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The Effects of Exercise on Cognition, Mobility, and Neuroimaging Outcomes in Older Adults without Dementia

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Abstract

Cognitive decline is increasing with the aging population and, at present, there is no effective pharmacologic treatment available. Exercise interventions may impart protection against cognitive decline. A novel exercise approach is multiple-modality exercise (MME; aerobic, resistance, and balance exercise) with mind-motor training. Mind-motor training is a promising intervention in the study of cognitive function. Combining MME with mind-motor training may improve or maintain cognition and provide prevention of dementia early in the course of cognitive decline. Individuals with subjective cognitive complaints (SCC) comprise an at-risk group early in the spectrum of cognitive decline that could be targeted for prevention. The objectives of this thesis were to report on the current state of evidence regarding the effects of MME in cognition and neuroimaging outcomes in older adults without dementia, and determine whether MME with mind-motor training benefit cognition, mobility, and neuroimaging outcomes in older adults with SCC. A scoping review of MME studies in older adults without dementia was conducted, as well as a 24-week randomized controlled trial (RCT) with a 28-week no-contact follow-up in community-dwelling older adults with SCC. Main findings were as follows: the scoping review concluded that although MME may improve cognition and neuroimaging outcomes compared to controls, confounding factors may account for these effects given that MME does not seem to evoke similar effects when compared to other interventions. Results from an RCT revealed that 24 weeks of MME with mind-motor training showed trends for greater improvements in global cognitive functioning and memory. These trends were confirmed after a 28-week no-contact follow-up. For mobility outcomes, MME alone was effective in improving gait performance under usual and dual-task conditions, while MME and mind-motor training did not seem to impart benefits to mobility. An exploratory study of memory and neuroimaging data revealed that MME and mind-motor training yielded greater benefits than MME alone in visuospatial memory, with changes in functional connectivity in brain areas of motor function and in brain regions relevant to Alzheimer's disease risk. In conclusion, MME with mind-motor training is a promising strategy to improve cognition

with potential to invoke neuroplasticity associated with improved memory, and reduce dementia risk.

Keywords

Exercise, Older Adults, Cognition, Mobility, Brain, Neuroplasticity, Neuroimaging.

Summary for Lay Audience

Older adults with memory complaints may be an ideal group to be targeted for dementia prevention programs, including multiple-modality exercise (MME) interventions (e.g., combining aerobic, resistance, and balance exercises). Mind-motor training is a promising intervention that could also reduce dementia risk. More research is needed to determine the effects of MME with mind-motor training in older adults with memory complaints. The objectives of this thesis were to summarize the results from studies published to date regarding effects of MME interventions in cognition and neuroimaging outcomes in older adults without dementia, and to determine whether MME with mind-motor training would benefit cognition, mobility, and neuroimaging outcomes compared to MME alone. A literature review of MME studies in older adults without dementia was conducted, as well as a 24-week exercise program in older adults with memory complaints. Main results were as follows: the literature review suggested that MME may improve cognition and neuroimaging outcomes compared to control groups that do not exercise. These effects, however, were not present when MME was compared to other interventions. The results from the exercise program revealed that 24 weeks of MME with mind-motor training showed trends for greater benefits in overall cognition and memory. These trends were confirmed after 28 weeks of no exercise. For mobility outcomes, MME alone benefited walking measures, but MME with mind-motor training did not seem to impart the same benefits. An exploratory study of memory and neuroimaging revealed that MME and mind-motor training benefited a specific type of memory (i.e., visuospatial), with changes in the connectivity of brain regions involved in motor function, and related to Alzheimer's disease risk. In conclusion, MME with additional mind-motor training is a promising strategy to improve cognition.

Co-Authorship Statement

I would like to thank the co-authors listed below for their contributions to this thesis. Without their help, the conclusion of this document would have not been possible.

Chapter 2: Dr. Dawn Gill and Dr. Robert Petrella contributed to the study concept, design and revised the final version of the manuscript.

Chapter 3: Dr. Dawn Gill contributed to study concept, design, implementation, data collection, data analysis and revised the final version of the manuscript. Dr. Adrian Owen, Dr. Teresa Liu-Ambrose, Dr. Vladimir Hachinski, and Dr. Ryosuke Shigematsu all contributed to study concept, design and revised the final version of the manuscript. Dr. Robert Petrella acquired funding for the study, contributed to study concept, design, implementation, data collection, data analysis and revised the final version of the manuscript.

Chapter 4: Dr. Dawn Gill contributed to study concept, design, implementation, data collection, data analysis and revised the final version of the manuscript. Dr. Michael Gregory and John Bocti, MSc both contributed to study concept, design and revised the final version of the manuscript. Dr. Robert Petrella acquired funding for the study, contributed to study concept, design, implementation, data collection, data analysis and revised the final version of the manuscript.

Chapter 5: Dr. Lindsay Nagamatsu contributed to study design, data cleaning and analysis, and revised the final version of the manuscript. Dr. Dawn Gill contributed to study design, implementation, data collection and revised the final version of the manuscript. Dr. Adrian Owen contributed to study concept and revised the final version of the manuscript. Dr. Robert Petrella acquired funding for the study, contributed to study concept, design, implementation, data collection, and revised the final version of the manuscript.

Dedication

To Rob Petrella who taught me

To my dad who believed in me

To my grandma who inspired me

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List of Abbreviations

AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale-cognitive subscale
AET	Aerobic exercise training
BA	Brodmann Area
BDNF	Brain-derived neurotropic factor
BOLD	Blood oxygenation level-dependent
CBS	Cambridge Brain Sciences
CCR	correct cognitive responses
CES-D	Centre for Epidemiological Studies Depression Scale
CI	Confidence interval
DMN	Default mode network
DS	Digit span task
ECB	Everyday Cognition Battery
EEG	Electroencephalogram
EF	Executive functioning
EPI	Echoplanar imaging
FC	Functional connectivity
FLIRT	FMRIB's Linear Image Registration Tool
fMRI	Functional magnetic resonance imagining
FOV	Field of view
FSL	FMRIB's Software Library
GCF	Global cognitive function
HR	Heart rate
HR_{max}	Maximum heart rate
ICA	Independent component analysis
IGF-1	Insulin-like growth factor 1
M2	Multiple-modality exercise comparator group
M4	Multiple-modality exercise with mind-motor training group
MELODIC	Multivariate Exploratory Linear Decomposition into Independent Components

ML	Monkey ladder
MME	Multiple-modality exercise training
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
NAI	Neuropsychological Aging Inventory
PA	Paired Associates task
PICO(T)	Population, intervention, comparison, outcome, and (type)
PRISMA-ScR	Preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews
pVO_2max	Predicted maximal oxygen consumption
QE	Quasi-experimental
RCT	Randomized controlled trial
RET	Resistance training
RM	Repetition maximum
RPE	Rate of perceived exertion
S7	Serial sevens task
SCC	Subjective cognitive complaints
SD	Standard deviation
SMI	Subjective memory impairment
SS	Spatial span task
SSE	Square-stepping exercise
VF	Verbal fluency task
WAIS-R	Wechsler Adult Intelligence Scale Revised
WMS	Wechsler Memory Scale

Chapter 1

1 Introduction

1.1 Cognitive impairment and dementia

Dementia is an umbrella term adopted to classify a series of neurodegenerative conditions marked by deterioration of cognitive function and yielding mobility impairment [1,2]. Alzheimer's disease (AD), vascular dementia, and Lewy Body dementia are the most prevalent causes of the disease in older adults [3]. As demonstrated by autopsy studies [4], dementia is a complex array of conditions, and mixed pathophysiological attributes of each subtype under the umbrella coexist in more than two-thirds of the cases.

Worldwide, the incidence of dementia is projected to reach nearly 75 million individuals by 2030, which could translate into an estimated cost of $2 trillion over the same period [1]. In Canada, nearly half-million people are currently living with AD and/or other dementias [5]. Approximately nine new cases are diagnosed per hour in those aged 65 or older, and the prevalence of the disease is expected to double within the next two decades [6]. This projected increase will be coupled with an economic burden that will reach an estimated $16.6 billion by 2031 in Canada alone [5,6]. Unfortunately, effective dementia treatment options are not yet available, and the prospectus for a single cure does not seem promising [7]. Targeting early stages of the disease would offer better hopes for preventing or deaccelerating disease progression.

Mild cognitive impairment (MCI) precedes the diagnosis of dementia, and is characterized by objective cognitive impairment in neuropsychological tests owing to underlying pathophysiological processes [8,9]. This prodromal stage of dementia affects 10% to 20% of older adults above the age of 65 [10,11], a portion of which (15% to 46%) will then progress into dementia diagnosis [12,13]. People living with MCI would comprise an ideal target group for preventive interventions aiming at alleviating and disease progression [8]. Unfortunately, MCI is already a marker of established neurodegeneration and may reflect irreparable damage [9]. This is further supported by meta-analytic studies showing unsuccessful attempts at treating MCI with pharmacological and non-

pharmacological therapies [14,15]. Under these circumstances, efforts have been made to identify and intervene with those who are at greater risk before the establishment of clinical impairment—that is, prior to MCI diagnosis [16]. Cognitively healthy older adults with subjective cognitive complaints* (SCC) [17,18] may represent a portion of the population experiencing early signs of cognitive decline due to underlying pathological changes, occurring before the onset of MCI (see **Figure 1.1**) [19,20]. These individuals do not meet the established criteria for MCI, but they often report cognitive complaints relating to worsening of their memory and other cognitive domains [21].

Despite lack of established cognitive impairment, individuals with SCC still present poorer scores on objective cognitive assessments compared to healthy controls of the same sex, age and education levels without SCC [17,18,22]. Further, SCC is associated with MCI or dementia diagnosis and greater health care utilization nearly two decades after initial self-reporting [23,24]. The rate of incident AD and other dementia (e.g., vascular dementia) are higher among those with SCC compared to controls [17]. Currently, evidence to determine the pathophysiological changes underlying SCC in clinically healthy older adults is still limited; however, recent reports suggest that SCC is likely caused by, or related to, neurodegeneration (e.g., hippocampal atrophy) [25–27], AD biomarker (i.e., tau and amyloid beta) deposition [28,29] and brain glucose hypometabolism [30]. These observations suggest that older adults with SCC compose a group of individuals at higher risk of AD and other dementias who do not yet demonstrate clinical symptoms, and therefore, may comprise an ideal target group for preventive interventions to mitigate or, at least, slow down disease progression. Targeting these individuals could culminate in the best clinical outcomes [31,32], and alleviate burdens on the health care systems worldwide [24].

*Also defined as: subjective or subtle cognitive decline, subjective cognitive impairment, or subjective memory complaints, or subjective memory impairment [17,18,24,32,120].

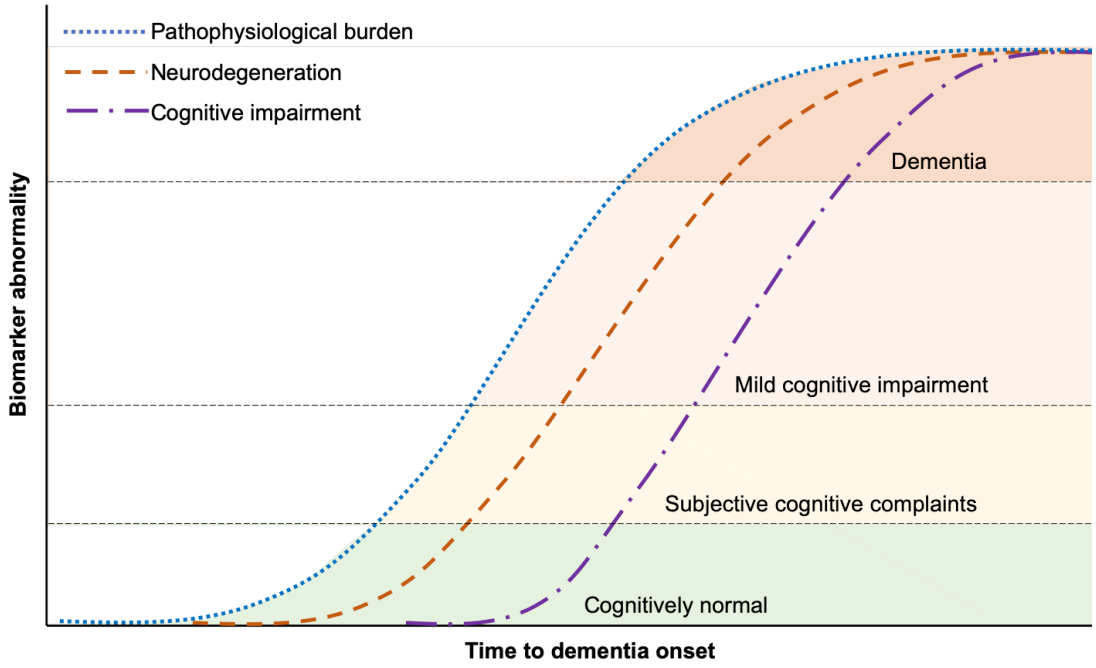

Figure 1.1. Simplified temporal illustration of biomarker abnormality and progression to dementia onset in older adults.

Note: Adapted from Jack Jr [33].

1.2 Cognitive function and mobility

Cognition and mobility are two clinically meaningful outcomes which are intrinsically associated [34]. Cognitive deficits in older adults have been strongly associated with slow gait velocity and increased stride time variability [35]. Slow gait velocity is an indicator of cognitive impairment [36] and is related to shortened life span [37]. Further, higher gait variability is associated with increased risk of falls [38,39] and greater degree of cognitive impairment [40]. Decline in executive functioning (EF) has been postulated as a possible mechanism for mobility impairment in healthy older adults [41] and those with cognitive impairment, including AD [42]. The importance of preserved EF in the cognitive control of gait becomes more evident under dual-task (DT) conditions (e.g., walking and preforming a concurrent cognitive task) [43–45], where individuals with poorer EF demonstrate the most dramatic gait impairment [46]. Clinically, poorer DT gait outcomes can even predict progression to dementia in older adults with MCI [47].

It is certainly challenging to determine the mechanisms underlying the co-occurring decline in both cognition and gait performance; however, evidence suggests the presence of neurodegenerative processes affecting brain structure (e.g., grey and white matter), as well as functional changes in cortical activity [41,48,49]. Brain structural changes such as smaller cortical and subcortical grey matter volume (e.g., parahippocampal gyrus) have been shown to predict poorer gait velocity and step length in older adults [49]. Poorer microstructural white matter integrity along with small vessel disease burden (i.e., white matter lesions) seem to also increase mobility impairment [48,50–52]. Specific brain functional networks during imagery of gait are less efficient in older adults compared to younger adults, including regions associated with EF (e.g., dorsolateral frontal cortex) and memory (e.g., hippocampus) [41].

With cognitive and mobility impairment co-occurring as a result of underlying neurodegenerative and pathological processes, it is imperative to consider these as target outcome measures for preventive intervention programs. For instance, it would be of particular clinical relevance to explore whether non-pharmacological strategies, such as exercise, aimed at improving cognitive function would also result in gait improvements,

reduce falls risk and delay institutionalization [34,36]. A systematic review has shown promising evidence of synergistic effects of exercise on cognition and mobility [53].

1.3 Exercise and cognition in older adults

Physical exercise may be an important strategy to prevent or slow the progression of dementia in the aging population [3,54,55], even in those with high genetic risk [56]. As recently estimated, more than a third of dementia cases worldwide might theoretically be prevented if effective preventive strategies take place before establishment of MCI [3]. Exercise has been associated with preserved cognitive functioning in observational studies [55,57–60] and improved cognition [61], as well as positive functional [62,63] and structural [64] brain changes in longitudinal interventional studies. More specifically, aerobic exercise training (AET) appears to benefit cognition and brain function in individuals with or without known cognitive impairment [65–67]. For instance, 6 months of a moderate-intensity AET yielded improvements in cognitive scores in older adults with cognitive impairment compared to a usual care group [61]. AET also yields brain structural changes such as hippocampal growth in healthy older adults [64], with similar effects in those with MCI [68]. Brain functional changes, measured via functional magnetic imagining (fMRI), have also been reported, including markers of neuroplasticity [69,70].

Despite promising evidence, the impact of AET on cognitive function in the aging population remains equivocal [71], and research is limited in those with SCC. Moreover, a Cochrane review suggests there is insufficient evidence to conclude that cognitive improvements are solely attributable to improved fitness [72]. Therefore, the current state of knowledge allows for considering exercise interventions that could have additive benefits to cognition beyond AET alone. Encouraging findings suggest resistance exercise training (RET) is an effective exercise modality to impart benefits to cognition [73,74]. Although research in RET as preventive or therapeutic approach for cognitive impairment is outnumbered by AET studies, RET yields positive changes in cognition (e.g., EF) [73,74], measures of brain function (e.g., plasticity) [75], and structure (e.g., reducing progression of white matter lesions) in older adults [76].

Nonetheless, findings from meta-analytic studies indicate lack of consistency across different exercise studies leading to mixed results. Variability in cognitive tests applied, sensitivity of cognitive tests to detect treatment effects, cognitive and physical health at baseline, as well as properties of the exercise programs administered may influence results [71,77]. As well, most studies have failed to comply with current guidelines for both AET and RET to improve overall health in older adults with regards to exercise type, intensity, frequency and duration [78]. Furthermore, these guidelines highly emphasize the importance of multiple-modality exercise (MME) programs (i.e., combining AET and RET) over single-modality exercise to enhance overall health and quality of life in the aging population [78,79].

A recent meta-analysis demonstrated the potential of MME to induce clinically relevant fitness improvements in older adults, including maximal oxygen uptake, and surrogate measures of cardiovascular fitness and functional capacity; however, no measures of cognition (or other brain function outcomes) were included [80]. Considering the physiological mechanisms underlying exercise improvements in cognition and brain function—which seem to be modality-specific[†]— is plausible that a combined intervention would yield cumulative benefits [81]. Yet, evidence suggests divergent findings regarding MME to improve cognition in older adults [82,83]. For instance, MME seems to be effective only when compared to no-treatment control groups (e.g., wait-list, no-contact, etc.) [84–89], while findings are inconclusive when considering active control groups (e.g., health education sessions, etc.) [90–94] or competing treatment groups (e.g., cognitive training) [95–100]. Under these considerations, even though MME may be effective in improving cognition, the quality of the evidence is limited, and more high-quality randomized controlled trials are warranted, particularly in older adults with SCC.

[†] Two main neurotrophic factors underlying neurophysiological changes are upregulated by exercise. AET increases brain-derived neurotropic factor (BDNF) [64,121,122], while RET increases expression of insulin-like growth factor 1 (IGF-1) [123].

1.4 Exercise and mobility in older adults

Preventive strategies that effectively improve mobility outcomes, such as usual and DT gait performance, in those at greater risk for dementia may preserve functional independence and reduce falls risk [101,102]. Ultimately, such strategies would aid in attenuating the increasing burden on health care systems associated with mobility disability and dementia [1,31]. Evidence suggest that exercise may impart improvements in usual and DT gait parameters [103,104], static and dynamic balance [105]; with a greater effect on frail individuals (e.g., fallers, musculoskeletal disorders) and in those with neurological conditions (e.g., mild to moderate dementia) [105,106]. These effects in DT gait performance seem to be related to improving walking speed, but not underlying cognitive processes [107].

In previous studies [107,108], single-modality exercise with additional DT gait training has been associated with improved mobility outcomes. These interventions often combine individualized supervised programs, conducted in a laboratory setting. Typically, these programs entail walking and at the same time performing a concurrent cognitive task (e.g., arithmetic operations, categorical naming), which are administered by a trained instructor [107,108]. Due to practical limitations, it is challenging to consider that such interventions would be feasible in community-based settings and impart long-term effects. Therefore, more practical solutions could be considered. Further, the majority of studies investigating changes in mobility following exercise does not seem to fully comply with guidelines for exercise prescription in older adults [104,107] and more evidence of MME over single-modality exercise interventions is warranted [78,79]. For instance, a recent systematic review revealed that in individuals with MCI or dementia, MME programs seemed to have mixed effects in mobility outcomes [109]. While another meta-analysis reported improvements in gait velocity following exercise to be negligible and unlikely to be clinically relevant [107]. As well, when comparing the effects of DT cost[‡] of

[‡] DT cost is a measure of interference of a secondary task (e.g., counting backwards) on a primary competing task (e.g., walking) [34,43]. Higher DT cost would indicate higher risk of mobility impairment [124] and progression to dementia in older adults with MCI [47].

gait velocity, subgroup analysis revealed exercise was not superior to competing treatment groups or even inactive control groups [107].

Therefore, it seems as though the specific components of a feasible exercise intervention that would impart the greatest benefit to mobility, while also influencing cognition (e.g., DT performance) warrant further investigation [107,109,110]. The limitations and contradictory findings from previous investigations create an opportunity for further studying alternative and/or novel interventions to improve mobility and cognition in older adults at risk of dementia (e.g., those with SCC).

1.5 Mind-motor training

Exploring the combination of MME with novel and feasible forms of simultaneous physical and cognitive training (e.g., mind-motor training[§]) may provide further support for designing optimal exercise interventions in at-risk older adults [78]. A feasible program would comprise a group-based, low-cost, and easily administered intervention to be implemented in the community. Such programs combining MME and mind-motor training might impart larger benefits than those focusing on single strategies alone [78,111].

Square-stepping exercise (SSE) [112] is a type of mind-motor training that has been associated with positive effects cognition and mobility in older adults [112–115]. It can be characterized as a visuospatial working memory task with a stepping response on a gridded floor mat [116]. The SSE program is a simple, low-cost, indoor, group-based program designed to serve as a strategy to improve mobility and prevent falls in older adults [112,113]. Preliminary findings from short-term, limited studies showed that the SSE was effective in reducing fall risks, with spillover effects in global and domain-specific cognitive function (including EF) in older adults [112–115]. Therefore, SSE is a novel and easily employed intervention that may be incorporated into standard exercise programs for community-dwelling older adults [116], and for those in assisted living [117]. Nonetheless, strong evidence from high-quality RCTs is needed to determine the effects of SSE on

[§] We adopted the term “mind-motor” and not “dual-task” owing to the distinct nature of our intervention.

cognition, mobility and neuroimaging outcomes (e.g., neuroplasticity) in those with SCC.

1.6 Thesis overview

Strategies to prevent or, at least, slow the rate of cognitive decline have gained increased attention [31]. Considering that underlying pathophysiological processes of dementia may take place decades before the disease diagnosis [118], the focus of experimental studies for dementia prevention is shifting to preclinical, asymptomatic stages [3]. Consequently, the identification of high-risk groups (e.g., SCC) and administration preventive strategies (e.g., MME and mind-motor training) seem to be of highest priority [31,119]. Therefore, the overarching goal of this thesis was to study whether combining MME (i.e., RET plus AET) with mind-motor training (i.e., SSE) would yield benefits in cognition, mobility and neuroplasticity in community-dwelling older adults with SCC.

A scoping review was conducted to report on the current state of evidence regarding the effects of MME in cognition and neuroimaging outcomes (Chapter 2). Further, it was reported the influence of MME with or without additional mind-motor training in global and domain-specific cognition outcomes. With the goal to establish whether older adults with SCC receiving MME and mind-motor training would demonstrate superior improvements in global cognitive function, memory, concentration, planning and reasoning (Chapter 3). Next, the effects of this intervention in mobility outcomes were explored, including usual and DT gait measures. The aim was to determine whether those receiving MME and mind-motor training would show superior improvements in usual and DT gait spatiotemporal characteristics at the end of the program (Chapter 4). Finally, an exploratory analysis was conducted to determine whether MME and mind-motor training would yield changes in surrogate neuroimaging measures of neuroplasticity (Chapter 5).

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Chapter 2

2 A scoping review of multiple-modality exercise studies to improve cognition in older adults without dementia: Implications for exercise prescription and future research

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2.1 Introduction

The current research in pharmacological strategies for the treatment of dementias, such as Alzheimer's disease, has proven challenging and unfruitful, with the possibility of a single pharmacological cure being very unlikely [1,2]. Consequently, efforts to prevent or reduce the rate of cognitive decline as well as identify and manage modifiable risk factors have become a priority [2,3]. For instance, the focus of experimental studies is starting to shift towards preclinical or asymptomatic stages, given that underlying pathophysiological processes of dementia may take place decades before diagnosis [4]. In this context, changes to lifestyle such as engaging in regular physical activity and exercise is postulated as an important strategy to prevent or slow the progression of dementia in the aging population [5–7]. This includes those with high genetic risk [8]. As recently estimated, more than a third of dementia cases worldwide might theoretically be prevented if effective preventive strategies are initiated early in life [5]. Exercise has been associated with preserved age-related cognitive functioning in observational studies [7,9–12] and has improved cognition [13], as well as shown positive functional[14,15] and structural [16] brain changes in longitudinal interventional studies.

Most literature has focused on aerobic exercise training (AET) interventions alone [17], with some evidence suggesting that AET appears to benefit cognition in individuals without known cognitive impairment and in those with dementia [18]. Improvements have been observed in cognitive function [13], particularly executive functioning [19], as well as neuroplasticity [20], neural efficiency [21], and hippocampal size in healthy older adults [16] and those and with mild cognitive impairment (MCI) [22]. Despite promising evidence, the impact of AET on cognitive function in the aging population remains equivocal [23]. A recent Cochrane review suggests there is insufficient evidence to conclude that cognitive improvements following AET are solely due to AET itself, even when improvement in cardiovascular fitness is observed [24]. Therefore, the current state of knowledge allows for exploration of exercise interventions that could have additive benefits to cognition beyond AET alone. Encouraging findings have suggested resistance exercise training (RET) as an effective exercise modality to impart benefits to cognition. Although research in RET as a preventive or therapeutic approach for cognitive impairment in older adults is limited, work by Liu-Ambrose and colleagues have consistently shown positive effects of RET on cognition (e.g., executive functioning) [25,26], as well as measures of brain function (e.g., functional plasticity) [27], and structure (e.g., reducing progression of white matter lesions) measured via neuroimaging techniques [28].

Findings from other meta-analytic studies have indicated a lack of consistency across different exercise studies, which could be due to variability in cognitive tests applied, sensitivity of cognitive tests in detecting treatment effects, cognitive and physical health at baseline, as well as characteristics of the exercise programs administered (e.g., single-modality, exercise intensity) [23,29]. Furthermore, several aspects of these investigations may raise concerns regarding the feasibility of exercise protocols to be translated to real world settings. Moreover, most studies have failed to comply with current guidelines for exercise in older adults with regards to exercise type, intensity, frequency and duration [30,31].

These guidelines highly emphasize the importance of multiple-modality exercise (MME) programs over single-modality exercise programs to enhance overall health and quality of life in the general population of older adults [31]. A recent meta-analysis demonstrated the

potential of MME to induce clinically relevant fitness improvements in older adults, and reported on MME effectively improving measures of maximal oxygen consumption, and surrogate measures of cardiovascular fitness and functional capacity (e.g., 6-minute walk test, timed up-and-go test) [32]. However, no previous literature review has focused solely on investigating effects of MME on cognition and neuroimaging outcomes, as such, further evidence is needed [33,34].

The objectives of this scoping review were to: 1) document the current state of evidence of the impact of MME on cognition and neuroimaging in older adults without dementia; 2) discuss the current state of evidence with regards to exercise prescription and implementation in these studies; and 3) propose future directions for research in the field.

2.2 Methods

2.2.1 Study Protocol and search strategy

The PICO(T) (population, intervention, comparison, outcome, and [type]) [35] approach was used to develop our research question, while the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [35] were utilized as a guideline in this review. Our research question was as follows: "What are effects of multiple-modality exercise interventions aimed at improving cognition and neuroimaging outcomes in older adults without dementia?". Between August and October 2019, we searched the following bibliographical databases for potentially relevant documents: Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE and Scopus. We also contacted authors directly to identify additional relevant material and to further determine eligibility of articles selected for full-text review. The final search strategy for MEDLINE can be found in **Supplementary Table 2.1 in Appendix A** [35].

2.2.2 Eligibility criteria

We selected peer-reviewed, published randomized controlled trials (RCTs) and non-randomized intervention studies (i.e., quasi-experimental) examining the effects of MME interventions on cognition (i.e., global and domain-specific cognitive function) and/or

neuroimaging (e.g., brain function and structure) outcomes. We defined MME interventions as those that included a combination of the following main exercise modalities: 1) AET aimed at improving aerobic capacity or cardiovascular fitness in which participants engaged in exercise involving large muscle groups, yielding substantial increase in heart rate and energy consumption (e.g., running, cycling, walking, dancing) [31,32]; 2) RET aimed at improving muscle strength, endurance or power, defined as any type of muscle strengthening exercise in which participants moved against external resistance (e.g., machine-based weightlifting, free-weight training, rubber bands) [31,32]. We also included studies that combined AET and RET with balance or flexibility exercises as complementary training. Balance and/or flexibility training was defined as activities aimed at increasing balance (e.g., static and dynamic balance exercises, single-leg stance standing, tandem walk) and flexibility (e.g., stretching, range of motion, and mobility exercises) [31,32]. Other actives referred to as 'warm-up', 'cool-down' or 'recovery' were not considered. Considering the nature of this scoping review, we did not specify minimum or maximum length of exercise programs, whether components of AET or RET were administered in the same session or different sessions, and whether interventions were supervised, home-based or both.

We included studies that met the following inclusion criteria: 1) MME studies combining both AET and RET with or without additional balance/flexibility training, as defined above; 2) included older adults aged ≥ 55 years; 3) included individuals with or without cognitive impairment, but not dementia (i.e., cognitively healthy, self-reported cognitive or memory complaints, subjective cognitive/memory decline or impairment [SMI, MCI]); included at least one measure of cognition (e.g., global or domain-specific cognitive function), and/or neuroimaging outcomes relevant to cognitive function (e.g., functional network connectivity, grey matter volume); 5) included a comparator group (i.e., competing treatment group, active control group, or no-treatment control group); 6) published in English between January 1990 and October 2019; and 7) published in a peer-reviewed journal. We also included other articles from the same parent study that reported different relevant outcomes from the original publication; however, we excluded those reporting sensitivity analyses of primary outcomes already reported in the original publication.

2.2.3 Data charting process

A data charting form was created to determine which variables to extract. The first author (NCBSS) reviewed and updated the data charting form continuously to capture the most relevant information on study characteristics, including study design, population (e.g., age, cognitive status), experimental and control conditions, detailed exercise intervention, study outcomes, and main findings.

For the purpose of the outcomes of this review, we captured and reported on the cognitive domains assessed in each study and the specific tests employed to assess these domains. We defined global and domain-specific cognition as a broad range of neuropsychological constructs measured using instruments based on individual performance. For example, global cognitive functioning can be measured via the Mini-Mental State Examination (MMSE) [36], while executive functioning is measured by the Trail-Making Test, Part B [37]. For the purpose of summarizing and contextualizing the evidence, we classified measures employed in the included studies under four cognitive domains: global cognitive functioning, executive functioning, memory, and processing speed, following previous methods [34]. In addition, we were particularly interested in the elements of the MME interventions employed in these studies to aid in contextualizing our results in light of the current guidelines for exercise prescriptions in older adults, as well as to facilitate recommendations for translation of the evidence. Therefore, when available, we extracted detailed information from each exercise training component administered (i.e., frequency, intensity, time [duration] and type) [30].

2.2.4 Synthesis of results

We organized our results based on study design. That is, reporting the evidence in the context of MME compared to the following conditions: a) competing treatment, defined as other experimental intervention aimed at improving cognition (e.g., cognitive training); b) active control, defined as conditions (e.g., education sessions) administered to control for confounding variables (e.g., socialization, attention); and c) no-treatment control, defined as a no-contact, no-intervention control conditions. Additionally, whenever applicable, we also contextualized the evidence based on participant cognitive

status and other demographic characteristics. The details of each study, including intervention, assessment and main findings were reported in summary tables.

2.3 Results

2.3.1 Selection of sources of evidence

Our search results including identification, screening, eligibility and selected articles are presented in **Figure 2.1**. The original search led to 2945 results; a total of 2073 citations were identified and included for title and abstract review, after removal of duplicates (n=872). We then excluded 1992 citations that did not meet the study inclusion criteria. As such, 106 articles retrieved from the original search (n=81) and added from other sources (e.g., from previous reviews, articles reference list, n=25) were selected for full text review and eligibility. Of these, 73 were excluded due to the following reasons: intervention protocol combined exercise and cognitive training (n=25); no MME program (n=22); sensitivity analysis of primary outcomes (n=6); no cognition or neuroimaging outcomes included (n=6); dementia patients included (n=7); full publication unavailable (n=4); combined nutrition and exercise program (n=1); insufficient information (n=1); and no control group (n=1). The remaining 33 studies (original search=25; added from other sources=8) were considered eligible for inclusion in this scoping review.

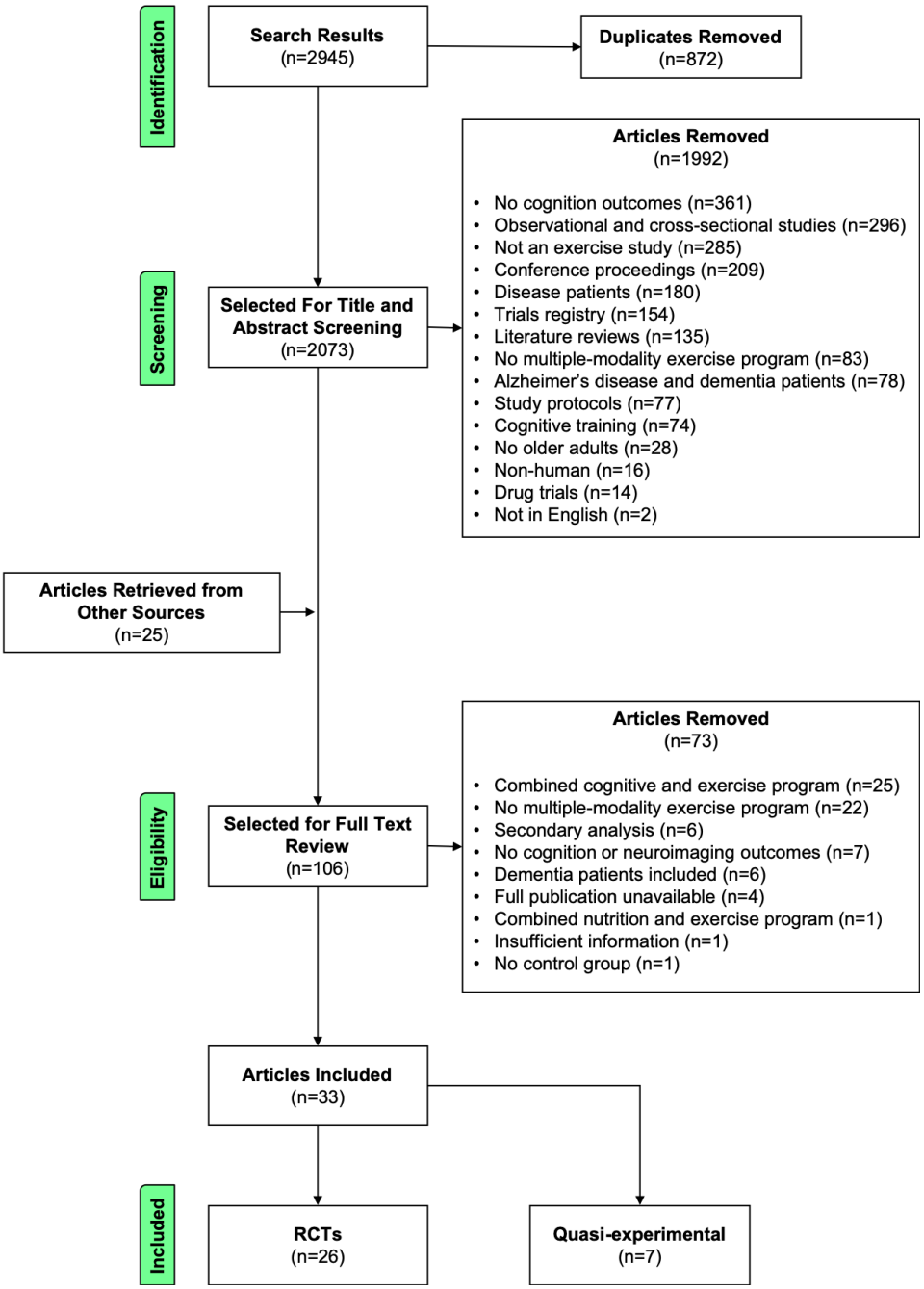

Figure 2.1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-ScR) flow diagram for the scoping review process

2.3.2 Characteristics of Sources of Evidence

Study design, sample size, and participant characteristics (i.e., age, sex, and baseline cognitive status) are reported in **Table 2.1**. We included 33 studies [38–70] of which 26 were RCT studies [38,39,51–57,60–62,40,64–68,70,41,43–45,48–50] and seven were quasi-experimental studies [42,46,47,58,59,63,69]. We included data from 30 original research articles [38,39,48–57,40,58,61–69,41–47] and three articles that were analyses of secondary outcomes [44,59,70]. A total of 4458 individuals (excluding counts from secondary outcomes articles) were studied. Sample sizes varied between 19 and 1476 (mean [standard deviation, SD]=148.6 [270.8]), with age range between 62.2 and 82.3 years of age (mean [SD]=72.5 [4.8]) and the majority of participants being females (mean [SD]=71.3% [16.8]). Most studies included healthy populations of older adults (e.g., preserved physical and cognitive function, n=13), followed by studies including older adults who were sedentary (n=8); had cognitive impairment but not dementia (i.e., SCC, SMI, and MCI, n=7); were frail (n=3); had diabetes (n=1) or were obese (n=1). Further, considering the study groups (i.e., comparators), the majority of study designs included no-treatment control groups (n=23), followed by at least one competing treatment group (n=17), and an active control group (n=9)

Table 2.1. Study and participant baseline characteristics.

First Author (Year)	Study Design	Population	Sample N	Age mean (SD)	Females N (%)	MMSE [a] or equivalent
Ansai (2015)[56]	RCT, 16-wk intervention with 6-wk follow-up	Sedentary older adults	69	82.4 (2.4)	47 (68.1)	24.9 (3.3)
Berryman (2014)[67]	RCT, 8-wk intervention	Healthy older adults	51	70.6 (5.6)	29 (56.9)	23.8 (1.1)
Boa Sorte Silva (2018)[51]	RCT, 24-wk intervention, single-blind with 28-wk follow-up	Older adults with SCC	127	67.5 (7.3)	90 (70.9)	29.1 (1.1)
Callisaya (2017)[39]	RCT, 6-mo intervention, single blind	Older adults with diabetes	50	66.2 (4.9)	24 (48)	≥28 [b]
Carral (2008)[57]	RCT, 5-mo intervention	Community-dwelling women	62	68.4 (3.4)	62 (100)	23.2 (3.9)
Damirchi (2018)[49]	RCT, 8-wk intervention with 6-mo follow-up	Sedentary older women with MCI	54	68.4 (4.3)	54 (100)	23.4 (2)
Eggenberger (2015)[48]	RCT, 6-mo intervention with 1-yr follow-up	Healthy older adults	71	78.9 (5.4)	46 (64.8)	28.2 (1.4)
Fissler (2017)[59]	QE, 10-wk intervention with 3-mo follow-up	Older adults with SMI	39	72 (5.3)	23 (59)	28 (1.9)
Gajewski (2012, 2018)[44,60]	RCT, 4-mo intervention	Healthy older adults	141	70.9 (5.2)	84 (59.6)	28.5 (1.7)
Ji (2017)[46]	QE, 6-wk intervention	Healthy older adults	24	70 (7.2)	12 (50)	≥24
Klusmann (2010)[62]	RCT, 6-mo intervention, single-blind	Healthy older women	259	73.6 (4.2)	259 (100)	28.8 (1)
Küster (2016)[63]	QE, 6-mo intervention with 3-mo follow-up	Older adults with SMI	54	71.4 (5.8)	30 (55.6)	27.9 (2.2)
Langlois (2013)[45]	RCT, 3-mo intervention	Nonfrail and frail older adults	72	72.4 (5.7)	56 (77.8)	≥25
Leon (2015)[54]	RCT, 12-wk intervention	Healthy older adults	138	71.4 (5.6)	106 (76.8)	Not reported
Linde (2014)[38]	RCT, 4-mo intervention, single-blind with 12-wk follow-up	Healthy older adults	55	67 (3.34)	41 (74.5)	Not reported
Lord (2003)[43]	Cluster RCT, 12-mo intervention	Frail older adults	551	79.5 (6.4)	474 (86)	≥20
Napoli (2014)[65]	RCT, 12-mo intervention, single-blind	Sedentary obese older adults	107	69.9 (4)	67 (62.6)	95.7 (0.8) [c]
Nascimento (2014)[69]	QE, 16-wk intervention, single-blind	Older adults with and without MCI	67	67.6 (6.2)	44 (65.7)	23.8 (4.3) [d]
Okumiya (1996)[52]	RCT, 6-mo intervention, single-blind	Healthy older adults	42	78.8 (4.7)	24 (57.1)	27.9 (2.6)
Rehfeld (2018)[41]	RCT, 6-mo intervention	Healthy older adults	38	68.4 (3.5)	20 (52.6)	28.6 (0.9)
Rosano (2017)[70]	RCT, 24-mo intervention, single-blind	Sedentary older adults	26	75.1 (7.7)	21 (80.8)	92.3 (8.5) [e]
Shah (2014)[47]	QE, 16-wk intervention	Healthy older adults	222	67.6 (5.2)	153 (68.9)	28.6 (1.4)

Table 2.1. (Contd.)

First Author (Year)	Study Design	Population	Sample N	Age mean (SD)	Females N (%)	MMSE [a] or equivalent
Silva (2019)[68]	RCT, 3-mo intervention, single-blind	Older adults with MCI	19	75 (5.5)	11 (57.9)	29 (26-30) [f]
Sink (2015)[66]	RCT, 24-mo intervention, single-blind	Sedentary older adults	1476	78.9 (5.2)	999 (67.7)	91.7 (5.4) [g]
Styliadis (2015)[42]	QE, 8-wk intervention	Older adults with MCI	70	70.6 (5.2)	45 (64.3)	25.7 (2.3)
Tarazona-Santabalbina (2016)[40]	RCT, 24-wk intervention, single-blind	Frail sedentary older adults	100	80 (3.65)	54 (54)	26.9 (5.6)
Taylor-Piliae (2010)[61]	RCT, 12-mo intervention, single-blind	Sedentary older adults	132	69.1 (5.7)	92 (69.7)	Not reported
Teixeira (2018)[58]	QE, 26-wk intervention, single-blind	Sedentary older adults	40	69.2 (5.4)	24 (60)	25.9 (2.2)
Vaughan (2014)[50]	RCT, 16-wk intervention, single-blind	Sedentary older women	49	68.9 (3.3)	49 (100)	37.6 (3.6) [h]
Vedovelli (2017)[55]	RCT, 3-mo intervention	Healthy older women	29	80.2 (8.2)	29 (100)	24.4 (3.3)
Williams (1997)[64]	RCT, 12-mo intervention	Healthy older women	187	71.7 (5.4)	187 (100)	No reported
Williamson (2009)[53]	RCT, 12-mo intervention, single-blind	Sedentary older adults	102	77.4 (4.3)	72 (70.6)	≥21

[a] MMSE score (or equivalent test) to indicate cognitive status of participants at baseline. Data reported as mean (standard deviation) or otherwise indicated. [b] Telephone Interview for Cognitive Status–Modified score. [c] Modified MMSE, reported as mean (standard error). [d] Montreal Cognitive Assessment, reported as median (interquartile range). [e] Modified MMSE, reported as median (interquartile range). [f] MMSE, reported as median (minimum – maximum). [g] Modified MMSE, reported as mean (standard deviation). [h] Telephone Interview for Cognitive Status, reported as mean (standard deviation). Abbreviations: MMSE = Mini-Mental State Examination; RCT = randomized controlled or clinical trial; QE = quasi-experimental; SCC = subjective cognitive complaint; MCI = mild-cognitive impairment; SMI = subjective memory impairment.

2.3.3 Multiple-modality exercise protocols

Of the MME protocols included in the 33 studies, 18 involved a combination of AET, RET, plus balance/flexibility training, while 15 studies included AET and RET only (see **Table 2.2** for more details). The MME protocols administered varied from 1 to 7 days/week (mean [SD]=3.1 [1.5]), and between 30 and 90 minutes/day (mean [SD]=62.7, [15.5]) from 1.5 to 24 months (mean [SD]=6.8 [6.3]). Due to limited reporting of measures of exercise intensity (AET [n=21 reported], RET [n=18] and balance/flexibility [n=3]) and high inconsistency in methods employed to prescribe and monitor intensity, it was not feasible to summarize exercise intensity for all studies; however, intensities varied between low and high for the exercise components. Below we further describe each component individually.

2.3.3.1 Aerobic exercise training

Across all studies, the AET component was prescribed on average 3.1 days/week (SD=1.6, n=33 reported), for an average of 32.6 minutes/day (SD=13, n=27), with studies employing low (n=2), moderate (n=12), and moderate to high (n=7) intensity. As mentioned earlier, 21 studies reported measures of AET intensity with high variability in tracking methods, which consisted of rate of perceived exertion (RPE, n=7), percentage of maximum heart rate (HR, n=6), percentage of HR reserve (n=3), percentage of HR peak (n=1), and other methods (n=4). AET types included continuous endurance activities such as walking, cycling, and dancing (**Table 2.2**).

2.3.3.2 Resistance exercise training

RET was prescribed on average 3.2 days/week (SD=1.5, n=33), lasting on average 23.6 minutes/day (SD=11.3, n=25), with studies employing low to moderate (n=2), moderate (n=8), moderate to high (n=6), and high (n=2) intensity. Only 18 studies measured RET intensity, using a diversity of methods, which included RPE (n=8), maximum repetitions (n=6), and others (n=4). RET type included bodyweight, machine-based, and free-weights, with 1 to 4 sets and 4 to 30 repetitions per muscle group.

2.3.3.3 Balance and flexibility exercise training

For the 18 studies that included balance and flexibility training components, these were administered on average 3.4 days/week (SD=1.8, n=18), on average 16.9 minutes/day (SD=10.3, n=13) at low (n=1) to moderate (n=2) intensity. Only three studies reported measures of intensity and these were either verbally described as "moderate intensity" (n=2) or reported as RPE (n=1). Balance and flexibility training type involved activities such a static and dynamic balance, postural sway, double- and single-leg stance variations, range of motion exercises, stretching and mobility of main muscle joints.

2.3.4 Overall effects of multiple-modality exercise on cognition

Details on study intervention, comparator, cognitive domains and tests, as well as main findings are summarized in **Table 2.3**. When compiling evidence from the 33 included studies, the effects of MME on cognition were considered mixed and heavily dependent on study designs, comparators, and outcomes. Aiming to facilitate coherence and to contextualize the evidence, we stratified our findings based on the differences between MME and comparators (i.e., competing treatment, active control, and no-treatment control groups) on the outcomes of interest (i.e., cognitive domains and tests used in the studies). Evidence from studies that included two or more comparators were considered separately for each applicable comparison, where multiple comparisons were reported by authors (e.g., MME vs active control, or competing treatment). Results are reported in the following subsections.

2.3.4.1 Multiple-modality exercise compared to competing treatment

A total of 17 studies included one or more competing treatment groups. These included varied forms of cognitive training (n=8) [38,42,44,47,49,59,60,62,63], physical training (n=6) [41,48,56,57,61,67], combined physical and cognitive training (n=7) [38,42,47–49,51,54], or combined physical training and diet (n=1) [65]. In only two studies, MME imparted similar improvements to competing treatment compared to no-treatment control group [62,65]. For example, one study reported that MME was of similar effectiveness compared to cognitive training in improving executive functioning and memory [62]. Another study showed that MME was equally effective compared to combined physical exercise and diet intervention in improving global cognitive functioning and executive functioning [65]. No other studies reported superiority of MME in improving cognition when

compared with competing treatment groups. Furthermore, the overall effects of the competing treatment groups were seen to be either superior to (n=7) [38,44,47,49,54,60,61], or equivalent (n=8) [41,42,48,51,56,57,63,67] to MME in the remaining studies (as reported in **Table 2.3)**. For studies showing superiority of competing treatment groups, the findings showed that cognitive training alone was superior to MME in improving measures of processing speed [44] and executive functioning [60], and one study showed that physical training (i.e., Tai Chi) was superior to MME in improving measures of executive functioning [61]. Furthermore, combining physical (i.e., MME) and cognitive training seemed to yield the greatest benefits in measures of executive functioning [49], processing speed [38,49], and memory [47].

2.3.4.2 Multiple-modality exercise compared to active control

Nine of 33 studies included an active control group and reported cognition outcomes [39,42–44,53,60,61,66,67]. Of these, one study indicated that MME was effective in improving measures of global cognitive function, executive functioning and memory [39], and another study reported improvements in measures of processing speed[43]. All other studies did not report results supporting MME imparting superior effects in cognition when compared with active control groups (n=7) [42,44,53,60,61,66,67].

2.3.4.3 Multiple-modality exercise compared to no-treatment control

Twenty-three studies included a no-treatment control group. The overall evidence suggested that MME was effective in improving many aspects of cognitive function. For instance, a number of studies reported improvements in measures of memory (n=4) [46,55,58,62], processing speed (n=5) [43,45,50,55,64], executive functioning (n=7) [45,50,55,62,64,65,68] and global cognitive functioning(n=3) [40,65,69]. The remaining studies did not report significant results (n=11) [38,42,63,44,47,49,52,54,56,59,60].

2.3.5 Overall effects on cognitive tests

In **Table 2.4** we report a summary of the tests employed to assess cognitive function across all studies stratified by cognitive domains, and the overall effects of MME compared to competing treatment, active control, and no-treatment control groups.

Among nine different tests, the MMSE was the most common test used to assess global cognitive functioning across all studies (n=7). Further, Digit Span Test (n=12), varied forms of the Stroop

Test (n=10), and Trail-Making Test (Part B, n=10) were commonly utilized as measures of executive functioning from a total of 31 different tests. For memory assessment among 15 tests, the most common measures were Rey Auditory Verbal Learning Test (n=4), Rey-Osterrieth Complex Figure Test (n=4), and Hopkins Verbal Learning Test (n=3). For processing speed, Trail-Making Test (Part A, n=10) and varied forms of Simple Reaction Time (n=4) were most utilized amidst a total of six different measures reported.

In summary, across all studies and comparators, MME showed superior improvements in three measures of global cognitive functioning(MMSE [n=1], Montreal Cognitive Assessment [n=1], and modified-MMSE [n=1]); seven measures of executive functioning (Digit Span Test [n=2], Stroop Test [n=5], Trail-Making Test [Part B, n=5], Semantic Fluency [n=1], Digit Symbol Coding Test [2], Controlled Oral Word Association Test [n=2], and Verbal Fluency [n=1]); seven measures of memory (Rey Auditory Verbal Learning Test [n=1], Rey-Osterrieth Complex Figure Test [n=1], Hopkins Verbal Learning Test – Revised [n=1], Logical Memory [n=1], Emotional Memory Task [n=1], Free and Cued Selective Reminding Test [n=1], and Rivermead Behavioural Memory Test [n=1]); and four measures of processing speed (Trail-Making Test [Part A, n=3], Simple Reaction Time [n=3], Choice Reaction Time [n=1], and Choice Movement Time [n=1]).

2.3.6 Multiple-modality exercise and neuroimaging outcomes

Nine studies included neuroimaging outcomes [39,41,42,44,46,58–60,70]. These involved structural (n=6) [39,41,46,58,59,70] and functional (n=1) [46] magnetic resonance imaging (MRI) data, as well as electroencephalogram (EEG, n=3) [42,44,60] data (see **Table 2.3** for details).

For MRI outcomes, one study reported no significant differences between MME compared to cognitive training and no-treatment control [59] in white matter integrity (i.e., fractional anisotropy). Another study, however, reported MME was associated with improvements in grey matter (occipital and cerebellar regions) and white matter (right temporal and right occipital regions) volumes, compared to dance training [41]. Compared to active control groups, two studies reported that MME was associated with greater improvements in hippocampal volume [39,70], and one study reported increased white matter integrity (i.e., fractional anisotropy) and total brain

volume [39]. Furthermore, compared to no-treatment control groups, MME yielded increases in cortical grey matter [46] and hippocampal volume [58] in two studies.

For EEG outcomes, two studies reported that MME was not effective in improving event-related brain action potentials (i.e., peak and amplitude of activations) in two executive functioning tasks [44,60] compared to cognitive training, active control and no-treatment control groups. Similarly, another study reported greater improvements in resting-state EEG brain activity (precuneus/posterior cingulate cortex) following a combined cognitive and physical training group compared to MME alone [42].

Table 2.2. Multiple-modality exercise intervention details, including frequency, intensity, time and type, and comparator(s).

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Ansai (2015)[56]	Aerobic, resistance, and balance training (60 min/d, 3 d/wk) for 16 wk (N=23) Adherence=34.7%	**Frequency:** 3 d/wk for 16 wk **Intensity:** 60-85% HRR **Time:** 13 min/d **Type:** Cycling	**Frequency:** 3 d/wk for 16 wk **Intensity:** 14-17 RPE (20-pt Borg) **Time:** 15-20 min/d, ≤15 reps, ≤3 sets **Type:** Free-weights, bodyweight	**Frequency:** 3 d/wk for 16 wk **Intensity:** Not reported **Time:** 10 min/d **Type:** Static balance, dynamic and static weight transfer	**Comparator 1:** Resistance training, machine-based (60 min/d, 3 d/wk) for 16 wk (N=23) Adherence=56.5% **Comparator 2:** No-treatment control group (N=23) Adherence=Not applicable
Berryman (2014)[67]	Aerobic, resistance (lower body), and balance training (60 min/d, 3 d/wk) for 2 mo (N=16) Attendance=96.9%	***High-intensity interval training*** **Frequency:** 2 d/wk for 2 mo **Intensity:** Maximal aerobic power **Time:** 4-7 min (2 sets, 15s on 15s off) **Type:** Cycling ***Continuous training*** **Frequency:** 1 d/wk for 2 mo **Intensity:** 60% maximal aerobic power **Time:** 20 min/d **Type:** Cycling	**Frequency:** 3 d/wk for 2 mo **Intensity:** RM **Time:** 4 sets, 4-6 or 12-20 reps **Type:** Upper or lower-body, machine-based	Not applicable	**Comparator 1:** Aerobic, resistance (upper body), and balance training (60 min/d, 3 d/wk) for 2 mo (N=15) Attendance=96.9% **Comparator 2:** Stretching, relaxation and ball manipulation exercises (60 min/d, 3 d/wk) for 2 mo (N=16) Attendance=96.9%
Boa Sorte Silva (2018)[51]	Aerobic, resistance, and balance training (60 min/d, 3 d/wk) for 24 wk (n=64) Adherence=68%	**Frequency:** 3 d/wk for 24 wk **Intensity:** 65-85% HRmax **Time:** 20 min/d **Type:** Walking, marching and sequenced aerobics	**Frequency:** 3 d/wk for 24 wk **Intensity:** Not reported **Time:** 10 min/d **Type:** Resistance bands, wall or chair exercises	**Frequency:** 3 d/wk for 24 wk **Intensity:** Not reported **Time:** 15 min/d **Type:** Balance, range of motion, and breathing exercises	Aerobic and resistance training combined with mind-motor training (60 min/d, 3 d/wk) for 24 wk (n=63) Adherence=72%

Table 2.2. (Contd.)

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Callisaya (2017)[39]	Aerobic and resistance training (60 min/d, 3 d/wk) for 6 mo (N=26) Attendance=79%	**Frequency:** 2 d/wk (supervised) plus 1 d/wk (home-based) for 6 mo **Intensity:** 12-16 RPE (20-pt Borg) **Time:** 30 min/d (supervised) plus 60 min/d (home-based) **Type:** Cycling, cross trainer, rower or treadmill	**Frequency:** 3 d/wk for 6 mo **Intensity:** 14-17 RPE (20-pt Borg) **Time:** 30 min/d, 3 sets, 8-12 reps **Type:** Upper and lower extremity, bodyweight, machine and free weights	Not applicable	Upper and lower limb stretching and gentle movement program (60 min/d, 3 d/wk) for 6 mo (N=24) Attendance=76%
Carral (2008)[57]	Water-based aerobic and resistance training (90 min/d, 3 d/wk) for 5 mo (N=27) Adherence=Unclear	**Frequency:** 2 d/wk for 5 mo **Intensity:** Not reported **Time:** 45 min/d **Type:** Water-based movements and continuous swimming	**Frequency:** 3 d/wk for 5 mo **Intensity:** 75% 1RM **Time**: 45 min/d**,** 3 sets, 10 reps **Type:** Machine-based	Not applicable	Water-based aerobic training and calisthenic training (90 min/d, 3 d/wk) for 5 mo (N=29) Adherence=Unclear
Damirchi (2018)[49]	Aerobic and resistance training (60 min/d, 3 d/wk) for 8 wk (N=11) Adherence=73.3%	**Frequency:** 3 d/wk for 8 wk **Intensity**: 55-75% HRR **Time:** 6-25 min/d **Type:** Walking	**Frequency:** 3 d/wk for 8 wk **Intensity**: 13 to 15 RPE (20-pt Borg) **Time:** 30 min/d **Type:** Muscular strength and range of motion exercises	Not applicable	**Comparator 1:** Cognitive training (30-60 min/d, 3 d/wk) for 8 wk (N=11) Adherence=73.3% **Comparator 2:** Aerobic and resistance training plus cognitive training (90-120 min/d, 3 d/wk) for 8 wk (N=13) Adherence=86.6% **Comparator 3:** No-treatment control group (N=9) Adherence=Not applicable

Table 2.2. (Contd.)

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Eggenberger (2015)[48]	Aerobic, resistance, and balance training (60 min/d, 1 d/wk) for 6 mo (N=25) Adherence=85.3%	**Frequency:** 2 d/wk for 6 mo **Intensity:** 5-7 RPE (10-pt Borg) **Time:** 20 min/d **Type:** Treadmill walking	**Frequency:** 2 d/wk for 6 mo **Intensity**: 5-7 RPE (10-pt Borg) **Time:** 20 min/d, 1-3 sets, 8-12 reps **Type:** Bodyweight, rubber bands, weight vests	**Frequency:** 2 d/wk for 6 mo **Intensity:** Not reported **Time:** 20 min/d **Type:** Double- and single-leg stance variations, on the floor or unstable surfaces	**Comparator 1:** Video game dancing, strength and balance training (60 min/d, 1 d/wk) for 6 mo (N=24) Adherence=82.1% **Comparator 2:** Treadmill walking with verbal memory exercise, strength and balance training (60 min/d, 1 d/wk) for 6 mo (N=22) Adherence=88.1%
Fissler (2017)[59] [a]	Aerobic, resistance, coordination, balance, and flexibility training (60 min/d, 2 d/w) for 10 wk (N=12) Adherence=Not reported	**Frequency:** 2 d/wk (supervised) plus 3 d/wk (home-based) for 10 wk **Intensity:** Not reported **Time:** Not reported **Type:** Not reported	**Frequency:** 2 d/wk (supervised) plus 3 d/wk (home-based) for 10 wk **Intensity:** Not reported **Time:** Not reported **Type:** Not reported	Not applicable	**Comparator 1:** Cognitive training (60 min/d, 5 d/wk) for 10 wk (N=11) Adherence=Not reported **Comparator 2:** No-treatment control group (N=16) Adherence=Not applicable

Table 2.2. (Contd.)

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Gajewski (2012, 2018)[44,60 b]	Aerobic and resistance training (90 min/d, 2 d/wk) for 4 mo (N=35) Adherence=Not reported	**Frequency:** 2 d/wk for 4 mo **Intensity:** Not reported **Time:** 30 min/d (cardiovascular) plus 30 min/d (aerobic) **Type:** Treadmills, bicycles, cross trainers, easy step and floor movement sequences	**Frequency:** 2 d/wk for 4 mo **Intensity:** Not reported **Time:** 30 min/d, 3 sets, 15 reps **Type:** Machine-based	Not applicable	**Comparator 1:** Cognitive training (90 min/d, 2 d/wk) for 4 mo (N=32) Adherence=Not reported **Comparator 2:** Relaxation training (90 min/d, 3 d/wk) for 4 mo (N=34) Adherence=Not reported **Comparator 3:** No-treatment control group (N=40) Adherence=Not applicable
Ji (2017)[46]	Aerobic, resistance, and balance training via Nintendo Wii Fit (30 min/d, 7 d/wk) for 6 wk (N=12) Adherence=Not reported	**Frequency:** 7 d/wk for 6 wk **Intensity:** Not reported **Time:** Not reported **Type:** Nintendo Wii fit exercises	**Frequency:** 7 d/wk for 6 wk **Intensity:** Not reported **Time:** Not reported **Type:** Nintendo Wii fit exercises	Not applicable	No-treatment control group (N=12) Adherence=Not applicable
Klusmann (2010)[62]	Aerobic, resistance, balance, and flexibility training (90 min/d, 3 d/wk) for 6 mo (N=80) Adherence=Not Reported	**Frequency:** 3 d/wk for 6 mo **Intensity:** Not reported **Time:** 30 min/d **Type:** Cycling	**Frequency:** 3 d/wk for 6 mo **Intensity:** Not reported **Time:** Not reported **Type:** Not reported	**Frequency:** 3 d/wk for 6 mo **Intensity:** Not reported **Time:** Not reported **Type:** Not reported	**Comparator 1:** Cognitive training (90 min/d, 3 d/wk) for 6 mo (N=81) Adherence=Not Reported **Comparator 2:** No-treatment control group (N=69) Adherence=Not Applicable

Table 2.2. (Contd.)

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Küster (2016)[63]	Aerobic, resistance, coordination, balance, and flexibility training (60 min/d, 2 d/w) for 10 wk (N=18) Adherence=77.1%	**Frequency:** 2 d/wk (supervised) plus 3 d/wk (home-based) for 10 wk **Intensity:** Not reported **Time:** Not reported **Type:** Not reported	**Frequency:** 2 d/wk (supervised) plus 3 d/wk (home-based) for 10 wk **Intensity:** Not reported **Time:** Not reported **Type:** Not reported	Not applicable	**Comparator 1:** Cognitive training (60 min/d, 5 d/wk) for 10 wk (N=16) Adherence=99.8% **Comparator 2:** No-treatment control group (N=20) Adherence=Not applicable
Langlois (2013)[45]	Aerobic and resistance training (60 min/d, 3 d/wk) for 12 wk (N=36) Adherence=84%	**Frequency:** 3 d/wk for 12 wk **Intensity:** Moderate to hard intensity RPE (10-pt Borg) **Time:** 10-30 min/d **Type:** Treadmills, recumbent bikes, and elliptical	**Frequency:** 3 d/wk for 12 wk **Intensity:** Not reported **Time:** 10 min/d **Type:** Not reported	Not applicable	No-treatment control group (N=36) Adherence=Not Applicable
Leon (2015)[54]	Aerobic and resistance training (60 min/d, 2 d/wk) for 12 wk (N=46) Adherence=Not Reported	**Frequency:** 2 d/wk for 12 wk **Intensity:** Not reported **Time:** 30 min/d **Type:** Dancing and circuit training	**Frequency:** 2 d/wk for 12 wk **Intensity:** Not reported **Time:** 15 min/d **Type:** Bodyweight, elastic bands	Not applicable	**Comparator 1:** Aerobic and resistance training combined with cognitive training (60 min/d, 2 d/wk) for 12 wk (N=57) Adherence=Not Reported **Comparator 2:** No-treatment control group (N=35) Adherence=Not Applicable

Table 2.2. (Contd.)

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Linde (2014)[38]	Aerobic and resistance training (60 min/d, 2 d/wk) for 16 wk (N=15) Adherence=81%	**Frequency:** 2 d/wk for 16 wk **Intensity:** 40-70% HRR **Time:** 40 min/d **Type:** Walking or running	**Frequency:** 2 d/wk for 16 wk **Intensity:** Moderate intensity **Time:** 20 min/d, 10-20+ reps **Type:** Not reported	Not applicable	**Comparator 1:** Cognitive training (30 min/d, 1 d/wk) for 16 wk (N=11) Adherence=81% **Comparator 2:** Aerobic and resistance training (60 min/d, 2 d/wk) combined with cognitive training (30 min/d, 1d/wk) for 16 wk (N=16) Adherence=81% **Comparator 3:** No-treatment control group (N=13) Adherence=Not Applicable
Lord (2003)[43]	Aerobic, resistance, and balance training (60 min/d, 2 d/wk) for 12 mo (N=259) Adherence=42.3%	**Frequency:** 2 d/wk for 12 mo **Intensity:** Not reported **Time:** Not reported **Type:** Leg, trunk, and arm exercises	**Frequency:** 2 d/wk for 12 mo **Intensity:** Not reported **Time:** 4 to 30 reps **Type:** Bodyweight	**Frequency:** 2 d/wk for 12 mo **Intensity:** Not reported **Time:** Not reported **Type:** Tandem foot standing, standing on one leg, altering the base of support, etc.	**Comparator 1:** Flexibility and relaxation exercises (60 min/w, 2 d/wk) for 12 mo (N=80) Adherence=45.4% **Comparator 2:** No-treatment control group (N=169) Adherence=Not applicable

Table 2.2. (Contd.)

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Napoli (2014)[65]	Aerobic, resistance, and balance training (90 min/d, 3 d/wk) for 12 mo (N=26) Adherence=88%	**Frequency:** 3 d/wk for 12 mo **Intensity:** 65 to 85% HRpeak **Time:** 30 min/d **Type:** Walking, cycling and stair climbing	**Frequency:** 3 d/wk for 12 mo **Intensity:** 65 to 80% 1RM **Time:** 30 min/d, 1-3 sets, 6-12 reps **Type:** Machine-based	**Frequency:** 3 d/wk for 12 mo **Intensity:** Not reported **Time:** 15 min/d **Type:** Not reported	**Comparator 1:** Diet that provided energy deficit of 500-750 kcal/d with goal to achieve ~10% weight loss (N=26) Adherence=83% **Comparator 2:** Aerobic, resistance, and balance training (90 min/d, 3 d/wk) combined with diet for 12 mo (N=28) Adherence=83% **Comparator 3:** No-treatment control group (N=27) Adherence=Not applicable
Nascimento (2014)[69]	Aerobic, resistance, and balance training (60 min/d, 3 d/wk) for 16 wk (N=35) Adherence ≥75%	**Frequency:** 1 d/wk for 16 wk **Intensity:** 60-80% HRmax **Time:** 45 min/d **Type:** Walking and marching	**Frequency:** 1 d/wk for 16 wk **Intensity:** RM **Time:** 45 min/d, 3 sets, 15-20 reps **Type:** Free weights (e.g., rubber-bands)	**Frequency:** 1 d/wk for 16 wk **Intensity:** Moderate intensity **Time:** 45 min/d **Type:** Recreational activities stimulating visual, vestibular and somatosensory systems	No-treatment control group (N=32) Adherence=Not applicable
Okumiya (1996)[52]	Aerobic, resistance, and balance training (60 min/d, 2 d/wk) for 24 wk (N=21) Adherence=86%	**Frequency:** 2 d/wk for 24 wk **Intensity:** Light **Time:** Not reported **Type:** Walking, game playing	**Frequency:** 2 d/wk for 24 wk **Intensity:** Light **Time:** Not reported **Type:** Bodyweight	**Frequency:** 2 d/wk for 24 wk **Intensity:** Not reported **Time:** Not reported **Type:** Not reported	No-treatment control group (N=21) Adherence=Not applicable

Table 2.2. (Contd.)

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Rehfeld (2018)[41]	Aerobic, resistance, and balance training (90 min/d, 2 d/wk) for 6 mo (N=18) Attendance ≥70%	**Frequency:** 2 d/wk for 6 mo **Intensity:** Not reported **Time:** 20 min/d **Type:** Bicycle ergometers	**Frequency:** 2 d/wk for 6 mo **Intensity:** Not reported **Time:** 20 min/d **Type:** Free weights (e.g., barbells, rubber bands, etc.)	**Frequency:** 2 d/wk for 6 mo **Intensity:** Not reported **Time:** 20 min/d **Type:** Not reported	Dance training (90 min/d, 2 d/wk) for 6 mo (N=18) Adherence= ≥70%
Rosano (2017)[70 c]	Aerobic, resistance, balance, and flexibility training (≤50 min/d, 2 d/wk [supervised] and 3-4 d/wk [home-based]) for 24 mo (N=10) Adherence=66.7%	**Frequency:** 2 d/wk (supervised) plus 3-4 d/wk (home-based) for 24 mo **Intensity:** 13 RPE (20-pt Borg) **Time:** ≤30 min/d **Type:** Walking	**Frequency:** 2 d/wk (supervised) plus 3-4 d/wk (home-based) for 24 mo **Intensity:** 15-16 RPE (20-pt Borg) **Time:** 10 min/d, 2 sets, 10 reps **Type:** Lower-extremity, ankle weights	**Frequency:** 2 d/wk (supervised) plus 3-4 d/wk (home-based) for 24 mo **Intensity:** Not reported **Time:** 10 min/d **Type:** Balance and larger muscle flexibility	Health and education sessions (60-90 min/d, weekly to monthly) for 24 mo (N=16) Adherence=90.6%
Shah (2014)[47]	Aerobic (60 min/d, 3 d/wk) and resistance training (40 min/d, 2 d/wk) for 16 wk (N=42) Adherence=Not reported	**Frequency:** 3 d/wk for 16 wk **Intensity:** Low intensity **Time:** 60 min/d **Type:** Walking	**Frequency:** 2 d/wk for 16 wk **Intensity:** Not reported **Time:** 40 min/d **Type:** Free weights and bodyweight	Not applicable	**Comparator 1:** Cognitive training (60 min/d, 5 d/wk) for 16 wk (N=51) Adherence=Not reported **Comparator 2:** Aerobic and resistance training (60 min/d, 5 d/wk) combined with cognitive training (60 min/d, 5 d/wk) for 16 wk (N=44) Adherence=Not reported **Comparator 3:** No-treatment control group (N=35) Adherence=Not applicable

Table 2.2. (Contd.)

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Silva (2019)[68]	Aerobic, resistance, and balance training (60 min/d, 2 d/wk) for 12 wk (N=7) Adherence=90%	**Frequency:** 2 d/wk for 12 wk **Intensity:** 80% HRmax **Time:** 30 min/d **Type:** Treadmill training	**Frequency:** 2 d/wk for 12 wk **Intensity:** Not reported **Time:** 20 min, 3 sets, 8-12 reps **Type:** Machine-based	**Frequency:** 2 d/wk for 12 wk **Intensity:** Not reported **Time:** 10 min/d **Type:** Static balance exercises and stretching prioritizing mobility of the main joints	No-treatment control group (N=12) Adherence=Not applicable
Sink (2015)[66]	Aerobic, resistance, balance, and flexibility training (≤50 min/d, 2 d/wk [supervised] and 3-4 d/wk [home-based]) for 24 mo (N=735) Adherence=71%	**Frequency:** 2 d/wk (supervised) plus 3-4 d/wk (home-based) for 24 mo **Intensity:** 13 RPE (20-pt Borg) **Time:** ≤30 min/d **Type:** Walking	**Frequency:** 2 d/wk (supervised) plus 3-4 d/wk (home-based) for 24 mo **Intensity:** 15-16 RPE (20-pt Borg) **Time:** 10 min/d, 2 sets, 10 reps **Type:** Lower-extremity, ankle weights	**Frequency:** 2 d/wk (supervised) plus 3-4 d/wk (home-based) for 24 mo **Intensity:** Not reported **Time:** 10 min/d **Type:** Balance and larger muscle flexibility	Health and education sessions (60-90 min/d, weekly to monthly) for 24 mo (N=741) Adherence=Not reported

Table 2.2. (Contd.)

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Styliadis (2015)[42]	Aerobic, resistance, and balance training via Nintendo Wii (60 min/d, 5 d/wk) for 8 wk (N=14) Adherence=65.2%	**Frequency:** 5 d/wk for 8 wk **Intensity:** Not reported **Time:** 20 min/d **Type:** Exergaming via Nintendo Wii	**Frequency:** 5 d/wk for 8 wk **Intensity:** Not reported **Time:** 8-10 min/d, 8-10 exercises **Type:** Exergaming via Nintendo Wii	**Frequency:** 5 d/wk for 8 wk **Intensity:** Not reported **Time:** 10 min/d **Type:** Exergaming via Nintendo Wii	**Comparator 1:** Cognitive training (60 min/d, 3-5 d/wk) for 8 wk (N=14) Adherence=60.9% **Comparator 2:** Aerobic, resistance, and balance training via Nintendo Wii (60 min/d, ≤5 d/wk) plus Cognitive (60 min/d, ≤5 d/wk) for 8 wk (N=14) Adherence=65.5% **Comparator 3:** Active control group (e.g., watching documentaries 60 min/d, 5 d/wk) for 8 wk (N=14) Adherence=67.1% **Comparator 4:** No-treatment control group (N=14) Adherence=Not applicable
Tarazona-Santabalbina (2016)[40]	Aerobic, resistance, balance, and flexibility training (65-70 min/d, 5 d/wk) for 24 wk (N=51) Adherence=47.3%	**Frequency:** 3 d/wk for 24 wk **Intensity:** 40-65% HRmax **Time:** 40 min/d **Type:** Walking and climbing stairs	**Frequency:** 2 d/wk for 24 wk **Intensity:** 25-75% 1RM **Time:** 40 min/d **Type:** Resistance bands, isometric, concentric and eccentric exercises	**Frequency:** 5 d/wk for 24 wk **Intensity:** Not reported **Time:** 5-15 min/d **Type:** Postural sway and dynamic balance, coordination, and flexibility	No-treatment control group (N=49)

Table 2.2. (Contd.)

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Taylor-Piliae (2010)[61]	Aerobic, resistance, balance, and flexibility training (60 min/d, 1-2 d/wk [supervised] plus 3 d/wk [home-based]) for 12 mo (N=39) Adherence=68%	**Frequency:** 1-2 d/wk (supervised) 3 d/wk (home-based) for 12 mo **Intensity:** Moderate **Time:** 15-25 min/d (supervised) plus ≥30 min/d (home-based) **Type:** Walking and calisthenics performed to music	**Frequency:** 1-2 d/wk (supervised) 3 d/wk (home-based) for 12 mo **Intensity:** Moderate **Time:** 15-20 min/d (supervised) plus 10-25 min/d (home-based) **Type:** Calisthenics, free-weight and rubber bands	**Frequency:** 1-2 d/wk (supervised) 3 d/wk (home-based) for 12 mo **Intensity:** Moderate **Time:** Not reported **Type:** Not reported	**Comparator 1:** Tai Chi (60 min/d, 1-2 d/wk [supervised] plus 3 d/wk [home-based]) for 12-mo (N=37) Adherence=77% **Comparator 2:** Healthy aging classes (90 min/d, 1 d/wk) for 6 mo (N=56) Adherence=67%
Teixeira (2018)[58]	Aerobic and resistance training (20-30 min/d, 3 d/wk) for 6 mo (N=20) Adherence=66.8%	**Frequency:** 1 d/wk for 6 mo **Intensity:** 70-90% HRmax **Time:** 20-30 min/d **Type:** Outdoor walking and jogging, circuit training	**Frequency:** 2 d/wk for 6 mo **Intensity:** 70-90% HRmax **Time:** 20-30 min/d **Type:** Circuit training including resistance exercises using rubber bands	Not applicable	No-treatment control group (N=20) Adherence=Not applicable
Vaughan (2014)[50]	Aerobic, resistance, balance, and flexibility training (60 min/d, 2 d/wk) for 16 wk (N=25) Adherence=85.7%	**Frequency:** 2 d/wk for 16 wk **Intensity:** 3-6 RPE (10-pt Borg) **Time:** 10-15 min/d **Type:** Freestyle aerobics and circuit training	**Frequency:** 2 d/wk for 16 wk **Intensity:** 4-6 RPE (10-pt Borg) **Time:** 10-15 min/d **Type:** Free-weights, bodyweight	**Frequency:** 2 d/wk for 16 wk **Intensity:** 3-4 RPE (10-pt Borg) **Time:** 7-30 min/d **Type:** Static and dynamic balance, coordination and agility, and reaction time	No-treatment control group (N=23) Adherence=Not applicable
Vedovelli (2017)[55]	Aerobic and resistance training (60 min/d, 3 d/wk) for 3 mo (N=22) Adherence=100%	**Frequency:** 3 d/wk for 3 mo **Intensity:** 75-85% HRmax **Time:** ≤30 min/d **Type:** Walking	**Frequency:** 3 d/wk for 3 mo **Intensity:** 50-75% 1RM **Time:** 30 min/d, 3 sets, 10 reps plus 10s isometric holds **Type:** Resistance bands, bodyweight	Not applicable	No-treatment control group (N=9) Adherence=Not applicable

Table 2.2. (Contd.)

First author (Year)	Multimodality exercise intervention summary	Aerobic training details	Resistance training details	Balance and/or flexibility training details	Comparator(s)
Williams (1997)[64]	Aerobic, resistance, and balance training (60 min/d, 2 d/wk) for 12 mo (N=94) Adherence=72%	**Frequency:** 2 d/wk for 12 mo **Intensity:** Not reported **Time:** Not reported **Type:** continuous movement of the legs and trunk and intermittent arm movement	**Frequency:** 2 d/wk for 12 mo **Intensity:** Not reported **Time:** Not reported **Type:** Bodyweight	**Frequency:** 2 d/wk for 12 mo **Intensity:** Not reported **Time:** Not reported **Type:** Standing on one leg, ball games, hand-eye and foot-eye coordination	No-treatment control group (N=93) Adherence=Not applicable
Williamson (2009)[53]	Aerobic, resistance, balance, and flexibility training (40-60 min/d, 1-3 d/wk [supervised] and 1-5 d/wk [home-based]) for 24 mo (N=50) Adherence=Not reported	**Frequency:** 2-3 d/wk (supervised) plus 1-3 d/wk (home-based) for 24 mo **Intensity:** 13 RPE (20-pt Borg) **Time:** 40 min/d **Type:** Walking	**Frequency:** 2-3 d/wk (supervised) plus 1-3 d/wk (home-based) for 24 mo **Intensity:** 15-16 RPE (20-pt Borg) **Time:** 10 min/d, 2 sets, 10 reps **Type:** Lower extremity, free weights	**Frequency:** 1-3 d/wk (supervised) plus 1-5 d/wk (home-based) for 24 mo **Intensity:** Not reported **Time:** 10 min/d **Type:** Not reported	Health and education sessions (weekly to monthly) for 24 mo (N=52) Adherence=Not reported

Note: [a] Secondary outcomes from Küster et al 2016. [b] Secondary outcomes from Gajewski et al 2012. [c] Secondary outcomes from Sink et al 2015. Abbreviations: d = day, wk = week(s); HRmax = maximum heart rate; RM = maximum repetition; RPE = rate of perceived exertion.

Table 2.3. Summary of study interventions, outcomes and main findings.

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Ansai (2015)[56]	Aerobic, resistance, and balance training (60 min/d, 3 d/wk) for 16 wk (N=23) Adherence=34.7%	**Comparator 1:** Resistance training, machine-based (60 min/d, 3 d/wk) for 16 wk (N=23) Adherence=56.5% **Comparator 2:** No-treatment control group (N=23) Adherence=Not applicable	(1,2) Global cognitive function (3) Executive function	(1) Montreal Cognitive Assessment (2) Clock Drawing Test (3) Verbal Fluency	No within- or between-group differences at follow-up.
Berryman (2014)[67]	Aerobic, resistance (lower body), and balance training (60 min/d, 3 d/wk) for 2 mo (N=16) Attendance=96.9%	**Comparator 1:** Aerobic, resistance (upper body), and balance training (60 min/d, 3 d/wk) for 2 mo (N=15) Attendance=96.9% **Comparator 2:** Stretching, relaxation and ball manipulation exercises (60 min/d, 3 d/wk) for 2 mo (N=16) Attendance=96.9%	(1) Inhibition under single-task condition (2) Working memory under single-task condition (3) Inhibition under dual-task condition (4) Working memory under dual-task condition	(1,2) Random Number Generation Task (3,4) Random Number Generation Task while walking on treadmill	Improvements in inhibition (single-task), inhibition and working memory (dual-task) in all groups. No between-group differences at follow-up.
Boa Sorte Silva (2018)[51]	Aerobic, resistance, and balance training (60 min/d, 3 d/wk) for 24 wk (n=64) Adherence=68%	Aerobic and resistance training combined with mind-motor training (60 min/d, 3 d/wk) for 24 wk (n=63) Adherence=72%	(1) Global cognitive function (2) Concentration (3) Reasoning (4) Planning (5) Memory	(1-5) Cambridge Brain Sciences Cognitive Battery	Improvements in global cognitive function, concentration and reasoning in both groups. Improvements in planning and memory in combined multiple-modality and mind-motor training group. No between-group differences at follow-up.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Callisaya (2017)[39]	Aerobic and resistance training (60 min/d, 3 d/wk) for 6 mo (N=26) Attendance=79%	Upper and lower limb stretching and gentle movement program (60 min/d, 3 d/wk) for 6 mo (N=24) Attendance=76%	**Cognition:** (1-7) Global cognitive function (1-5) Executive function (6,7) Memory **Neuroimaging:** (8) Brain total volume (9) White matter volume (10) Hippocampal volume (11) Cortical thickness (12) Fractional anisotropy (13) Mean diffusivity	**Cognition:** (1) Victoria Stroop Test (Part C-D) (2) Trail Making Test (Part B-A) (3) Digit Symbol Coding Test (4) Digit span Test (WAIS-III) (5) Controlled Oral Word Association Test (6) Hopkins Verbal Learning Test – Revised (7) Rey Complex Figure Test **Neuroimaging:** (8-13) MRI	Greater improvements in cognition (global cognitive function, executive function, and memory) and brain structure (fractional anisotropy, total and hippocampal brain volume), compared to control group.
Carral (2008)[57]	Water-based aerobic and resistance training (90 min/d, 3 d/wk) for 5 mo (N=27) Adherence=Unclear	Water-based aerobic training and calisthenic training (90 min/d, 3 d/wk) for 5 mo (N=29) Adherence=Unclear	Global cognitive function	Mini-Mental State Examination	No between-group differences at follow-up.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Damirchi (2018)[49]	Aerobic and resistance training (60 min/d, 3 d/wk) for 8 wk (N=11) Adherence=73.3%	**Comparator 1:** Cognitive training (30-60 min/d, 3 d/wk) for 8 wk (N=11) Adherence=73.3% **Comparator 2:** Aerobic and resistance training plus cognitive training (90-120 min/d, 3 d/wk) for 8 wk (N=13) Adherence=86.6% **Comparator 3:** No-treatment control group (N=9) Adherence=Not applicable	(1) Working memory (2) Processing speed (3) Reaction time (4) Inhibition (error number)	(1) Digit Span Test (WAIS-III) (2) Digit Symbol Coding Test (WAIS-III) (3,4) Stroop Test	Greater improvements in working memory and processing speed in combined multiple-modality exercise and cognitive training compared to multiple-modality exercise group.
Eggenberger (2015)[48]	Aerobic, resistance, and balance training (60 min/d, 1 d/wk) for 6 mo (N=25) Adherence=85.3%	**Comparator 1:** Video game dancing, strength and balance training (60 min/d, 1 d/wk) for 6 mo (N=24) Adherence=82.1% **Comparator 2:** Treadmill walking with verbal memory exercise, strength and balance training (60 min/d, 1 d/wk) for 6 mo (N=22) Adherence=88.1%	(1) Executive function (2) Working memory (3) Long-term visual memory (4) Long-term verbal memory (5) Short-term verbal memory (6) Attention and concentration (7,8) Processing speed	(1) Trail-Making Test (Part B) (2) Executive Control Task (3) Paired-Associates Learning Task (4) Logical Memory (Story recall, WMS-R) (5) Digit Span Test (WMS-R) (6) Age Concentration Tests A and B (7) Trail-Making Test (Part A) (8) Digit Symbol Substitution Task (WAIS-R)	Improvements in executive function, working memory, long-term visual and verbal memory, attention and processing speed in all groups. No between-group differences at follow-up.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Fissler (2017)[59 a]	Aerobic, resistance, coordination, balance, and flexibility training (60 min/d, 2 d/w) for 10 wk (N=12) Adherence=Not reported	**Comparator 1:** Cognitive training (60 min/d, 5 d/wk) for 10 wk (N=11) Adherence=Not reported **Comparator 2:** No-treatment control group (N=16) Adherence=Not applicable	Fractional anisotropy	Diffusion Tensor Imaging via MRI	No within- or between-group differences at follow-up.
Gajewski (2012)[44]	Aerobic and resistance training (90 min/d, 2 d/wk) for 4 mo (N=35) Adherence=Not reported	**Comparator 1:** Cognitive training (90 min/d, 2 d/wk) for 4 mo (N=32) Adherence=Not reported **Comparator 2:** Relaxation training (90 min/d, 3 d/wk) for 4 mo (N=34) Adherence=Not reported **Comparator 3:** No-treatment control group (N=40) Adherence=Not applicable	**Cognition:** (1) Reaction times (2) Executive function **Neuroimaging:** (3) Peak and amplitude of electrophysiological brain activity	**Cognition:** (1,2) Task Switching Test **Neuroimaging:** (3) EEG	Greater improvements in reaction time variability in cognitive training group compared to multiple-modality exercise training and no-treatment control group. EEG results suggested higher improvements in event-related brain action potentials associated with response selection, allocation of cognitive resources and error detection in cognitive training group.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Gajewski (2018)[60 b]	Aerobic and resistance training (90 min/d, 2 d/wk) for 4 mo (N=35) Adherence=Not reported	**Comparator 1:** Cognitive training (90 min/d, 2 d/wk) for 4 mo (N=32) Adherence=Not reported **Comparator 2:** Relaxation training (90 min/d, 3 d/wk) for 4 mo (N=34) Adherence=Not reported **Comparator 3:** No-treatment control group (N=40) Adherence=Not applicable	**Cognition:** (1) Immediate verbal memory and delayed word recognition (2) Long-term semantic memory (3) Short-term memory (4) Visuospatial memory (5,6) Working memory **Neuroimaging:** (7) Electrophysiological brain activity	**Cognition:** (1) Verbal Learning and Memory Test (2) Word Fluency Test (3) Digit Span Test (4) Rey-Osterrieth Complex Figure Test (5) Digit Span Test (6) n-Back Task **Neuroimaging:** (7) EEG	Improvements in reaction time in multiple-modality exercise group at follow-up, no change in other groups. Greater improvements in working memory in cognitive training group compared to multiple-modality exercise and both control groups. EEG suggested improvements in underlying processing associated with working memory.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Ji (2017)[46]	Aerobic, resistance, and balance training via Nintendo Wii Fit (30 min/d, 7 d/wk) for 6 wk (N=12) Adherence=Not reported	No-treatment control group (N=12) Adherence=Not applicable	**Cognition:** (1) Immediate, delayed and recognition recall (2) Immediate and delayed story recall (3,4) Executive function (5) Working memory (6,7) Processing speed (8) Emotional memory recall **Neuroimaging:** (9) Grey matter volumes (10) Resting state amplitude of low-frequency fluctuations (11) Regional homogeneity (12) Functional connectivity	**Cognition:** (1) Hopkins Verbal Learning Test – Revised (2) Rivermead Behavioural Memory Test (3) Trail-Making Test (Part B) (4) Stroop Test (5) Digit Span Test (6) Digit Symbol Substitution Test (7) Trail-Making Test (Part A) (8) Emotional Memory task **Neuroimaging:** (9) Structural MRI (10-12) Resting-state functional MRI	Greater improvements in emotional memory recall, grey matter volume, and increased functional connectivity in multiple-modality exercise group compared to control group.
Klusmann (2010)[62]	Aerobic, resistance, balance, and flexibility training (90 min/d, 3 d/wk) for 6 mo (N=80) Adherence=Not Reported	**Comparator 1:** Cognitive training (90 min/d, 3 d/wk) for 6 mo (N=81) Adherence=Not Reported **Comparator 2:** No-treatment control group (N=69) Adherence=Not Applicable	(1) Semantic verbal fluency (2,3) Episodic memory (4,5) Executive function	(1) Verbal Fluency (2) Story Recall (RBMT) (3) Free and Cued Selective Reminding Test (4) Trail-Making Test (Part A/B) (5) Stroop Test	Greater improvements in memory (immediate and delayed story recall, as well as delayed free recall) and executive function in multiple-modality exercise group as well as cognitive training group compared to no-treatment control group.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Küster (2016)[63]	Aerobic, resistance, coordination, balance, and flexibility training (60 min/d, 2 d/w) for 10 wk (N=18) Adherence=77.1%	**Comparator 1:** Cognitive training (60 min/d, 5 d/wk) for 10 wk (N=16) Adherence=99.8% **Comparator 2:** No-treatment control group (N=20) Adherence=Not applicable	(1-9) Global cognitive function (1-6) Executive function (6-8) Memory	(1) Phonematic Fluency (2) Semantic Fluency (3) Digit Span Test (WAIS-III) (4) Trail-Making Test (Part A and B) (5) Digit Symbol Coding Test (WAIS-III) (6) Computation Span (ECB) (7) Free Recall (ADAS-cog) (8) Munich Verbal Learning Test	No between-group differences at follow-up.
Langlois (2013)[45]	Aerobic and resistance training (60 min/d, 3 d/wk) for 12 wk (N=36) Adherence=84%	No-treatment control group (N=36) Adherence=Not Applicable	(1) Global cognitive function (2) Abstract verbal reasoning (3-5) Processing speed (6,7) Working memory (8) Episodic memory (9,10) Executive function	(1) Mini-Mental State Examination (2) Similarities Test (WAIS-III) (3) Digit Symbol Coding Test (4) Trail-Making Test (Part A) (5) Stroop Test (6) Letter-Number Sequencing (7) Digit Span Test (WAIS-III) (8) Rey Auditory Verbal Learning Test (9) Trail-Making Test (Part B-A) (10) Stroop Test	Greater improvements in processing speed, working memory, and executive function in multiple-modality exercise compared to no-treatment control group.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Leon (2015)[54]	Aerobic and resistance training (60 min/d, 2 d/wk) for 12 wk (N=46) Adherence=Not Reported	**Comparator 1:** Aerobic and resistance training combined with cognitive training (60 min/d, 2 d/wk) for 12 wk (N=57) Adherence=Not Reported **Comparator 2:** No-treatment control group (N=35) Adherence=Not Applicable	(1) Simple reaction time (2) Choice reaction time (3) Simple movement time (4) Choice movement time	(1-4) Vienna Test System	Improvements in simple reaction time and choice movement time in multiple-modality exercise group at follow-up. Greater improvements in simple movement time, choice reaction and movement time in combined multiple-modality exercise and cognitive training group compared to multiple-modality exercise and no-treatment control.
Linde (2014)[38]	Aerobic and resistance training (60 min/d, 2 d/wk) for 16 wk (N=15) Adherence=81%	**Comparator 1:** Cognitive training (30 min/d, 1 d/wk) for 16 wk (N=11) Adherence=81% **Comparator 2:** Aerobic and resistance training (60 min/d, 2 d/wk) combined with cognitive training (30 min/d, 1d/wk) for 16 wk (N=16) Adherence=81% **Comparator 3:** No-treatment control group (N=13) Adherence=Not Applicable	(1) Reasoning (2) Spatial relations (3) Concentration (4) Processing speed (5) Cognitive speed (6) Short-term memory	(1, 2) Leistungs-Prüf System 50+ (3) d2: Test of Attention (4) Trail-Making Test (Part A) (5) Digit Symbol Substitution Test (NAI) (6) Word List Test (NAI)	No between-group differences in treatment groups. Greater improvements in cognitive speed in combined multiple-modality exercise and cognitive training compared to no-treatment control. Greater improvements in concentration in cognitive training group compared to no-treatment control group.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Lord (2003)[43]	Aerobic, resistance, and balance training (60 min/d, 2 d/wk) for 12 mo (N=259) Adherence=42.3%	**Comparator 1:** Flexibility and relaxation exercises (60 min/w, 2 d/wk) for 12 mo (N=80) Adherence=45.4% **Comparator 2:** No-treatment control group (N=169) Adherence=Not applicable	(1) Choice reaction time (2) Simple reaction time	(1) Stepping on rectangular panels as quickly as possible (2) Seated, using a light as the stimulus and a hand press as the response	Greater improvements in multiple-modality exercise group in choice and simple reaction time compared to no-treatment control group, and flexibility and relaxation group, respectively.
Napoli (2014)[65]	Aerobic, resistance, and balance training (90 min/d, 3 d/wk) for 12 mo (N=26) Adherence=88%	**Comparator 1:** Diet that provided energy deficit of 500-750 kcal/d with goal to achieve ~10% weight loss (N=26) Adherence=83% **Comparator 2:** Aerobic, resistance, and balance training (90 min/d, 3 d/wk) combined with diet for 12 mo (N=28) Adherence=83% **Comparator 3:** No-treatment control group (N=27) Adherence=Not applicable	(1) Global cognitive function, (2) Processing speed (3,4) Executive function	(1) Modified Mini-Mental State Examination (2) Trail-Making Test (Part A) (3) Word List Fluency Test (4) Trail-Making Test (Part B)	Greater improvements in global cognitive function all treatment groups compared to no-treatment control group. Greater improvements in executive function in multiple-modality exercise group and combined group compared to no-treatment group.
Nascimento (2014)[69]	Aerobic, resistance, and balance training (60 min/d, 3 d/wk) for 16 wk (N=35) Adherence ≥75%	No-treatment control group (N=32) Adherence=Not applicable	Global cognitive function	Montreal Cognitive Assessment	Greater improvements in global cognitive function in MCI participants in multiple-modality exercise group compared to no-treatment control group.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Okumiya (1996)[52]	Aerobic, resistance, and balance training (60 min/d, 2 d/wk) for 24 wk (N=21) Adherence=86%	No-treatment control group (N=21) Adherence=Not applicable	(1,2) Global cognitive function (3) Visual orientation	(1) Mini-Mental State Examination (2) Hasegawa Dementia Scale Revised (3) Visuospatial Performance Test	No within- or between-group differences at follow-up.
Rehfeld (2018)[41]	Aerobic, resistance, and balance training (90 min/d, 2 d/wk) for 6 mo (N=18) Attendance ≥70%	Dance training (90 min/d, 2 d/wk) for 6 mo (N=18) Adherence ≥70%	**Cognition:** (1) Attention (2) Processing speed (3) Verbal fluency, short-term and working memory (4) Verbal episodic memory (5) Visuospatial memory **Neuroimaging:** (6) Grey matter volume (7) White matter volume	**Cognition:** (1) Alertness, Go/Nogo, Divided Attention, and Flexibility Tasks (2) Trail-Making Test (3) Digit Span Test (WMS) (4) Verbal Learning and Memory Task (5) Rey-Osterrieth-Complex – Figure Test **Neuroimaging:** **(**6,7) MRI	Improvements in attention, immediate and delayed recall in both groups. No between-group differences. Greater increases in dance group in gray matter (frontal and temporal cortical areas) and white matter (truncus and splenium in corpus callosum) volumes. Greater changes in multiple-modality exercise in grey matter (occipital and cerebella regions) and white matter (right temporal and right occipital) volumes.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Rosano (2017)[70 c]	Aerobic, resistance, balance, and flexibility training (≤50 min/d, 2 d/wk [supervised] and 3-4 d/wk [home-based]) for 24 mo (N=10) Adherence=66.7%	Health and education sessions (60-90 min/d, weekly to monthly) for 24 mo (N=16) Adherence=90.6%	(1) Hippocampal volume (2) Dentate gyrus (3) Cornu ammonis	(1-3) MRI	Greater improvements in left and right hippocampus and left cornu ammonis in multiple-modality exercise group compared to active control group. After adjustments, only changes in left hippocampus remained statistically significant.
Shah (2014)[47]	Aerobic (60 min/d, 3 d/wk) and resistance training (40 min/d, 2 d/wk) for 16 wk (N=42) Adherence=Not reported	**Comparator 1:** Cognitive training (60 min/d, 5 d/wk) for 16 wk (N=51) Adherence=Not reported **Comparator 2:** Aerobic and resistance training (60 min/d, 5 d/wk) combined with cognitive training (60 min/d, 5 d/wk) for 16 wk (N=44) Adherence=Not reported **Comparator 3:** No-treatment control group (N=35) Adherence=Not applicable	(1) Premorbid IQ (2) Verbal episodic memory (3) Verbal fluency (4) Processing speed (5) Attention (6) Executive function (7) Visual memory	(1) Cambridge Contextual Reading Test (2) Rey Auditory Verbal Learning Test (3) Control Word Association Test (4) Detection (CogState Battery) (5) One Back Memory (CogState Battery) (6) Groton Maze Learning (CogState Battery) (7) Visual Memory Index Score (CogState Battery)	Greater improvements in verbal episodic memory in combined multiple-modality exercise and cognitive training group compared to no-treatment control group.
Silva (2019)[68]	Aerobic, resistance, and balance training (60 min/d, 2 d/wk) for 12 wk (N=7) Adherence=90%	No-treatment control group (N=12) Adherence=Not applicable	(1,2) Global cognitive function (3,4) Executive function (5) Inhibition	(1) Clinical Dementia Rating (2) Mini-Mental State Examination (3) Clock Drawing Test (4) Verbal Fluency (5) Stroop Test	Greater improvements in executive function in multiple-modality exercise group compared to no-treatment control group.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Sink (2015)[66]	Aerobic, resistance, balance, and flexibility training (≤50 min/d, 2 d/wk [supervised] and 3-4 d/wk [home-based]) for 24 mo (N=735) Adherence=71%	Health and education sessions (60-90 min/d, weekly to monthly) for 24 mo (N=741) Adherence=Not reported	(1) Psychomotor speed, attention and working memory (2) Word list learning and recall (3) Visuospatial function and figural memory (4) Language (5) Concentration, attention and psychomotor speed (6-10) Executive function (1,2,8-10) Global cognitive function	(1) Digit Symbol Coding Task (2) Hopkins Verbal Learning Test – Revised (3) Rey-Osterrieth Complex Figure Test (4) Boston Naming Test (5) Trail-Making Test (Part A) (6) Trail-Making Test (Part B) (7) Category Fluency Test (8) n-Back Task (9) Eriksen Flanker Task (10) Task Switching Exercise	No main effects of multiple-modality exercise on any of the cognition outcomes. Subgroup analysis revealed greater improvements in executive function in participants with poorer physical function at baseline or aged 80+, in the multiple-modality exercise group.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Styliadis (2015)[42]	Aerobic, resistance, and balance training via Nintendo Wii (60 min/d, 5 d/wk) for 8 wk (N=14) Adherence=65.2%	**Comparator 1:** Cognitive training (60 min/d, 3-5 d/wk) for 8 wk (N=14) Adherence=60.9% **Comparator 2:** Aerobic, resistance, and balance training via Nintendo Wii (60 min/d, ≤5 d/wk) plus Cognitive (60 min/d, ≤5 d/wk) for 8 wk (N=14) Adherence=65.5% **Comparator 3:** Active control group (e.g., watching documentaries 60 min/d, 5 d/wk) for 8 wk (N=14) Adherence=67.1% **Comparator 4:** No-treatment control group (N=14) Adherence=Not applicable	**Cognition:** (1) Global cognitive function **Neuroimaging:** (2) Electrophysiological brain activity	**Cognition:** (1) Mini-Mental State Examination **Neuroimaging:** (2) EEG, resting state	No within- or between group differences in global cognitive function. Greater improvements in resting-state electrophysiological brain activity in the precuneus/posterior cingulate cortex in combined multiple-modality exercise and cognitive training group compared to multiple-modality exercise group.
Tarazona-Santabalbina (2016)[40]	Aerobic, resistance, balance, and flexibility training (65-70 min/d, 5 d/wk) for 24 wk (N=51) Adherence=47.3%	No-treatment control group (N=49)	Global cognitive function	Mini-Mental State Examination	Greater improvements in global cognitive function in multiple-modality exercise compared to no-treatment control group.

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Taylor-Piliae (2010)[61]	Aerobic, resistance, balance, and flexibility training (60 min/d, 1-2 d/wk [supervised] plus 3 d/wk [home-based]) for 12 mo (N=39) Adherence=68%	**Comparator 1:** Tai Chi (60 min/d, 1-2 d/wk [supervised] plus 3 d/wk [home-based]) for 12 mo (N=37) Adherence=77% **Comparator 2:** Healthy aging classes (90 min/d, 1 d/wk) for 6 mo (N=56) Adherence=67%	(1) Semantic fluency (2) Attention, concentration, and mental tracking	(1) 60-s Animal Naming Test (2) Digit Span Test	Greater improvements in attention, concentration and mental tracking in the Tai Chi compared to multiple-modality exercise and no-treatment control groups (6 and 12 months). Improvements in both multiple-modality exercise and Tai Chi groups in semantic fluency at 12 months compared to baseline.
Teixeira (2018)[58]	Aerobic and resistance training (20-30 min/d, 3 d/wk) for 6 mo (N=20) Adherence=66.8%	No-treatment control group (N=20) Adherence=Not applicable	**Cognition:** (1) Global cognitive function (2) Memory encoding (3) Memory delayed recall (4) Memory recognition **Neuroimaging:** (5) Cortical and hippocampal volume	**Cognition:** (1) Mini-Mental State Examination (2-4) Rey Auditory Verbal Learning Test **Neuroimaging:** (5) Structural MRI	Greater improvements in memory delayed recall and increase in hippocampal volume in multiple-modality exercise group compared to no-treatment control group.
Vaughan (2014)[50]	Aerobic, resistance, balance, and flexibility training (60 min/d, 2 d/wk) for 16 wk (N=25) Adherence=85.7%	No-treatment control group (N=23) Adherence=Not applicable	(1) Inhibition (2) Verbal fluency (3) Working memory (4) Reaction time (5) Processing speed (6) Executive function	(1) California Older Adults Stroop Test (2) Controlled Oral Word Association Test (3) Letter-Number Sequencing (4) Deary-Liewald Reaction Time Task (5) Trail-Making Test (Part A) (6) Trail-Making Test (Part B)	Greater improvements in inhibition, verbal fluency, processing speed and executive function in the multiple-modality exercise group compared to no-treatment control group

Table 2.3. (Contd.)

First author (Year)	Treatment group(s)	Comparator(s)	Cognitive domain(s) assessed (outcomes)	Cognitive test(s) (measures employed)	Main findings
Vedovelli (2017)[55]	Aerobic and resistance training (60 min/d, 3 d/wk) for 3 mo (N=22) Adherence=100%	No-treatment control group (N=9) Adherence=Not applicable	(1) Attention and working memory (2) Processing speed (3) Executive function (3) Immediate and delayed recall (4) Inhibition	(1) Digit Span Test (WAIS) (2) Trail-Making Test (Part A) (3) Trail-Making Test (Part B) (4) Logical Memory Test I and II (5) Stroop Test	Greater improvements in all cognition outcomes in multiple-modality exercise group compared to no-treatment control group.
Williams (1997)[64]	Aerobic, resistance, and balance training (60 min/d, 2 d/wk) for 12 mo (N=94) Adherence=72%	No-treatment control group (N=93) Adherence=Not applicable	(1) Short-term acquisition and retrieval (2) Nonverbal reasoning ability (3) Nonverbal reasoning ability and problem solving (4) Simple reaction time	(1) Digit Span Test (WAIS-R) (2) Picture Arrangement (WAIS-R) (3) Cattell's Matrices (4) Reaction Time Task	Greater improvements in reaction time and short-term acquisition and retrieval in multiple-modality exercise group compared to no-treatment control group.
Williamson (2009)[53]	Aerobic, resistance, balance, and flexibility training (40-60 min/d, 1-3 d/wk [supervised] and 1-5 d/wk [home-based]) for 24 mo (N=50) Adherence=Not reported	Health and education sessions (weekly to monthly) for 24 mo (N=52) Adherence=Not reported	(1) Psychomotor speed and working memory (2) Inhibition (3) Global cognitive function (4) Short and long-term verbal memory	(1) Digit Symbol Test Substitution (2) Modified Stroop Test (3) Modified Mini-Mental State Examination (4) Rey Auditory Verbal Learning Test	No between-group differences in any of the cognition outcomes.

Note: [a] Secondary outcomes from Küster et al 2016. [b] Secondary outcomes from Gajewski et al 2012. [c] Secondary outcomes from Sink et al 2015. Abbreviations: EEG = electroencephalography; MRI = magnetic resonance imaging; MCI = mild-cognitive impairment; NAI = Neuropsychological Aging Inventory; WMS = Wechsler Memory Scale; WAIS-R = Wechsler Adult Intelligence Scale.

Table 2.4. Overall effects of multiple-modality exercise on cognitive tests compared to competing treatment, active control, and no-treatment control groups.

			Competing treatment		Active control group		No-treatment control		Total	
Cognition Measures	**Studies**	**Sample**	No effect	Improvement	No effect	Improvement	No effect	Improvement	No effect	Improvement
Global cognitive function										
Mini-Mental State Examination	7	405	2	–	1	–	5	1	8	1
Modified Mini-Mental State Examination	2	209	1	–	1	–	–	1	2	1
Montreal Cognitive Assessment	2	136	1	–	–	–	1	1	2	1
Clock Drawing Test	2	88	1	–	–	–	2	–	3	–
Cambridge Contextual Reading Test	1	224	1	–	–	–	1	–	2	–
Clinical Dementia Rating	1	19	–	–	–	–	1	–	1	–
Global Cognitive Function (CBS)	1	127	1	–	–	–	–	–	1	–
Hasegawa Dementia Scale Revised	1	42	–	–	–	–	1	–	1	–
Visuospatial Performance Test	1	42	–	–	–	–	1	–	1	–
Executive function										
Digit Span Test	12	993	7	–	4	–	6	2	17	2
Stroop Test	10	730	2	–	2	–	3	5	7	5
Trail-Making Test (Part B)	10	2191	4	–	1	–	2	5	7	5
Semantic Fluency	6	2169	5	–	3	–	3	1	11	1
Digit Symbol Coding Test	5	1706	2	–	2	–	2	2	6	2
Digit Symbol Substitution Test	4	252	2	–	1	–	1	–	4	–
Controlled Oral Word Association Test	3	323	1	–	–	–	1	2	2	2
Verbal Fluency	3	142	2	–	–	–	2	1	4	1
Letter-Number Sequencing	2	121	–	–	–	–	2	–	2	–
N-Back Task	2	1617	1	–	2	–	1	–	4	–
Task Switching Test	2	1617	1	–	2	–	1	–	4	–
Age Concentration Tests A and B	1	71	1	–	–	–	–	–	1	–
Alertness	1	38	1	–	–	–	–	–	1	–
Boston Naming Test	1	1476	–	–	1	–	–	–	1	–
Cattell's Matrices	1	187	–	–	–	–	1	–	1	–

Table 2.4. (Contd.)

			Competing treatment		Active control group		No-treatment control		Total	
Cognition Measures	**Studies**	**Sample**	No effect	Improvement	No effect	Improvement	No effect	Improvement	No effect	Improvement
Computation Span (ECB)	1	54	1	–	–	–	1	–	2	–
Concentration (CBS)	1	127	1	–	–	–	–	–	1	–
d2: Test of Attention	1	55	1	–	–	–	1	–	2	–
Divided Attention	1	38	1	–	–	–	–	–	1	–
Eriksen Flanker Task	1	1476	–	–	1	–	–	–	1	–
Executive Control Task	1	71	1	–	–	–	–	–	1	–
Flexibility	1	38	1	–	–	–	–	–	1	–
Go/Nogo	1	38	1	–	–	–	–	–	1	–
Groton Maze Learning (CogState Battery)	1	224	1	–	–	–	1	–	2	–
Leistungs-Prüf System 50+	1	55	1	–	–	–	1	–	2	–
One Back Memory (CogState Battery)	1	224	1	–	–	–	1	–	2	–
Picture Arrangement (WAIS-R)	1	187	–	–	–	–	1	–	1	–
Planning (CBS)	1	127	1	–	–	–	–	–	1	–
Random Number Generation Task	1	51	1	–	1	–	–	–	2	–
Reasoning (CBS)	1	127	1	–	–	–	–	–	1	–
Similarities Test (WAIS-III)	1	72	–	–	–	–	1	–	1	–
Memory										
Rey Auditory Verbal Learning Test	4	438	1	–	1	–	2	1	4	1
Rey-Osterrieth Complex Figure Test	4	1705	2	–	2	–	1	1	5	1
Hopkins Verbal Learning Test – Revised	3	1550	–	–	1	–	–	1	1	1
Logical Memory	2	100	1	–	–	–	–	1	1	1
Verbal Learning and Memory Test	2	179	2	–	1	–	1	–	4	–
Emotional Memory Task	1	24	–	–	–	–	–	1	–	1
Free and Cued Selective Reminding Test	1	259	1	–	–	–	–	1	1	1
Free Recall (ADAS-cog)	1	54	1	–	–	–	1	–	2	–
Memory (CBS)	1	127	1	–	–	–	–	–	1	–

Table 2.4. (Contd.)

			Competing treatment		Active control group		No-treatment control		Total	
Cognition Measures	**Studies**	**Sample**	No effect	Improvement	No effect	Improvement	No effect	Improvement	No effect	Improvement
Munich Verbal Memory Test	1	54	1	–	–	–	1	–	2	–
Paired-Associates Learning Task	1	71	1	–	–	–	–	–	1	–
Rivermead Behavioural Memory Test	2	24	1	–	–	–	–	1	1	1
Visual Memory Index Score (CogState Battery)	1	224	1	–	–	–	1	–	2	–
Word List Test (NAI)	1	55	1	–	–	–	1	–	2	–
Processing speed										
Trail-Making Test (Part A)	10	1975	5	–	1	–	3	3	9	3
Simple Reaction Time	4	925	1	–	–	1	2	2	3	3
Choice Reaction Time	3	738	1	–	1	–	2	1	4	1
Choice Movement Time	1	138	1	–	–	–	–	1	1	1
Detection (CogState Battery)	1	224	1	–	–	–	1	–	2	–
Simple Movement Time	1	138	1	–	–	–	1	–	2	–

Note: Empty cells (–) indicate either that the comparison is not applicable, or no significant result were reported. Abbreviations: CBS = Cambridge Brain Sciences cognitive battery; ECB = Everyday Cognition Battery; NAI = Neuropsychological Aging Inventory; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; WAIS-III = Wechsler Adult Intelligence Scale.

2.4 Discussion

In this review, we explored the overall effects of MME compared to competing treatment, active control, and no-treatment control conditions in global and domain cognitive function, and neuroimaging outcomes in older adults without dementia. We also had interest in the characteristics of the MME programs administered in the studies (i.e., frequency, intensity, time and type) with hopes that our findings would aid in informing translation of current findings into practice and provide direction for future research. Our main findings and recommendations are discussed below.

2.4.1 Multiple-modality exercise and cognitive function

Our findings indicated that when compared to competing treatment groups (i.e., cognitive training, physical training, or combined cognitive and physical training), apart from two studies [62,65], the majority of studies indicated that MME was inferior to competing treatments in improving cognition outcomes [38,41,57,59–61,63,67,42,44,47–49,51,54,56]. Similarly, only two studies reported that MME was superior to active control groups (e.g., health and education, stretching and relaxation) in improving cognition [39,43], while the remaining studies including active control groups did not find MME to be superior [42,53,60,61,66,67]. The only scenario in which MME was primarily effective in improving global and domain-specific cognitive function was when compared to no-treatment control groups [40,43,68,69,45,46,50,55,58,62,64,65]. Moreover, as reported in **Table 2.4**, most studies investigated changes in measures of executive functioning, followed by measures of memory, global cognitive function, and processing speed. In all of these measures, apart from one study in which processing speed [43] was improved compared to active control groups, MME was only superior in improving global or domain-specific cognitive function when compared to no-treatment control group.

Important considerations must be made when discussing the lack of superiority of MME in improving cognition when compared to competing treatment or active control groups. For instance, many studies included competing treatment groups that combined both cognitive and physical training [38,42,47–49,51,54]. Considering the studies showing superiority of combining both treatments when compared to MME alone, we observed improvements

in measures of executive functioning [49], processing speed [38,49], and memory [47]. One confounding aspect of these findings is that by receiving both physical and cognitive training, study subjects would receive prolonged exposure to treatment effects during each session. As identified in the study by Damirchi and colleagues [49], participants in the combined treatment group received prolonged intervention (90 to 120 minutes/day, 3 days/week) compared to the MME group (60 minutes/day, 3 days/week). Similarly, two studies showed superiority of cognitive plus physical training sessions lasting longer (i.e., minutes/day) than the MME session (i.e., Linde et al [38] and Shah et al [47], see also **Table 2.3** for more details). Therefore, it remains to be investigated whether a combination of cognitive and physical training can impart improvements to cognition due to intrinsic aspects of these interventions only, or due to prolonged exposure to treatment stimuli.

Nevertheless, considering that MME was not superior to active control groups in seven [42,44,53,60,61,66,67] of nine studies included, we must also consider other factors influencing the effects of MME beyond prolonged exposure to treatment. Active control groups aid in controlling for confounding effects of exercise programs. Effects such as socialization are present when these interventions are administered in sessions with multiple participants exercising together (as reported in the majority of studies included in this section [44,53,60,61,67]). In fact, social interaction may provide significant cognitive stimulation [66] and partially account for improvements in cognition in older adults undergoing intervention programs [71,72]. Furthermore, in a previous review [33], greater effect sizes were observed following exercise in older adults compared to no-treatment control groups, but not in comparison to active control groups [33]. Therefore, the lack of superiority of MME when compared to active control groups could be attributed to effects of socialization. Moreover, for the two studies that showed superiority of MME in comparison to active control groups, one included diabetics [39] and the other included frail older adults [43], which may represent populations suffering from greater health burden, and therefore, are more susceptible to benefit from the MME program. The other studies showing lack of effects of MME in cognition outcomes included healthy or sedentary older adults [44,53,60,61,66,67], and one enrolled patients with MCI [42].

Our findings suggested that only when compared to no-treatment control groups, MME yielded improvements in cognition (i.e., memory [46,55,58,62], processing speed [43,45,50,55,64], executive functioning [45,50,55,62,64,65,68] and global cognitive functioning[40,65,69]). These findings suggest the potential of MME to impart improvements in cognition in individuals with different clinical characteristics, given that the studies included healthy or sedentary older adults [46,50,55,58,62,64], as well as frail [40,43,45], obese [65], and MCI [69] individuals. Nevertheless, caution must be exercised when interpreting these findings, as essential limitations must be considered. For instance, three of the included studies were non-randomized (i.e., quasi-experimental), and therefore, bias is inflicted in study results owing to confounding factors (e.g., selection bias). Another confounding variable introduced by including no-treatment control groups is that participants exposed to MME interventions are also exposed to other factors such as, attention and social interaction (as mentioned above). This is a crucial aspect of the studies included, since six [40,43,45,50,62,69] of the included studies explicitly reported that the MME sessions were administered in groups of at least 3 participants.

Altogether, the literature suggests MME may be an effective strategy to improve global and domain-specific cognitive function; albeit, there is limited evidence from studies including active control or competing treatment groups. Considerations and limitations regarding the MME protocols administered in these studies are discussed in the subsequent sections.

2.4.2 Effects of multiple-modality exercise in neuroimaging outcomes

Among the secondary objectives of our review was to report and discuss the current evidence on the effects of MME on neuroimaging outcomes. Evidence from nine of 33 studies suggested mixed effects of MME on white matter structure, but more consistent effects on cortical and subcortical grey matter, as discussed below.

Fissler and colleagues [59] reported no differences in white matter integrity (i.e., fractional anisotropy) in older adults with SMI following cognitive training or MME, compared to a no-treatment control group. Conversely, Callisaya and colleagues [39] reported

improvements in fractional anisotropy in older adults with diabetes compared to an active control group, and Rehfeld and colleagues [41] noted greater increases in white matter in temporal and occipital lobes following MME compared to dance training. Dance training, nonetheless, yielded greater changes in the white matter of other brain regions (see **Table 2.3**) suggesting training-specific adaptations. Although the evidence is limited, these findings suggest that MME may be effective in imparting improvements in white matter, however, the extent to which these improvements are superior to other interventions (e.g., dance training or cognitive training) warrants further exploration. Some relevant contrasts among these studies must also be considered. Fissler and colleagues [59] included older adults with SMI, a marker of increased risk of dementia [73], while Callisaya [39] studied older individuals with diabetes—comprising a different risk profile for dementia [74]—and Rehfeld and colleagues included only healthy individuals [41]. The most notable difference between studies, however, could be the length of these programs, with one lasting only 10 weeks [59], while the other two studies [39,41], which showed in part positive effects of MME on white matter outcomes, lasted 6 months. As such, longer intervention periods may result in greater positive changes in white matter.

Regarding changes in the grey matter of cortical and subcortical structures, compared to no-treatment control groups, Ji and colleagues [46] reported that MME was associated with increases in cortical grey matter (e.g., dorsolateral prefrontal cortex, posterior cingulate/precuneus cortex), while Teixeira and colleagues [58], reported increases in hippocampal volume. In comparison to active control groups [39,70], MME was associated with greater increases in total brain volume [39] and hippocampal volume [39,70]. Furthermore, among the studies included, Ji and colleagues [46] were the only ones to investigate functional connectivity changes via fMRI. Using a resting-state fMRI protocol, the authors reported increased functional connectivity between the posterior cingulate cortex/precuneus and the right striatum, and other regions compared to controls—while controls suffered atrophy of the striatum region, suggesting protective effects of MME.

Altogether, the main findings of MRI and fMRI studies point towards MME imparting positive changes in brain function and structure, particularly marked by multiple studies

reporting significant increases in hippocampal volume [39,58,70]. Clinically, these results could have relevance to prevent and/or delay onset of cognitive impairment. Both hippocampi are implicated in memory function [75–77], and are hallmark regions where pathophysiological changes in MCI and early/prodromal stages of Alzheimer's disease occur (e.g., amyloid beta deposition) [78], including cortical atrophy proceeding Alzheimer's disease diagnosis [79]. Nonetheless, three of the studies reporting positive effects of MME were non-randomized interventions [46,58,59] and their findings should be interpreted with caution. We must also acknowledge that the neuroimaging findings reported in this review are limited owing to the unclear association, or pathway, underlying changes in neuroimaging outcomes that result in cognitive changes. For example, it is not possible to establish a direct connection between increased hippocampal volume and improved memory performance based on the results we gathered from these studies. That is, most studies either did not show [46,59] (or report [39,41,58,70]) a direct statistically significant association between changes in both outcomes. Granted, with small sample sizes, these associations would most likely be underpowered. With these considerations, future research is necessary.

Finally, three studies explored EEG outcomes as surrogate measures of brain activity [42,44,60]. All three studies included competing treatment groups and their results suggested that MME was not superior to other treatment conditions in improving resting-state and task-based brain activity. For instance, in an early study Gajewski and Falkenstein [44] reported that cognitive training yielded higher improvements in event-related brain action potentials associated with response selection, allocation of cognitive resources, and error detection compared to MME. Similarly, in a secondary study, the same authors [60] reported improvements in underlying processing associated with working memory following cognitive training only. Accordingly, Styliadis and colleagues reported additive effects of combining cognitive and physical training in resting-state electrophysiological brain activity in the precuneus/posterior cingulate cortex compared to MME alone [42]. Overall, these findings suggest that MME alone has limited influence in brain activity measured via EEG outcomes when compared to competing treatment groups. Owing to limited literature included in this review, this topic needs to be further explored.

2.4.3 Recommendations and future directions

In this review, we report that when compared to no-treatment control groups, MME seems to impart positive effects in various cognitive domains [40,43,68,69,45,46,50,55,58,62,64,65]. Owing to limitations and confounding factors, however, the quality of the evidence is uncertain, and more research is necessary.

One key aspect to be further investigated is whether compliance with international guidelines for exercise in older adults and increasing adherence to exercise will aid in strengthening the effects of MME on cognitive function. For example, for the studies included in this review, the average frequency of MME sessions was 3.1 (SD=1.5) days/week, lasting on average 62.7 (SD=15.5) minutes/day. However, the average time spent in each MME component was 32.6 (SD=13) minutes/day for AET, 23.6 (SD=11.3) minutes/day for RET, and 16.9 (SD=10.3) minutes/day for balance/flexibility component. In this context, the average time per component is relatively low compared to recommendations of exercise frequency, intensity and time for older adults by the American College of Sports Medicine and the American Heart Association [31,80]. It is important that future research addresses whether complying with recommendations would yield greater benefits to cognition above and beyond confounding variables influencing cognition (e.g., socialization). This is pertinent when contemplating that previous studies have provided strong evidence for the positive effects of AET [20] and RET [26] on cognition. These are examples of well-conducted RCTs, with detailed exercise programs, and measures of cognitive function sensitive to the effects of exercise [20,26]. Consequently, with a detailed MME program, administered with appropriate frequency, duration and intensity, it is plausible to expect additive effects of combining AET and RET, and potentially balance/flexibility training, on physical function and performance. These effects could then translate into improvements in the underlying neurophysiological mechanisms evoking positive cognitive changes [5,81].

The exercise literature has suggested two main neurotrophic factors underlying neurophysiological changes upregulated by exercise: brain-derived neurotropic factor (BDNF) [16,82], and insulin-like growth factor 1 (IGF-1) [83]. Only six of the 33 studies included in this review measured changes in BDNF [40,41,49,50,55,69]. In part of these studies,

MME was associated with improvements in BDNF in cognitively healthy individuals [40,50,55,69], and in those with MCI [69]. In neither of these studies, did the authors comment on whether changes in cognitive function were statistically associated with changes in BDNF levels, which would strengthen BDNF as a mediator of treatment effects [50,55,69]. Further, all of these studies included only no-treatment control groups. When compared to competing treatment groups, MME did not have the same effects in BDNF [41,49]. Unfortunately, only one study included IGF-1 [65] as an outcome, and no differences between groups were seen. Thus, the effects of MME on neurotrophic factors warrants further investigation.

Finally, due to heterogeneity across studies, it was challenging to gather and harmonize information on the elements of the exercise programs administered (i.e., frequency, intensity, time and type). In this perspective, future studies should consider a standardised and detailed method of reporting exercise training protocols, which will facilitate appreciation and understanding of the effects of exercise on variables of interest [32]. To this end, we suggest reporting on exercise training variables following previous recommendations [31,32], including the following: a) exercise frequency (e.g., days/week); b) objective or subjective measures of intensity (e.g., target HR, RPE, maximum repetitions etc.); c) time allocated to each component (e.g., minutes/day) and d) type of exercise administered (e.g., running, walking, machine-based, bodyweight). We hope these recommendations will aid future research and improve the current evidence on the effects of MME to cognition and overall brain health in older adults without dementia. If with stronger study designs, clearer training methodology and well-defined study populations, MME is proven to be efficient, it will then be plausible to discuss long-term effects and follow-ups, feasibility, and translation of these programs in real world community-settings [32].

2.4.4 Limitations

Our scoping review has important limitations. We only included articles published in English between 1990 and 2019. We also included quasi-experimental studies that otherwise met the inclusion criteria. While the results from these non-randomized intervention studies aid in understanding the current state of the evidence, they have the

potential to be strongly bias and should be interpreted with caution. The studies included in this review mostly enrolled women and no sex- or gender-based sensitivity analysis were considered in the majority of the studies, apart from Sink and colleagues [66]. Therefore, we were not able to consider how these factors can influence our results and conclusions. Furthermore, many studies included different types of tests to assess cognitive function with inconsistences between the cognitive outcomes and domains being measured. We classified these cognition tests under four broader domains (i.e., global cognitive function, executive functioning, memory, and processing speed) to facilitate and contextualize our results, which limits our ability to report on the effects of MME on subdomains as originally intended in each study. Nonetheless, we provide details of each specific test and main findings (see **Tables 2.3** and **2.4**). In addition, a scoping review is an enormous undertaking and only one of the co-authors was able to perform the literature search (NCBSS) under the supervision of the senior author (RJP), which creates the risk for missing potential papers for inclusion—although to minimize this risk, we searched previous reviews and articles for potentially eligible sources of evidence [35].

2.5 Conclusions

We investigated the effects of MME on cognition and neuroimaging outcomes in older adults without dementia. Our findings indicated that MME has the potential to impart positive changes in global and domain-specific cognitive function, as well as white matter, cortical grey matter and hippocampal volume when compared to no-treatment control groups. The lack of superiority of MME when compared to competing treatment (e.g., cognitive training) or active control (e.g., health education programs) suggests that extrinsic factors could yield improvements independent of MME-induced neurophysiological effects. Noteworthy, summary data from the MME protocols administered, including frequency, intensity and time of MME programs administered in the studies did not seem to be fully aligned with current guidelines for exercise for older adults, which could have hindered MME effects in the outcomes studied. Additionally, it is plausible that combining different treatment conditions may provide additive effects to

cognitive function, however, the feasibility of such programs to be translated to real world settings remains to be explored in future research.

Summary

In this chapter, a report was provided on the current state of evidence regarding the influence of multiple-modality exercise on cognition and neuroimaging outcomes in older adults without dementia. The literature search was conducted for studies investigating the effects of multiple-modality exercise on global and domain-specific cognitive function (e.g., executive functioning, memory), as well as neuroimaging of brain structure and function. The findings of these studies suggested that multiple-modality exercise improved global cognition, executive functioning, processing speed, and memory largely when compared to no-treatment control groups. Additionally, multiple-modality exercise improved white matter, cortical grey matter, and hippocampal volumes when compared to no-treatment control groups. When compared to active control groups (e.g., health education programs) or competing treatment groups (e.g., cognitive training), multiple-modality exercise was not effective in improving these outcomes.

Ultimately, the findings from this chapter suggest that although multiple-modality exercise may improve cognition and neuroimaging outcomes in older adults without dementia, confounding factors may account for these effects. This is supported by findings showing that multiple-modality exercise does not seem to evoke similar effects in studies including competing treatment or active control groups. Within this context, Chapter 3 reported whether combining multiple-modality exercise with mind-motor training would impart greater benefits to cognition compared to multiple-modality alone, and later, in Chapter 5, these effects where explored in neuroimaging outcomes in older adults with subjective cognitive complaints.

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Chapter 3

3 Cognitive changes following multiple-modality exercise and mind-motor training in older adults with subjective cognitive complaints: The M4 Study

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3.1 Introduction

Findings from laboratory work and clinical trials for the treatment of dementias (e.g., Alzheimer's disease) have consistently produced disappointing results, with the possibility of a single cure being very unlikely [1,2]. As a result, strategies to prevent and treat cognitive decline early in life have gained increased attention [2]. Indeed, the focus of research has started to shift from stages in which the disease has been established to preclinical or even asymptomatic stages [3]. This shift is extremely important since underlying pathophysiological process of dementia may take place decades before disease diagnosis occur [3]. In this perspective, the identification of biomarkers and the management of modifiable risk factors seem to be of greatest priority [2,4]. Of particular interest, cognitively healthy older adults with subjective cognitive complaints (SCC) [5] may represent a portion of the population experiencing early signs of cognitive decline due to underlying pathological changes before the onset of clinical impairment [6,7].

Although these individuals demonstrate preserved cognitive function in traditional neuropsychological tests—therefore, not meeting the criteria for mild-cognitive impairment (MCI) or dementia—they often report cognitive complaints relating to worsening of memory and thinking skills [8]. In fact, SCC has been associated with poorer scores in objective cognitive assessments [9], the establishment of clinical impairment

nearly 2 decades after first report [10], and greater health care utilization [11]. More strikingly, older adults with SCC show patterns of cortical and hippocampal atrophy similar to that of patients with the diagnosis of MCI [12]. These observations suggest that older adults with SCC compose an ideal target group for early-in-life intervention programs aiming at mitigate cognitive impairment, which could culminate in the best clinical outcomes [2,13] and alleviate burdens on the health care systems worldwide [11].

Habitual participation in aerobic exercise (AET) interventions alone [14] or combined with mind-motor training [15] appears to benefit cognition in individuals without known cognitive impairment and in those with dementia [16]. Despite promising evidence, the impact of AET on cognitive function in the aging population remains equivocal [17], particularly in those with SCC. Colcombe and Kramer [18] conducted a meta-analysis of 18 interventions and found a significant effect of AET on cognition, with a greater effect on executive functioning. Colcombe et al [19] also observed improvements in brain plasticity after 6 months of progressive AET compared to a stretching group. Similarly, after 6 months of a moderate-intensity exercise program, Lautenschlager et al [20] observed improved cognitive scores in older adults with cognitive impairment compared to a usual care group. Erickson et al [21] found that following a 12-month moderate-intensity AET regimen, healthy older adults showed growth in volume in anterior hippocampal regions, while hippocampal atrophy was seen over the same period in the active control group. Smith et al [22] observed improvements in neural efficiency during semantic memory retrieval tasks in older adults with MCI following a 12 week moderate intensity, treadmill-based AET regimen. Finally, Ten Brinke et al [23] found that 6-months of moderate intensity, walking-based exercise increased hippocampal volume among older adults with probable MCI compared to a balance and toning control.

Although AET training is related to improvements in cognition, a recent Cochrane review suggests there is insufficient evidence to conclude that cognitive improvements are solely attributable to improved cardiovascular fitness [24]. As well, findings from other meta-analytic studies indicate lack of consistency across different exercise studies, which could mostly be due to variability in cognitive tests applied, sensitivity of cognitive tests to detect treatment effects, and cognitive and physical health at baseline [17,25]. Furthermore,

several aspects of these investigations may raise concerns regarding the feasibility of exercise protocols administered in such laboratory settings (i.e., real-world applicability and translation to community settings). Moreover, most studies have failed to comply with current guidelines for exercise in older adults with regards to exercise type, intensity, frequency and duration [26].

These guidelines also emphasize the importance of multiple-modality exercise programs over single-modality exercise programs to enhance overall health and quality of life in the general population of older adults [26,27], although evidence is still limited in more specific groups (e.g., individuals with SCC). The evidence is even more scarce with regards to multiple-modality exercise interventions and cognitive function in older adults at risk for dementia. As such, more research is warranted. In addition, from a clinical and scientific perspective, exploring the combination of multiple-modality exercise with alternative, and perhaps more feasible (e.g., group-based, low-cost, and easily administered), forms of mind-motor training (simultaneous cognitive and physical engagement) on cognitive outcomes may provide further support for optimal exercise interventions to improve overall health and promote additive benefits to cognitive function in older adults at risk for cognitive impairment [26].

Square-stepping exercise (SSE) [28] is a novel form of mind-motor training that has been associated with positive effects on global [29] and domain-specific cognitive functioning [29,30] in older adults. Although no investigation on the specific physiological mechanisms were conducted in these studies, we postulate that these improvements could be attributable to increased neuroflexibility and/or plasticity, which in turn is a result of exercise-induced synaptogenesis and angiogenesis in the brain, particularly in brain regions associated with executive functioning and working memory[14,31]. The SSE program is a simple, low-cost, indoor, group-based exercise program designed to improve fitness of the lower extremities and serve as a strategy to prevent falls in older adults [28,32].

Results from short-term studies [28,32] showed that the SSE was equally as effective as strength training and more effective than a weekly walking session to improve lower-extremity function and reduce fall risk factors. Although the impact of SSE on cognitive

function remains relatively unknown, pilot work suggests the potential for SSE to benefit cognition. Teixeira et al [29] observed improvements in global cognition, attention, and mental flexibility among cognitively healthy older adults following 16-weeks of SSE. These findings were advanced by Shigematsu et al [30] who investigated the cumulative impact of SSE training over 6 months on cognition among non-demented, community-dwelling older adults. Although improvements in memory were observed following both training regimens, improved executive functioning was reserved for those performing SSE on a weekly basis. Moreover, SSE is an innovative, inexpensive, and easily employed group exercise program, lending itself as a mind-motor task that may be easily incorporated into standard exercise programs for older adults.

There is some research to support the notion that aerobic and other forms of exercise may impart improvements to cognition in older adults; as well, the preliminary findings suggest the potential utility of SSE as an exercised-based cognitive intervention; it remains unclear, however, whether older adults showing signs of early cognitive deterioration are susceptible to improvements in cognition following multiple-modality exercise with additional mind-motor training. Thus, we investigated the effects of group-based based, multiple-modality exercise with additional SSE on cognition compared to multiple-modality exercise alone in older adults with SCC living in the community.

3.2 Methods

3.2.1 Study design

The M4 Study was a two-arm randomized controlled trial (RCT) implementing a 24-week intervention program with a 28-week no-contact follow-up [33]. Assessments were performed at baseline, 24 weeks (intervention endpoint) and 52 weeks (study endpoint). After baseline assessments, participants were randomized to either the multiple-modality exercise with mind-motor training intervention group (Multiple-Modality, Mind-Motor [M4]) or to the multiple-modality exercise active control group (Multiple-Modality [M2]). The randomization sequence was computer generated and concealed envelopes were used to assign group status. All assessors were blinded to group assignment.

3.2.2 Participants

Details of the M4 Study participants and eligibility criteria have been published [33,34]. The study included community-dwelling older adults aged 55 years or older, who self-reported a cognitive complaint (defined answering positively to the question "Do you feel like your memory or thinking skills have got worse recently?") [35]. Subjective cognitive complaints are defined as a subjective perception of cognitive deterioration by an individual or their peers, even though the individual may seem to perform well in neuropsychological tests, and may not demonstrate signs of objective cognitive impairment [13,36,37]. As well, we included individuals who were fully independent in functional activities (maximum score in the Lawton-Brody Instrumental Activities of Daily Living scale [8/8]) [38]. Individuals were excluded if they had a diagnosis of dementia and/or scored < 24 on the Mini-Mental State Examination (MMSE) [39], had major depression, recent history of severe cardiovascular conditions, any neurological and/or psychiatric disorders, or were unable to comprehend the study letter of information.

The study was registered with ClinicalTrials.gov on 29 April 2014 (Identifier: NCT02136368). The Western University Health Sciences Research Ethics Board approved this project and all participants provided written informed consent prior to participating in the study.

3.2.3 Multiple-modality exercise intervention

Participants in both groups received 45 minutes of group-based, standardized, multiple-modality exercise (described below) [33]. The M4 group performed an additional 15 minutes of mind-motor training (i.e., SSE), whereas the M2 group underwent 15 minutes of active control condition focused on balance, range of motion, and breathing exercises. In total, participants in both groups exercised 60 minutes/day, 3 days/week for 24 weeks.

The multiple-modality exercise intervention incorporated a 5-minute warm-up, 20-minute AET, 5-minute cool down, followed by 10 minutes of resistance training (see **Supplementary Table 3.1 in Appendix B**) and 5 minutes of stretching. We prescribed AET intensity via target heart rates (HR) determined at baseline using the STEP^{TM} tool

[40]. During the AET component, participants were encouraged to keep their HR at 65-85% of their predicted maximum HR (HRmax) and/or at a rating of 5-8 on the 10-point modified Borg Rating of Perceived Exertion (RPE) scale [27]. We conducted HR monitoring part way through and at the end of the AET component during each exercise session. Participants were instructed to record HR and RPE immediately after each monitoring in a training log provided by the research team. Target HR was recalculated at 12 weeks to adjust for short-term cardiorespiratory adaptations.

3.2.4 Comparator intervention

The comparator group underwent additional 15 minutes of balance, range of motion, and breathing exercises, prior to the 5 minutes of stretching. This component of the intervention was focused on low-intensity exercises without use of any additional loading (e.g., hand weights or resistance bands), with HR maintained below target zone, and was deemed as a suitable active control condition, as these exercises have not been found to impart cognitive benefits [33]. Participants performed 10 minutes of static (e.g., postures in narrow stance, tandem stance and single leg stance), dynamic (e.g., walk tandem line on heels or toes) and functional balance (e.g., changing direction on cue, walking with head turns). The session ended with 5 minutes of range of motion exercises (e.g., shoulder, hip and wrist circles) and was accompanied by either standing or sitting breathing exercises.

3.2.5 Mind-motor training intervention

In addition to the multiple-modality exercise intervention, participants within the M4 group also performed SSE training [28], prior to the 5 minutes of stretching. The SSE program is a group-based intervention performed on a gridded floor mat (2.5 m × 1 m) containing 10 rows with 4 equal-sized squares per row. The training protocol entails the reproduction of previously demonstrated complex stepping patterns on the SSE mat (see **Figure 3.1**). The stepping patterns are demonstrated by an instructor and participants are expected to memorize, and further attempt to reproduce each stepping pattern by memory. Instructors could not physically intervene, but in instances where participants were having difficulty reproducing the SSE patterns, they were provided oral cues.

There are more than 200 stepping patterns created for SSE [28], and the complexity of these stepping patterns is given according to the number of steps per pattern, as well as the order and direction of foot placement across the SSE mat. In our study, the SSE sessions were carried out in groups of no more than 6 participants per mat. To ensure equal group progression throughout the program, the complexity of the stepping patterns within each session was increased only when the majority of participants (i.e., 75%) had successfully performed a given stepping pattern at least four times. The goal was to progress through as many SSE patterns as possible over the 24-week intervention period. Additionally, to create a positive social atmosphere, participants were encouraged to assist one another other as necessary, by providing cues to accurately perform the stepping patterns.

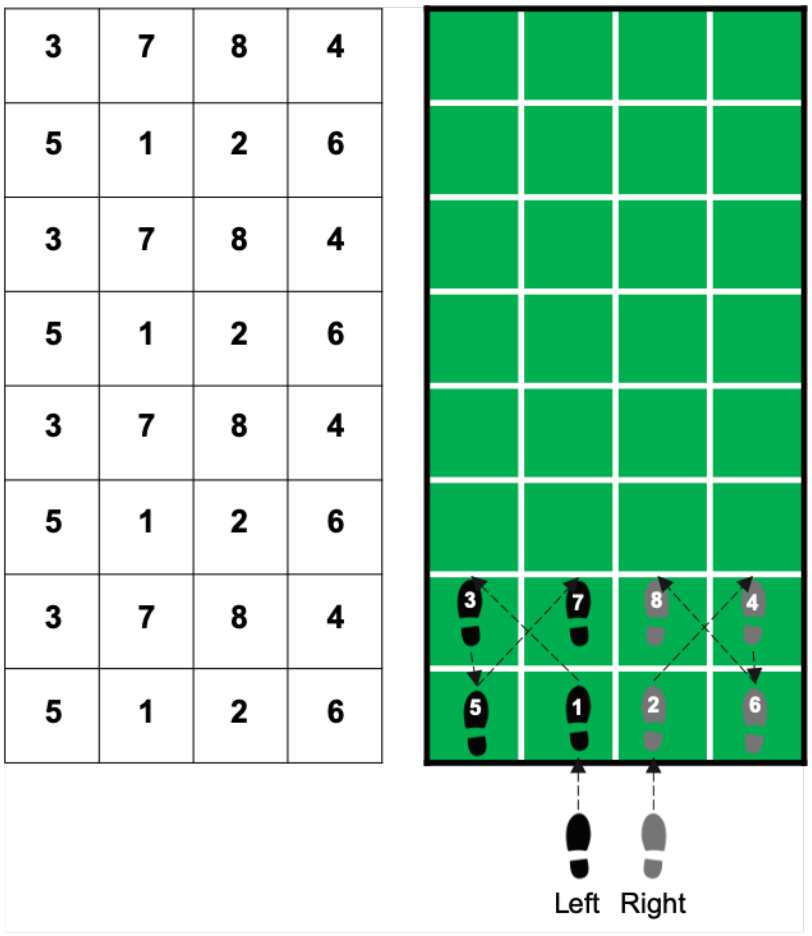

Figure 3.1. Square-stepping exercise.

Note: Illustration of the square-stepping exercise training protocol. The numbers indicate the order in which the steps are performed, the arrows indicate the sequence.

3.3 Study assessments

3.3.1 Descriptive variables

Baseline assessments were performed after obtaining written informed consent and prior to participant randomization. Neuropsychological assessments were performed using the MMSE, the Montreal Cognitive Assessment (MoCA), [41] and the Centre for Epidemiological Studies Depression Scale [42]. Participant clinical and demographic data included: age, sex, race, medical history, weight, height, body mass index, and 24-hour blood pressure. Additionally, we assessed cardiorespiratory fitness (predicted maximal oxygen consumption [pVO_2 max]) at baseline, and again 24 and 52 weeks for further exploratory analyses using the STEP tool [40].

3.3.2 Cognition outcomes

Outcome assessment was performed at baseline, 24 weeks (intervention endpoint) and 52 weeks (after a 28-week no-contact follow-up) using the Cambridge Brain Sciences (CBS) computerized cognitive battery [43] (https://www.cambridgebrainsciences.com/). The CBS contains 12 non-verbal cognitive tasks that cover four broad cognitive domains (i.e., concentration [3 tasks], reasoning [3 tasks], planning [2 tasks], and memory [4 tasks]) and correlates highly with measures of general fluid intelligence [44] (see [33] for full CBS description). These tasks are fully automated and have been used to effectively evaluate cognition in several large-scale, population-based studies [43]. It is an adaptive testing platform that randomly generates novel versions of the tasks between individual trials and can be administered within 60 minutes, thereby, it is believed that the CBS can minimize practice effects and participant fatigue compared to paper-based neuropsychological assessments.

The CBS was administered on the first day of assessments for familiarization purposes (short version) and re-administrated on the second day of assessments for data collection (full version). We used data gathered from participants' performance in the CBS to create composite scores [45]. These composites scores were derived by first converting all individual outcomes from the CBS tasks to standardized *z* scores. Next, standardized scores were averaged within each one of the four cognitive domains, then domain-

specific composite scores were averaged to create a global cognitive functioning (GCF) score, ensuring that the four cognitive domains were weighted equally.

The study primary outcome was differences between groups in estimated mean change from baseline to 24 weeks in GCF. Secondary outcomes included changes at 52 weeks in GCF and changes in composites scores of concentration, reasoning, planning, and memory at 24 and 52 weeks.

3.3.3 Sample size

Results from a previous meta-analysis indicated that exercise would have an overall effect on cognition with a moderate effect size ($d = 0.48$) [18]. No study to date, however, has observed the effect of a 24-week multiple-modality exercise program with mind-motor training on GCF in community-dwelling older adults. In addition, although the CBS is grounded in well-validated neuropsychological tests [43], it has not been used to date as an outcome in published exercise intervention studies. For these reasons, sample size for the proposed study was approximated by using the effect size approach, combined with feasibility and comparisons to sample sizes used in other similar studies [20,35]. Hence, we determined that a sample size of 52 participants per group would have an 80% power at the 5% significance level to detect an effect size of $d = 0.55$. Considering a dropout rate of 20%, our final sample size was estimated at 65 participants per group.

3.3.4 Statistical analysis

We conducted linear mixed models for repeated measurements [46] to assess differences between groups in mean change from baseline to 24 weeks. Within the models, we also examined differences between groups from baseline to 52 weeks, and differences within groups from baseline to 24 and 52 weeks. The terms included in the models were: group, time, and group × time. Time was modeled categorically using two indicator variables representing each time point (baseline as reference category). All analyses were performed using the intent-to-treat approach, including all randomized participants, regardless of compliance with the program and follow-up assessments [46]. An advantage of the mixed effects regression modeling approach is that it does not require each participant to have the same number of measurements, provided that data are missing at

random (i.e., after taking observed data into account, there are no systematic differences between participants with complete data as compared to those with missing data). This is also an assumption made by most multiple imputation methods [46]. We also performed a sensitivity analysis including only those who completed the study assessments at all time points. As well, for the main outcomes of the study, we conducted analyses adjusting for global cognitive functioning at baseline (MoCA scores). Interpretation of study results were primarily based on mean estimation and associated 95% confidence intervals.

Finally, additional analyses were conducted using linear regression models to investigate whether change in cardiorespiratory fitness (pVO_2max) would be associated with change in the study outcomes following previous methods [21,47]. For this purpose, change scores from baseline to 24 and 52 weeks for all cognition outcomes as well as for pVO_2max were calculated and included in the models adjusting for age, gender, and years of education. If pVO_2max significantly predicted changes in cognition, a mediation effect would be assumed. All analyses were performed using IBM® SPSS® Statistics for Mac, Version 21 (Armonk, NY: IBM Corp).

3.4 Results

3.4.1 Enrollment, randomization, and adherence

This study was conducted between January 13, 2014 and March 14, 2016. Participants were enrolled in 4 waves of assessments and intervention over a period of 14 months. During the screening process, 169 individuals were assessed for eligibility; 11 did not meet the inclusion criteria and 31 declined to participate. Thus, 127 participants were included and randomized to either the M2 (n=64) or M4 (n=63) groups,109 participants attended assessments at 24 weeks, and 102 returned for the final assessments at 52 weeks (see **Figure 3.2**). Participants had completed the study and the average attendance to the exercise sessions was 72% for the M2 group (52 out of 72 sessions) and 68% for the M4 group (49 out of out of 72 sessions).

A two-sided independent samples t-test revealed no significant differences between groups in participant average attendance (p = .3). At the end of the intervention, participants in the M4 group had achieved the Advanced Level 3 of the SSE program,

with stepping patterns ranging from 12 to 16 steps, and with steps performed in a broad range of directions (backwards, diagonal, and backwards diagonal), as well as with stepping patterns incorporating wide and long steps (3 to 5 squares between feet). Considering attendance level and program achievement, the SSE program was shown to be feasible in this specific population (i.e., older adults with SCC) and no study-related adverse events were recorded.

Table 3.1 provides the baseline descriptive characteristics of the 127 participants. Overall, the study participants were mostly Caucasian, highly educated and presented with signs of cognitive deterioration based on mean MoCA scores. Further observation of the domain-specific MoCA scores revealed that participants in both groups showed low scores in the delayed-recall memory composite, which indicates memory loss may possibly be underlying the nature of the self-reported SCC. As well, even though participants involved in the study were high-functioning and lived independently in the community, pVO_2max assessment yielded classification of 'poor' to 'fair' cardiorespiratory fitness compared to age and gender reference values [48].

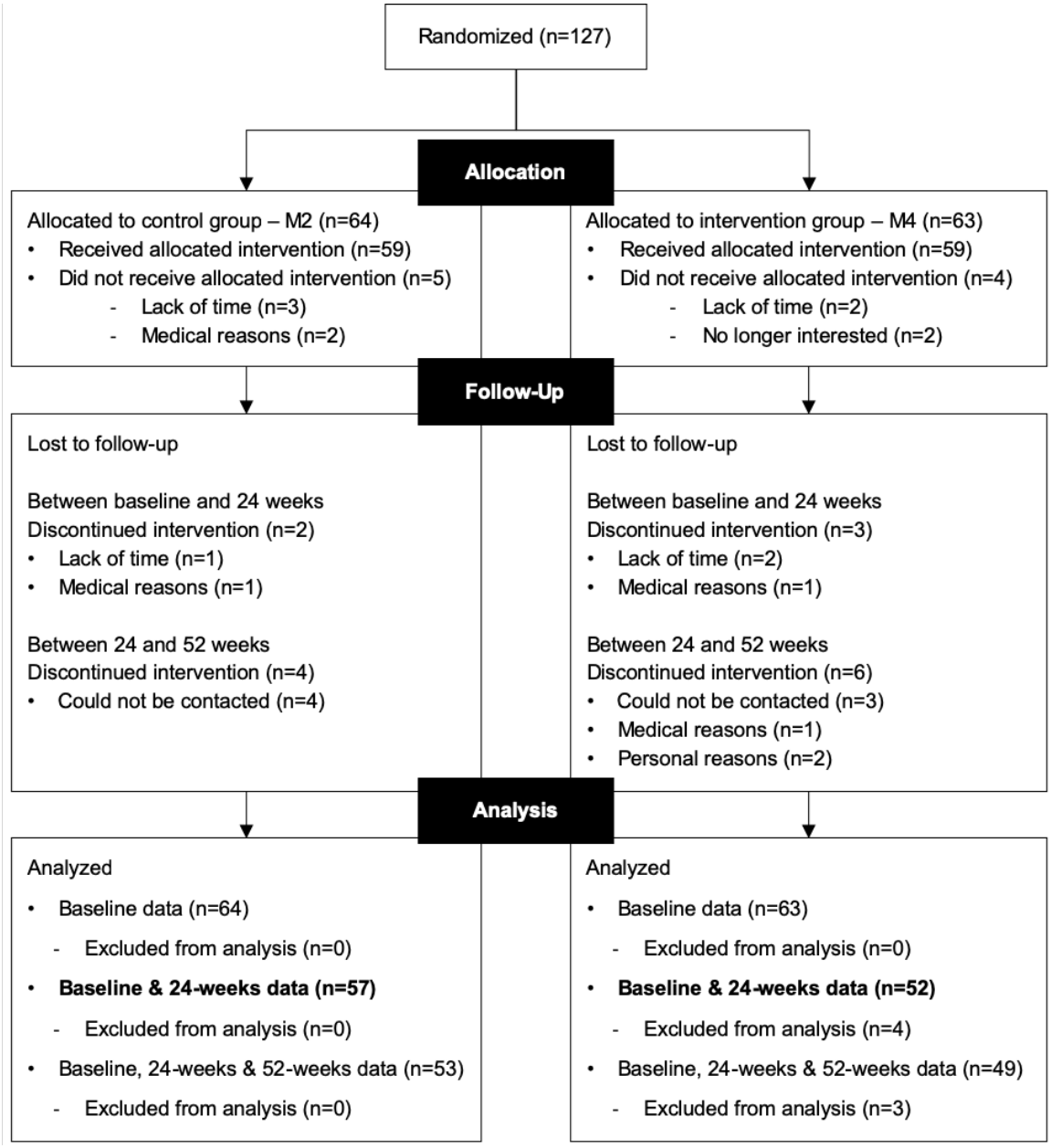

Figure 3.2. Flow of participants in the 24-week randomized controlled trial with a 28-week no-contact follow-up.

Note: For the M4 group, data from 4 participants were missing at 24 weeks and, therefore, not included in analyses.

Table 3.1. Baseline characteristics of study participants by randomization group.

Variables [a]	M2 (n = 64)	M4 (n = 63)
Demographics		
Age, yr	67.4 (7.2)	67.6 (7.5)
Women	46 (71.9%)	44 (69.8%)
Caucasian	62 (98.4%)	61 (96.8%)
Education, yr	13.8 (3)	13.3 (2.7)
MoCA, score	25.6 (2.4)	25.3 (2.7)
Visuospatial/Executive (/5)	4 (2)	4 (2)
Naming (/3)	3 (0)	3 (0)
Attention (/6)	6 (1)	6 (1)
Language (/3)	3 (0)	3 (0)
Abstraction (/2)	2 (0)	2 (0)
Delayed recall (/5)	3 (2)	3 (2)
Orientation (/6)	6 (0)	6 (0)
≤ 12 years of education	19 (30%)	15 (24%)
MMSE, score	29.2 (1)	29 (1.2)
CES-D, score	9.4 (7.4)	10 (8.9)
24-hour systolic BP, mmHg	129.6 (15.2)	126.5 (11.3)
24-hour diastolic BP, mmHg	74.2 (8.3)	72.2 (8.1)
Weight, kg	80.8 (17.7)	80 (13.8)
Height, m	1.65 (0.1)	1.65 (0.1)
BMI, kg/m^2	29.7 (6.2)	29 (4.1)
pVO_2max, ml/kg/min	26.8 (8)	27.1 (7.9)
Medical history, *n* (%)		
Hypertension	32 (50%)	36 (57.1%)
Hypercholesterolemia	23 (35.9%)	28 (44.4%)
Type 2 diabetes	5 (7.8%)	7 (11.1%)
Myocardial infarction	4 (6.3%)	5 (7.9%)
Atrial fibrillation	-	3 (4.8%)
Angina/coronary artery disease	1 (1.6%)	2 (3.2%)
Aneurysm	1 (1.6%)	2 (3.2%)
Former smoker	28 (44.4%)	29 (46%)
Current smoker	1 (1.6%)	1 (1.6%)
Study outcomes, z scores		
GCF	.058 (.638)	–.047 (.687)
Concentration	.008 (.788)	–.008 (.746)
Reasoning	.041 (.707)	–.041 (.838)
Planning	.091 (.76)	–.092 (.96)
Memory	.091 (.824)	–.047 (.803)

Note: [a] Data presented either as mean (standard deviation) or no. (%) where applicable. [b] Domain-specific MoCA scores presented as median and interquartile range.

Abbreviations: GCF = global cognitive functioning; M2 = multiple-modality group; M4

= multiple-modality, mind-motor group; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; CES-D = Centre for Epidemiological Studies Depression Scale; BP = blood pressure; pVO_2max = predicted maximal oxygen consumption.

3.4.2 Study outcomes

At 24 weeks, no significant differences between groups in estimated mean change from baseline were observed for any outcomes (**Table 3.2**). The M4 group, however, demonstrated trends for greater improvements in GCF ($p = .07$) and memory ($p = .07$) compared to the M2 group. Although there were only trends for statistically significant differences between groups, both groups demonstrated improvements in GCF (**Figure 3.3),** concentration, and reasoning, and the M4 group also showed improvements in planning and memory at 24 weeks (**Figure 3.4**). At 52 weeks, the M4 group showed greater GCF ($p = .02$) and memory ($p = .03$) scores compared to the M2 group (**Table 3.2**). Both groups also retained improvements in GCF (**Figure 3.3**), concentration, reasoning, and planning, and the M4 group retained improvements in memory (**Figure 3.4**). Complete case analysis resulted in similar findings to those from the intent-to-treat analysis (**Table 3.2**).

3.4.3 Secondary analyses

Additional analyses were conducted to understand possible associations between cardiorespiratory fitness (i.e., pVO_2max) and cognition. At baseline, pVO_2max was positively associated with GCF ($r = .20$, $p = .006$), concentration ($r = .24$, $p = .004$), planning ($r = .18$, $p = .02$) and memory ($r = .17$, $p = .025$), but not reasoning. Following the 24-week intervention period, change in pVO_2max was positively associated with change in concentration ($r = .23$, $p = .02$), but unrelated to change in the remaining outcomes. The association between changes in pVO_2max and concentration was driven by the M4 group, showing a significant effect ($F_{(1, 45)} = 4.8$, $p = .03$, $r = .30$), whereas the M2 group did not ($p = .33$). No other associations were observed either at 24 or 52 weeks. **Table 3.3** shows the results of the regression models.

Table 3.2. Differences between groups in the study outcomes.

	Differences between groups (95% confidence interval) [a]			
Outcomes [b]	24 weeks	*p* Value	52 weeks	*p* Value
GCF				
Intent-to-treat analysis	.11 (–.01 to .23)	.07†	.17 (.025 to .31)	.02‡
Complete case analysis	.11 (–.01 to .24)	.08†	.17 (.03 to .32)	.02‡
Concentration				
Intent-to-treat analysis	–.012 (–.24 to .21)	.9	.17 (–.1 to .44)	.2
Complete case analysis	.04 (–.2 to .28)	.75	.23 (–.05 to .51)	.1
Reasoning				
Intent-to-treat analysis	.04 (–.15 to .23)	.7	.07 (–.15 to .28)	.5
Complete case analysis	.01 (–.19 to .21)	.9	.056 (–.16 to 27)	.6
Planning				
Intent-to-treat analysis	.21 (–.06 to .48)	.1	.16 (–.13 to .45)	.3
Complete case analysis	.22 (–.08 to .52)	.15	.16 (–.15 to .47)	.3
Memory				
Intent-to-treat analysis	.17 (–.01 to .36)	.07†	.25 (.03 to .47)	.03‡
Complete case analysis	.18 (–.02 to .38)	.08†	.25 (.02 to .48)	.03‡

Note: [a] Calculated from linear mixed effects regression models that included group (M2 or M4), time (baseline, 24 and 52 weeks), and group × time interaction terms. Differences between groups calculated as M4 – M2. [b] Data presented as *z* scores. †Trends for differences between groups in estimated mean change from baseline. ‡Significant differences between groups in estimated mean change from baseline. Abbreviations: GCF = global cognitive functioning; M2 = multiple-modality group; M4 = multiple-modality, mind-motor group.

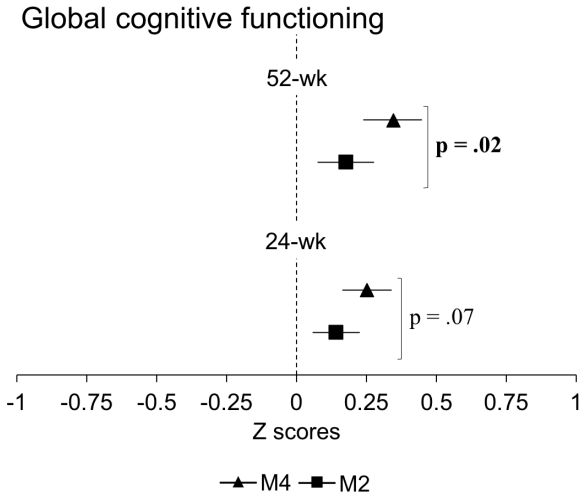

Figure 3.3. Changes in global cognitive functioning.

Note: Solid squares (M2) and triangles (M4) represent point estimated group mean change from baseline; bars represent associated 95% confidence intervals. P value indicates significant differences between groups in estimated mean change from baseline. Abbreviations: M2 = multiple-modality group; M4 = multiple-modality, mind-motor group; 24-wk = intervention endpoint; 52-wk = study endpoint.

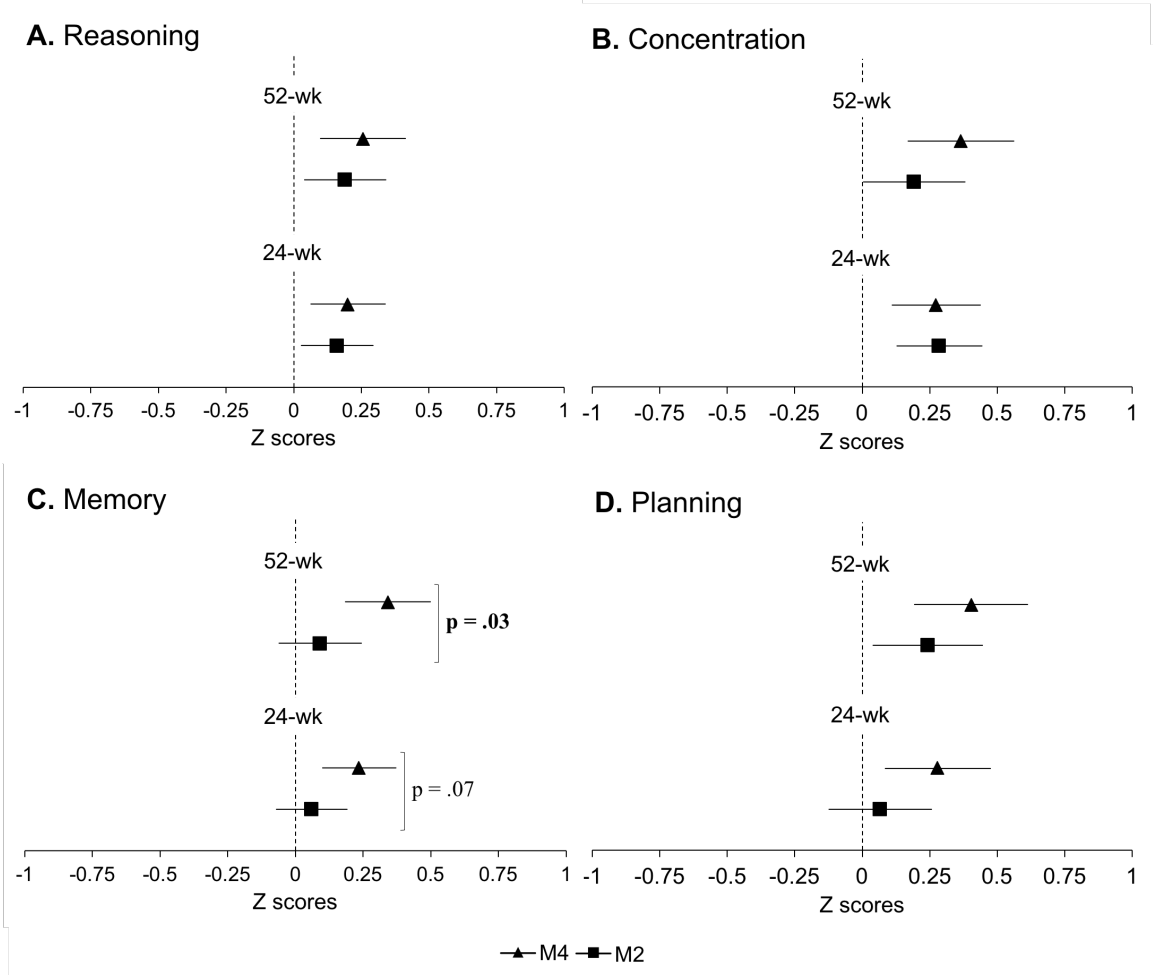

Figure 3.4. Changes in domain-specific cognitive function.

Note: Solid squares (M2) and triangles (M4) represent point estimated group mean change from baseline; bars represent associated 95% confidence intervals. P value indicates significant differences between groups in estimated mean change from baseline. Abbreviations: M2 = multiple-modality group; M4 = multiple-modality, mind-motor group; 24-wk = intervention endpoint; 52-wk = study endpoint.

Table 3.3. Associations between cardiorespiratory fitness and study outcomes at baseline and with change scores over time.

Outcomes [a]	pVO_2max (baseline)	ΔpVO_2max (24 weeks) [b]	ΔpVO_2max (52 weeks) [c]
GCF	$F_{(1, 120)} = 7.9$, p = .006, $r^2 = .042$†	$F_{(1, 101)} = .85$, p = .36, $r^2 = .001$	$F_{(1, 88)} = 2.3$, p = .13, $r^2 = .02$
Concentration	$F_{(1, 120)} = 8.5$, p = .004, $r^2 = .059$†	$F_{(1, 102)} = 5.8$, p = .018, $r^2 = .052$†	$F_{(1, 89)} = 2.1$, p = .15, $r^2 = .02$
Reasoning	$F_{(1, 120)} = .92$, p = .34, $r^2 = .01$	$F_{(1, 102)} = 1.6$, p = .20, $r^2 = .02$	$F_{(1, 89)} = .01$, p = .91, $r^2 = .000$
Planning	$F_{(1, 120)} = 5.2$, p = .024, $r^2 = .032$†	$F_{(1, 102)} = .03$, p = .86, $r^2 = .01$	$F_{(1, 89)} = .003$, p = .95, $r^2 = .000$
Memory	$F_{(1, 120)} = 5.1$, p = .025, $r^2 = .028$†	$F_{(1, 102)} = .64$, p = .43, $r^2 = .01$	$F_{(1, 88)} = .61$, p = .43, $r^2 = .007$

Note: [a] Statistics are presented as F_{change} and r^2_{change} from hierarchical regression models and represent the unique contribution of pVO_2max to the model, after adjustments for age, gender and years of education. [b] Change scores from baseline to 24 weeks. [c] Change scores from baseline to 52 weeks. †Significant associations adjusting for age, gender and years of education. Abbreviations: GCF = global cognitive functioning; pVO_2max = predicted maximal oxygen consumption

3.5 Discussion

The results of our study did not provide support for the hypothesis that multiple-modality exercise with additional mind-motor training yields greater improvements in cognitive function compared to multiple-modality exercise with additional balance, range of motion, and breathing exercises. We did note, however, positive changes over time as result of the intervention. Aligning with previous research in individuals with SCC [35], our results indicated that a 24-weeks of exercise yielded improvements in GCF, concentration, reasoning, planning and memory. Furthermore, additional mind-motor training only demonstrated trends for greater improvements in GCF and memory (both p = .07) at 24 weeks. Even though significant differences between groups were not detected, it is possible that the additional 15 minutes of SSE may have positively influenced these outcomes. This partially corroborates previous studies demonstrating that SSE may benefit GCF, attention, mental flexibility [29], memory and executive functioning [30] in cognitively healthy older adults.

Compared to those previous studies, the lack of superior effects of the SSE to drive between-group differences in our investigation may be attributed to the short duration and different frequency in which the mind-motor component was administered. Furthermore, other factors may have influenced our results. The current study adopted a RCT design, whereas those previous investigations followed either a quasi-randomized [29] or non-randomized [30] design, which may have resulted in bias. Additionally, discrepancies may have also occurred due to the methodology applied to evaluate cognition in our study (i.e., the CBS battery) compared to the traditional paper-based assessment administered previously [29,30].

In our study, both groups retained the gains in GCF and domain-specific cognitive functioning 28 weeks following the end of the exercise intervention. This is in contrast with the LIFE trial [49], where participants who completed a two-year multicomponent exercise program were not able to retain any gains in cognition after the end of the study. The improved performance within both groups in this study, and particularly in the M4 group, may be partially explained by extraneous factors, such as continuation in self-

selected exercise practice or engagement in cognitive training following the end of our intervention. Despite our promising findings, not many studies have investigated the decay of exercise-induced cognitive improvements in older adults after exercise cessation, thus, more research is warranted [17,25].

In our secondary analysis, we sought to explore whether changes in cognition were associated with changes in cardiorespiratory fitness. This set of analyses would allow us to infer a more causal relationship between both exercise interventions and the study outcomes, as observed in previous studies [21,50]. When exploring the cardiovascular outcomes from M4 study in a previous investigation [34], it was observed that both groups demonstrated significant improvements in pVO_2max after the invention and at 52 weeks, similar to the findings for cognition in the current study. Regardless of these similar changes, no significant associations were found between changes in pVO_2max and changes in cognition when adjusting for age, gender and years of education, except for concentration at 24 weeks.

This suggests that the changes in cognition were not uniquely driven by improvements in fitness, but may have been influenced by other factors. A plausible hypothesis is that such changes may have occurred due to the influence of increased socialization. In fact, social interaction may provide significant cognitive stimulation [49] and partially account for improvements in cognition in older adults [47,51]. Furthermore, in a recent meta-analysis [52] greater effect sizes were observed following exercise in older adults compared to education or no-contact control groups, but not in comparison to active or social engagement control groups [52]. The underlying physiological and neurophysiological changes accountable for improvements in cognition following exercise certainly deserve further investigation particularly in this population of individuals with SCC.

3.5.1 Limitations

The following limitations should be considered when interpreting the results of our study. Our inclusion criteria may have not been stringent enough to determine the nature, diversity and influence of SCC in cognition function in our sample; a more comprehensive assessment of the SCC would have provided a more homogenous sample.

Therefore, our results should be considered carefully. Although the CBS is grounded in well-validated neuropsychological tests [43], this is the first study to apply this method to evaluate the effects of exercise in cognition in older adults. Participants could have also had access to the online version of the CBS and practiced the games before, during, or at the end of the study. Although, we administered an offline version of the CBS, which participants only had access to during the study assessment period. Nonetheless, if participants accessed the games on their own, this access was most likely at random and would not affect the primary outcome of the study (i.e., differences between groups at 24 weeks). Also, participants included in this study were predominantly Caucasian, well educated, and functionally independent, thus, our results may not be generalizable. In addition, we used a surrogate, although validated, measure of cardiorespiratory fitness (pVO_2max), which could lack precision in comparison to other more objective measures.

3.6 Conclusions

Results from our study indicate that a 24-week, group-based multiple-modality exercise intervention can yield improvements in cognition in older individuals with SCC. Additional mind-motor training only led to trends for greater benefits, particularly in GCF and memory. Future studies could investigate whether individuals presenting additional risk factors for future dementia (e.g., family history of AD, *APOE* ε4 carriers) would respond differently to an exercise intervention similar to what was presented in the current study. As well, it is paramount to investigate whether individuals with SCC who engage in regular exercise can reduce the risk of objective cognitive impairment later in life. As indicated by the results of this study, exercise may preserve cognitive function in this population; however more robust evidence is warranted. Also, in the future, including neuroimaging methods to explore changes in brain function (e.g., cortical plasticity) not captured via behavioural data in individuals with SCC would provide a more comprehensive assessment of the effects of exercise in this particular population.

Summary

This chapter reported on the effects of a 24-week multiple-modality exercise with additional mind-motor training intervention, compared to multiple-modality exercise alone in older adults with subjective cognitive complaints. Main findings revealed that additional mind-motor training yielded trends for significant improvements in global cognitive functioning and memory. After a 28-week no-contact follow-up, individuals who received additional mind-motor training during the 24-week intervention phase, demonstrated significantly greater performance in global cognitive functioning and memory compared to the control group. These changes after the 28-week no-contact follow-up might have been influenced by participation in the study intervention, as well as continuation in self-selected exercise practice or engagement in cognitive training following the end of the intervention program.

The mind-motor training program employed in this study (e.g., square-stepping exercise) was originally developed to impart mobility changes in older adults with higher risk of falling, with potentially additive benefits to cognitive function. Mobility decline is concomitant to cognitive decline and its plausible to hypothesize that by addressing cognitive function, changes in mobility would also occur in older adults at risk of cognitive impairment. To test this hypothesis, Chapter 4 addressed whether multiple-modality exercise and mind-motor training would yield benefits to mobility outcomes in a sample of older adults with subjective cognitive complaints.

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Chapter 4

4 Multiple-modality exercise and mind-motor training to improve mobility in older adults: A randomized controlled trial

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4.1 Introduction

Older adults with subjective cognitive complaints (SCC) are at increased risk for future mobility impairment [1] and cognitive decline [2,3]. Self-reported SCC may be the first indicator of underlying cognitive impairment [4–6] and have been associated with poorer scores on objective cognitive assessments [7], as well as cortical and hippocampal atrophy [8]. In this perspective, SCC is a clinically-relevant phenomenon that can serve to identify individuals at-risk for more serious forms of cognitive impairment and dementia, and these cognitive complaints have been found to predict future neuropathological progression towards the establishment of dementia [3]. The current efforts to improve cognition and mobility in Alzheimer's disease and other dementias have been met with relatively little success [9,10]. Thus, directing interventions towards individuals who are at increased risk for future pathological cognitive decline (e.g., those with SCC) prior to the establishment of underlying neuropathological changes to the brain may provide the greatest clinical benefit [11].

Cognitive deficits in older adults have been strongly associated with poor performance in several spatiotemporal gait characteristics, including slow velocity and increased stride time variability [12]. Moreover, slow gait velocity is an early indicator of cognitive impairment [13] and is related to shortened life span [14]. Further, gait variability is associated

with increased risk of falls [15,16], and higher gait variability is more apparent in those with a greater degree of cognitive impairment [17]. In fact, slower gait velocity and increased gait variability were linked to accentuated cognitive decline 25 years after baseline assessment in a recent retrospective investigation [18]; however, the relationship between cognitive functioning and gait performance has yet to be fully understood. This relationship is thought to be mediated, at least in part, by poor executive functioning (EF) [19] among healthy individuals [20] and those with severe cognitive impairment (e.g., Alzheimer's disease) [21]. The importance of preserved EF in the cognitive control of gait becomes more evident under dual-task (DT) conditions (e.g., walking and preforming a concurrent cognitive task) [22,23], where individuals with poorer EF demonstrate the most dramatic gait impairments [24].

Early prevention strategies (prior to the establishment of permanent cognitive impairment) that effectively improve usual and DT gait performance in those at greater risk for cognitive impairment may preserve functional independence, reduce fall risk [25,26], and attenuate the increasing burden on health care systems associated with mobility disability and dementia [10,27]. Thus far, increasing evidence has suggested that habitual participation in exercise programs may lead to improvements in usual and DT gait parameters [28,29], static and dynamic balance [30]; with a greater effect on frail individuals (e.g., fallers, musculoskeletal disorders) and in those with neurological conditions (e.g., mild to moderate dementia) [30,31]. For instance, in a recent laboratory-based investigation conducted by our research group, older adults with cognitive impairment, not dementia (CIND) [32] who underwent a combined 26-week DT gait and aerobic exercise (AET) intervention (40 min/day, 3 days/week) demonstrated significant improvements in usual and DT gait velocity and step length [33].

Despite promising evidence, the specific components of an exercise intervention that would impart the greatest benefit to mobility impairments in older adults are yet to be defined [34]. Furthermore, evidence is insufficient to conclude that a specific program of cognitive training and/or exercise warrants prescription in individuals with SCC [35]. Although the administration of exercise with [36] or without [29] additional DT gait training in previous exercise studies has been associated with improved usual and DT gait

performance, several aspects of these investigations may raise concerns regarding the feasibility of exercise protocols administered in such laboratory settings (i.e., translation to community settings).

Further, most studies have failed to comply with current guidelines for exercise in older adults with regards to exercise intensity, frequency, and duration [29,36]. These guidelines also emphasize the importance of multiple-modality exercise programs over single-modality exercise programs to enhance overall health and quality of life in the general population of older adults [37,38], although evidence is still limited in more specific groups (e.g., individuals with SCC). In addition, exploring the combination of multiple-modality exercise with alternative, and perhaps more feasible (e.g., group-based, low-cost, and easily administered), forms of mind-motor training (simultaneous cognitive and physical engagement) on mobility outcomes may provide further support for optimal exercise interventions in older adults at risk for cognitive and mobility impairment [37].

Square-stepping exercise (SSE) is a group-based, low-intensity exercise program that has been associated with improvements in lower extremity functional fitness and reduced fall risk in older adults at high risk of falling [39]. The SSE intervention is best characterized as a visuospatial working memory task with a stepping response on a gridded floor mat, and thus, may be considered as a novel form of mind-motor training [40]. Recent evidence suggests that SSE may yield improvements in global and domain-specific cognitive functioning, including EF subdomains (i.e., attention and mental flexibility) in older adults free of dementia [41,42]. Nonetheless, the additive effects of SSE on usual and DT spatiotemporal gait characteristics in combination with multiple-modality exercise warrants further investigation.

Hence, the purpose of this study was to examine the influence of group-based, multiple-modality exercise combined with mind-motor training (i.e., SSE), in comparison to multiple-modality exercise with additional balance, range of motion, and breathing exercises on spatiotemporal gait characteristics in community-dwelling older adults with SCC. We hypothesized that the addition of a mind-motor component to the multiple-modality exercise intervention would lead to greater improvements in the study outcomes

compared to multiple-modality exercise alone, particularly by influence of SSE on neural control of gait.

4.2 Methods

4.2.1 Study design and participants

As reported in Chapter 3, the M4 Study was a two-arm randomized controlled trial (RCT) implementing a 24-week intervention program with a 28-week no-contact follow-up [43]. Assessments were performed at baseline, 24 weeks (intervention endpoint) and 52 weeks (study endpoint). After baseline assessments, participants were randomized to either the multiple-modality exercise with mind-motor training intervention group (Multiple-Modality, Mind-Motor [M4]) or to the multiple-modality exercise active control group (Multiple-Modality [M2]).

Details of the M4 Study participants and eligibility criteria have been reported in Chapter 3 and published elsewhere [43,44]. Briefly, the study included community-dwelling older adults aged 55 years or older, who self-reported a cognitive complaint [4–6,45]. As well, we included individuals who were fully independent in functional activities (maximum score in the Lawton-Brody Instrumental Activities of Daily Living scale [8/8]) [46]. Individuals were excluded if they self-reported a diagnosis of dementia and/or scored < 24 on the Mini-Mental State Examination (MMSE) [47], had major depression, recent history of severe cardiovascular conditions, any neurological and/or psychiatric disorders, or were unable to comprehend the study letter of information.

The study was registered with ClinicalTrials.gov on 29 April 2014 (Identifier: NCT02136368). The Western University Health Sciences Research Ethics Board approved this project and all participants provided written informed consent prior to taking part in the study.

4.2.2 Multiple-modality exercise intervention

Participants in both groups received 45 minutes of group-based, standardized, multiple-modality exercise, as reported in Chapter 3 (see **Supplementary Table 3.1 Appendix B)** [43]. The M4 group performed an additional 15 minutes of mind-motor training (i.e., SSE),

whereas the M2 group underwent 15 minutes of training focused on balance, range of motion, and breathing exercises (i.e., active control condition). In total, participants in both groups exercised 60 minutes/day, 3 days/week for 24 weeks.

4.2.3 Comparator intervention

The comparator group underwent 45 minutes of multiple-modality exercise with additional 15 minutes of balance, range of motion, and breathing exercises, prior to the 5 minutes of stretching (see Chapter 3).

4.2.4 Mind-motor training intervention

In addition to the multiple-modality exercise intervention, participants within the M4 group also performed SSE training (as described in detail in Chapter 3) [39], prior to the 5 minutes of stretching (**Figure 4.1**). Briefly, the SSE program entails the reproduction of previously demonstrated complex stepping patterns on the SSE mat. The stepping patterns are demonstrated by an instructor and participants are expected to memorize, and further attempt to reproduce each stepping pattern by memory. The goal was to progress through as many SSE patterns as possible over the 24-week intervention period.

Figure 4.1. Participants performing stepping patterns during a square-stepping exercise session.

4.3 Study assessments

4.3.1 Descriptive variables

Baseline assessments were performed after obtaining written informed consent and prior to participant randomization. Neuropsychological assessments were performed using the MMSE, the Montreal Cognitive Assessment (MoCA), [48] and the Centre for Epidemiological Studies Depression Scale [49]. Participant clinical and demographic data included: age, sex, race, medical history, weight, height, body mass index (BMI), and 24-hour blood pressure. Additionally, cardiorespiratory fitness was assessed at baseline (predicted maximal oxygen consumption [pVO_2 max]) using the STEP tool [50].

4.3.2 Mobility outcomes

Spatiotemporal gait characteristics were collected using a portable electronic walkway system (GAITRite® System, 580 × 90 × 0.63 cm (L × W × H), scanning frequency of 60 Hz, Software Version 4.7.1, CIR Systems, Peekskill, NY, USA). The GAITRite® is valid and reliable for gait assessment in various populations, including older adults with and without mobility impairment [51,52]. Participants completed two usual walking trials (i.e., walking at usual pace), followed by two separated walking trials under DT conditions (i.e., phonemic verbal fluency [VF] and serial sevens [S7] tasks) at a self-selected walking velocity. In the DT gait VF task, participants were instructed to name as many animals (baseline), vegetables (24 weeks), and countries (52 weeks) as possible. For the S7 task, participants were instructed to perform subtractions by sevens starting at 100 (baseline), 90 (24 weeks), and 80 (52 weeks). No instructions to prioritize gait performance or responses to the cognitive tasks during the DT conditions were given to the participants. In each trial, participants were instructed to start walking 1 m before and continue to walk until 1 m beyond the electronic walkway, in order to measure steady-state walking. Gait performance over two walking trials were averaged and used for analysis. The measures of interest were usual and DT (VF and S7) gait velocity (cm/s), step length (cm), and cycle time variability (coefficient of variation [%]) [12].

In addition, we were interested in cognitive performance under the DT gait conditions (i.e., accuracy). As such, following previous methods [53], DT cognitive accuracy while dual-tasking was measured based on the number of correct cognitive responses (ccr) provided by each participant during the two DT gait assessments. This number was then divided by the time (s) taken for each individual DT condition. To adjust for performance errors, ccr/s was finally multiplied by the ratio of correct responses to total responses. We discarded repeated answers during each trial and did not consider answers that were deemed to be inappropriate or incorrect (e.g., naming 'cities' instead of 'countries' during the DT gait VF trial at 52 weeks).

4.3.3 Sample size calculations

The sample size included in this study was calculated based on the primary outcome from the larger RCT (i.e., difference between groups at 24 weeks in global cognitive functioning derived from the computer-based Cambridge Brain Sciences cognitive battery) [43,54]. Briefly, results from a previous meta-analysis indicated that exercise could improve cognition with an moderate effect size ($d = 0.48$) [55]. Although our study has a different design (e.g., intervention and outcome), we decided to take this number into account. Therefore, a sample size of 52 participants per group would have an 80% power at the 5% significance level to detect a moderate effect size of 0.55 in cognition. Considering a dropout rate of 20% during the 24-week intervention period, our final sample size was estimated at 130 participants (65 in each group). In a recent meta-analysis [29], multiple-modality exercise was associated with improvements in usual gait velocity in healthy older adults with an effect size of $d = .77$. Thus, if gait velocity were used to estimate the study sample size as the primary outcome, considering an 80% power at 5% significance level and a dropout rate of 20%, we would need only 25 participants per group (50 participants in overall) to detect a significant treatment effect—so our analysis is fully powered to detect significant changes in gait outcomes.

4.3.4 Statistical analysis

Similar described in Chapter 3, we conducted linear mixed models for repeated measurements [56] to assess differences between groups in mean change from baseline to

24 weeks. Within the models, we also examined differences between groups from baseline to 52 weeks, and differences within groups from baseline to 24 and 52 weeks. The terms included in the models were: group, time, and group × time. Time was modeled categorically using two indicator variables representing each time point (baseline as reference category). All analyses were performed using the intent-to-treat approach, including all randomized participants, regardless of compliance with the program and follow-up assessments [56]. An advantage of the mixed effects regression modeling approach is that it does not require each participant to have the same number of measurements provided data are missing at random (i.e., after taking observed data into account, there are no systematic differences between participants with complete data as compared to those with missing data). This is also an assumption made by most multiple imputation methods [56]. We also performed a sensitivity analysis including only those who completed the study assessments at all time points. As well, for the main outcomes of the study, we conducted analyses adjusting for global cognitive functioning at baseline (MoCA scores). Interpretation of study results were primarily based on mean estimation and associated 95% confidence intervals. All analyses were performed using IBM® SPSS® Statistics for Mac, Version 21 (Armonk, NY: IBM Corp).

4.4 Results

4.4.1 Enrollment, randomization, and adherence

This study was conducted between January 13, 2014 and March 14, 2016. Participants were enrolled in 4 waves of assessments and intervention over a period of 14 months. During the screening process, 169 individuals were assessed for eligibility; 11 did not meet the inclusion criteria and 31 declined to participate. Thus, 127 participants were included and randomized to either the M2 (n=64) or M4 (n=63) groups,109 participants attended assessments at 24 weeks, and 102 returned for the final assessments at 52 weeks (see **Figure 4.2**). Participants had completed the study and the average attendance to the exercise sessions was 72% for the M2 group (52 out of 72 sessions) and 68% for the M4 group (49 out of 72 sessions).

A two-sided independent samples t-test revealed no significant differences between groups in participant average attendance ($p = .3$). At the end of the intervention period, participants in the M4 group had achieved the Advanced Level 3 of the SSE program, with stepping patterns ranging from 12 to 16 steps, and with steps performed in a broader range of directions (backwards, diagonal, and backwards diagonal), as well as with stepping patterns incorporating wider and longer steps (3 to 5 squares between feet). Considering attendance level and program achievement, the SSE program was shown to be feasible in this specific population (i.e., older adults with SCC) and no study-related adverse events were recorded.

Table 4.1 provides the baseline descriptive characteristics of the 127 participants. In overall, the study participants were mostly Caucasian, highly educated and presented with signs of cognitive deterioration based on mean MoCA scores. Further observation of the domain-specific MoCA scores revealed that participants in both groups showed low scores in the delayed-recall memory composite, which indicate memory loss possibly underlying the nature of the self-reported SCC. As well, even though participants involved in the study were high-functioning and lived independently in the community, pVO_2max assessment yielded classification of 'poor' to 'fair' cardiorespiratory fitness compared to age and gender reference values [57]. The study outcomes at baseline are presented in **Table 4.2**, participants demonstrated high gait velocity and low cycle time variability for age, indicating preserved function [14].

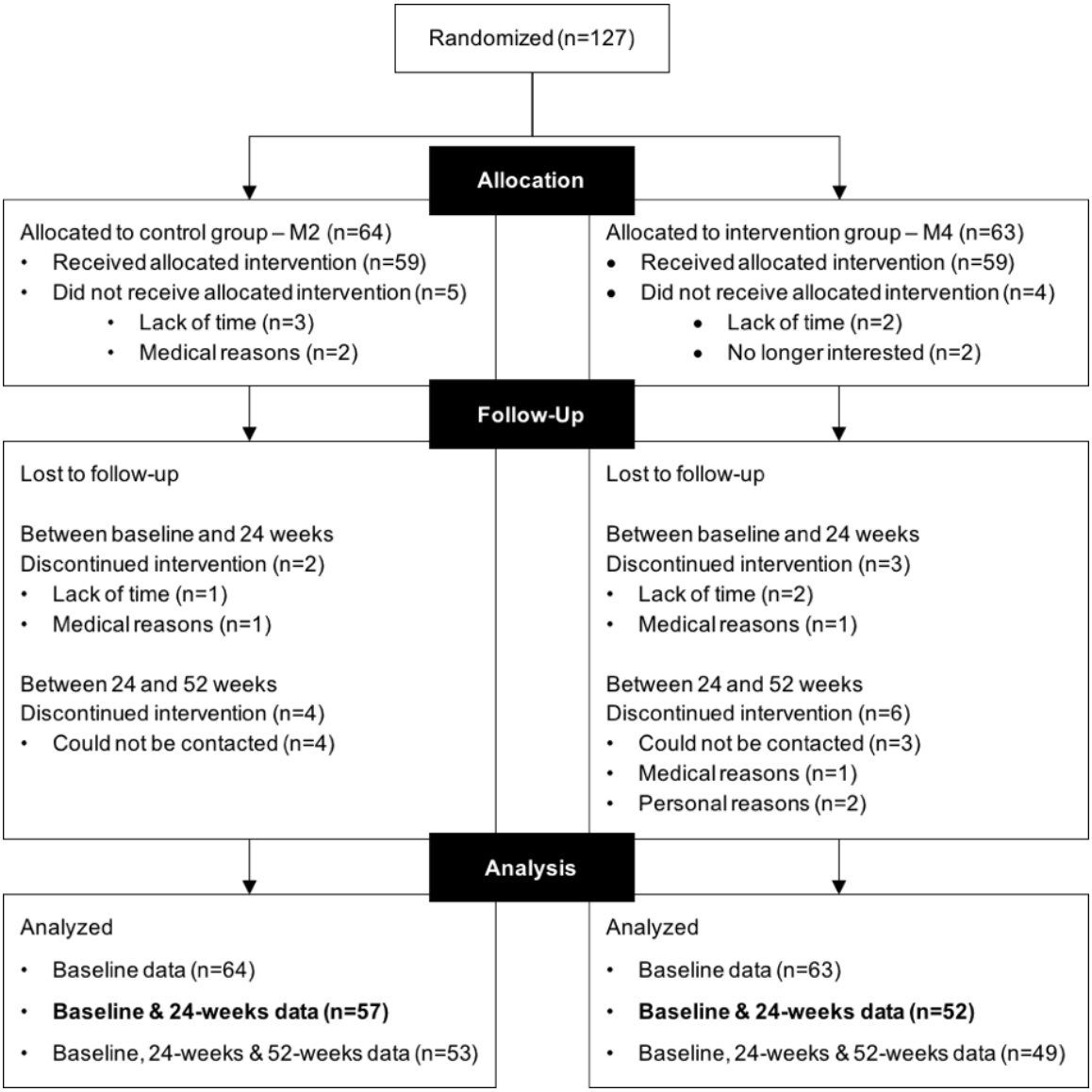

Figure 4.2. Flow of participants

Note: For the M4 group, data from 4 participants were missing at 24 weeks and, therefore, not included in analyses.

Table 4.1. Baseline demographics and clinical characteristics.

Variables [a]	M2 (n = 64)	M4 (n = 63)
Demographics		
Age, yr	67.4 (7.2)	67.6 (7.5)
Females	46 (71.9%)	44 (69.8%)
Caucasian	62 (98.4)	61 (96.8)
Education, yr	13.8 (3)	13.3 (2.7)
MoCA, score (/30) [b]	25.6 (2.4)	25.3 (2.7)
Visuospatial/Executive (/5)	4 (2)	4 (2)
Naming (/3)	3 (0)	3 (0)
Attention (/6)	6 (1)	6 (1)
Language (/3)	3 (0)	3 (0)
Abstraction (/2)	2 (0)	2 (0)
Delayed recall (/5)	3 (2)	3 (2)
Orientation (/6)	6 (0)	6 (0)
≤ 12 years of education	19 (30%)	15 (24%)
MMSE, score	29.2 (1)	29 (1.2)
CES-D, score	9.4 (7.4)	10 (8.9)
24-hour systolic BP, mmHg	129.6 (15.2)	126.5 (11.3)
24-hour diastolic BP, mmHg	74.2 (8.3)	72.2 (8.1)
Weight, kg	80.8 (17.7)	80 (13.8)
Height, m	1.65 (0.1)	1.65 (0.1)
BMI, kg/m^2	29.7 (6.2)	29 (4.1)
pVO_2max, ml/kg/min	26.8 (8)	27.1 (7.9)
Medical history, *n* (%)		
Hypertension	32 (50%)	36 (57.1%)
Hypercholesterolemia	23 (35.9%)	28 (44.4%)
Type 2 diabetes	5 (7.8%)	7 (11.1%)
Myocardial infarction	4 (6.3%)	5 (7.9%)
Atrial fibrillation	-	3 (4.8%)
Angina/coronary artery disease	1 (1.6%)	2 (3.2%)
Aneurysm	1 (1.6%)	2 (3.2%)
Former smoker	28 (44.4%)	29 (46%)
Current smoker	1 (1.6%)	1 (1.6%)

Note: [a] Data presented either as mean (standard deviation) or no. (%) where applicable. [b] Domain-specific MoCA scores presented as median and interquartile range.

Abbreviations: M2 = multiple-modality group; M4 = multiple-modality, mind-motor group; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; CES-D = Centre for Epidemiological Studies Depression Scale; BP = blood pressure; pVO_2max = predicted maximal oxygen consumption.

Table 4.2. Baseline study outcomes.

Outcomes [a]	M2 (n = 64)	M4 (n = 63)
Usual gait		
Gait velocity, cm/s	116.5 (16.7)	116.6 (20.9)
Step length, cm	64.7 (7.9)	64.03 (9.8)
Cycle time variability, %, Mdn (IQR)	1.8 (1.5, 2.3)	2.08 (1.5, 2.8)
DT Gait (VF)		
Gait velocity, cm/s	97.6 (23.5)	94.6 (26.7)
Step length, cm	61.2 (8.7)	59.7 (10.8)
Cycle time variability, %, Mdn (IQR)	3.8 (2.3, 7)	4 (2.1, 8.1)
DT Gait (S7)		
Gait velocity, cm/s	88.9 (26.7)	85.4 (28.2)
Step length, cm	59.9 (10.2)	58.4 (10.6)
Cycle time variability, %, Mdn (IQR)	5 (2.7, 8.1)	4.6 (3, 7.1)
Secondary outcomes		
DT cognitive accuracy (VF), ccr/s	1.16 (.33)	1.02 (.33)
DT cognitive accuracy (S7), ccr/s	.40 (.35)	.37 (.36)

Note: [a] Data presented as mean (standard deviation) or otherwise indicated.

Abbreviations: M2 = multiple-modality group; M4 = multiple-modality, mind-motor group; Mdn = median; IQR = interquartile range; VF = verbal fluency task; S7 = serial sevens task; CCR = rate of correct cognitive responses.

4.4.2 Study outcomes

Table 4.3 shows differences between groups in estimated mean change from baseline to 24 and 52 weeks in the study outcomes. At 24 weeks, the M4 group demonstrated inferior performance in usual gait velocity, usual step length, and DT gait velocity (VF) compared to the M2 group. Differences between groups in usual gait velocity remained significant and 52 weeks, favouring the M2 group. No other differences were seen in the remaining outcomes; however, the M4 group demonstrated a trend for higher DT cycle time variability (VF) at 24 weeks ($p = .054$) compared to the M2 group.

Regarding within-group analyses, **Figure 4.3** shows the estimated mean change from baseline to 24 and 52 weeks. At 24 weeks, improvements were observed in usual gait velocity and usual step length among participants in the M2 group; whereas the M4 group demonstrated decline in DT step length (VF) at the same time point. Lastly, the M4 group demonstrated a trend for increased DT cognitive accuracy (VF) at 52 weeks ($p = .052$). In addition, the sensitivity analysis, which included only participants who completed the study, did not change the main findings, except that it confirmed the trend for increased DT cycle time variability (VF) at 24 weeks ($p = .049$) in the M4 group compared to the M2 group (see **Supplementary Table 4.1 in Appendix C**). As well, the results remained the same when adjusting for global cognitive functioning at baseline (MoCA scores).

Table 4.3. Differences between groups in the study outcomes.

Outcomes [b]	Difference between groups in estimated mean change (95% CI) [a]					
	24 weeks	*p* Values		52 weeks	*p* Values	
Usual gait						
Gait velocity, cm/s	–10.1 (–15.8 to –4.4)	<.001†	.001‡	–6.7 (–13.4 to –.05)	.048†	.044‡
Step length, cm	–2.9 (–4.8 to –1)	.003†	.003‡	–2.1 (–4.2 to .1)	.06	.06‡
Cycle time variability, % [c]	.02 (–.08 to .11)	.74	.72	–.01 (–.11 to .09)	.86	.89
Dual-task gait (VF)						
Gait velocity, cm/s	–7.9 (–15.5 to –.3)	.043†	.039‡	–4.8 (–14.7 to 5)	.33	.32
Step length, cm	–1.8 (–4 to .5)	.11	.11	–.4 (–3 to 2.2)	.76	.74
Cycle time variability, % [c]	.15 (–.002 to .29)	.054	.052	.11 (–.06 to .27)	.19	.18
DT gait (S7)						
Gait velocity, cm/s	–7.3 (–15.9 to 1.2)	.09	.085	–7.5 (–17 to 1.9)	.11	.11
Step length, cm	–1.5 (–4 to 1)	.23	.22	–2.2 (–4.7 to .3)	.09	.085
Cycle time variability, % [c]	.11 (–.05 to .27)	.17	.15	.1 (–.07 to .27)	.23	.21
Secondary outcomes						
DT cognitive accuracy (VF), ccr/s [d]	–.05 (–.23 to .14)	.62	.58	.13 (–.04 to .31)	.14	.16
DT cognitive accuracy (S7), ccr/s [d]	–.04 (–.22 to .13)	.62	.64	.02 (–.16 to 19)	.86	.84

Note: [a] Calculated from linear mixed effects regression models that included group (M2 or M4), time (baseline, 24 and 52 weeks), and group × time interaction terms. A total of 13 models were conducted, corresponding to each outcome listed in the first column. Differences between groups calculated as M4 – M2. [b] M4 group: baseline, n=63; 24 weeks, n=52; 52 weeks, n=49. M2 group: baseline, n=64; 24 weeks, n=57; 52 weeks, n=53. [c] Log transformation applied. [d] Square root transformation applied. † Significant differences between groups in estimated mean change from baseline. ‡ Significant differences between groups in estimated mean change from baseline adjusted for MoCA scores. Abbreviations: 95% CI = confidence interval; M2 = multiple-modality group; M4 =

multiple-modality, mind-motor group; DT = dual-task; VF = verbal fluency task; S7 = serial sevens task; CCR = rate of correct cognitive response.

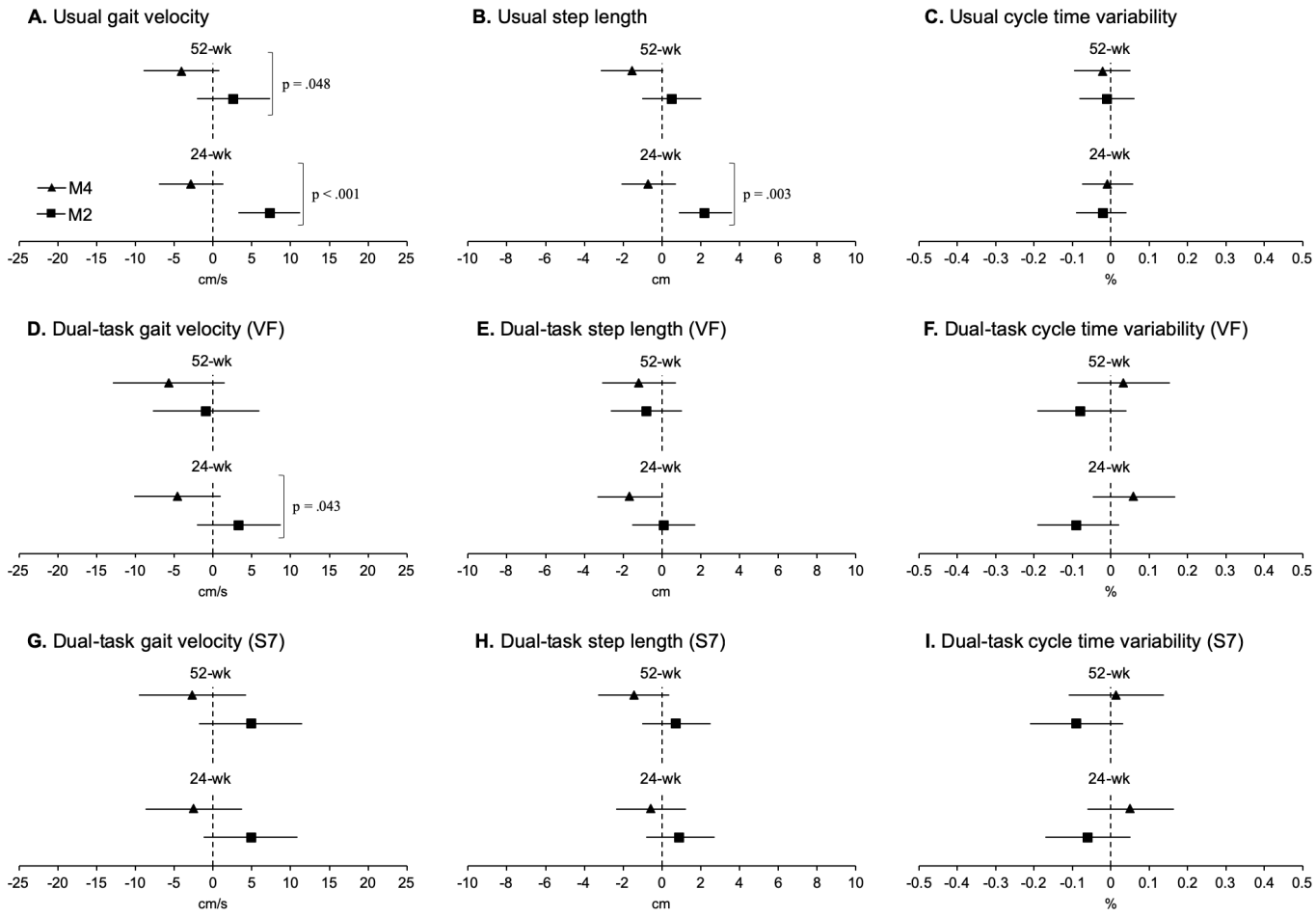

Figure 4.3. Within-group estimated mean changes from baseline in the study primary outcomes.

Note: Solid squares (M2) and triangles (M4) represent point estimated group mean change from baseline; bars represent associated 95% confidence intervals. Confidence intervals not including zero (i.e., not crossing the vertical dotted line) indicate significant

differences from baseline. P value indicates significant differences between groups in estimated mean change from baseline (see **Supplementary Table 4.2 in Appendix D** for specifics). Abbreviations: M2 = multiple-modality group; M4 = multiple-modality, mind-motor group. 24-wk = intervention endpoint; 52-wk = study endpoint; VF = verbal fluency task; S7 = serial sevens task.

4.5 Discussion

The results of the current study indicated that the addition of mind-motor training (i.e., SSE) to a standardized multiple-modality exercise intervention did not yield further improvements in spatiotemporal gait characteristics and DT cognitive accuracy. Nonetheless, the multiple-modality exercise intervention with additional balance, range of motion, and breathing exercises (i.e., M2) did impart improvements to usual gait velocity, step length, and DT gait velocity (VF) at 24 weeks, and did retain the gains in usual gait velocity at 52 weeks. The changes observed in the M2 group are in accordance with previous investigations [29,36]. Results from a systematic review and meta-analysis indicated that multiple-modality exercise interventions may yield clinically significant changes in gait velocity in older adults (mean change 0.09 m/s or 8.4%) similar to our findings (0.07 m/s or 6.25%) [29].

A surprising finding of the current study is that despite the fact that SSE was developed to promote improvements in lower extremity functioning in at-risk older fallers [39], it did not provide additional benefits to gait performance when added to the M2 exercise component. From a neuromuscular point of view, the lack of improvement within the M4 group may indicate that the specific biomechanical and/or physical requirements of SSE are not intrinsically associated with the mechanisms underlying exercise-induced changes in gait dynamics in older adults [58]. Further, the fact that M2 group received additional balance exercises may account for the superior gait performance in comparison to the M4 group. Indeed, positive changes in gait performance following balance training in older adults have been widely reported in the literature [29], and have been associated with reduced risk for mobility impairment and falls [59]. Taking this perspective, even though previous studies [39,60,61] indicated that SSE improved balance in older adults–which was the basis of our hypothesis that SSE would impart similar or greater benefits than the additional balance exercises–we failed to report such improvements.

It is important to mention, however, that the SSE program encompasses gradual progression in complexity to perform the stepping patterns; this complexity is determined by the number of steps performed, as well as the direction and length of the steps.

Therefore, at a certain point in the program (advanced phase), participants did perform stepping patterns requiring wider and lengthier steps and thus, improvements in spatiotemporal gait characteristics could be expected. As the key component of SSE is its simultaneous cognitive-physical demand, we argue that it was a valid hypothesis to expect favourable changes in the study outcomes, particularly with regards to DT gait measures.

In addition, it was hypothesized that the specific requirements of the SSE exercise would not directly train the specific gait outcomes that were considered for this study, but would act more specifically to train the control of gait on a more global scale. Among healthy populations, the control of gait is rather automatic and very little attention and/or effort is needed for habitual daily ambulation [62]. However, the SSE removes the habitual automatic walking response, and forces participants to actively modify their gait to successfully complete the task. This active modification of gait was also thought to be the key to the potential effectiveness of the SSE among relatively pre-clinical patient populations; a conscious modification of gait would potentially serve to strengthen the neural control of global gait performance.

Exercise-induced improvements in gait performance are primarily attributed to gains in muscle strength and neuromuscular control of the lower extremities [58,63–65], especially with respect to gait velocity [29]. For instance, gains in gait velocity over a 22-week exercise intervention program were associated with increased muscle strength in the hip flexors and ankle dorsiflexors muscles [66]. In the SSE sessions, the main goal was to complete the stepping pattern accurately, however, time to complete the tasks was not a main priority of the program. In this scenario, participants were expected to observe and retain information about the stepping patterns, then proceed to their execution in order to maintain forward gait, at a relatively slow gait velocity, regardless of participants' individual abilities. This may be understood as a lower-intensity set of stimuli that did not reach the threshold to impart muscle adaptions and induce gains in gait performance compared to the M2 group, which received additional balance exercises. Additionally, the SSE stepping patterns were executed in a way that does not necessarily correspond to the configuration of normal walking (e.g., backwards, lateral, and diagonal steps) and may

have negatively influenced the results within the M4 group, ultimately indicating task-specific effects of the SSE intervention unrelated to normal walking.

Looking at our findings from a neurological/cognitive perspective, it was also expected that SSE would improve DT gait parameters to a greater extent in the M4 group compared to the M2 group. Previous studies reported that SSE has been associated with improvements in EF subdomains (i.e., attention and mental flexibility) [41,42], which are understood as primary cognitive functions and/or brain networks involved in DT gait functioning [22]. Therefore, it was believed that even though SSE is of lower physical intensity, it would enhance DT gait parameters by benefiting EF, via a more neurological/cognitive pathway as opposed to a neuromuscular pathway, due to its high cognitive demand. In reality, we observed that the M4 group showed a decay in one of the DT gait velocity (VF) outcomes after the intervention, which led to statistically significant differences between groups at 24 weeks.

Given that no changes in any other DT gait parameters (under either VF or S7 conditions) were noted, it is possible that this singular between-group difference in DT gait velocity (VF) could be explained by the same neuromuscular mechanisms described previously. That is, participants had slower DT gait velocity (VF) probably due to the lack of an overall effect of SSE on gait, and thus, the DT component did not change that relationship. If SSE had a negative effect on the cognitive aspect of the DT, it would have likely appeared in the other DT gait parameters, particularly under the serial sevens condition (S7), since this task has been shown to be more cognitively demanding than the VF task [67]. Furthermore, the measures of cognitive accuracy recorded from both DT gait VF and S7 conditions did not differ between groups at 24 weeks, which supports this hypothesis.

Nonetheless, we observed a trend for increased DT cycle time variability (VF) in the M4 group that is worth discussing. Increased variability in gait parameters may be indicative of impairment in cognitive control of gait, particularly EF [68], and has been associated with increased risk of falling [65]. Although this finding may indicate an adverse effect of SSE in the M4 group, it should be interpreted with caution. We did not measure EF in the

current study, therefore it is unknown whether adverse changes in DT cycle time variability was associated with unfavorable changes in EF. Nonetheless, this assumption is unlikely given that SSE has been associated with improved EF in previous studies [41,42]. Rather, we argue that because of the above described characteristics of the SSE program, increased gait variably would likely result from a more cautious gait pattern developed in response to performing stepping patterns requiring increased attention and concentration. In fact, increased gait variability is a marker of cautious gait in fallers [69]. It is paramount, however, to bear in mind that the trends for increased DT cycle time variability were nonexistent at 52 weeks, suggesting that, if any, the adverse effects of SSE on gait variability would not permanent and would wear off after program cessation.

After the no-contact follow-up period, the M4 group demonstrated trends for improvements in DT cognitive accuracy (VF); this was not seen in the M2 group. Aerobic-based and multiple-modality exercise interventions have been shown to improve VF in this population under single task conditions [70,71]; however, under DT conditions, exercise-induced changes in DT cognitive accuracy has not been fully explored. Thus, the trend for improved performance of the M4 group in the VF task may be indicative of delayed-treatment impact of the exercise intervention with additional SSE [41], although this requires further exploration particularly with regards to clinical meaningfulness of these measures. This finding would implicate superior efficiency in proper allocation of attention resources to the cognitive task while maintaining stable gait velocity, which may be an encouraging sign of improvements in EF, particularly in our sample of older adults with SCC [53].

In sum, we speculate that the lack of SSE superior effects to drive between-group differences in DT gait parameters may be due to two main reasons: 1) the short duration and different frequency in which the mind-motor component was administered compared to previous studies [40,41], along with the low-intensity aspect of the SSE component; and 2) SSE could target specific cognitive functions/brain networks different from those required under DT gait conditions and, therefore, a significant treatment effect could not be expected under these circumstances. Another relevant factor to be taken into account when interpreting our findings is participants' baseline characteristics. This is particularly

important given that participant health and functional status prior to the beginning of any given exercise regimen can mediate the effect of exercise on gait performance [29]. For instance, in a study including patients with objective cognitive impairment, poorer baseline motor performance was the only factor related to greater response to the exercise training [72]. In this study, we recruited high-functioning community-dwelling older adults who, despite reporting signs of early cognitive deterioration (i.e., SCC), already presented relatively higher gait velocity and lower gait variability before the program, compared to population parameters [14]. Consequently, the lack of improvement in the M4 group may also be due the high-functioning aspect of our sample that would limit the extent to which the relatively low-intensity SSE would impart additional benefits to gait performance [58,73]. In other words, this could indicate a dose-response relationship, where a higher-intensity intervention would be necessary to observe significant changes in gait parameters in high-functioning older adults, even in those with SCC [29,74]. Moreover, past studies have shown that higher intensities of AET may yield functional and morphological alterations in brain regions associated with the cognitive control of gait [75] and improve usual gait and DT gait performance [35,76].

4.5.1 Limitations

This study presents several limitations. The lack of a non-exercising control group impaired our ability to control for the possible influence of external factors. Further, limitations regarding the DT assessments are also noted, including: 1) the task performance was not randomized (i.e., usual gait followed by DT gait VF, and then DT gait S7); 2) performance on the secondary cognitive tasks within the DT gait evaluation was not methodologically controlled (i.e., VF and S7 tasks isolated, without the walking task). Thus, our ability to determine whether changes in DT gait performance were similar to change in cognitive task (isolated VF and S7 tasks) is limited. In addition, AET intensity was controlled based on participants indirectly monitoring their own HR (i.e., via radial artery pulse), which could have created room for underestimations and participants may have exercised at different intensities from what was prescribed. In addition, due to our group-based intervention, we were not able to monitor progression in both exercise groups to an individual level; therefore, it cannot be concluded with high

confidence that each individual performed at their optimal performance. Finally, individuals in this study were predominantly Caucasian, well educated, functionally independent, and relatively healthy; thus, results may not be generalized to other populations.

4.6 Conclusions

The current investigation explored the influence of multiple-modality exercise with either additional mind-motor training or an active control intervention (e.g., additional balance, range of motion, and breathing exercise) on mobility outcomes in older adults with SCC. Our findings demonstrated that additional SSE training was not effective to improve usual and DT spatiotemporal gait characteristics compared an active control intervention. In fact, participants enrolled in the active control group experienced greater changes in usual gait velocity, step length and DT gait velocity after the 24-week intervention program.

Summary

In older adults with subjective cognitive complaints, 24 weeks of multiple-modality exercise with mind-motor training did not seem to impart improvements in mobility, as indexed by lack of changes in gait performance. Contrary to the original hypothesis, multiple-modality exercise alone imparted significantly superior changes in mobility. It is plausible that the mind-motor training (i.e., square-stepping exercise) component was not sufficiently intense to incite neuromuscular adaptations that would reflect better gait performance at the end of the program. Furthermore, the nature of the program did not specifically involve gait training, which could have hindered any potential benefits to gait performance. Based on these findings, along with findings from Chapter 3, it is likely that the effects of the intervention were primarily seen in cognitive function, particularly memory, and these effects did not translate to changes in mobility outcomes.

Therefore, a deeper understanding of the effects of the intervention program would be made possible by investigating underlying changes in neural correlates of cognition (i.e., measures of neuroplasticity). It would be relevant to determine whether adaptations in patterns of brain activation during cognitive tasks would have occurred as a result of multiple-modality exercise and mind-motor training. These investigations would also allow for exploration of whether the program brought about changes in brain regions associated with control of gait function or dual-task ability—despite lack of changes in behavioural measures. In this perspective, in Chapter 5 addressed changes in behavioural measures of memory function, as well as memory-related brain functional connectivity via analysis of functional resonance magnetic imaging (fMRI) data. Data were included from a subsample of participants attending the multiple-modality exercise and mind-motor training program who underwent fMRI data collection.

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Chapter 5

5 Memory function and brain functional connectivity adaptations following multiple-modality exercise and mind-motor training in older adults at risk of dementia: an exploratory sub-study

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5.1 Introduction

Findings from laboratory work and clinical trials for the treatment of dementias, such as Alzheimer's disease, have consistently produced disappointing results, with the possibility of a single cure being very unlikely [1,2]. Efforts have been made to identify and intervene with those who are at greater risk of cognitive decline and dementia before the establishment of clinical impairment [3]. Older adults with subjective cognitive complaints (SCC) [4,5] may represent a portion of the population experiencing early signs of cognitive decline due to underlying pathophysiological changes before clinical impairment is obvious [6,7]. The focus on preclinical stages of dementia has included the impact of preventive measures such as exercise and cognitive training years prior to disease onset [8]. If prevention programs could delay the onset of dementia even in part of the at-risk population, this could decrease the disease prevalence significantly [9,10]. Healthy lifestyle choices, including exercise, may be an important strategy to prevent or slow the progression of dementia in the aging population [8,11,12], even in those with high genetic risk [13].

Exercise has been associated with preserved age-related cognitive functioning in observational studies [12,14–17] and improved cognition [18], as well as positive functional [19,20] and structural [21] brain changes in longitudinal interventional studies. The positive effects of exercise on behavioural and neuroimaging outcomes in older adults are well-documented, but less is known about the effects of exercise in brain functional connectivity (FC). Brain FC can be understood as temporal and functional correlations of spatially distinct cortical and subcortical structures active at rest and/or during task in blood oxygenation level-dependent (BOLD) functional resonance imaging (fMRI) [22,23]. Intrinsic FC consists of anatomically and/or functionally distinct neuronal networks underlying neural function, particularly necessary to higher order cognitive processes [22,23]. From a clinical perspective, FC can also aid in identification of neurodegenerative processes occurring early on in the spectrum of dementia. For instance, Song and colleagues (2015) reported resting-state FC disruption in the medial temporal lobe associated with Alzheimer's disease biomarker deposition in cognitively healthy older adults [24]. Others have postulated that resting-state FC disruption in the default mode network (DMN) is evident in Alzheimer's disease patients compared to healthy controls [25,26], which is also pronounced in individuals with mild cognitive impairment (MCI), along with changes in the medial temporal lobe (MTL) network, prior to Alzheimer's disease diagnosis [27].

Exploring changes in FC in older adults at risk of Alzheimer's disease and dementia is, therefore, imperative. Of particular interest, previous resting-state fMRI studies have shown that exercise might impart positive effects in enhancing FC in resting-state networks in healthy individuals and in those with MCI [19,20]. These studies have primarily focused on the effects of aerobic exercise (AE) on FC changes within the DMN and MTL networks in healthy and MCI patients, due to the clinical relevance of these networks in the context of Alzheimer's disease [25–27]. Despite promising research with resting-state FC studies, less is known on the effect of multiple-modality exercise on task-related FC in older adults at risk of dementia. Focusing on task-related FC could aid in understanding the influence of exercise in FC underlying neurocognitive processes in those at higher risk of dementia. In addition, as we progress towards more comprehensive interventions that impart improvements to overall health in older adults, it is of interest to investigate

whether multiple-modality exercise training (e.g., AE, resistance or balance training) along with cognitively engaging tasks (i.e., mind-motor training), could have a different impact on FC in these individuals beyond traditional AE alone [28]. Unfortunately, very few studies have explored the effects of combining different exercise modalities (i.e., multiple-modality exercise) and mind-motor training in brain functional and/or structural outcomes [29–32]. Only a short-term (6 weeks), quasi-experimental study included FC as an outcome with results indicating increased FC between the posterior cingulate cortex with cingulate, temporal, parietal, and occipital regions in the multiple-modality exercise group compared to a control group [30]. Due to limited evidence, further research is warranted.

Square-stepping exercise (SSE) [33] is a novel form of mind-motor training, which has been associated with positive effects on global and domain-specific cognitive functioning in older adults [34,35]. Although the impact of SSE on cognitive function remains relatively unknown, evidence suggests the potential for SSE to benefit cognition, especially by improving memory [36,37]. Our group has investigated the effects SSE in cognition, mobility, and oculomotor function in older adults with and without cognitive impairment [34,35,38,39]. Nevertheless, the effects of SSE on task-related FC remains to be determined.

Therefore, the objective of this exploratory study was to investigate changes in memory function in a group of older adults following multiple-modality exercise with mind-motor training, compared to multiple-modality exercise alone. Further, we investigated task-related FC changes in memory in a subsample of older adults with SCC derived from our full randomized controlled trial (RCT) [35].

5.2 Methods

5.2.1 Study design

Our study design, recruitment and inclusion criteria has been reported previously [35]. This study is a secondary analysis of memory function outcomes from our full RCT (Chapter 3) as well as an exploratory study involving a subsample of individuals who underwent fMRI assessment at baseline and 24 weeks. Participants in the experimental group were randomized to a 24-week intervention (**m**ultiple-**m**odality exercise and **m**ind-**m**otor

training [M4 group]) targeted at improving cognitive function, mobility and cardiovascular health [40]. Participants in the control group received an active control intervention (multiple modality exercise plus balance, range of motion and breathing exercise [M2 group]). A subsample of participants from the experimental arm (M4 group) underwent fMRI assessment at baseline and 24 weeks later. The study was registered with ClinicalTrials.gov in April 2014 (Identifier: NCT02136368). The Western University Health Sciences Research Ethics Board approved this project and all participants provided written informed consent prior to taking part in the study.

5.2.2 Participants

For this secondary analysis of memory function, we examined data from 127 participants, while for the exploratory fMRI study, we examined fMRI data from 9 participants who completed both baseline and 24-week assessments. As applied in our full trial [40], the study included community-dwelling individuals aged 55 years or older with self-reported SCC (defined as answering positively to the question "Do you feel like your memory or thinking skills have got worse recently?") [41], and with preserved instrumental activities of daily living [40]. In addition to the full trial inclusion criteria, only right-handed participants were included in this sub-study. Individuals with a diagnosis of dementia and/or scoring < 24 on the Mini-Mental State Examination (MMSE) [40], history of stroke or transient ischemic attacks or presented with MRI contraindications were also excluded.

5.2.3 Multiple-modality exercise intervention

Participants in both groups received 45 minutes of group-based, standardized, multiple-modality exercise, as reported in Chapter 3 (see **Appendix B)** [40]. The M4 group performed an additional 15 minutes of mind-motor training (i.e., SSE), whereas the M2 group underwent 15 minutes of training focused on balance, range of motion, and breathing exercises (i.e., active control condition). In total, participants in both groups exercised 60 minutes/day, 3 days/week for 24 weeks.

5.2.4 Comparator intervention

The comparator group underwent 45 minutes of multiple-modality exercise with an additional 15 minutes of balance, range of motion, and breathing exercises, prior to the 5 minutes of stretching (see Chapter 3).

5.2.5 Mind-motor training intervention

In addition to the multiple-modality exercise intervention, participants within the M4 group also performed SSE training (as described in detail in Chapter 3) [33], prior to the 5 minutes of stretching. Briefly, the SSE program entails the reproduction of previously demonstrated complex stepping patterns on the SSE mat. The stepping patterns are demonstrated by an instructor and participants are expected to memorize, and further attempt to reproduce each stepping pattern by memory. The goal was to progress through as many SSE patterns as possible over the 24-week intervention period

5.2.6 FMRI data collection

Participants were invited to attend a one-hour fMRI session at the Robarts Research Institute at Western University. Image acquisition was performed in a Siemens MAGNETOM Fit whole-body 3 Tesla MRI scanner with in-plane acceleration (GRAPPA = 2). Structural MR images (T1-weighted anatomical images) were acquired for each participant lying passively in the magnet with the following parameters: echo time (TE): 2.98 ms, repetition time (TR): 2300 ms, time for inversion (TI): 900 ms, and flip angle = 9 deg, field of view (FOV) = 256 mm, voxel size: 1 x 1 x 1 mm. Whole-brain, task-related functional imaging was performed using a gradient-echo echoplanar imaging (EPI) sequence (36 slices) sensitive to BOLD contrast with the following parameters: TE: 30 ms, TR: 2000 ms, flip angle = 70 deg, FOV = 240 mm, voxel size: 3 x 3 x 3 mm.

The procedure allowed us to acquire 145 functional MR images over 5 minutes of continuous data collection while the participants were presented with each cognitive task. Tasks were displayed on a projector screen, visible from the bore of the MRI scanner via a mirror. In each task, participants were required to click on the screen to select their

answers using an MRI compatible tracker ball mouse. The tasks were programmed in the Adobe Flex development environment and were administered as a stand-alone software within the Adobe Integrated Runtime (AIR) environment. The study experiment consisted of a design-free, data driven approach where a specific design (e.g., block or event-related) was not established [42,43]. The tasks used have been adapted from tests used in previous neuroimaging and patient studies at our institution [44,45]. Tasks were behaviourally piloted by volunteers prior to scanning in order to ensure optimal performance for generating fMRI contrasts of interest (i.e., BOLD). The general approach used for task design was standardized across all four memory tasks described in the subsequent sections.

5.2.7 Behavioural tasks

The four cognitive tasks were administered in this study at baseline and 24 weeks and were derived from the Cambridge Brain Sciences (CBS) computerized cognitive battery [44]. Although we collected data from 12 cognitive tasks within the CBS cognitive battery, for this secondary analysis we decided to focus only on four memory tasks, namely Monkey Ladder, Spatial Span, Digit Span and Paired Associates. We had data available from 127 participants at baseline, collected over two days using a computer laptop (see our published protocol for more details [40]). The rationale to focus on these memory tasks is based on the fact that for our full RCT, the memory composite derived from these four tasks showed trends for greater changes following the 24-week exercise program and showed significant changes 56-weeks after baseline assessments [35]. However, data from each individual task, as well as the fMRI data have not yet been published. Below is the description of each individual task:

a) Monkey Ladder is based on a task from the animal literature (non-human primates) and assesses working memory ability [46]. In this task, sets of numbered boxes are all displayed at the same time at random locations within a grid. After a variable interval (number of boxes multiplied by 900 ms), the numbers are removed leaving just the blank boxes visible. Participants are requested to respond by clicking on the boxes in ascending numerical sequence. The difficulty of the task is modulated as follows: the number of boxes presented increases by

one if the participant answers correctly and decreases by one if the participant makes a mistake. The outcome measure is the length of the longest sequence successfully remembered.

b) Spatial Span is a task to measure spatial short-term memory capacity in humans [47]. In this task, 16 boxes are displayed in a grid. A sequence of randomly selected boxes flashes one at a time at a rate of 900 ms per box. Subsequently, a tone cues the participant to repeat the sequence by clicking on the boxes in the same order in which they flashed. The difficulty of the task is modulated as follows: the number of boxes that flash increases by one if the participant answers correctly and decreases by one if the participant makes a mistake. The outcome measure is the length of the longest sequence successfully remembered.

c) Digit Span is based on the verbal working memory component of the WAIS-R intelligence test [48]. In this task, participants view a sequence of digits that appear on the screen one at a time. Subsequently, participants are required to repeat the sequence of numbers by using the mouse cursor to click a series of numbered buttons that appear along the bottom of the screen. The difficulty of the task is modulated as follows: the sequence of numbers on the screen increases by one if the participant answers correctly and decreases by one if the participant makes a mistake. The outcome measure is the length of the longest digit sequence successfully remembered.

d) Paired Associates is a visuospatial paired associate learning task [49]. In this task, boxes are displayed at random locations on a grid. The boxes open one after another to reveal an enclosed icon, after which they close. Subsequently, the icons are displayed in random order in the centre of the grid and the participant must click on the boxes that contained them. The difficulty of the task is modulated as follows: if the participant remembers all the icon-location pairs correctly, then the next trial will have one more box. If a mistake is made, the next trial has one less box. The outcome measure is the length of the longest sequence successfully remembered.

5.2.8 Behavioural data analysis

All behavioural data collected from our full sample were analyzed using linear mixed models for repeated measurements [50] to assess differences between groups in mean change from baseline to 24 weeks. In the models, we also examined differences within groups from baseline to 24 weeks. The terms included in the models were: group, time, and group × time interaction. Time was modeled categorically using two indicator variables representing each time point (baseline as reference category). Task scores were z transformed. All analyses were performed using the intent-to-treat approach, including all randomized participants, regardless of compliance with the program and follow-up assessments [50]. Behavioural data collected during fMRI image acquisition in our exploratory analysis were analyzed via paired samples t-tests in SPSS®. We also calculated Cohen's *d* for paired-samples t-tests at *post-hoc* using the formula $d = t / \sqrt{n}$, where *d* corresponds to Cohen's *d*, *t* represents t-scores and *n* is the sample size [51]. Analysis of behavioural data was done in order to inform and contextualize results from fMRI data.

5.2.9 FMRI data analysis

All data analysis was performed using FMRIB's Software Library (FSL) tools (www.fmrib.ox.ac.uk/fsl). *Post hoc* analysis was performed in SPSS® for Mac, Version 21 (Armonk, NY). The study pipeline for image acquisition and data analysis is illustrated in **Figure 5.1**.

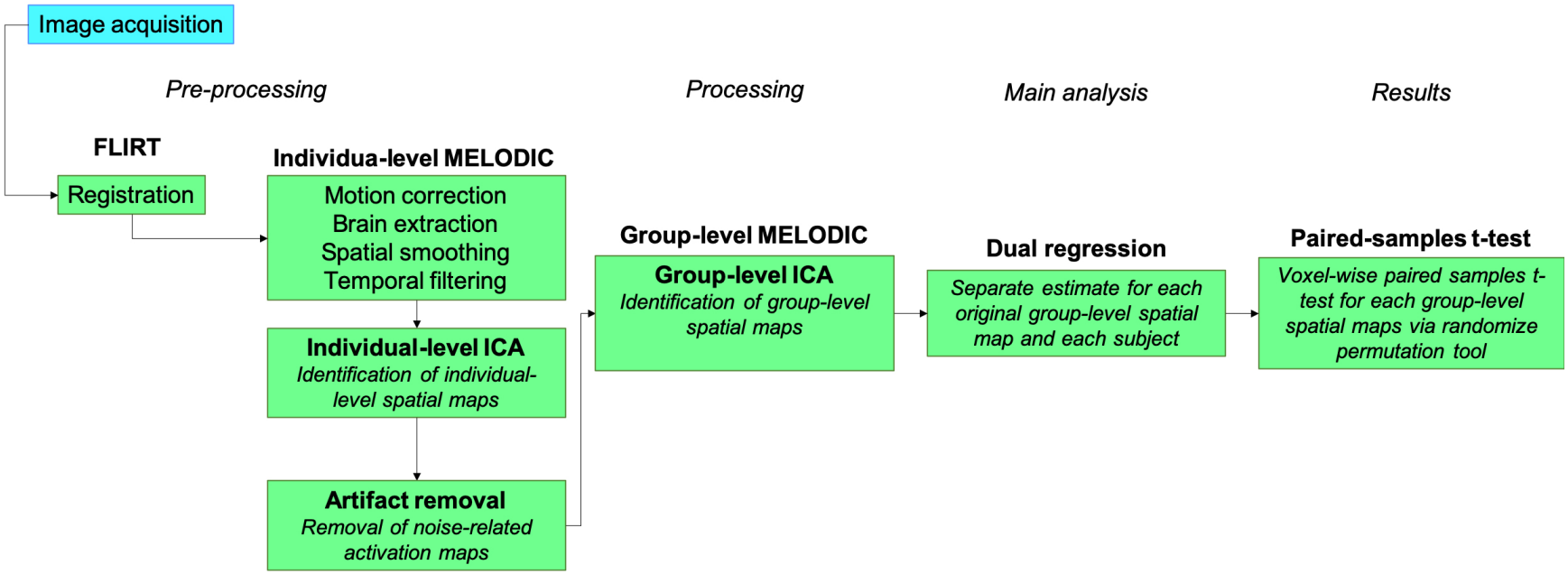

Figure 5.1. FMRI data analysis pipeline.

5.2.9.1 Preprocessing

Structural images were brain-extracted using an in-house script and inspected for optimal extraction. Functional images were registered using FLIRT linear registration to each individual's structural image and then a 2 mm MNI template registration. We then applied motion correction, brain extraction, spatial smoothing (5 mm FWHM Gaussian kernel) and high-pass temporal filtering [52,53].

5.2.9.2 Processing

Functional data analysis was performed using Probabilistic Independent Component Analysis [54] as implemented in FSL's Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC) Version 3.15 [54–56]. At the subject level, MELODIC results were decomposed into independent components that represent large-scale patterns of functional network connectivity using independent component analysis (ICA). Individual-level ICA maps were inspected to identify components that were considered noise using a visually inspected structured artifact removal approach (i.e., hand removal) [57], as previously applied in a similar exercise study [58]. All independent components that were identified as noise were removed from individual-level data via spatial regression using FSL's *fsl_regfilt* tool. These components were composed of noise due to several sources such as head motion, cerebral spinal fluid signal, respiratory and cardiac rhythms, scan parameters and others.

5.2.9.3 Main analysis

Following individual-level MELODIC, we then performed group-level ICA to identify independent components that represent large-scale patterns of FC within the group-level spatial maps, and the independent components were set at 40 per task, based on inspection of individual-level ICA results to inform optimal fitting of the data. Results from group-level MELODIC were further analyzed using FSL's dual regression tool. In this approach, the set of spatial maps from the group-average analysis was used to generate subject-specific versions of the spatial maps, and associated timeseries [59]. Primarily, for each individual in the study, the group-average set of spatial maps is

regressed (as spatial regressors in a multiple regression) into the subject's 4D space-time dataset; this results in a set of subject-specific timeseries, one per group-level spatial map. Later, those timeseries are regressed (as temporal regressors in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map. This procedure ultimately unfolds in a separate estimate for each original group-ICA map and each subject. In the final step of our analysis, we then performed paired samples t-tests in a voxel-wise analysis for each of the group-level spatial maps using FSL's randomise permutation-testing tool (5000 permutations, threshold-free cluster enhancement) corrected for voxel-wise multiple comparisons. Our goal was to identify any significant changes in the group-level spatial maps from baseline to 24 weeks. If any changes were identified, our results could indicate that the exercise program might have imparted adaptations in FC.

5.2.10 Post hoc analysis

We further performed *post hoc* analysis using subject-specific spatial maps (stage 2 outputs from dual regression) to quantify changes in the strength of connectivity within a group-level spatial map from baseline to 24 weeks, following previous methodology [60]. To accomplish this, we used the group-level spatial map as binary network masks and calculated an index that would indicate, on average, how strongly the voxels within a group-level spatial map are related to each other for each individual (via FSL's *fslmeants*). We were interested in knowing whether this FC index would have changed following the exercise program [58,60]. We also performed a similar procedure to quantify the changes in specific regions that showed significant changes from baseline to 24 weeks in the main analysis. Instead of using a binary mask, this was accomplished by extracting a voxel connectivity index from the exact location where changes from baseline to 24 weeks occurred (i.e., by using MNI152 coordinates in *fslmeants*); the coordinates were defined based on significant or borderline significant results of dual regression. The indices calculated as result of these procedures were then analyzed in a paired samples t-test in SPSS®.

5.3 Results

Details regarding study enrollment, randomization and adherence have been reported elsewhere [35,38]. Briefly, 169 individuals were assessed for eligibility; 11 did not meet the inclusion criteria and 31 declined to participate. Thus, 127 participants were included and randomized to either the M2 (n=64) or M4 (n=63) groups,109 participants attended assessments at 24 weeks. Demographic characteristics for our full sample are shown in **Table 5.1**. For our fMRI exploratory study, the sample was composed of mostly females who were approximately 70 years of age and with a Montreal Cognitive Assessment (MoCA) score of approximately 25, suggesting presence of objective cognitive impairment in addition to the self-reported SCC but with no indication of dementia (mean MMSE score of 29) [61]. Participant demographic and clinical characteristics for this subsample are presented in **Supplementary Table 5.1 in Appendix E**.

Table 5.1. Baseline characteristics of study participants by randomization group.

Variables [a]	M4 (n = 63)	M2 (n = 64)
Demographics		
Age, yr	67.6 (7.5)	67.4 (7.2)
Women	44 (69.8%)	46 (71.9%)
Caucasian	61 (96.8%)	62 (98.4%)
Education, yr	13.3 (2.7)	13.8 (3)
MoCA, score	25.3 (2.7)	25.6 (2.4)
MMSE, score	29 (1.2)	29.2 (1)
Weight, kg	80 (13.8)	80.8 (17.7)
Height, m	1.65 (0.1)	1.65 (0.1)
BMI, kg/m^2	29 (4.1)	29.7 (6.2)
Medical history, *n* (%)		
Hypertension	36 (57.1%)	32 (50%)
Hypercholesterolemia	28 (44.4%)	23 (35.9%)
Type 2 diabetes	7 (11.1%)	5 (7.8%)
Myocardial infarction	5 (7.9%)	4 (6.3%)
Atrial fibrillation	3 (4.8%)	-
Angina/coronary artery disease	2 (3.2%)	1 (1.6%)
Aneurysm	2 (3.2%)	1 (1.6%)
Former smoker	29 (46%)	28 (44.4%)
Current smoker	1 (1.6%)	1 (1.6%)
Memory tasks, z scores		
Monkey Ladder	.05 (1.03)	-.05 (.97)
Spatial Span	-.04 (1.05)	0.04 (.95)
Digit Span	-.1 (1.03)	.28 (1.75)
Paired Associates	-.09 (0.95)	.09 (1.05)

Note: [a] Data presented either as mean (standard deviation) or no. (%) where applicable.

Abbreviations: M2 = multiple-modality group; M4 = multiple-modality, mind-motor group; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; BMI = body mass index.

5.3.1 Behavioural results

For our full sample (n = 127), the M4 group showed greater improvements in the Paired Associates tasks compared to the M2 group at 24 weeks (mean difference: 0.47, 95% confidence interval [CI]: .08 to .86, p = 0.019, see **Table 5.2**), which resulted from an improvement in the M4 group from baseline to 24 weeks (p = 0.001), while changes in the M2 group were not observed (p = .93). Participants in both groups showed improvements in the Monkey ladder task ($p \leq 0.01$), however there were no differences between groups at follow-up. No within- or between-group changes were observed for the Spatial Span and Digit Span tasks, however the M4 group showed trends for improvements in the Digit Span task (p = 0.06).

For our subsample of participants in the fMRI exploratory study (n = 9), the results indicated no significant differences from baseline to 24 weeks in all of the tasks studied. For the Paired Associates task, however, we observed a trend for significant differences compared to baseline for the task max score (mean difference: 0.75, 95% CI: -0.1 to 1.6, t[7] = 2.05, p = 0.08, Cohen's d = 0.72) and task mean score (mean difference: 0.4, 95% CI: -0.1 to 0.8, t[7] = 0.08, Cohen's d = 0.74), corroborating the results from our full sample. The results are presented in **Supplementary Table 5.2 in Appendix F**.

Table 5.2. Within- and between-group differences from baseline to 24 weeks by randomization group

	Within-group differences (95% CI)				Between-group differences (95% CI)	
Outcomes [a]	M4 (n = 63)	*p* Value	M2 (n = 64)	*p* Value	24 weeks (n = 127)	*p* Value
Monkey Ladder	.23 (.05 to .41)	.01†	.29 (.12 to .47)	.001†	-.07 (-.32 to .19)	.6
Spatial Span	-.07 (-.25 to .12)	.47	.04 (-.14 to .22)	.67	-.11 (-.36 to .15)	.42
Digit Span	.33 (-.02 to .69)	.06	-.06 (-.4 to .29)	.75	.39 (-.1 to .88)	.12
Paired Associates	.48 (.2 to .76)	.001†	.01 (-.26 to .28)	.93	.47 (.08 to .86)	.019†

Note: [a] Calculated from linear mixed effects regression models that included group (M4 or M4), time (baseline and 24 weeks), and group × time interaction terms. A total of 4 models were conducted—corresponding to each memory task listed in the first column. Results are represented as intent-to-treat approach. †Significant differences within- or between-groups where applicable.

Abbreviations: M2 = multiple-modality group; M4 = multiple-modality, mind-motor group.

5.3.2 fMRI results

Group-level ICA via MELODIC identified several independent components across all four tasks; one component included previously studied networks such as the DMN (**Supplementary Figure 5.1 in Appendix G**). Considering the exploratory nature of the study, we investigated significant and borderline significant changes across all independent components identified across all four tasks. Dual regression results indicated significant change in FC after the 24-week program within only one of the group-level spatial maps in the Spatial Span task, along with overall borderline significant changes in eight other regions in the brain (of which seven were further explored and one was excluded as it was considered not relevant for the purposes of this study). The results for each task are reported in further detail below, except for the Monkey Ladder task as no differences were observed at post-test.

For the Spatial Span task across all 40 group-level spatial maps (i.e., Spatial Span independent components [SS]), dual regression revealed significantly decreased co-activation in the right precentral/postcentral gyri (MNI: 36, -22, 58) after the exercise program within SS16 (corrected p = 0.008), as shown in **Figure 5.2A**. There were also borderline significant differences suggesting increased co-activation in the left frontal orbital cortex ([MNI: -36, 27, -22], corrected p = 0.08), with participants showing increased activation at post-test compared to baseline within SS06, please see **Figure 5.2B**. Similarly, borderline significant decreased co-activation in the left frontal lobule/superior frontal gyrus ([MNI: -18, 42, 31], Brodmann Area [BA] 9, corrected p = 0.09) within SS23, as show in **Figure 5.2C**. Additionally, borderline increased co-activation was seen following the exercise program in the left occipital fusiform gyrus/lateral occipital cortex ([MNI: -40, -74, -16], BA 19, corrected p = 0.07) within SS30, as shown in **Figure 5.2D**. The brain regions identified to be involved in each independent component for the Spatial Span task are reported in **Table 5.3.**

Table 5.3. Brain regions composing the Spatial Span independent components (group-level spatial maps) identified via independent component analysis.

Brain Regions	MNI Coordinates (x, y, z)	Z Score
SS06		
Cerebellum	23, -36, -32	11.3
Fontal Lobule (BA 10), R	5, 57, 34	9.1
Inferior Frontal Gyrus, R	56, 28, 25	13.2
Lateral Occipital Cortex, R	56, -63, -14	10.1
Middle Frontal Gyrus, R	50, 33, 33	15.1
Precentral Gyrus, R	51, 10, 30	13.9
Precentral Gyrus, L	-52, -0, 50	9.9
Precuneus Cortex, L	-2, -78, 42	10.5
Supramarginal Gyrus, R	59, -40, 44	12.5
SS16		
Angular Gyrus, L	-43, -53, 19	10.7
Inferior Frontal Gyrus, R	48, 8, 15	10.1
Lateral Occipital Cortex, L	-23, -89, 13	11.5
Lateral Occipital Cortex, R	56, -60, 13	13.4
Middle Frontal Gyrus, R	33, 5, 65	13.1
Occipital Pole, R	18, -98, 7	12.6
Precentral Gyrus, L	-44, -2, 35	11.2
Superior Frontal Gyrus, R	22, -6, 74	10.9
Superior Parietal Lobule, L	-24, -54, 55	10.3
SS23		
Cerebellum	42, -51, -49	14.3
Lateral Occipital Cortex, R	12, -63, 64	9.4
Postcentral Gyrus, R	28, -37, 75	9.8
SS30		
Central Opercular Cortex, L	-47, 3, 3	9.8
Inferior Frontal Gyrus, L	-57, 22, 14	9.4

Note: Regions reported as peak of cluster activation (Z score) within each component.

Abbreviations: SS = Spatial Span independent components (group-level spatial maps); BA = Brodmann Area; L = left hemisphere; R = right hemisphere.

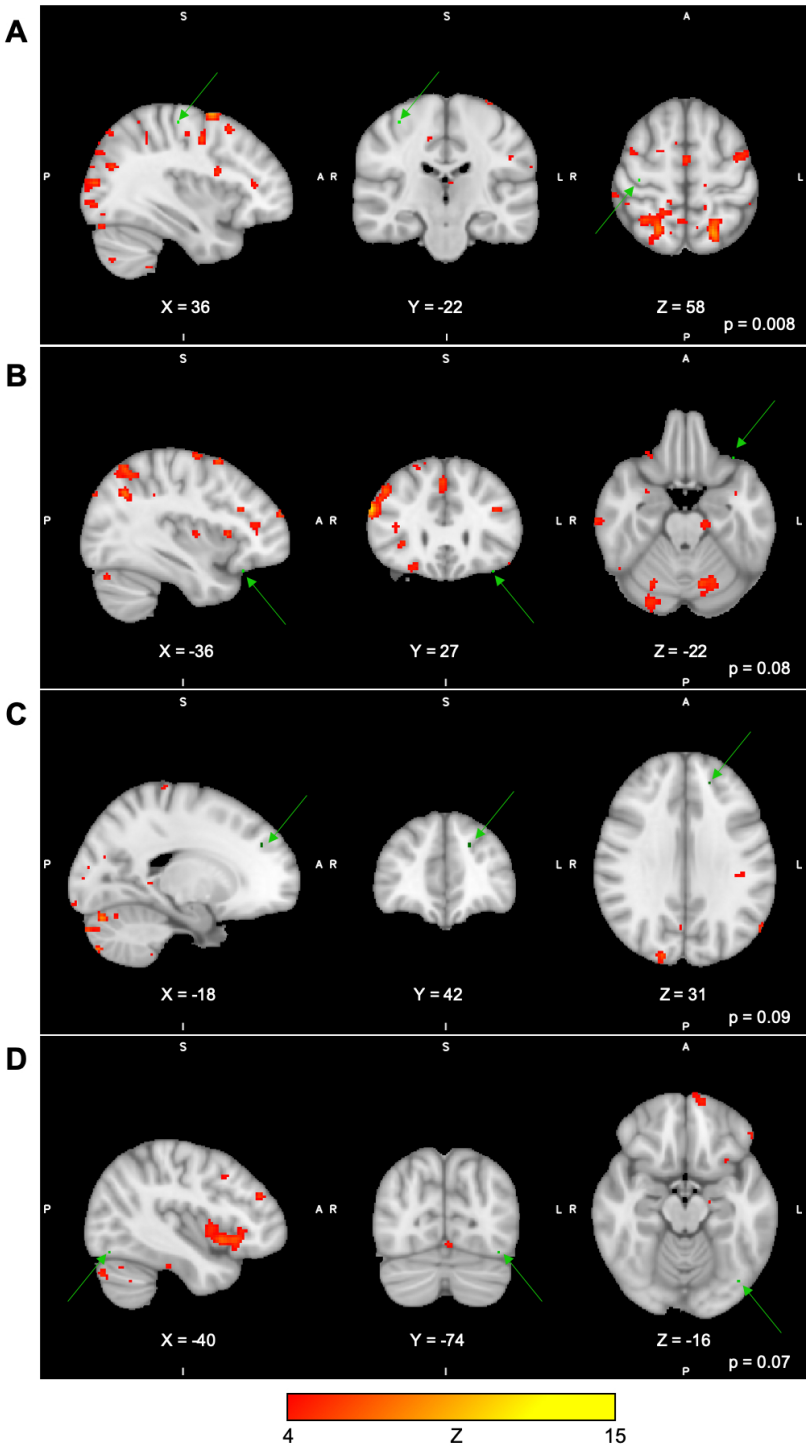

Figure 5.2. Changes within group during Spatial Span task.

Note: In red-yellow contrast are Spatial Span independent components 16 (A), 06 (B), 23 (C), and 30 (D). In dark-light green are regions with changes in group-level spatial maps co-activation after the exercise program (green arrows).

For the Digit Span task, there were no significant differences following the exercise program across all 40 group-level spatial maps (i.e., Digit Span independent components [DS]). However, borderline significant differences were found in the DS06 in which increased co-activation was seen in the left occipital fusiform gyrus ([MNI: -40, -68, -22], corrected p = 0.08), see **Figure 5.3A**. As well, increased co-activation was seen within the DS08 located in the left inferior temporal gyrus ([MNI: -48, -10, -32], corrected p = 0.09), see **Figure 5.3B.** The brain regions identified to be involved in each independent component for the Digit Span task are reported in **Table 5.4**.

Table 5.4. Brain regions composing the Digit Span independent components (group-level spatial maps) identified via independent component analysis.

Brain Regions	MNI Coordinates (x, y, z)	Z Score
DS06		
Supramarginal Gyrus, R	51, -44, 43	9.7
Supramarginal Gyrus, L	-45, -49, 42	9.7
Superior Parietal Lobule, L	-31, -55, 44	13.2
Lateral Occipital Cortex, R	31, -64, 58	9.9
Lateral Occipital Cortex, L	-24, -60, 44	12.3
Angular Gyrus, R	45, -57, 44	12.2
DS08		
Subcallosal Cortex, L	-10, 23, -17	11.9
Frontal Medial Cortex, R	10, 34, -20	12.5
Frontal Medial Cortex, L	-7, 38, -17	10.8

Regions reported as peak of cluster activation (Z score) within each component.

Abbreviations: DS = Digit Span independent components (group-level spatial maps); L = left hemisphere; R = right hemisphere.

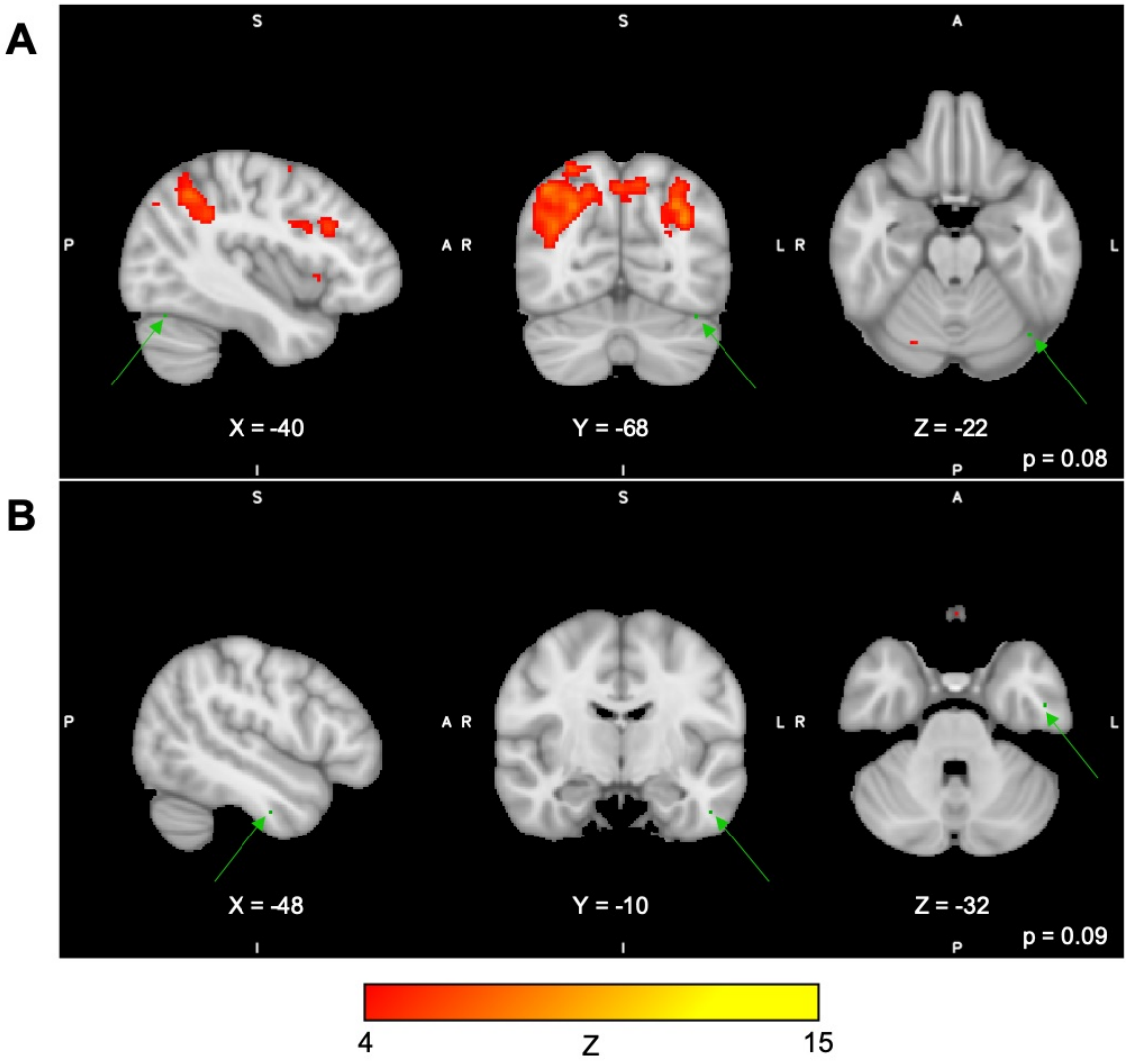

Figure 5.3. Changes within group during the Digit Span task.

Note: In red-yellow contrast are Digit Span independent components 06 (A) and 08 (B). In dark-light green are regions with changes in group-level spatial maps co-activation after the exercise program (green arrows).

For Paired Associates task across all 40 group-level spatial maps (i.e., Paired Associates independent components [PA]), there were no significant differences following the exercise program. However, borderline significant differences were found in PA15 in which increased co-activation was seen in the right temporal lobe ([MNI: 46, 18, -40], BA 38, corrected $p = 0.07$), as well as in the PA34, where decreased co-activation was seen in the left middle temporal gyrus ([MNI: -60, -32, -8], corrected $p = 0.06$) following the exercise program, please see **Figure 5.4A** and **B.** The brain regions identified to be involved in each independent component for the Paired Associates task are reported in **Table 5.5**.

Table 5.5. Brain regions composing the Paired Associates independent components (group-level spatial maps) identified via independent component analysis.

Brain Regions	MNI Coordinates (x, y, z)	Z Score
PA15		
Cerebellum	-30, -51, 43	17.4
Lingual Gyrus, L	-6, -52, -2	10.7
Supramarginal Gyrus, R	53, -41, 20	9.7
Middle Temporal Gyrus, R	52, -48, 6	9.2
PA34		
Temporal Pole (BA21), L	-25, 3, -36	8.2
Parahippocampal Gyrus, L	-24, 1, -36	8.1

Note: Regions reported as peak of cluster activation (Z score) within each component. Abbreviations: PA = Paired Associates independent components (group-level spatial maps); L = left hemisphere; R = right hemisphere.

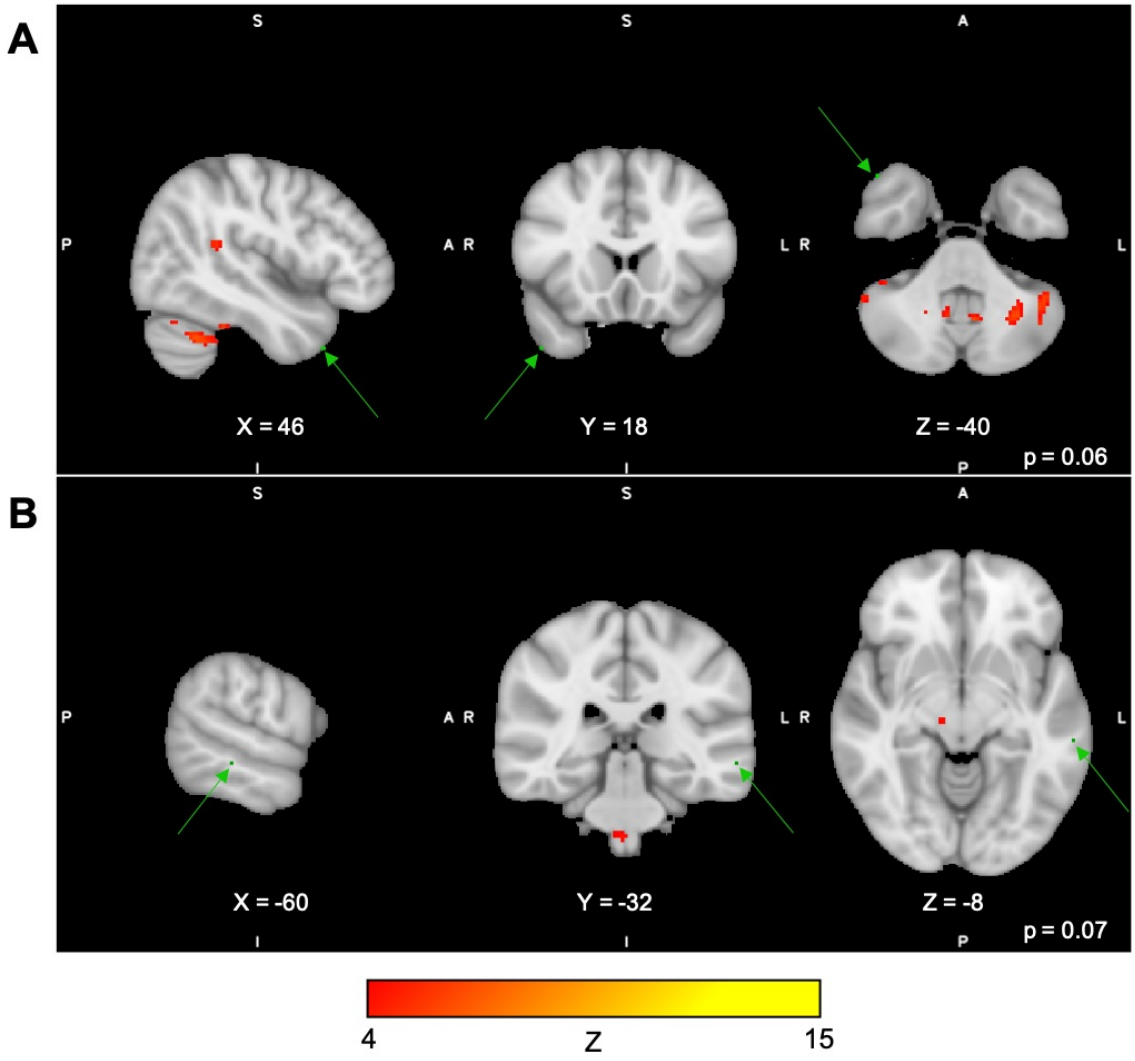

Figure 5.4. Changes within group during the Paired Associates task.

Note: In red-yellow contrast are IC15 (A), IC08 (B). In dark-light green are regions of decreased co-activation after the exercise program (green arrows).

5.3.3 Post hoc analysis

In our *post hoc* analysis (using dual regression stage 2 outputs) we explored within group-level spatial map by extracting summary values that indicated how strongly the voxels of a given map were associated with the time course for that map (e.g., Spatial Span 16) and whether those values changed over time. This *post hoc* analysis was limited to group-level spatial maps that were significant in our main analysis (i.e., dual regression). We extracted summary values from the entire group-level spatial maps as well as for the specific locations that showed changes over time using MNI coordinates. For example, we looked at the average connectivity change within the right precentral/postcentral gyri (MNI: 36, -22, 58) for SS16 from baseline to 24 weeks.

Our results indicated that there were no significant changes in group-level spatial maps average FC from baseline to 24 weeks across all three tasks. When only considering the regions where significant or borderline significant changes occurred in the main analysis, we noted changes in the average FC from baseline to 24 weeks, which confirmed the results from dual regression. The results are summarized in **Figure 5.5** and **5.6**.

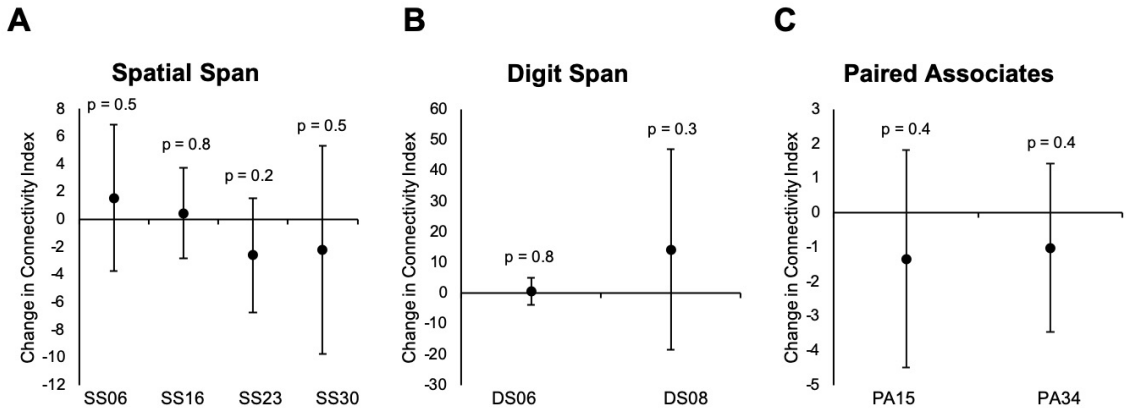

Figure 5.5. Changes overtime in the average strength of functional connectivity within each group-level spatial maps.

Note: Changes overtime in the average strength of functional connectivity within each group-level spatial maps for each task that showed significant changes from baseline to 24 weeks in the main analysis. Data are presented as mean difference from baseline to 24 weeks and associated confidence interval, along with *p* values for significant changes. Abbreviations: SS = Spatial Span independent components; DS = Digit Span independent components; PA = Paired Associates independent components.

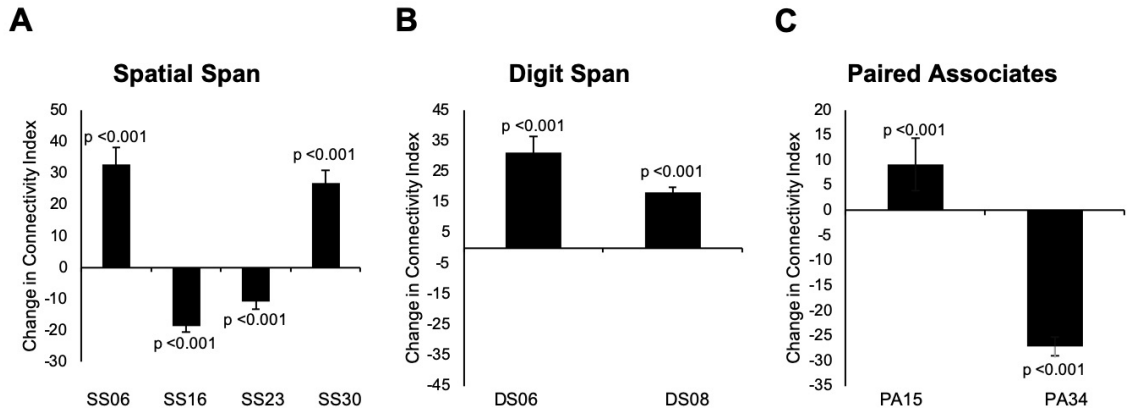

Figure 5.6. Changes overtime in the average strength of functional connectivity for specific regions.

Note: Changes overtime in the average strength of functional connectivity for the specific region where changes from baseline to 24 weeks in group-level spatial map co-activation were observed. Graph A illustrates changes in the left frontal orbital cortex (MNI: -36, 27, -22) for SS06; right precentral/postcentral gyri (MNI: 36, -22, 58) for SS16; left frontal lobule/superior frontal gyrus (MNI: -18, 42, 31, BA 9) for SS23, and left occipital fusiform gyrus/lateral occipital cortex (-40, -74, -16, BA 19) for SS30. Graph B illustrates changes in the left occipital fusiform gyrus (MNI: -40, -68, -22) for DS06, and left inferior temporal gyrus (MNI: -48, -10, -32) for DS08. Graph C illustrates changes in the right temporal lobe (MNI: 46, 18, -40, BA 38) for PA15, and left middle temporal gyrus (MNI: -60, -32, -8) for PA34. Data are presented as mean difference from baseline to 24 weeks and associated confidence interval, along with p values for significant changes. Abbreviations: SS = Spatial Span; DS = Digit Span; PA = Paired Associates independent components; MNI: Montreal Neurological Institute coordinates; BA = Brodmann Area.

5.4 Discussion

We conduced secondary analysis of four memory tasks following a 24-week multiple-modality exercise and with or without additional mind-motor training. We also conducted a data-driven exploratory analysis of task-related cortical FC changes as a result of multiple-modality exercise and mind-motor training (M4 group) in older adults with SCC at increased risk for dementia. Following 24 weeks of intervention, we observed significant differences between groups in the Paired Associates tasks, favouring the experimental group, which received additional mind-motor training (i.e., M4 group) compared to the active control group. Further, our exploratory analysis revealed borderline significant changes in FC during three of the four memory tasks administered in our study. Owing to the approach used in our investigation, results from our fMRI substudy must be interpreted within the context of each task and each independent component derived from the ICA. Our analysis was aimed at exploring within group-spatial maps FC changes after the intervention. Using MELODIC ICA, we were able to identify independent components that included brain regions that were temporally associated (i.e., co-activation) during each task, and therefore, could be understood as functionally associated [62,63]. It is relevant to note that some of the regions also co-active during a task (temporally, but not functionally correlated) might not necessarily be a result of task-related processes, but rather the result of other neuronal processes concurrent to task performance [64]. With these considerations, it is then possible to question whether the intervention had any impact within the FC of the brain for a given task in our study.

Overall, the results from our full sample suggested that additional mind-motor training yielded greater changes in memory measured in the Paired Associates task superior to multiple-modality exercise without mind-motor training, with trends for significant changes in the Digit Span task at the follow-up. Results from our exploratory, data-driven fMRI analysis indicated that our experimental condition might have imparted divergent effects on cortical FC across the tasks employed, however results must be considered with caution. More specifically, for the Spatial Span task, we observed decreased co-activation in the precentral/postcentral gyri (corrected $p = 0.008$) and left frontal

lobe/superior frontal gyrus (trend), as well as increased co-activation in the left frontal orbital cortex and left occipital fusiform gyrus/lateral occipital cortex (trend). For the Digit Span task, we observed increased co-activation in the left occipital fusiform gyrus and left inferior temporal gyrus (trend). Lastly, for the Paired Associates task, we observed increased co-activation in the right temporal lobe (trend) and decreased co-activation in the left middle temporal gyrus (trend). Our *post hoc* analysis investigating changes in FC strength across the entire group-level spatial maps following previous methodology [60], revealed no significant differences following the program. Although, when exploring each specific cortical region within the group-level spatial maps for connectivity strength, we encountered statistical significance, suggesting confirmation of the changes in the co-activation in the spatial maps (please see **Figure 5.6**).

Across all four tasks, significant changes were seen only for the Spatial Span task in the right precentral/postcentral gyri. For this task, we observed decreased co-activation within the group-level spatial maps from baseline to 24 weeks. The group-level spatial map (SS16) in which this change occurred involves co-activation of brain regions previously associated with executive control (e.g., superior parietal lobule), working memory (e.g., superior frontal gyrus), as well as sensorimotor and visuospatial areas [65]. In the context of this group-level spatial map, it is possible to suggest that the decreased FC of the precentral/postcentral gyri with the other cortical regions did not have an imperative effect on task performance at 24 weeks, owing to the fact that there were no significant changes in the behavioural scores for the Spatial Span task for our full sample, nor for our subsample in this M4 group.

The Spatial Span task is believed to measure spatial short-term memory ability [47]. It is noteworthy that our program included a 15-minute block of SSE, in which participants are expected to memorize and reproduce increasingly complex stepping patterns on a gridded floor map [33]. Arguably, the SSE program demands increased attention and short-term spatial memory recall, which could lead to improvements in overall spatial memory performance. Although speculative, it is possible that the SSE program, in addition to the multiple-modality exercise program, could have yielded FC changes involving co-activation of the precentral/postcentral gyri during Spatial Span task performance in the

current study. This could be further supported by trends of increased co-activation observed in the left inferior temporal gyrus during another task in this study, the Digit Span task, a region engaged in motor function and known to show decreased connectivity in older adults compared to young individuals in resting-state fMRI [66]. Due to methodological limitations, these interpretations must be interpreted with caution.

It is, however, undoubtedly challenging to attribute changes in FC of motor-related regions (i.e., precentral/postcentral gyri and left inferior temporal gyrus) during computer-based memory tasks to the effects of our program, since we are unable to establish a direct connection between changes in the co-activity and task performance, in addition to estimating region engagement from resting to task-related states [64]. Due to a lack of significant changes in the behavioural measures for the Spatial Span and Digit Span tasks (trend for significant changes in the full sample), it is also difficult to suggest whether increases in co-activation would indicate negative changes in FC due to aging or disease-related processes and/or whether decreases in co-activation would indicate efficiency during task performance due to the intervention applied in our study. Moreover, as mentioned above, these processes could also be considered task-irrelevant, which might or might not be detrimental to task performance [64]. In addition, a previous study did not observe changes in FC of motor regions following 6 and 12 months of AE in older adults [19]. Voss and colleagues (2010) reported that the exercise program did not lead to any changes in regional FC in motor areas such as the right precentral gyrus and left inferior temporal gyrus. There is evidence from animal literature suggesting brain plasticity identified as increased synaptic density and expression of proteins associated with dendritic growth in motor-related regions following treadmill exercise [67,68], and even more so with more complex motor training [69].

Therefore, in our limited design, we cannot determine with certainly if the task-related FC changes observed in our study are due to the intervention itself and whether these are positive meaningful changes. In the context of previous studies adopting a similar data analysis methodology, Chirles and colleagues (2017) investigated FC changes in older adults diagnosed with MCI following a 12-week AE program [20]. The authors were mainly interested in exploring FC of the posterior cingulate cortex and precuneus within the

DMN. The authors reported increased co-activation in resting-state FC between the posterior cingulate cortex and precuneus regions and the several other cortical regions, including the right postcentral gyrus. This suggested that the aerobic program enhanced recruitment of preserved brain regions in MCI patients, which possibly reflected in improvements in behavioural measures of cognitive function. The FC improvements were not seen in the healthy control group—despite improvements in behavioural measures in these participants [20].

Noteworthy, we reported borderline significant changes (confirmed in our *post hoc* region-specific analysis) in FC in the right temporal lobe (BA 38) and left middle temporal gyrus during the Paired Associates task, two regions heavily involved in memory processes [65]. Moreover, our behavioural data showed greater changes in the Paired Associates tasks for our full sample analysis and also borderline significant changes in the task performance in our subsample. Under these considerations, we can postulate that our multiple-modality exercise and mind-motor training program might have had a positive effect in FC underlying visuospatial memory, as measured by improved performance in the full sample, and in our 9 participants from the M4 group (trend at $p = 0.08$) in the Paired Associates task with a medium to large effect size (i.e., Cohen's d for max score = 0.72, and 0.74 for mean score, **Supplementary Table 5.2 in Appendix G**). More importantly, results from our full sample analysis revealed that there were indeed significant improvements in Paired Associates task performance above and beyond the active control group ($p = 0.001$ for changes overtime, and $p = 0.019$ for difference between groups at 24 weeks). The data from our full sample offers confirmation and strengthens our borderline significant changes in the Paired Associates behavioural data within our subsample. This can then provide context and assist in interpretation of the borderline significant changes in FC observed in this fMRI sub-study.

Cortical regions involved in the group-level spatial maps where the FC changes occurred, that is, independent components PA15 and PA34 (please see **Table 5.5**) were predominately located in the medial temporal lobe, including left and right hippocampi, parahippocampal gyri, and middle temporal gyrus (please see **Supplementary Figure 5.2**

in Appendix H). It is well-known that these regions have been implicated in memory function [65,70,71], and have been observed to be heavily involved in the Paired Associates task memory encoding and retrieval [72]. From a clinical perspective, these findings could have important implications, considering that these aforementioned regions are hallmarks of pathophysiological changes (e.g., amyloid beta deposition) in MCI and early/prodromal stages of Alzheimer's disease [73], including cortical atrophy proceeding Alzheimer's disease diagnosis [74], and disruption of resting-state FC possibility due to Alzheimer's disease biomarker deposition [24]. Moreover, performance on a variant of the Paired Associates task employed in this study demonstrated marked differences between MCI patients and healthy controls, characterized by decreased bilateral hippocampal and parahippocampal activation during task in MCI patients compared to controls [72].

Here, we were able to demonstrate significant changes in the behavioural component of memory function measured via the Paired Associates task, this is an encouraging result and future research could investigate the effects of multiple-modality exercise and mind-motor training in medial temporal lobe regions, employing a full RCT design and including resting state and task-related FC as main outcomes. It would be relevant to use a task such as the Paired Associates task to explore such effects, as postulated by De Rover and colleagues (2011) regarding the relevance of the task as a possible biomarker of Alzheimer's disease risk [72].

5.4.1 Limitations

Our findings should be interpreted with caution and in the context of our limitations. Although the CBS is grounded in well-validated neuropsychological tests [44], this is the first study to apply this method to evaluate the effects of exercise in memory function in older adults with SCC. Also, participants included in this study were predominantly Caucasian, well educated, and functionally independent, thus, our results may not be generalizable to other populations. Four our exploratory fMRI substudy, our data analysis was restricted to nine subjects only, a very small sample size, limiting our ability to generalize the results. We had limited resources to collect fMRI data from our active control group, and, therefore, we cannot establish certainty on whether our findings were due to main effects of the intervention program—even though the results from the

experimental group in our full data analysis of memory tasks showed greater changes in memory following the program (driven by changes in the Paired Associates task), superior to the active control group. As well, we did not include resting-state data in our study, impairing our ability to determine which regions identified in the task-derived independent components were in fact relevant to task performance or were a result of other processes irrelevant to task performance [64]. Importantly, our group-level results were also susceptible to artifacts, and the group-level maps could have included regions in which co-activation was seen due to noise, despite our efforts to correctly identify and remove artifact-driven independent components at the individual level. As well, despite our efforts to mitigate sources of noise and variability influencing the BOLD response, we acknowledge that this is still a possibility. However, it is unlikely that the individual-level and group-level maps would significantly suffer from, or be heavily influenced by, variability of BOLD response or non-task processes, as BOLD variability would be a product of random noise, and not a specific pattern equally present in all individuals during assessment.

Another limitation of our study was that we adopted a model-free approach to analyze the task-related fMRI data [75]. We used this approach to investigate whole-brain, voxel-wise FC maps that could have been active for the duration of each task, and therefore, our methods were restricted to data-driven exploratory analysis as opposed to a hypothesis-driven approach (where previous knowledge would have informed the decision of limiting analysis to a set of cortical and subcortical regions of interest) [75]. In addition, our model-free design only allowed us to collect data during a single 5-minute block of ongoing trials for each task and, consequently, we were not able to time-lock stimulus and data collection of each single trial within the block (as commonly done in event-related or block design studies), this could have ultimately reduced our power to detect true significant treatment effects [43].

In addition, FC data is particularly sensitive to head motion and physiological artifacts linked to respiratory and cardiac rhythms [23]. Furthermore, FC data provide essential insights into cortical and subcortical coupling at rest and during task-related fMRI, however, is unknown whether observed FC within a group-level spatial map in this study

reflect stable or temporary connectivity configurations in the brain [23]. Finally, our study employed a multi-domain intervention, involving components of aerobic training, resistance training, as well as mind-motor training. This is a novel approach, and to our knowledge, no previous neuroimaging studies have been conducted to investigate changes in FC during memory tasks in older adults with SCC following a multi-domain program such as ours. Therefore, methodological differences between our study and previous studies create a barrier to draw conclusions regarding our results.

5.5 Conclusions

Our aim was to explore the effects of 24 weeks of multiple-modality exercise with or without additional mind-motor training in four memory tasks, and explore task-related, cortical and subcortical FC changes in older adults with SCC. Our findings indicated that multiple-modality exercise with additional mind-motor training yielded greater changes in memory function during the Paired Associates task compared to an active control group. Further, our intervention might have resulted in divergent FC adaptations, including significant decreased co-activation in the precentral/postcentral gyri during the Spatial Span task. Of particular interest, we also reported borderline significant increased co-activation in the right temporal lobe, accompanied by decreased co-activation in the left middle temporal gyrus within two group-level spatial maps involving regions of the medial temporal lobe during the Paired Associates task. These findings provide insight into the potential of our multiple-modality exercise and mind-motor training intervention to promote improvements in behavioural measures of visuospatial memory, as well as impart FC adaptations in brain regions relevant to Alzheimer's disease risk. Future research should emphasize the clinical relevance of these FC changes following exercise in the context of disease prevention and treatment.

Summary

This chapter reported on changes in memory function following multiple-modality exercise with or without additional mind-motor training (i.e., square-stepping exercise). The findings from a secondary analysis revealed that additional mind-motor training imparted a specific effect in the Paired Associates memory task following the 24-week exercise program. Furthermore, an exploratory analysis of functional magnetic resonance imaging data suggested that the experimental group underwent alterations in functional connectivity within brain activation maps in motor function regions. Importantly, trends for changes in functional connectivity in memory-related regions during the Paired Associates task were also reported. These changes at the cortical level could represent specific adaptations following the intervention program, and account for the improvements in behavioural measure observed in the study full sample. Therefore, it is plausible that the program had a very specific effect in visuospatial memory function as assessed by the changes in the Paired Associates task. Considering the clinical relevance of the regions where functional changes occurred during this task, these findings suggest the potential of additional mind-motor training to impart protective effects against neurodegenerative processes in regions sensitive to Alzheimer's disease pathophysiology.

Ultimately, the findings from this study indicate that combining non-pharmacological strategies to improve cognition in older adults with subjective cognitive complaints may have greater benefits to cognition, particularly memory function. Future research should consider experimenting with other possible combinations of these strategies (e.g., diet, multiple-modality exercise, cognitive training) and could target other populations with added risk for dementia beyond subjective cognitive complaints (e.g., those with multimorbidity or cardiovascular disease burden).

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Chapter 6

6 Thesis discussion

6.1 Summary of findings

The overall aim of this thesis was to study the effects of multiple-modality exercise (MME) and mind-motor training in mobility, cognition, and neuroimaging outcomes in a population of older adults at risk of dementia. It was also important determine whether a novel intervention believed to provide simultaneous cognitive and physical engagement, that is, square-stepping exercise (SSE), would impart additive benefits to MME in this population. A scoping review (Chapter 2) reported current evidence on MME effects in cognition and neuroimaging outcomes in older adults without dementia. The subsequent chapters reported findings from a 24-week randomized controlled trial (RCT) investigating the effects of MME and mind-motor training on cognition (Chapter 3) and mobility outcomes (Chapter 4) compared to MME without additional mind-motor training. Further, based on findings from Chapter 2, an exploratory study was conducted to investigate the effects of MME and mind-motor training on memory as well as associated markers of neuroplasticity, by analyzing functional magnetic resonance imagining data (Chapter 5).

The main findings of this thesis are as follows: 1) a scoping review of the literature concluded that MME is beneficial to global and domain-specific cognitive function in older adults without dementia across a myriad of cognitive measures. However, these benefits were evident when studies compared MME to no-treatment control groups, which is an important limitation—raising the hypothesis that such improvements could partially result from confounding factors, such as socialization; 2) in a 24-week RCT, additional mind-motor training seemed to benefit global cognitive functioning and memory outcomes—this was confirmed after a 28-week no-contact follow-up; 3) additional mind-motor training did not seem to be effective in improving mobility outcomes, as no improvements were seen in any of the usual and dual-task (DT) gait measurements explored; 4) additional mind-motor training seemed to specifically affect

visuospatial memory performance, as well as impart adaptations in functional connectivity involving mainly areas of the motor function (decreased co-activation of the right precentral/postcentral gyri) and memory processing (right temporal lobe, and middle temporal gyrus).

The main findings from this thesis revealed that MME with additional mind-motor training led to trends for greater benefits in global cognitive functioning and memory, corroborating previous evidence [1]. However, the results from the main analysis including all memory tasks in a single composite score did not reach statistical significance. In previous investigations, SSE was administered for longer duration and frequency [1,2], while only 15 minutes per session, 3 days/week, was administered in this study. This could suggest a dose-response relationship in which longer exposure to SSE would reflect greater cognitive changes. The exploratory analysis conducted of each memory task individually, revealed that the intervention resulted in significant changes in the Paired Associates task only, a visuospatial memory task. This suggests a specific effect of SSE on memory function, but not other cognitive domains.

For mobility outcomes, SSE probably lacked enough intensity to promote functional changes in usual and DT gait performance, such as increasing muscle strength and neuromuscular control, in the lower extremities [3–6]. As the development of physical performance during the SSE portion of the intervention was not prioritized, participants were expected to focus on memorization and accuracy while repeating each stepping pattern. Thus, it is plausible that the program did not impart muscle adaptions that would reverberate gait improvements superior to the control condition (i.e., balance, range of motion, and breathing exercises). Furthermore, the lack of significant changes in other cognitive domains related to executive functioning (i.e., concentration, reasoning and planning) may also explain the lack of changes in the mobility outcomes, particularly DT gait performance following the intervention.

A neuroimaging exploratory study provided insight into the impact of the intervention on memory function and underlying functional connectivity changes. During one of the memory tasks, Spatial Span, significant decreased co-activation in the right

precentral/postcentral gyri was observed at the end of the study. Trends were also noted for significant changes during the Digit Span and Paired Associates tasks. Arguably, the SSE program demands increased attention and short-term visuospatial memory recall, which could lead to improvements in overall visuospatial memory performance as demonstrated by changes in the Paired Associates task. The findings suggest the potential of this intervention to yield neuroplasticity in mechanisms associated with memory performance. Contemplating the limitations in the exploratory study for the neuroimaging outcomes (e.g., small sample size, no control group), the implications and relevance of these findings remain to be further explored. For instance, it would be important to determine whether the presence of neuroplasticity despite change in behaviour culminates in overall neuroprotective effects, such as increased brain reserve and resilience to neuropathophysiological changes [7,8].

6.2 Future directions

Evidence from histological studies suggest that dementia has multietiological cause, is diverse and complex in nature, and its impact varies from individual to individual [9]. This complexity creates a challenge to prevent, treat, or care for dementia with unilateral and isolated strategies, such as exercise, diet, or cognitive training alone [10]. Therefore, it seems necessary to emphasize multidomain approaches targeting multiple aspects of health and disease prevention [11,12].

Promising evidence from a multidomain trial administering diet, exercise, cognitive training, and vascular risk monitoring suggested large improvements over time in global cognitive function, processing speed, and executive functioning in older adults at risk of dementia [13]. New trials around the world are now under development to replicate these findings [11,12], including in Canada [14]. The current scenario is encouraging, and it is possible that with replication of the evidence, future research could then start tailoring/manipulating specific elements of these multicomponent interventions. For instance, some may benefit more from dietary changes, while others from exercise programs, or cognitive training. Thus, each multicomponent intervention could be individualized, with emphasis on particular elements from which individuals would most likely benefit, while still being exposed to other components.

It is also relevant to identify target populations at higher risk in order to refine prevention strategies. In this perspective, targeting individuals with other non-communicable chronic conditions could also aid in more effective preventive strategies [15,16]. Chronic conditions such as hypertension are believed to increase the risk of cognitive impairment and dementia incidence [15,17]. In fact, the deleterious effects of hypertension on cognition have been particularly observed in executive functioning, processing speed, and memory [18,19]. Hypertension is a major precursor of strokes [20] and vascular cognitive impairment [17], manifestations of cerebral small vessel disease, such as white matter hyperintensities [21–23], and is linked to hippocampal atrophy [24], as well as Alzheimer's disease pathophysiology [25].

Hypertension can be managed with exercise, and high-intensity interval training shows potential for greater benefits over other strategies (e.g., regular continuous aerobic training) [26–28]. We are currently investigating whether individuals with diagnosis of hypertension and subjective cognitive complaints benefit from high-intensity exercise combined with mind-motor training (i.e., SSE) in measures of global and domain-specific cognitive function, vascular health, and mobility (ClinicalTrials.gov Identifier: NCT03545958). The results from this trial will aid in determining whether these individuals, who are at higher risk of Alzheimer's disease and vascular dementia [29], can benefit from a tailored intervention targeted at reducing blood pressure and improving cognition. Recently, results from the SPRINT-MIND trial showed that intensive hypertension treatment with medication over three to five years significantly reduced the risk of mild-cognitive impairment [30], although no changes in gait were observed [31]. This certainly offers encouragement for more research with non-pharmacological interventions targeting this population.

Furthermore, other markers of vascular function associated with hypertension seem to show promising significance for clinical investigation. Fluctuations in blood pressure over 24 hours, known as blood pressure dipping, can indicate cardiovascular disease risk and mortality [32,33]. In individuals in which blood pressure levels from daytime to nighttime experience no decline, that is, no dipping, this blunted response has been associated with an increased risk of cerebrovascular events and dementia risk [32,33]. For

example, we conducted a preliminary cross-sectional data analysis from 333 community-dwelling older adults recruited from three studies in our laboratory, using standardized methods [34,35]. Lower blood pressure dipping from daytime to nighttime was associated with poorer usual and DT gait parameters (i.e., verbal fluency task), independent of hypertension diagnosis. The associations remained significant even after adjustment for other important confounding variables, i.e., age, sex, global cognitive functioning, body mass index, and diabetes diagnosis (F_{change} [1,325] = 7.1, p = 0.008, R^2 = 0.019, data not published). Furthermore, in a subsample of these participants who underwent magnetic resonance imaging (n=31), lower blood pressure dipping was associated with smaller hippocampal volume (F_{change} [1,26] = 5.5, p = 0.027, R^2 = 0.11, data not published).

These preliminary findings suggest that lower blood pressure dipping may be a marker of higher risk of mobility disability and hippocampal atrophy among community-dwelling older adults. In this perspective, individuals with blunted blood pressure response could be considered ideal candidates for interventions aimed at reducing dementia risk by managing cardiovascular disease burden in future studies.

6.3 Conclusions

In this thesis, a scoping review on the effects of MME in older adults without dementia was conducted, as well as a 24-week, two-arm RCT with a 28-week no-contact follow-up in community-dwelling older adults with subjective cognitive complaints. Overall, findings ultimately suggest that MME may benefit cognition, brain structure, and function, however more high-quality evidence is warranted. Further, MME with additional mind-motor training is beneficial to cognition, does not seem to impact mobility, but may potentially influence neuroplasticity in older adults at risk of dementia. These findings are encouraging as dementia burden continues to increase worldwide, and without a cure, effective preventive strategies must be prioritized.

The challenge is to develop and implement high-quality interventions through research that can be easily translated into real-world settings, with potential for long-lasting impact. The studies involved in this thesis aimed to develop such research. A pragmatic, community-based intervention was employed in a group setting requiring minimum

equipment and basic training. With a distinctive approach in combining MME and mind-motor training, the intervention program administered in this thesis could be a step forward in the search for an optimal non-pharmacological alternative to aid in dementia prevention. Future research should investigate the effects of non-pharmacological interventions such as combined exercise, cognitive training and diet in individuals with added risk of dementia, including those with cardiovascular disease burden.

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Appendices

Appendix A: Final search strategy for MEDLINE

MEDLINE search parameters
1. Aged/ or Aging/ or older adults.mp.
2. (Elderly or Elders).mp.
3. Seniors.mp.
4. Multiple-Modality.mp.
5. Combined.mp.
6. Global.mp.
7. Integrated.mp.
8. (Multi-component or Multicomponent).mp.
9. (Multi-domain or Multidomain).mp.
10. (Multi-faceted or Multifaceted).mp.
11. (Multi-modal* or Multimodal).mp.
12. Exercise/
13. (Aerobic exercise or Aerobic training).mp.
14. (Balance exercise or Balance training).mp.
15. (Cardiovascular exercise or Cardiovascular training).mp.
16. Endurance exercise.mp. or Endurance Training/
17. (Functional exercise or Functional training).mp.
18. (Physical activity or Physical exercise or Physical training).mp.
19. Resistance training.mp. or Resistance Training/
20. (Strength exercise or Strength training).mp.
21. Walking.mp. or Walking/
22. Cognition/
23. Brain/
24. Brain function*.mp.
25. Cognitive function*.mp.
26. Global cognitive function*.mp.
27. Mental ability.mp.
28. Neurocognition.mp.
29. Neurocognitive function*.mp.
30. Attention/
31. Concentration.mp.
32. Decision Making/
33. Dual-task*.mp.
34. Executive function*.mp. or Executive Function/
35. (Information processing speed or Processing speed).mp.
36. Memory/
37. Memory function*.mp.
38. Mental flexibility.mp.
39. Problem Solving.mp. or Problem Solving/
40. Reasoning.mp.
41. Thinking/
42. Thinking ability.mp.
43. Alzheimer's disease/
44. (Cognitive complaint* or Subjective cognitive complaint*).mp.
45. Cognitive Dysfunction/
46. Cognitive impairment.mp.
47. Dementia/
48. Healthy.mp.

49. (Mild-cognitive impairment or MCI).mp.
50. Memory impairment.mp.
51. Dementia, Vascular/
52. Subjective memory impairment.mp.
53. (Memory complaint* or Subjective memory complaint*).mp.
54. or/1-3 [**Older adults]
55. or/4-11 [**Multiple-modality]
56. or/12-21 [**Exercise types]
57. or/22-42 [**Cognition, all terms]
58. or/43-53 [**Clinical status]
59. and/54-58 [**All]

Appendix B: Supplementary Table 3.1

Description of the Cambridge Brain Sciences cognitive battery.

M2: Multiple-modality exercise group (comparison group)	**M4: Multiple-modality, mind-motor exercise group** (intervention group)
Warm-up (5 minutes) • Light aerobics • Dynamic range of motion of the major joints	**Warm-up (5 minutes)** • Light aerobics • Dynamic range of motion of the major joints
Aerobic Exercise (20 Minutes) • Large rhythmical endurance activities (e.g., walking, marching, • sequenced aerobics) • Keep HR continuously in target zone (i.e., not interval training) • Moderate to vigorous intensity • RPE: 5–8 on scale of 0–10 • Participants to check HR ½ way through and at end of AE.	**Aerobic Exercise (20 Minutes)** • Large rhythmical endurance activities (e.g., walking, marching, • sequenced aerobics) • Keep HR continuously in target zone (i.e., not interval training) • Moderate to vigorous intensity • RPE: 5–8 on scale of 0–10 • Participants to check HR ½ way through and at end of AE.
Aerobic Cool Down (5 minutes) • Safely bringing heart rates down	**Aerobic Cool Down (5 minutes)** • Safely bringing heart rates down
Strength Training (10 minutes) • Therabands, wall or chair exercises, core strengthening • Day 1 – Upper body focus • Day 2– Lower body focus • Day 3 – Core focus	**Strength Training (10 minutes)** • Therabands, wall or chair exercises, core strengthening • Day 1 – Upper body focus • Day 2– Lower body focus • Day 3 – Core focus
Balance, Range of Motion & Breathing (15 minutes) • Keep HR below target zone • Dynamic, static and functional balance • Breathing and relaxation exercises • Finger exercises • Range of motion (e.g., arm circles)	**Mind-Motor Training (15 minutes)** • Keep HR below target zone • Progressive, group-based, Square Stepping Exercise (SSE) • Stretching (5 minutes) Stretching (5 minutes)
Total: 60 min exercise intervention	Total: 60 min exercise intervention

Abbreviations: HR = heart rate; RPE = rating perceived exertion.

Appendix C: Supplementary Table 4.1

Differences between groups in the study outcomes for all completers.

Outcomes	Difference between groups in estimated mean change (95% CI) [a]			
	24 weeks	*p* Value	52 weeks	*p* Value
Usual gait				
Gait velocity, cm/s	–10.1 (–.16.2 to –3.9)	.001*	–7.5 (–14.4 to –.5)	.035*
Step length, cm	–2.7 (–4.8 to –.6)	.011*	–1.9 (–4.2 to .4)	.10
Cycle time variability, % [b]	.01 (–.09 to .11)	.87	–.002 (–.11 to .11)	.97
DT gait (VF)				
Gait velocity, cm/s	–.8.3 (–16.5 to –.1)	.048*	–5.9 (–16 to 4.3)	.30
Step length, cm	–1.8 (–4.2 to .6)	.10	–.5 (–3.2 to 2.2)	.70
Cycle time variability, % [b]	.16 (.0001 to .33)	.049*	.12 (–.05 to .29)	.16
DT gait (S7)				
Gait velocity, cm/s	–.5.7 (–15.1 to 3.6)	.22	–7.2 (–17 to 2.6)	.15
Step length, cm	–.8 (–3.5 to 1.8)	.53	–1.5 (–4.2 to 1.2)	.26
Cycle time variability, % [b]	.10 (–.07 to .27)	.25	.11 (–.07 to .29)	.23
Secondary outcomes				
DT cognitive accuracy (VF), ccr/s [c]	–.03 (–.22 to .17)	.78	.15 (–.04 to .33)	.12
DT cognitive accuracy (S7), ccr/s [c]	–.04 (–.23 to .15)	.67	.02 (–.16 to .21)	.79

Note: Reference category = M2. 103 participants who completed the study were included in this sensitivity analysis (M2 = 53; M4 = 50). [a] Calculated from linear mixed effects regression models that included group (M2 or M4), time (baseline, 24 and 52 weeks), and group × time interaction terms. A total of 13 models were conducted, corresponding to each outcome listed in the first column. [b] Log transformation applied. * Significant differences between groups in estimated mean change from baseline. Abbreviations: 95% CI = confidence interval; M2 = multiple-modality group; M4 = multiple-modality, mind-motor group; 24-wk = intervention endpoint; 52-wk = study endpoint; DT = dual-task; VF = verbal fluency task; S7 = serial sevens task; CCR = rate of correct cognitive response.

Appendix D: Supplementary Table 4.2

Within-group estimated mean changes from baseline in the study primary outcomes.

	M2 (n=64)		M4 (n=63)	
Outcomes [a]	Estimate (95% CI)	*p* Value	Estimate (95% CI)	*p* Value
Usual gait				
Velocity, cm/s				
24-wk	7.28 (3.33 to 11.23)	< .001*	-2.78 (-6.86 to 1.29)	.18
52-wk	2.63 (-1.98 to 7.25)	.26	-4.09 (-8.91 to 0.73)	.09
Step length, cm				
24-wk	2.23* (0.9 to 3.57)	.001*	-0.68 (-2.06 to 0.69)	.33
52-wk	0.52 (-0.98 to 2.04)	.49	-1.52 (-3.1 to 0.05)	.06
Cycle time variability, % [b]				
24-wk	-0.02 (-0.08 to 0.03)	.45	-0.008 (-0.07 to 0.05)	.80
52-wk	-0.01 (-0.08 to 0.05)	.70	-0.02 (-0.09 to 0.05)	.54
DT gait (VF)				
Velocity, cm/s				
24-wk	3.34 (-1.97 to 8.66)	.21	-4.56 (-10.04 to 0.92)	.10
52-wk	-0.86 (-7.67 to 5.94)	.80	-5.7 (-12.85 to 1.45)	.12
Step length, cm				
24-wk	0.1 (-1.45 to 1.66)	.89	-1.67 (-3.29 to -0.05)	.042*
52-wk	-0.79 (-2.59 to 1.01)	.39	-1.18 (-3.06 to 0.68)	.21
Cycle time variability, % [b]				
24-wk	-0.08 (-0.18 to 0.01)	.10	0.05 (-0.04 to 0.16)	.27
52-wk	-0.07 (-0.18 to 0.03)	.19	0.03 (-0.08 to 0.15)	.58
DT gait (S7)				
Velocity				
24-wk	4.86 (-1.08 to 10.82)	.11	-2.48 (-8.62 to 3.65)	.43
52-wk	4.87 (-1.68 to 11.43)	.14	-2.65 (-9.46 to 4.16)	.44
Step length				
24-wk	0.93 (-0.79 to 2.65)	.28	-0.56 (-2.35 to 1.21)	.53
52-wk	0.71 (-1.02 to 2.45)	.42	-1.45 (-3.26 to 0.35)	.11
Cycle time variability (S7), % [b]				
24-wk	-0.05 (-0.16 to 0.04	.29	0.05 (-0.06 to 0.16)	.37
52-wk	-0.09 (-0.2 to 0.02)	.13	0.01 (-0.1 to 0.13)	.83
DT cognitive accuracy (VF), ccr/s				
24-wk	–.003 (–.13 to .12)	.96	–.05 (–.18 to .08)	.46
52-wk	–.01 (–.13 to 12)	.92	.13 (–.001 to .26)	.052**
DT cognitive accuracy (S7), ccr/s				
24-wk	.08 (–.04 to .20)	.21	.03 (–.09 to .16)	.60
52-wk	–.01 (–.14 to 11)	.83	.002 (–.13 to .13)	.96

Note: [a] Data displayed as means estimate and 95% confidence interval. [b] Log transformation applied. [c] Square root transformation applied. * Significant changes from baseline; ** trend for significant changes from baseline. Abbreviations: 95% CI = confidence interval; M2 = multiple-modality group; M4 = multiple-modality, mind-motor group; 24-wk = intervention endpoint; 52-wk = study endpoint; VF = verbal fluency task; S7 = serial sevens task; CCR = rate of correct cognitive response.

Appendix E: Supplementary Table 5.1

Baseline demographic and clinical characteristics.

Variables	Study sample (n = 9)
Demographics	
Age, yr	67.8 (8.8)
Women, *n*	8
Caucasian, *n*	9
Education, yr	14.1 (3.1)
MoCA, score	24.9 (2.9)
MMSE, score	29.2 (0.7)
Hypertension, *n*	5
Hypercholesterolemia, *n*	2
Type 2 diabetes, *n*	1

Note: Data presented either as mean (standard deviation) or *n* where applicable. Abbreviations: MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment.

Appendix F: Supplementary Table 5.2

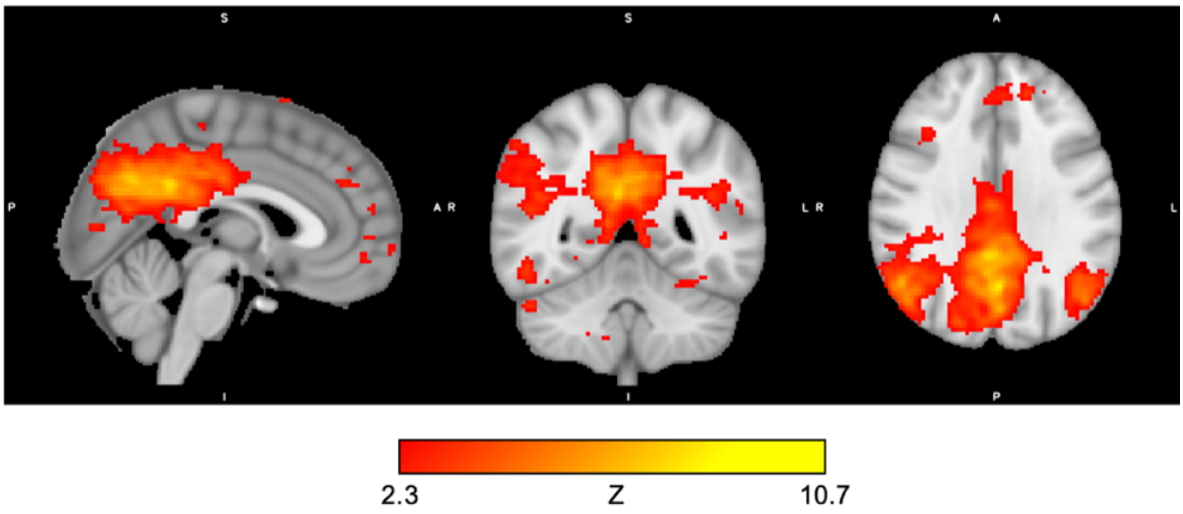
Changes in behavioural cognitive tasks from baseline to 24 weeks.

Behavioural tasks	Baseline	24 weeks	Differences from baseline (95% confidence interval)	*t* Value	*p* Value	Cohen's *d*
Monkey Ladder †						
Max score	5.8 (.7)	6 (1.1)	0.3 (-0.3 to 0.8)	1	0.35	0.35
Mean score	4 (0.5)	4.4 (0.6)	0.4 (-0.1 to 0.9)	1.7	0.12	0.62
Spatial Span †						
Max score	4.4 (1.3)	4.3 (0.9)	-0.1 (-1.3 to 1)	-0.3	0.80	-0.09
Mean score	3.5 (0.9)	3.5 (0.8)	0.01 (-0.8 to 0.8)	-0.02	0.99	-0.01
Digit Span						
Max score	6.2 (1.6)	6.3 (1.1)	0.1 (-0.4 to 0.6)	0.6	0.59	0.18
Mean score	5.1 (1.2)	5 (0.9)	-0.1 (-0.5 to 0.3)	-0.7	0.49	-0.24
Paired Associates †						
Max score	3.9 (0.8)	4.6 (0.9)	0.8 (-0.1 to 1.6)	2	0.08	0.72
Mean score	2.9 (0.4)	3.3 (0.6)	0.4 (-0.1 to 0.8)	2.1	0.08	0.74

Behavioural tasks are expressed in arbitrary units. Data presented as mean (standard deviation) or otherwise indicated. †Behavioural data missing for 1 participant in each task.

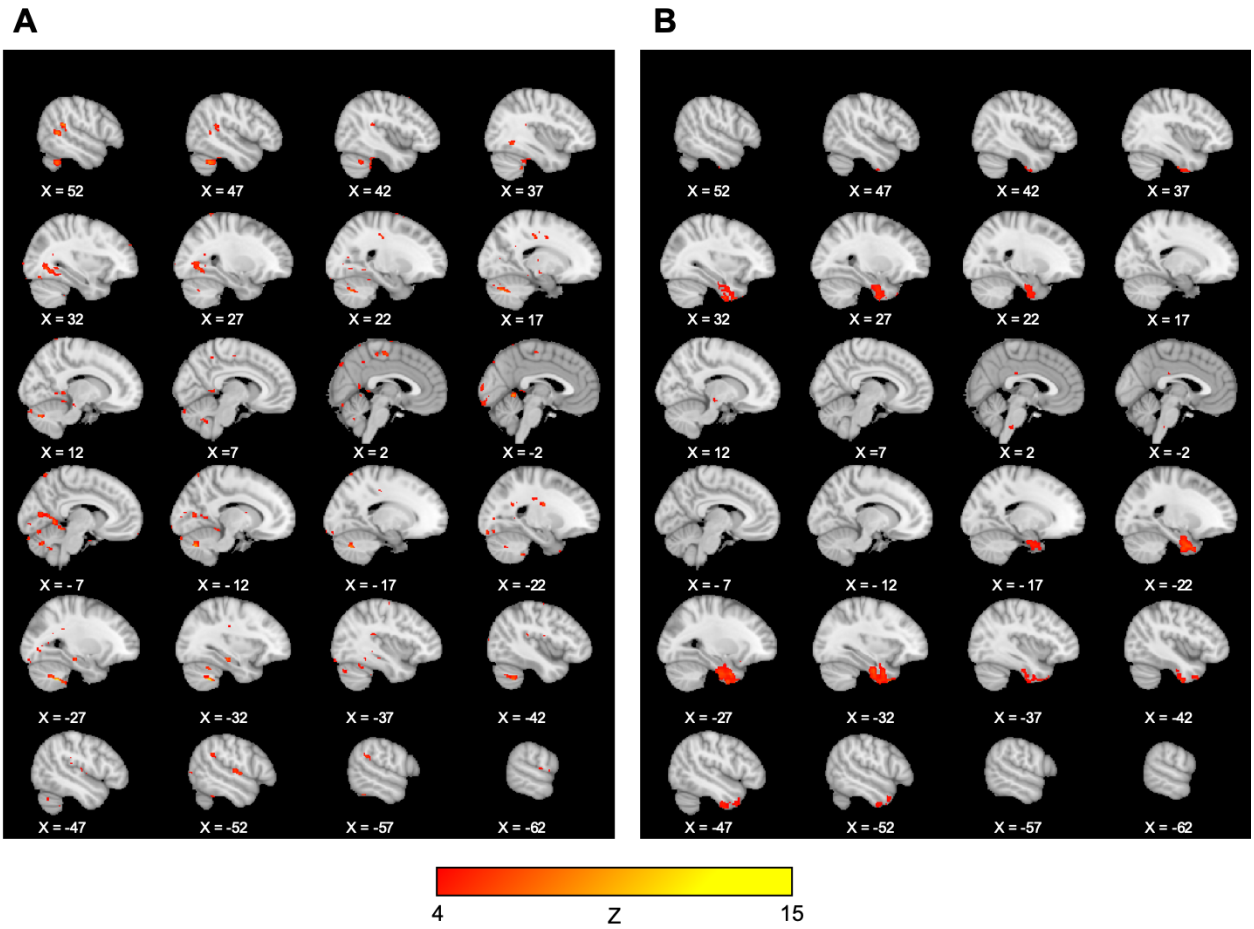
Appendix G: Supplementary Figure 5.1

Default mode network (DMN) identified via group independent component analysis (ICA) during Monkey Ladder task.



Appendix H: Supplementary Figure 5.2

Group-level spatial maps (A = PA15; B = PA34) identified via independent component analysis (ICA) during Paired Associates task.



Appendix I: Ethics Approvals

Ethics Approval 1: Original submission

Research Western

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Robert Petrella
File Number:102434
Review Level: Full Board
Approved Local Adult Participants:126
Approved Local Minor Participants:0
Protocol Title:HM2: Healthy Mind, Healthy Mobility â€“ Dual-task Aerobic Exercise for Older Adults with Cognitive Impairment. (REB# 18858)
Department & Institution: Schulich School of Medicine and Dentistry\Family Medicine,Western University
Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: May 31, 2012
Ethics Expiry Date: March 31, 2014

Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Western University Protocol	(including instruments noted in section 8.1)	
Letter of Information & Consent		2012/03/05
Letter of Information & Consent	Informant	2012/05/04
Advertisement		
Other	Telephone Script	

This is to notify you that the University of Western Ontario Health Sciences Research Ethics Board (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 study on the approval date noted above. The membership of this HSREB 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.

Member of the HSREB that are named as investigators in research studies, or declare a conflict of interest, do not participate in discussions 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.

[redacted]

Signature

Ethics Officer to Contact for Further Information

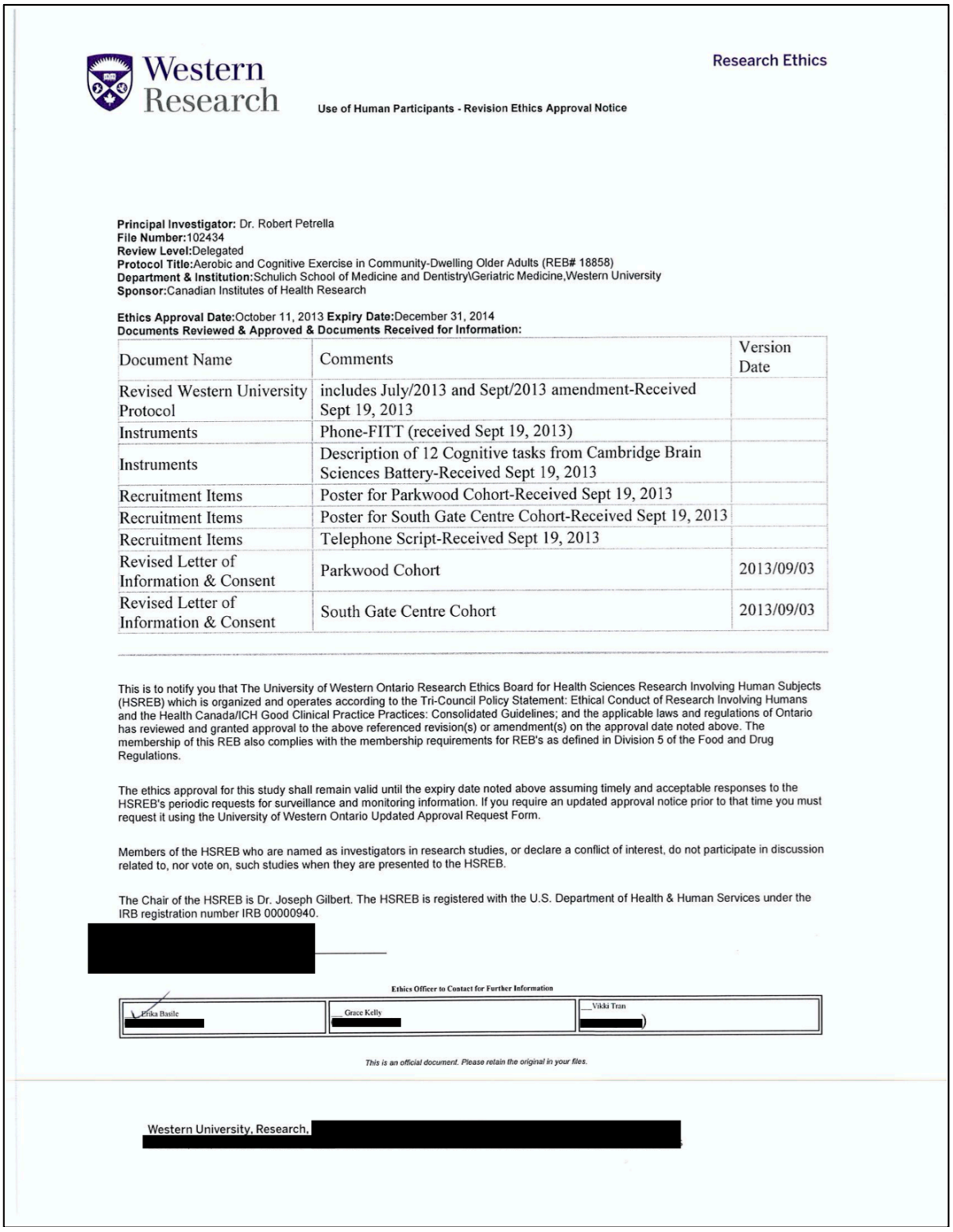
Janice Sutherland	Grace Kelly	Shantel Walcott
[redacted]	[redacted]	[redacted]

This is an official document. Please retain the original in your files.

The University *of* Western Ontario
Office of Research Ethics

[redacted]

Ethics Approval 2: Amendment to include Woodstock Cohort



Western Research

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.

[redacted]

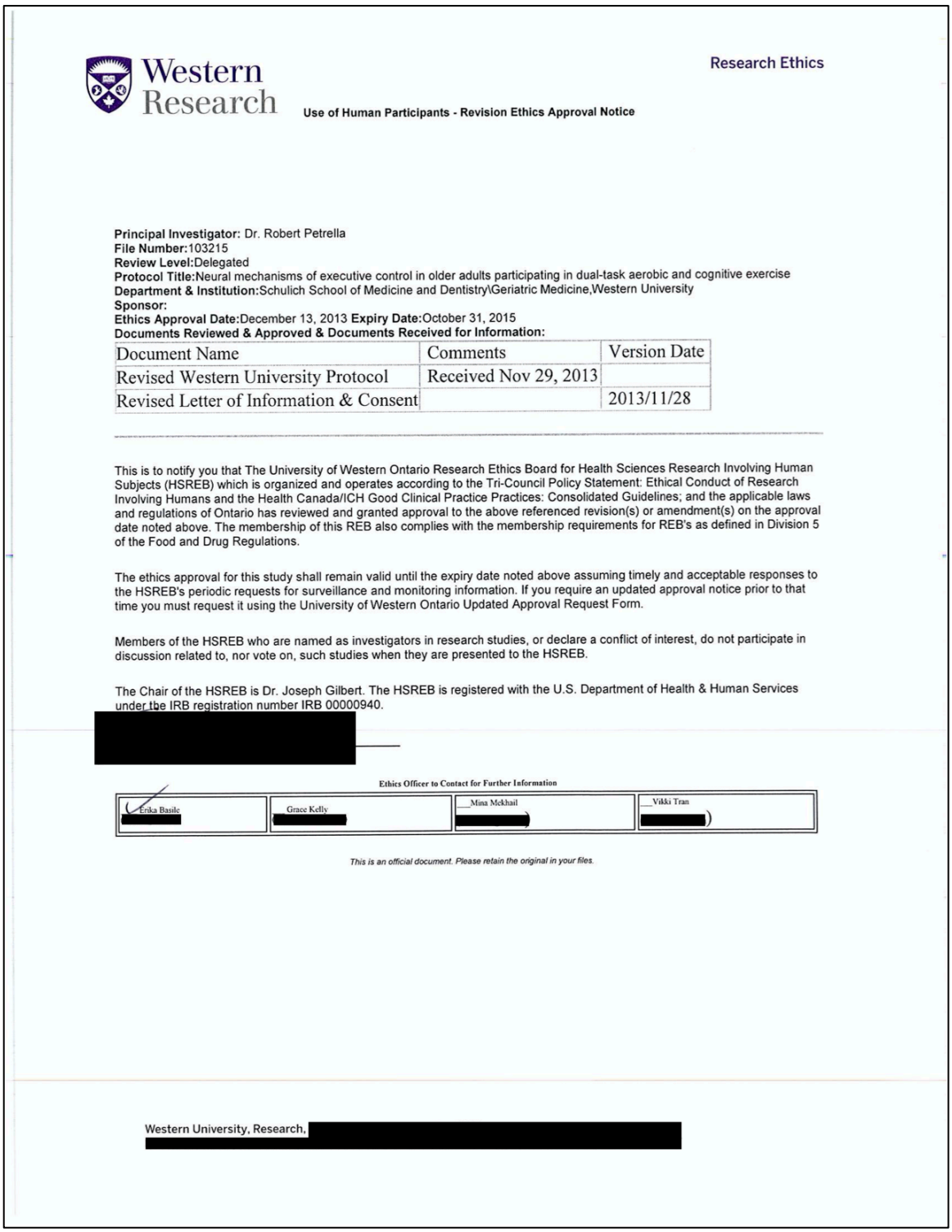
Ethics Officer to Contact for Further Information

Erika Basile [redacted] | Grace Kelly [redacted] | Vikki Tran [redacted]

This is an official document. Please retain the original in your files.

Western University, Research, [redacted]

Ethics Approval 3: Amendment to include functional Magnetic Resonance Imagining substudy



Western Research

Research Ethics

Use of Human Participants - Revision Ethics Approval Notice

Principal Investigator: Dr. Robert Petrella
File Number:103215
Review Level: Delegated
Protocol Title: Neural mechanisms of executive control in older adults participating in dual-task aerobic and cognitive exercise
Department & Institution: Schulich School of Medicine and Dentistry\Geriatric Medicine,Western University
Sponsor:
Ethics Approval Date: December 13, 2013 **Expiry Date:**October 31, 2015
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Received Nov 29, 2013	
Revised Letter of Information & Consent		2013/11/28

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.

[redacted]

Ethics Officer to Contact for Further Information

Erika Basile [redacted]	Grace Kelly [redacted]	Mina Mckhail [redacted]	Vikki Tran [redacted]

This is an official document. Please retain the original in your files.

Western University, Research, [redacted]

Appendix J: Letters of Information and Consent Forms

Letter of Information and Consent Form 1: Woodstock Cohort

Aerobic and Cognitive Exercise in Community-Dwelling Older Adults (Woodstock Cohort)

Letter of Information

Principal Investigator: Robert Petrella, MD, PhD
Aging, Rehabilitation & Geriatric Care Research Centre
Lawson Health Research Institute
[redacted]

Co-Investigators: Dawn Gill, PhD
Aging, Rehabilitation & Geriatric Care Research Centre
Lawson Health Research Institute
[redacted]

Vladmir Hachinski, CM, MD, FRCPC, DSc
Western University
Department of Clinical Neurological Science
[redacted]

Teresa Liu Ambrose, PhD
Centre for Hip Health and Mobility
Vancouver, BC
[redacted]

Kevin Shoemaker, PhD
Western University
School of Kinesiology
[redacted]

Guang Yong Zou, PhD
Western University
Department of Epidemiology & Biostatistics
[redacted]

Sponsor: The Canadian Institute of Health Research is funding this study.
[redacted]

About the Study

You are being invited to participate in this research study because you are 55 years of age or older and you have self-reported a concern about your memory or thinking skills. As we age, the way we walk, also known as gait, becomes less automatic and it requires more attention to move around safely. Cognitive decline and related gait impairments may be accelerated by cardiovascular risk factors, specifically high blood pressure, and it is becoming widely accepted that healthy lifestyle choices are an important strategy to slow or prevent cognitive decline. Regular physical activity has been recommended to lower blood pressure, and has recently been demonstrated to maintain or improve cognitive function in older adults. Furthermore, exercise involving cognitive engagement may have greater effects.

This study was designed to: 1) Determine whether adding thinking tasks to a standard exercise program for older adults (including aerobic exercise) can improve brain function and mobility, over and above a standard exercise program alone; and 2) Determine whether either a standard exercise program combined with thinking tasks or a standard exercise program alone improves blood vessel function. We hypothesize that adding thinking tasks to a standard exercise program for older adults will lead to improvements in cognition, mobility and vascular function.

This letter contains information to help you decide whether or not to participate in this research study. It is important for you to be aware of why the study is being done and what it will involve. Please take the time to read this carefully and feel free to ask questions if anything is unclear or there are words or phrases you do not understand. Please take your time to make a decision and feel free to discuss this letter with your personal doctor, family members and friends.

Number of Participants

We plan to enroll a total of 140 participants in this study (70 participants per group).

Study Procedures and Schedule

If you choose to consent and participate in this study, today will be considered your screening visit. We will collect a medical history, take your blood pressure, and ask you questions about your memory and thinking skills. The visit will include an assessment of your cognitive function using standardized questionnaires including the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), and an assessment of your ability to engage in daily activities using the Lawton-Brody – Instrumental Activities of Daily Living Scale. We will also determine if the presence of depression exists by administering the Center for Epidemiologic Studies – Depression Scale (CES-DS). If you are found to have severe depression, your family physician will be contacted and informed of this matter. Dr. Petrella and your family physician will then determine a course of action to treat your depression.

If you are still eligible for the study you will be asked to undergo a baseline assessment that will be conducted over three days (in a row). The first day will be devoted to general questions about your health and becoming familiar with the cognitive measures that will be administered on Day 2. Day 1 will last approximately 1.5 hours. On Day 2, you will complete the cognitive measures and you will be required to wear a blood pressure monitor for 24 hours and then return it to us

the next day. Day 2 will last approximately 1 to 1.5 hours. On Day 3, mobility and cardiovascular health will be assessed and will last approximately 1 to 1.5 hours in length. This three-day assessment will be repeated 6 months (end of training) and one year (follow up) later.

On Day 1, we will ask you a few questions about yourself, your general health and your current level of physical activity using the Phone-FITT questionnaire. We will also ask you to complete several tasks on a computer that will measure different aspects of thought, including attention, planning, and memory. On Day 1 you will simply be introduced to and familiarized with all of the computer-based tasks with a member of our research team. In total, there are 12 different cognitive tasks. As an example, in the Digit Span Task, you will view a sequence of numbers on the computer screen and then you will be required to remember and repeat this number sequence by entering them on the keyboard.

On Day 2, you will be asked to complete the 12 different cognitive tasks that you were introduced to on Day 1. A member of our research team will be there to assist you as needed. At the end of Day 2, you will be asked to wear a 24-hour Ambulatory Blood Pressure Monitor, which is a small monitoring device attached to a cuff. Multiple blood pressure measurements will be taken at regular intervals (every 30 minutes during the day and every 60 minutes during the night) over a 24-hour period. The Ambulatory Blood Pressure Monitor will be brought back on the following day so results can be analyzed.

On Day 3, after the study staff member has collected the 24-hour Ambulatory Blood Pressure Monitor, you will undergo ultrasound measurements to determine the health of the blood vessels that supply your neck, and measure the blood flow to the brain. This will require you to lay on a bed for approximately 30 minutes, with gel placed on your neck while a probe is manipulated over the gel to find a good image of your arteries. You will be given a comfortable bed and pillow to minimize any discomfort associated with the procedure.

Following these tasks you will undergo height, weight, and waist circumference measurements. In order to assess your cardiorespiratory fitness, we will ask you to complete a STEP test that will require you to walk up and down a set of two stairs, twenty times. Next, your gait will be assessed using the GAITRite system, where you will walk across a ten-metre mat that will record your walking characteristics. We will ask you to walk first at a normal pace, then while counting backwards and finally while naming certain objects aloud. Finally, we will assess your balance using the Fullerton Advanced Balance Scale, which will involve holding your balance while attempting certain tasks (i.e., closing eyes, turning head).

Once you have completed your baseline assessment, you will be randomized (like the flip of a coin) to one of the two groups described below.

Group 1 – Multiple-Modality (M2) Exercise Group: Individuals assigned to this group will take part in a multiple-modality exercise program led by a certified Seniors Fitness Instructor. Each 60-minute class will include: i) a 5 minute warm up incorporating light aerobic training and dynamic range of motion of the major joints to slowly increase heart rate; ii) 25 minutes of moderate to vigorous intensity aerobic exercise, which includes large rhythmical repetitive

endurance activities such as walking, marching, and sequenced aerobics; iii) 5 minute aerobic cool down to decrease heart rate safely; iv) 10 minutes of resistance training of all major muscle groups, including core strengthening exercises; v) 5 minutes of balance training; and vi) 10 minutes of stretching and breathing exercises **Classes will run 3 times per week for 6 months and each class will be 60 minutes in length.**

Group 2 – Multiple-Modality Plus Mind-Motor (M4) Exercise Group: Individuals assigned to this group will take part in a similarly structured class, with modifications (i.e., 5 min removed from each of: resistance, balance, and stretching/breathing exercises) to allow for the incorporation of a 15-minute mind-motor component. Similar to the M2 group, the multiple-modality exercise program will be led by a certified Seniors Fitness Instructor. A Western University Health Sciences Graduate Student will lead the mind-motor component of the program, with assistance from a certified Seniors Fitness Instructor. The mind-motor exercise involves a mat with a grid on top of it and stepping protocols that instruct foot placement. This will be done in small group formats and in a welcoming and non-competitive atmosphere. **Classes will run 3 times per week for 6 months and each class will be 60 minutes in length.**

Research Techniques

It is important to know that following your baseline visit you will be randomly assigned to one of the two groups (exercise programs). Your chance of being randomized to one of the two groups is 50%.

Location

The screening visit, Days 1 & 2 of each assessment, and the entire exercise program will take place at the South Gate Centre or Woodstock Health & Fitness (Woodstock, ON). For Day 3 of each assessment (3 days in total in 1-year), we will require you to come to the Aging, Rehabilitation and Geriatric Care Research Centre at Parkwood Hospital ([redacted]).

Risks

Regarding risks for participation in physical activity, the absolute risk of an exercise-related cardiovascular event varies with the prevalence of cardiac disease, but appears to be extremely low in supposedly healthy people. However, the incidence of sudden death, serious arrhythmias, and myocardial infarction in connection with both recreational and rehabilitative physical activity is small. Although the incidence of sudden death is several times higher in exercise than at other times, the vast majority of cases result from underlying advanced coronary heart disease. The addition of cognitive tasks while exercising may also pose a risk, as older adults are more prone to falls when they are multi-tasking. We will implement strategies to reduce the risk of the aforementioned events even further, such as screening individuals before participation in exercise, excluding high-risk individuals from certain activities, careful supervision, promptly evaluating possible early symptoms, training fitness personnel for emergencies, and encouraging participants to avoid high-risk activities.

Potential Benefits

There may be no direct benefit to you associated with your participation in this study. You may experience improved cardiovascular fitness, improved cognitive function, and improved mobility. The benefits to society at large stem from our goals of working towards developing strategies to prevent or reduce cognitive impairment in older adults by managing cardiovascular risk factors. In addition, we are working towards determining how maintenance of cognitive function, with improved cardiovascular health, may in turn improve mobility function.

Cardiovascular, cognitive, and mobility complications are overriding concerns to older adults and their families. Consequently, determining how to maintain cognitive and mobility function in older adults through improved cardiovascular health not only benefits the population of people at risk for future cognitive impairment, but also the global society as a whole, whose members all have goals of successfully aging.

Withdrawal/Voluntary Participation

Participation in the study is voluntary. You may refuse to participate, refuse to answer any questions, or withdraw from the study at any time with no effect on your future care. You have the right to be given information on the exercise interventions, the study, and what you will be asked to do. You should only agree to take part if you are satisfied that you know enough about these things. You do not have to take part in the study if you do not want to. Dr. Petrella may withdraw you from the study at any time should he feel it is in your best interest.

Participation in Concurrent or Future Studies

If you are participating in another study at this time, please inform Dr. Petrella right away to determine if it is appropriate for you to participate in this study.

New Findings

If, during the course of this study, new information becomes available that may relate to your willingness to continue to participate, this information will be provided to you.

Confidentiality

Every effort will be made to keep your study records confidential. Representatives of the Western University Health Sciences Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research. Additionally, the research team may contact you or require access to your study-related records to monitor the conduct of the research.

Your research results will be stored in the following manner: locked in a cabinet in a secure office, and password protected on Parkwood Hospital's computer network drive, allowing access only to those researchers directly involved with analysis. If the results of the study are published, your name will not be used and no information that discloses your identity will be released or published without your explicit consent to the disclosure. Withdrawal of your participation does not necessarily include withdrawal of any data compiled up to that point. If for any reason you are withdrawn prior to completion of the study, you may be asked to come in for a final study

visit. If we find information we are required by law to disclose, we cannot guarantee confidentiality. For example, we are required to report anyone who we believe may have a reportable or communicable disease to the local Medical Officer of Health.

Contact Person for Participants

If you have any questions about your rights as a research participant or the conduct of the study, you may contact Dr. David Hill, Scientific Director, Lawson Health Research Institute ([redacted] If you have any questions about the study or have a research-related injury, please do not hesitate to contact Dr. Dawn Gill, Research Associate with Dr. Rob Petrella at Parkwood Hospital ([redacted]).

Compensation & Costs

You will not be paid to take part in the study. The exercise program, assessments (including parking at Parkwood hospital) and all procedures required by the study will be provided at no cost to you. The only costs you may incur include your own transportation. For the 3 days that we require you to come to Parkwood hospital, we will reimburse you for your mileage from South Gate Centre to Parkwood hospital (and back).

In the event that you experience an adverse (unfavourable) reaction, you should immediately contact the research team. You will be reimbursed, through the use of funds allocated for the research study, for reasonable medical expenses incurred by you for medical care. This includes hospitalization for the treatment of adverse reactions arising directly from devices following their administration or use in accordance with the protocol (study plan). These expenses are those that would not be covered by your medical or hospital insurance coverage or other third party payer. The adverse event must in no way be attributable to your own failure to follow instructions. No other compensation of any type will be provided to you.

No Waiver of Rights

You do not waive any legal rights by signing the consent form.

Publication of Results

The results of this study are expected to be published in a peer reviewed medical journal. If you would like to receive a copy of the overall results, please notify the study investigator.

Copy of Information/Consent Documentation

You will be given a copy of this letter of information and consent form once it is signed.

Consent Form

Project Title: Aerobic and Cognitive Exercise in Community-Dwelling Older Adults (Woodstock Cohort)

Study Principal Investigator: Dr. Robert Petrella

I have read the Letter of Information and have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Participant's Name (please print): _____

Participant's Signature: _____

Date: _____

Person Obtaining Informed Consent (please print): _____

Signature: _____

Date: _____

Are you interested in being contacted about future research studies being done by this research team?

☐ Yes Participant's Signature: _____

☐ No

Letter of Information and Consent Form 2: Functional Magnetic Resonance Imaging substudy

Western

Letter of Information

Neural Mechanisms of Executive Control in Older Adults Participating in Aerobic and Cognitive Exercise

You are being invited to participate in a research study. This letter provides preliminary information regarding the study.

Purpose of the Study

What is MRI scanning?
We can learn a great deal about how the brain works by looking at the blood flow to different parts of the brain whilst the brain performs different tasks.

We measure brain function using images taken with a magnetic resonance imaging scanner. This scanner uses a strong magnetic field to create detailed images of brain structure and function. By taking a series of images whilst you perform a task we can build up a picture of the brain areas activated by this type of function. The scan does not involve any injections or X-rays and MRI is thought to be a safe, non-invasive imaging technique. The entire research project will involve approximately 42 people.

Like faces, brains come in all shapes and sizes, so that there are many normal variations of what the scan shows. There is a chance of less than 1:100 that your MR scan may show a significant abnormality of which you are unaware. It should be emphasised that the scan is not for medical purposes. However, if one of the technical or research staff finds an abnormality, your scans will be forwarded to a consultant neurologist who will contact you should counselling be appropriate. Such early detection has the benefit of starting treatment early but, in a small number of cases, may have implications for future employment and insurance.

What does the study involve?
Scanning will be undertaken in the 3 Tesla Siemens MRI scanner at the Robarts scan facility. This type of scanner is a standard machine that is used widely for both medical and research purposes. Before your scan, a member of staff will ask you some questions to ensure that you have no metal within you before you enter the strong magnetic field. You will then be asked to lie in the scanner and the scanning will start.

The scanning can be noisy and so we shall give you ear plugs as well as headphones to reduce this noise. It may not be appropriate for you to be scanned if you are very claustrophobic. We do not scan women who are pregnant. During some of the scans we will ask you to perform simple tasks, described below. The scanning session will take about one and a half hours, although you will not actually be scanned for more than 75 minutes of

this time. The first 15 minutes will be for setting up, then brain function will be imaged for 60 minutes, and the final 15 minutes will be used to collect a very detailed picture of your brain. While measuring brain function we will use several different imaging sequences.

What will you be doing during the study?
In this study, we are investigating the processes by which you are able to willfully control your thoughts and actions. Your task will involve looking at pictures displayed via a projector screen, or listening to words played via headphones, and you will have to react to them using a button box according to certain rules.

If you decide to take part in this study, you will be asked to sign a consent form.

Risks
Part of your participation in this study will involve a research test with Magnetic Resonance Imaging (MRI) system, a common medical diagnostic tool that uses a strong magnetic field, a low frequency magnetic field, and a radio frequency field. No X-rays are used. As with any technology there is a risk of death or injury. For MRI the risk of death is less than 1 in 10 million and the risk of injury is less than 1 in 100,000. These risks do not arise from the MRI process itself, but from a failure to disclose or detect MRI incompatible objects in or around the body of the participant or the scanner room. It is therefore very important that you answer all the questions honestly and fully on the MRI screening questionnaire. Almost all the deaths and injuries related to MRI scans have occurred because the MRI operator did not know that surgically implanted metal hardware (such as a cardiac pacemaker) was present inside the participant during the MRI scan.

Other remote risks involve temporary hearing loss from the loud noise inside the magnet. This can be avoided with ear headphone protection that also allows continuous communication between the participant and staff during the scan. For comparison, the risk of death in an MRI is similar to travelling 10 miles by car, while the risk of injury during an MRI is much less than the risks associated with normal daily activities for 1 hour.

You may not be allowed to continue in this research study if you are unable to have a MRI scan because, for example, you have some MRI incompatible metal in your body, you may be pregnant or attempting to become pregnant, or you may have a drug patch on your skin that contains a metal foil. Should you require a medically necessary MRI scan in the future, the final decision as to whether you can be scanned will be made by a qualified physician considering all the risks and benefits.

MRI exclusion criteria
If you have any history of head or eye injury involving metal fragments, if you have some type of implanted electrical device (such as a cardiac pacemaker), if you have severe heart disease (including susceptibility to heart rhythm abnormalities), you should not have an MRI scan unless supervised by a physician. Additionally you should not have a MRI scan if you have conductive implants or devices such as skin patches, body piercing or tattoos

containing metallic inks because there is a risk of heating or induction of electrical currents within the metal element causing burns to adjacent tissue.

Participation
Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at anytime with no effect on your future care. You may withdraw from the study at any time without explaining why. You do not waive any of your legal rights by signing the consent form.

Compensation
There is no financial compensation for taking part in this study; however, parking costs will be covered.

Confidentiality
All the information we collect is kept confidential and is only seen by members of the research team. The results will be kept securely for a minimum of 5 years. Representatives of the University of Western Ontario Health Sciences Research Ethics Board may contact you or may require access to your study related records to monitor the conduct of the research. Any report published about this study will not identify you by name.

Benefits
You will not receive any direct benefit by participating in this study.

Contact Information
If you would like further information or would like to discuss any aspect of volunteering, then please contact either of the following:

Dr. Robert Petrella
University of Western Ontario &
Lawson Health Research Institute
St. Joseph's Parkwood Hospital
[redacted]

Dr. Dawn Gill
Lawson Health Research Institute
St. Joseph's Parkwood Hospital
[redacted]

If you have any questions about your rights as a research participant or the conduct of the study you may contact The Office of Research Ethics [redacted]

You will receive a copy of this letter of information and the signed consent form.

Consent Form

Neural Mechanisms of Executive Control in Older Adults Participating in Aerobic and Cognitive Exercise

I have read the letter of information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Printed Name of Participant

_____

Signature of Participant Date

_____ _____

Printed Name of the Person Obtaining Consent

_____

Signature of the Person Obtaining Consent Date

_____ _____

Appendix K: Permission to Reproduce Published Materials

Chapter 2:

The content in Chapter 2 has been accepted for publication by *Current Sports Medicine Reports.* Authors are authorized the reproduction of the accepted manuscript for inclusion in a thesis dissertation 12 months following the data of original publication of the manuscript by journal. The final version of the manuscript will be published in *Current Sports Medicine Report* in the August 2020 issue of the journal. This thesis dissertation will be under embargo until September 1st, 2021.

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Curriculum Vitae

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Honours and Awards:	Globalink Research Internship Award (B.Sc.) MITACS 2014 Globalink Graduate Fellowship Award (M.Sc.) MITACS 2015-2016 Lawson Internal Research Fund Studentship Award (M.Sc.) Lawson Health Research Institute 2016-2017 Western Graduate Research Scholarship (M.Sc. and Ph.D.) The University of Western Ontario 2016-2020 Globalink Graduate Fellowship Award (Ph.D.) MITACS 2017-2018 Province of Ontario Graduate Scholarship (Ph.D.) The University of Western Ontario 2018-2019
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Experience

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Boa Sorte Silva, N. C., Nagamatsu, L. S., Gill, D. P., Owen, A. M., & Petrella, R. J. (2020). Memory Function Brain Functional Connectivity Adaptations Following Multiple-Modality Exercise and Mind-Motor Training in Older Adults at Risk of Dementia: An Exploratory Sub-Study. Frontiers in Aging Neuroscience, 12(February), 22. https://doi.org/10.3389/FNAGI.2020.00022

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Presentations:

Boa Sorte Silva N. C., Gill D. P., Petrella R. J. The influence of hypertension diagnosis on cognition and dual-task gait in community dwelling adults at increased risk for dementia. *Oral presentation at*: Canadian Association on Gerontology 47th Annual Scientific and Educational Meeting. Vancouver, Canada, Oct 2018.

2017

Boa Sorte Silva N. C., Gill D. P., Petrella R. J. Dual-task gait and cardiorespiratory fitness, but not vascular health, predict cognitive function in community-dwelling older adults with subjective cognitive complaints. *Poster presentation at*: 2018 Alzheimer's Association International Conference. Chicago, United States, Jul 2018.

Boa Sorte Silva N. C., Gill D. P., De Cruz A., Petrella R. J. Gender-specific effects in cognition and mobility following exercise in older adults at risk for dementia. *Poster presentation at*: American College of Sports Medicine 66th Annual Meeting. Minneapolis, United States, May 2018.

Boa Sorte Silva N. C., Gill D. P., Petrella R. J. Systolic blood pressure dipping in older adults: implications for mobility and cognition outcomes. *Poster presentation at*: Canadian Association on Gerontology 46th Annual Scientific and Educational Meeting. Winnipeg, Canada, Oct 2017.

Boa Sorte Silva N. C., Gill D. P., Petrella R. J. Multi-modality exercise and mind-motor training to improve cognition in older adults: results from the M4 Study. *Oral presentation at*: 2017 Alzheimer's Association International Conference. London, England, Jul 2017.

Boa Sorte Silva N. C., Gill D. P., Petrella R. J. Does a 6-month dual-task gait and aerobic exercise intervention differentially impact older adults with normal vs. non-normal blood pressure dipping status? *Poster presentation at*: 2017 Alzheimer's Association International Conference. London, England, Jul 2017.

Boa Sorte Silva N. C., Gill D. P., Gregory M. A., De Cruz A., Petrella R. J. Multi-modality exercise training may decrease risk for dementia and improve mobility in older adults with subjective cognitive complaints. *Oral presentation at*: Canadian Association on Gerontology 45th Annual Scientific and Educational Meeting. Montreal, Canada, Oct 2016.

Boa Sorte Silva N. C., Gill D. P., Gregory M. A., De Cruz A., Petrella R. J. The efficacy of a multi-modality exercise program combined with mind-motor task training for older adults at risk of cognitive impairment on usual and dual-task gait: a randomized controlled trial. *Oral presentation at*: 2016 Alzheimer's Association International Conference. Toronto, Canada, Jul 2016.