of falls (age 64-84). Theill and colleagues (2010) added to this notion; they found 10 weeks (2 times per week for 30 minutes) of simultaneous physical and cognitive training improved cognitive functions (executive function and paired associates task) to a greater degree than the passive control group in sixty-three healthy older adults (age 65-84). Furthermore, larger changes were seen for executive functioning in the dual-task group than the single task group and control group. Finally, Dorfman et al (2014) observed beneficial changes in cognitive performance, as measured by the Trails Making Test B, following a 6-week progressive intensive (17- 47mins) treadmill and dual task exercise program (3 times a week) among older adults with a history of repeated falls (aged 65 – 85).

Suzuki and colleagues (2012) studied older adults with mild cognitive impairment and examined the effectiveness of a 12-month multicomponent exercise program. Participants

were either divided into a multicomponent exercise program consisting of aerobic, strength, postural and dual task exercises (2 days a week; 90 min/d) or an educational control group. Improvements in memory recall and letter fluency were observed following the end of the treatment. Schwenk et al (2010) saw improvements in dual-task performance, specifically serial 3's (walking whilst subtracting 3), among geriatric patients with dementia following 12 weeks (2 hours, twice a week) of progressive resistance training and functional-balance training with additional simultaneous concurrent motor or cognitive tasks. Lastly, Shigematsu and colleagues found improvements in executive functioning and memory following 6-months, 50-60 minutes of either weekly or fortnightly SSE in healthy community-dwelling older adults. These findings highlight dual tasking as a successful intervention in more advanced stages of cognitive decline.

1.5.6 Square Stepping Exercises (SSE)

One interesting and novel form of cognitive exercise is the utilization of SSE interventions (Shigematsu et al, 2008) to improve cognitive status among older adults. The SSE is understood to be beneficial through its multifaceted impact on cognition, such as the social benefits ascertained from performing the SSE in a group environment (Shigematsu et al, 2008). Some recent intervention based studies have attempted to gather insight into the degree SSE interventions have on the aging population. One recent study by Teixeira et al (2013) saw positive influences on global cognitive function (MMSE score), concentrated attention (Toulouse-Pierón Attention Test) and mental flexibility (Modified Card Sorting Test) following 4-months (3 times a week; 40 minutes a day) of SSE among community-dwelling healthy older adults. Taken together, the literature behind the inclusion of dual-task exercises in preventing cognitive decline is scarce, yet, promising in the healthy and cognitively declining older adult population.

Exercise as an impact on overall cognitive status and health looks promising given the influence various exercise modalities have on cognition. Combing the exercise modalities looks the most effective way to augment the amelioration of cognitive decline in older adults. As previously highlighted, not all the literature is in accordance with utilizing exercise as an effective approach in alleviating cognitive decline (Young et al, 2014). However, Van Uffelen and colleagues highlight and suggest possible causes as to why

exercise in some cases has been shown to null effect on cognitive outcomes, including; lack of high-quality studies, the large variability in study populations, exercise protocols, and outcome measures. One outcome measure that could be studied further is inhibitory control.

1.6 Exercise and Inhibitory Control

Inhibitory control has been identified as a key component of executive function (Padilla et al, 2014). Inhibitory control refers to the ability to voluntarily control behavior that conflicts with an otherwise automatic response (MacLeod, 1991) This skill or task has been demonstrated as requiring a higher-level of cognitive function. With regards to age-related changes in inhibitory control it is seen to deteriorate with age. In addition, the deterioration has been correlated to reductions in overall cognitive health. In its entirety, there is not only an age related response to inhibitory control but also a cognitive link between the two. Boucard et al (2012) & Padilla et al (2014) show that inhibitory control can be mediated via previous levels of physical activity. In accordance with this notion, a recent cross-sectional study from Prakash et al (2010) highlights the role of physical exercise on inhibitory control, suggesting, that levels of physical fitness have a direct relation to prefrontal and parietal regions of the brain.

The extent to which exercise interventions impact inhibitory control has been a focus of recent interest. The Stroop and Eriksen flanker task can be seen to be forms of inhibitory control (Erickson et al, 2009; Eriksen & Eriksen, 1974). Stroop task involves asking participants to indicate the color of the ink that a word appears in (i.e. “Red” in the colour blue, the correct verbal response would be “blue” . The challenge to this task arises when the ink color does not match the identity of the color word (for review of task see Stroop, 1935). The flanker task requires participants to indicate the identity of a centralized stimulus while managing to ignore distracting stimuli on the outside. There are two main trials types related to the flanker task: congruent and incongruent. On congruent trials the distractors are associated with the same response as the target; on incongruent trials the distractors are related to a different response than that required by the target. The most common version of the flanker task involves presenting participants with five arrowheads and then being tasked with determining the central stimulus (for review of task see Eriksen & Eriksen, 1974).

1.6.1 Aerobic Training and Inhibitory Control

Dustman et al (1984) analyzed stroop task performance in sedentary older adults (age 55-70). After 4 months of aerobic exercise (60 minutes a day, 3 days a week), the intervention group showed increased ability in stroop task performance (reduced interference). Colcombe et al (2004) showed that a 6-month aerobic exercise program (3 times a week at intensities increasing to 60-70% of heart rate reserve), improved Flanker task scores among 29 community-dwelling older adults when compared to participants in a stretching/ toning control group. More recently, Smiley-Oyen and colleagues (2008) saw reduced interference and improved accuracy in stroop task performance, following 10 months brisk walking (30 minutes a day, 3 days a week) in healthy older adults. Collectively these results demonstrate aerobic exercise as a possible cause for improvements in inhibitory control processes in healthy older adults. In addition it seems that aerobic exercise specifically influences reduced interference in stroop task performance.

1.6.2 Resistance Training

Liu-Ambrose et al (2012) observed improvements in inhibitory control processes (modified Flanker Task) after a 12-month (twice-weekly) resistance-training program among older women (age 65-75 years). Specific changes in increased engagement of response inhibition processes when needed, and a decreased tendency to prepare response inhibition as a default state, were observed. Additionally, Davis and colleagues (2013) found improvements in stroop task performance following a 6 months (twice a week, 60 minutes a day) of high intensity progressive resistance training, among community-dwelling women with mild cognitive impairment aged 70 – 80. Interestingly, resistance training was responsible for greater changes in stroop task performance than the aerobic and balance/ stretching training. Lastly Forte et al (2013) observed similar improvements in inhibition following 3-months, (2 times a week, 60 minutes a day) of either multicomponent training involving neuromuscular coordination, balance, agility, and cognitive executive control or progressive resistance training, in healthy community

dwelling older adults (age 65-75). Taken together, inhibitory control can be impacted through resistance-based interventions in healthy and cognitively declined older adults. To conclude, inhibitory control is influenced through various exercise modalities that seem to impact different cognitive abilities. Although there is little literature on combined exercise and cognitive tasks, inhibitory control, through the suppression of a prepotent response, can be impacted positively.

1.7 Antisaccade Task (AS)

The ability to suppress reflexive responses in favor of voluntary movements is vital for everyday life functionality (Everling and Fischer, 1998). As aforementioned in the literature previously, exercise can have beneficial impacts on inhibitory control. One particular method for assessing inhibitory control and thus with it cognitive impairment, is through assessing oculomotor control. Everling & Fischer (1998) & Heuer et al (2013) have identified the antisaccade task as an efficient way in assessing inhibitory control. Furthermore, age-related declines in this task have also been observed (Eenshuistra et al 2004). To further understand the importance of this task with its relation to cognition, the procedure in performing this task, followed by the neural mechanisms involved must first be understood.

The antisaccade task is a construct whereby subjects are required to generate an eye-movement in the direction opposite of a peripherally presented cue. The ability to perform this task adequately relies on effectively suppressing an innate response or so called reflexive saccade, to a stimulus. The antisaccade task is usually compared to a prosaccade whereby the subjects look as quickly and as accurately as they can towards the stimulus. Typically performed using a computer monitor, whereby the stimulus is presented either side of a fixation cross on the screen, the participant will either look as quickly and as accurately at the stimulus (prosaccade) or in the mirror-symmetrical location of where the stimulus was presented (antisaccade).

The antisaccade task can offer several measures that can provide important insight into cognitive integrity responsible for the proficiency of the task. These include latencies of saccades, errors, movement time and spatial accuracy measures. When comparing the two tasks (pro vs anti) certain differences can be seen, the antisaccade task usually relates

to longer latencies (i.e. the subject takes a longer time to initiate the antisaccade response than the prosaccade response). In addition a common characteristic of the antisaccade task is increased errors, both corrected and uncorrected, in that subjects will perform a prosaccade instead of an antisaccade. These characteristics are also seen to exacerbate with aging (Munoz et al, 1998; Eenshuistra et al, 2004).

1.7.1 Neural Mechanisms for the Antisaccade task

The neural mechanisms associated with performing the antisaccade task have been described through recent advancements in fMRI research. Different mechanisms are activated, when compared to the prosaccade task, indicating that different processes are required for inhibition. The main regions associated with antisaccade performance involve the fronto-parietal subcortical networks (Hutton & Ettinger, 2006). Furthermore, different regions of the brain are seen to be associated with specific processes involved in the task performance such as the preparation versus execution of the antisaccade. For example Connolly and colleagues (2002) demonstrated higher levels of frontal eye field activation during the seconds leading up to the saccadic response.

Research among non-human primates have further highlighted successful antisaccade performance is mediated by the inhibition of saccade neurons in frontal eye fields (FEF) and superior colliculus (SC). Additional brain regions such as the DLPFC are required to inhibit the prepotent response, while parietal areas may be responsible for visuospatial sensorimotor transformations (Zhang & Barash, 2000; Munoz & Everling, 2004).

1.7.2 Antisaccade Task and Cognitive Decline

The antisaccade task can be broken down into two components: the first being, the actual suppression of the innate response (response suppression), and the second being, successfully mirroring the stimulus in the opposite direction (vector inversion). These two requirements for the task display a necessity for higher cognitive function. The nature of the task allows for any deficiencies in cognitive function, specifically pertaining to inhibitory control, to be distinguished. Heuer and colleagues examined the cognitive function of various cognitively-based populations including normal elderly persons, patients with mild cognitive impairment and AD in an attempt to evaluate AS performance as determined by task latencies and errors. AS performance was negatively

impacted by the severity of cognitive decline, normal elderly subjects performed best at the task whilst the AD subjects performed the worse. Furthermore, MRI data obtained for subjects showed lower hippocampal volumes for MCI and AD patients compared to the normal elderly subjects. Adding to this evidence, Kaufman et al (2012) showed significantly more antisaccade errors for Alzheimer disease patients relative to age-matched controls. Taken together these findings highlights the sensitivity of the antisaccade task across the cognitive spectrum and how it may reflect the disease impact upon cortical regions.

To summarize, the antisaccade task requires the efficient ability to firstly suppress an innate response and secondly adept vector inversion capability; thus the AS task has been deemed an effective tool in assessing inhibitory control. The AS task has also been shown to have age and cognitive-related correlations in that task functionality is impeded with increased age. Furthermore, the neurological processes responsible for performing an antisaccade task are relatively well understood. Taken together, it could highlight direct saccadic performance as one of the earliest indicators or biomarkers for cognitive decline in aging.

1.7.3 Exercise and Antisaccade Task

With regards to exercise and the antisaccade task, we are unaware of any significant research that has been performed on older adults and the aging population. The research is promising however; one recent randomized control trial study from Krafft and colleagues (2014) saw antisaccade task improvements following 8 months, (5 days per week, 40 minutes a day) of aerobically-based exercise in children aged 8-11.

Furthermore, there was a correlation between reduced activation in the regions of the brain associated with performance on the antisaccade task. Given the nature of the antisaccade task and its ability to underline declines in cognition, coupled with the role of exercise in alleviating cognitive decline, the possibility for the antisaccade task to be utilized in such a study, involving older adults, could be promising.

1.8 Summary

Implementing exercise interventions as an instrument for alleviating cognitive decline in older adults can be seen to be effective. The current literature review highlights areas of research that are lacking and require further investigation. Knowledge pertaining to the extent exercise can be utilized is still limited; future research in the direction could assess the extent of the new cognitive based modalities, such as SSE, in a combined exercise intervention. Furthermore investigating the novel exercise modalities arising should be studied further through in-depth, longer exercise interventions combining the modalities. The outcome measure for assessing cognitive decline/ improvement, or the earlier detection of this pathology is still ambiguous in nature, and thus has been suggested as a reason for improper findings in previous literature. Future studies should attempt to develop standardized tools in assessing cognitive decline.

The literature and the scarcity of research in certain areas opens the possibility of the current exercise intervention, whereby a 6-month multiple modality exercise program with a mind-motor component to be utilized in alleviating cognitive decline.

Furthermore, suggestions from the research pertaining to enhanced modes of assessing cognitive decline have been noted; the utilization of sensorimotor function and the antisaccade task has been shown to be promising as a novel mode of assessment. Taken together, the current study can be seen to develop new steps in addressing the prominent issues related to mitigating cognitive decline.

Chapter 2

2 The effect of a combined multi-modality exercise intervention on sensorimotor function in community dwelling older adults, with a subjective cognitive complaint: the M4 study (multi-modal; mind motor)

2.1 Introduction

The findings from the aforementioned literature outline the necessity for an intervention-based study in older adults. Therefore, the purpose of this study was to investigate the impact of a multiple-modality plus mind motor (M4: intervention group) exercise program, compared to a multiple-modality (M2: exercise control group) exercise alone group on sensorimotor control in community-dwelling older adults with a subjective cognitive complaint. The hypotheses being tested were that 1) The M4 group will display improved reaction times after 6 months, when compared to the M2 exercise group; 2) That the M4 group will have less errors after 6 months when compared to M2 group; and 3) That the M4 group will show improved movement times after 6 months, when compared to the M2 group.

2.2 Methods

The following section outlines and explains the methods used in the study including the subjects, measures and procedural protocol

The current study was a sub-study of a larger randomized control trial, whereby the assessors were blinded, conducted out of Woodstock, Ontario, Canada. Approval was met through Health Sciences Research Ethics Board at Western University (ethics approval) and then further regulatory approval from Lawson's Clinical Research Impact Committee. All participants provided written informed consent prior to enrolling into the study. Outcome measures were recorded prior to the exercise intervention at baseline (V0) and at 6-months (intervention end point; V1).

Subjects

A total of 47 community-dwelling based participants aged 55 years and over with a subjective cognitive complaint (i.e. answering yes to “do you think your memory or thinking skills have become worse recently?”) were recruited from the Woodstock area via adverts in newspapers, flyers and radio. Once informed consent was completed and the participants were deemed eligible through a screening process, participants were invited to a 3-day baseline assessment period. Participants were then randomized into one of the two exercise groups

Location

Screening and baseline day 1 & 2 visits were conducted at the Salvation Army Church, Woodstock, Ontario, Canada. Day 3 of the assessments were administered at Parkwood Insitute, London, Ontario, Canada. The exercise classes were held in the gymnasium at The Maranatha Christian Reformed Church, Woodstock, Ontario, Canada.

Screening

Screening visits were implemented to ensure subjects met the correct inclusion criteria. Current health conditions, history of diseases, any medications being taken, as well as three blood pressure readings (average of 2 and 3 taken) were obtained. Screening visits consisted of a variety of tests and questionnaires including the MMSE, the Montreal Cognitive Assessment (MoCA), as an assessment of cognitive function, the Lawson-Brody – Instrumental Activities of Daily Living Scale (IADL), assessing the ability to engage in daily activities, and the Center for Epidemiologic Studies – Depression Scale (CES-DS) to determine the presence of severe depression.

Inclusion/ Exclusion Criteria

Participants were deemed eligible to participate in the study if they were 55 years of age or older, answered “yes” to the question “Do you feel like your memory or thinking skills have become worse recently?” and scored 8/8 on the IADL, demonstrating full independence and autonomy. Participants were excluded, if they displayed any of the following criteria: presence of dementia either through previous diagnosis or MMSE

score < 24; presence of other significant neurological disorders or psychiatric disorders; severe sensory impairment (i.e. blind); a previous history of severe heart conditions (i.e. myocardial infarction in the past year, end stage congestive heart failure, end stage renal disease); significant orthopedic conditions (severe arthritis); Blood pressure reading >180/100mmHg or <100/60mmHg; and severe depression (CES-DS score ≥ 16 and clinical judgment of the study physician). If the participants were deemed eligible they were invited back for the 3-day baseline assessment period.

3-Day Baseline Assessment period

Once deemed eligible, a 3-day baseline assessment period was scheduled. Day 1 and 2 involved participants coming into Woodstock; day 3 assessments were administered at Parkwood Institute, London, Ontario.

Day 1: Demographic information including age, sex, ethnicity, marital status and years of education were recorded. A Phone-FITT was used to assess baseline levels of physical activity (Gill et al, 2008). Smoking status and drinks consumed in a “typical” week were obtained. Participants were introduced to twelve Cambridge brain science (CBS) computer games assessing different levels of cognitive functions. Dell PC laptops were used with a track mouse. Participants were explained each game by a research assistant, following the explanation the game was then played until the subject understood the game. The assessment lasted approximately 45 minutes. Either on Day 1 or Day 2 subjects were fitted with a 24-hour ambulatory blood pressure monitor.

Day 2: Participants played each of the 12 CBS games in full, each game lasting approximately 4 minutes. After completion of the 12 games, the scores for each game were recorded and saved. The assessment lasted approximately 60 minutes.

Day 3: Participants were assessed at Parkwood Institute in London, Ontario for the remainder of the assessments where the eye tracking assessment (explained below, see *Instruments and Measures* section) was performed. In addition to this participants were taken through a battery of assessments that pertained to the larger study outcomes and will not be included in this current paper. Firstly subjects received an ultrasound of the carotid artery, a gait assessment using a GaitRite system. After these assessments had been completed, participants were given further tests assessing balance (Fullerton

Advanced Balance Scale), submaximal levels of fitness and training heart rate for the exercise program. (STEP test) and blood pressure. Height, weight, waist circumference and body mass index (BMI) were also collected. The assessments lasted approximately 1.5 – 2 hours. collected. Once participants had completed the three-day assessments, they were randomized into one of the two exercise classes via concealed envelopes by the study coordinator who was not involved with generating the randomization sequences. Randomization was performed in private to ensure that the assessors were blinded to the group allocation.

Intervention

The exercise classes, comprising of 10-20 subjects in each class, were offered in a class format, 3 times a week, Mondays, Tuesdays and Thursdays for 6 months at Woodstock Maranatha Church. Exercise classes were 60 minutes in length and led by certified senior fitness instructors. The subjects were randomized into one of two exercise groups: multiple modality plus mind motor exercise group (M4) or multiple modality exercise group (M2).

Multiple Modality Exercise group (M2)

The exercise class incorporated a 5 minute warm up involving light aerobic training and dynamic stretches, 20 minutes of moderate to vigorous intensity aerobic exercise, followed by an aerobic cool down, 10 minutes of resistance training (using therabands and wall and chair exercises), 15 minutes of balance, range of motion and relaxation exercises and 5 minutes of stretching exercises.

Multiple Modality plus Mind Motor Exercise group (M4)

The structure for the exercise class was similar, 5 minute warm up, 20 minutes moderate-vigorous intensity of aerobic exercise, 10 minutes of resistance training, 5 minutes of stretching and a 5 minute cool down, with the only difference being that the 15-minute balance exercises were replaced with 15 minutes of mind-motor exercise (Square Stepping Exercise).

M4: Square Stepping Exercise

The exercise intervention group completed 15 minutes of square stepping exercises (SSE). The SSE is a novel mind motor task developed by Shigematsu and Okura (For review of procedure, see Shigematsu & Okura, 2006). SSE was performed on a gridded mat, 250cm by 100cm, and each square being 25cm each side. Participants were given a variation of progressive patterns involving forward, backward, lateral and oblique movements, which were memorized and then performed. Step patterns were developed and categorized as beginner, intermediate and advanced. SSE were performed in a group environment, whereby 4-5 participants were on a mat at one time, support from participants was encouraged.

Follow-up Procedures

During the exercise program participants were contacted monthly by phone via a research member to collect data regarding the levels of physical activity in a typical week for the month. Halfway through the intervention (3-months) a STEP test was performed so as to determine any changes in cardiovascular fitness corresponding to changes in the participants training heart rate and to ensure the aerobic exercise was progressive.

Instruments and Measures

Participants performed an eye-tracking procedure as a measurement of cognitive function, more specifically observing the adeptness of the pre-frontal cortex, and the ability of response suppression (Eenshuistra et al, 2004). Eye movements were recorded in a darkened room to reduce light pollution. Participants performed discrete eye movements (i.e., saccades) and responses were recorded via a video-based eye-tracking system (i.e., EyeLink 1000, SR Research Ltd. Mississauga, Canada) sampling at 500 Hz. Participants sat in front of the monitor and were positioned 60cm from a LCD monitor. The right eye was tracked for consistency unless other circumstances, such as mild ptosis, inhibited accurate readings.

The procedure involved flashes of crosses appearing on the peripheral area of the screen and then participants were instructed to either look at the stimulus (prosaccade) or in the mirror symmetrical location (antisaccade). Participants performed a total of 160 saccades across two different blocks. In one block participants completed prosaccades whereby the task was to look as quickly and as accurately at where the yellow cross flashed up. In turn, the other block entailed antisaccades wherein participants had to look in the mirror symmetrical location to where the yellow cross was presented. The two blocks entailed a collection period between 15-30 minutes depending on calibration efficiency and participant breaks. Saccadic movements were 2 blocks, 80 prosaccades, 80 antisaccades randomized through computer software, MATLAB (7.6: The MathWorks, Natick, MA, USA) and the Psychophysics Toolbox extensions (ver 3.0; see Brainard 1997). MATLAB was used so as to allow the assessor more manipulation of variables as well as enabling the assessor the flexibility to change certain aspects of the test paradigm if required. Each trial started with the appearance of a green (prosaccade) or red (antisaccade) fixation cross in the center of the screen. Participants were instructed to direct their gaze to the fixation and following a stable gaze duration (i.e., ± 1 degrees for 400 ms) the fixation cross disappeared. After a 200 ms interval after fixation extinction, a target stimulus (i.e., yellow cross: 12 degrees) appeared left or right of the former fixation at one of two eccentricities (i.e., 12 and 15 degrees from fixation). The onset of the target stimulus served as the imperative to pro- or antisaccade “quickly and accurately”.

Data Reduction

Data was filtered offline. Saccade onset was determined on the basis of velocity and acceleration values that exceeded $30^\circ/\text{s}$ and $8,000^\circ/\text{s}$ respectively. Trials that involved missing data, noise trials, (i.e. a blink) or an anticipatory saccade (i.e. $\text{RT} < 85\text{ms}$) were excluded from the analyses. Trials where a directional error was performed (i.e. prosaccade instead of an antisaccade) were recorded and presented as the percentage of directional errors below; however, trials involving an error were not included in the analysis for both reaction time (RT) and movement time (MT).

Analysis of Saccades

Eye movement data were analyzed offline for reaction time (RT: time from target stimulus presentation to saccade onset), movement time (MT: time from saccade onset to saccade offset) and errors [(the completion of a prosaccade instead of an antisaccade, or vice versa and an anticipatory saccade <85ms (Munoz et al, 1998)].

Statistical Analysis: RT & MT

Statistical analyses were run through IBM SPSS software (IBM) version 20. An alpha-level of 0.05 was used for all omnibus tests and only significant effects are reported. A mixed model analysis of variance was selected to determine the effect of a 6-month multiple modality exercise program between M2 and M4 groups for both RT and MT, constructed of a 2 (task: prosaccade, antisaccade) by 2 (space: left, right) by 2 (target: near, far) by 2 (time: pre, post) by 2 group (M2, M4). A 2x2 mixed analysis of variance was conducted to compare the number of errors made at baseline and post intervention, constructed of a 2 (group: M2, M4) by 2 (time: pre, post). Analysis of the studentized residuals showed there was normality, as assessed by the Shapiro-Wilk test of normality and no outliers as assessed by no studentized residuals greater than ± 3 standard deviations. Data are mean (standard deviation), unless otherwise stated. Significant main effects and interactions were broken down through simple effects analysis.

2.3 Results

Participant Flow

Participants were enrolled from December 2013, through June 2015 in a wave format. Figure 1 shows the flow of participants through the study. A total of 33 participants were excluded from the study, 10 were excluded due to not meeting the inclusion criteria: no cognitive complaint (n=2), depression (n=1), significant neurological conditions (n=5), MMSE <24 (n=1) and high blood pressure >180/100 (n=1). 23 participants declined to participate. A total of 47 participants were randomized into the current sub-study (2 out of the 4 waves) for baseline assessments. 17 were allocated to M2 and 30 to M4. 47 were used for the current sub-study comprised of 2 waves. Insufficient eye data occurred for 5

participants, 4 were unable to be ‘tracked’ (the camera could not accurately locate the eye), 1 participant had a blepharospasm (eye twitch) and 1 participant had insufficient trials once data outliers were accounted for. 8 participants did not attend baseline and 6-month assessments. A total of 33 participants were used for the analysis of the current study¹; 14 for M2 and 19 for M4.

Baseline Characteristics

Table 1 describes the baseline characteristics for each individual intervention group. Participants were all living independently and were autonomous. Characteristics pertaining to the two groups are as follows. Overall, participants had a mean age of 66.76 and 14.15 years of education; 26.47% of the participants were male and 73.53% were female. Participants had a relatively high level of global cognitive function with a mean MMSE score of 29.21 and a corresponding moCA score of 26.18. Mean BMI for participants was 27.56kg/m². Average waist circumference was 91.16cm. Participants had good overall fitness with consequent mean VO₂max scores of 34.48 for males and 26.07 for females (Petrella et al, 2003). Nearly 56% (55.9%) of participants had reported hypertension, 11.8% had a cardiac related issue, 35.3% had high cholesterol and just short of 3% (2.9%) of participants had diabetes. There were significant differences in baseline characteristics between M2 and M4 groups for the percent of participants diagnosed with high cholesterol and diabetes.

¹ 32 participants were included for RT and MT analysis as 1 participant had insufficient number of trials once errors and outliers were removed. Error analysis included 33 as including errors ensured the participant had sufficient number of trials for analysis

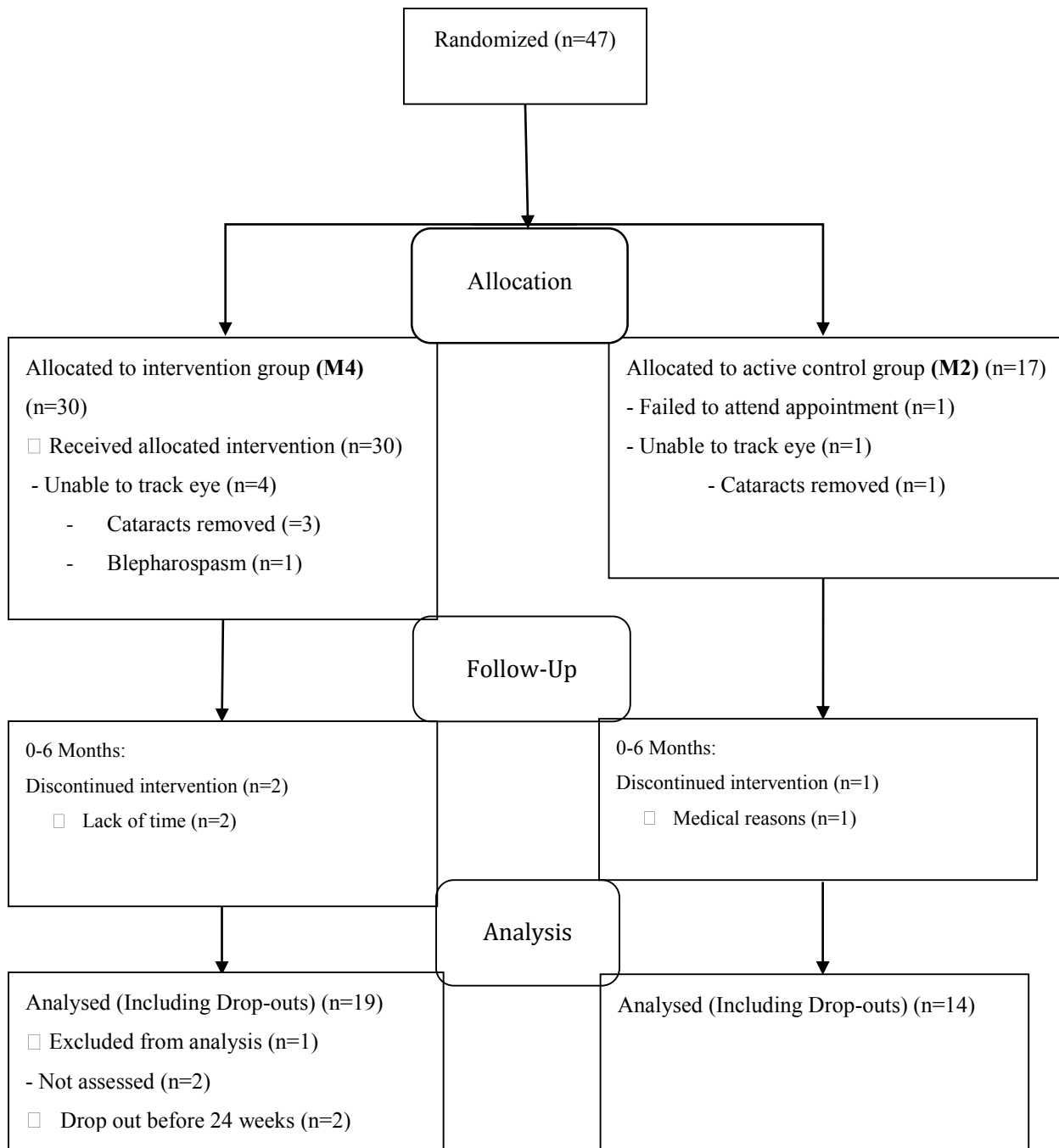


Figure 1: Participant Flow

Table 1: Baseline Characteristics of the M2 and M4 Intervention Groups, M (SD).

Demographics	M2 (n=14)	M4 (n=19)
Gender (%)		
Men	14.3	35
Women	85.7	65
Age (yrs)	68.01 (5.61)	66.38 (7.32)
MMSE	28.86 (1.61)	29.43 (0.93)
MoCA	25.21 (2.26)	26.86 (2.46)
Education (yrs)	14.36 (3.59)	14.10 (2.62)
BMI (kg/m²)	27.71 (5.15)	27.50 (3.32)
WC (cm)	93.07 (14.77)	90.02 (8.96)
VO₂ Max (ml/kg/min)	25.11 (6.84)	29.90(8.16)
Medical history (%)		
Hypertension	50	60
Heart problem	14.29	10
High cholesterol	42.86	30
Diabetes	7.14	0
All data is presented as mean (SD)		

Key: MMSE, Mini mental state examination; MoCA, Montreal cognitive assessment; BMI, body mass index; WC, waist circumference

Primary Outcome: Reaction Time

Figure 2 shows the characteristics for pro and antisaccade trials within each group. Results for RT showed a main effect for task $F(1,31) = 319.936$, $p < 0.001$, as well as a task by time interaction, $F(1,31) = 8.185$, $p = 0.007$. As shown in figure 3 prosaccade RTs at the 6-month assessment did not differ from prosaccades at baseline $t(31) = 0.743$, $p = 0.463$, whereas, antisaccade RTs at the 6-month assessment were shorter than their baseline counterparts, $t(31) = 2.176$, $p = 0.037$. In addition, and given the primary goals of this study, results for RT did not produce a main effect for group $F(1,31) = 0.042$, $p = 0.839$, or involve any higher order interactions concerning group $F_s < 1$.

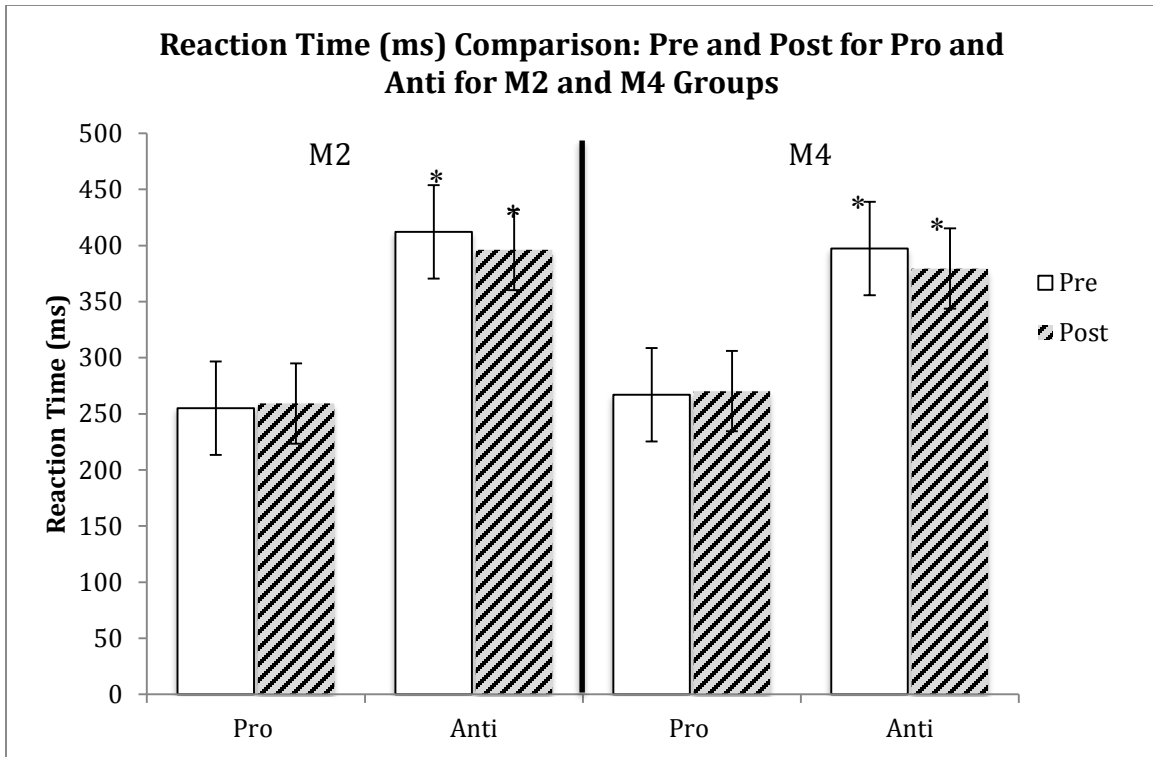


Figure 1: Reaction Time (ms) for Prosaccade and Antisaccade task (x-axis) Trials for Pre (white bar) and Post (shaded bar) for M2 (left) and M4 (right) Groups; * = significantly slower than prosaccades $p < 0.05$, CI 95%.

A sensitivity analysis was performed for compliance concerning the exercise program. 70% was set as an appropriate cut-off. No changes in the interactions were seen when after accounting for participants who did not make 70% minimum compliance. M2 group showed 74.6 % compliance and M4 group showed 75.5 % compliance.

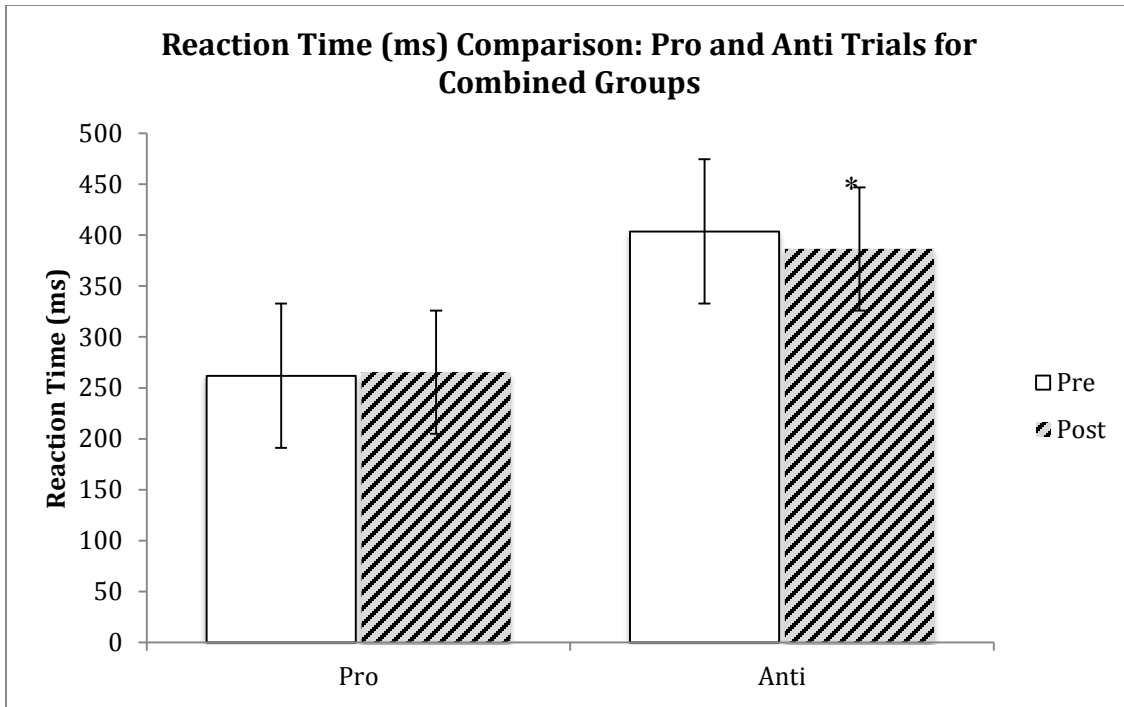


Figure 2: Reaction Time for Prosaccade and Antisaccade Trials (x-axis) for Pre (white bar) and Post (shaded bar) for Combined Groups; * = significantly different from baseline, $p < 0.05$, CI 95%.

Errors

There was no significant interaction between group and time, $F(1, 32) = 0.636$, $p = 0.431$. M2 baseline errors were 16.86% (8) and M4 was 10.78% (7). After the 6-month assessment M2 errors were 17.82% (12.04) and M4 was 9.41% (7.45). M4 and M2 did not see any significant changes in the reduction of errors following 6 months of the exercise program. Figure 4 shows the % errors between each group.

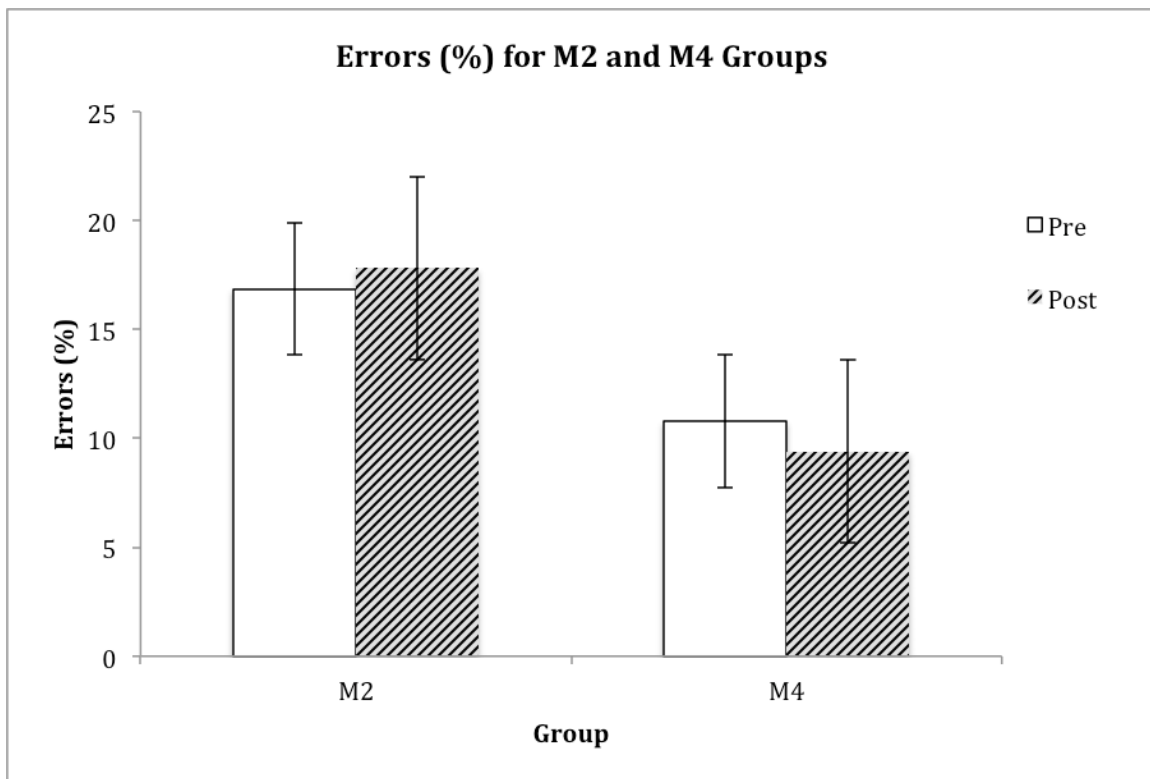


Figure 4: Errors (%) Pre (white bar) and post (shaded bar) for M2 and M4 Groups

Movement Time

Results showed a main effect for task $F(1,31) = 15.442$, $p < 0.001$, as well as a main effect for target (near or far) $F(1,31) = 36.765$, $p < 0.001$. There were no statistically significant interactions between groups $F(1,31) = 0.118$, $p = 0.773$. In addition there was no interaction for time $F(1,31) = 0.218$, $p = 0.644$. Figure 5 shows the MTs between groups at baseline and 6-months assessments for prosaccade and antisaccade task.

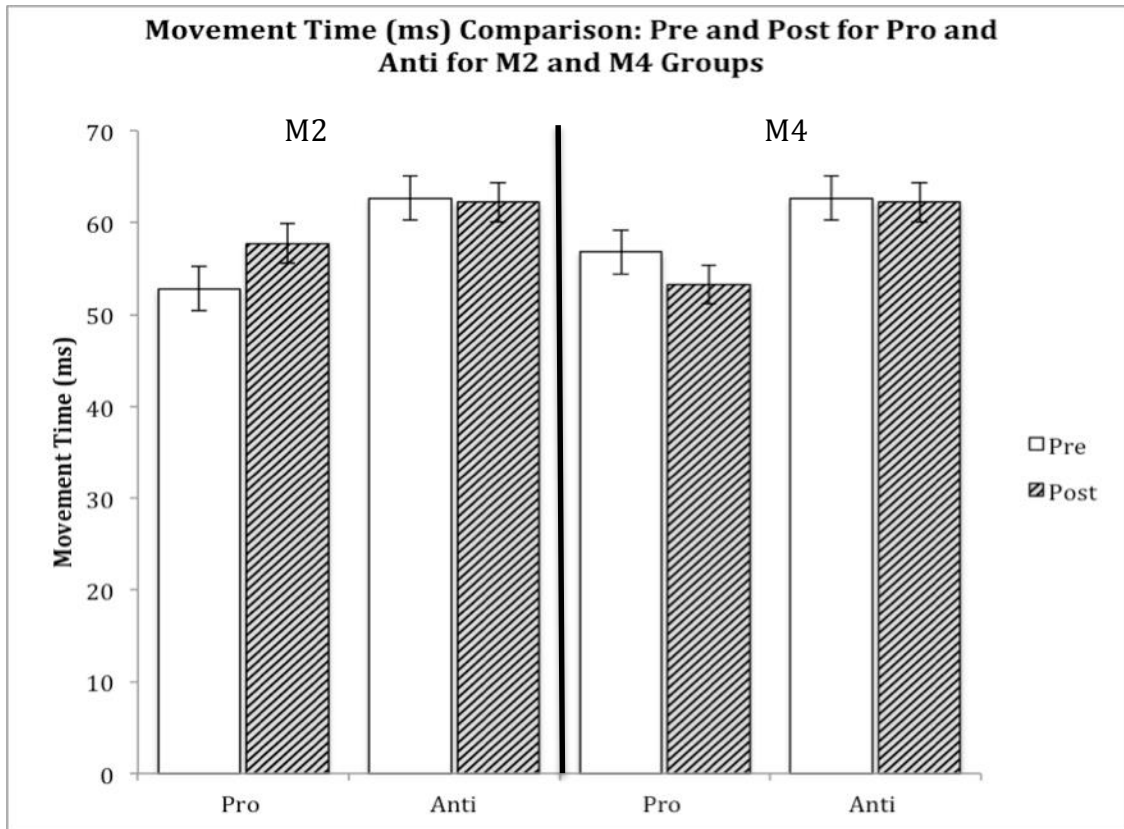


Figure 3: Movement Time (ms) Pre (white bar) and Post (shaded bar) for Prosaccade and Antisaccade Trials (x-axis) for M2 (left) and M4 (right) Groups

2.4 Discussion

The purpose of this study was to investigate the impact of a multiple modality plus mind motor (M4) exercise program compared to a multiple modality (M2) exercise program alone, on sensorimotor control in community-dwelling older adults with a subjective cognitive complaint. The current paper focuses on the primary outcome of reaction time; followed by percent of errors made and movement time.

Reaction Time

Reaction time characteristics supplement previous literature pertaining to saccade research in older adults with and without cognitive impairment. The current study saw prosaccade RTs that were significantly faster than antisaccade RTs at baseline and post intervention for both groups. These typical findings concur with research from Everling

and Fischer (1998) and Munoz and Everling (2004); suggesting that the antisaccade task is more cognitively challenging when compared to the prosaccade task. The prosaccade is understood to be an automatic or innate response to a presentation of a stimulus; the antisaccade task relies on the suppression of this response with the additional requirements involved for vector inversion.

The influence of exercise on inhibitory control has been reasonably well documented; furthermore, it is understood that individuals participating in regular physical activity will see improvements in cognitive functioning (Boucard et al, 2012). However, to the current knowledge of this study, distinguishing the impacts of an exercise intervention on sensorimotor functioning, specifically pertaining to the antisaccade task, in older adults is limited. Thus, elucidating the current findings of this study can be observed through looking at previous interventions observing changes in inhibitory control processes and functions, as well as further exploring the intricacies of the antisaccade task.

The primary research question of this study was to elucidate towards whether a multiple modality plus mind motor exercise intervention could positively influence sensorimotor functioning in older adults; yet, no statistical interaction was discovered regarding group x time. In addition, it was seen that there were no differences between group's pre and post. The current study showed the additional mind-motor task (M4) had minimal impact on the antisaccade RTs performance. This finding disagrees with the hypothesis of this study as well as some literature. Bamidis' et al (2014) recent review that looked at the impact of multimodal exercise training in elderly individuals found that the utilization of multimodal exercise programs induced more beneficial cognitive effects than cognitive and exercise training alone. Furthermore, they add, that greater cognitive benefits will be seen if the cognitive intervention aspect is provided in a socially challenging way. The SSE offered in this study can be categorized as one of these forms of cognitive training. It should be noted that incorporation of cognitive training simultaneously alongside exercise based interventions displays some disparities in findings. A review from Snowden et al 2011, found positive but not sufficient evidence that exercise interventions improved cognitive ability in older adults. However, other reasons concerning the lack of

effect could possibly be attributed to sample size (i.e. lack of statistical power), monitoring the progress of the SSE, so as to progressively exert the participants cognitively, and due there only being 15 minutes of SSE in each class.

These discrepancies highlight the need for additional research to be carried out on the prescription, frequency and intensity of multiple modality exercise programs, with specific focus on the mind-motor component.

When combining both the M2 and M4 groups together a statistically significant reduction in antisaccade RTs from baseline to post intervention was seen. These findings indicate towards exercise as the primary contributor towards improving sensorimotor functioning in community dwelling older adults with a subjective cognitive complaint. The antisaccade task is the higher cognitively demanding task, when comparing the prosaccade and antisaccade task. Thus, to see improvements in this task, via improved RTs, would suggest improvements in sensorimotor functioning (Mirsky et al, 2011).

As previously mentioned exercise can positively influence cognitive functioning; consequently, to see the improvements in antisaccade RTs are anticipated. Colcombe et al (2004) findings concur with that of the current study, whereby they saw improvements on the flanker task that correlated with greater levels of task-related activity in attention control areas. Additionally, Voss et al (2010) found improvements in functional brain regions associated with cognitive functioning and inhibitory control processes following 12 months of aerobic exercise in older adults.

Liu-Ambrose et al (2012) found improvements on the flanker task and functional changes in brain plasticity following 12 months of twice-weekly resistance based training in older women. Lastly, Suzuki and colleagues found improvements in stroop task ability following 12 months of combined aerobic and resistance-based exercise.

The flanker and stroop tasks require similar activation of brain regions that are found on the antisaccade task (Munoz & Everling, 2004). The findings mentioned above outline the direct correlations between positive functional changes in areas associated with inhibitory control and the flanker and stroop task as a result of exercise. Although the

current study did not include the use of fMRI imaging, the improvements in the antisaccade RTs could be attributed to these functional adaptations. The antisaccade task requires two main processes 1) response suppression and 2) vector inversion. The efficiency of these two processes are understood to account for the corresponding RTs (Everling and Fischer, 1998; Zhang & Barash, 2000; & Everling & Munoz, 2004). The corresponding improvements found within this study generate the question of whether it is an increased ability in response suppression, or, that the improved antisaccade reaction times were as a result of a faster vector inversion? Research from primate (Everling & Munoz, 2000) and human fMRI studies by Souza et al (2003) suggest that efficiency on the antisaccade task corresponds to processes preceding the antisaccade task. In other words, certain processes, involving the FEF, SC and DLPFC, leading up to the presentation of the peripheral target in an antisaccade task are responsible for how efficiently it is performed. The DLPFC is known to play a role with the first process (response suppression) (Pierrot-Deseilligny et al, 2003), specifically; the DLPFC is thought to be responsible in the top-down processes that are required for the inhibition of the response. FEF and SC are responsible for vector inversion through interactions of neurons between them (Munoz et al, 2000). Given that general deficits in inhibitory control, and in AD populations, have been associated with reductions in prefrontal cortices, and that studies involving lesions, or damages to these regions showed poorer performance on the antisaccade task, it can be suggested that the improved antisaccade RTs are as a result of neurophysiological adaptations and improvements in signaling pathways. In addition, it highlights the evaluation of antisaccade RTs as an adequate indication of improvements in sensorimotor function, in older adults.

An additional result of exercise interventions amongst older adults is increased cerebral blood flow (Swain, 2003; Akazawa, 2012). Early imaging studies involving fMRI and positron emission tomography (PET) show that when performing the antisaccade task, there is an increase of cerebral blood flow to parietal and frontal areas, in addition when comparing the two tasks (pro and anti) higher levels of cerebral blood flow are recorded for the antisaccade task in FEF and DLPFC regions. Therefore, could the exercise intervention have improved overall cerebral blood flow, and caused an improvement in

blood flow efficiency required for the antisaccade task? Further research is required into this interesting consideration

The role of BDNF in improved cognitive functioning has also been seen to attenuate cognitive decline in rodent models. Furthermore, the up-regulation of BDNF can be seen as a result of exercise and exercise interventions (Knaepen et al, 2010; Erickson et al, 2011). The possible increase of certain growth factors such as BDNF could have allowed for neurogenesis of prefrontal cortices and corresponding improvements in sensorimotor functioning. Thus, the better efficiency in the functioning of these regions could possibly account for faster antisaccade RTs.

Errors

The percent of errors made had no change over the exercise intervention from baseline to post intervention. These findings somewhat contradict the literature and the hypothesized findings of this paper. Mirsky et al (2011) argue that antisaccade performance predicts executive functioning and brain structure in normal elderly participants. In addition, research with AD populations have demonstrated a reduced performance on the AS task (Kaufman, 2012). The percent of errors made are strongly related to inhibitory control. Response suppression directly relates to the function and capability of the DLPFC. Moreover, research has shown that exercise can have a positive impact on the DLPFC. However it should be noted that to date, no research has attempted to show the influence of an exercise intervention on percent errors. Although the percent of errors made is strongly related to brain atrophy and function, does this study show the first indication that it is not influenced through exercise? Findings from Heuer and colleagues (2013) could indicate as to why no changes in errors were seen. They found stochastic responses for errors across the spectrum of the disease, suggesting that the initial pathology associated with cognitive decline may cause for a wider response in errors. The participants recruited for this study were at the earliest stage of cognitive decline, although considerations should be made towards the impact of age on cognitive decline. Age can be seen to be a risk factor for cognitive decline; the current study recruited participants from 55 years and older. It could be possible that some of the older

participants had a varied range of error responses and thus more stochastic responses. Another consideration is findings from Mirsky et al (2011) who found that the inferior frontal junction and supplementary eye field were responsible for the performance of AS % errors. Although the literature is in agreement that the DLPFC is responsible for the inhibition of prosaccades on the antisaccade task, it suggests that additional regions may play a role in the % of correct errors. Moreover, it posits the question of whether the current exercise intervention targeted those regions. Future research should try and identify the specific region(s) involved in antisaccade inhibition and the impact of exercise on these regions.

Studies involving patients with lesions to the DLPFC show an increase of errors made (Pierrot-Deseilligny et al, 2003), however, an important finding to note is that lesions in the FEF do not relate to inhibitory control (inability to suppress the response), instead, they have been linked with the impaired ability to generate the voluntary antisaccade (increased reaction times) (Gaymard et al, 1999). Although successful performance of the antisaccade task relies on a collaboration of the neural circuits associated, these findings show the segregation of different brain regions as well as their individual roles in the performance of the antisaccade task.

Taken together these findings indicate that the exercise intervention improved AS RT as a result of improved SC and FEF functioning and not DLPFC functions, related to improved vector inversion. In addition, possible adaptations allowing for improved blood flow during antisaccade task functions and increased BDNF levels could have accounted for these improvements. These findings elucidate the regions of the brain that are improved through exercise. However, it should be noted that in order to clarify these findings, fMRI and PET studies should be implemented to suitably explain and understand the functional improvements.

Movement Time

Recall how movement time was characterized: the time from the initiation of the saccade to the termination. There was a significant interaction for task, in that antisaccade MT's were slower than prosaccade counterparts. This finding agrees with previous studies pertaining to movement time (Heath et al, 2010) in that it suggests that the combination of increased task difficulty and vector inversion to no spatial or peripheral target is what causes increased antisaccade MT. A main effect for target was also discovered, this aligns with Fitts' speed accuracy trade off law (Fitts, 1954) There were no significant differences between groups following the intervention. The hypothesized findings were that MT would improve following a 6-month exercise intervention. Whilst there is literature that shows age-related changes in movement time as a result of either a reluctance to produce errors and/ or as a result of age related declines in brain connectivity (Forstmann et al, 2011), there is also a strong body of research that suggests that MT is impervious to age-related declines (Pratt et al, 2006). Furthermore, improvements in cognition would not automatically necessitate improvements in MT given the fact that the processes required to perform the eye movements are related to neural activity involving motor control; however, limited studies are yet to observe the impact of cognitive decline on MT. Pratt et al (2006) note that constant saccadic activity could be what keeps saccadic motor systems more fit than other motor systems that are seen to decline with age. Individuals make approximately 200,000 saccades a day; such levels of activity may maintain this motor system.

Limitations and Future Research

This novel study has developed knowledge on exercise and sensorimotor functioning; however, there are some limitations towards the current study and there are possible future directions that could further help elucidate the nature of cognitive decline, as well as to develop preventative interventions. Firstly, it should be recognized that these improvements in antisaccade RT are without a non-exercise control to fully determine if it was solely exercise alone that mediated the improvements. The gold standard used for interventions is that of a RCT, however the smaller sub-sample used for this current study may not have mediated the desired effects, balancing all known and unknown

confounders, of randomization. It should also be highlighted that although efforts to maintain adherence to the exercise program were made, not everyone managed to attend all the classes.

The future for research in this area is appealing. The antisaccade task has been used in many cognitively impaired populations; further research could look at the relationship between cognitive scores and performance on the antisaccade task following the exercise intervention. The utilization of fMRI should definitely be used in tandem with the antisaccade task following an intervention-based study. This will help to elucidate towards the exact functional changes that occur as a result of the exercise. In addition the use of fMRI during the antisaccade task should be performed to possibly explain any task-related functionality changes. This current study recommends that future intervention-based studies should look at variations of cognitive training in tandem with exercise to observe and explain the true effects of multiple modality plus mind motor exercise interventions on cognition. Lastly, research pertaining to the chronic effects of exercise interventions on sensorimotor functioning should be considered. Does a multiple modality plus mind motor exercise intervention have longer-term effects (6-month follow-up) on sensorimotor performance?

2.5 Conclusion

In conclusion, the implementation of a 6-month exercise program incorporating aerobic and resistance training can be seen to have a positive influence on sensorimotor performance in older adults with subjective cognitive complaints. Furthermore, these findings highlight the sensitivity of antisaccade RT performance as an effective diagnostic tool. Taken together, these findings indicate the use of a multiple modality exercise program as being neuroprotective for older adults with the first indications of cognitive impairment; thus mitigating the cognitive decline process.

2.6 References

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Appendices

Appendix A: Lawson Health Research Health Institute Final Approval

LAWSON HEALTH RESEARCH INSTITUTE

FINAL APPROVAL NOTICE

RESEARCH OFFICE REVIEW NO.: R-12-265

PROJECT TITLE: HM2: Healthy Mind, Healthy Mobility - Dual-task Aerobic Exercise for Older Adults with Cognitive Impairment

PRINCIPAL INVESTIGATOR: Dr. Robert Petrella

DATE OF REVIEW BY CRIC: June 12, 2012

Health Sciences REB#: 18858

Please be advised that the above project was reviewed by the Clinical Research Impact Committee and the project:

Was Approved

PLEASE INFORM THE APPROPRIATE NURSING UNITS, LABORATORIES, ETC. BEFORE STARTING THIS PROTOCOL. THE RESEARCH OFFICE NUMBER MUST BE USED WHEN COMMUNICATING WITH THESE AREAS.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

All future correspondence concerning this study should include the Research Office Review Number and should be directed to Sherry Paiva, CRIC Liaison, LHSC, Rm. C210, Nurses Residence, South Street Hospital.

cc: Administration

Appendix B: Ethics Approval Form



Research Ethics

Use of Human Participants - Revision Ethics Approval Notice

Principal Investigator: Dr. Robert Petrella
 File Number: 102434
 Review Level: Delegated
 Protocol Title: Aerobic and Cognitive Exercise in Community-Dwelling Older Adults (REB# 18858)
 Department & Institution: Schulich School of Medicine and Dentistry/Geriatric Medicine, Western University
 Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: October 11, 2013 Expiry Date: December 31, 2014
 Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	includes July/2013 and Sept/2013 amendment-Received Sept 19, 2013	
Instruments	Phone-FITT (received Sept 19, 2013)	
Instruments	Description of 12 Cognitive tasks from Cambridge Brain Sciences Battery-Received Sept 19, 2013	
Recruitment Items	Poster for Parkwood Cohort-Received Sept 19, 2013	
Recruitment Items	Poster for South Gate Centre Cohort-Received Sept 19, 2013	
Recruitment Items	Telephone Script-Received Sept 19, 2013	
Revised Letter of Information & Consent	Parkwood Cohort	2013/09/03
Revised Letter of Information & Consent	South Gate Centre Cohort	2013/09/03

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer in Contact for Further Information

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