COMPUTERIZED COGNITIVE TRAINING AND PHYSICAL EXERCISE: EFFECTS ON COGNITIVE AND BRAIN FUNCTION IN OLDER ADULTS

by

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Abstract

Since the world is aging at an unprecedented rate, it is important to identify and evaluate strategies that promote healthy cognitive aging. In addition to exercise, computerized cognitive training (CCT) is an emerging and promising strategy to promote cognitive function. Therefore, the aim of my dissertation is four-fold: 1) To provide a detailed review of literature examining the underlying neural changes of CCT in older adults; 2) To examine the effects of CCT, alone and when immediately preceded by a 15-minute brisk walk, on cognitive function; 3) To identify the neural correlates of CCT-induced cognitive benefits; and 4) To examine whether CCT impacts these neural correlates. Firstly, a systematic review examining the underlying neural mechanisms of CCT showed that, despite promising benefits on for example functional connectivity, there is a need for more high-quality studies in order to draw sound conclusions. Secondly, I addressed the remaining three aims by developing an 8-week randomized controlled trial of CCT examining the impact of CCT, alone and when immediately preceded by a single bout of aerobic exercise, on cognitive function compared with an active control in community-dwelling older adults. Results demonstrated that those assigned to CCT showed cognitive benefits compared with those assigned to the active control. More widespread cognitive benefits were seen for those assigned to the combined exercise and CCT group. In addition, using resting-state functional magnetic resonance imaging, I examined inter-network functional connectivity over the course of the eight weeks. I was able to identify inter-network functional connectivity correlates of change in cognitive performance observed after the 8-week intervention. Moreover, those assigned to purely CCT improved regional inter-network functional connectivity compared with the active control. My work confirms and extends on previous work, suggesting that CCT benefits cognitive function. A novel finding is the additional cognitive benefit elicited when preceding CCT with a single bout

of exercise. Additionally, new insights into the potential neural mechanisms underlying CCT-induced benefits on cognitive function are presented. Overall, results from my dissertation contribute to this emerging field, suggesting CCT as a promising strategy to promote healthy cognitive aging.

Lay Summary

There is currently no pharmacological therapy available for dementia. Hence, it is important to focus on lifestyle strategies that can help delay or prevent cognitive decline in later life. The current thesis aims to summarize current literature and investigate whether computerized cognitive training, alone and when preceded by a short walk, benefits cognitive and brain function in community-dwelling older adults. The key findings of my thesis are: 1) More high-quality studies are needed to uncover how the brain might change as a result of cognitive training; 2) Cognitive training improves executive functions, where combined exercise and cognitive training results in more widespread benefits; 3) Connections between different brain areas are related to improved executive functions; cognitive training improves connections between these areas compared with groups without cognitive training. In summary, computerized cognitive training is a potential strategy to prevent or delay cognitive decline.

Preface

This dissertation consists of materials written and compiled by Lisanne ten Brinke. The content of this dissertation was reviewd by Professors Teresa Liu-Ambrose, Todd Handy, and Kirk Erickson; provided comments were taken into consideration for the final version of the dissertation.

For chapters 3 – 5 of this dissertation, ethical approval for the 8-week randomized controlled trial (ClinicalTrials.gov identifier: NCT02564809) was obtained from the University of British Columbia's Clinical Research Ethics Board (H14-02438) and the Vancouver Coastal Health Research Institute ethics board (V14-02438). The research took place at the Djavad Mowafaghian Centre for Brain Health at the University of British Columbia and the Research Pavilion and Centre for Hip Health and Mobility at Vancouver General Hospital. Lisanne ten Brinke, Professor Teresa Liu-Ambrose, and Dr. John Best were involved in protocol development. For this trial, we partnered with Rosetta Stone Canada, at the time owners of the cognitive training platform (i.e., Fit Brains®) used for this trial. As per contract, the industry partner did not have any influence in the research findings. Lisanne ten Brinke coordinated the 8-week trial, and was assisted with recruitment and classes by Joey Chan and Cheyenne Ghag. Data analysis of the 8-week RCT was performed by Lisanne ten Brinke, Professor Teresa Liu-Ambrose, and Dr. John Best.

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List of Abbreviations

6-MWT: 6-Minute Walk Test
AD: Alzheimer's Disease
AxD: Axial Diffusivity
AI: Anterior Insula
aMCI: Amnestic Mild Cognitive Impairment
ANCOVA: Analysis of Covariance
AUC: Area Under the Curve
BA: Brodmann Area
BAT: Balanced And Toned
BDNF: Brain Derived Neurotrophic Factor
BET: Brain Extraction Tool
BF: Brain Fitness
BOLD: Blood Oxygen Level Dependent
CBF: Cerebral Blood Flow
CCT: Computerized Cognitive Training
CEN: Central Executive Network
CI: Confidence Interval
CONSORT: Consolidated Standard of Reporting Trials
CSF: Cerebrospinal Fluid
dACC: dorsal Anterior Cingulate Cortex
DCCS: Dimensional Change Card Sort
DMN: Default Mode Network
DTI: Diffusion Tensor Imaging
EE: Environmental Enrichment
EF: Executive Functions
Ex-FBT: Exercise-Fit Brains® Training
FA: Flip Angle
FA: Fractional Anisotropy
FBT: Fit Brains® Training
FCI: Functional Comorbidity Index
fMRI: functional Magnetic Resonance Imaging
FoV: Field of View
FPN: Frontoparietal Network
FSL: FMRIB's Software Library
FWHM: Full-Width-Half-Maximum
IADL: Independent Activities of Daily Living
ICA: Independent Component Analysis
IGF-1: Insulin-like Growth Factor-1
IPL: Inferior Parietal Lobe
ITL: Inferior Temporal Lobe
LALPFC: Left Anterolateral Prefrontal Cortex
LdlPFC: Left dorsolateral Prefrontal Cortex
LMTG: Left Medial Temporal Gyrus

MCI: Mild Cognitive Impairment
MD: Mean Diffusivity
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
mPFC: medial Prefrontal Cortex
MRI: Magnetic Resonance Imaging
NIH: National Institute of Health
naMCI: Non-Amnestic Mild Cognitive Impairment
PA: Physical Activity
PASE: Physical Activity Scale for the Elderly
PCC: Posterior Cingulate Cortex
PEDro: Physiotherapy Evidence Database
PRT: Progressive Resistance Training
RALPFC: Right Anterolateral Prefrontal Cortex
RAVLT: Rey Auditory Verbal Learning Test
RCT: Randomized Controlled Trial
RdlPFC: Right dorsolateral Prefrontal Cortex
RIPS: Right Inferior Parietal Sulcus
RMTG: Right Medial Temporal Gyrus
ROI: Region Of Interest
RON: Rise Of Nation
rs-fMRI: resting-state functional Magnetic Resonance Imaging
RVAI: Right Ventral Anterior Insula
SBA: Seed Based Analysis
SF: Space Fortress
SN: Salience Network
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SPL: Superior Parietal Cortex
SPPB: Short Physical Performance Battery
TE: Echo Time
TR: Repetition Time
UBC: University of British Columbia
UBCCREB: University of British Columbia Clinical Research Ethics Board
VCHRI: Vancouver Coastal Health Research Institute
VCI: Vascular Cognitive Impairment
VEGF: Vascular Endothelial Growth Factor
VGH: Vancouver General Hospital
WHO: World Health Organization
WM: Working Memory
WMH: White Matter Hyperintensity

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Dedication

I dedicate this thesis to my parents, who have always encouraged and supported me along the way – despite me moving to another continent.

Lieve pap en mam, bedankt voor jullie liefde, steun, en vertrouwen tijdens deze jaren. Naast dat jullie altijd klaar stonden met advies en een luisterend oor, ben ik ook dankbaar voor al jullie geweldige bezoekjes aan Canada.

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Chapter 1: Introduction

The World Health Organization (WHO) is emphasizing the urgency to focus on healthy cognitive aging as the population is aging at an unprecedented rate. Age is the most important factor for dementia and it is expected that 22% of the world population is over 60 years of age by the year 2050.[1] Dementia is a global research and public health priority as there are currently 50 million people living with the condition, with numbers expected to triple by 2050.[2] To reduce both the social and economic burden of dementia, the WHO aims to increase awareness, target risk-reduction, diagnosis, treatment, and research efforts.[3] Since an effective pharmaceutical therapy does not currently exist, there are growing efforts to prevent or delay age-related cognitive impairment and dementia via lifestyle strategies.[4] Even when an effective pharmacological approach is available, lifestyle approaches (i.e., exercise, nutrition, and cognitive training) can be used as a complementary approach; many lifestyle interventions have multidimensional benefits.[5]

The main objective of my thesis is to examine the effects of computerized cognitive training on cognitive and brain function in older adults. In addition, I will examine whether exercise immediately prior to cognitive training can potentially result in broader benefits of cognitive training. I will start my thesis by discussing the following: 1) Concepts of cognition; 2) Aging and cognition; 3) Aging and the brain; 4) Non-pharmaceutical strategies to promote healthy cognitive aging; and 5) Functional magnetic resonance imaging.

1.1 Cognition

Cognition can be defined as intellectual or mental processes whereby the individual becomes aware or obtains knowledge.[6] Cognition is a comprehensive concept and consists of multiple domains with each its associated function. The DSM-5 Work Group classified six important key domains within the concept of cognitive function: 1) complex attention; 2) executive function (EF); 3) learning and memory; 4) language; 5) perceptual-motor function; and 6) social cognition.[7] These six domains each contain basic and more complex subdomains. For the purpose of this thesis, I will focus on executive functions and learning and memory, two domains of cognition greatly susceptible to age-related decline and often examined in relation to cognitive training.[8]

1.1.1 Executive Function

Executive functions are a set of higher-order cognitive processes involved in goal-directed behavior, requiring concentration and attention. Executive functions are commonly divided into inhibition, working memory, set-shifting, reasoning, problem solving, and planning.

1.1.1.1 Inhibition

Inhibition, or also response inhibition, refers to the ability to suppress inappropriate actions, impulses, or irrelevant information and is one of the three core domains of EF.[9,10] Inhibition is an overall domain that can be divided into inhibitory control (e.g., controlling attention, emotions, and behaviours) and interference control (e.g., selectively attending or suppressing stimuli, cognitive inhibition).[9] Commonly used measures for inhibition are the Stroop test[11] and the Flanker test.[12] Performance of inhibition tends to decline with age; specifically a decline in the ability to

suppress irrelevant information is visible in older adults.[13,14] The prefrontal cortex is a critical region for EF, such as response inhibition.[15]

1.1.1.2 Working Memory

Working memory (WM), another core domain of EF, was first defined by Baddeley and Hitch as a "mental workspace" for both the storage and manipulation of information when needed.[16] WM can be divided into several subdomains, such as verbal and visuospatial tasks.[9] WM does not have unlimited resources, and therefore has limits regarding capacity. Both cross-sectional data, as well as data from a meta-analysis show that WM capacity declines with age.[17,18] Neural substrates of WM include the inferior frontal and fusiform gyrus during maintenance of information; activation in the hippocampus, superior parietal gyrus, and bilateral insula increases while making correct decisions during WM tasks.[19]

1.1.1.3 Set-Shifting

Set-shifting is the last of three core cognitive domains.[10] For this EF process, one requires the ability to divide attention, to use one's WM, and the ability to adapt based on inputs, and therefore shift between response sets.[9] Set-shifting is often measured by tasks such as the Trail Making Test (Part A & B)[20] and the Dimensional Change Card Sort Test.[21] In accordance with the two previously mentioned key EF, the frontal brain regions are of great importance for tasks of set-shifting.

1.1.1.4 Reasoning, Problem-Solving, and Planning

Reasoning is a marker of fluid intelligence and refers to the ability to integrate information from different sources in order to problem solve.[22] Reasoning is closely tied to WM.[9,23] and can be divided into inductive and deductive reasoning, which encompasses the ability to draw conclusions based on facts or inferences. Similar to reasoning, problem solving is a higher-order EF that arises from the core processes (i.e., inhibition, WM, and set-shifting).[24] and falls under the concept of fluid intelligence.[22] A commonly used measure to assess reasoning and problem-solving (i.e., higher-level EFs: fluid intelligence) is the Raven's Progressive Matrices.[25] Due to its complexity, fluid intelligence involves a wide range of brain regions, including the frontal, and parietal brain regions, as well as the insular and posterior cingulate cortices, and subcortical structures.[26]

Planning is the last marker of fluid intelligence in the realm of EF, and aims to achieve a goal through the selection, formulation, and evaluation of a set of actions and thoughts.[27] Planning commonly gets assessed in the literature using the Tower of London[28] and evokes activity in the dorsolateral prefrontal cortex,[29] lateral premotor areas, the anterior cingulate and the caudate nucleus,[30] regions part of the frontostriatal system.[31,32]

1.1.2 Learning and Memory

Episodic memory is the ability to encode, store, and retrieve personal experiences from our daily life.[33,34] Encoding refers to the ability to perceive and learn new information, which we maintain over time through the process of storing. The ability to access this stored information happens via the third process of retrieval. Successful episodic memory depends on the correct functioning of these three processes.[35] Episodic memory, including all three processes, undergoes changes

throughout the lifespan, showing decreases in performance starting in adulthood, which accelerate in old age.[36,37] Brain regions involved in episodic memory are the medial temporal lobe, including structures such as the hippocampus, and the prefrontal cortex.

1.2 Aging and Cognition

Aging is characterized by multifaceted changes in cognition, brain structure, and brain function. Cognitive abilities susceptible to aging include EF, speed, and memory.[8,38] In contrast, verbal ability and general knowledge stay relatively spared with aging.[8] However, due to the vast number of aspects that can impact the course of cognitive and brain aging, there is a large variability observed between individuals.

The research chapters included in this dissertation focus largely on a healthy older adult population, including those who experience cognitive decline greater than expected given an individual's age and education, also referred to as mild cognitive impairment (MCI). Therefore, in this section I will summarize the existing understanding of normal cognitive aging as well as MCI. In addition, I will discuss common and current methods to detect MCI.

1.2.1 Normal Aging

Normal aging is commonly defined as aging without the presence of overt diseases of the nervous system.[39] Changes in cognition are a normal part of the aging process; however, it is important to realize that 'normal' cognitive aging and its trajectory of decline differs vastly between individuals (see Figure 1.1). Many factors, such as genetics, medical status, vascular health, diet, and lifestyle,

all impact the course of cognitive aging.[8] Nevertheless, age itself is the greatest risk for cognitive decline.[8]

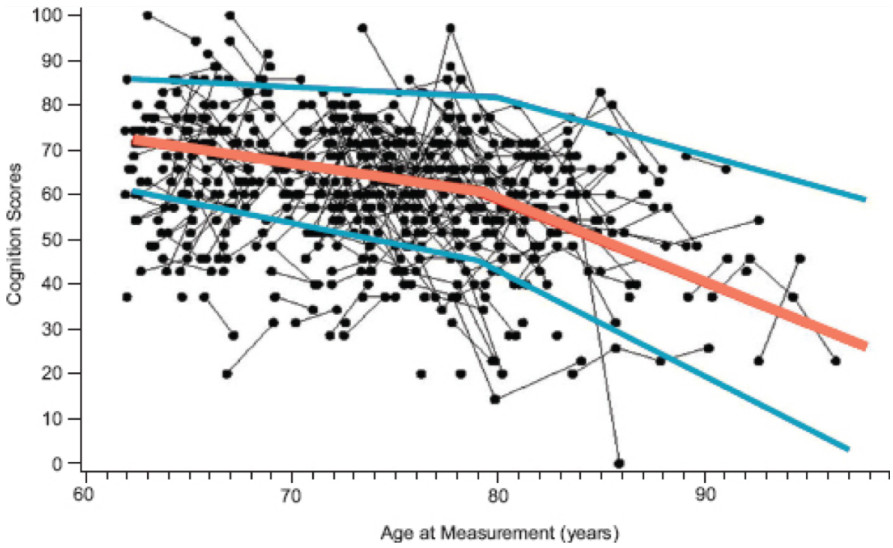

Figure 1.1 Variability in Cognitive Aging (McArdle, Advances in Statistical Analysis, 2011[40])

Processes of neurological diseases such as Alzheimer's disease (AD) happen slowly over time, and sometimes its symptoms coincide with those of normal aging, making it hard to distinguish normal aging versus disease-related aging.[39] In contrary to age-related neurodegenerative disease, loss of neurons in normal aging does not exceed 10% of neurons compared with young adults,[41,42] and is mostly present in the dorsolateral prefrontal cortex and hippocampus (i.e., medial temporal lobe).[38,41,42] Thus, neuronal loss in normal aging is limited, however aging is moreso characterized by changes in neuronal structure (e.g., dendritic shortening, dendritic loss, axonal loss, and increased axonal demyelination),[42] with synaptic loss being an important marker of normal aging.[43] Additionally, literature suggests that normal aging affects the organization and function of neural networks throughout life.[44] Specifically, a recent study in a healthy older adult population

showed that age was associated with both decreased connectivity (intra-network and inter-network) and increased connectivity (inter-network), depending on networks involved.[45] These changes in functional reorganization happen more rapidly in diseases such as AD.[46]

When taking into consideration that brain structure and function changes with age, the key to normal or successful cognitive aging is the maintenance of cognitive function in the presence of these changes. This is also referred to as "cognitive reserve" and is defined by Stern as "differences in cognitive processes as a function of lifetime intellectual activities and other environmental factors that explain differential susceptibility to functional impairment in the presence of pathology or other neurological insult".[47] A current method to quantify cognitive reserve is functional magnetic resonance imaging (fMRI), and more specifically resting-state fMRI (rs-fMRI) – a measure of spatial and temporal synchronous activity across brain regions in the absence of a task. This can provide information on functional reorganization (i.e., functional compensation) of the brain to maintain cognitive performance in the presence of brain pathology,[44] which I will discuss in more detail in section 1.3.2.

Evidence shows common declines in different domains of cognition, such as EF, memory, and processing speed.[8,38] For example, in complex attention, aging is related to decreases in processing speed. This decrease in processing speed could potentially be linked to an increased presence of white matter hyperintensities[48] and decreases in white matter structural connectivity.[49] Furthermore, brain regions involved in tasks of complex attention, such as temporal, prefrontal, and parietal regions[50] are prone to age-related declines.[15]

The three core domains of EF (i.e., inhibition, working memory, and set shifting) show age-related declines in performance and changes in its neural substrates. The prefrontal cortex, a critical region for these three core EFs, is susceptible to age-related structural declines.[15] For inhibition, involvement of additional brain regions (e.g., inferior frontal gyrus and motor-planning regions) slightly changes as a function of age, where adolescents recruit more brain regions (e.g., temporal and parietal regions) and at an earlier time during task execution compared with adults, indicating brain systems are still developing through adolescent years.[51] In turn, declines in working memory, the second key EF, may be associated with decreased performance of EF, such as inhibition.[52] Comparing WM performance between healthy young and older adults showed overall declines in WM with age; specifically, in more complex tasks (i.e., higher memory load) a greater age-related decline was visible.[53] Finally, set-shifting has been found to develop throughout middle childhood and declines with aging, specifically the time it takes to switch (i.e., switch cost) increases from approximately age 60.[54]

Reasoning is prone to relatively early age-related decline, starting in the mid-sixties.[55] The process of problem solving is believed to change throughout life; older adults increasingly depend on acquired knowledge to compensate for losses in fluid intelligence, where younger adults rely mostly on aspects of fluid intelligence.[56] For planning, studies show that older adults were less accurate on task execution, required more moves and time to complete the task compared with young adults,[57-59] however the onset of age-related decline varies among studies.

The hippocampus is a key structure for memory, such as episodic and spatial memory, and in late adulthood hippocampal volume declines annually with approximately 1-2% in older adults without

dementia.[15] This decline in hippocampal volume is reversible, where increases in volume, as a result of aerobic exercise (i.e., walking program 3x/week for 12 months), are associated with increases in spatial memory performance.[60]

1.2.2 Mild Cognitive Impairment

Worldwide, the prevalence of cognitive impairment varies largely due to variation in criteria used. However, a recent study taking into account various geographical locations concluded that among adults 60 years and older, approximately 6 – 12% were classified with MCI.[61] MCI is conceptually defined as a clinical entity characterized by cognitive decline greater than that expected for an individual's age and education level but does not interfere notably with everyday function.[62] MCI is characterized by both subjective and objective changes in cognitive function.[63,64] Subjective cognitive decline refers to older adults who notice and express concerns about declines in cognitive performance,[65] and despite a difficulty to predict the course of decline, those with subjective cognitive decline are 1.5 – 3 times more likely to develop objective cognitive impairment, such as MCI.[66,67] Current evidence suggests that MCI may represent the prodromal stage of AD.[68,69] Those with MCI are at increased risk (i.e., 6-15% annually) to develop AD,[70] compared with those without MCI (1-2% annually).[64]

If diagnosed, MCI can be classified as either amnestic MCI (aMCI) or non-amnestic MCI (naMCI). When memory impairment is present, we speak of aMCI; if not, it can be diagnosed as naMCI.[71] Both categories (i.e., aMCI or naMCI) can be divided into either single-domain or multiple-domain MCI. For example, in single domain aMCI, memory is the only impaired domain, whereas in multiple domain aMCI, other domains beside memory are impaired. Similar diagnosis

can be made in the naMCI; when only one non-memory domain is impaired we speak of single-domain naMCI, but when more than one non-memory domain is impaired we refer to multiple-domain naMCI.[71] Amnestic MCI is a prodromal stage of AD, and approximately 10-15% annually progress to AD.[72]

Overall, MCI is an evolving clinical entity and depicts an intermediate state between normal cognitive aging and dementia; therefore, MCI represents a great window of opportunity to evaluate dementia prevention strategies, with the possibility of reversion to a cognitively intact status.[73]

1.2.2.1 Detection of Mild Cognitive Impairment

The Mini-Mental State Examination (MMSE)[74] has been one of the most widely-used screening tools for cognitive decline, including MCI. The MMSE consists of seven domains, including orientation of time and place, word registration and recall, attention and calculation, language and visuospatial construction; and has a maximum score of 30 points. A cut-off score of 24/30 or more is generally used to indicated "normal" cognition; anything below that could indicate MCI. A recent review showed that despite a good test-retest reliability (0.80 – 0.95) to detect those with mild to moderate dementia, the MMSE has been less sensitive to detect MCI.[75] It has been suggested that those with higher levels of education reach a ceiling effect due to the lack of difficulty on items in the MMSE, which could be one of the factors the MMSE is less sensitive to detect more subtle changes in cognition.[76] A more recently developed screening tool for MCI is the Montreal Cognitive Assessment (MoCA).[77] The MoCA is a valid (criterion validity ranging from 0.79 – 0.86 area under the curve (AUC) for different domains)[78] and reliable (test-retest reliability of 0.92) measure,[77] and assesses eight cognitive domains such as attention,

concentration, EF, memory, language and visuo-constructional skills. The total possible score is 30 points. Initially, a cutoff score of 26 was recommended for indication of MCI, as it showed a 90% sensitivity to for detecting MCI.[77] However, recent studies suggested that the current cutoff might not be the most accurate. A recent meta-analysis revealed that a cutoff score of 23 would be more appropriate for diagnosing MCI, as it lowered false positives and demonstrated better diagnostic accuracy.[79] Moreover, it has been suggested that age and education are important factors to take into consideration for cutoff scores; therefore Borland and colleagues recently developed cutoff scores taking into account these factors.[80]

A diagnosis of MCI can be made when an individual meets a set of developed criteria such as the Petersen criteria:[71,81] 1) Presence of a cognitive complaint; 2) Presence of an objective cognitive impairment, such as lower general cognitive function than normal, as measured with the MoCA;[77] 3) Essentially normal function of activities of daily living (i.e., mild difficulties permitted);[82] and 4) No dementia diagnosis.[83] To determine whether MCI is due to AD, the use of AD biomarker data (e.g., amyloid beta deposition, medial temporal atrophy) is required.[81]

1.3 Aging and the Brain

As section 1.2 briefly addressed, age-related changes in the brain can manifest itself in different manners, such as decreases in brain volume (i.e., atrophy), changes in white matter integrity, the development of lesions in the brain, as well as changing patterns of brain activity such as structural and functional connectivity as a result of underlying pathology. In this section, I will specifically focus on structural (i.e., volume and structural integrity) and functional changes (i.e., resting-state

functional connectivity) in the aging brain by discussing some of the basic concepts involved in these neuroimaging techniques in more detail.

1.3.1 Structural Changes: Volume and Integrity

The central nervous system consists of the brain and the spinal cord. The brain can be subdivided into the medulla, pons, cerebellum, the diencephalon, midbrain, the two cerebral hemispheres, and the ventricular system. Brain matter is composed of grey matter and white matter. Grey matter is found in the (sub)cortical areas of the brain and consists of neuronal cell bodies and dendrites, whereas the white matter consists of axons that are surrounded by a myelin sheath (i.e., tracts).[84] Aging is associated with atrophy within the gray matter and subcortical structures, especially in the prefrontal regions and regions in the medial temporal lobe such as the hippocampus and entorhinal cortex.[85] Alzheimer's disease is characterized by declines in memory, which are associated with decreased hippocampal volume, a crucial brain region for memory. In healthy older adults, hippocampal volume declines approximately 1-2% annually,[15] compared with an average annual loss of approximately 3.5-4% in those with AD.[86,87] Therefore, hippocampal volume is used as a common imaging biomarker for AD,[88] where those with MCI and smaller hippocampal volumes are at greater risk for developing AD.[89] In addition to hippocampal volume, the annual rate of ventricular space expansion, which results in increased levels of cerebrospinal fluid (CSF), is much higher in older adults (4.25%) compared with younger adults (0.43%)[8,85] and has been associated with decreased global cognition, memory, and EF.[90]

White matter volume is relatively stable in older adults; however, aging and risk factors for cerebrovascular disease (e.g., high blood pressure) are associated with changes in white matter

integrity. White matter integrity is important for higher order cognitive functions, as it is responsible for signal transmission between different cortical regions of the brain.[91] Loss of white matter integrity can be caused by the development of white matter lesions, which result from degeneration of white matter (i.e., demyelination) due to for example axonal loss, myelin or oligodendrocyte pathology and show up as white matter hyperintensities on T2-weighted or FLAIR images via MRI.[92,93] White matter hyperintensities (WMH) become more prevalent with aging. The most common type of WMH are periventricular and deep lesions localized in the genu of the internal capsule, in the anterior corona radiate, and the anterior centrum semiovale. Even though WMHs are also found in asymptomatic older adults, white matter lesions are associated with cognitive decline, specifically in EF.[94,95] Progression of periventricular WMHs were found to be associated with declines in cognitive function,[96] such as declines in processing speed.[97]

1.3.2 Functional Changes: Resting-State Functional Connectivity

In addition to age-related structural changes, aging has also been found to impact functional connectivity, which can be measured using rs-fMRI and task-based fMRI. Task-based functional connectivity measures activity of brain regions during a specific task in the scanner, whereas resting-state functional connectivity is able to measure synchronous fluctuations of intrinsic neural activity between regions at rest (i.e., in absence of a task). This thesis focuses on resting-state functional connectivity, as it provides the possibility to look at the functional organization of brain networks at rest that underlie higher order cognitive functions and help provide insight in experience-dependent plasticity. During resting-state functional connectivity, brain regions that show temporally correlated activity are captured as neural networks. For this purpose of this thesis, I will focus on four prominent neural networks due to their involvement in cognition, specifically

EF: 1) the default mode network (DMN); 2) the fronto-parietal network (FPN); 3) the central executive network (CEN); and 4) the salience network (SN).

The DMN is a brain system with a set of interacting brain regions that are functionally connected and distinct from other brain systems. The DMN is activated in passive (cognitive) states, when individuals are not occupied by external tasks (i.e., task-negative) and is involved in self-referential processes[98] and mind wandering.[99] More specifically, for successful task execution, the DMN decreases activation when on-task, to ensure network efficiency. The core region of the DMN is considered the posterior cingulate cortex,[98,100] but the network also includes areas such as the hippocampus and the adjacent medial temporal lobe which are associated with episodic memory.[101] Comparison of multiple methods aiming to define the DMN showed that in addition the medial prefrontal cortex (MPFC) and the inferior parietal lobe (IPL) were also involved in the network. Taking into consideration the regions are involved in this network, the network is considerably prone to aging.[102]

The CEN is involved in executive functioning, providing error feedback for top-down control, and also with the maintenance of associations between action and outcome.[103-105] Brain regions involved in this network are the prefrontal cortex, interior sulcus, anterior cingulate gyrus, and interior frontal gyrus.[103] Dysfunction in this network was found to be associated with age-related cognitive decline.[106]

The FPN is involved in attention and executive control and is able, through communication with other control and processing networks, to adjust and fine-tune control processes with changing

demands.[107,108] The FPN is, in contrast with the DMN, a task-positive network and therefore should be anti-correlated with the DMN to ensure well-executed task performance. Decreases in FPN connectivity have been associated with age-related declines in set-switching.[109] Reineberg and colleagues confirmed the networks involvement in EF. Specifically, they showed that higher performance on executive tasks of set-shifting was associated with increased positive connectivity between the FPN and visual networks.[110]

The SN consists of two main hubs, the anterior insula (AI) and the dorsal anterior cingulate cortex (dACC). The overall function of the SN is its involvement in attention and cognitive control, with its goal to identify relevant stimuli to help guide behaviour.[105] Specifically, the two main hubs of the network contribute to its general network function in their own way. The AI is the network's main hub and plays a role in integration of information from sensory and emotional inputs as well as cognitive information, and therefore plays a critical role in switching between the DMN and CEN.[111] The dACC seed of the network is more involved in response selection and conflict monitoring,[112] as well as facilitating motor responses.[111]

Thus far, the overall consensus currently is that during "healthy" aging intra-network activity generally decreases, whereas inter-network activity is found to both increase or decrease, depending on networks involved.[45,113] Changes in functional connectivity are hypothesized to reflect a decrease in segregation of brain networks due to changes in functional specialization that are evoked during a reorganization process of the brain throughout aging.[44] Functional connectivity within the DMN, one of the most commonly researched resting-state networks, has been found to be impacted by the aging process.[113-115] A recent review demonstrated that in normal

aging, various regions of the DMN (e.g., posterior cingulate cortex, superior and middle frontal gyrus, and superior parietal cortex) show decreased connectivity.[114] Besides overall decreases in DMN connectivity with aging, differences in age-associated changes in connectivity were also found between the anterior versus the posterior DMN.[46,116] In the anterior DMN, both increases and decreases in connectivity were found in the frontal lobe, whereas the posterior DMN only demonstrated age-associated decreases in overall connectivity.[46,117] It is hypothesized that increased connectivity in the anterior DMN could be a compensatory response for losses of cognitive function.[46,117,118] In addition to the DMN, age has also found to impact other networks such as the SN[119] and the FPN.[113] The latter networks are, in contrast to the DMN, considered task-positive networks and generally show decreased intra-network connectivity at rest compared with the DMN. However, with increased age, functional connectivity between task-negative and task-positive networks is susceptible to be less anti-correlated (i.e., increased connectivity), which could result in decreased cognitive performance.

1.4 Non-Pharmaceutical Strategies to Promote Healthy Cognitive Aging

While aging is associated with declines in cognitive performance, not all individuals equally experience these declines, as there is a significant proportion of the population who maintain cognitive function, even in the face of significant brain pathology. This suggests healthy cognitive aging is possible and that cognitive impairment, or dementia, can be delayed or even averted. Importantly, because an effective treatment or cure for dementia remains elusive, there are increased efforts to establish the efficacy of non-pharmaceutical strategies, such as targeted exercise training and cognitive training, on cognitive health in older adults.

Research investigating lifestyle approaches to delay or prevent cognitive decline has shown a great interest in exercise and cognitive training interventions. In this section, I will first address definitions and potential mechanisms of cognitive training, and its effects on both cognitive and brain function by providing evidence from epidemiology studies and randomized controlled trials (RCTs), followed by current limitations in cognitive training literature. Then, I will discuss the effects of physical activity (PA) and exercise on cognition in epidemiological studies and RCTs and its underlying mechanisms. Finally, I will discuss how a combined approach (i.e., exercise and cognitive training) might broaden benefits of cognitive training.

1.4.1 Cognitive Training

Cognitive training is based on the notion that the brain, even with age, can change for the better, if given the appropriate environmental stimuli, thoughts, and emotions.[120] This capacity of the brain is called "neuroplasticity". In the same way that physical training improves physical abilities, cognitive training may induce neuroplastic changes in the brain, resulting in improved cognitive abilities. One of the fundamental principles of neuroplasticity is the concept of synaptic plasticity – the notion that individual connections within the brain are constantly being removed or recreated, largely dependent upon how they are used.[121] Cognitive training aims to harness this principle of neuroplasticity by using guided practice on a set of tasks related to memory, attention, EF, or other cognitive processes.

Computerized cognitive training (CCT) is one example of complex mental activity that could be used to promote healthy cognitive aging. The working definition for CCT for this thesis is the following: CCT is defined as cognitive training on an individual electronic device (e.g., computer,

laptop, tablet/iPad) that requires a physical response such as a button press, and excludes training that primarily requires an individual to perform two tasks simultaneously, in order to compare performance with single-task conditions (i.e., dual-task training). Notably, CCT is an approach that could be used by those who are limited in their ability to physically participate in other strategies, such as exercise.

Animal studies have focused on the underlying mechanisms evoked by environmental enrichment (EE),[122] a form of stimulation most similar to cognitive training in humans. Studies have shown increased hippocampal neurogenesis after exposure of complex EE in adult mice[123,124] and rats.[125] Research suggests that EE could elicit neuronal changes by differentiation and survival, whereas PA might predominantly evoke cell proliferation.[126-128] In addition to neurogenesis, evidence from rodent studies show an increase in synaptogenesis after EE.[129] Specifically, Gelfo and colleagues[130] found synaptogenesis after EE in adult rats was most pronounced via increased dendritic length and spine density. In addition, EE-induced gliogenesis was seen the neocortex[127] and the hippocampus[131-133] in rodents. Besides impacting cellular mechanisms, EE was found to increase levels of brain derived neurotrophic factor (BDNF) after a year of EE in male rats.[134] Despite the efforts thus far in examining the underlying mechanisms of CCT in human studies, more evidence is needed to better understand these neural processes. By addressing this knowledge void, I aim to provide more insight of the potential mechanisms by which CCT exerts an impact on brain function by using resting-state functional connectivity in the current thesis.

1.4.1.1 Type of Training

Computerized cognitive training can be divided into either single-domain or multi-domain training. Single-domain CCT can be defined as training that focuses on one specific cognitive domain (e.g., working memory) for the duration of the training, whereas multi-domain CCT trains multiple cognitive domains by performing a set of activities that each tap into a different domain. Multi-domain training evokes a wider range of cognitive challenges compared with single-domain, which might result in enhanced stimulation of neuroplasticity.[135] A review of cognitive training literature (not specific CCT) suggested that multi-domain cognitive training improved global cognitive function and was able to delay or slow down cognitive decline in MCI,[135,136] whereas single-domain cognitive training has little evidence of increased cognitive function.[137] Also, multi-domain cognitive training was better able to maintain gains acquired during training compared with single-domain cognitive training.[138] In addition, transfer effects to other cognitive domains or to tasks of daily living could be less likely to occur after single-domain training versus multi-domain training as it mainly calls on one type of cognitive ability.[138]

1.4.2 Cognitive Training and Cognitive Outcome

In animal studies, cognitive training or enrichment is often referred to as EE, and involves living circumstances with increased stimulation of the animals (i.e., inclusion of sensory, cognitive and motor stimulation).[139] Studies show that animals exposed to an enriched environment improve performance on tasks of spatial learning (e.g., Morris water maze); specifically, the environmentally enriched animals showed a more targeted response (i.e., shorter swim path) compared with those in a standard environment.[123,140] A recent review on EE and set-shifting (i.e., domain of EF) demonstrated that EE induces cognitive improvements in animal models.[141]

However, it is important to note that, even though there is consistent evidence that EE elicits both behavioural and mechanistic changes in the brain, it is hard to distinguish which aspects of EE (i.e., cognitive, physical, or combination) elicit these changes.[139,142]

Evidence from animal models has led to a growing interest in complex mental activity as a strategy to promote healthy cognitive aging in humans. Complex mental activity comprises all activities that are cognitively challenging for an individual,[143] such as memory and EF training, or dance. A meta-analysis of human cohort studies provides robust evidence that complex patterns of mental activity in early-life, mid-life, and late-life stages is associated with a significant reduction in dementia incidence.[144] Furthermore, they found an association between increased levels of complex mental activity in late life and lower dementia rates, independent of other predictors. Specifically, it showed a dose-response relationship between the amount of complex mental activities in late life and dementia risk.[144]

In addition, recent RCTs showed that complex mental activities such as computer lessons[145] and playing a real-time strategy video game[146] provide cognitive benefits for older adults, such as improvements in episodic memory (e.g., delayed word and story recall). Playing a real-time strategy video game for 23.5 hours improved performance in EF, indicating transfer of training after participating in complex mental activities.[146] Similar effects were demonstrated for complex skill acquisition training (i.e., far transfer of training and changes in neural networks). Thus, a demonstrated benefit of complex mental activities is transfer of training,[146,147] such that a skill learned in one situation is applied to a different but similar situation. Additionally, regarding the retainment of benefits over time, an RCT showed that CCT resulted in improvements in memory

and processing speed which were still visible twelve months post-training,[148] and shows that CCT is able to maintain its benefits.

A recent meta-analysis of cognitive-based training in healthy older adults found that over the 31 included RCTs, benefits were found for overall cognitive function (Hedges' $g = 0.42$). In addition they found cognitive-based training improved EF (Hedges' $g = 0.42$), memory (Hedges' $g = 0.35$), attention (Hedges' $g = 0.22$), and visuospatial abilities (Hedges' $g = 0.18$); with greater benefits seen in studies with a duration of eight or more weeks, 24 or more sessions, and three or more sessions per week.[149] The beneficial effect of cognitive training on EF were supported by other systematic reviews and meta-analyses,[150-152] including in those with MCI.[153] However, other meta-analyses showed no beneficial effects of CCT on EF in older adults.[154,155] According to Harvey and colleagues[156] the current controversy of the efficacy of CCT might be due to inconsistencies in defining CCT, where either definitions or outcomes measures are defined too narrowly. They recommend, in addition to more efficacy studies, a shift in outcome measures to ensure the inclusion of measures that reflect its potential effect on real-world setting. In addition to an otherwise healthy older adult population, more studies have focused on the effects of CCT in more targeted populations, such as those with cognitive impairment, showing overall benefits for global cognition.[157-160]. Thus, current evidence suggests that CCT is a promising strategy for promoting healthy cognitive aging in healthy older adults and those at risk for dementia. However, it is important to note that when critically reviewing the quality and findings of the current systematic reviews and meta-analysis examining the effects of CCT, there is not a clear consensus as to what aspects of cognition might benefit from CCT. For example, the earlier reviews showed benefits of CCT on memory, but not EF.[151,155] More recent reviews included CCT-induced benefits on

EF.[149,150] Thus, even though evidence of CCT on cognitive function is promising, evidence regarding the type of cognitive domain benefited is inconsistent and more high-quality studies are needed to examine this effect more closely.

1.4.3 Cognitive Training and Neuroimaging

To gain more insight in what potential neuroplastic changes CCT by itself may induce; incorporating different neuroimaging techniques in studies could be a good approach to help demonstrate these changes in the brain. For example, synaptic plasticity as a result of stimulation by CCT could potentially be captured by functional connectivity, measured with rs-fMRI, by strengthening connections within and between networks.[161] Work among younger adults illustrated changes in functional activity in the middle frontal gyrus and superior and inferior parietal cortices after working memory training;[162] however these findings do not necessarily translate to an older adult population. Despite increased efforts over the last years, it is not yet well established how CCT impacts regional brain volume, functional activity, and functional or structural connectivity in older adults.

Recently, more studies have focused on providing insight on the potential underlying mechanisms of CCT by including neuroimaging outcomes in trials of solely CCT or combined CCT and PA. Li and colleagues[163] focused on the effects of a multimodal intervention on resting-state functional connectivity. They found that those assigned to a 6-week multimodal intervention, including cognitive training, altered functional connectivity between the medial prefrontal cortex and the medial temporal lobe, which was associated with cognitive performance. However, the majority of studies including neuroimaging outcomes have been performed in older adults with cognitive

impairment (i.e., MCI and vascular cognitive impairment, VCI). Suo and colleagues[164] examined the effects of 6 months of progressive resistance training (PRT), CCT, or a combined intervention (i.e., PRT+CCT) compared with an active control on cognitive function and its underlying mechanisms. Results showed that even though CCT did not improve global cognition, CCT was able to attenuate declines in memory, and this decline was mediated by enhanced connectivity between the hippocampus and the superior frontal cortex. Additionally, a study by Tang et al.[160] examined the effects of a 7-week multi-domain CCT intervention on global cognition and functional connectivity in older adults with VCI. They found that those assigned to the CCT significantly improved global cognition compared with the control group. Moreover, the CCT group showed significant increases in functional connectivity between the medial prefrontal and the left dorsolateral prefrontal cortex, which was correlated with global cognition.

In addition, in a more network-based approach, Chapman and colleagues[165] found that a 12-week program of thrice weekly cognitive training (i.e., total of 35 hours) significantly increased global and regional cerebral blood flow (CBF), particularly in the DMN and the CEN. Moreover, aging has been associated with changes in other networks such as the SN and the FPN. As these functional networks mediate higher order cognitive control processes (i.e., EF), the current thesis will focus on these four prominent resting-state networks: the DMN, CEN, SN, and FPN.

1.4.4 Limitations in Cognitive Training

The current body of research investigating the effects of computerized training is lacking high-quality study designs (i.e., RCTs) that include a well-designed control group. Specifically, studies either only include a passive control group (i.e., usual care) or did not include a control group (i.e.,

comparing different interventions) in their study design. The inclusion of a control group, with a preference for the so-called active control groups (compared with for example wait-list controls), is recommendable in future studies, as the lack of randomization to a proper control group makes it difficult to draw proper conclusion about the efficacy of CCT.

In addition, vast differences in total intervention duration (i.e., number of weeks), frequency of training (i.e., number of sessions), and session duration (i.e., number of minutes per session) exist across studies. Intervention duration varies from only a couple of days to as long as 4 months.[155] This variation in design, as well as the discrepancy in terminology between studies, makes it difficult to compare training effects across studies and make a collective conclusion about the efficacy of CCT.

1.4.5 Physical Activity and Exercise

Physical activity (PA) is defined as activity that is performed as part of an individual's daily life and involves any movement of the body including the use of skeletal muscles.[166] Exercise is a subcategory of PA, and is considered PA that is specifically planned and structured in order to improve physical function.[166]

Based on evidence from both animal and human studies, there are different ways how PA can impact cognition. Firstly, PA can improve brain health by the reduction of chronic diseases that increase the risk of cognitive impairment (e.g., hypertension, diabetes, and depression).[167] In addition, PA can impact mechanisms on cellular levels such as angiogenesis, neurogenesis, synaptic plasticity, and synaptogenesis.[122,168] Vascular health is key to successful brain functioning

as it is responsible for the oxygen and nutrient supply to neurons via blood flow; therefore, PA induced increased vascularization (i.e., angiogenesis) could promote cognitive function. The process of generating new neurons, also referred to as neurogenesis, is also promoted by PA. Neurogenesis predominantly happens in the dentate gyrus (i.e., subgranular zone and granule cell layer) of the hippocampus.[168] The role of PA on synaptogenesis is less well defined and consistent compared with cognitive enrichment; however, some animal studies have shown benefits on synaptic and dendritic structure as a result of PA.[169] These above-mentioned neuroplastic processes could be a result of exercise-induced levels of neurotrophic growth factors, such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF). A review by Cotman and colleagues, examining both animal and human studies, demonstrated the pivotal role of growth factors such as BDNF in exercise-induced changes in cognition, brain function and structure.[170] Van Praag and colleagues[124] established that voluntary wheel running in adult rodents stimulated levels of BDNF in the hippocampus, as well as neurogenesis, cell proliferation, and neuronal survival. In humans, twelve months of aerobic exercise lead to increased hippocampal volume in healthy older adults, which was associated with improvements in spatial memory.[60] Moreover, Erickson and colleagues found that these increases in hippocampal volume were associated with greater levels of serum BDNF. Furthermore, comparing mechanisms of aerobic and resistance exercise-induced memory benefits in rodents, Cassilhas and colleagues[171] found increased levels of hippocampal BDNF and IGF-1 in those assigned to aerobic exercise, where the animals assigned to resistance exercise only showed increases in hippocampal IGF-1. In addition to rodent studies, evidence from human studies showed exercise-induced benefits for memory[172] and EF[173] in older adults. These exercise-induced

levels of BDNF and IGF-1 have been associated with the promotion of neurogenesis and angiogenesis (see Figure 1.2).[168,174]

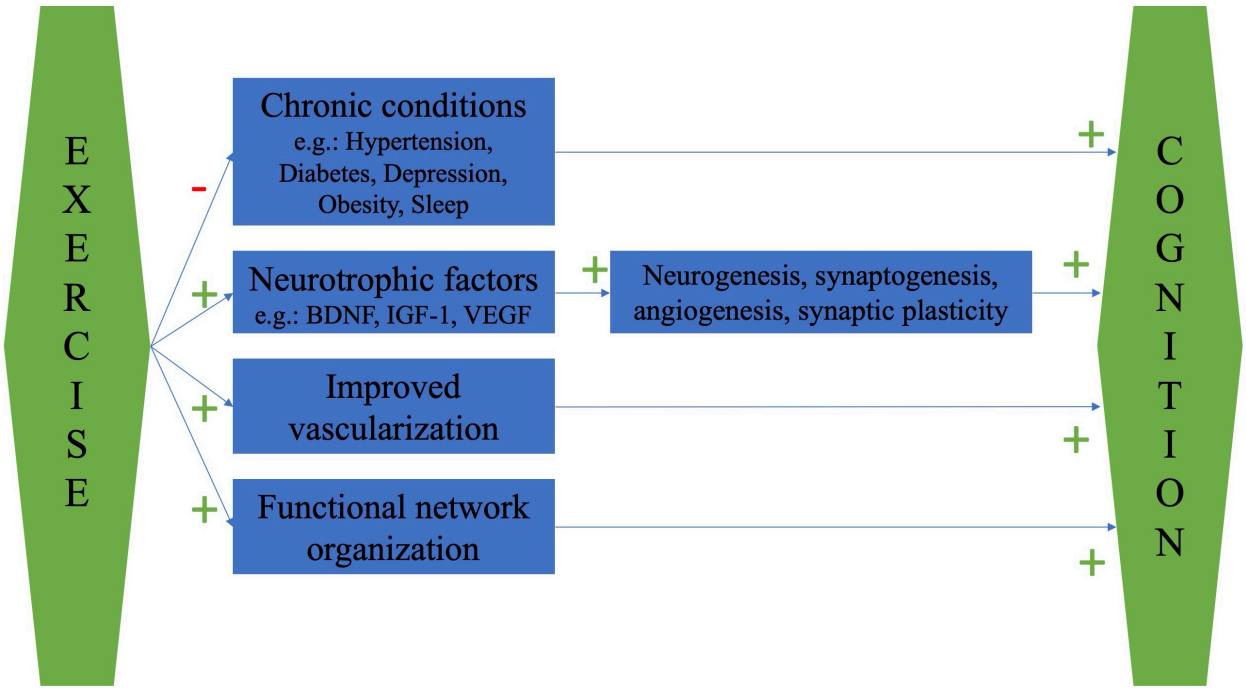

Figure 1.2 Exercise-Induced Mechanisms for Promoting Cognition

In addition to neurotrophic factors, a recent review by Stillman and colleagues[175] demonstrated another pathway how exercise may affect cognition. In both "normal" cognitive aging as well as in AD, processes that underlie the development of amyloid pathology impact the functional organization of neural networks such as the DMN.[100] Studies show that exercise is able to modify this impacted functional organization, especially in networks sensitive to age-related changes (e.g., the DMN and FPN).[98,175,176] The process of this exercise-induced modification is referred to as the restoration of network integrity and is linked to changes in cognitive function.[174] More research needs to examine what type of exercise and its dosage are able to elicit the most optimal benefits

for strengthening neural networks and thus maintain cognitive function throughout the aging process.

1.4.6 Physical Activity and Cognition

Evidence from epidemiological and experimental studies over the past decades shows that PA can help prevent and treat cognitive impairment, and that PA throughout one's lifetime is beneficial for cognitive performance in later life.[177] A 25-year prospective study of 3,247 young adults (age 18-30 years) showed that those who participated in high television watching and low PA in early adulthood showed poorer performance on tests of EF (i.e., response inhibition) and processing speed in midlife compared with those who reported low television watching and high PA.[178] A meta-analysis of non-demented older adults showed that both low-to-moderate as well as higher levels of PA were associated with a reduced risk to develop cognitive impairment (-35%, and -38%, respectively).[179] In addition, a systematic review focusing on PA and the risk of developing neurogenerative disease showed an inverse relationship between PA and dementia risk, such that PA decreased dementia risk (28%) and risk of Alzheimer's disease (45%).[180] A recent longitudinal study showed that over a 10-year follow-up, PA was associated with preserved cognitive function. Specifically, at year 10, preserved memory and EF were found in active individuals where a decline was found in inactive individuals. These findings were broader in females versus males; where active females showed maintenance for both memory and EF versus solely maintenance in EF in men.[181]

1.4.7 Exercise and Cognition

Aerobic and resistance exercise are the most-researched strategies, and evidence shows both types are promising strategies to promote cognitive health, while benefiting cardiovascular function at the same time.[182] In addition to reducing risk factors for cognitive decline, such as high blood pressure, exercise can also alter brain structure and function. Several meta-analyses showed that exercise was beneficial for cognition in older adults.[183,184] Specifically, Kramer and Colcombe[183] demonstrated that aerobic exercise benefited cognition, in particular performance on EF. However, they found that combined aerobic and resistance training showed even greater effects than aerobic exercise alone. In addition, Smith and colleagues showed that aerobic exercise, such as walking, could benefit cognition such as EF (e.g., inhibition, processing speed) and memory.[185] An early study showed that a four-month aerobic training program improved cardiorespiratory function as well as the performance on a simple reaction time task compared with age-matched controls who performed strength and flexibility exercises.[186] These findings were supported by studies investigating the effects of a six-month aerobic training (i.e., walking) intervention compared with age-matched controls performing flexibility exercises. Results showed that the aerobic training group improved reaction time on multiple aspects of cognitive control compared with the control group.[182,187]

However, not all studies find the same beneficial effect of exercise on cognition. A recent study reviewed the effects of exercise on cognitive function in 754 participants over twelve RCTs with training duration varying between eight and twenty-six weeks.[188] Analysis showed that aerobic exercise, compared with any control (i.e., active or no-treatment control), did not benefit cognitive performance. A meta-analysis of exercise training and cognition in individuals with MCI showed

similar results, where findings from 14 RCTs demonstrated limited evidence of cognitive benefits due to exercise.[189] Finally, a recent cohort study examining the link between physical activity, cognitive decline and dementia risk, demonstrated that at a 28-year follow-up on over 10,000 individuals there was no association between level of physical activity and cognitive decline or risk of dementia.[190]

Conversely, studies investigating the effect of resistance exercise on cognition have found promising results.[172,173] A 12-month once or twice weekly progressive resistance training intervention demonstrated improved selective attention and conflict resolution in community-dwelling woman aged 65 to 75 years old.[173] In addition, an RCT of mental and resistance training showed that 2-3x/week of resistance training over 6 months was able to improve global cognitive function at the six month time point and maintain performance on global cognitive function as well as EF measured at 18-month follow-up.[191]

A more recent meta-analysis by Northey and colleagues[184] demonstrated positive effects on cognition after various types of exercise, such as aerobic and resistance exercise, multicomponent training, and tai chi. Besides type of exercise, they also found that exercise performed for 45-60 minutes at moderate or higher intensity showed cognitive benefits. In addition to changes in cognitive functioning, recent research demonstrated that a 12-month, 3 times weekly walking intervention increased both left and right hippocampal volume (2.12% and 1.97%, respectively), which led to increases in spatial memory performance.[60] Finally, improved functional connectivity was found in the default mode network and the executive control network in sedentary older adults after 12-months 3x/week hourly aerobic exercise classes.[174]

1.4.8 Combined Approach to Increase Benefits of CCT

To maximize the potential benefits of CCT, adding exercise immediately prior to CCT might augment any potential benefits of CCT on cognition. Individually, both exercise and CCT are promising strategies to prevent or delay cognitive decline in older adults.[192] Recently more studies have focused on combining different lifestyle strategies to maximize benefits on cognition, but to my knowledge no study has focused on the effects of a single bout of exercise and CCT in immediate succession. A current limitation in the CCT literature is the lack of transfer of benefits to untrained domains (i.e., far transfer).[193] In order to obtain transfer of training, trained and untrained tasks should overlap in activation of brain regions,[194] or trained and untrained skills should be structurally similar.[195] Potentially, priming the brain for CCT using a moderate bout of aerobic exercise could broaden patterns of regional activation and lead to more widespread benefits.

The current literature is addressing the limitation of lack of transfer by combining lifestyle strategies, however they are usually not in immediate succession and more classified as multimodal interventions.[196] For example, in a 16-week trial of PA and cognitive training, Shah and colleagues[197] assigned community-dwelling older adults to one of four groups; exercise (i.e., brisk walk plus resistance training), cognitive training (auditory and visual CCT), combined training (i.e., exercise plus CCT), or a control group. Participants trained five days per week; each training component (i.e., exercise or CCT) was one-hour in duration. They found that those assigned to the combined training group significantly improved performance on the Rey Auditory Verbal Learning Test, a measure of verbal memory and learning, compared with the control group.

However, certain limitations could have impacted these results, such as the lack of true randomization and the unequal number of sessions between groups; the combined training group received twice the number of sessions compared with the exercise group, and fourfold of sessions compared with the control group.

Mechanistically, evidence shows that both aerobic exercise and complex cognitive activities can elicit neuronal changes. Though it is believed both strategies elicit neural changes through different pathways; aerobic exercise stimulates neurogenesis (cell proliferation) via exercise-induced increases of BDNF, whereas cognitive stimulation or cognitive enrichment increases neuronal survival, neuronal differentiation,[122,198] and promotes synaptic plasticity.[198] Aerobic exercise-induced increases in neurotrophic factors, such as BDNF, remain elevated in the brain for approximately one hour post-exercise.[199] Possibly, the immediate succession of CCT-induced plasticity (e.g., neuronal differentiation and synaptic plasticity) after a single bout of moderate-intensity exercise could augment the potential benefits of CCT by enhancing neural plasticity. In addition to neurotrophic factors, mechanisms that could underlie potential enhanced benefits of a single bout of aerobic exercise before CCT could be that of arousal.[200] An early animal model of arousal and cognitive performance showed that learning a difficult cognitive task was optimal after moderate levels of arousal.[201] However, there is still much unknown about the potential arousal effect of PA on cognitive performance as measures of arousal (e.g., heart rate, skin conductance) quickly revert back to normal levels after PA.[202] More research needs to focus on the impact of PA duration and intensity on the concept of arousal and its underlying mechanism. Finally, one neuroimaging study in young females showed that those who completed a working memory task in the scanner following a single session of exercise (20 minutes, moderate intensity) showed

increased activity in the prefrontal and occipital cortices compared to those who rested before completing the task in the scanner.[203] Unfortunately, the increased activity was not linked to behavioural performance. However, the increased activity in the prefrontal cortex on-task suggests that a 20-minute moderate bout of exercise prior to a cognitively demanding tasks alters brain function for a period of time after exercise cessation. Perhaps physical activity may be a promising approach to prime the brain for cognitive training. However, to our knowledge, no studies to date have tested this hypothesis in the field of CCT.

1.5 Functional Magnetic Resonance Imaging

The current thesis focuses on the effects of CCT on functional connectivity, as measured with rs-fMRI. In this section, I will describe some of the key principles and methodology of rs-fMRI.

Using fMRI, we are able to look at in-vivo activity of the brain at rest or while performing a task. The principle used to capture functional brain activity is by measuring changes in the blood-oxygen level dependent (BOLD) signal. These changes in the BOLD signal occur when neural activity changes as a result of for example task execution. Different behaviors (i.e., rest or functional task) call on different brain regions, which interact through various brain networks.[204] The BOLD signal is characterized by a time delay of several seconds, also referred to as the hemodynamic response, due to time required for the physiological response of vasodilation after stimulation.[205] Resting-state fMRI makes it possible to look at the 'spontaneous' activity of the brain when at rest, or in other words, when we are not thinking about anything in particular or executing a task.

1.5.1 Resting-State fMRI: Functional Connectivity

The brain consists of functional and structural networks that are interconnected. Communication between different networks is a key process during complex cognitive processes, by using and integrating information from different neural regions.[206] This is also referred to as functional connectivity; the temporal dependency between spatially remote neurophysiological events.[207] However, using rs-fMRI it is possible to measure co-activation of spontaneous neural activity during rest (i.e., when thinking about nothing in particular), also referred to as resting-state functional connectivity.[100,206] As previously discussed in section 1.3.2, functional connectivity is prone to be impacted by the "normal" aging process. In addition, it is hypothesized that with disease, the connectivity between brain regions is disrupted. Using rs-fMRI, studies have looked at resting-state functional connectivity within networks (e.g., the default mode network, described in section 1.3.2) in AD. Results showed that compared with a healthy population, individuals with AD showed decreases in functional connectivity within the default mode network, specifically a decreased resting-state connectivity between the posterior cingulate cortex (PCC) and the hippocampus.[101] As mentioned previously, resting-state functional connectivity data provides information on how different brain regions behave in absence of a task, and how regions correlate with each other temporally. Therefore, it does not directly provide information regarding neural mechanisms underlying these functional behaviours.[208] We can only hypothesize, based on the current knowledge of cellular changes with aging or impairment, what underlying cellular changes are responsible for changes in functional connectivity. In addition, in order to help advance this field of research, it is essential to combine behavioural data with rs-fMRI data in order to make any assumptions or draw conclusions about favorable directionality.

There are different methods to process rs-fMRI data, such as seed-based analysis (SBA, model-dependent) or independent component analysis (ICA, model-free). In short, SBA focuses on the correlation between resting-state time series of different regions of interest (i.e., the seeds). With SBA a functional connectivity map can be created that maps out all the present regions that show functional connections with the chosen seed region. ICA is a more data-driven process that looks for underlying sources that can explain the connectivity patterns by focusing on the presence of spatial sources of resting-state signals that are maximally independent from each other.[206]

1.6 Thesis Overview

There is much interest in lifestyle strategies to help prevent or delay cognitive decline in older adults with or without cognitive impairment. Exercise is a well-established and well-accepted strategy for the promotion of cognitive health in the current literature. A relatively new but explosive field has emerged as there has been a large influx of commercialized CCT programs on the market over the last few years. Therefore, the objective of this thesis is to examine the efficacy of CCT programs in relation to cognitive health, by means of the following aims:

1. To provide a detailed review of the current state of the literature examining the underlying neural changes of CCT in adults aged 55 years and older.
2. To examine the effects of an eight-week RCT of CCT, alone and when immediately preceded by a 15-minute brisk walk, on verbal memory and learning and executive functions, compared with an active control in older adults aged 65 – 85 years old.
3. To identify relevant changes in inter-network functional connectivity that correlate with changes in executive functions.
4. To examine whether CCT benefits changes in inter-network functional connectivity compared with an active control.

Chapter 2: Effects of computerized cognitive training on neuroimaging outcomes in older adults: A systematic review

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2.1 Introduction

With our ageing population, the incidence of dementia is rising rapidly. Currently, over 47 million people worldwide are diagnosed with dementia and this number is expected to triple by 2050.[209] In 2010 it was estimated that the worldwide cost of dementia was 604 billion US dollars.[209] Thus, it is imperative to find strategies that promote cognitive healthy aging to minimize the projected societal, health, and economic burden by reducing or delaying the potential progression to mild cognitive impairment or dementia.

Currently, there is no pharmaceutical cure for dementia. As such, identifying lifestyle approaches that may prevent, delay, or even treat cognitive impairment and dementia in older adults is becoming increasingly important.[4] Even when an effective pharmacological therapy is available, lifestyle approaches (i.e., exercise, nutrition, and cognitive training) can be used in conjunction as lifestyle interventions result in multidimensional benefits.[5] In recent years, there is growing interest in complex mental activity as a strategy to promote healthy cognitive aging. Complex

mental activity comprises all activities that are cognitively challenging for an individual,[143] such as memory and executive functioning training, or dance. A meta-analysis of human cohort studies provides robust evidence that complex patterns of mental activity in early, mid-life, and late-life stages is associated with a significant reduction in dementia incidence.[144] Furthermore, they found an association between increased levels of complex mental activity in late life and lower dementia rates, independent of other predictors. Finally, it showed a dose-response relationship between the amount of complex mental activities in late life and dementia risk.[144]

Computerized cognitive training (CCT) is one example of complex mental activity that could be used to promote healthy cognitive aging. CCT is defined as cognitive training on an individual electronic device (e.g., computer, laptop, tablet/iPad) that requires a physical response such as a button press, and excludes training that primarily requires an individual to perform two tasks simultaneously, in order to compare performance with single-task conditions (i.e., dual-task training). Notably, CCT is an approach that could be used by those who are limited in their ability to physically participate in other strategies, such as exercise. A meta-analyses shows that CCT improved overall cognitive performance in older adults.[155] Specifically it showed improvements in verbal and non-verbal memory, working memory, processing speed, and visuospatial skills.[155] Recent randomized controlled trials (RCTs) of CCT in older adults showed that both two and three months of training resulted in improved global cognition compared with an active control group.[148,210] Additionally, an RCT showed that CCT resulted in improvements in memory and processing speed which were still visible twelve months post-training,[148] and shows that CCT is able to maintain its benefits. Playing a real-time strategy video game for 23.5 hours improved performance in executive functions, indicating transfer of training after participating in complex

mental activities.[146] Thus, current evidence suggests that CCT is a promising strategy for promoting healthy cognitive aging.

Cognitive training is based on the notion that the brain, even with age, can change for the better, if given the appropriate environmental stimuli, thoughts, and emotions.[120] This capacity of the brain is called "neuroplasticity". In the same way that physical training improves physical abilities, cognitive training (or brain training) may induce neuroplastic changes in the brain, resulting in improved cognitive abilities. One of the fundamental principles of neuroplasticity is the concept of synaptic plasticity – the notion that individual connections within the brain are constantly being removed or recreated, largely dependent upon how they are used.[121] Cognitive training aims to harness this principle of neuroplasticity by using guided practice on a set of tasks related to memory, attention, or other cognitive processes.

To gain more insight in what potential neuroplastic changes CCT may induce; incorporating different neuroimaging techniques in studies could be a good approach to help demonstrate these changes in the brain. For example, synaptic plasticity as a result of stimulation by CCT could potentially be captured by functional connectivity, measured with resting-state functional magnetic resonance imaging (rs-fMRI), by strengthening connections within and between networks.[161] To date, it is not well established how CCT impacts regional brain volume, functional activity, and functional or structural connectivity in older adults. Although work has been done among younger adults illustrating changes in functional activity in the middle frontal gyrus and superior and inferior parietal cortices after working memory training,[162] these findings don't necessarily translate to an older adult population. Therefore, gaps remain in understanding the

underlying mechanisms of training-induced neuroplasticity in older adults. Addressing this knowledge void, this systematic review aims to ascertain the mechanisms by which CCT exerts an impact on brain structure and function by using different neuroimaging techniques such as volumetric magnetic resonance imaging (MRI), task-based functional MRI (fMRI), rs-fMRI, and diffusion tensor imaging (DTI). Through understanding the underlying neural mechanisms of CCT, our goal is to provide knowledge on how to design improved and targeted interventions that help combat or prevent cognitive decline throughout life.

2.2 Methods

2.2.1 Search Strategy

In accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement,[211] we conducted a comprehensive search of MEDLINE, EMBASE, and CINAHL databases to identify all the studies that investigated neuroimaging outcomes resulting from CCT interventions. We limited our search to adults aged 55 years and older with and without cognitive impairment, who have not been diagnosed with dementia. We did not limit the search based on publication date, as CCT is a relative novel research topic. The final search (see Figure 2.1A for search strategy) was done on July 7 (2016) and included a check for recent publications in PubMed.

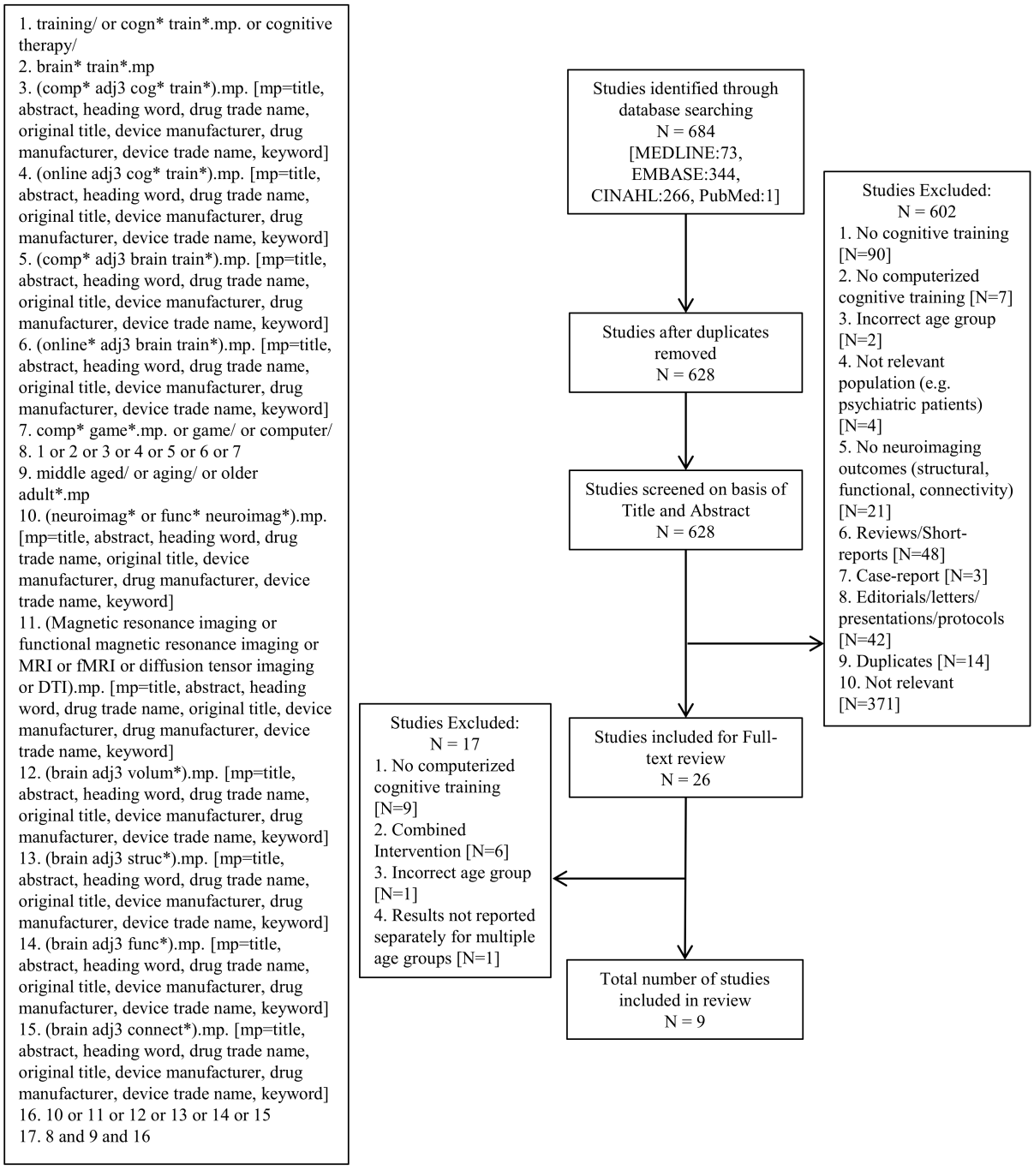

Figure 2.1 (A) Search Strategy Retrieved from Ovid; (B) Exclusion Pathway for Study Selection

2.2.2 Study Selection

We selected studies that had a CCT intervention with neuroimaging outcomes (e.g. volumetric structural MRI, functional MRI, DTI) in an older adult population (age 55 years and older). Study designs included in this systematic review were RCTs and quasi-experimental studies. Studies that used samples of younger and older adults but reported group results separately were included in this systematic review. We included studies that focused on both single- and multi-domain CCT programs. We considered single-domain CCT training as training that targeted a specific cognitive ability, such as working memory. In contrast, multi-domain CCT was considered training that consisted of a series of tasks that targeted multiple cognitive abilities (e.g., executive functions and memory). We excluded studies that did not focus on CCT or studies that used CCT in combination with other types of intervention (e.g., non-CCT, exercise), reviews and short reports. A full list of exclusion criteria and the exclusion pathway is displayed in Figure 2.1B. Critical review of titles and abstracts resulted in 22 articles for full-text review.

2.2.3 Data Extraction and Quality Assessment

We developed a list of data extraction items. This list included reference, study sample, study design, MRI magnet, neuroimaging outcomes, cognitive function measured, training program/task, cognitive domain trained, description of training, training frequency and duration, total hours of training, supervised/home-based training, and control group. Two authors [LTB and CKB] independently extracted the data from the included studies. Discrepancies were discussed and solved by two authors [JCD and TLA].

The Physiotherapy Evidence Database (PEDro) scale[212] was used to assess the quality of the included studies. We [LTB and TLA] added three additional items to the PEDro scale to ensure a proper assessment of intervention studies using neuroimaging outcomes. These three items included were: 1) cognition measured to assist the interpretation of neuroimaging results; 2) sample size calculation; and 3) compliance reported (yes/no). To answer the items in the quality assessment, we used a '+' for items that were present and a '-' for items that were absent. The quality assessment was performed independently by two authors [LTB and CKB]. Discrepancies were discussed and reviewed by two authors [JCD and TLA]. Consensus between two authors [LTB and CKB] was achieved after discussion (K=0.98). Because item one of the PEDro scale is related to external validity, it is not included in the overall PEDro score. Therefore, the maximum quality assessment score calculated by the PEDro was 10 points (each '+' indicates one point) and will be reported in the results. Studies with a PEDro score of 6/10 or higher were considered studies of moderate to high quality. The additional item list had a maximum score of three points and trends from this list will be descriptively discussed in the results.

2.3 Results

2.3.1 Overview of Studies Included

Of the 684 articles identified, nine were included in this systematic review (Table 2.1). These nine papers included four RCTs[164,213-215] and five quasi-experimental studies;[147,216-219] all nine studies had a different study duration. Details of the interventions included are provided in Table 2.2. The results are categorized into four categories: 1) Volumetric structural imaging (n=4);[164,213,216,218] 2) Task-based fMRI (n=3);[215,217,218] 3) Connectivity (n=7);[147,164,213,214,216,218,219] and 4) Correlation

between imaging outcomes and cognitive function outcomes (n=8),[147,164,213-218] (Table 2.3). Results are reported in order of study quality, starting with the highest quality.

Table 2.1 Characteristics of Studies Included

Reference	Study Sample[a]	Study Design Length of follow-up	MRI Magnet	Neuroimaging Outcome Measures	Cognition measured (test name)
Suo et al.[164] ***2016***	Older adults with MCI N=100 70.1 ± 6.7 years Completed MRI: N=79	RCT Assessments at baseline and 6 months	3T	• Volumetric Structural MRI • Resting-state fMRI	Global Cognition (ADAS-Cog)[220] o Memory Domain o Executive Function o Attention-Speed
Rosen et al.[215] ***2011***	Older adults with MCI N=12 74.34 ± 9.25 years Training N = 6 70.67 ± 10.58 years Control N=6 78 ± 7.92 years	RCT Assessments conducted on average 72 ± 26 days apart	3T	• Task-based fMRI · *Incidental Auditory-Verbal Repetition paradigm*	Memory (Repeatable Battery for the Assessment of Neuropsychological Status: RBANS)[221]
Lampit et al. [213] ***2015***	Healthy older adults: Subsample from Timecourse Trial N=12 71.43 ± 7.48 years	RCT Assessments at baseline, 3 weeks: Follow Up 1(FU1), 3 months:	3T	• Volumetric Structural MRI • Resting-state fMRI • Proton Magnetic Resonance Spectroscopy • DTI	Global Cognition: Composite of memory and information processing speed (Mindstreams battery)[222] as well as executive function (Average Mindstreams Stroop Interference test for Inhibition[222] and

Reference	Study Sample[a]	Study Design Length of follow-up	MRI Magnet	Neuroimaging Outcome Measures	Cognition measured (test name)
	Training N=7 72.3 ± 8 years Control N=5 70.2 ± 6.7 years	Follow Up 2 (FU2) Secondary analysis			Cambridge Neuropsychological Test Automated Battery (CANTAB) Stockings of Cambridge problems solving)[223,224]
Belleville et al.[217] ***2014***	Healthy community-dwelling older adults N = 40 69 ± 6.27 years Training group 1 N=12 68.58 ± 8.16 years Training group 2 N=14 69.57 ± 5.81 years Training group 3 N=14 68.79 ± 5.13 years	Quasi-experimental Pre-post Assessments 1 week before and 1 week after training	3T	• Task-based fMRI · Alphanumeric equation task · Visual detection task Tasks performed as single-task and dual-task	Reaction Time (Alphanumeric equation task and visual detection task) Accuracy (Alphanumeric equation task and visual detection task)

Reference	Study Sample[a]	Study Design Length of follow-up	MRI Magnet	Neuroimaging Outcome Measures	Cognition measured (test name)
Lin et al.[214] ***2014***	Older adults with a history of a stroke N=34 69.21 ± 4.93 years Training N=16 62.4 ± 6.0 years Control N=18 63.2 ± 5.7 years	RCT Assessments at baseline and 10 weeks	3T	• Resting state fMRI	Memory (Wechsler Memory Scale)[225] Executive Function (Trail Making Test)[226]
Strenziok et al.[147] ***2014***	Healthy older adults N = 42 69.21 ± 4.93 years Training group 1 N=14 69.70 ± 6.9 years Training group 2 N=14 68.52 ± 5.6 years Training group 3 N=14 69.41 ± 2.3 years	Quasi-experimental Pre-post Length of follow up: Not stated	Not stated	• Resting-state fMRI • DTI	Reasoning/Problem Solving (WAIS III Matrix Reasoning subtest,[227] Everyday problems Test,[228] Word Series and Letter Series Tests)[229] Episodic Memory (Wechsler Memory Scale Logical Memory Subtest)[230,231] Spatial Working Memory (Information-processing Visuo-Spatial Delayed Match-to-Sample Test)[232,233] Auditory Working Memory (Letter Number Sequencing subtest of WAIS III)[227]

Reference	Study Sample[a]	Study Design Length of follow-up	MRI Magnet	Neuroimaging Outcome Measures	Cognition measured (test name)
Lövden et al.[219] ***2010***	Healthy older adults*: Subsample COGITO study N = 25 69.32 ± 3.12 years Training N = 12 68.9 ± 2.7 years Control N=13 69.7 ± 3.5 years	Quasi-experimental Pre-post Training: Pre-post MRI on average 179 ± 25.2 days apart Control: Pre-post MRI on average 184 ± 15.0 days apart	1.5T	• DTI	Spatial Working Memory (3-Back)** Numerical Working Memory (Memory Updating)** Figural-Spatial Episodic Memory (Object-Position Memory)** Numerical Episodic Memory (Number-noun pairs)** Verbal Episodic Memory (Wordlist)** Perceptual Speed (Choice Reaction Task, Comparison tasks) **
Antonenko et al.[216] ***2016***	Healthy older adults N = 25 69 ± 6 years	Quasi-experimental Pre-post Assessments 1 day before (pre), 1 day after (post) and 1 month after (follow-up) training***	3T	• Volumetric Structural MRI • DTI	Cued recall (3-alternative-forced-choice recall task (AFC); main outcome)[234] and recognition Episodic Memory control task (German Rey Auditory Verbal Learning Test)[235]

Reference	Study Sample[a]	Study Design Length of follow-up	MRI Magnet	Neuroimaging Outcome Measures	Cognition measured (test name)
Heinzel et al.[218] ***2014***	Healthy older adults** N=19 65.95 ± 3.73 years	Quasi-experimental Pre-post Subset of 15 older individuals performed pre-post MRI Length of follow up: Not stated	3T	• Volumetric Structural MRI • Task-based fMRI · *N*-back [236]: two runs (16 blocks/ run) with 4 working memory loads (0,1, 2,3) • Functional Connectivity (PPI)	Relative Working Memory Training gain (*n*-Back)[236] Short-term memory (Digit span Fwd and Bwd WAIS III)[230] Processing Speed (Digit Symbol WAIS III,[230] D2 Test[237]) Executive Functions: Verbal Fluency (Controlled Oral Word Association Test)[238] Inhibition (Stroop)[239] Abstract Reasoning (Raven's SPM[240], Figural Relations subtest[241])

[a] Mean age ± standard deviation
* A sample of young adults was included in the study as well
** Behavioural outcomes only measured for intervention groups
*** Only cognitive assessments at one-month follow-up (no MRI)
MRI: Magnetic Resonance Imaging
DTI: Diffusion Tensor Imaging
fMRI: functional Magnetic Resonance Imaging
RCT: Randomized Controlled Trial

Table 2.2 Details of the Computerized Cognitive Training Intervention for the Studies Included

Reference	Training program/ task Cognitive Domain Trained	Description of Training	Training Frequency Training Duration	Total hours of training Supervised/ Home-based	Control Group
Suo et al.[164] ***2016***	COGPACK Multidomain: memory, attention, response speed, executive functions, language	COGPACK: Exercises focused on memory, attention, response speed, executive functions, and language	26 weeks 52 sessions 90 min/session	78 Supervised	Active: watched videos on computer, followed by questions
Rosen et al.[215] ***2011***	Posit Science Multidomain: processing speed, accuracy in auditory processing	Auditory verbal repetition paradigm: 7 exercises aimed at improving processing speed and accuracy in auditory processing	5 weeks 24 sessions 100 min/session	36 Home	Active: 3 different computer-based activities (listening to audiobooks, reading online news, playing visuospatial computer game)
Lampit et al.[213] ***2015***	COGPACK Multidomain: memory, attention, response speed, executive functions, language	Exercises focused on memory, attention, response speed, executive functions, and language	12 weeks 3x/week 60min/session	36 Supervised	Active: viewed 7 National Geographic videos per session on a computer with multiple choice questions

Reference	Training program/ task Cognitive Domain Trained	Description of Training	Training Frequency Training Duration	Total hours of training Supervised/ Home-based	Control Group
Belleville et al.[217] ***2014***	Customized program Executive Function: Attention	*Alphanumeric equation task:* judge accuracy of visually presented letter and number equations. *Visual detection task:* detect the red rectangles (press a button) in a series of white and red rectangles Groups: 1.Single repeated: Complete both tasks individually (focused attention) 2. Divided fixed: Complete 2 tasks simultaneously with divided attention (50%) 3. Divided variable: Complete two tasks simultaneously with different attention allocation levels (80%, 50%, 20%)	2 weeks 3x/week 1 hour/session	6 Supervised	No Control
Lin et al.[214] ***2014***	RehaCom Executive Function and memory	Computer-assisted exercise focused on memory and executive function	10 weeks 6x/week 60 min/session	60 Supervised	Passive

Reference	Training program/ task Cognitive Domain Trained	Description of Training	Training Frequency Training Duration	Total hours of training Supervised/ Home-based	Control Group
Strenziok et al.[147] ***2014***	Multidomain: Brain Fitness (BF): auditory perception; Space Fortress (SF): visuomotor and working memory Rise of Nation (RoN): attention, motor processing, working memory, reasoning, visuospatial short-term memory, task-switching	1. Brain Fitness (BF): Adaptive auditory perception computer game 2. Space Fortress (SF): Complex skill acquisition computer game 3. Rise of Nations (RoN): Off-the shelf real-time strategy computer game	6 weeks 36 sessions 60 min/session	36 Supervised + Home (50-50%)	No Control
Lövden et al.[219] ***2010***	Customized program Multidomain: working memory, episodic memory, perceptual speed	Working Memory (3-Back, Memory updating, Alpha span) Episodic memory (Object-position memory, Number-noun pairs, Word lists) Perceptual speed (Choice reaction tasks, Comparison Tasks)	>4 months Average of 100 ± 3.7 sessions 60 min/session	Average of 100 Supervised	Passive: Pre-post MRI only

Reference	Training program/ task Cognitive Domain Trained	Description of Training	Training Frequency Training Duration	Total hours of training Supervised/ Home-based	Control Group
Antonenko et al.[216] ***2016***	Object-location Learning Paradigm Memory	*Object-location Learning Paradigm:* Learn the correct spatial locations of buildings on a street map. Five blocks of 120 stimulus-location pairing with a response interval of 3 seconds. Each block was followed by a cued recall and a recognition task	3 consecutive days 5 learning blocks/day	Unknown Unspecified	No Control
Heinzel et al.[218] ***2014***	*n*-Back training Executive Function: Working Memory	Adaptive *n*-back training, 3 runs (12 blocks/run) each session. Difficulty level increased according to individual performance (higher working memory load, shortened interstimulus interval (ISI). ISI ranged from 1500-500ms in steps of 500ms.	4 weeks 3x/week 45 min/session	9 Supervised	No control

2.3.2 Structural Imaging (n=4)

Four studies[164,213,216,218] reported volumetric and cortical thickness outcomes (Table 2.3). A randomized controlled study (full factorial design) multi-domain cognitive training study using Cogpack,[164] older adults with mild cognitive impairment (MCI) trained for a total of 78 hours over a period of 6 months under supervision. Combined cognitive training with resistance training resulted in increased cortical thickness in the posterior cingulate cortex. However, in the same study they found that cognitive training alone led to a decrease in the posterior cingulate cortex thickness. However, there was no difference in decrease in thickness compared with the control group.

In addition, a twelve-week supervised multi-domain CCT study[213] using the same program (CogPack) showed that 36 hours of training resulted in an increase in grey matter density in the right post-central gyrus compared with a decrease in the active control group. Additionally, the training resulted in a difference in rate of thickness change over time in both the left fusiform gyrus and the supramarginal and post-central gyri.

In contrast, in an object-location learning paradigm study[216] participants performed training on three consecutive days where they had to learn the correct spatial location of buildings on a street map. On each training day, the training was followed by a cued recall and recognition task. Hippocampal volumes was measured pre- and post-training. The authors found that the object-location learning paradigm did not lead to changes in hippocampal volume.

In another quasi-experimental study,[218] participants performed an adaptive working memory training (*n*-Back) for twelve 45-minute sessions over 4 weeks. Difficulty level of the training was based on individual performance and increases over time. Results showed that the training did not result in changes in grey matter volume in the working memory network.

In summary, one RCT[164] found cortical thinning as a result of cognitive training alone. In contrast, another RCT[213] found an increase in grey matter density following training. Finally, one study[218] found that cognitive training did not result in changes in grey matter, and one study[216] found that cognitive training did not lead to changes in hippocampal volume.

2.3.3 Task-Based fMRI (n=3)

Three[215,217,218] of the eight included studies examined the effect of a CCT intervention on brain function as measured via task-based fMRI (Table 2.3). An RCT[215] showed that 2200 minutes of cognitive training over a period of 5 weeks resulted in a significant increase in left anterior hippocampus activity compared with an active control group. The cognitive training consisted of seven games aimed to improve auditory processing speed and accuracy. Task difficulty was adjusted throughout the training based on individual performance. The active control group performed computer-based activities such as reading online newspapers and playing computer games targeting visuospatial abilities.

A two-week quasi-experimental study looked at focused and divided (fixed and variable) attention training.[217] In the focused attention training, two tasks (i.e., alphanumeric task and a visual detection task) were performed back to back but separate so participants focused on one task at a

time. In the divided attention training, participants performed two tasks at the same time with an equal amount of attention (fixed) or under different attention allocations (variable). Results showed that training a single alphanumeric task for 6 hours over two weeks decreased activation in the inferior and right middle frontal gyrus, in the left middle frontal gyrus and in the left thalamus. No differences in functional brain activation were found after performing the single visual detection task or the in the dual task condition. Participants who were assigned to training where they performed both the alphanumeric task and the visual detection task at the same time (i.e., dual task) did not show differences in performance during the alphanumeric task in the scanner. However, participants showed decreased functional brain activation at post-training compared with pre-training in the cerebellum and right middle occipital gyrus during the single visual detection task. Additionally, participants showed a slight increase in activation in both the right and left middle frontal gyrus. Finally, participants who were assigned to the training group where they had to perform dual tasks under different attention allocation levels (i.e., 80%, 50%, or 20%), showed increased activation in the right middle frontal gyrus (area 10) for 20% and 50% attention allocation when performing the dual task. No significant changes in functional brain activation were found during the 80% attention allocation task, neither during the alphanumeric single task, nor during the visual detection single task performance.

In an adaptive *n*-back training program,[218] participants performed 12 sessions of approximately 45 minutes each over 4 weeks. The difficulty level of the training was based on individual performance and was increased across training sessions by increasing working memory load and decreasing the interstimulus interval. Results of this study showed a non-significant time (2) by working memory load (3) interaction, with a significant main effect of time. This main effect of

time demonstrates a reduction in working memory network functional brain activity measured by the Blood Oxygen Level Dependent (BOLD) signal after 12 training sessions. Only decreases in the 1-back (and not 2-back or 3-back) condition were significant, which indicates this main effect of time is driven by the BOLD signal during the 1-back condition.

In summary, an RCT[215] showed that 2200 minutes of CCT resulted in increased in left anterior hippocampus activity compared with an active control group. One quasi-experimental study[217] showed that depending on the task and region of interest, all training conditions resulted in both increased and decreased activity. Finally, a second quasi-experimental study[218] found that 12 sessions of *n*-back training resulted in a significant decrease in working memory activity; however decrease in activity was driven by performance on the 1-back condition.

2.3.4 Connectivity

2.3.4.1 Resting-State fMRI (n=5)

Five studies[147,164,213,214,218] looked at changes in functional connectivity after CCT (Table 2.3). An RCT[164] examined the effect of progressive resistance training (PRT), computerized multi-domain cognitive training (CCT), or a combined intervention on brain structure and function in older adults with mild cognitive impairment (MCI). The study duration was 26 weeks, with a total of 78 hours of training. In the cognitive training groups (i.e., PRT+CCT, and CCT+Sham), the posterior cingulate cortex showed significant decreases in resting-state functional connectivity with both the superior frontal lobe and the anterior cingulate cortex. In addition, increases in resting-state functional connectivity between the hippocampus and the left superior frontal lobe were found compared with groups without CCT.

A second RCT of 12 weeks of multimodal CCT[213] showed that 36 hours of cognitive training resulted in decreases in resting-state functional connectivity between the posterior cingulate and the right superior frontal gyrus, while the control group showed significant increases in resting-state functional connectivity. In contrast, CCT resulted in increased resting-state functional connectivity between the right hippocampus and the left superior temporal gyrus compared with a decrease in connectivity in the control group.

Another RCT[214] looked at the effects of a 10-week computer assisted training focused on executive functioning and memory in older adults with a history of stroke. The authors found that training, compared with a passive control group, significantly increased resting-state functional connectivity in multiple areas. The left hippocampus showed significantly increased connectivity with the right inferior frontal gyrus and the right middle frontal gyrus. Additionally, the right hippocampus showed increased resting-state functional connectivity with the left middle frontal gyrus, the left inferior frontal gyrus, the left superior frontal gyrus and the left parietal lobe. In contrast, the control group showed significant decreases in resting-state functional connectivity over the 10 weeks (see Table 2.3 for connectivity decreases).

A quasi experiment investigating the effect of three different computer programs[147] found an increased resting-state functional connectivity in the dorsal network between the right superior parietal cortex (SPC) and left posterior inferior temporal lobe (ITL) in Rise Of Nation (RON) compared with a decrease in Space Fortress (SF). Finally, Brain Fitness (BF) resulted in

significantly decreased resting-state functional connectivity between the right SPC and the left anterior ITL compared with an increase in RON.

Finally, a quasi-experimental study[218] looking at the effects of an adaptive *n*-back training program in older adults found that the 5-week training did not result in changes in task-based functional connectivity in the working memory network.

2.3.4.2 Structural Connectivity (n=4)

Four studies[147,213,216,219] examined changes in structural connectivity, using DTI, after CCT (Table 2.3). Whole brain diffusion tensor imaging (DTI) of an RCT of 12 weeks of multimodal CCT[213] showed that 36 hours of cognitive training did not result in changes in structural connectivity after training.

A quasi-experiment in healthy older adults looked at the effect of three different training protocols on brain structure.[147] The participants trained for 36 hours over a period of 6 weeks; half of the training was supervised, and the other half was performed at their own homes. One training group performed BF, an auditory perception game; the second training group performed SF, a complex skill acquisition game focused on visuomotor and working memory skills; and the third group performed RON, an off-the shelf real-time strategy game focused on for example attention, motor processing, working memory and reasoning. The authors found changes in the ventral and dorsal network. Axial diffusivity (AxD) was increased in the right occipito-temporal white matter in the BF group, compared with a decrease in SF and RON.

Another quasi-experimental study[219] of approximately 100 hours of multi-domain cognitive training in both young and healthy older adults performed Diffusion Tensor Imaging (DTI) to look at the effects of training on structural connectivity in the brain. Result showed a significant decrease in MD in the genu of the corpus callosum compared with a passive control group who showed no changes in MD. They also found a significant increase of fractional anisotropy (FA) in the genu of the corpus callosum compared with the control group.

Diffusion Tensor Imaging results from a third quasi-experimental study[216] that involved 3 consecutive days of training an object-location learning paradigm, showed that the 3-day training resulted in a significant decrease in mean diffusivity (MD) in the fornix at post-training compared with pre-training. No changes in MD were found in the hippocampus as a result of the training. In addition, the results showed an increase in FA in the fornix, however this increase was not significant.

In summary, the seven[147,164,213,214,216,218,219] above mentioned rs-fMRI and DTI studies showed both increases and decreases in functional and structural connectivity after CCT. The variety in study protocol (i.e., training type, duration) and the regions of interest chosen for neuroimaging analysis makes the comparison between studies difficult.

2.3.5 Correlation Between Imaging Outcomes and Cognitive Function Outcomes (n=8)

Eight studies[147,164,213-218] assessed the association between cognitive performance and neuroimaging findings (Table 2.3). An RCT in older adults with a history of stroke[164] found that increases in posterior cingulate grey matter were associated with improvements in global

cognition. Additionally, a cognitive training by time interaction showed that the increased connectivity between the hippocampus and the left superior frontal lobe was related to increased memory domain performance. However, this interaction takes into account all training groups that had a cognitive training component (i.e., also cognitive training combined with resistance training). The inclusion of the combination group might have influenced this interaction.

In contrast, an RCT looking at CCT in older adults with MCI[215] found no significant correlations between neuroimaging and cognitive results. However, the authors found a non-significant trend suggesting that, in both groups, increases in hippocampal activity might be related to improved memory scores on the RBANS.

An RCT of multimodal CCT[213] found that increased grey matter density in the right posterior central gyrus was associated with improved global cognition at 3 weeks and 3 months. This association was found in both the training and control group. In addition, it was found that a decrease in resting-state functional connectivity between the posterior cingulate and the superior frontal gyrus after 3 weeks of training was related to an increased change in global cognition after 3 months of training. Increased resting-state functional connectivity between the right hippocampus and the left superior temporal gyrus measures after three weeks of training was associated with increases in global cognition after 3 months of training.

A quasi-experimental study[217] found that in participants performing the alphanumeric task in the single task condition (i.e., focus on one task at the time), there was a significant positive correlation between both the right inferior and the middle frontal gyrus activation and reaction time. Thus

shorter reaction time (i.e., better performance) was associated with a decrease in brain activation. In the divided variable condition (i.e., dual task with different attention allocation levels), there was a negative correlation between activation of the right superior and middle frontal gyrus and attentional cost post training. This correlation indicates that a better training performance (i.e., lower attentional cost during dual task performance) was associated with higher levels of brain activation.

An RCT in older adults with a history of stroke[214] revealed that in the multimodal cognitive training group, resting-state functional connectivity between the left hippocampus and both the right frontal lobe and right parietal lobe, was associated with improved performance in memory and executive function respectively. Additionally, increases in resting-state functional connectivity between the right hippocampus and the left frontal lobe and the left parietal lobe were associated with increases of memory and executive functioning. No significant associations between functional connectivity and behavioural performance were found in the control group.

A quasi-experimental study looking at the effect of three different types of cognitive training on brain structure and function[147] found that in the BF training group an increase in thalamic AxD was associated with an increase in working memory performance. By comparing BF and SF, the authors found that an increase in occipito-temporal AxD was associated with a decrease in everyday problem solving time. Additionally, they found an association between the increase in both the occipito-temporal AxD and occipito-temporal-parietal AxD and accuracy of spatial working memory tasks, indicating that a greater AxD was associated with a smaller increase in accuracy on the memory task. Finally, looking at the contrast between SF and RON, functional

connectivity decreases between the superior parietal cortex (SPC) and the posterior inferior temporal lobe (ITL) were related to better performance on every day problem solving tasks (i.e., decrease in time for task completion).

In another quasi-experimental study[216], participants training for 3 consecutive days on an object-location learning paradigm. The authors found that the previous mentioned increase in fornix FA on the post-test compared with pre-test was significantly associated with better recall performance. Thus, a higher increase in fornix FA over the course of the training resulted in a better recall performance on the object-location learning paradigm task. Changes in fornix MD, hippocampal MD, and hippocampal volume were not associated with recall performance. Performance on the episodic memory control task was not associated with changes in fornix FA.

The last quasi-experimental study[218] looked at changes in short term memory (digit span) and found a non-significant trend between task-based functional activation at baseline and improvement in digit span, which indicates that an increased activation might lead to increased short term memory performance.

In summary, eight[147,164,213-218] of the nine studies[147,164,213-219] included demonstrated an association between changes in neuroimaging measures (volumetric or connectivity) and changes in behavioural outcomes. Depending on the region of interest (i.e., both volumetric and connectivity), both increases and decreases in activity resulted in improved cognitive performance. One study[215] found no significant association between neuroimaging and behavioural measures. One study[219] did not report the association between neuroimaging and cognition in older adults specifically.

Table 2.3 Results for Imaging Outcomes

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
Suo et al. [164] ***2016***	Combined cognitive training and progressive resistance training led to increased cortical thickness in posterior cingulate cortex. Cognitive training alone led to atrophy.	-	Cognitive training groups showed Group X Time interaction indicating decreased connectivity between the posterior cingulate and superior frontal lobe ($F(67)=31.7$, $p<0.001$) and between the posterior cingulate and the anterior cingulate cortex ($F(67)=13.9$, $p<0.001$)* Cognitive training group (alone or combined with exercise) showed a Group X Time interaction indicating increased connectivity between hippocampus and the left superior frontal lobe compared with non-computerized cognitive training ($p=0.012$)*	Computerized cognitive training (alone and with resistance training): Memory domain: Group X Time interaction ($F(90)=5.7$, $p<0.02$) showing no decline in cognitive training group compared to non-cognitive training groups* ADAS-Cog: No effect of cognitive training	Change in posterior cingulate grey matter correlated with improvement in the ADAS-Cog ($r=0.25$, $p=0.030$)* Increased connectivity between hippocampus and superior frontal lobe was correlated with improved memory domain performance ($r=0.33$, $p=0.005$)*

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
Rosen et al. [215] ***2011***	-	Significant increase of activation in left anterior hippocampus in experimental group compared with controls.	-	A non-significant but greater gain in memory performance in experimental group compared with control group ($F(1,10)=4.76$, $p=0.054$). Change scores showed improved memory performance in intervention group compared with decrease in performance in the control group ($t(10)=2.61$, $p<.0027$, Cohen's $d= 1.38$)	Non-significant trend showing changes in hippocampal activation correlated positively with changes in memory score on RBANS in all participants ($r=0.49$, $p=0.10$, Cohen's $d=1.14$)
Lampit et al. [213] ***2015***	Significant increase in grey matter density in right post-central gyrus in training group compared with a decrease in control	-	Group x Time interaction showed functional connectivity decrease between posterior cingulate and right superior frontal gyrus in training group while functional connectivity increased in the control group ($p=.006$) at FU1.	Repeated-measured ANOVA showed improved global cognition in training group compared to control (Group X Time, $F=7.833$, $p=0.003$)	Significant positive correlation between change in grey matter density in right post-central gyrus at FU2 and change in global cognition at FU1($r=0.647$, $p=.023$) and FU2 ($r=0.584$,$p=0.046$) in

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
	Vertex-based analysis showed significant difference in rate of thickness change over time between training and control in both the left fusiform gyrus (T>3.39) and the supramarginal and post-central gyri (T>2.24).		Group x Time interaction showed functional connectivity increase between right hippocampus and left superior temporal gyrus in CCT, while decreased in control at first FU1 (p=.029) No significant Group x Time interactions found for Magnetic Resonance Spectroscopy (MRS) and whole brain Diffusion Tensor Imaging (DTI)	Effect size on Global Cognition (d=0.94 baseline versus FU1 and d=2.18 baseline versus FU2)	both training and control Inverse correlation between functional connectivity between posterior cingulate and right superior frontal gyrus at FU1 and change in global cognition at FU2 (r=-.771, p=.003) Significant positive correlation in functional connectivity between the right hippocampus and left superior temporal gyrus at FU1 and change in global cognition at FU2 (r=0.591, p=.043).

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
Belleville et al. [217] ***2014***	-	<u>Single Repeated:</u> *Alphanumeric single task:* Decreased post-training activation in inferior and right middle frontal gyrus (t=5.91), left middle frontal gyrus (t=4.57) and left thalamus (t=5.37). *Visual detection single task* : no change *Dual task*: no change <u>Divided Fixed</u> *Alphanumeric single task:* no change *Visual detection single task:* Decreased post-training activation in right cerebellum	-	*Alphanumeric single task:* All groups showed improved reaction time (RT; $F(1,34)=9.75$, $p<.001$, $\eta^2=.22$) and accuracy (AC; $F(1,34)=14.8$, $p=.001$, $\eta^2=.30$) *Visual detection single task*: No change *Dual task (cost score)***: <u>Single repeated:</u> No improvements in dual tasking <u>Divided Fixed:</u> Reduced dual-task cost ($F(1,34)=6.97$, $p<.001$, $\eta^2=.45$) <u>Divided Variable:</u> Reduced dual-task cost and were able to modify attentional priority ($F(2,33)=5.17$,$p<.001$, $\eta^2=.34$)	<u>Single Repeated</u>: *Alphanumeric single task:* Significant positive correlation between right inferior and middle frontal gyrus activation and reaction time (r=.56, $p<.05$). <u>Divided Variable</u>: Significant negative correlation (post training) between activation of right superior and middle frontal gyrus (Brodmann area 10) and attentional cost (r= -.55, $p<.05$)

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
		(*t*=4.73) and right middle occipital gyrus (*t*=4.68) when performing the visual detection task. *Dual task (50/50):* *S*mall increase in post-training activation in right and left middle frontal gyrus (areas 11, 47; *t*=4.41 and *t*=4.52 respectively). <u>Divided Variable</u> *Alphanumeric single task:* no change *Visual detection single task:* no change *Dual task:* Significant increased activation in right			

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
		middle frontal gyrus (area 10; for 20% attention allocation t=5.35 and 50% attention allocation t=4.78). No reduced post-training activation in 80% attention allocation.			
Lin et al. [214] ***2014***	-	-	Training group: Significant increased functional connectivity in (all p's<0.005): 1.Left hippocampus-right inferior frontal gyrus 2.Left hippocampus-right middle frontal gyrus 3.Right hippocampus-left middle frontal gyrus 4.Right hippocampus-left inferior frontal gyrus 5.Right hippocampus-left superior frontal gyrus	Training group: 1. Significant improved scores on 5/7 subtests from Wechsler Memory Scale, namely: Mental control (p=0.003), Logical memory (p<0.001), Digits forward and backward (p=0.014), Visual reproduction (p=0.008), and Associated learning (p<0.001). 2. Improved Memory quotient (p=0.005) 3. Improved performance on Trail	Training group: significant positive correlations between (all p's<0.001): 1. Memory quotient and functional connectivity of left hippocampus-right frontal lobe (r=0.64) 2. Memory quotient and functional connectivity of right hippocampus-left frontal lobe (r=0.85) 3. Memory quotient and functional connectivity of right hippocampus-left parietal lobe (r=0.79)

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
			6.Right hippocampus-left parietal lobe <u>Control group:</u> Significantly decreased functional connectivity (all *p*'s<0.005): 1.Left hippocampus-right middle occipital gyrus 2.Right hippocampus-right posterior lobe or cerebellum 3.Right hippocampus-left superior temporal gyrus	Making Test-A (p<0.001) <u>Control group:</u> no significant changes between baseline and 10-week scores	4. Trail Making Test-A score and functional connectivity of left hippocampus-right frontal lobe (r=0.94) 5. Trail Making Test-A and functional connectivity of right hippocampus-left frontal lobe (r=0.68) Control group: no significant correlations between cognition and functional connectivity***
Strenziok et al. [147] ***2014***	-	-	<u>Ventral Network:</u> Axial diffusivity (AxD) in the right occipito-temporal white matter significantly increased after BF compared with a decrease after SF and RON (p<0.05) <u>Dorsal Network:</u> Functional connectivity between right superior	Univariate ANOVA showed main effects of training group: <u>Reasoning on Everyday Problems Test:</u> Main effect of training group ($F(2,39)=5.34$, $p< 0.01$, partial $\eta^2=0.215$).	<u>Cognition and White Matter Integrity</u> Positive correlation between change in thalamic AxD and change in working memory performance in all participants (r=0.44, p<0.005).

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
			parietal cortex (SPC) and left posterior inferior temporal lobe (ITL) decreased in SF and increased in RON (p=0.02) Functional connectivity between right SPC and left anterior ITL decreased in BF and showed an increase in RON (p=0.03)	BF and SF showed improved performance after training and RON showed no effect <u>Spatial Working Memory:</u> Main effect of training group (F(2,39)=5.03, p< 0.001, partial η^2=0.205). SF improved performance after training, RON decreased performance, and BF showed no effect <u>Matrix Reasoning:</u> Main effect of training group (F(2,39)=3.40, p< 0.044, partial η^2=0.148). Largest gains seen in BF and a smaller gain in RON. The SF group showed a decrease in	Negative correlation between changes in occipito-temporal AxD and everyday problem solving (r=-0.32, p<.05) and spatial working memory accuracy (r=-0.35, p<.05) Negative correlation between changes in occipito-temporal-parietal AxD and spatial working memory accuracy (r=-0.40, p<0.05) <u>Cognition & Functional Connectivity</u>Positive correlation between changes in SPC-posterior ITL connectivity and changes in everyday problem solving time (r=-0.57, p<.001).

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
				reasoning after training	
Lövden et al. [219] ***2010***	-	-	<u>Mean Diffusivity (MD)</u> Group X Time interaction found for segment 1 (genu) of corpus callosum, showing a decrease in MD ($t(11)=2.39$, $p=.036$). No changes in control group <u>Fractional Anisotropy (FA)</u> Group X Time interaction found for segment 1 of corpus callosum, showing an increase in FA ($t(11)=3.12$, $p=.010$)	Unknown: analysis combined younger and older subsets	Unknown: analysis combined younger and older subsets
Antonenko et al. [216] ***2016***	Hippocampal volume: no difference pre to post training (p=0.505)	-	<u>Mean Diffusivity (MD):</u> A significant decrease in fornix MD was found at post-training compared with pre-training ($p=0.036$). No difference in hippocampal MD from	*% Correct during training:* Task performance significantly improved in a curvilinear convex manner over the 3 training days learning	- Higher increase in fornix FA from pre to post assessment was significantly related to better average recall performance on the object-location task during training, at 1-

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
			pre- to post-training (p=0.669) <u>Fractional Anisotropy (FA):</u> A non-significant increase in fornix FA was found between pre- and post-training (p=0.114)		day post and follow-up (r=0.431, p=0.031) - Change in fornix FA did not correlate with episodic memory performance on the control task (Rey Auditory Verbal Learning Test; p=0.214) - Change in fornix MD did not correlate with recall performance p=0.728 - Change in hippocampal MD or volume did not correlate with recall performance (p=0.688 and p=0.758, respectively)

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
Heinzel et al. [218] ***2014***	No significant change in grey matter volume of working memory network post training ($t(14)$= 0.83, p=.421)	No significant 2(time) x3(working memory load) interaction (F= .24, p=.714, partial η^2=.024). Significant main effect of time (F=12.68, p= .003, Partial η^2=.475) driven by BOLD decrease in 1-back (t=.99, p=.029).	A 2(time)x3(load) repeated measures ANOVA showed no changes in connectivity in working memory network (F(2,28)=1.08, p=.355, partial η^2=.071)	*n*-Back: paired t-tests showed improved performance on 1-Back (t(18)=3.37, p=.003), 2-ack (t(18)=7.47, p<.001), and 3-Back (t(18)=4.86, p<.001)**** Repeated-measures MANOVA (factor time) showed improvements in neuropsychological measures after training. Post hoc paired t-tests showed improvements in Digit Span Fwd (t(18)=2.97, p=0.008), D2 test (t(18)=6.48, p<0.001), Digit Symbol (t(18)=2.76, p=0.013), Stroop Interference (t(18)=3.28, p=0.004), and Figural Relations (t(18)=4.73, p<0.001). No improvements after training were	Non-significant trend between BOLD activation at baseline and relative improvement in Digit Span Fwd (r=.43, p=.067)

Reference	Structural changes	Functional changes	Changes in connectivity	Cognition Outcome	Cognition related to imaging outcome
				found in Digit Span Bwd, Verbal Fluency, and Raven's SPM.****	

* This study was a full factorial design
**This dual-task cost represents the proportional loss of performance in the dual-task condition as a function of performance in the single-task condition. A larger score represents a larger dual-task cost.
*** Not specified whether correlations were based on change scores or scores at week 10
**** Results reported for all older participants (N=19)

2.3.6 Quality Assessment of the Included Studies

The quality of studies included in this systematic review varied substantially (Table 2.4). On average, the nine included studies met 7 of the 11 PEDro criteria. Two studies of the highest quality[164,215] meeting 9 of the 10 PEDro criteria; however, five[147,214,216,218,219] studies failed to meet five or more study quality criteria. Item 11 (i.e., included point measures and variability measures) was met for all nine studies. Item 8 (key outcome for measured for 85% of subject) and nine (outcome data analyzed by intention to treat) were met by seven of the nine studies.[147,164,215-219] Item 6, (i.e., blinding of all who administered the training) commonly received a negative response (i.e., one of the studies[164] blinded training administers). Frequent issues were failure to meet or report: 1) allocation concealment (n=4);[147,216,218,219] 2) blinding of all subjects (n=6);[147,214,216-219] 3) blinding of all who administered the training (n=8);[147,213-219] 4) blinding of assessors who measured at least one key outcome (n=5);[147,216-219] and 5) between-group statistical comparisons for at least one key outcome (n=4).[214,216-218] Item 9 (participants with available outcome measures received the treatment or control condition allocated) received 78% overall rater agreement between the authors [LTB and CKB], where the remaining questions received a 100% overall rater agreement between the authors [LTB and CKB].

Of the three additional items, selected by the authors [LTB and TLA], item 12 (inclusion of cognitive outcomes to assist neuroimaging interpretation) was addressed by all nine studies.[147,164,213-219] Items 13 (sample size calculation) and 14 (reported compliance) were not addressed by eight studies.[147,213-219]

Table 2.4 Quality Assessment of Included Studies (N=9)

Quality item	Suo et al. [164] *2016*	Rosen et al. [215] *2011*	Lampit et al. [213] *2015*	Belleville et al. [217] *2014*	Lin et al. [214] *2014*	Strenziok et al. [147] *2014*	Lövden et al. [219] *2010*	Antonenko et al. [216] *2016*	Heinzel et al. [218] *2014*
PEDro Scale Items									
1	+	+	+	+	+	-	+	+	-
2	+	+	+	+	+	+	-	-	-
3	+	+	+	+	+	-	-	-	-
4	-	+	+	+	+	+	+	-	-
5	+	+	+	-	-	-	-	-	-
6	+	-	-	-	-	-	-	-	-
7	+	+	+	-	+	-	-	-	-
8	+	+	-	+	-	+	+	+	+
9	+	+	-	+	-	+	+	+	+
10	+	+	+	-	-	+	+	-	-
11	+	+	+	+	+	+	+	+	+
Additional Items									
12	+	+	+	+	+	+	+	+	+
13	+	-	-	-	-	-	-	-	-
14	+	-	-	-	-	-	-	-	-

PEDro scoring system: receive a point (+) for each item that is met. When criteria were not met (-), no points were given.
The maximum number of points is 10, which means excellent quality based on PEDro's quality assessment.
Additional Quality Assessment Items: Maximum score of 3.

PEDro Scale
1. Eligibility criteria were specified (this item is not used to calculate the PEDro score).
2. Subjects were randomly allocated to groups
3. Allocation was concealed
4. The groups were similar at baseline regarding the most important prognostic indicators
5. There was blinding of all subjects

6. There was blinding of all therapists who administered the therapy
7. There was blinding of all assessors who measured at least one key outcome
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat"
10. The results of between-group statistical comparisons are reported for at least one key outcome
11. The study provides both point measures and measures of variability for at least one key outcome

Additional Items
12. Was cognition measured to assist the interpretation of neuroimaging results?
13. Was there a sample size calculation?
14. Was the compliance reported?

2.4 Discussion

Findings from two high-quality studies examining the effect of CCT on *volumetric changes*, suggest that multi-domain CCT programs with a duration ranging from 12 to 26 weeks could result in an increase in grey matter density,[213] but in contrast could also result in a decrease in cortical thickness in the posterior cingulate.[164] This indicates that in a relatively short time span, multi-domain CCT might be able to alter brain structure. However, the overall heterogeneity of the findings between studies (i.e., potential functional improvements versus declines), which could be in part due to the differences in region of interest, makes it difficult to draw definitive conclusions regarding the effect of CCT on brain structure.

Task-based functional brain activity decreased after training of a single task;[217] however, an increase in task-based brain activation was found in a more complex dual-task training[217] and a multi-domain CCT program.[215] This highlights that the CCT method (i.e., multi-domain versus single domain CCT) may play a critical role in task-based functional brain activity. Conversely, multi-domain CCT did not result in changes in *structural connectivity*,[213] where an auditory perception-training program resulted in increased AxD.[147] *Resting-state functional connectivity* was found to increase[164,213] or decrease[147,164,213] depending on training type (e.g., single- versus multi-domain) and region of interest. Below, we will discuss as to why we might see a discrepancy between single- and multi-domain CCT effects, and why this discrepancy might affect both structural and resting-state functional connectivity differently.

2.4.1 Task-Based Functional Activity

Functional activation patterns in the brain change with aging as a result of neurophysiological changes. Compared with younger adults, functional activation patterns become less coordinated and localized in older adults, which result in loss of cognitive performance.[242] In the current review, three studies looked at functional activity in the brain while performing a task in the scanner. Activity levels in the brain while performing a task were both increased and decreased, depending on the type of training and region of interest. All three studies focused on different brain regions, which makes comparison difficult. However, results suggest that engaging in a more diverse or complex training (e.g., multi-domain CCT or dual-task training) might lead to an increased functional activation[215,217] compared with training of a single task.[217,218] In contrast, a short report focusing on transfer of training showed results that five weeks of training (i.e., letter memory and updating tasks) resulted in increases in task-related functional activity in the striatum compared with a passive control group.[194] Though, besides the focus on different brain regions, the vast differences in study design, such as the training duration, the presence or absence of a control group, and the small number of studies ask for prudence for making assumptions.

2.4.2 Structural Connectivity and Type of Training

DTI is an imaging technique used to determine the white matter microstructure of the brain by looking at how water molecules diffuse within the brain (i.e., the direction and amount of diffusion).[243,244] DTI is often quantified by measures such as FA and MD; which provide information about the direction of diffusivity and molecular diffusion rate, respectively. Decreases in FA and increases in MD might indicate lower levels of myelin or the presence of axonal injury, as water molecules are able to diffuse more freely (i.e., isotropic).[245,246] However, rather than

looking at one specific DTI scalar (e.g., FA, MD), scalars need to be combined with other neuroimaging measures (e.g., T2, PD, FLAIR) to give a more detailed and accurate picture of for example white matter abnormalities that might occur within the brain.[246] Studies have linked loss of white matter integrity, as measured with DTI, to be associated with age-related cognitive decline in otherwise healthy older adults.[247] In addition, a meta-analysis focusing on DTI in MCI and Alzheimer's Disease found increased MD in both MCI and Alzheimer's Disease, as well as decreased FA in Alzheimers' Disease compared with controls. More severe levels of Alzheimer's Disease (i.e., lower scores on the Mini-Mental State Examination) were associated with reductions in FA.[248]

Few studies looked at the effect of CCT on structural connectivity using DTI. One study of moderate-to-high quality (PEDro score of 7/10) found no changes in structural connectivity after 12 weeks of multi-domain CCT, which could be due to the small sample size.[213] These findings are in contrast with a quasi-experimental study[218] that found that an average of 100 hours of training over four months resulted in decreased MD and increased FA in the genu of the corpus callosum. These findings suggest that multi-domain CCT is able to alter white matter microstructure in the brain in older adults. This finding could be promising as disruptions in white matter organization are often paired with cognitive decline.[249] However, a limitation of this quasi-experimental study is the lack of an active control group. Thus, we need more high-quality studies to replicate these findings and to examine how multi-domain CCT might be able to alter white matter microstructure.

Increases in AxD in the right occipito-temporal white matter were found in a study examining the effect of an adaptive auditory perception computer game (i.e., single-domain). This increased AxD was correlated with a lower score in everyday problem solving and spatial working memory accuracy.[147] However, due to the absence of an included control group, this study used contrasts between the three training groups to look at improvements between groups. Therefore, results will more likely provide information about the effect of the training groups in relation to each other (i.e., which intervention shows the best results), than give information whether the intervention actually works.

2.4.3 Functional Connectivity and Type of Training

Resting-state fMRI is used to map networks in the brain, such as the well-established Default Mode Network (DMN) and the Central Executive Network (CEN). These networks are activated in both the presence[105] or the absence of a (cognitive) task.[98,250] In patients with MCI or Alzheimer's Disease, these functional networks in the brain are found to be disrupted.[251,252] In addition, we can measure functional networks in the brain while performing a task with task-based fMRI.

Two studies[164,213] showed that a multi-domain CCT intervention resulted in increased resting-state functional connectivity of the hippocampus. One high quality study (i.e., PEDro score of 9/10) found that a 26-week multi-domain CCT program alone (versus combination of CCT with resistance training) resulted in increased resting-state functional connectivity between the hippocampus and the left superior frontal lobe.[164] Additionally, a study with the same CCT program (i.e., COGPACK) found that multi-domain CCT resulted in increased resting-state functional connectivity between the right hippocampus and the left superior temporal gyrus after

only three weeks of training.[213] These improvements in resting-state functional connectivity were significantly correlated with improved memory performance[164] and changes in global cognition at follow-up,[213] respectively.

In accordance, an RCT of multi-domain CCT in older adults with a history of a stroke[214] found that CCT increased resting-state functional connectivity between the hippocampus and both the inferior frontal gyrus and the middle frontal gyrus. These increases in resting-sate functional connectivity were associated with significant positive changes in memory quotient and processing speed (Trail Making Test-A). Literature shows that resting-state functional connectivity between the hippocampus and the superior frontal lobe is reduced in MCI.[251,252] Therefore, the current findings might indicate that multi-domain CCT could lead to improved cognitive performance through strengthening hippocampal functional networks and preventing memory loss that might be manifested by loss in hippocampal functional connectivity. However, the biological underpinnings of this change in connectivity are still unclear. Current histological findings suggest training induced neuroplasticity could be a result of dendritic branching, synaptogenesis or other factors such as angiogenesis.[253] Besides more human studies, we need to combine knowledge acquired from both human and animal (histological analyses), to help understand how multi-domain CCT could result in these functional changes in the brain.

Immediate comparison between the results of a single- versus multi-domain program can be made within one quasi-experimental study.[147] Participants in this study were randomly assigned to one of three included cognitive training programs. Participants who were randomized in Brain Fitness, a training program considered more single-domain in nature, showed decreased resting-state

functional connectivity between the superior parietal cortex and the inferior temporal lobe. In contrast, participants who were assigned to Rise of Nation, a more multi-domain training, showed increased resting-state functional connectivity between the superior parietal cortex and the inferior temporal lobe. This contrast could be due to the nature of the training (i.e., single-domain versus multi-domain), as another quasi-experimental study[218] of single-domain CCT showed no changes in task-based functional connectivity following training.

A recent study[138] comparing non-computerized single-domain and multi-domain training found that multi-domain cognitive training mainly resulted in increased memory proficiency, while single-domain training primarily – but not only - enhances visuospatial and attentional benefits. Results of the current systematic review are in accordance with these findings, as the multi-domain CCT shows improvements in resting-state functional connectivity of hippocampus-frontal lobe and hippocampus-temporal lobe, which was associated with improvements in memory. Single-domain CCT did not result in similar findings. Gains in cognition resulting from multi-domain were more prone to sustain compared to gains acquired in single-domain cognitive training. Thus, multi-domain cognitive training might result in more widespread gains in cognitive functions, which maintain visible over a longer period of time compared to single-domain cognitive training.

2.4.4 Quality Assessment

The quality of studies was heterogeneous. Commonly missed criteria, were those that focused on blinding of participants, blinding of individuals who delivered the CCT, and blinding of the assessors. These issues could result into bias (i.e., either positively or negatively) during training and follow-up measurements due to expectations of both study examiners (treatment delivery or

assessors) and participants. However, five[147,216-219] of the nine included studies were quasi-experimental and therefore the key characteristic of the more superior RCT, randomization into either an experimental or a control group, was lacking in these studies. The absence of a proper control group in these five quasi-experimental designs affects the interpretation of the results of the study; instead of whether a treatment works, quasi-experimental studies provide information on whether an intervention is more effective than a standard or alternative treatment.

Finally, of the three additionally included quality assessment criteria (i.e., item 12-14) two criteria (i.e., sample size calculation, compliance reported) were only met by one study.[164] The absence of sample size calculations and reported compliance in the remaining studies,[147,213-219] could result in a lack of power, which increases the chances of false negatives (i.e., type-II errors). This could mean that potential effects of CCT on neuroimaging parameters simply could not be detected due to a small sample size, and not because they were not present.

2.4.5 Limitations

The studies included in this systematic review varied vastly in study design and CCT delivery, which resulted in a great deal of heterogeneity mainly in outcomes of functional and structural connectivity. Only four of the nine included studies were RCTs.[164,213-215] However, the type of control group used varied; some studies included active controls, whether other control groups were of a passive nature (i.e., usual care). The inclusion of a control group, with a preference for the so-called active control groups, is recommendable in future studies. In addition, the heterogeneity of the findings in this systematic review might also be due to the large variability in type of training (single- versus multi-domain) and the dosage and duration of training (i.e., days

versus months). Thus, the heterogeneous nature of the study designs in this review makes it difficult to draw conclusions. To better understand the relevant mechanisms of CCT, neuroimaging outcomes need to be accompanied with behavioural data. Furthermore, there are limited investigations regarding the transfer effects of CCT and the pattern of neuroplasticity associated with transfer. A high-quality study design, which includes for example an active control group, a literature-based training duration and dosage, and a sample size calculation, would help increase the consistency and comparability of findings, which in turn would help increase the ability to draw appropriate conclusions.

2.4.6 Conclusions and Future Directions

This systematic review is an essential first step towards understanding the complex volumetric and functional changes, as well as changes in structural and functional connectivity that underlie CCT in older adults. However, the highly heterogeneous nature of the results in this systematic review, potentially due to the large variability in study design, indicates that more high-quality studies are needed to confirm and expand upon these findings. In addition, these studies do not provide information regarding the physiological and cellular mechanisms causing these structural changes. More histological studies are needed to gain insight whether these CCT induced changes might be a result of for example neurogenesis or synaptic plasticity. Future studies should focus on multi-domain CCT, since this type of training has the potential to induce more widespread and long-lasting effects on cognition.

Chapter 3: The Effects of an 8-Week Computerized Cognitive Training Program in Older Adults: A Study Protocol for a Randomized Controlled Trial

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3.1 Introduction

The world's population is aging, and the promotion of active aging is a global priority.[254] Cognitive impairments and dementia are now the leading cause of disablement and death in later life. The incidence of dementia is rising rapidly, and over 47 million people worldwide are diagnosed with dementia and this number is expected to triple by 2050.[254] As an effective treatment or cure for dementia remains elusive, there are increased efforts to establish the efficacy of non-pharmaceutical strategies, such as targeted exercise training and cognitive training, on cognitive health in older adults. Even when an effective pharmacological therapy is available, lifestyle approaches (i.e., exercise, nutrition, and cognitive training) can be used as a complementary approach, as lifestyle interventions result in multidimensional benefits.[5]

Interest in strategies such as cognitive training, a form of complex mental activities, has increased over the last decade. Tasks aimed to train for example executive functions, memory, or learning a

language are considered complex mental activities, as long as they challenge an individual cognitively.[143] Improvements in cognitive function, such as episodic memory (e.g., delayed recall), were found in older adults who participated in videogames[146] or computer lessons.[145] Moreover, auditory perception training for 6 weeks, 1 hour per day, resulted in improvements in problem solving and reasoning,[147] which is considered to be positive far transfer. Thus, besides improvements in the trained domains, cognitive training could also show benefits of transfer.[146,147] Aside from immediate benefits, the ACTIVE study[255] found that ten years post intervention, participants who received either speed-of-processing training or reasoning training for 5-6 weeks maintained effects of targeted cognitive abilities (i.e., speed-of-processing, reasoning). A meta-analysis of human cohort studies demonstrates that the amount of time involved in complex mental activities in early, mid- and late-life, was associated with a reduction in dementia incidence in later life.[144] Specifically, they found that increased complex mental activity in later life was associated with lower dementia rates, independent of other predictors, where more involvement in complex mental activities was found to lower dementia risk.[144]

One example of complex mental activity that received increasing attention as a strategy to promote healthy cognitive aging is computerized cognitive training (CCT). The number of commercialized CCT programs has increased rapidly over the last years. A meta-analysis of CCT in older adults showed that CCT is able to improve overall cognitive function, memory (verbal, non-verbal), processing speed, working memory and visuospatial skills.[155] No improvements were found for executive functions and attention.[155] A recent randomized controlled trial (RCT) comparing multidomain CCT with an active control group found improvements in global cognition, memory and processing speed.[148] Improvements in memory and processing speed were maintained at 1-

year follow up, indicating maintenance of CCT benefits.[148] Thus, CCT is a promising strategy to promote healthy cognitive aging and is also a feasible strategy for those who are limited in their abilities to participate in other lifestyle strategies, such as exercise.

Aerobic exercise is a promising strategy to promote cognitive health, while benefiting cardiovascular function at the same time.[182] Research shows that aerobic exercise, such as walking, could benefit cognitive functions such as executive functions (e.g., inhibition, processing speed), memory,[60,182,185,187] as well as brain structure[60,256] and function.[174] As both exercise and cognitive training are promising strategies to prevent or delay cognitive decline,[192] perhaps by combining them the benefit may be increased. Importantly, whereas aerobic exercise can facilitate neuroplasticity by increasing the number of newly formed neurons, additional experience-dependent cognitive activity is necessary to promote synaptic plasticity and the survival and functional integration of the newly formed neurons into neural networks.[198,257-259] Moreover, due to the transient nature of the upregulation of neurotrophic factors[260] it has been suggested that cognitive training preferably takes place in temporal proximity to exercise training.[199]

The objective of the current proof-of-concept RCT will be to examine the effect of CCT, alone and preceded by a 15-minute brisk walk, on cognitive function and to explore the underlying neural mechanism in community dwelling older adults. Therefore, our aim is four-fold: 1) To compare the effects of an 8-week computerized cognitive training program (i.e., Fit Brains® Training: FBT), as well as the effects of a 15-minute brisk walk prior to FBT (i.e., Ex-FBT), with an active control (i.e., BAT) on cognitive performance in older adults aged 65-85 years old; 2) Using structural and functional Magnetic Resonance Imaging (MRI), to explore the effect of FBT and Ex-FBT

compared with BAT on brain structure and function; 3) To explore whether the effects of FBT and Ex-FBT are moderated by baseline cognitive status (i.e., Mild Cognitive Impairment (MCI) versus non-MCI); 4) To explore whether Ex-FBT has additional benefits compared with FBT; and 5) To explore whether potential benefits from CCT are maintained at 1-year follow-up.

3.2 Methods

3.2.1 Trial Design

This proof-of-concept RCT in community-dwelling older adults will have three experimental arms. We will include 120 community-dwelling adults aged 65-85 years old who will be randomized to one of three experimental groups: 1) Computerized cognitive training (FBT); 2) Exercise plus computerized cognitive training (Ex-FBT); or 3) Balanced and Toned (BAT, i.e., active control, see Figure 3.1). There will be three measurement sessions, baseline, trial completion (i.e., 8 weeks), and 1-year follow-up. The study protocol follows the Consolidated Standard of Reporting Trials (CONSORT) statement[261] and basic requirements from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).[262] The trial is registered at ClinicalTrials.gov (NCT02564809).

3.2.2 Study Setting

The study will be conducted at two locations in Metro Vancouver, BC (Canada), the Djavad Mowafaghian Centre for Brain Health at the University of British Columbia (UBC) as well as the Centre for Hip Health and Mobility at Vancouver General Hospital (VGH).

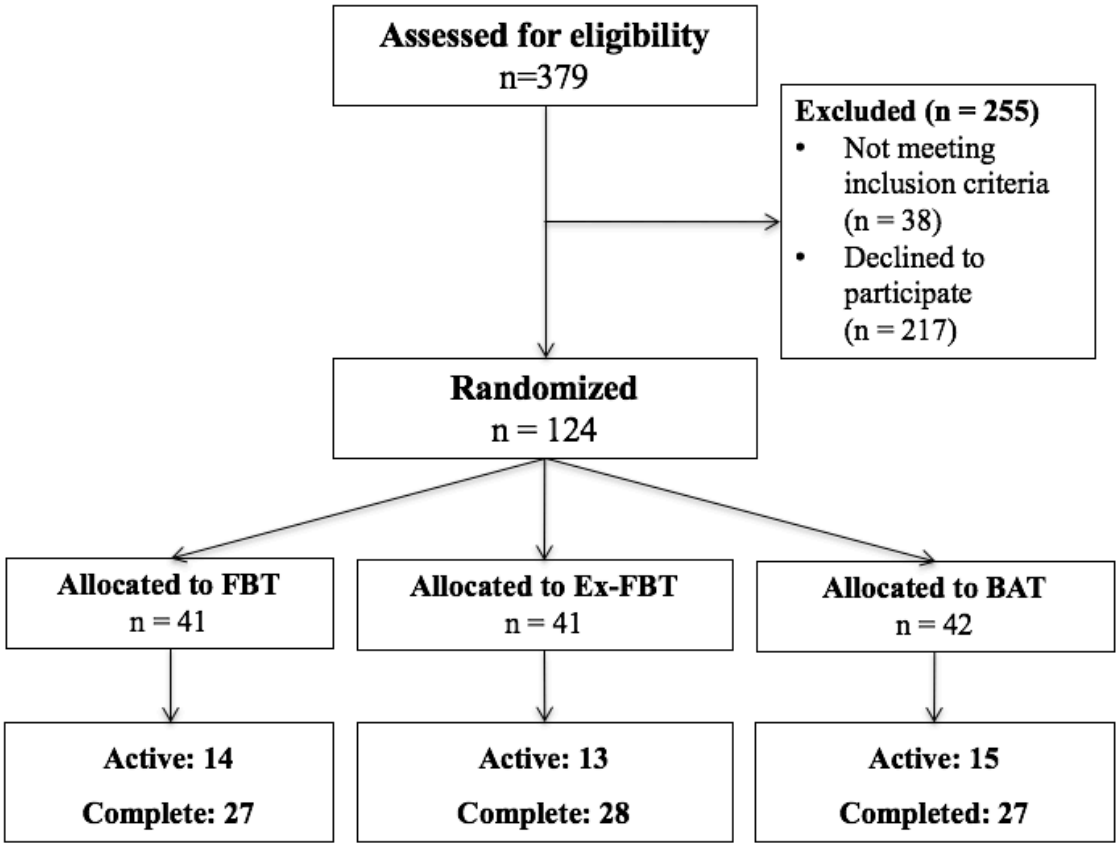

Figure 3.1 Overview of Participant Flow

3.2.3 Participants

Participants will be recruited from the community (Greater Vancouver, BC Canada) as well as through our database of previous research participants. Individuals showing interest in the study via advertisements in community centres or local newspapers will receive a short summary of the study and if still interested, will be screened over the telephone to determine eligibility. Participants from previous studies in our laboratory who expressed interest in future studies will be contacted either via mail or email.

3.2.4 Eligibility

3.2.4.1 Inclusion Criteria

For this study, we will include individuals who are: 1) are aged between 65 and 85 years; 2) completed high school education; 3) live in their own home; 4) read, write, and speak English with acceptable visual and auditory acuity; 5) have preserved general cognitive function as indicated by a Mini-Mental State Examination[74] score of ≥ 24/30; 6) score > 6/8 on the Lawton and Brody Instrumental Activities of Daily Living Scale;[82] 7) are not expected to start or are stable on a fixed dose of anti-dementia medications (e.g., donepezil, galantamine, etc.) during the 8-week study period; 8) are able to walk independently; 9) are suitable to engage in 15 minutes of brisk walking based on the Physical Activity Readiness Questionnaire;[263] and 10) provide a personally signed and dated informed consent document indicating that the individual (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

3.2.4.2 Exclusion Criteria

We will exclude individuals who are: 1) diagnosed with dementia of any type; 2) clinically suspected to have neurodegenerative disease as the cause of MCI that is not AD, vascular dementia (VaD), or both (e.g. multiple sclerosis, Parkinson's disease, Huntington's disease, fronto-temporal dementia, etc.); 3) have clinically significant peripheral neuropathy or severe musculoskeletal or joint disease that impairs mobility, as determined by his/her family physician; 4) taking medications that may negatively affect cognitive function, such as anticholinergics, including agents with pronounced anticholinergic properties (e.g., amitriptyline), major tranquilizers (i.e., typical and atypical antipsychotics), and anticonvulsants (e.g., gabapentin, valproic acid, etc.) and 5) planning to participate, or already enrolled in, a concurrent clinical drug trial.

A subset of participants will undergo MRI scanning. For this MRI subset, we will exclude individuals to participate in the optional MRI if they do not meet the specific scanning requirements of the UBC MRI Research Centre. Specifically, we will exclude anyone with: pacemaker, brain aneurysm clip, cochlear implant, surgery or tattoos within the past 6 weeks, electrical stimulator for nerves or bones, implanted infusion pump, history of any eye injury involving metal fragments, artificial heart valve, orthopedic hardware, other metallic prostheses, coil, catheter or filter in any blood vessel, ear or eye implant, bullets, or other metallic fragments.

3.2.5 Classification by Baseline Cognitive Status

To explore whether the intervention effects (i.e., FBT and Ex-FBT) are moderated by baseline cognitive status, we will classify individuals based on their baseline Montreal Cognitive Assessment (MoCA).[77] The MoCA is a 30-point test that covers multiple cognitive domains.[77] The MoCA has been found to have good internal consistency and test-retest reliability and was able to correctly identify 90% of a large sample of individuals with MCI from two different clinics.[77] Thus, participants with a baseline MoCA score $\leq$ 26/30 will be classified as probable MCI and those with a MoCA score > 26/30 will be classified as cognitively normal.

3.2.6 Interventions

For the 8-week intervention period, all participants will be asked to come to the study location (i.e., VGH or UBC) 3 times per week for 1 hour. Thus, all participants will attend 24 one-hour classes at VGH or UBC. These classes will have a set time, and thus after randomization; participants will come in on Monday, Wednesday and Friday at the same time each day. Over the

course of the four study cohorts, group times will be kept consistent (+/- 15 minutes). In addition, study staff will be kept consistent over all four cohorts to ensure training consistency. Depending on group size, students/staff will help facilitate study classes to meet the participants' needs.

3.2.6.1 Fit Brains® Training

Participants who are randomized to Fit Brains® Training, FBT, will be required to attend 3 formal training sessions per week, for 8 weeks, at the Djavad Mowafaghian Centre for Brain Health or the Centre for Hip Health and Mobility (VGH). Each session will be for 60 minutes. In addition, they will be asked to complete 3 additional one-hour training sessions at home per week. Thus, FBT participants will complete a total of 48 hours of cognitive training over 8 weeks.

There is currently no consensus as to the "best dosage". However, we based our proposed dosage on the collective work by Strenziok and colleagues,[147] Basak and colleagues,[146] Engvig and colleagues,[264] and Smith and colleagues.[210] Overall, the total number of training hours ranged from 23.5 hours to 40 hours, each training session ranged from 60 minutes to 90 minutes, and total intervention period ranged from 5 weeks to 8 weeks. Importantly, the study population included by Envig and colleagues[264] (i.e., older adults with subjective memory complaints) is the most similar to our target population. They employed an 8-week intervention period with one formal training session of 90 minutes and five at home sessions. Each at home session was approximately 30 minutes. Thus, their total number of training hours was ~ 32 hours (12 hours of formal training and 20 hours of at home training). Notably, Envig and colleagues[264] demonstrated that after 8-weeks of training, there was significant improvement in verbal memory (i.e., long verbal delay recall) and increases in gray matter volumes. To be conservative, we increased our total number

of training hours to 48 hours as data extracted from existing Fit Brains® subscribers suggest that compared with young adults, older adults may require more frequent cognitive training to maintain benefit.[265]

Fit Brains®, a program by Rosetta Stone Inc., offers 59 different training games, of which 38 are available on the mobile platform (e.g., iPad). The games are designed to be targeting one of six cognitive domains – focus, speed, memory, visual, problem solving, and language. The majority of the games last exactly 60 seconds during which individual aims to answer as many questions as quickly and accurately as possible. Other games have a set number of trials the participants have to complete before moving on to the next game. The difficulty of the game increases after each correct answer. Each game has three levels of difficulty: 1) novice; 2) intermediate; and 3) advanced.

During the FBT intervention, all participants will begin the training at the beginner level. Difficulty will increase throughout the intervention period based on their performance. At the end of each training session, FBT game progress will be saved and participants will begin the next session at that point. Each block of games consists of 5 games. The first 5 blocks of games are prescribed to offer an introduction to the user. After that, the sequencing of the games will be random, where in each block the games presented will be games that need the most attention (i.e., games that showed the lowest performance), and games will be randomly selected based on a set algorithm. Game performance will be recorded for each participant. Moreover, for their training sessions at home, participants will be asked to train at the same time of the day as their study classes at VGH/UBC. Please see Appendix A for a more detailed protocol.

3.2.6.2 Exercise + Fit Brains® Training (Ex-FBT)

Participants randomized to Exercise and Fit Brains® Training, Ex-FBT, will be required to attend 3 formal training sessions per week, for 8 weeks, at the Djavad Mowafaghian Centre for Brain Health (UBC) or the Centre for Hip Health and Mobility (VGH). Each session will be for 1 hour. Participants will start the training with a 15-minute walk outside. Participants will monitor their intensity of their walk by 20-point Borg's Rating of Perceived Exertion.[266] For the first two weeks the participants will aim for a 10-11 on the Borg scale (i.e., between very light and fairly light). The following 2 weeks the aim is to reach for 12 – 13 on the Borg scale (i.e., up to somewhat hard) During the remaining 4 weeks the participants will aim for 13-14 on the Borg scale (i.e., somewhat hard). The 15-minute walk is followed by a 45-minute Fit Brains® training session (see FBT program, mentioned above) on the iPad. Additionally, participants will be asked to complete 3 additional 1-hour training sessions at home (i.e., 15-minute walk followed by 45-minutes of FBT training). The participants will be recording their Borg-scale scores and the number of steps they walked during their 15-minute walks on a calendar that will be provided at the start of the study. Please see Appendix B for a more detailed protocol.

3.2.6.3 Balanced and Toned (BAT)

Participants who are randomized to the Balanced and Toned group, BAT, will be required to attend 3 formal 1-hour training sessions per week, for 8 weeks, at the Djavad Mowafaghian Centre for Brain Health (UBC) and/or the Centre for Hip Health and Mobility (VGH). Specifically, the BAT participants will complete a total of 8 hours of sham cognitive training, 8 hours of sham exercise training, and 8 hours of education regarding brain health over the 8-week training.

We have largely designed the sham cognitive training of the BAT protocol based on the work of Baniqued and colleagues[267] who examined the nature of cognitive abilities tapped by casual online games. They identified online games that largely tapped solely into visuo-motor speed, such as Alphattack and Crashdown. Alphattack requires players to prevent bombs from landing by pressing the character specified by the approaching bomb (source: miniclip.com). Crashdown requires players to prevent the wall from reaching the top of the display by clipping on three or more adjacent same-coloured bricks to remove them (source: miniclip.com). As these online games do not significantly tap into memory abilities, we used similar online games in our BAT protocol. In addition to exercises on the iPad we have included group-based games, such as drawing using both their dominant and non-dominant hand, writing captions on cartoons, and word games.

The exercise component of the BAT program will consist of once weekly balance and tone classes. The BAT program will be led by certified fitness instructors (i.e., CPR certified and NCAA certified or equivalent) and include stretching exercises, range of motion exercises, basic core-strength exercises including kegals (i.e., exercises to strengthen the pelvic floor muscles), balance exercises and relaxation techniques. Key balance exercises include Tai Chi-based forms (i.e., Crane, Tree Pose), tandem stand, tandem walking, and single leg stance (eyes open and closed). Previous use of this protocol showed no improvements of cognitive functioning as a result of the BAT program.[173] These sessions will be held at the Centre for Hip Health and Mobility.

Additionally, once a week the participants will attend educational classes. For the first four one-hour education sessions, participants will attend lectures relating to brain health, such as sleep and

goal setting. During the remaining four weeks, participants will create their individual photo book using the iPad. Please see Appendix C for a more detailed protocol.

3.2.6.4 Adherence

Participants' adherence to the interventions will be recorded using three methods. First, class attendance will be recorded by study team members. Second, monitoring CCT training at home will be done by the study team using the number of minutes trained per day registered by the program and provided by Rosetta Stone Inc. Third, we will ask participants to record their training minutes on a homework calendar provided by the study team.

3.2.7 Outcome Measures

All participants in the current study will attend three measurement sessions at VGH: baseline, trial completion, and 1-year follow-up. Each visit to VGH will be up to 3 hours in duration. In addition, if interested and eligible, a subset of participants will attend two MRI scans (1.5 hours per appointment) at UBC over the duration of the study (i.e., before and at trial completion). Our trained research staff, which will assess enrolled participants at baseline and trial completion, will be blinded to group allocation.

3.2.7.1 Descriptive Measures

At baseline, general health, demographics, socioeconomic status, and education will be ascertained by a questionnaire. Descriptive measures such as age in years, standing and sitting height in centimetres, mass in kilograms, and waist and hip circumference in centimetres will be obtained.

3.2.7.1.1 Global Cognitive Function

Global cognitive function will be measured using both the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). The MoCA is a valid and reliable measure,[77] and assesses eight cognitive domains such as attention, concentration, executive functions, memory, language and visuoconstructional skills. The total possible score is 30 points; a score of less than 26 points indicates MCI. The MoCA has with a score of 26 a 90% sensitivity to for detecting MCI.[77]

3.2.7.1.2 General Health, Falls History, and Socioeconomic Status

We will administer questionnaires to obtain information about their level of education, employment status and general health information (e.g., medication, fall and fracture history).

3.2.7.1.3 Instrumental Activities of Daily Living Scale

The Lawton and Brody Instrumental Activities of Daily Living (IADL)[82] Questionnaire will be administered to assess the participants' ability to perform tasks of daily living such as housekeeping, laundry, transportation, and management of finances. The questionnaire looks at eight different types of daily activities, and therefore it has a maximum achievable score of eight.

3.2.7.1.4 Co-morbidity

To assess the presence of any medical conditions, the functional comorbidity index (FCI)[268] will be used. In this scale, which contains 18 conditions, participants can indicate whether the condition is present currently, in the past or not at all.

3.2.7.1.5 Cognitive Activity over Lifetime

At baseline, we will administer a questionnaire focusing on lifetime stimulation of cognitively stimulating activities in a subset of participants.[269] This questionnaire measures the involvement in cognitively stimulating activities during their lifetime, namely at age 6, 12, 18, 40, and at their present age. Cognitively stimulating activities include visits to the library, read a newspaper, read a book, write a letter, and play a game. The involvement on all 25 items included will be rated on a 5-point scale, with 1) Once per year or less; 2) Several times per year; 3) Several times per month; 4) Several times per week; or 5) Every day or nearly every day.

3.2.7.2 Primary Outcome: Verbal Memory and Learning

Our primary cognitive outcome will be (verbal) episodic memory as measured by the Rey Auditory Verbal Learning Test (RAVLT).[270] The RAVLT is a valid, reliable, and widely used instrument of (verbal) episodic memory. Notably, a 2013 prospective study showed that among a combination of neuropsychological, neuroimaging, and cerebrospinal fluid markers, RAVLT performance was the best individual predictor of MCI conversion to dementia.[271] For the RAVLT, a list of 15 common words (List A) is read to participants five times. Immediately after each time, they are required to recall as many words as possible. After the fifth trial, an interference list (List B) is presented, after which participants are asked to spontaneously recall the words form the original list (List A). Then, participants are asked to spontaneously recall the original words (List A) after a 20-minute delay (i.e., long delay free recall), and finally, they are asked to circle words from the original list (List A) in a paragraph of texts containing thirty underlined words (i.e., words from the original list plus distractor words). Scores were calculated as the total number of words recalled: 1) across the five trials (total acquisition); 2) after the interference list (recall after

interference); 3) on the fifth trial minus after the interference (loss after interference); 4) at recognition (number of words correctly identified from list A); and 5) after the 20-minute delay (long delay free recall – our primary RAVLT measure of interest). We will focus on changes in memory (trial completion minus baseline) over the course of the study.

3.2.7.3 Secondary Outcome Measures

3.2.7.3.1 Comprehensive Neuropsychological Battery (iPad)

We will use the National Institute of Health (NIH) Toolbox Cognition Battery,[272-274] a comprehensive neuropsychological battery with normative values. The cognitive battery of this toolbox includes tests that measure: *1) Executive Functions*: Executive functions is the capacity to plan, organize, and monitor the execution of behaviours that are strategically directed in a goal-oriented manner. The NIH Toolbox measures two components of executive functions: 1) inhibition and 2) set shifting. The NIH Toolbox focuses on the inhibition of automatic response tendencies that may interfere with achieving a goal. Set shifting is considered the capacity for switching among multiple aspects of a strategy or task. Inhibition is measured with the NIH Toolbox Dimensional Change Card Sort Test. Set shifting is measured with the NIH Toolbox Flanker Inhibitory Control and Attention Test; *2) Attention*: Attention refers to the allocation of one's limited capacities to deal with an abundance of environmental stimulation. It is the foundation for all other types of mental processes. Attention is measured with the NIH Toolbox Flanker Inhibitory Control and Attention Test*; 3) Episodic Memory*: Episodic memory refers to cognitive processes involved in the acquisition, storage and retrieval of new information. It involves conscious recollection of information learned within context. Episodic memory can be verbal (i.e., remembering a conversation or list of grocery items) or nonverbal (i.e., imagining a picture one

saw a week ago). Episodic memory is assessed with the NIH Toolbox Picture Sequence Memory Test. As a supplemental measure we will use the NIH Toolbox Auditory Verbal Learning Test (Rey)*; 4) Language*: Language refers to a set of mental processes that translate into symbols (words, gestures) that can be shared among individuals for purposes of communication. The NIH Toolbox focuses on two aspects of language: 1) Vocabulary knowledge, which is measured with the NIH Toolbox Picture Vocabulary Test, and 2) Oral reading skill, which is assessed by the NIH Toolbox Oral Reading Recognition Test; *5) Processing Speed*: Processing speed refers to either the amount of time it takes to process a set amount of information, or the amount of information that can be processed within a certain unit of time. It is a measure that reflects mental efficiency and is central for many cognitive functions and domains. Processing Speed is measured by the NIH Toolbox Pattern Comparison Processing Speed Test; and *6) Working Memory*: Working Memory refers to a limited-capacity storage buffer that becomes overloaded wen the amount of information exceeds capacity. Working Memory refers to the capacity of an individual to process information across a series of tasks, hold information in a short-term buffer, manipulate the information, and hold the products in the same short-term buffer. Working Memory is assessed with the NIH Toolbox List Sorting Working Memory Test.

3.2.7.3.2 Executive Functions

For executive functions, we include three executive cognitive processes based on the work of Miyake and colleagues[275] and frequency of inclusion in clinical batteries:[270] 1) response inhibition, 2) set shifting; and 3) working memory. Response inhibition involves deliberately inhibiting dominant, automatic, or prepotent responses. Set shifting requires one to go back and forth between multiple tasks or mental sets.[275] Working memory involves monitoring incoming information for

relevance to the task at hand and then appropriately updating the informational content by replacing old, no longer relevant information with new incoming information. We will assess: 1) response inhibition using the Stroop Colour-Word Test;[11] 2) set shifting using the Trail Making Test (Parts A & B);[20] and 3) working memory using the Digit Symbol Substitution Test (DSST; 90 seconds).[276]

3.2.7.3.3 Balance and Mobility

The Short Physical Performance Battery (SPPB)[277] will be used to capture domains of strength, gait speed and balance, by performing standing balance, walking and sit-to-stand exercises. The SPPB is scored out of 4 points per component and has a maximum score of 12. Low scores on the SPPB reflect poor performance.

3.2.7.3.4 Cardiovascular Capacity

The Six Minute Walk Test (6-MWT)[278] will be used to measure cardiovascular capacity. This test asks participants to walk as far as they can (meters) in six minutes (breaks allowed). Before and after the walk, the participants' blood pressure will be measured. The participants will be asked to rate their walk on the Borg Rating of Perceived Exertion.[266] The score on the 6MWT is the distance (meters) covered during six minutes.

3.2.7.3.5 Physical Activity Level

To obtain information about their physical activity, the Physical Activity Scale for the Elderly (PASE)[279,280] will be administered. This 12-item questionnaire assesses the amount of time spent

per day in the previous week on leisure activity time (light, moderate and strenuous activities), household work, and time spent volunteering.

3.2.7.3.6 Magnetic Resonance Imaging

Prior research has demonstrated that significant changes in brain volume can be observed after 32 hours of computer-based cognitive training over a span of 8 weeks among older adults with subjective memory complaints[264] – a population very similar to ours. Thus, we will include neuroimaging outcomes in our proposed proof-of-concept RCT. Our neuroimaging outcomes will include: 1) hippocampal volume and cortical thickness as determined by structural MRI; and 2) functional connectivity as determined by resting state functional MRI and seed-based approach. If interested and eligible, a subset of participants will be asked to do one MRI scan before and one after the completion of the 8-week training. Participants will come to the UBC for 1.5 hours each visit. The scanning protocol will take approximately 50 minutes, and a series of anatomical scans will be performed in addition to a resting-state functional MRI scan.

Acquired structural and functional neuroimaging data will be analyzed using different pipelines. The Freesurfer image analysis suite[281] will be used for structural data analysis. Freesurfer is developed at the Martinos Center for Biomedical Imaging by Laboratory for Computational Neuroimaging (http://surfer.nmr.mgh.harvard.edu/). Data processing will include skull-stripping,[282] motion correction,[283] Talairach transformation,[284,285] atlas registration,[286] and brain parcellation.[285,287] The data will be manually checked, and if necessary corrected. Functional connectivity analysis will be using resting-state functional MRI (rs-fMRI) data to investigate the effect of CCT (alone and preceding a 15-minute walk) on functional connectivity. Resting-state

fMRI data will be preprocessed using FSL (FMRIB's Software Library). Data processing will include skull-stripping using Brain Extraction Tool (BET), motion correction using MCFLIRT, and spatial smoothing. Data will be manually checked, and if necessary corrected. Model-free independent component analysis (ICA) will be performed using FSL-MELODIC to examine whole-brain connectivity patterns, and with selecting independent resting-state components, we will look at between group differences. Seed-based functional connectivity analysis (SBA) will be performed to look at the correlations between regions of interest within and between networks. Connectivity maps will be created to show connections with the seed region (i.e., region of interest).

3.2.8 Participant Timeline

Eligible participants will attend a one-hour information session at either the UBC or at VGH. In this one-hour information session, the study coordinator will give a short presentation that provides the potential participants with important details of the study. During this one-hour session, the potential participants will receive a copy of the consent form. Once written consent is obtained, a research assistant will schedule a baseline assessment. After completion of baseline assessment, participants will be randomized into one of 3 training groups (i.e., FBT, Ex-FBT, or BAT), after which they will attend the final assessment session(s). For a complete timeline, see Figure 3.2.

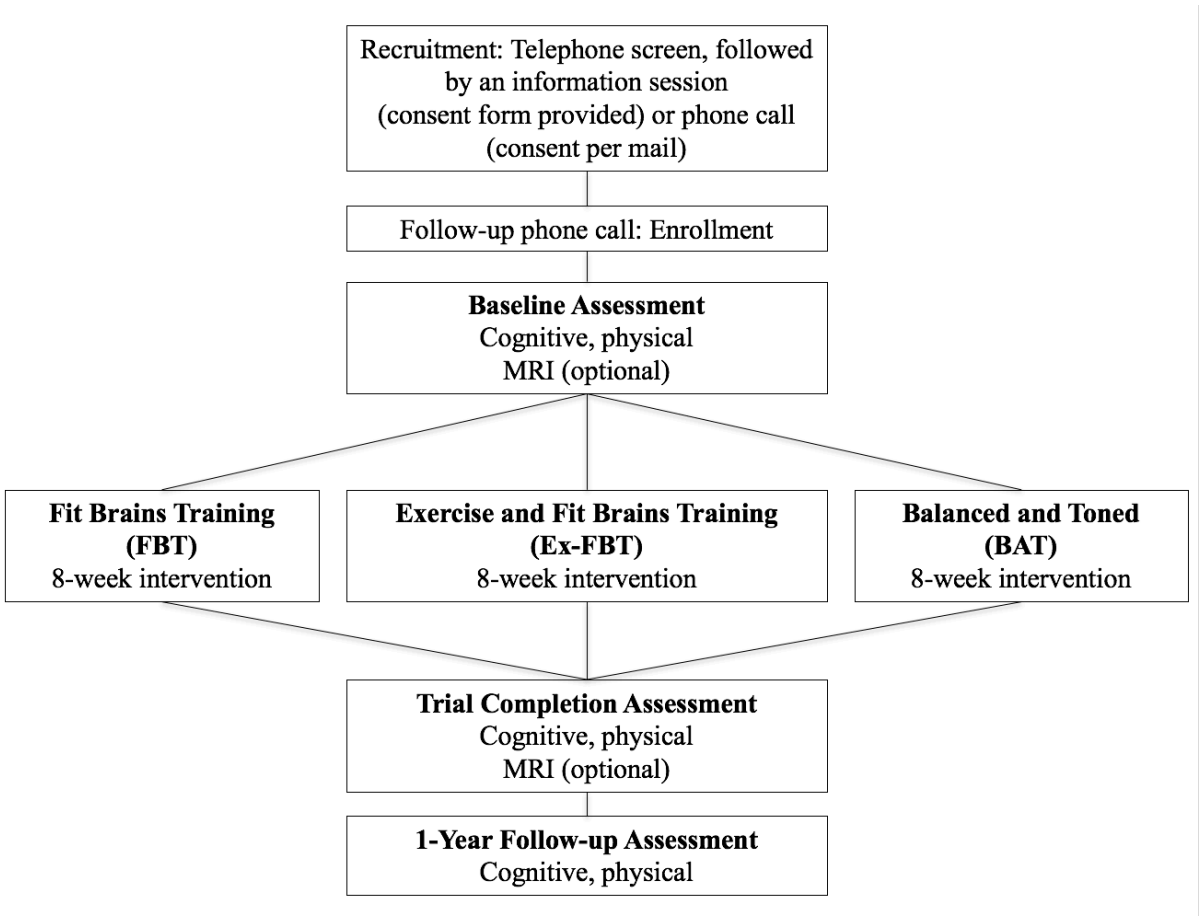

Figure 3.2 Participant Timeline

3.2.9 Sample Size and Randomization

The required sample size for this study was calculated based on changes in the RAVLT (retention score). Specifically, we predicted a mean change of 0.31 for the FBT group, a mean change of 0.40 for the Ex-FBT group, and a mean change of -0.31 for the BAT group. We made these estimates based on the work of Diamond and colleagues.[288] With a pooled standard deviation of 1.1, and alpha of 0.05, 36 participants are needed for a power of 0.80. To accommodate for a 10% drop-out rate, our total sample size comes to 120 participants (i.e., 40 FBT, 40 Ex-FBT, and 40 BAT).

Participants will be randomly allocated (1:1:1) to FBT, Ex-FBT, or BAT. The randomization sequence will be generated by an independent member of the team using computer software (www.randomization.org). Blocked randomization will be used, with a block size of 12. The group allocation will be concealed for the study coordinator. After enrolment, performed by a research assistant, and completion of the baseline assessment, the study coordinator will send a list of participant identification numbers to the independent member responsible for the randomization, who will provide the study coordinator with the group assignment for the enrolled participants. After completion of baseline assessment at VGH, the participants will be informed of their group assignment. Outcome assessors were blinded after treatment allocation.

3.2.10 Adverse Events Monitoring

Adverse events will be monitored using adverse event forms. All adverse events will be discussed with the principal investigator and the study team to see whether any adaptations to the protocol or program should be made as a result of the adverse event and to ensure safety for all participants.

3.2.11 Data Management

Data will be entered ongoing over the study period. Data will be securely stored in a locked cabinet and in a secured online database. Random data checks will be performed promote data quality.

3.2.12 Statistical Analysis

3.2.12.1 Effects of CCT

The primary and secondary outcomes will be analyzed using an identical analytic model, which will follow the intention-to-treat principle, such that all randomized participants will be included to estimate treatment effects irrespective of deviations from treatment protocol (e.g., loss to follow-up, non-compliance). This will be done using linear mixed models using maximum likelihood estimation. The model will include random intercepts, and fixed effects of time (baseline, trial completion), intervention assignment (FBT, Ex-FBT, BAT), and their interaction. Baseline MoCA score and age will also be included as fixed effect covariates. Treatment effects are indicated by a statistically significant treatment by time interaction. Two planned simple contrasts will be performed to assess differences in changes in the primary and secondary outcomes between: 1) the FBT group and the BAT group; and 2) the ex-FBT group and the BAT group. A secondary planned contrast will determine whether FBT and ex-FBT differ in changes in the primary and secondary outcomes over time. To explore maintenance of treatment effects, we will perform repeated measures with linear mixed models using maximum likelihood estimation. The models will include random intercepts, and fixed effects of time (baseline, trial completion, 1-year follow up), intervention assignment, and their interaction. Baseline MoCA score and age will also be included as fixed effect covariates.

Follow-up sensitivity analyses will restrict the study sample to individuals with valid data at all three time points (baseline, trial completion, and 1-year follow-up). The same linear mixed models describe above will be employed to determine whether inferences are similar for the intention-to-treat and complete-case study samples.

3.2.12.2 Baseline Cognitive Status as a Moderator

To determine whether treatment effects are similar for individuals identified as having MCI, we will add MCI status as an additional fixed effect in the linear mixed models described above. Moderation will be indicated by a statistically significant MCI status by treatment by time interaction. In the presence of moderation, the planned contrasts described above will be re-computed after stratifying by MCI status. This will identify how MCI status moderated the effects of treatment on the outcome of interest.

3.3 Discussion

Currently there is are a limited number of high-quality studies investigating the efficacy of CCT programs; therefore, findings from this randomized controlled trial will contribute to the existing research. In addition, a gap currently exists in literature investigating the effect of these programs in an older adult population with MCI. If this research demonstrates benefits of an 8-week CCT intervention, both short-term (i.e., trial completion) and long-term (1-year follow-up), CCT might serve as an easy accessible strategy to combat cognitive decline in healthy older adults and a potential effective way to alter the trajectory of cognitive decline in older adults with MCI.

3.3.1 Neural Mechanisms

Evidence regarding the underlying neural mechanisms of CCT in both healthy older adults and older adults with MCI is limited. If the current study would provide evidence of changes in neural structure or neural activity (e.g., functional connectivity), it would be a considerable contribution to research in this field.

Chapter 4: The Effects of Computerized Cognitive Training With and Without Physical Exercise on Cognitive Function in Older Adults: An 8-Week Randomized Controlled Trial

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4.1 Introduction

The world's population is aging at an unprecedented rate.[289] Thus, the promotion of healthy cognitive aging is of critical importance.[254] Currently, over 47 million people worldwide are diagnosed with dementia, and this number is expected to triple by 2050.[254] As effective pharmacological treatments are not currently available, there are growing efforts to establish the efficacy of lifestyle strategies in promoting cognitive health in older adults. Even when an effective pharmacological treatment is available, lifestyle strategies can be recommended as complementary approaches, providing multidimensional benefits.[5]

In the last decade, there has been significant interest in cognitive training as an approach to promote cognitive health. The number of commercially available computerized cognitive training (CCT) products has grown rapidly over recent years. However, the evidence for these commercial

products, while promising, is limited and equivocal. Thus, considerable research is still needed to better understand the efficacy of CCT on cognitive function, and to better understand underlying neural mechanisms.[290]

For example, one meta-analysis of randomized controlled trials (RCT) of CCT in older adults (RCTs=31) showed benefits for overall cognitive function (Hedges' g = 0.42), executive functions (g = 0.42), memory (g = 0.35), attention (g = 0.22) and visuospatial ability (g = 0.18).[149] Additionally, benefits were stronger for attention when training occurred over 8 weeks or more, and for executive functions when training occurred three times or more per week. However, two other meta-analyses of CCT in older adults concluded that CCT had no benefit for executive functions.[154,155] Notably, a common conclusion of systematic reviews and meta-analyses of CCT is that more high-quality studies, such as RCTs, are needed. CCT is attractive as a strategy for healthy cognitive aging as it can be widely accessible and it is a feasible approach for those having physical limitations to participate in lifestyle strategies, such as exercise.

Current evidence suggests that exercise has a positive impact on cognitive and brain health.[185] In RCTs of older adults with and without mild cognitive impairment, aerobic exercise significantly improved memory and executive functions,[60,185,256] as well as brain structure[60,256] and function.[174] Specifically, Erickson and colleagues demonstrated that a moderate-intensity aerobic exercise program increased hippocampal volume in otherwise healthy older adults, which was associated with improved spatial memory performance.[60] Moreover, ten Brinke and colleagues showed that a twice-weekly brisk walking (i.e., moderate-intensity) program increased hippocampal volume and improved verbal memory and learning as measured by the Rey Auditory Verbal Learning Test

in older adults with mild cognitive impairment.[256,291] Based on the meta-analysis by Northey and colleagues, the effect of aerobic exercise does not significantly vary between cognitive domains, such that it is equally beneficial for global cognition, attention, executive functions, memory, and working memory.[184]

There is growing evidence that multimodal interventions may be more efficacious than singular interventions for cognitive health.[196] For example, Shah and colleagues assigned healthy community-dwelling older adults to 16 weeks of exercise (brisk walking and resistance training), cognitive training (auditory- and visual-based CCT), combined training (i.e., CCT and exercise), or control and found that those in the combined training significant improved on verbal memory and learning, as measured by the Rey Auditory Verbal Learning Test, compared with those in the control group.[197] Thus, combining CCT with exercise is an approach currently being investigated in healthy aging research.[292] Mechanistically, aerobic exercise increases the number of newly formed neurons within the dentate gyrus of the hippocampus.[258] Additional cognitive activity promotes further synaptic plasticity and the survival and functional integration of the newly formed neurons into neural networks.[198,258] Aerobic exercise transiently upregulates neurotrophic factors such as brain-derived neurotrophic factor (BDNF),[260] with levels remaining elevated for one hour post exercise.[199] The promotion of brain plasticity, in part elicited through mechanisms such as BDNF, could therefore be most effective during or directly after exercise training. As such, cognitive training may be more beneficial for augmenting cognitive function if it occurs subsequent to exercise training;[199] however, to our knowledge, this immediate succession of exercise and CCT has not been investigated in the current literature.

The aim of this study was to examine the effects of an 8-week CCT program (i.e., Fit Brains® Training: FBT), with or without a 15-minute brisk walk prior to FBT, compared with an active control on memory and executive functions in community-dwelling older adults. We hypothesized that an 8-week CCT program would benefit memory and executive functions, and that priming the brain with a short bout of aerobic exercise immediately prior to CCT could result in additional gains in cognitive function.

4.2 Methods

The protocol for this study has been published.[293] We summarize the key aspects of the study protocol in the following sections.

4.2.1 Study Design

We conducted an 8-week, single-blinded, proof-of-concept RCT (ClinicalTrials.gov identifier: NCT02564809) at the University of British Columbia and Vancouver General Hospital campus with assessments at baseline and trial completion (i.e., 8 weeks). Assessors were trained and blinded to group allocation.

4.2.2 Participants

Participants were recruited between September 2015 and April 2017 from the community in metro Vancouver, British Columbia using newspaper advertisement and flyers in local community centres. Individuals were screened over the phone and were invited to an information session to discuss additional study information and the consent form. In Figure 4.1, the CONSORT (Consolidated Standards of Reporting Trials) flow chart provides more information on participant

flow and distribution. Ethical approval was obtained from the University of British Columbia Clinical Research Ethics Board (UBCCREB) and the Vancouver Coastal Health Research Institute (VCHRI) ethics boards. All participants provided signed consent prior to study commencement.

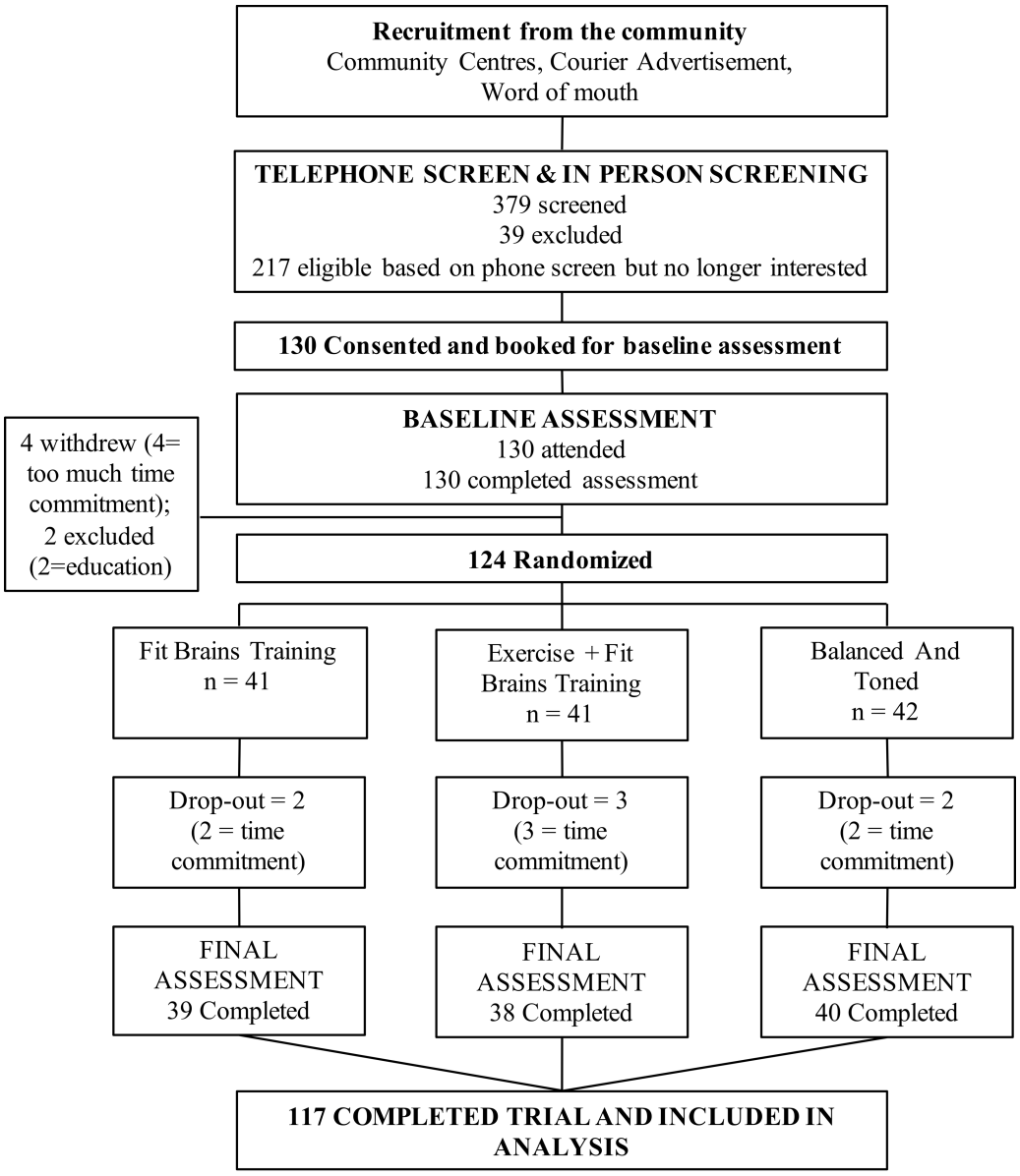

Figure 4.1 CONSORT Flow Diagram

4.2.2.1 Inclusion and Exclusion Criteria

We included community-dwelling older adults who: 1) were aged between 65 and 85 years; 2) completed high school education; 3) had preserved general cognitive function as indicated by a Mini-Mental State Examination (MMSE)[74] score $\geq$ 24/30; 4) scored $\geq$ 6/8 on the Lawton and Brody[82] Instrumental Activities of Daily Living Scale; 5) were not expected to start or are stable on a fixed dose of anti-dementia medications (e.g., donepezil, galantamine, etc.) during the study period; and 6) were suitable to engage in 15 minutes of brisk walking based on the Physical Activity Readiness Questionnaire.[263] We excluded individuals who: 1) were diagnosed with dementia of any type; 2) had a neurodegenerative disease as the cause of mild cognitive impairment that is not Alzheimer's disease, vascular dementia, or both (e.g. multiple sclerosis, Parkinson's disease, etc.); 3) experienced clinically significant peripheral neuropathy or severe musculoskeletal or joint disease that impairs mobility, as determined by his/her family physician; and 4) were taking medications that may negatively affect cognitive function, such as anticholinergics, tranquilizers, and anticonvulsants.

4.2.3 Descriptive Variables

We measured age in years, standing height in centimetres, and mass in kilograms. The Lawton and Brody Instrumental Activities of Daily Living (IADL) Scale[82] assessed IADL ability. The Functional Comorbidity Index (FCI)[268] was calculated to assess the degree of comorbidities present at baseline. A 25-item questionnaire[269] quantified lifetime involvement in cognitively stimulating activities. Current level of physical activity was assessed by the Physical Activities Scale for the Elderly (PASE).[279] Global cognition was assessed using the Montreal Cognitive Assessment (MoCA)[77] and the MMSE[74].

4.2.4 Primary Outcome: Verbal Memory and Learning

Our primary outcome measure was the retention score for verbal memory and learning, as assessed by the Rey Auditory Verbal Learning Test (RAVLT).[270] The RAVLT is a valid, reliable, and widely-used instrument of verbal memory and learning,[294] with normative values.[270] Retention score was chosen as a measure of memory consolidation, and percentage retention (% retention) was calculated as ([Trial 7/ Trial 5]*100). Scores were calculated as the total number of words recalled: 1) after the interference list (% retention); 2) across the five trials (total acquisition); 3) after the 20-minute delay (long delay free recall); and 4) at recognition.

4.2.5 Secondary Outcomes: Executive Functions

The Stroop Colour-Word Test[11] was used to assess response inhibition, by calculating incongruent condition completion time minus congruent condition completion time. To assess set shifting, the Trail Making Test (Parts A&B)[20] was used, where we calculated Trails B – Trails A. In addition to standard paper and pen tests of executive functions, we administered two additional measures of response inhibition and set shifting from the Cognition battery of the National Institute of Health (NIH) Toolbox[273] – the Flanker Inhibitory Control and Attention Test and the Dimensional Change Card Sort Test (DCCS).

4.2.6 Randomization

Participants were randomly allocated to either Fit Brains® Training (FBT), Exercise plus Fit Brains® Training (Ex-FBT), or Balanced And Toned (BAT; i.e., control) with a ratio of 1:1:1 using the web application www.randomization.com. A research team member not involved with

the study held this sequence at a remote location. Assessors were blinded to group allocation of the participants.

4.2.7 Sample Size

Sample size calculations were based on predictions of changes in RAVLT (retention score) in the absence of previous trials testing the effects of FBT on memory and learning. Specifically, we predicted a mean change (i.e., z-scores) of 0.31 for the FBT group, a mean change of 0.40 for the Ex-FBT group, and a mean change of -0.31 for the BAT group. We made these estimates based on the work of Diamond and colleagues.[288] With a pooled standard deviation of 1.1, and a two-sided alpha of 0.05, 36 participants per group were needed for a power of 0.80, based on a two-group comparison (i.e., FBT vs. BAT; Ex-FBT vs. BAT). To accommodate an expected 10% drop-out rate, our total targeted sample size came to 120 participants (i.e., 40 FBT, 40 Ex-FBT, and 40 BAT).

4.2.8 Interventions

The protocol for each intervention arm is published elsewhere for a more detailed description.[293]

4.2.8.1 Fit Brains® Training

Participants randomized to Fit Brains® Training (FBT) performed computerized cognitive training 3x/week for 60 minutes at the research centre, as well as 3x/week at home for 60 minutes. Games were performed on an iPad and consisted of 38 games targeting one of six domains – focus, speed, memory, visual, problem solving, and language. Games were individualized and adaptive throughout the 8-week program.

4.2.8.2 Exercise plus Fit Brains® Training

Participants randomized to the Exercise + Fit Brains® Training (Ex-FBT) came to the research centre 3x/week for 60 minutes, consisting of a 15-minute brisk walk perceived as somewhat hard (i.e., up to 13-14 on the 6-20 Borg's Rating of Perceived Exertion scale)[266] followed by a 45-min session of computerized cognitive training. Additionally, they repeated the same 60-minute training (i.e., 15-minute walk + FBT training) 3x/week at home for 8-weeks. Please see Figure 4.2 for a detailed overview of walking intensity progression.

Figure 4.2 Target Borg Rate of Perceived Exertion

4.2.8.3 Balanced and Toned

The Balanced and Toned (BAT) group attended three 60-minute sessions/week at the research centre for 8 weeks. Specifically, participants completed 8 hours of sham cognitive training (e.g., word and drawing games, and creativity exercises), 8 hours of sham exercise training (e.g., stretching, balancing, and core strength exercises), and 8 hours of education regarding brain health (e.g., lectures on sleep, goal setting, mindfulness, and an educational project). Participants were asked to complete homework in order to complete their educational project.

4.2.9 Compliance

Compliance was recorded for group-based training as well as home-based training via diaries and time stamped data recorded by the CCT platform and was reported as percentage of training completed.

4.2.10 Adverse Events

Participants were asked about the presence of any adverse effects throughout the study, such as musculoskeletal pain or discomfort following the sham exercise portion (i.e., BAT) and the 15-minute brisk walk (i.e., Ex-FBT). Participants were monitored for shortness of breath during the sham exercise and brisk walks.

4.2.11 Statistical Analysis

Statistical analyses were conducted using R version 3.5.1 (r-project.org). Analysis of covariance (ANCOVA) evaluated treatment effects on the primary and secondary variables. Change in each outcome (post-test minus pre-test) was regressed on the baseline outcome score, baseline MoCA score, age, and a categorical treatment variable (BAT vs. FBT vs. Ex-FBT). In addition, we conducted a post-hoc, exploratory comparison between Ex-FBT vs. FBT for both primary and secondary outcome variables. Undue influence of outliers was tested by calculating Cook's distance for each observation in each ANCOVA model. One outlier for Stroop Incongruent – Congruent performance (Cook's $d > 0.5$) and one outlier for the Trail Making B-A performance (Cook's $d > 1.0$) were identified and removed from the relevant ANCOVA model.

Seven individuals had missing scores across the outcome measures at post-test. Little's MCAR test was non-significant (χ^2 [16] = 25.55, p = .06). The statistical plan evaluated treatment effects under the assumption that the data were missing at random by addressing missingness in two ways. First, we imputed missing data using multivariate imputation by chained equations with the R package *mice* 3.1.0.[295] This allowed us to include the entire randomized sample of 124 and is appropriate when data are missing at random or are missing completely at random.[295] Forty imputed data sets were created following 40 iterations of a Gibbs sampler for each imputed data set. Proper convergence of the Gibbs sampler was confirmed by visual inspection of trace plots of each imputed variable, which revealed proper mixing and the absence of spikes or systematic trends across iterations. The results of each ANCOVA model were pooled across the 40 imputed data sets. Second, we restricted the sample to 117 individuals with complete data at both timepoints and ran the ANCOVA models on this restricted sample. Across all models, the primary comparison was the comparison of FBT to BAT and Ex-FBT to BAT on adjusted change in the outcome measure. Statistical significance of each comparison was set at a two-tailed $p < .05$. No adjustment for multiple outcomes was made since in a proof-of-concept study a Type II error is of more concern than a Type I error.[296]

4.3 Results

4.3.1 Participants

A total of 124 participants completed baseline assessment and were randomized, of which 117 participants completed the trial (Figure 4.1). Baseline characteristics of all 124 participants are reported in Table 4.1. The mean age was 72.4 +/- 4.8 years. Except for Trail Making Test B-A, there were no notable between-group baseline differences.

Table 4.1 Participant Characteristics at Baseline (N=124)

Variable	BAT (n=42) Mean (SD)	FBT (n=41) Mean (SD)	Ex-FBT (n=41) Mean (SD)
Age (years)	71.36 (5.14)	72.88 (5.17)	72.46 (4.11)
Weight (kg)	74.35 (18.30)	67.46 (14.41)	72.61 (17.20)
Height (cm)	166.06 (10.48)	163.36 (10.82)	166.27 (10.25)
Sex (f, %)	23 (55%)	30 (73%)	22 (54%)
Education (%)			
High school certificate or diploma	12.0	12.2	9.8
Trades or professional certificate or diploma	19.0	7.3	14.6
University certificate or diploma	19.0	26.8	29.3
University degree	50.0	53.7	46.3
Instrumental Activities of Daily Living	7.88 (0.40)	7.95 (0.22)	7.95 (0.22)
Functional Comorbidity Index	2.52 (1.78)	1.88 (1.47)	2.00 (1.53)
Lifetime cognitively stimulating activities	84.10 (14.07)[a]	83.89 (14.20)[c]	81.95 (14.21)[a]
Physical Activity Scale for the Elderly	116.88 (54.52)	116.22 (47.45)	116.44 (46.92)
Montreal Cognitive Assessment	25.12 (3.10)	25.49 (3.16)	24.63 (3.87)
Mini-Mental State Examination	28.36 (1.56)	28.78 (1.39)	28.68 (1.39)
Rey Auditory Verbal Learning Test			
% Retention (%)	78.09 (26.96)	81.22 (18.31)	75.46 (22.72)
Total Acquisition (n)	41.17 (9.92)	42.61 (9.35)	40.93 (9.91)
Long Delay Free Recall (n)	8.02 (3.89)	8.34 (3.10)	7.66 (3.43)
Recognition (n)	12.93 (2.31)	13.10 (1.93)	13.02 (1.93)
Stroop Incongruent – Congruent (s)	52.54 (27.47)	45.85 (32.45)	54.20 (29.79)[a]
Trail Making Test B-A (s)	67.50 (70.48)[b]	36.54 (29.43)	40.85 (32.27)
Flanker score	90.55 (11.36)	95.32 (9.37)	97.83 (12.25)
Dimensional Change Card Sort score	103.17 (16.99)	102.98 (15.04)	107.43 (17.57)

Note. FBT = Fit Brains® Training; Ex-FBT = Exercise plus Fit Brains® Training; BAT = Balanced And Toned (i.e., control)
[a] n = 40; [b] n= 41; [c] n = 37

4.3.2 Compliance

Compliance for the group-based training was 93.2 % for the FBT group, 91.2% for the Ex-FBT group, and 95.3% for the BAT group. Compliance for the home-based Fit Brains® training was 94.8% for the FBT group and 92.1% for the Ex-FBT group.

4.3.3 Adverse Events

Over the course of the study, we had one fall in the facility during the cognitive training classes which resulted in some bruising – this participant remained in the program. This fall was not directly a result of the program (i.e., fell whilst leaving the room); thus, no adjustments to the protocol were necessary to ensure participant safety. No participants reported musculoskeletal-related issues (e.g., muscle strain and soreness) throughout the study.

4.3.4 Verbal Memory and Learning

Change scores for verbal memory and learning, as well as the contrasts between both CCT intervention groups with BAT, are reported in Table 4.2 and include both complete case and multiple imputation analyses. Results from analysis of complete case and multiple imputation data sets reveal a very similar pattern of results, with no significant between-group differences at post-intervention for % retention (i.e., primary outcome), total acquisition, long delay free recall, and recognition.

Table 4.2 Estimated Mean Change in Verbal Memory and Learning: Rey Auditory Verbal Learning Test

	Within-group adjusted change from baseline to post-test (95% CI)			Adjusted Between-group contrast (95% CI) and Standardized Mean Difference (SMD) [1]		
Outcome [#]	BAT	FBT	Ex-FBT	FBT vs. BAT	Ex-FBT vs. BAT	Ex-FBT vs. FBT
% Retention						
Complete Case	-1.20 (-7.59, 5.18)	1.48 (-5.06, 8.01)	-5.65 (-12.24, 0.94)	2.68 (-6.50, 11.86) SMD = 0.11	-4.45 (-13.63, 4.74) SMD = -0.18	-7.13 (-16.55, 2.30) SMD = -0.28
Multiple Imputation	-1.89 (-8.16, 4.39)	2.07 (-4.26, 8.41)	-5.44 (-11.95, 1.06)	3.96 (-5.03, 12.94) SMD = 0.16	-3.56 (-12.58, 5.46) SMD = -0.12	-7.01 (-16.03, 2.01) SMD = -0.28
Total Acquisition						
Complete Case	2.37 (0.31, 4.43)	2.66 (0.56, 4.76)	1.48 (-0.63, 3.59)	0.29 (-2.66, 3.25) SMD = 0.04	-0.89 (-3.85, 2.06) SMD = -0.12	-1.19 (-4.20, 1.83) SMD = -0.16
Multiple Imputation	2.29 (0.22, 4.35)	2.73 (0.64, 4.83)	1.32 (-0.82, 3.45)	0.45 (-2.50, 3.39) SMD = 0.08	-0.97 (-5.19, 3.25) SMD = -0.10	-1.42 (-4.41, 1.56) SMD = -0.19
Long Delay Free Recall						
Complete Case	0.25 (-0.47, 0.97)	0.73 (-0.002, 1.46)	-0.13 (-0.87, 0.60)	0.48 (-0.55, 1.51) SMD = 0.20	-0.38 (-1.41, 0.65) SMD = -0.16	-0.86 (-1.91, 0.18) SMD = -0.35
Multiple Imputation	0.21 (-0.50, 0.93)	0.72 (-0.02, 1.46)	-0.13 (-0.88, 0.62)	0.51 (-0.51, 1.53) SMD = 0.23	-0.34 (-1.38, 0.70) SMD = -0.08	-0.86 (-1.89. 0.17) SMD = -0.35
Recognition						
Complete Case	0.12 (-0.39, 0.64)	0.50 (-0.03, 1.03)	0.54 (0.01, 1.07)	0.38 (-0.36, 1.12) SMD = 0.21	0.41 (-0.33, 1.16) SMD = 0.23	0.04 (-0.71, 0.79) SMD = 0.02
Multiple Imputation	0.14 (-0.36, 0.65)	0.50 (-0.01, 1.02)	0.53 (0.003, 1.06)	0.36 (-0.36, 1.08) SMD = 0.21	0.39 (-0.34, 1.12) SMD = 0.24	0.04 (-0.70, 0.78) SMD = 0.02

[#] Higher scores reflect better performance.

[1]Standardized mean differences were calculated by dividing the adjusted between-group difference by the standard deviation in changes in the outcome from baseline to post-test. To facilitate interpretation, positive SMD values favour FBT or Ex-FBT vs. BAT and Ex-FBT vs. FBT for all variables.

4.3.5 Executive Functions

Change scores for each measure of executive function, as well as the contrasts between each CCT intervention group with BAT, are reported in Table 4.3 and include both complete case and multiple imputations analyses. Results from analysis of complete case and multiple imputation data sets reveal a very similar pattern of results (see Table 4.3), and results reported below are based on complete-case analysis.

Table 4.3 Estimated Mean Change for Secondary Outcomes: Executive Functions

	Within-group adjusted change from baseline to post-test (95% CI)			Adjusted Between-group contrast (95% CI) and Standardized Mean Difference (SMD) [1]		
Outcome	BAT	FBT	Ex-FBT	FBT vs. BAT	Ex-FBT vs. BAT	Ex-FBT vs. FBT
Stroop 3-2						
Complete Case	-3.44 (-7.47, 0.59)	-14.16 (-18.29, -10.02)	-11.39 (-15.58, -7.20)	-10.72 (-16.53, -4.91)*** SMD = 0.42	-7.95 (-13.77, -2.13)** SMD = 0.31	2.77 (-3.21, 8.74) SMD = 0.11
Multiple Imputation	-4.82 (-8.90, -0.74)	-15.63 (-19.93, -11.33)	-12.84 (-17.20, -8.49)	-10.81 (-16.75, -4.87)*** SMD = 0.33	-8.02 (-13.98, -2.07)** SMD = 0.24	3.15 (-2.82, 9.13) SMD = 0.09
Trails B-A						
Complete Case	2.90 (-5.81, 11.61)	-5.72 (-14.37, 2.93)	-10.75 (-19.41, -2.10)	-8.62 (-21.11, 3.86) SMD = 0.17	-13.65 (-26.09, -1.22)* SMD = 0.27	-5.03 (-17.37, 7.30) SMD = -0.10
Multiple Imputation	-2.30 (-11.03, 6.44)	-11.03 (-19.91, -2.15)	-15.47 (-24.24, -6.71)	-8.73 (-21.31, 3.84) SMD = 0.11	-13.18 (-25.77, -0.59)* SMD = 0.15	-3.78 (-16.21, 8.65) SMD = -0.04
Flanker						
Complete Case	4.05 (1.22, 6.87)	7.30 (4.48, 10.12)	10.76 (7.86, 13.66)	3.26 (-0.76, 7.27) SMD = 0.33	6.72 (2.55, 10.88)** SMD = 0.67	3.46 (-0.63, 7.55) SMD = 0.35
Multiple Imputation	4.17 (1.34, 7.01)	7.34 (4.49, 10.18)	10.59 (7.70, 13.49)	3.17 (-0.89, 7.22) SMD = 0.34	6.42 (2.25, 10.60)** SMD = 0.66	3.19 (-0.88, 7.26) SMD = 0.32
Dimensional Change Card Sort						
Complete Case	5.44 (1.49, 9.40)	8.32 (4.26, 12.38)	12.19 (8.08, 16.30)	2.88 (-2.79, 8.54) SMD = 0.22	6.75 (0.99, 12.50)* SMD = 0.51	3.87 (-2.02, 9.77) SMD = 0.29
Multiple Imputation	5.29 (1.36, 9.22)	8.35 (4.37, 12.32)	12.06 (8.05, 16.07)	3.06 (-2.53, 8.65) SMD = 0.23	6.77 (1.14, 12.41)* SMD = 0.51	3.85 (-1.89, 9.59) SMD = 0.29

*$p < .05$; **$p < .01$; ***$p < .001$

[1]Standardized mean differences were calculated by dividing the adjusted between-group difference by the standard deviation in changes in the outcome from baseline to post-test. To facilitate interpretation, positive SMD values favour FBT or Ex-FBT vs. BAT and Ex-FBT vs. FBT for all variables.

4.3.5.1 Response Inhibition

For Stroop Incongruent minus Stroop Congruent, planned contrasts showed significant improvements in FBT (-10.72, 95% CI [-16.53, -4.91]), and in Ex-FBT (-7.95, 95% CI [-13.77, 2.13]) compared with BAT.

For Flanker, planned contrasts showed no significant improvements in FBT (3.26, 95% CI [-0.76, 7.27]), but significant improvements in Ex-FBT (6.72, 95% CI [2.55, 10.88]) compared with BAT.

4.3.5.2 Set Shifting

For Trail Making Test B-A, planned contrasts showed no significant improvements in FBT (-8.62, 95% CI [-21.11, 3.86]) compared with BAT. However, planned contrasts showed significant improvements for set shifting in Ex-FBT (-13.65, 95% CI [-26.09, -1.22]) compared with BAT.

For DCCS performance, planned contrasts showed no improvements in FBT (2.88, 95% CI [-2.79, 8.54]) compared with BAT. In contrast, planned contrasts showed significant improvements in Ex-FBT (6.75, 95% CI [0.99, 12.50]) compared with BAT.

4.3.5.3 Post Hoc Analyses

Results from the exploratory analysis (i.e., comparison Ex-FBT vs. FBT) are displayed in Table 4.2 and Table 4.3. There were no significant differences between the two interventions groups at post intervention for verbal memory and learning or executive functions.

4.4 Discussion

In community-dwelling older adults aged 65 to 85 years old, an 8-week CCT program improved response inhibition, relative to an 8-week sham exercise and cognitive training program. Moreover, a 15-minute brisk walk prior to CCT provided additional benefits for set shifting. However, we did not find any benefit of CCT, with or without exercise, for verbal memory and learning. To our knowledge, this is the first study that has examined the effect of a single bout of aerobic exercise prior to CCT on cognitive function in community-dwelling older adults.

The lack of improvements in memory in this study contrasts with the results of a systematic review that showed CCT benefits memory.[155] The majority of the studies included in the systematic review used a memory-based training task, or had a strong memory-component in their multi-domain CCT program. In contrast, the Fit Brains® training program does not have a primary focus on memory; memory is one of six cognitive domains the program targets. Therefore, the total training time for memory was likely substantially less than those studies included in the systematic review.[155] This may, in part, explain the discrepancy in findings.

Moreover, the majority of the memory games in the Fit Brains® training program targeted visuospatial memory. The RAVLT is a measure of verbal memory and learning and thus, is not an ideal measure to detect potential gains in visuospatial memory from the 8-week training. Also, neural circuits for verbal memory and learning are different than those for visuospatial memory.[297] So, if this training had regionally specific neural effects than brain processes associated with verbal memory and learning might not have been sufficiently affected to see a response on this test. In

addition, a non-significant trend towards memory decline is visible in the Ex-FBT group. We encourage future studies to examine this potential trend.

Our finding of improved response inhibition with CCT concurs and extends previous findings from a recent meta-analysis,[150] which reviewed the effects of CCT on executive functions by classifying and redistributing cognitive outcome factors more carefully. The differences in findings between memory and executive functions could be explained by the higher frequency and overall duration of Fit Brains® Training games targeting executive functions (i.e., four out of six domains).

We also found that implementing a 15-minute brisk walk with CCT had broader benefits for executive functions, such that there were significant benefits for both response inhibition and set shifting. A recent review[298] demonstrated that a single bout of exercise benefits cognitive processes dependent on the prefrontal cortex, such as executive functions. Moreover, a single bout of moderate-intensity exercise prior to cognitive training stimulates the Hypothalamic-Pituitary-Adrenal axis, which in turn increases levels of cortisol.[299] Cortisol supports learning and memory and its levels remain elevated for up to two hours after exercise cessation,[298] and therefore could positively impact CCT training in the Ex-FBT group. However, it is important to note that we were not adequately powered to establish a potential additive effect of Ex-FBT.

Potentially, effects of CCT on EF could vary by MCI status and sex (see Appendices D and E), thus future studies are encouraged to investigate these potential moderators. In addition, we are cautious about results from Trail Making Test B-A as examination of baseline data suggested that the control group had poorer performance on this task, and the ANCOVA model assumes that

baseline differences are random in nature.[300] In RCTs it is best practice to maintain consistency in regard to time of day while performing cognitive assessments as well as keeping consistent assessors to minimize bias during assessments. For the current RCT we tried to address these aspects as best we could, however it was not feasible to completely adhere to these concepts. Finally, the absence of recorded compliance data for homework completion in the control group (i.e., BAT) did not ensure accurate comparison of hours spent working at home between control and CCT groups.

Conclusions and Future Recommendation

Finding successful lifestyle strategies to promote healthy cognitive aging in later life is of great importance. In addition to existing evidence showing beneficial effects of exercise, results from our proof-of-concept RCT suggest that CCT immediately preceded by aerobic exercise improved multiple cognitive processes of executive functions. Computerized cognitive training alone also provided benefit for executive functions, but only for response inhibition. Executive functions are an important facet of cognitive performance, though they are highly susceptible to aging.[8] Therefore, benefits gained after CCT are of great value. Future studies with larger sample sizes are needed to examine the additive or interactive effect of exercise and CCT.

Chapter 5: Resting-State Functional Connectivity and Response Inhibition: Effects of an 8-Week Randomized Controlled Trial of Computerized Cognitive Training

5.1 Introduction

Over the last decades, there have been increased efforts in finding strategies to combat cognitive decline as a result of a rapidly aging world population.[4] Aging negatively impacts multiple cognitive domains, such as memory, processing speed, and executive functions.[8] Executive functions (EF) are higher order cognitive processes involved in goal-directed behaviour,[9] and thus, are critical for one's capacity to remain functionally independent. Current evidence supports the role of lifestyle strategies, such as exercise and cognitive training, in promoting cognitive function in older adults.[149,184,255] However, the underlying neural mechanisms are not well understood. A better understanding of underlying mechanisms will aid in the refinement of lifestyle strategies.

Previously, we demonstrated that an 8-week randomized controlled trial (RCT) of computerized cognitive training (CCT), with or without exercise, significantly improved EF in community-dwelling older adults. Specifically, compared with an active control group, CCT, with or without exercise, significantly improved the executive cognitive process of response inhibition. The underlying neural mechanisms of how CCT improves EF are not well examined.[290] We propose changes in inter-network functional connectivity as potential neural mechanisms.

The brain consists of functional networks that are interconnected; communication within and between these networks is crucial for cognitive performance.[206] Functional connectivity analysis examines the strength of the connections between brain regions that show temporally correlated activity and is measured using rs-fMRI. Well-established neural networks include the default mode network (DMN), the fronto-parietal network (FPN), the salience network (SN), and the central executive network (CEN). The DMN is a network distinct from other brain systems, and is active in a task-negative state and inactive in task-positive states.[101] The network is involved in self-referential processes[98] and mind wandering.[99] The FPN is a task-positive network and is involved in attention and executive control, and is able to adjust and control processes based on changing demands.[107] The SN aims to identify relevant stimuli and helps guide behaviour, and thus plays a role in processes of attention and cognitive control.[105] The main hub of the network, the anterior insula, is critical for the ability to switch between the DMN and the CEN by integrating information from multiple sources (e.g., emotional, sensory, and cognitive).[111] The main function of the CEN is its involvement in EF, providing error feedback for top-down control, and help maintain associations between action versus outcome.[104,105]

Functional connectivity, both within and between these neural networks, is sensitive to aging effects.[116] Regions of the neural networks can either correlate positively or negatively (i.e., anti-correlation) with each other. When focusing on inter-network functional connectivity, specifically between task-negative (i.e., DMN) and task-positive (i.e., FPN, CEN, and SN) networks; an anti-correlation is favourable for cognitive performance.[301] The degree of anti-correlation appears to vary across the lifespan; positive correlations are observed in early childhood, and evolve into anti-correlations in young adulthood.[302] With older age, the developed anti-correlation between neural

networks tends to diminish.[45,116,303] For example, Geerligs and colleagues[113] showed that in adults aged 18 – 26, the FPN and DMN acted as separate networks, while in older adults (aged 59 – 74) the two networks act functionally more as one coherent network (i.e., reduced anti-correlation). These age-related decreases in anti-correlation between task-negative and task-positive networks have been linked to decreased network modularity (i.e., less segregation of networks[44]) and efficiency,[113,304] and are associated with reduced cognitive performance.[305] Studies suggest these age-related changes in inter-network functional connectivity reflect changes in the brain's underlying architecture such as structural connectivity.[206]

We hypothesize CCT could impact inter-network functional connectivity in the older adult brain by improving structural connectivity of the brain. Evidence from rodent models shows that environmental enrichment (without exercise) is able to promote the functional neuronal structure through neuronal survival and stimulating synaptic plasticity; for example by increasing dendritic length and spine density.[130] These beneficial neuroplastic changes after environmental enrichment may enhance structural connectivity by improving neuronal connectivity, as dendrites and dendritic spines are a vital part of neuronal connection.[122] Similarly to environmental enrichment, CCT in older adults may result in enhanced structural connectivity, which provides the basis of functional connectivity in the brain.[306]

Therefore, the aim of this secondary analysis of an 8-week trial of CCT is two-fold: 1) To identify relevant changes in inter-network functional connectivity, specifically between task-positive (FPN, SN, and CEN) and task-negative (DMN) networks, that correlate with changes in EF; and 2) To examine the effects of an 8-week RCT of CCT on changes in regional inter-network

functional connectivity (i.e., task-negative vs. task-positive networks) compared with an active control group. We hypothesize that: 1) Improved response inhibition will be associated with increased anti-correlation between task-positive and task-negative networks; and 2) Compared with those assigned to the active control group, those assigned to the CCT groups will show increased anti-correlation between task-positive and task-negative networks on an overall-network level as well as a regional level.

5.2 Methods

The study protocol[293] and the primary findings[307] of the study have been published previously (chapters 3 and 4). A summary with key aspects of the protocol is described in the following sections; for more detailed information we refer to the protocol paper (i.e., chapter 3).[293]

5.2.1 Study Design

This is a secondary analysis of a previously published 8-week, single-blinded, proof-of-concept RCT (ClinicalTrials.gov identifier: NCT02564809) at the University of British Columbia and Vancouver General Hospital campus with assessments at baseline and trial completion (i.e., 8-weeks). MRI data were acquired at baseline and trial completion in a subset of eligible participants.

5.2.2 Participants

Sixty-eight community-dwelling older adults were included in this planned secondary analysis. Participants were recruited from metro Vancouver, British Columbia between September 2015 and April 2017 using advertisements in newspapers, flyers and brochures in local community centres. We included community-dwelling older adults who: 1) were aged between 65 and 85 years; 2)

completed high school education; 3) had preserved general cognitive function as indicated by a Mini-Mental State Examination (MMSE)[74] score ≥ 24/30; 4) scored ≥ 6/8 on the Lawton and Brody[82] Instrumental Activities of Daily Living Scale; 5) were not expected to start or are stable on a fixed dose of anti-dementia medications (e.g., donepezil, galantamine, etc.) during the study period; and 6) were suitable to engage in 15 minutes of brisk walking based on the Physical Activity Readiness Questionnaire.[263] We excluded individuals who: 1) were diagnosed with dementia of any type; 2) had a neurodegenerative disease as the cause of mild cognitive impairment (MCI) that is not AD, vascular dementia, or both (e.g. multiple sclerosis, Parkinson's disease, etc.); 3) experienced clinically significant peripheral neuropathy or severe musculoskeletal or joint disease that impairs mobility, as determined by his/her family physician; 4) were taking medications that may negatively affect cognitive function, such as anticholinergics, tranquilizers, and anticonvulsants; and 5) were ineligible for MRI scanning.

Following screening over the phone, eligible participants came in for an information session to discuss additional study information as well as the consent form. Figure 5.1, the CONSORT (Consolidated Standards of Reporting Trials) flow chart, provides information about participant flow and distribution. Ethical approval was obtained from both the University of British Columbia Clinical Research Ethics Board as well as from the Vancouver Coastal Health Research Institute (VCHRI) ethics board.

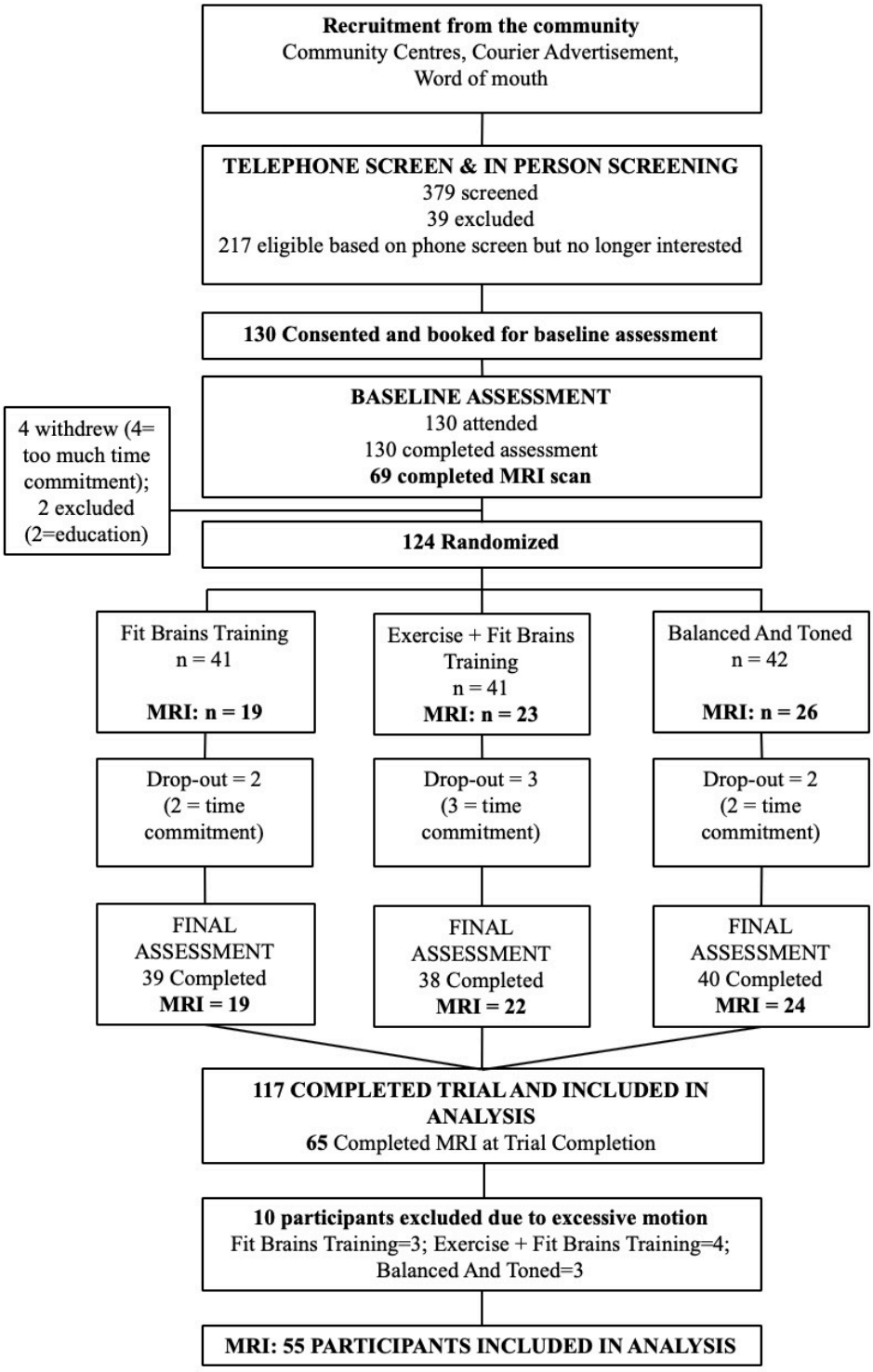

Figure 5.1 CONSORT Flow Diagram

5.2.3 Descriptive Variables

At baseline, general health, demographics, socioeconomic status, and education were ascertained by a questionnaire. Descriptive measures such as age in years, standing and sitting height in centimeters, mass in kilograms, and waist and hip circumference in centimeters were obtained. Global cognitive function was measured using both the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). The MoCA is a valid and reliable measure,[77] and assesses eight cognitive domains such as attention, concentration, EF, memory, language and visuo-constructional skills. The total possible score is 30 points; a score of less than 26 points indicates MCI. The MoCA has with a score of 26 a 90% sensitivity to for detecting MCI.[77]

5.2.4 Executive Function: Response Inhibition

The Stroop Colour-Word Test[11] was used to assess response inhibition, by calculating incongruent condition completion time minus congruent condition completion time. In addition to standard paper and pen tests of response inhibition, we administered the Flanker Inhibitory Control and Attention Test from the cognition battery of the National Institute of Health (NIH) Toolbox.[273]

5.2.5 Functional MRI Acquisition

Participants completed an MRI scan at baseline and trial completion at the UBC MRI Research Centre on a 3.0 Tesla Intera Achieva MRI Scanner (Philips Medical Systems, Best, The Netherlands) using an 8-channel SENSE head coil. The twelve-minute resting-state fMRI scan consisted of 360 dynamic images of 36 slices (thickness of 3 mm) which were acquired using the following imaging parameters: repetition time (TR) of 2000ms, echo time (TE) of 30ms, flip angle (FA) of 90 degrees, field of view (FoV) of 240mm, and an acquisition matrix of 80x80. During

the rs-fMRI scan, no music was played, and participants were asked to keep their eyes open while focusing on a point outside the scanner without thinking of anything in particular. The anatomical T1-weighted images were acquired using the following imaging parameters: 170 slices (thickness of 1mm), TR of 7.7ms, TE of 3.6ms, FA of 8 degrees, FoV of 256mm, and an acquisition matrix of 256x200.

5.2.6 Randomization

Participants were randomly allocated to either Fit Brains® Training (FBT), Exercise plus Fit Brains® Training (Ex-FBT), or Balanced And Toned (BAT; i.e., control) with a ratio of 1:1:1 using the web application www.randomization.com. A research team member not involved with the study held this sequence at a remote location. Assessors were blinded to group allocation of the participants.

5.2.7 Sample Size

Sample size calculations were based on predictions of changes in RAVLT (retention score) in the absence of previous trials testing the effects of FBT on memory and learning. Specifically, we predicted a mean change (i.e., z-scores) of 0.31 for the FBT group, a mean change of 0.40 for the Ex-FBT group, and a mean change of -0.31 for the BAT group. We made these estimates based on the work of Diamond and colleagues.[288] With a pooled standard deviation of 1.1, and a two-sided alpha of 0.05, 36 participants per group were needed for a power of 0.80, based on a two-group comparison (i.e., FBT vs. BAT; Ex-FBT vs. BAT). To accommodate an expected 10% drop-out rate, our total targeted sample size came to 120 participants (i.e., 40 FBT, 40 Ex-FBT, and 40 BAT).

5.2.8 Interventions

A succinct description of the intervention is described below. A more detailed description of the protocol is published elsewhere (i.e., chapter 3).[293]

5.2.8.1 Fit Brains® Training

Participants randomized to Fit Brains® Training (FBT) performed multi-domain computerized cognitive training 3x/week for 60 minutes at the research centre, as well as 3x/week at home for 60 minutes. Games were performed on an iPad and consisted of 38 games targeting one of six domains – focus, speed, memory, visual, problem solving, and language. Games were individualized and adaptive throughout the 8-week program.

5.2.8.2 Exercise plus Fit Brains® Training

Participants randomized to the Exercise + Fit Brains® Training (Ex-FBT) came to the research centre 3x/week for 60 minutes, consisting of a 15-minute brisk walk perceived as somewhat hard (i.e., up to 13-14 on the 6-20 Borg's Rating of Perceived Exertion scale)[266] followed by a 45-min session of multi-domain computerized cognitive training. Additionally, they repeated the same 60-minute training (i.e., 15-minute walk + FBT training) 3x/week at home for 8-weeks. Please see Figure 5.2 for a detailed overview of walking intensity progression.

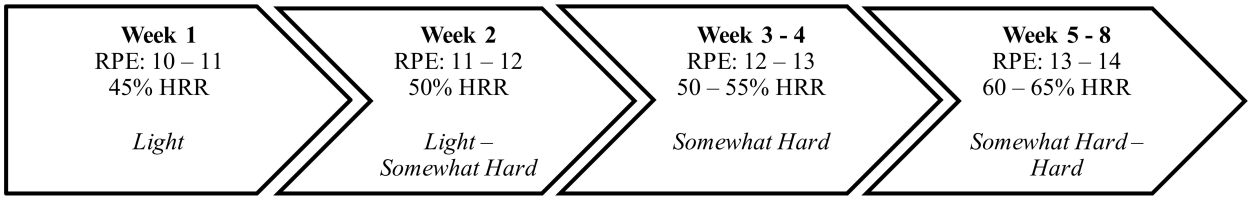

Figure 5.2 Target Borg Rate of Perceived Exertion

5.2.8.3 Balanced and Toned

The Balanced and Toned (BAT) group attended three 60-minute sessions/week at the research centre for 8 weeks. Specifically, participants completed 8 hours of sham cognitive training (e.g., word and drawing games, and creativity exercises), 8 hours of sham exercise training (e.g., stretching, balancing, and core strength exercises), and 8 hours of education regarding brain health (e.g., lectures on sleep, goal setting, mindfulness, and an educational project). Participants were asked to complete homework in order to complete their educational project.

5.2.9 Adverse Events

Participants were asked about the presence of any adverse effects throughout the study, such as musculoskeletal pain or discomfort following the sham exercise portion (i.e., BAT) and the 15-minute brisk walk (i.e., Ex-FBT). Participants were monitored for shortness of breath during the sham exercise and brisk walks.

5.2.10 Functional MRI Data Analysis

5.2.10.1 Preprocessing

Processing of the images was done using FEAT[308] (version 6.00), which is part of FSL (FMRIB Software Library; version 6.0),[309] MATLAB (Matrix Laboratory), and toolboxes from SPM (Statistical Parametric Mapping). Brain extraction in high resolution T1-weighted images was performed using optiBET[310] to remove unwanted structures (e.g., bones, skull). Manual checks were performed to ensure all brain tissue was included in the extraction; optiBET masks were edited where necessary by one individual to ensure rater consistency. Using the "*fslmaths"* function, final brain extraction was calculated by multiplying T1-weighted scans with the edited optiBET masks. FSL FLIRT[311-313] and "*fslmaths*" functions were used to create a study-specific template image (instead of MNI152 average brain) to ensure best template representation of the current study population. Registration with the study-specific average brain was checked manually by one individual for gross errors. Rigid body motion correction was completed using MCFLIRT;[312] participants were excluded when an absolute displacement of 2.0 mm or a relative displacement of 0.2 mm was exceeded. Spatial smoothing was carried out using a Gaussian kernel of 6.0 mm Full-Width-Half-Maximum (FWHM). A high-pass filter with a cut-off of 120 seconds was used for temporal filtering. Preprocessed functional data were registered to personal high-resolution T1-weighted anatomical images, which in turn were registered on the average study-specific space. In addition, excess noise originating from movement, physiological noise generated from cerebral-spinal fluid, and white matter was regressed out of the signal.

5.2.10.2 Functional Connectivity Analysis

The choice of resting-state networks and their corresponding regions of interest (ROI; i.e., seeds) are based on previous studies in aging.[100,111,116,314] The networks and their corresponding key ROIs are displayed in Table 5.1. The DMN included the posterior cingulate cortex (PCC) and the right and left middle temporal gyrus (RMTG and LMTG, respectively). The FPN included the right inferior parietal sulcus (RIPS) and the right anf left dorsolateral prefrontal cortex (RdlPFC and LdlPFC, respectively). The CEN included the right and left anterolateral prefrontal cortex (RALPFC and LALPFC, respectively). The SN included the right ventral anterior insula (RVAI) and the dorsal anterior cingulate cortex (dACC). For each ROI, 5mm radius spherical regions (i.e., diameter of 10mm) were drawn on the study-specific average brain, from which preprocessed time-series data were extracted. A radius of 5mm was chosen to avoid overlap of ROIs, which could lead to similar correlations between different ROIs. Subsequently, correlation-matrices were obtained between all ROIs, which contained Fisher's *z* transformed correlations.

Table 5.1: Included Resting-State Networks and Included Regions of Interest

Network	ROI
DMN	PCC
	RMTG
	LMTG
FPN	RIPS
	RdlPFC
	LdlPFC
CEN	RALPFC
	LALPFC
SN	RVAI
	dACC

Note**:** DMN=Default Mode Network; FPN=Fronto-Parietal Network; CEN=Central-Executive Network; SN=Salience Network; ROI=Region Of Interest; PCC=Posterior Cingulate Cortex; RMTG=Right Medial Temporal Gyrus; LMTG=Left Medial Temporal Gyrus; RIPS=Right Inferior Parietal Sulcus; RdlPFC=Right dorsolateral Prefrontal Cortex; LdlPFC=Left dorsolateral Prefrontal Cortex; RALPFC=Right Antero-Lateral Prefrontal Cortex; LALPFC=Left Antero-Lateral Prefrontal Cortex; RVAI=Right Ventral Anterior Insula; dACC=dorsal Anterior Cingulate Cortex.

Guided by previous work,[314] overall inter-network connectivity between the task-positive (FPN, SN, CEN) and task-negative (DMN) networks was calculated by categorically computing the average of all the pairwise ROI-ROI correlations with similar spatial designation to generate a network level correlation coefficient. For example, for overall DMN-CEN connectivity, we calculated it as ((V3+V4+V11+V12+V18+V19)/6); see Figure 5.3. Changes in inter-network connectivity were then calculated as trial completion value minus baseline value.

To examine inter-network (DMN – FPN) functional connectivity on the ROI level, we used a total of 9 Fisher's *z* transformed correlations (V7 – V9, V15 – V17, and V22 – V24; see Figure 5.3).

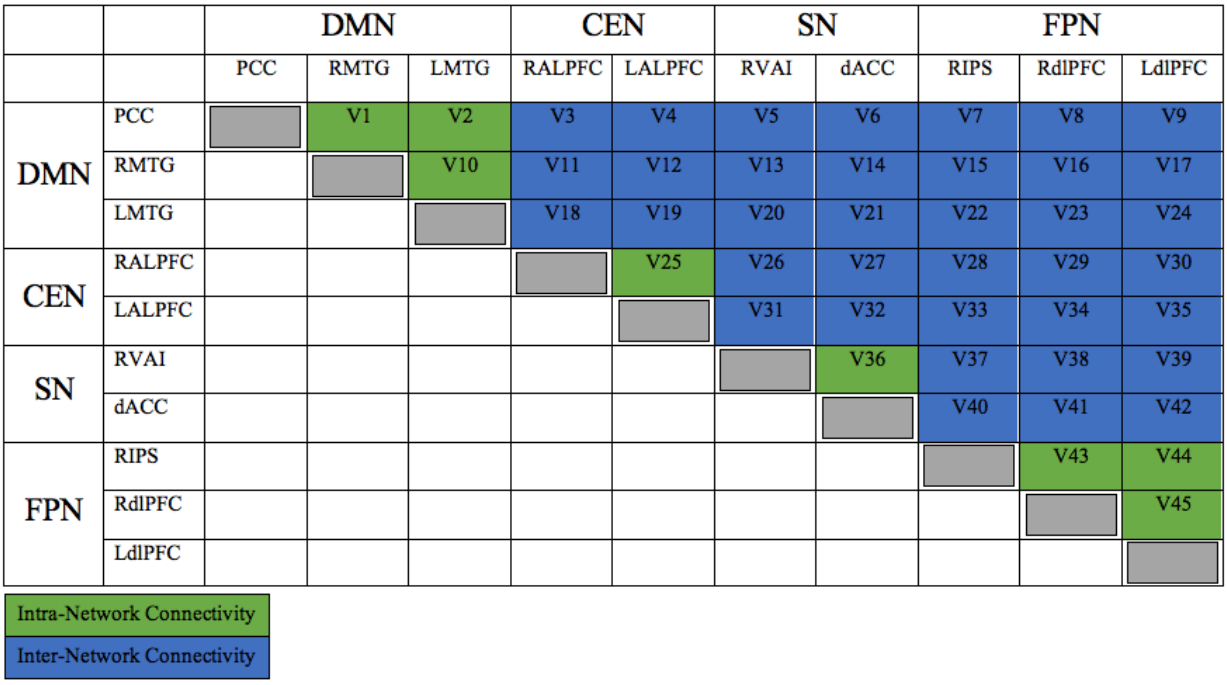

Figure 5.3 Correlation Matrix of Regions of Interest Included in Analysis

Note**:** DMN=Default Mode Network; CEN=Central-Executive Network; SN=Salience Network; FPN=Fronto-Parietal Network; PCC=Posterior Cingulate Cortex; RMTG=Right Medial Temporal Gyrus; LMTG=Left Medial Temporal Gyrus; RVAI=Right Ventral Anterior Insula; dACC=dorsal Anterior Cingulate Cortex; RALPFC=Right Antero-Lateral Prefrontal Cortex; LALPFC=Left Antero-Lateral Prefrontal Cortex; RIPS=Right Inferior Parietal Sulcus; RdlPFC=Right dorsolateral Prefrontal Cortex; LdlPFC=Left dorsolateral Prefrontal Cortex;

5.2.11 Statistical Analysis

All analyses were "full set analysis"[315] (i.e., defined as the analysis set which is as complete and as close as possible to the intention-to-treat ideal of including all randomized participants). Statistical analysis was performed using the statistical package SPSS 26.0 (IBM Corporation, Armonk, NY). The overall alpha was set at $p < 0.05$.

To examine whether changes in response inhibition in the overall sample were associated with changes in the overall inter-network resting-state connectivity between task-positive and task-

negative networks, we conducted a partial correlation analysis between change scores of response inhibition, as measured by the both the Stroop Colour-Word Test and the Flanker Inhibitory Control and Attention Test, and changes in overall inter-network functional connectivity between task-negative and task-positive (i.e., DMN – FPN; DMN – CEN; DMN – SN) networks. We controlled for baseline MoCA, baseline systolic blood pressure, and experimental group in these analyses.

After identifying the inter-network resting-state connectivity relevant to changes in response inhibition, we: 1) examined the effect of FBT and Ex-FBT, compared with BAT, on changes in overall inter-network connectivity (i.e., DMN – FPN), and 2) examined the effect of FBT and Ex-FBT, compared with BAT, on changes in the 9 ROI pairs that exist in the relevant overall inter-network connectivity of the DMN and FPN. We performed an ANCOVA, adjusting for baseline MoCA and baseline systolic blood pressure.

5.3 Results

5.3.1 Participants

Sixty-eight out of the 124 participants who consented and were randomized in the parent study underwent scanning at baseline. Three of the 68 MRI participants dropped out over the course of the study (1 = Ex-FBT, and 2 = BAT) and 65 participants completed a scan at trial completion. Scans of 10 participants (3 = FBT, 4 = Ex-FBT, and 3 = BAT) were excluded due to excessive motion. Baseline characteristics of the 55 participants, with both scans at baseline and trial completion, are reported in Table 5.2.

Table 5.2 Participant Characteristics at Baseline (N = 55)

Variable	BAT (n = 21) Mean (SD)	FBT (n = 16) Mean (SD)	Ex-FBT (n = 18) Mean (SD)	Total (N = 55) Mean (SD)
Age (years)	71.43 (5.81)	70.75 (4.87)	72.44 (3.37)	71.56 (4.81)
Weight (kg)	72.18 (17.83)	69.26 (14.08)	73.46 (16.26)	71.75 (16.09)
Height (cm)	166.96 (11.16)	166.32 (12.36)	168.91 (10.94)	167.41 (11.29)
Sex (f, %)	10 (47.60)	10 (62.5)	7 (38.9)	27 (49.1)
Education (%)				
High school certificate or diploma	3 (14.3)	1 (6.3)	1 (5.6)	5 (9.2)
Trades or professional certificate or diploma	3 (14.3)	-	4 (22.2)	7 (12.7)
University certificate or diploma	2 (9.5)	6 (37.5)	5 (27.8)	13 (23.6)
University degree	13 (61.9)	9 (56.3)	8 (44.4)	30 (54.5)
Instrumental Activities of Daily Living (max. 8 pts)	7.81 (0.51)	7.94 (0.25)	7.94 (0.24)	7.89 (0.37)
Functional Comorbidity Index (max. 18 points)	2.29 (1.45)	1.87 (1.36)	1.56 (1.25)	1.93 (1.37)
Physical Activity Scale for the Elderly	108.71 (46.08)	119.27 (40.21)	130.91 (46.26)	119.05 (44.70)
Systolic blood pressure (mmHg)	133.48 (19.39)	131.50 (16.70)	142.94 (25.02)	136.00 (20.94)
Montreal Cognitive Assessment (max. 30 pts)	24.90 (3.75)	27.19 (2.76)	24.78 (3.87)	25.53 (3.64)
Mini-Mental State Examination (max. 30 pts)	28.10 (1.79)	29.25 (0.86)	28.39 (1.50)	28.53 (1.53)
Stroop Incongruent – Congruent (s)	59.91 (32.33)	56.87 (41.34)	65.78 (37.16)	60.95 (36.19)
Flanker score	90.71 (11.25)	94.38 (7.10)	99.00 (9.96)	94.49 (10.22)

Note: BAT = Balanced And Toned; FBT = Fit Brains Training; Ex-FBT= Exercise + Fit Brains Training

5.3.2 Compliance

The parent study[307] reported compliance for the group-based training (i.e., in-class) 93.2% for the FBT group, 91.2% for the Ex-FBT group, and 95.3% for the BAT group. Home-based Fit Brains® training compliance for the FBT and Ex-FBT was 94.8% and 92.1%, respectively.

5.3.3 Partial Correlation: Changes in Response Inhibition and Functional Connectivity

Table 5.3 reports correlations between changes in performance on tasks of response inhibition (i.e., Stroop 3 – Stroop 2, Flanker) and changes in inter-network functional connectivity (i.e., DMN-FPN, DMN-CEN, DMN-SN) in the overall sample. For the Stroop Colour-Word Test, there was a significant positive partial correlation between behavioural performance and functional connectivity between DMN and FPN (Pearson's $r = .358$, $p = .009$; Table 5.3), such that improved behavioural performance over the course of the intervention was associated with increased anti-correlation between the DMN and FPN (Figure 5.4). In addition, a significant negative partial correlation between Flanker test performance and functional connectivity between the DMN and FPN was observed (Pearson's $r = -.275$, $p = .048$; Table 5.3), indicating that improved performance on the Flanker test was associated with increased anti-correlation between the DMN and FPN (Figure 5.5). No significant associations were found between changes in response inhibition and changes in DMN-CEN, and DMN-SN (Table 5.3).

Table 5.3 Partial Correlations Between Change in Response Inhibition - Change in Functional Connectivity

Variable†	Mean Change	Δ DMN – FPN	Δ DMN – CEN	Δ DMN – SN
	Mean (SD)	Pearson's *r*	Pearson's *r*	Pearson's *r*
Δ Stroop (s)	-17.230 (29.643)	.358**	.189	.079
Δ Flanker	9.200 (9.132)	-.275*	-.193	-.023

†Stroop = Stroop 3 – Stroop 2 (seconds); DMN = Default Mode Network; FPN = Fronto-Parietal Network; CEN = Central Executive Network; SN = Salience Network.
Change calculated at trial completion minus baseline
Correlations adjusted for: baseline Montreal Cognitive Assessment, baseline systolic blood pressure, and group
Δ Stroop interference: negative value represents improvement
Δ Flanker: positive value represents improvement
*$p < .05$; **$p < .01$

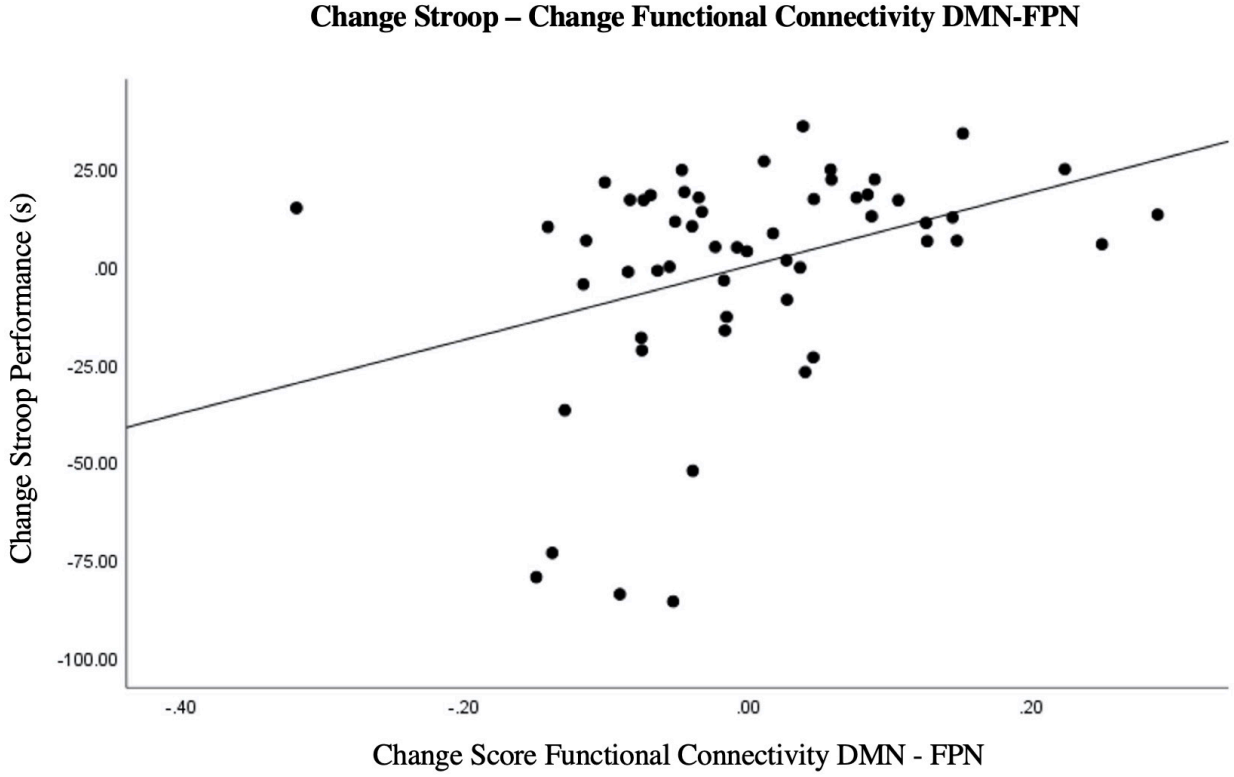

Figure 5.4 Partial Correlation of Stroop and Overall DMN-FPN Functional Connectivity

Note: DMN= Default Mode Network; FPN = Frontoparietal Network.
Change in Stroop Performance: Negative scores reflect better performance

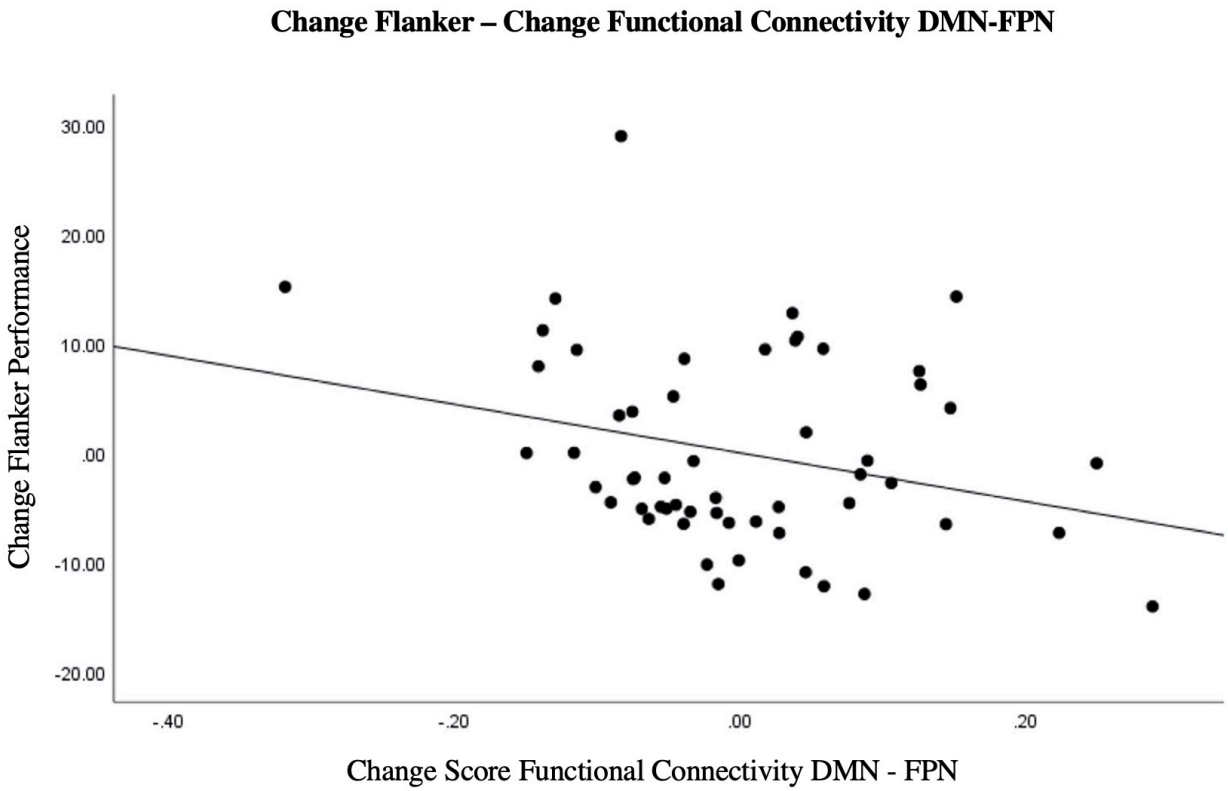

Figure 5.5 Partial Correlations of Flanker and Overall DMN-FPN Functional Connectivity

Note: DMN= Default Mode Network; FPN = Frontoparietal Network.
Change in Flanker Performance: Positive scores reflect better performance

5.3.4 ANCOVA: Effect of FBT and Ex-FBT on Regional DMN-FPN Connectivity

No significant differences were found for overall inter-network DMN-FPN connectivity between FBT vs. BAT and Ex-FBT vs BAT (p = .277 and p = .944, respectively). There were significant differences between FBT and BAT for the 9 ROI DMN-FPN pairs; results are displayed in Table 5.4. Specifically, there was a significant difference between FBT compared with BAT in connectivity between the RMTG and LdlPFC (p = .014; Table 5.4); where FBT demonstrated increased anti-correlation between RMTG and LdlPFC, ROI of the DMN and FPN respectively, whereas BAT showed decreased anti-correlation (Figure 5.6). In addition, there was a significant difference between FBT and BAT for the LMTG and LdlPFC (p = .043; Table 5.4); where FBT

increased anti-correlation between both ROIs of the DMN and FPN compared with a decreased anti-correlation in BAT (Figure 5.7). No significant differences were found when comparing changes in functional connectivity between the Ex-FBT and BAT groups after the intervention (Table 5.4).

Table 5.4 Regional Inter-Network Functional Connectivity (DMN – FPN) Results

ROI Pairs†	BAT		FBT		Ex-FBT		*p*-value	
	Mean	SE	Mean	SE	Mean	SE	FBT vs. BAT	Ex-FBT vs. BAT
PCC – RIPS	-.037	.038	-.028	.045	.066	.042	.880	.078
PCC – RdlPFC	.009	.041	.066	.049	.072	.045	.383	.316
PCC – LdlPFC	.066	.046	-.063	.054	.019	.050	.078	.493
RMTG – RIPS	.006	.036	-.006	.042	.035	.039	.835	.585
RMTG – RdlPFC	.043	.040	.030	.046	.014	.043	.834	.624
RMTG – LdlPFC	.077	.036	-.066	.042	.012	.039	.014*	.228
LMTG – RIPS	.000	.032	-.042	.038	.044	.035	.405	.367
LMTG – RdlPFC	.032	.038	.052	.044	.028	.041	.745	.940
LMTG - LdlPFC	.040	.038	-.083	.045	-.029	.042	.043*	.226

† DMN=Default Mode Network
FPN=Fronto-Parietal Network
PCC=Posterior Cingulate Cortex
RIPS=Right Inferior Parietal Sulcus
RdlPFC= Right dorsolateral Prefrontal Cortex
LdlPFC=Left dorsolateral Prefrontal Cortex
RMTG=Right Medial Temporal Gyrus
LMTG=Left Medial Temporal Gyrus
BAT=Balanced and Toned (i.e., active control)
FBT=Fit Brains Training
Ex-FBT=Exercise + Fit Brains Training.
*p <.05; controlled for baseline Montreal Cognitive Assessment and systolic blood pressure

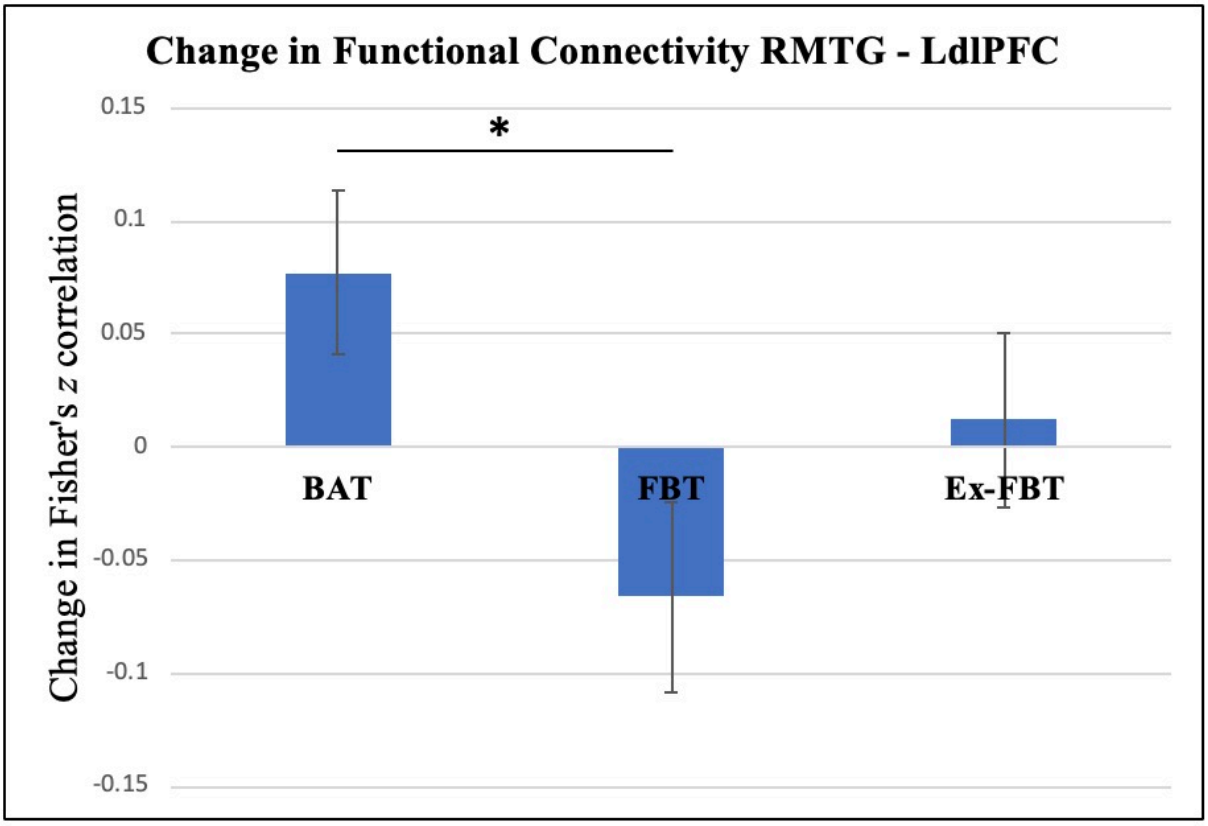

Figure 5.6 Between-Group Regional Differences in Inter-Network Functional Connectivity of DMN – FPN

Note: RMTG= Right Medial Temporal Gyrus (i.e., Default Mode Network)
LdlPFC= Left dorsolateral Prefrontal Cortex (i.e., Frontoparietal Network)
DMN = Default Mode Network
FPN = Frontoparietal Network
BAT = Balanced And Toned (i.e., control)
FBT = Fit Brains Training
Ex-FBT= Exercise + Fit Brains Training

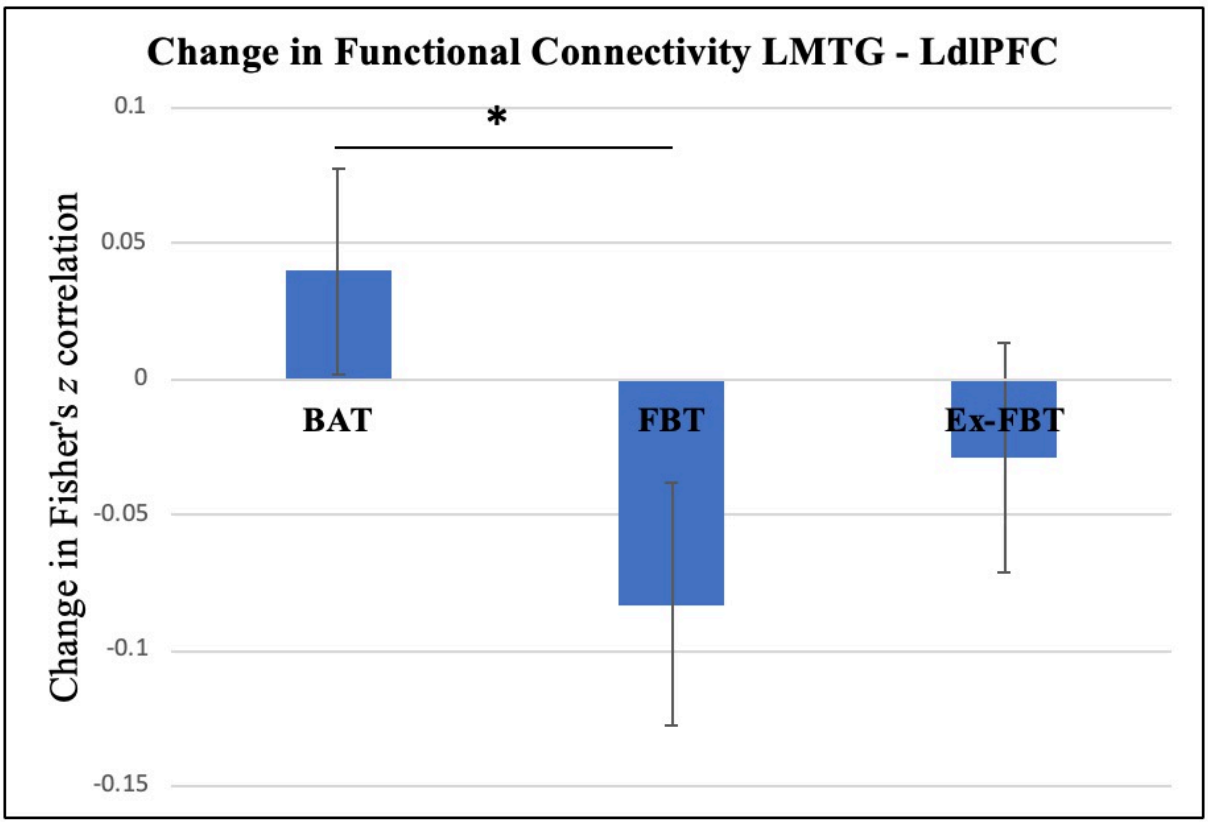

Figure 5.7 Between-Group Regional Differences in Inter-Network Functional Connectivity of DMN – FPN

Note: LMTG= Left Medial Temporal Gyrus (i.e., Default Mode Network)
LdlPFC= Left dorsolateral Prefrontal Cortex (i.e., Frontoparietal Network)
DMN = Default Mode Network
FPN = Frontoparietal Network
BAT = Balanced And Toned (i.e., control)
FBT = Fit Brains Training
Ex-FBT= Exercise + Fit Brains Training

5.3.5 Adverse Events

There was one adverse event over the course of the 8-week trial; a participant fell in the facility during the cognitive training classes which resulted in some bruising. This adverse event was not directly a result of the program (i.e., the participant fell whilst leaving the room); thus, no adjustments to the protocol were necessary to ensure participant safety. No participants reported musculoskeletal-related issues (e.g., muscle soreness or muscle strain) throughout the study.

5.4 Discussion

This secondary analysis investigating the effects of an 8-week RCT of CCT in otherwise healthy older adults showed that: 1) improvements in executive functions, specifically response inhibition, were associated with increased inter-network anti-correlation between the DMN and FPN, and 2) compared with an 8-week sham exercise and cognitive training program, CCT alone significantly increased anti-correlation between the left dorsolateral prefrontal cortex and both right and left medial temporal gyrus regions.

These findings complement and advance current research investigating potential underlying mechanisms of CCT in otherwise healthy older adults. In a recent systematic review,[290] we summarized the current status of the neuroimaging literature in CCT, and demonstrated evidence to date is equivocal. Five of the nine included studies examined resting-state functional connectivity after CCT; results were very heterogeneous, with both increased and decreased levels of connectivity after the intervention, which were linked to maintained or improved cognitive performance. A consistent finding across two studies was increased functional connectivity between the hippocampus and both the frontal and temporal lobes which was associated with

improved memory and global cognition.[164,213] More recently, a study in older adults with vascular cognitive impairment showed that a 7-week study of multi-domain CCT increased inter-network functional connectivity between the medial prefrontal and left dorsolateral prefrontal cortex, which was associated with improved global cognition.[160] Thus, the current RCT extends on the excisting literature with quality evidence by examining inter-network changes in resting-state functional connectivity, specifically functional connectivity between task-positive and task-negative networks. One study[316] examined changes in functional connectivity between neural networks in older adults after 3 months of CCT (24 sessions), and showed maintained anti-correlation between the DMN and CEN. However, resting-state data were collected at baseline and 1-year post training cessation, and therefore the demonstrated effects could be due to other factors. In addition, the study did not compare CCT effects with an active control group, but rather included a wait-list control.

The current analysis focused on changes between measures of response inhibition and inter-network functional connectivity. Specifically, we focused on functional connectivity between task-positive and task-negative networks, as age-related changes (i.e., increased connectivity) between those networks could contribute to impaired cognitive functioning.[113,116] The FPN is a task-positive network involved in higher order cognitive functions[110] and a network of interest as the current analysis focused on changes in EF. We showed that an increase in anti-correlation of functional connectivity between the DMN-FPN was associated with increased performance on tasks of response inhibition, a core aspect of EF.[10] Generally, less segregation between the DMN and FPN is present with increasing age.[116,303] This inability to segregate the networks is detectable by increased functional connectivity (i.e., decreased anti-correlation) between the networks; and this

increased functional connectivity was visible in our control group after the 8-week intervention. The current findings are in accordance with results of a study showing that, compared with older adults, younger adults showed more segregation of the DMN and FPN, which was linked to increased performance on tasks of response inhibition.[305] Therefore, this study showed that 8-weeks of CCT is potentially able to reverse some of this functional desegregation occurring during the process of aging.

In contrast, we found no significant effect of CCT when combined with exercise (i.e., Ex-FBT group) on DMN-FPN functional connectivity. Previous literature indicates that changes evoked on a neural level are different for exercise versus cognitive training; where exercise is known to stimulate the growth of new neurons (i.e., neurogenesis),[122,124,168] cognitive training promotes the functional neuronal structure via neuronal survival and differentiation (e.g., synaptogenesis, spine density, dendritic length).[122,129,130,198] Recently, a review by Stillman and colleagues[175] focused on the effects of exercise on functional connectivity. The authors concluded that, despite vast differences in intervention characteristics, there is consistent evidence that exercise benefits functional connectivity within networks such as the DMN, sensory-motor network, and the executive control network. Results from studies examining inter-network functional connectivity are more inconsistent. In general, the vast differences in study design (i.e., exercise duration, content, and sample size) could contribute to these inconsistencies. Therefore, the authors recommended more high-quality RCTs are needed to explore the effects of exercise on functional connectivity and advance the field of research. Potentially, by taking into account the relatively short duration of the current intervention (i.e., 8 weeks), underlying mechanisms of CCT, such as increased dendritic length, might be observed at a faster rate compared to those elicited by exercise.

Resting-state fMRI could capture neuroplastic changes resulting in improved efficiency of inter-neuronal communication, such as increased length of dendrites or increased spine density. Possibly, removing 15 minutes of CCT per session in the combined exercise and CCT group could have impacted the lack of changes in inter-network functional connectivity in the combined group. Where the purely CCT group received 48 hours of CCT over the 8-week intevention, the combined exercise plus CCT group received 36 hours of CCT; maybe the lower dosage of CCT could have resulted in less CCT-induced plasticity.

To limit multiple comparisons, the current study focused on ROI analysis between the DMN and FPN as the analysis demonstrated an association between changes in response inhibition and inter-network connectivity of the DMN and FPN. However, 9 ROI-pairwise comparisons were still performed, making the results susceptible to Type-I error. Notably, the current results would no longer be statistically significant when a Bonferroni correction (i.e., dividing alpha by number of comparisons) would be applied. Furthermore, as this is a secondary analysis of a proof-of-concept study, future studies with larger sample sizes are needed to confirm these findings. Finally, by performing seed-based functional connectivity analysis, we limited our findings to the predetermined regions of interest. By implementing a more data-driven approach (e.g., Independent Component Analysis, ICA), future studies could extend our results outside the realm of these specific regions of interest.

In summary, results from this secondary analysis showed that increased performance on tasks of EF was related to improved functional connectivity (i.e., increased anti-correlation) between task-negative and task-positive networks in community-dwelling older adults. This suggests that those

who are able to better functionally segregate off-task and on-task neural networks with age, might be better able to preserve performance on tasks requiring high-order cognitive functions. Specifically, those who engaged in CCT showed the best segregation of off- and on-task networks compared to those without the same level of cognitive stimulation. Therefore, CCT might be a promising strategy to promote the functional organization of the brain. However, we would encourage future studies with larger samples to replicate and extend on these exploratory findings.

Chapter 6: General Discussion and Conclusion

The overarching theme of my thesis was to better understand the effect of CCT on cognitive function in community-dwelling older adults and explore possible neural mechanisms using neuroimaging. The aim of this last chapter is to summarize and integrate the research presented in this thesis thus far. Firstly, I will provide a brief recapitulation of all research studies included in this thesis. Secondly, the overall aims of the thesis, stated in chapter 1, will be reviewed and discussed; and finally, I will address some of the strengths and limitations of the research, and conclude this thesis with future directions for this field of research.

6.1 Summary of Research Chapters

The first research study, discussed in chapter 2, was a systematic review aimed to examine the effect of CCT on brain structure and function. Results of this systematic review showed that there is a dearth of studies investigating the underlying mechanisms of CCT. Moreover, among the scarce number of studies addressing this gap in the literature, there is a shortage of high-quality studies. Of the mere 9 studies included in the systematic review, only two were high-quality RCTs. Results from the higher-quality studies showed that CCT could potentially impact grey matter and resting-state functional connectivity. However, due to the lack of high-quality studies and considerable differences in study design, it was difficult to systematically examine the effect of CCT on brain structure and function. More high-quality studies with similar methodology and outcomes that examine the association between imaging data and behavioural data are needed to better understand the underlying mechanisms of CCT in older adults.

Chapter 3 was the study protocol of an 8-week proof-of-concept RCT (NCT02564809) aimed to examine the effects of CCT, alone and when preceded by a 15-minute brisk walk, on cognitive and brain function in community-dwelling older adults. Randomized controlled trials are considered the gold standard for clinical research studies, and thus the objective was to design rigorous and robust methods to ensure contribution of high-level evidence to the current field of CCT research. Important issues addressed in the current design were the inclusion of an active control group, randomization, and appropriate sample size. In addition to a purely CCT group, an additional intervention group was designed to examine whether potential cognitive benefits of CCT could be enhanced or broadened by preceding CCT with a 15-minute brisk walk, a novel aspect in the field of cognitive training.

Chapter 4 reported the primary findings of the 8-week proof-of-concept RCT (NCT02564809). Results showed that both CCT groups (i.e., FBT and Ex-FBT) improved response inhibition, compared with an active control. Moreover, those assigned to a brisk 15-minute walk immediately prior to CCT showed more widespread benefits on multiple tests and processes of EF. No benefits of either CCT intervention group were found on verbal memory and learning. It is important to consider the content of the CCT intervention when determining its efficacy on cognitive outcomes. The CCT program used in the 8-week proof-of-concept RCT had proportionally more content targeting EF compared with memory, this could explain the observed benefits for EF and the lack of benefit for memory. In summary, the results of this 8-week RCT of CCT suggest that CCT is a potential strategy to promote cognitive function by improving performance on tasks of EF, higher order cognitive processes important in goal-directed behaviour. Moreover, benefits of CCT could be augmented when CCT is immediately preceded by a 15-minute brisk walk.

Chapter 5 was a secondary analysis of rs-fMRI data acquired from the 8-week proof-of-concept RCT of CCT (NCT02564809). I first aimed to identify relevant changes in inter-network functional connectivity that correlate with changes in EF found in chapter 4. Secondly, I examined the effects of CCT, alone and when preceded by a 15-minute brisk walk, on relevant changes in inter-network resting-state functional connectivity in community-dwelling older adults. Results from this study demonstrated that improved response inhibition was associated with increased anti-correlation between the DMN and the FPN. Subsequently, analysis using ROI pairs showed that compared with BAT, CCT alone (i.e., FBT) increased anti-correlation in specific ROI pairs between the DMN and FPN. Specifically, increased anti-correlation was observed between the left dorsolateral prefrontal cortex and both the right and left medial temporal gyrus (i.e., LdlPFC-RMTG, and LdlPFC-LMTG). These results suggest that CCT alone can alter the neural organization by improving segregation of task-negative (i.e., DMN) and task-positive (i.e., FPN) neural networks. Decreased segregation between task-negative and task-positive networks as a result of strengthening connectivity between networks is associated with increased age or disease,[44,113] and could negatively impact cognitive functioning. Thus, improved segregation of the DMN and FPN, observed via increased anti-correlation, could result in less inter-network disturbances and therefore promote cognitive performance. The absence of significant change in inter-network connectivity in the Ex-FBT group compared with the active control, could be due to CCT volume. Compared with FBT, the Ex-FBT group participated in 75% of the overall CCT time. Thus, CCT training dose (i.e., volume) may be a critical factor for eliciting changes in functional connectivity.

6.2 Review of Thesis Aims

The central research aims of the current dissertation were summarized in chapter 1. In this section, I will readdress each aim, discuss how the findings fit the existing evidence in the current field of research, and provide a concluding statement.

First research aim: To provide a detailed review of the current state of the literature examining the underlying neural changes of CCT in adults aged 55 years and older.

As there is currently no pharmacological cure available for cognitive impairment and dementia, there has been an increased focus on lifestyle strategies such as exercise and cognitive training. In particular, in the last decade there has been an explosive growth in the development of commercialized CCT programs. However, evidence supporting the efficacy of these available products was present but limited, resulting into controversy in the field of CCT.[156] Findings from recent systematic reviews and meta-analyses showed that, depending on training type and duration, CCT could elicit changes in global cognition,[149] memory,[149] and executive functions.[149-152] In addition to studies investigating the effects on cognitive function, it is important to investigate the potential underlying neural mechanisms by which CCT could improve cognition. Potentially, a greater understanding of neural changes elicited by CCT could help tailor and design these programs to ensure maximal benefits from this category of lifestyle intervention.

Chapter 2 aimed to summarize the current literature focusing on underlying neural changes in CCT. As discussed, evidence regarding the underlying neural mechanisms thus far is very limited and inconsistent, with few studies demonstrating benefits for grey matter[213] and resting-state

functional connectivity.[164,213] Of the nine included studies in the systematic review, only two were high-quality RCTs. Further, few studies included an active control group. In addition, vast differences in intervention duration, frequency, and type of training make comparison between studies challenging and is it difficult to draw any methodologically sound conclusions regarding the effects of CCT on brain structure and function. This led to the conclusion that more high-quality studies are needed to shed light to this area of research.

Second research aim: To examine the effects of an eight-week RCT of CCT, alone and when immediately preceded by a 15-minute brisk walk, on verbal memory and learning and executive functions, compared with an active control in older adults aged 65 – 85 years old.

In order to examine this second aim of the thesis, a study protocol for an 8-week RCT of CCT was developed and published (chapter 3). This protocol aimed to address important methodological aspects that were previously overlooked in some of the studies in the literature, such as a high-quality design (i.e., RCT) and the inclusion of an active control. A RCT, if designed and executed properly, is considered the most robust and reliable method for examining the efficacy of healthcare interventions.[317] Key aspects of RCT design include randomization, blinding, sample size, and adherence. Randomization assures that all participants enrolled have an equal chance of being assigned to either intervention group, and ensures equal distribution of participant characteristics between the intervention groups. This prevents bias from the investigators to impact the results of the study, also referred to as selection bias.[318,319] Adequate sample size is important to ensure the study is powered to detect an effect and avoid chances of type-II errors.[320-322] Another potential cause of bias in the outcomes could result from the absence of blinding, both from an

investigator and participant perspective. The gold standard in RCTs is double blinding, where both investigator and participant are unaware of group allocation. However, practically this is more difficult, and a more feasible approach is a single blinded trial, where only the participant is unaware of group allocation. In addition to these key concepts of RCT design, adherence to the trial protocol to avoid attrition is pivotal. All these key aspects were carefully taken into consideration when designing the study protocol in chapter 3.

Results of this 8-week RCT showed that in community-dwelling adults aged 65-85, a CCT program improved EF – specifically response inhibition compared with the active control group. These findings are consistent with recent systematic reviews and meta-analyses that show CCT benefits EF.[149-152] Furthermore, participants who completed a 15-min brisk walk immediately prior to the CCT session demonstrated additional benefits for set-shifting. A novel aspect of this study was the inclusion of a 15-minute brisk walk immediately prior to the CCT session. To my knowledge, no study has previously examined the potential effects of a single bout of moderate exercise immediately prior to CCT on cognitive function in community-dwelling older adults. Potentially, the additional benefits on EF found in the current study were induced through arousal. Animal models have shown that learning a difficult task was optimal after moderate levels of arousal.[201] However, much is unknown about arousal-induced effects on cognition, specifically how long these potential effects could last after exercise cessation.[202] Alternatively, combining different mechanisms of plasticity (i.e., aerobic exercise and CCT-induced plasticity) could result into these increased cognitive gains.

In contrast with previous findings, the current study did not find benefits for verbal memory and learning, the primary outcome of the study. Based on existing literature[288] at the time of study design, verbal memory and learning was chosen as the primary outcome; CCT studies showing benefits for EF were limited at the time of study planning and design. The CCT platform used in this RCT consisted of 38 games on the iPad, each targeting one of six domains – focus, speed, memory, visual, problem solving, and language. However, the CCT program did not have a primary focus on memory, and only a small portion of the games targeted this domain. Thus, the total training time for memory was most likely considerably less compared with studies included in the systematic review.[149] Moreover, the memory games included in the CCT program were more of a visuo-spatial nature compared with verbal nature of the primary outcome measure. Both these aspects could have contributed to the lack of memory benefits in the current study. This in turn could also indicate the lack of transfer of CCT to untrained domains, a topic that is commonly discussed in this field of literature.[156,323] This potential limitation of CCT will be addressed in more detail in section 6.3.2.

Third and fourth research aims: To examine whether changes in executive functions are associated with changes in inter-network resting-state functional connectivity. And furthermore, to examine whether CCT benefits changes in inter-network functional connectivity compared with an active control.

Chapter 5 of the current thesis addressed the last two research aims, and demonstrated that improvements in EF over the course of the 8-week RCT were associated with increased anti-correlation between the DMN and the FPN at rest. This increased anti-correlation between

networks could reflect a better segregation of task-negative (i.e., DMN) and task-positive (i.e., FPN) networks. Additionally, chapter 5 demonstrated that those assigned to the purely CCT group improved the anti-correlation between regions of the DMN and the FPN compared with the control group; specifically between the left dorsolateral prefrontal cortex (LdlPFC) and both the right medial temporal gyrus (RMTG) and the left medial temporal gyrus (LMTG). These improvements in functional connectivity might support the observed changes in EF described in chapter 4.

Integrating findings of chapter 4 and 5 suggests that CCT promotes EF in community-dwelling older adults, specifically response inhibition and set-shifting. This improvement may be linked to improved functional connectivity between task-positive and task-negative networks involved in this domain of cognition. Previous studies have observed a successful segregation of task-positive and task-negative networks in a younger population, and linked this to better performance on tasks of EF, specifically response inhibition as measured with the Flanker task.[305] With age, the functional segregation between these networks tends to decrease, resulting in less anti-correlation between the networks and poorer performance on cognitive tasks.[113,116,304] The FPN is a network involved in executive functions, and when this network is strongly correlated with an off-task network such as the DMN, the networks could disturb each other's functions, resulting in impeded cognitive performance. Chapters 4 and 5 demonstrated that CCT, compared with a control group, showed increased anti-correlation between regions of the DMN and FPN, which in turn reflected in improved response inhibition. The group that had combined exercise with CCT did not show significant regional increases in anti-correlation between the DMN and FPN compared with the control group. In comparison with the control group, they did demonstrate less correlation between the regions, however this was not significant. Potentially, both CCT groups in the current study

elicited neural changes differently, as literature shows that exercise and cognitive training may partially evoke neural changes through different pathways.[122] Compared with the control group, both FBT and Ex-FBT groups received CCT, however in different quantities. The FBT group received a total of 48 hours of CCT, whereas the Ex-FBT group received 75% (i.e., 36 hours) of the CCT as they engaged in 15 minutes of aerobic exercise prior to CCT in each session. These differences in dosage could contribute to the lack of changes in regional inter-network functional connectivity in the combined group. In addition to the smaller dosage of CCT, the volume and intensity of the included exercise might also be important to note. Compared with studies investigating the effects of aerobic exercise on cognition,[184] the short duration and dosage of the included aerobic exercise (i.e., 12 hours over 8 weeks) in the Ex-FBT group might not be sufficient to evoke aerobic-exercise induced plasticity. A recent systematic review[324] examined the effects of an acute bout of exercise on cognition, and showed that a single bout of acute exercise could benefit cognitive performance in healthy older adults. However, due to high variability in research protocols, including exercise intensity (i.e., sedentary (<40% of HRmax) - high (>90% HRmax)), conclusions should be viewed with prudence. Potentially, the light to moderate intensity of the single bout of exercise in the current thesis could have contributed to the absence of benefits in functional connectivity compared with the active control group. Alternatively, potential exercise-induced changes in neuroplasticity responsible for broadened benefits on EF. such as volumetric changes, were present but not captured with rs-fMRI. Overall, in the current thesis neural changes evoked by CCT (e.g., dendritic lengthening and dedifferentiation) might be observed faster with more exposure, and measured more directly with rs-fMRI as this neuroimaging technique is able to measure the strength of connections between different brain regions that show activity at the same time.

6.3 Strengths and Limitations

6.3.1 Strengths

The current thesis aimed to design a high-quality study to investigate the effects of an 8-week intervention of CCT. In addition to focussing on all key criteria necessary to provide methodologically sound evidence, adherence across all three intervention groups was considered high at approximately 93%. In addition, by incorporating both behavioural measurements as well as measures of neuroimaging, the current study was able to provide comprehensive evidence regarding the efficacy of CCT.

6.3.2 General Limitations

Limitations for each research study were provided in its corresponding chapter. Here, I aim to appoint some of the overarching limitations of the current dissertation.

Firstly, a common criticism over the past years in the field of CCT research was the absence of measures included that focus on transfer of training, in particular far transfer or environmental transfer. Harvey and colleagues[156] defined different levels of evidence of CCT, namely: level 1) improved performance on training tasks (i.e., training engagement); level 2) improved cognitive performance on tasks that are not trained (i.e., near transfer); level 3) improved performance on functional tasks that are cognitively demanding (i.e., far transfer); and level 4) improved everyday functioning (i.e., environmental transfer). The current study focused on measures of near transfer

(i.e., level 2 evidence from above-mentioned criteria), and did not include measures of far or environmental transfer.

Generally, the duration of CCT inteventions is, compared with for example exercise interventions, relatively short. CCT training can get fairly repetitive with only a limited number of tasks to be executed in a single session. Therefore studies of CCT with longer durations are less feasible as increased duration could strongly impact training adherence, which in turn could negatively effect the quality of the study findings. However, with longer duration of CCT interventions, findings for both behavioural performance as well as neuroimaging could potentially be more robust.

Finally, in chapter 5 we aimed to examine the underlying neural mechanisms of CCT by including measures of rs-fMRI. However, due to the high costs of neuroimaging measures such as MRI, only a subset of the complete sample completed scans at baseline and trial completion.

6.3.3 Limitations in Rs-fMRI

Neuroimaging measures allow us to look at brain function and structure in vivo. However, there is much variability in design and analysis of neuroimaging data. At different stages of data analysis, different parameters and methods can be used which could make replication of findings difficult. An important and inescapable issue of fMRI is head motion, with even small movements impacting the quality of the data. A common strategy used, is to extract motion parameters, such as cerebrospinal fluid (CSF) and white matter, by adding these parameters as confound variables in the model in order to regress them out of the signal. In addition to the CSF and white matter parameters, often 6 degrees of motion (i.e., translational and rotational motion) are included as

explanatory variables and are regressed out of the signal. Current literature suggests that the combination of "real-time" motion correction (i.e., sensors in scanner detecting participant motion) and retrospective methods leads to better motion correction, which in turn would lead to better sensitivity of the rs-fMRI signal.[325] However, much debate remains to find the best method to account for head motion. In the meantime, it is recommended that researchers report the procedures for motion correction in detail in order to improve comparison between studies.

In addition, seed-based analysis, as included in chapter 5 of the current dissertation, is a model-dependent method in which linear correlations between voxels from the entire brain and an a-priori selected region are sought. The a-priori selection makes it an appropriate and straightforward method to examine specific region-dependent aims; however, this specificity also his is limitations. Even though there might be valid reasons for focusing on these a priori determined regions, it is difficult to examine whole-brain functional connectivity and therefore the analysis might not pick up on other potential changes in functional connectivity. In contrast, independent component analysis is a more data-driven process and examines many voxel-voxel correlations of specific networks in the brain.

6.4 Future Directions

As the field of CCT is a very young and fast expanding field, this section of the thesis aims to provide some suggestions for future research examining the effects of CCT on cognitive function as well as its underlying neural mechanisms.

6.4.1 Lifestyle Strategy to Promote Healthy Cognitive Aging: Cognitive Training

Research investigating lifestyle strategies to prevent cognitive decline and promote healthy cognitive aging has exhibited increased interest in examining the efficacy of CCT. Despite much controversy in the field, findings from studies investigating its efficacy have been promising. Findings from chapters 3 and 4 of this dissertation confirmed and extended on evidence from this field of research by demonstrating benefits of CCT on EF. Thus, in accordance with current literature, findings from this research suggests that CCT might be a promising lifestyle strategy to promote healthy cognitive aging in addition to strategies such as exercise. The novel aspect of this thesis, a 15-minute brisk walk immediately preceding CCT, suggests that priming the brain with exercise might lead to broadened benefits. However, the current study was not able to establish the underlying mechanisms of these extended benefits on EF. Future studies with larger samples, increased intervention duration, and inclusion of blood biomarkers (e.g., BDNF, IGF-1, and VEGF) could help provide a better understanding of the underlying mechanisms by which CCT elicits changes in EF. In addition, to address current concerns about the lack of transfer of training in interventions of CCT, it is recommended that future studies include outcome measures focused on far transfer or environmental transfer. Finally, a recommendation for future CCT-intervention studies would be to include the analysis of intraindividual variability (IIV); where IVV describes the variability of an individual's performance across multiple trials (e.g., baseline and final). In older adults, this IVV has been shown to increase with age,[326] impacting performance on cognition and everyday functioning.[327] Moreover, reaction time IIV in older adults has been found predictive of long-term changes in cognition.[328] Thus, potentially those who benefit from CCT, demonstrate improved IIV.

6.4.2 Underlying Mechanisms of Computerized Cognitive Training

Chapter 2 of the current dissertation concluded that there is a lack of consistent evidence regarding the neural mechanisms by which CCT might affect cognitive function. Chapter 5, utilising rs-fMRI, suggested that CCT might improve functional connectivity (i.e., increased anti-correlation) between task-positive and task-negative neural networks after 8-weeks of CCT. As findings from chapter 5 were secondary and exploratory, it is encouraged that future studies keep examining this link of improved inter-network connectivity of networks, as maintenance or increased anti-correlation between these networks could be a potential underlying mechanism of cognitive improvement. Due to the exploratory nature of the study in chapter 5, neural networks were limited to include its key ROIs. Studies with larger samples could investigate additional seeds within networks for a more robust signal, and include networks that could help explore the facet of far transfer. Lastly, as this field of research is in its infancy, it is critical that future studies associate findings of rs-fMRI with behavioural data to best advance the knowledge in the field.

6.5 Final Conclusion

This dissertation has provided an overview of the current concepts of cognitive function, including the impact of aging on its performance. Evidence from the four research chapters suggests that CCT in community-dwelling older adults is a potential strategy to maintain or improve cognitive function, specifically executive functions. Lifestyle interventions as short as 8-weeks of CCT are able to demonstrate changes in the functional reorganization of the brain. These findings expand the relatively young but flourishing field of CCT research and help advance treatment strategies to promote healthy cognitive aging.

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Appendices

Appendix A: Study Protocol Fit Brains Training (FBT)

For the cognitive training (i.e. Fit Brains Training) program, the participants will perform a 60-minute cognitive training session for 6 days per week. Three (3) of those six training sessions will be performed at the Djavad Mowafaghian Center for Brain Health (CBH) at the University of British Columbia or at the Centre for Hip Health and Mobility (CHHM) at Vancouver General Hospital. The remaining three (3) sessions of 45-minutes of Fit Brains Training will be performed at home at approximately the same time of day.

The hourly session at CBH/CHHM consists of:

- 45-minutes of Fit Brains Training. During the 45-minute training sessions, the participant will play a sequence of Fit Brains games. The order of the game is individualized and based on individual performance (2 games in weakest area and 2/3 games randomized from remaining games).
- 10 minutes of games/puzzles for warm up (start class + end class)
- Physical/stretch break in the middle of class (~5 min)

Week 1

- **Monday:** Welcome/Introduction and start Fit Brains Training
    - Location: CBH/ CHHM
    - Duration: 60 minutes
        - 25 minutes: Welcome and introduction into program
            - Setting up iPads & Instructions
            - Explaining Fit Brains Application
            - Going through binder for homework
        - 10 minutes: Start-up Fit Brains together
        - 25 minutes: Fit Brains Training

- **Wednesday**: Fit Brains Training
    - Location: CBH/ CHHM
    - Duration: 60 minutes
        - 5 minutes: "Starts with the letter…" **Food** (3min)
        - 25 minutes: Fit Brains Training
        - 5 minutes: physical break
        - 20 minutes: Fit Brains Training
        - 5 minutes: "Starts with the letter…" **Cities** (3 min)

- **Friday**: Fit Brains Training
    - Location: CBH/ CHHM
    - Duration: 60 minutes
        - 5 minutes: Number Challenge
        - 25 minutes: Fit Brains Training
        - 5 minutes: Physical Break
        - 20 minutes: Fit Brains Training
        - 5 minutes: Number challenge (recall number: write & check)

- **Tuesday + Thursday + Sat/Sun**: Homework - Fit Brains Training
    - Location: at home
    - Duration: 45 minutes each day
        - Record on homework diary

Week 2

- **Monday:** Fit Brains Training – BC FAMILY DAY
    - Location: CBH / CHHM
    - Duration: 60 minutes
        - 10 minutes: word puzzle (Side Effects)
        - 20 minutes: Fit Brains Training
        - 10 minutes: Break and Draw (Starbucks $10)
        - 20 minutes: Fit Brains Training

- **Wednesday**: Fit Brains Training
    - Location: CBH/ CHHM
    - Duration: 60 minutes
        - 15 minutes: Neuroplasticity Talk
        - 25 minutes: Fit Brains Training
        - 5 minutes: Physical Break
        - 20 minutes: Fit Brains Training

- **Friday**: Fit Brains Training
    - Location: CBH / CHHM
    - Duration: 60 minutes
        - 5-10 minutes: immediate recall with words
        - 25 minutes: Fit Brains Training
        - 5 minutes: Physical Break
        - 20 minutes: Fit Brains Training

- **Tuesday + Thursday + Sat/Sun**: Homework - Fit Brains Training
    - Location: at home
    - Duration: 45 minutes each day
        - Record on homework diary

Week 3

- **Monday:** Fit Brains Training
  - Location: CBH / CHHM
  - Duration: 60 minutes
    - 5 minutes: Triangle Game
    - 25 minutes: Fit Brains Training
    - 5 minutes: Physical Break
    - 20 minutes: Fit Brains Training
    - 5 minutes: Feedback from last week:
      - ✓ Training minutes Week 1 + 2

- **Wednesday**: Fit Brains Training
  - Location: CBH / CHHM
  - Duration: 60 minutes
    - 5 minutes: word card: APOLOGY
    - 25 minutes: Fit Brains Training
    - 5 minutes: Physical Break
    - 20 minutes: Fit Brains Training
    - 5 minutes: game (counting numbers worksheet)

- **Friday**: Fit Brains Training
  - Location: CBH / CHHM
  - Duration: 60 minutes
    - 10 minutes: "Where do words go" Morse code worksheet
    - 25 minutes: Fit Brains Training
    - 5 minutes: Physical Break
    - 20 minute: Fit Brains Training

- **Tuesday + Thursday + Sat/Sun**: Homework - Fit Brains Training
  - Location: at home
  - Duration: 45 minutes each day
    - Record on homework diary

Week 4

- **Monday:** Fit Brains Training
    - Location: CBH / CHHM
    - Duration: 60 minutes
        - 5 minutes: word card BOB DYLAN
        - 25 minutes: Fit Brains Training
        - 5 minutes: Physical Break
        - 20 minutes: Fit Brains Training
        - 5 minutes: game (word teaser?)

- **Wednesday**: Fit Brains Training
    - Location: CBH / CHHM
    - Duration: 60 minutes
        - 5 minutes: game (matchsticks worksheet)
        - 25 minutes: Fit Brains Training
        - 5 minutes: Physical Break
        - 20 minutes: Fit Brains Training
        - 5 minutes: game (word teaser?)

- **Friday**: Fit Brains Training
    - Location: CBH / CHHM
    - Duration: 60 minutes
        - 5 minutes: Draw $10 Starbuck gift card
        - 25 minutes: Fir Brains Training
        - 5 minutes: Physical Break
        - 45 minutes: Fit Brains Training
        - 5 minutes: word teaser?

- **Tuesday + Thursday + Sat/Sun**: Homework - Fit Brains Training
    - Location: at home
    - Duration: 45 minutes each day
        - Record on homework diary

Week 5

- **Monday:** Fit Brains Training
  - Location: CBH / CHHM
  - Duration: 60 minutes
    - 5 minutes: word card PRELOAD
    - 25 minutes: Fit Brains Training
    - 5 minutes: Physical Break
    - 20 minutes: Fit Brains Training
    - 5 minutes: game/ Feedback from last week:
      - ✓ Training minutes week 3 + 4

- **Wednesday**: Fit Brains Training
  - Location: CBH / CHHM
  - Duration: 60 minutes
    - 5 minutes: game (word scramble – WINTER?)
    - 25 minutes: Fit Brains Training
    - 5 minutes: Physical Break
    - 20 minutes: Fit Brains Training

- **Friday**: Fit Brains Training
  - Location: CBH / CHHM
  - Duration: 60 minutes
    - 5 minutes: word card – BIG APPLE
    - 25 minutes: Fit Brains Training
    - 5 minutes: Physical Break
    - 20 minutes: Fit Brains Training
    - 5 minutes: game (Word List)

- **Tuesday + Thursday + Sat/Sun**: Homework - Fit Brains Training
  - Location: at home
  - Duration: 45 minutes each day
    - Record on homework diary

Week 6

- **Monday:** Fit Brains Training
    - Location: CBH / CHHM
    - Duration: 60 minutes
        - 5 minutes: word list – memory (7 words)
        - 25 minutes: Fit Brains Training
        - 5 minutes: Physical Break
        - 20 minutes: Fit Brains Training
        - 5 minutes: Recall words from start class

- **Wednesday**: Fit Brains Training
    - Location: CBH / CHHM
    - Duration: 60 minutes
        - 5 minutes: word card – PARACHUTE & Phlegm
        - 25 minutes: Fit Brains Training
        - 5 minutes: Physical Break
        - 20 minutes: Fit Brains Training
        - 5 minutes: game (portrait describing in partners)

- **Friday**: Fit Brains Training
    - Location: CBH / CHHM
    - Duration: 60 minutes
        - 5 minutes: game (mental rotation)
        - 25 minutes: Fit Brains Training
        - 5 minutes: Physical Break
        - 20 minutes: Fit Brains Training
        - 5 minutes: game (visual rotation)

- **Tuesday + Thursday + Sat/Sun**: Homework - Fit Brains Training
    - Location: at home
    - Duration: 45 minutes each day
        - Record on homework diary

Week 7

- **Monday:** Fit Brains Training
  - Location: CBH / CHHM
  - Duration: 60 minutes
    - 5 minutes: word card – POLITICS
    - 25 minutes: Fit Brains Training
    - 5 minutes: Physical Break
    - 20 minutes: Fit Brains Training
    - 5 minutes: game (Word Scramble)
    - Feedback from last week:
      - ✓ Training minutes week 5 + 6

- **Wednesday**: Fit Brains Training
  - Location: CBH / CHHM
  - Duration: 60 minutes
    - 5 minutes: Boggle worksheet
    - 25 minutes: Fit Brains Training
    - 5 minutes: Physical Break
    - 20 minutes: Fit Brains Training
    - 5 minutes: game (linking words worksheet)

- **Friday**: Fit Brains Training
  - Location: CBH / CHHM
  - Duration: 60 minutes
    - 5 minutes: Brain Teaser Sheet (he Σ art = broken heart)
    - 25 minutes: Fit Brains Training
    - 5 minutes: Physical Break
    - 20 minutes: Fit Brains Training
    - 5 minutes: game (top off the pyramid)

- **Tuesday + Thursday + Sat/Sun**: Homework - Fit Brains Training
  - Location: at home
  - Duration: 45 minutes each day
    - Record on homework diary

Week 8

- **Monday:** Fit Brains Training
    - Location: CBH / CHHM
    - Duration: 60 minutes
        - 5 minutes: game (telephone, on paper)
        - 25 minutes: Fit Brains Training
        - 5 minutes: Physical Break
        - 20 minutes: Fit Brains Training

- **Wednesday**: Fit Brains Training
    - Location: CBH / CHHM
    - Duration: 60 minutes
        - 5 minutes: word card – AMONGST (goats/gnats)
        - 25 minutes: Fit Brains Training
        - 5 minutes: Physical Break
        - 20 minutes: Fit Brains Training
        - 5 minutes: game (brain teasers)

- **Friday**: Fit Brains Training
    - Location: CBH
    - Duration: 60 minutes
        - 5 minutes: game (mental rotation)
        - 25 minutes: Fit Brains Training
        - 5 minutes: Physical Break
        - 20 minutes: Fit Brains Training
        - 5 minutes: word card CATS, DESPAIR

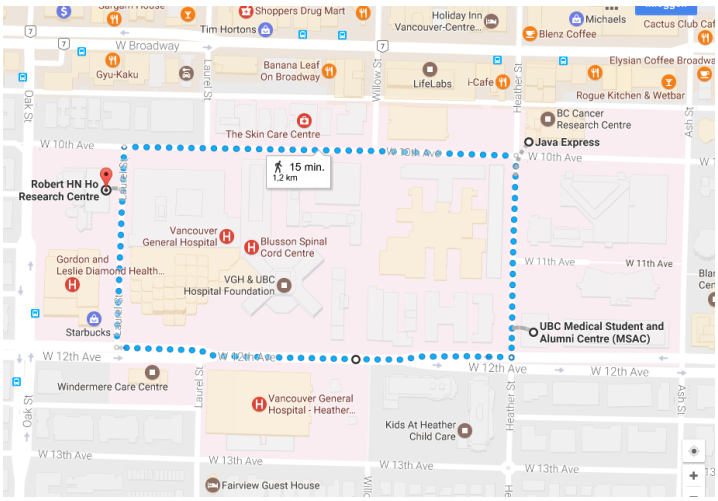
- **Tuesday + Thursday + Sat/Sun**: Homework - Fit Brains Training
    - Location: at home
    - Duration: 45 minutes each day
        - Record on homework diary

Appendix B: Study Protocol Exercise + Fit Brains Training (Ex-FBT)

For the combined training (i.e., aerobic exercise + cognitive training) group the participants will perform training sessions of 1 hour for 6 days per week. Three of the 6 training sessions will be held at the Djavad Mowafaghian Center for Brain Health (CBH) at the University of British Columbia. The remaining three sessions will be performed at home at approximately the same time of the day.

The hourly session will start with a **15-minute** walk to increase the arousal level. The participants will first meet in CHHM (5th floor) and will start the 15-minute walk as a group under the supervision of 4-5 individuals

Route example (Google maps – 15 min):



Once a week participants will wear a heart rate monitor to get an objective measure of their level of intensity. For the other training sessions, participants will be checking their heart rate manually. Additionally, the participants will report Borg-scale measures after each 15-minute walk. Participants will be wearing a pedometer to record the number of steps. After the walk, the participants will perform a 45-minute session of Fit Brain games. The training will be individual and the selection of games will be based on individual performance.

During their 'homework' days they will be wearing their pedometer during the 15-minute walk and record their number of steps, along with their Borg Scale Rating (aim for moderate activity), the time and duration of the walk.

Weeks 1-2: Aim for BORG 11-12
Weeks 3-4: Aim for BORG 12-13
Weeks 4-8: Aim for BORG 13-14

Week 1 and 2

- **Monday**: Welcome/ introduction (Week 1)
    - 15-min walk
        - Borg Scale after walk
        - Number of steps
    - 45-minutes of Fit Brains Training
    - Location: CHHM
    - Duration: 60 minutes
- **Wednesday**:
    - Week:
        - Week 1:
            - 15-min walk
            - Borg Scale after walk
            - Number of steps
        - Week 2:
            - 15-minute talk neuroplasticity
    - 45 minutes of Fit Brains Training
    - Location: CHHM
    - Duration: 60 minutes
- **Friday:**
    - 15-min walk
        - Borg Scale after walk
        - Number of Steps
    - 45 minutes of Fit Brains Training + word mixers
    - Location: CHHM
    - Duration: 60 minutes
- **Tuesday + Thursday + Sat/Sun**: Homework
    - Take a 15-min walk
        - Fill out diary:
            - Rating of Borg Scale
            - Time of the walk
            - Duration of the walk
            - Number of steps (pedometer)
    - 45 min of Fit Brains Training.
    - Location: At home
    - Duration: 1 hour each day.

Weeks 1-2: Aim for BORG 11-12

Low mood in the 45-minute session of Fit Brains: do a quick word teaser

Week 3 and 4

- **Monday**:
  - 15-min walk
    - Borg Scale after walk
    - Number of steps
  - 45-minutes of Fit Brains Training
    - Feedback from last week:
      - Training minutes Week 1 + 2
  - Location: CHHM
  - Duration: 60 minutes
- **Wednesday**:
  - 15-min walk
    - Borg Scale after walk
    - Number of steps
  - 45 minutes of Fit Brains Training
  - Location: CHHM
  - Duration: 60 minutes
- **Friday:**
  - 15-min walk
    - Borg Scale after walk
    - Number of Steps
  - 45 minutes of Fit Brains Training
  - Location: CHHM
  - Duration: 60 minutes
- **Tuesday + Thursday + Sat/Sun**: Homework
  - Take a 15-min walk
    - Fill out diary:
      - Rating of Borg Scale
      - Time of the walk
      - Duration of the walk
      - Number of steps (pedometer)
  - 45 min of Fit Brains Training.
  - Location: At home
  - Duration: 1 hour each day.

Weeks 3-4: Aim for BORG 12-13

Low mood in the 45-minute session of Fit Brains: do a quick word teaser

Week 5 - 8

- **Monday**:
  - 15-min walk (wear heart rate monitor)
    - Borg Scale after walk
    - Number of steps
  - 45-minutes of Fit Brains Training
    - Feedback from last week:
      - Training minutes Week Review 2 weeks
  - Location: CHHM
  - Duration: 60 minutes
- **Wednesday**:
  - 15-min walk (manually check HR)
    - Borg Scale after walk
    - Number of steps
  - 45 minutes of Fit Brains Training
  - Location: CHHM
  - Duration: 60 minutes
- **Friday:**
  - 15-min walk (manually check HR)
    - Borg Scale after walk
    - Number of Steps
  - 45 minutes of Fit Brains Training
  - Location: CHHM
  - Duration: 60 minutes
- **Tuesday + Thursday + Sat/Sun**: Homework
  - Take a 15-min walk (check HR manually)
    - Fill out diary:
      - Rating of Borg Scale
      - Time of the walk
      - Duration of the walk
      - Number of steps (pedometer)
  - 45 min of Fit Brains Training.
  - Location: At home
  - Duration: 1 hour each day.

Weeks 4-8: Aim for BORG 13-14

Low mood in the 45-minute session of Fit Brains: do a quick word teaser

Appendix C: Study Protocol Balanced And Toned (BAT; control)

Participants assigned to the BAT group will perform three 60-minute sessions per week. The three training sessions will be held at CHHM at Vancouver General Hospital. The three training sessions will look as followed: 1) On Monday the participants will attend an hour long educational lecture (sleep, goal setting, mindfulness etc.); 2) On Wednesday the participants will be performing Cognitive training; 3) On Friday the participants will perform an hour long sham exercise (balance and tone exercises, VGH).

Once a week they will attend an educational talk (Monday):
Week 1: Goal Setting
Week 2: Neuroplasticity
Week 3: Mindfulness
Week 4: Sleep
Week 5: Photo Book
Week 6: Photo Book
Week 7: Photo Book
Week 8: Photo Book

Weekly Program:

Week 1

- **Monday: Education/Lecture**
  - Goal Setting (Michelle)
- **Wednesday: Cognitive Training**
  - 10 minutes: 4 Pics 1 Word (iPad)
  - 15 minutes: Boggle (4 rounds of 3 min)
  - 5 minutes: Piano Tiles (iPad)
  - 10 minutes: Mastermind (iPad)
- **Friday: Exercise**
  - Balance Exercises

Week 2

- **Monday: Education/Lecture**
  - Neuroplasticity (Cindy)
- **Wednesday: Cognitive Training**
  - 2.5 minutes: Word List
  - 10 minutes: Three-Way Drawing
  - 15 minutes: Bananagrams
  - 10 minutes: Guess the code
  - 2.5 minutes: Word List
- **Friday: Exercise**
  - Strength

Week 3

- **Monday: Education/Lecture**
  - Mindfulness (Tracy)
- **Wednesday: Cognitive Training**
  - 10 minutes: Draw a difficult pattern (2X)
  - 10 minutes: Word Brain (iPad)
  - 15 minutes: SET
  - 10 minutes: Hangman
- **Friday: Exercise**
  - Balance

Week 4

- **Monday: Education/Lecture**
  Sleep (Glenn)
- **Wednesday: Cognitive Training**
  - 10 minutes: Word Scramble (paper)
  - 15 minutes: Heads Up
  - 10 minutes: Sudoku
  - 10 minutes: Cartoon Caption
  - 5 minutes: Anagram Twist
- **Friday: Exercise**
  - Strength

Week 5

- **Monday: Photo Book intro**
- **Wednesday: Cognitive Training**
  - 10 minutes: Starts with the Letter (food, cities, animals – 3 min each)
  - 10 minutes: Flow Free
  - 10 minutes: Draw a difficult pattern
  - 10 minutes: Pattern Recognition (triangles)
  - 10 minutes: Guess the code
- **Friday: Exercise**
  - Balance

Week 6

- **Monday: Photo Book**
- **Wednesday: Cognitive Training**
    - 2.5 minutes: Word List (cold > cook list)
    - 5 minutes: Three-Way Drawing
        - Building, animals, transport – non-dominant hand
    - 10 minutes: 4 Pics One Word
    - 15 minutes: Bananagrams
    - 10 minutes: Morse Code
    - 2.5 minutes: Word List
- **Friday: Exercise**
    - Strength

Week 7

- **Monday: Education/Lecture**
- **Wednesday: Cognitive Training**
    - 2.5 minutes: Number Challenge (4 digits + 3)
    - 10 minutes: Study the Masters
    - 15 minutes: Boggle
    - 5 minutes: 2 dots
    - 10 minutes: Guess the code (Mastermind)
    - 10 minutes: Say one thing do another
    - 2.5 minutes: Number Challenge
- **Friday: Exercise**
    - Balance

Week 8

- **Monday: Education**
- **Wednesday: Cognitive Training**
    - 10 minutes: word cards: PARACHUTE, word → book
    - 10 minutes: Jeopardy
    - 20 minutes: SET
    - 10 minutes: Gesture Building
    - 10 minutes: Flow Free
- **Friday: Exercise**
    - Strength

Appendix D: Executive Functions: Analysis Stratified by MCI Status

To examine whether CCT-induced benefits on executive function could vary by MCI status, I ran additional analysis stratifying EF outcomes based on MCI status (i.e., score of <26 on the Montreal Cognitive Assessment). Analaysis of covariance (ANCOVA) evaluated treatment effects on EF, stratified by MCI status. Change in EF (post-test minus pre-test) was regressed on baseline outcome scores, and baseline age. One outliner for Stroop 3 – 2 performance (Cook's d > 0.5), and one outlier for Trails B – A (Cook's d > 1.0) were removed from the relevant ANCOVA model.

Table D.1 Estimated Mean Change for Executive Functions by MCI Status

		Adjusted Between-Group Contrast (95% CI)	
Outcome	Sample Size	FBT vs. BAT	Ex-FBT vs. BAT
No MCI			
Stroop 3 – 2	61	-7.86 (-14.27, -1.44)*	-10.52 (-17.31, -3.74)**
Flanker	61	1.35 (-4.68, 7.38)	5.56 (-1.18, 12.30)
Trails B – A	61	-6.14 (-18.91, 6.63)	-4.58 (-18.09, 8.94)
DCCS	61	8.05 (0.30, 15.80)*	9.98 (1.85, 18.10)*
MCI			
Stroop 3 – 2	55[1]	-15.49 (-26.25, -4.74)**	-5.95 (-15.87, 3.98)
Flanker	56	5.62 (-0.49, 11.73)	7.37 (1.66, 13.08)*
Trails B – A	55[1]	-16.03 (-39.42, 7.37)	-24.41 (-46.02, -2.80)*
DCCS	56	0.85 (-8.52, 10.22)	3.47 (-5.19, 12.14)

* $p < .05$; ** $p < .01$

[1] Outlier (Cook's d > 0.5)

DCCS = Dimensional Change Card Sorting Test

Results are reported in Table D.1, and show that those assigned to FBT and Ex-FBT without MCI significantly improved performance on response inhibition (i.e., Stroop 3 – 2), and set-shifting (i.e., DCCS) compared with BAT ($p < .05$, $p < .01$, respectively). In contrast, those with MCI in the FBT group significantly improved performance on response inhinition (i.e., Stroop 3 – 2) compared with BAT ($p < .01$). In addition, those with MCI in the Ex-FBT group significantly improved performance on response inhibition (i.e., Flanker) and set-shifting (i.e., Trails B – A) compared with BAT ($p < .05$, $p < .05$, respectively).

Appendix E: Executive Functions: Analysis Stratified by Sex

To examine whether CCT-induced benefits on executive function could vary by sex, I ran additional analysis stratifying EF outcomes based on sex. Analaysis of covariance (ANCOVA) evaluated treatment effects on EF, stratified by sex. Change in EF (post-test minus pre-test) was regressed on baseline outcome scores, baseline MoCA, and baseline age. One outliner for Stroop 3 – 2 performance (Cook's d > 0.5), and one outlier for Trails B – A (Cook's d > 1.0) were removed from the relevant ANCOVA model.

Table E.1 Estimated Mean Change for Executive Functions by MCI Status

		Adjusted Between-Group Contrast (95% CI)	
Outcome	Sample Size	FBT vs. BAT	Ex-FBT vs. BAT
Male			
Stroop 3 – 2	45[1]	-6.95 (-18.35, 4.45)	-2.35 (-12.73, 8.04)
Flanker	46	5.18 (-1.70, 12.06)	12.13 (5.59, 18.66)**
Trails B – A	46	-9.79 (-28.57, 8.98)	-9.09 (-26.03, 7.84)
DCCS	46	8.39 (0.09, 16.68)*	17.39 (9.56, 25.22)***
Female			
Stroop 3 – 2	71	-13.59 (-20.64, -6.54)***	-12.13 (-19.56, -4.71)**
Flanker	71	1.90 (-3.29, 7.09)	2.18 (-3.55, 7.91)
Trails B – A	70[1]	-9.13 (-27.47, 9.22)	-16.48 (-35.66, 2.70)
DCCS	71	-2.36 (-9.81, 5.09)	-3.03 (-11.04, 4.98)

* $p < .05$; ** $p < .01$; *** $p < .001$

[1] Outlier (Cook's d > 0.5)

DCCS = Dimensional Change Card Sorting Test

Results are reported in Table E.1, and show that males assigned to FBT and Ex-FBT significantly improved performance on set-shifting (i.e., DCCS) compared with BAT ($p < .05$, $p < .001$, respectively). Additionally, males in the Ex-FBT group significantly improved response inhibition performance (i.e., Flanker) compared with BAT ($p < .01$). In contrast, females assigned to FBT and Ex-FBT only improved on response inhibition (i.e., Stroop 3 – 2) compared with BAT ($p < .001$, $p < .01$, respectively).