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Describing functional brain connectivity's role in the relationship of multimodal interventions to improve cognitive and physical function in vulnerable (frailty & mild cognitive impairment) older adults.

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ABSTRACT

Aging is associated with declining cognitive and physical function. The decline accelerates in older adults diagnosed with mild cognitive impairment (MCI), a pre-dementia state, and frailty, a state of decreased physiological reserve. Previous work shows that frailty modifies the relationship between dementia pathology and clinical symptoms. Functional brain network connectivity (FBNC) refers to brain areas that are anatomically separate but temporally related in their neural signaling; it is believed to enable the completion of complex cognitive and physical functions. FBNC is considered a sensitive biomarker for monitoring the progression of dementia syndromes and investigating the efficacy of interventional strategies. Therefore, this dissertation investigated if FBNC represents an underlying neurophysiological change responsible for alterations in the cognitive and physical function of vulnerable older adults after partaking in a lifestyle intervention. Furthermore, how improvements or lack thereof may reflect a relationship between frailty, sex, and dementia.

First, I conducted a systematic review on the effect of physical exercise with and without other interventional strategies on FBNC in older adults with and without cognitive impairment (Chapter 2). Included studies (10/12) demonstrated increased within-network FBNC. Conversely, control groups showed no or alternative changes in FBNC. Only one of the included studies showed a correlation between FBNC and cognitive outcomes, and they did not control for multiple comparisons.

Next, and given its inclusion in Chapter 4, I conducted an open-label feasibility study in older adults to test the feasibility and efficacy of high-dose vitamin D independently. The study sample experienced no adverse events but only participants with the greatest deficits (i.e., frail and insufficient ($\leq$ 75nmol/L) vitamin D serum levels) made significant improvements, and only in measures of physical performance.

Chapter 4's randomized controlled trial examined the impact of aerobic and resistance training separately and synergistically with cognitive training and/or high-dose vitamin D supplementation (multimodal intervention) on FBNC. I found that physical exercise increased connectivity between the Hippocampus and Angular Gyrus, representing regions within the Default Mode-Network. Adding cognitive training with or without high-dose vitamin D supplementation made some additional changes to exercise-induced FBNC alterations. Similar to our systematic review, FBNC showed no correlations with behavioral outcomes after controlling for multiple comparisons.

Chapter 5 was motivated by a desire to determine if frailty alters FBNC. I found increasing (worse) frailty is associated with what is believed to be increasing between-network connectivity. Furthermore, the relationship between frailty and FBNC differed by sex.

This dissertation provided support for FBNC as a potential biomarker to monitoring neural substrates vulnerable populations and their response to interventions. Specifically, lifestyle interventions, inclusive of exercise, are efficacious in increasing within-network FBNC, which is thought to reflect "better" brain function. Frailty status, sex, and baseline vitamin D levels appear

to confound or interact with the effect of exercise interventions on FBNC. As such, researchers should explore these in future studies.

Keywords

Cognitive Training, Cross-sectional, Frailty, Functional Magnetic Resonance Imaging, Mild Cognitive Impairment, Intervention, Physical Exercise, Randomized Controlled Trial, Systematic Review, Vitamin D

LAY SUMMARY

Decline in cognition and physical function (i.e., memory and muscle strength) is a normal part of aging. The decline is faster in vulnerable older adults diagnosed with mild cognitive impairment and/or frailty. Mild cognitive impairment is considered a pre-dementia state, and frailty is a decline in overall health. Older adults diagnosed with cognitive impairment are more likely to be frail and vice versa. Brain connectivity (i.e., areas of the brain that activate or "turn on" together) may be compromised in both groups. It may also help explain important behavioural changes (i.e., memory improvement) following physical exercise (i.e., jogging).

Chapter 2 showed that brain connectivity improves following physical exercise, but changes have very little impact on cognitive or physical function. Chapter 3 showed that high-dose vitamin D supplementation improved physical but not cognitive function, and only in those that were the most vulnerable (i.e., frail and/or low vitamin D levels). Chapter 3 also provided support for the inclusion of vitamin D in Chapter 4, where I explored the impact of various lifestyle interventions on brain connectivity. Physical exercise improved brain connectivity and adding cognitive training and vitamin D supplementation created some additional changes. Similar to chapter 2, changes in brain connectivity showed no relationship with changes in cognitive or physical performance. Pre-intervention differences in health status may have affected the results of chapter 2 and 4. So, in Chapter 5, I explored and then showed that frailty status is associated with brain connectivity, and the relationship differs by sex.

My studies revealed that interventions improve brain connectivity, but how these changes impact cognitive or physical function remains unclear. Vitamin D has some benefits on brain

connectivity and improves physical performance. Researchers should consider frailty status, sex and, vitamin D levels when measuring brain connectivity.

CO-AUTHORSHIP STATEMENT

This dissertation contains material from published manuscripts (Chapters 2 and 3). On both manuscripts, Nick W Bray is the first author, and Dr. Timothy J Doherty and Dr. Manuel Montero-Odasso are co-authors. Dr. Robert Bartha, Dr. Lindsay S Nagamatsu, and Dr. Frederico Pieruccini-Faria are co-authors on Chapter 2. All data in Chapter 2 (Systematic review) were collected, analyzed, and interpreted by Nick W Bray. Nick W Bray aided in data collection for Chapters 3 and 4 but was primarily responsible for data analysis and interpretation.

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A calm sea don't make a skilled sailor.

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LIST OF SUPPLEMENTAL MATERIALS

List of Abbreviations

m/sec, meter per second

ADAS, Alzheimer's Disease Assessment Scale

ANOVA, analysis of variance

BOLD, Blood Oxygen Level Dependent

CT, cognitive training

CTc, cognitive training control

FBNC, Functional Brain Network Connectivity

DMN, Default Mode Network

FDR, false discovery rate

fMRI, Functional Magnetic Resonance Imaging

HDR, Hemodynamic Response

iPTH, Intact Parathyroid Hormone

MANGO, Multi-image Analysis Graphical User Interface

MCG, Micrograms

MCI, Mild Cognitive Impairment

MMSE, Mini-Mental State Examination

MoCA, Montreal Cognitive Assessment

PASE, Physical Activity Scale for the Elderly

PC, pure control

PE, physical exercise

PEc, physical exercise control

ROI, region of interest

S-V, seed-to-voxel

SPPB, Short Physical Performance Battery

SPSS, Statistical Package for the Social Sciences

SYNERGIC or SYN, SYNchronizing Exercises, Remedies in GaIt and Cognition

VD, vitamin D

VDc, vitamin D control

CHAPTER 1: LITERATURE REVIEW

1.1 AGING & THE RELATIONSHIP WITH COGNITIVE AND PHYSICAL DECLINE

The average age of the world's population is increasing. The number of older adults (60+ years of age) will increase from 900 million (2015) to ~2 billion by 2050 and, in doing so, create unique economic and societal problems (1). One factor contributing to the rising aging population is increasing life expectancy (1). Unfortunately, longevity is not synonymous with quality of life (2,3), as even "healthy" aging is broadly characterized by a decline in two "geriatric giants" with an intricate relationship (4–13): cognitive and physical function. Importantly, the decline of both functions accelerates in vulnerable older adults with prevalent geriatric syndromes, including mild cognitive impairment (MCI) and frailty.

1.1.1 Mild Cognitive Impairment (MCI)

Cognitive decline is a normal part of aging and is appropriately termed "normal cognitive aging" (14). Declining cognitive function makes it more difficult to remember, pay attention, and/or problem-solve. Individuals living with a dementia syndrome suffer from accelerated declining cognitive function compared to their "normal cognitive aging" counterparts (Figure 1). Dementia is an umbrella term and includes the most well-known, Alzheimer's disease (15,16), as well as Cerebrovascular, Mixed pathology, Lewy body, and Frontotemporal (17).

Alzheimer's disease is ultimately due to neuronal death (18), caused by a combination of genetic (19), lifestyle (20), and environmental (21) factors. There are now several distinct phases before a formal diagnosis of Alzheimer's disease, each of which represents an opportunity to intervene:

- Preclinical: Measurable physiological changes (i.e., beta-amyloid accumulation) and genetic (i.e., apolipoprotein E type 4 allele) factors that have not yet resulted in cognitive decline (22,23), but are associated with greater risk of developing Alzheimer's disease (19);
- Subjective cognitive impairment: Includes frequent confusion and/or memory loss. Individuals often "have trouble remembering how to complete familiar tasks or things they usually know, and not just where they left their keys" (24,25);
- Mild cognitive impairment (MCI): Incorporates the first measurable changes in cognitive function, but it does not impact the ability to complete activities of daily living (24,26,27).

Conceptually, MCI was introduced in 1999 (27). The current criteria for MCI diagnosis, as per the National Institute on Aging-Alzheimer's Association Workgroups (28) is:

- Subjective cognitive impairment
- Objective cognitive impairment in one of the following four cognitive domains: memory, executive function, attention, and language, operationalized using one or more of the following:
    - Montreal Cognitive Assessment (29) scores ranging from 13 to 24/30,
    - Logical Memory below Alzheimer's disease Neuroimaging Initiative cut-offs (< 9 for 16+ years of education; < 5 for 8–15 years of education; < 3 for 0–7 years of education) (30),
    - Consortium to Establish a Registry for Alzheimer's disease word list recall < 6 (31).

- Preserved activities of daily living operationalized as a score > 14/23 on the Lawton-Brody Instrumental Activities Of Daily Living scale (32) and confirmed by clinician's interviews.
- Absence of dementia using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (33) and/or Global Clinical Dementia Rating ≤ 0.5 (34).

MCI can be further sub-divided into distinct sub-domains, including:

- Amnestic single-domain;
- Amnestic multi-domain;
- Non-amnestic single-domain;
- Non-amnestic multi-domain.

Memory is affected in amnestic MCI, whereas non-amnestic includes other cognitive domains. As the name implies, single-domain represents impairment in one cognitive function, whereas multi represents impairment in two or more (35,36). Single domain MCI is more common than multi. The estimated prevalence of MCI in population studies is 10-20% (37). Previously, research showed amnestic to be more prevalent (38), but more recent work suggests higher percentages of non-amnestic (39), particularly in females (40). The classification of MCI has also expanded to include early- and late-stage, based upon the extent of episodic memory impairment (41). Older adults with MCI, particularly late-stage (42), are at a much higher risk for progression to Alzheimer's disease or other dementia than those experiencing "normal cognitive aging" (43–45). Males appear to be at greater risk of developing MCI than females (46). More than half a million Canadians live with dementia, but this estimate increases by 50% when MCI is included (47). Dementia cases will increase absolutely with the rising aging

population, but this may multiply as a long-term consequence of the novel COVID-19 virus (48,49).

1.1.2 Frailty

Using the MeSH Term "frail elderly," PubMed shows that the first article on frailty was published in 1966 (50). There is still disagreement on what exactly constitutes frailty (51), despite clinicians agreeing that they "know frailty when they see it" (52). Generally, frailty is considered a decrease in physiological reserve that places the individual at an increased risk to respond to a stressor (53), such as the novel COVID-19 virus (54).

Today, there is an exhausting list of tools that can directly or indirectly measure frailty (55), but the Frailty Index (FI) (56) and Cardiovascular Health Study - Frailty Phenotype (57) are two of the most commonly utilized. The FI provides a score based upon the number of deficits accumulated. The FI is considered a health state measure that reflects vulnerability to adverse health outcomes and is calculated as:

$$FI = \frac{number\ of\ health\ deficits\ present}{number\ of\ health\ deficits\ measured}$$

The original FI encompassed 92 items from a variety of domains, and as a result, offered an extensive but time-consuming measure of frailty. Research has since demonstrated that as few as 30 items can obtain an accurate FI (58), and an even further abbreviated version permits classification by simply observing a participant (59). The Frailty Phenotype uses five indicators: 1) unexplained weight loss; 2) self-reported exhaustion; 3) physical inactivity; 4) weak grip strength; and 5) reduced gait speed. Individuals with 0 indicators are non-frail, whereas those

with 1-2 or >3 are pre-frail and frail, respectively. There are several variations of the original Frailty Phenotype (60), but researchers have advised that such modifications make it difficult to compare studies and obtain a comprehensive view of frailty prevalence (61,62).

Similar to MCI, the field has evolved to include sub-domains to aid in frailty classification. Physical frailty centers on observable physical characteristics of frailty and is the focus of the Frailty Phenotype (57). Conversely, the FI is unidimensional and, as a result, may show greater predictive value in community settings and for adverse outcomes (63). In 2013, researchers proposed cognitive frailty as a separate entity (64) in response to research showing an association between physical frailty and brain health, as well as a desire to include a cognitive element within the frailty domain (65–67). Other domains of frailty evolve around emotional and social status and further support the multidimensionality of frailty (68).

Frailty overlaps with other aging diseases and syndromes, such as sarcopenia (69,70) and/or MCI, but it is a distinct entity (71,72) with its own medical diagnostic code (73). Substantial differences exist between scales (74), but generally, higher (worse) frailty predicts adverse outcomes, such as surgical recovery time (75), disability, the need for long-term care, and even mortality (71,72). The risk of becoming frail rises with increasing age (53) (Figure 2). Females become frail earlier yet, live longer than their male counterparts (76). The source of the sex-specific experience of frailty is unknown, but it is an active area of research (77); it has been coined the male-female health survival paradox (78). The prevalence of frailty within community-dwelling older adults is ~10% (79), but this undoubtedly increases within institutional settings.

1.2 The Brain & Functional Magnetic Resonance Imaging (fMRI)

The brain weighs ~2% of our total body weight but utilizes ~20% of the oxygen we consume (80). The brain contains roughly 86 billion neurons with many more neuroglia and synapses to support and connect (81–84). Neurons vary in size and complexity, but they represent the basic processing units of the nervous system (85). Our brain makes us uniquely human, and its evolution has allowed us to move beyond our primitive ancestors (86,87). However, the brain still largely represents a mystery as essential questions remain to be solved (88,89).

The basis of magnetic resonance imaging was discovered in the late 1940s (90,91), but it was not until the 1970s that researchers imaged the first biological tissue (92). Furthermore, it was another ~20 years before researchers uncovered how blood oxygenation could influence MR images. Subsequently, functional magnetic resonance imaging (fMRI) was born and offered a new avenue for exploring brain health (93,94). The field's growth is reflected in PubMed indexing ~5000 manuscripts per year since 2014 with a title or abstract containing the keyword "fMRI" or "functional magnetic resonance imaging."

fMRI represents an intersection between physics, engineering, computer science, and neuroanatomy, in addition to the knowledge required to understand the clinical populations and interventional methods under investigation. The complexity of these areas relative to MR signal generation, image formation, and analysis is beyond this dissertation's scope. As such, the following sections focus on only the most critical concepts of fMRI and the brain.

1.2.1 Hemodynamic Response (HDR) & Blood Oxygen Level Dependent (BOLD)

At "Baseline," the human brain consumes the minimal amount of oxygen needed to maintain basic function. When a neuron up-regulates or activates, which may be sporadic or in response to

a specific event (i.e., visual stimulus), there is an "Initial Dip." The initial dip has not been consistently observed (95), but it likely reflects the immediate excess oxygen available and extracted. In response to the initial dip, there is an eventual "Rise" or increase in cerebral blood flow (i.e., functional hyperemia) (96) and thus, volume of oxygenated blood until a "Peak" is reached. Notably, the amount of blood provided far exceeds that required or extracted by the demanding biological tissue. Why exactly there is a mismatch between supply and demand is unclear, but it may reflect a safety margin (97,98) given that the brain can experience severe and permanent damage if not supplied with a relatively constant flow of nutrients (99). Following the peak, there is a return or "Fall" back to baseline, but not before a slight "Undershoot" occurs as the system attempts to re-establish balance (100). The entire process is known as the hemodynamic response (HDR – Figure 3), and in comparison to neural activation, it is quite slow (i.e., milliseconds versus ~12 seconds, depending on the study condition) (101). The neurovascular unit is a complex structure of closely linked cells that plays a crucial role in regulating the HDR (102–104).

fMRI is a "neuroimaging technique that uses standard MR scanners to investigate changes in brain function over time" (105). MRI characterizes tissue by two different relaxation times: T1 (longitudinal) and T2 (transverse). fMRI utilizes T2*-weighted images, which describes the decay of the transverse component of net magnetization due to: 1) accumulated phase differences (like T2); but also 2) the local magnetic field inhomogeneities (i.e., the degree of blood oxygen level dependent (BOLD) contrast via the amount of deoxygenated hemoglobin present) (106). Hemoglobin is a protein within red blood cells responsible for delivering oxygen throughout the human body (107). Oxygenated hemoglobin (i.e., hemoglobin with attached oxygen) is diamagnetic and weakly repels a magnetic field. Conversely, deoxygenated hemoglobin (i.e.,

hemoglobin without oxygen attached) is paramagnetic and is attracted to a magnetic field (108). Therefore, areas of the brain that are temporarily diamagnetic (i.e., relatively more oxygenated) show a "greater" MR signal than paramagnetic regions because the latter creates greater distortion in the nearby magnet (109). Oxygenated hemoglobin increases during the HDR, allowing researchers to indirectly interpret which neurons or areas of the brain are active. In summary, fMRI capitalizes on the mismatch between oxygen supply and demand during the HDR and the magnetic properties of blood (110). As such, it is a surrogate measure of neuronal activity that HDR mediates.

1.2.2 Contrast, Resolution & Alternative Neuroscience Techniques

fMRI's interest and growth can be attributed to several factors, including but not limited to access to scanners, availability of educational material, and decreasing costs. The most significant contributors to fMRI's popularity are likely the contrast it naturally provides and its balance between temporal and spatial resolution (Figure 4).

Unlike Positron Emission Tomography (111), fMRI does not require the injection of radioactive substances to generate images. Instead, it leverages biological tissue's intrinsic properties (i.e., endogenous contrast). As previously discussed, it capitalizes on the difference in magnetism between oxygenated and deoxygenated blood. As a result, fMRI is considered a safe imaging option, especially in the context of research.

Spatial and temporal resolution represents the ability to distinguish changes in a signal or images across space and time (112,113). The spatial resolution of fMRI is dependent on several factors, but one of the most important is voxel size; voxels are small cubes that comprise MR images.

The human brain spans from macroscopic anatomy to microscopic biology. fMRI is between these extremes as it measures on a scale of centimeters to millimeters depending on the organism (114). Typically, fMRI spatial resolution in humans is ~3mm (115), but this can be indirectly enhanced when "registered" to a high-resolution anatomical image and using a scanner with greater Tesla. As such, registration is often one of the many essential preprocessing steps in fMRI analysis (116).

The basic sampling unit of temporal resolution is the repetition time or the time interval between successive excitation pulses (113); stated differently, repetition time represents when the image acquisition procedure restarts at the initial slice or area of the brain at which it began. Similar to spatial, fMRI's temporal resolution is intermediary (i.e., milliseconds to seconds), and in human experiments, it is typically ~2 seconds (110). Improvement in resolution is an active area of research (117).

fMRI represents just one option in a list of techniques that can image or measure the brain. Diffusion Tensor Imaging can assess the white matter tracts of the brain (118). Together, Diffusion Tensor Imaging and fMRI can provide insight into the relationship between anatomical and functional connections. Electroencephalography places small electrodes on the scalp to record neurons' electrical activity (119). Although researchers must make additional efforts to ensure image quality, Electroencephalography and fMRI can be measured simultaneously (120). Ultimately, neuroimaging techniques are complementary as one often helps to ameliorate a shortcoming of another, and so, their simultaneous usage often improves the interpretation of findings.

1.2.3 (Dys)functional Connectivity

fMRI has provided a better understanding of the brain in a variety of demographics, including concussion (121), mental health (122,123), stroke (124), and many more (125–130). Broadly, fMRI experiments exist in two conditions: 1) Task-based (i.e., extrinsic activity) fMRI requires the participant to perform a task while in the scanner, such as pressing a button in response to a stimulus (131,132); and 2) Resting-state (i.e., intrinsic activity) requires the participant to sit inside the scanner (133,134) with eyes open or closed (135), and not think about or do anything in particular. Resting-state fMRI does not require the extra knowledge and work of being paired with a task, and for this reason, it has likely contributed to fMRI research growth.

Previously, research focused predominantly on localizing function (i.e., activation) (136) or assigning specific brain regions to a particular cognitive task. More recently, there is growing interest in functional brain network connectivity (FBNC) or areas of the brain that are anatomically separate but temporally correlated in their BOLD signaling (137) (Figure 5). FBNC is believed to reflect the completion of complex functions and enable information processing across the brain. Despite recently coming under criticism (138), FBNC is calculated by measuring the correlation (139,140), typically via Pearson (141), between BOLD signals from two brain regions; if signals are correlated, then the regions are considered functionally connected. Researchers can acquire FBNC during tasks or resting-state fMRI, but the latter may provide insight into the brain's basic architecture and general health. Networks represent a set of brain regions that consistently show temporal similarities in their BOLD signal across different demographics (139,142). Debatably, the most popular is the Default Mode Network (DMN) (143,144), which activates when engaged in episodic memory or future planning, but some others include Attention (145), Visual (146), and Salience (147).

Our understanding of networks is still evolving due to several factors, including regions belonging to more than one network (148,149), level of consciousness (150–152), emotional state (139), and nomenclature (154). Furthermore, not all network regions are created equal, as some are more critical to neuronal integration (155,156) (i.e., functional hubs hypothesis), or their functional relevance may depend on the "status" of other connected areas (i.e., neural context hypothesis) (157). What is consistent is that the connectivity of networks changes as we age (158,159), and changes accelerate in those with dementia syndromes. Changes in network connectivity are complex; initially, there appears to be a decrease in within- and increase in between-network connectivity (160–166); the latter is believed to reflect an attempt to maintain homeostasis via remodeling before an inevitable decrease (167). Notably, changes in FBNC precede structural changes and the manifestation of clinical symptoms, and as such, represent some of the earliest alterations in those living with or at risk of progressing to a dementia syndrome (Figure 6). Therefore, it represents a biomarker for those at risk of progressing to Alzheimer's disease or another dementia.

1.3 Previous Interventional & Cross-sectional Research Related to Brain Function

Our understanding of brain health is continuously evolving. Pharmacological agents can improve dementia symptoms, and various agents with different targets continued to be investigated (168), but a true cure remains elusive (17). It is becoming increasingly evident that many cases of dementia incorporate mixed pathology (i.e., Alzheimer's disease, vascular pathology, etc.) and that our search for a single treatment or "magic bullet" is inherently flawed (169). Combined with the growing aging population and increasing interest in biomarkers to identify at-risk

individuals (170), there has been a fundamental shift to early identification. Non-pharmaceutical interventions or lifestyle modifications have grown in popularity and may reduce the risk of dementia by up to 40% (171). Similarly, there is no medication to cure frailty, but prevention is also considered the best "medicine" (172).

1.3.1 fMRI & MCI

Several studies have investigated the efficacy of interventional strategies on FBNC and, by extension, cognitive function in those with MCI and across the dementia spectrum. Cognitive training appears to be one of the most common nonpharmacological interventional strategies (173–176). A 2020 systematic review found multi-domain cognitive training to counteract dysfunctional FBNC in normal aging and neurodegeneration (177). However, another review found little transfer of such training to behavioral outcomes (i.e., cognitive performance) (178). Physical exercise is also popular (179), but to date, no study has reviewed the literature on the role of physical exercise in altering FBNC in those that are cognitively healthy and impaired. Another interventional strategy is nutritional supplementation (180–182). Currently, the World Health Organization only recommends a Mediterranean diet (183). Despite conflicting evidence (184), Vitamin D supplementation, particularly in those with insufficient levels, is considered an open area of research (185) as it has been associated with negative brain changes and poor cognition (186). Other, more unique strategies include herbal medicine (187), acupuncture (188), and singing (189).

1.3.2 fMRI & frailty

Numerous studies have investigated interventional strategies in frailty, none more predominant and successful than physical exercise and nutrition modification (190–193). No previous research has simultaneously examined the impact of an intervention on FBNC and frailty status, but one is currently ongoing, albeit in cognitive frailty (194). Cross-sectional work demonstrated that pre-frail and frail older adults show less connectivity in the supplementary motor area but not the pre-supplementary motor area when compared to non-frail (195). A 2018 scoping review identified three cross-sectional studies that utilized an original frailty tool (i.e., Frailty Phenotype or FI) but only collected anatomical images (196); other included studies used surrogate measures of frailty such as grip strength and gait speed. Finally, studies have also shown that higher (worse) frailty is associated with adverse outcomes in white matter (196,197). The lack of research examining the relationship between brain function and frailty is interesting, given that frailty status modifies the relationship between Alzheimer's disease pathology and clinical manifestation (198,199) and is prevalent to varying degrees across neurodegenerative disorders (200).

1.4 Overview of Dissertation

1.4.1 Thesis Rationale

The previous sections outline the role of an interdisciplinary approach to understanding systemic aging and the promotion of successful aging, which involves maintaining physical mobility and cognitive function without impairment as per the World Health Organization (201). Essential knowledge gaps still exist, and as such, provide the objectives for this dissertation (see next section – 1.4.2 Objectives). FBNC represents a biomarker for understanding early biological and

pathological aging, brain function alterations via interventional strategies, and the neural substrate for cognitive and physical function (170).

1.4.2 Objectives

The objectives of this dissertation were:

Chapter 2

- To systematically review the effect of physical exercise with and without other interventions on FBNC (as assessed by fMRI) in older adults that are cognitively healthy and impaired;
- Given the established relationships between exercise and physical performance, as well as cognition and brain function, I also reviewed the effect of the proposed interventions on secondary outcomes of physical and cognitive function;
- Additionally, I reviewed the correlations between FBNC and secondary outcome changes to determine the behavioral implications of altered FBNC.

Chapter 3

- To determine if high-dose vitamin D supplementation (4000 IU/day) is safe and feasible for older adults;
- To establish the efficacy of this dose to improve physical and cognitive performance outcomes.

Chapter 4

- To evaluate the effect of aerobic and resistance training separately and synergistically with cognitive training and/or vitamin D supplementation (multimodal intervention) on FBNC in older adults with MCI;
- Similar to Chapter 2, I also aimed to determine if a change in FBNC correlated with a change in physical and cognitive performance outcomes.

Chapter 5

- To explore the relationship between frailty status and FBNC in individuals clinically classified with MCI;
- Given the well-established sex-specific experience of frailty, I also aimed to determine if the frailty-FBNC relationship differs between males and females.

1.4.3 Hypotheses

I hypothesized that:

Chapter 2

- Exercise would lead to changes in FBNC;
- FBNC would correlate with exercise-improved secondary outcomes.

Chapter 3

- 4000 IU/day of vitamin D would be safe for older adults;
- 4000 IU/day of vitamin D would lead to an improvement in physical and cognitive performance outcomes.

Chapter 4

- Based upon the results of our systematic review, exercise and multimodal interventions would significantly increase within-network FBNC;
- Changes in FBNC would significantly correlate with changes in physical and cognitive performance.

Chapter 5

- Frailty would be associated with FBNC in individuals with MCI;
- Due to the previously discussed male-female health survival paradox, patterns of association between frailty and FBNC would differ by biological sex.

1.5 GRAPHICS

1.5.1 Figures

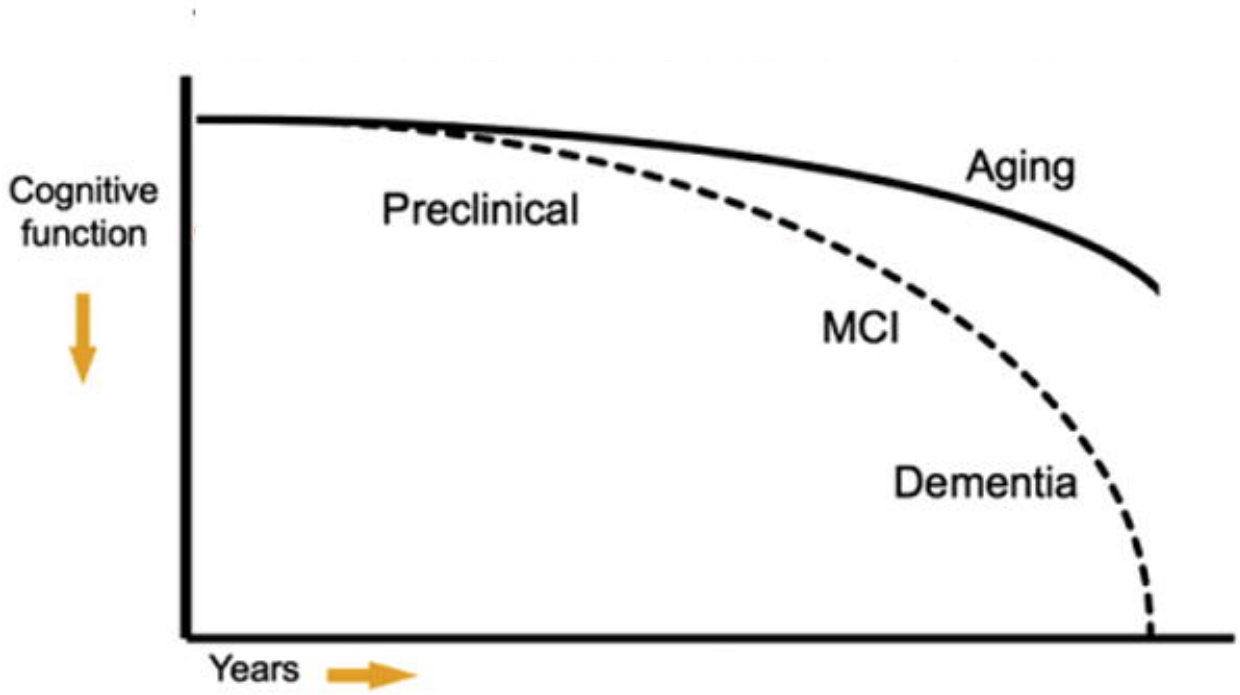

Figure 1.1 Normal cognitive aging vs. accelerated cognitive aging for those at risk for dementia (22).

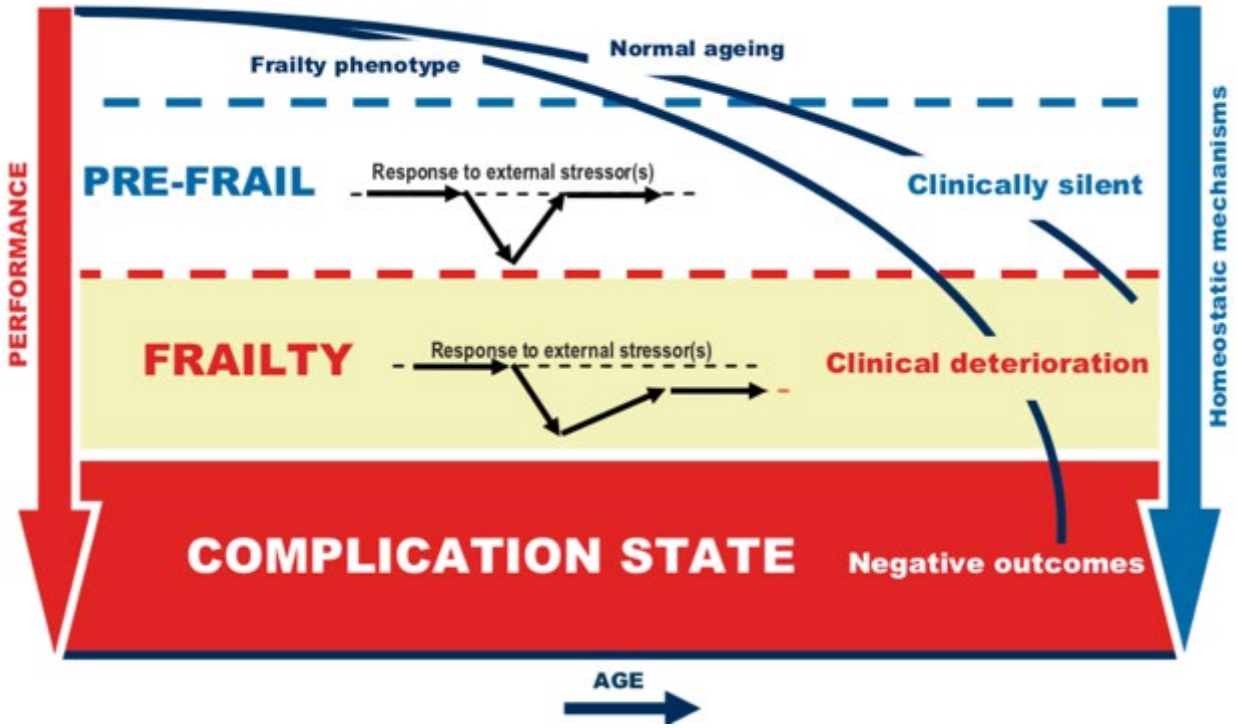

Figure 1.2 Normal aging versus aging in those that develop frailty (172).

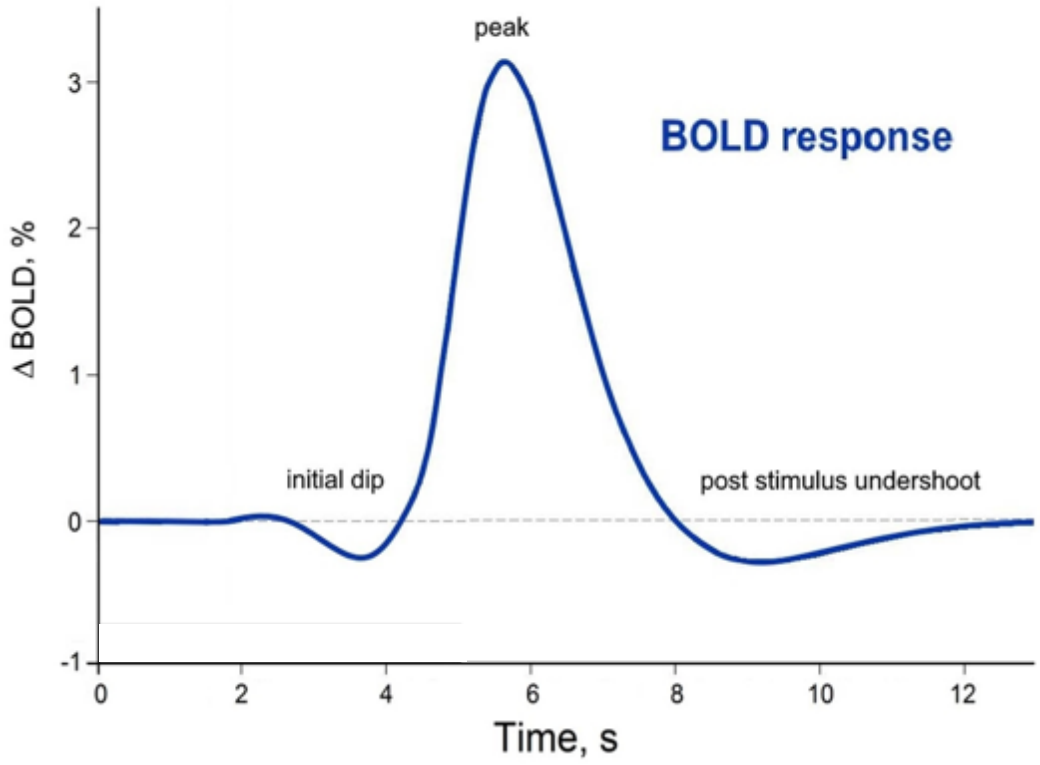

Figure 1.3 Schematic representation of the hemodynamic response (HDR) (202).

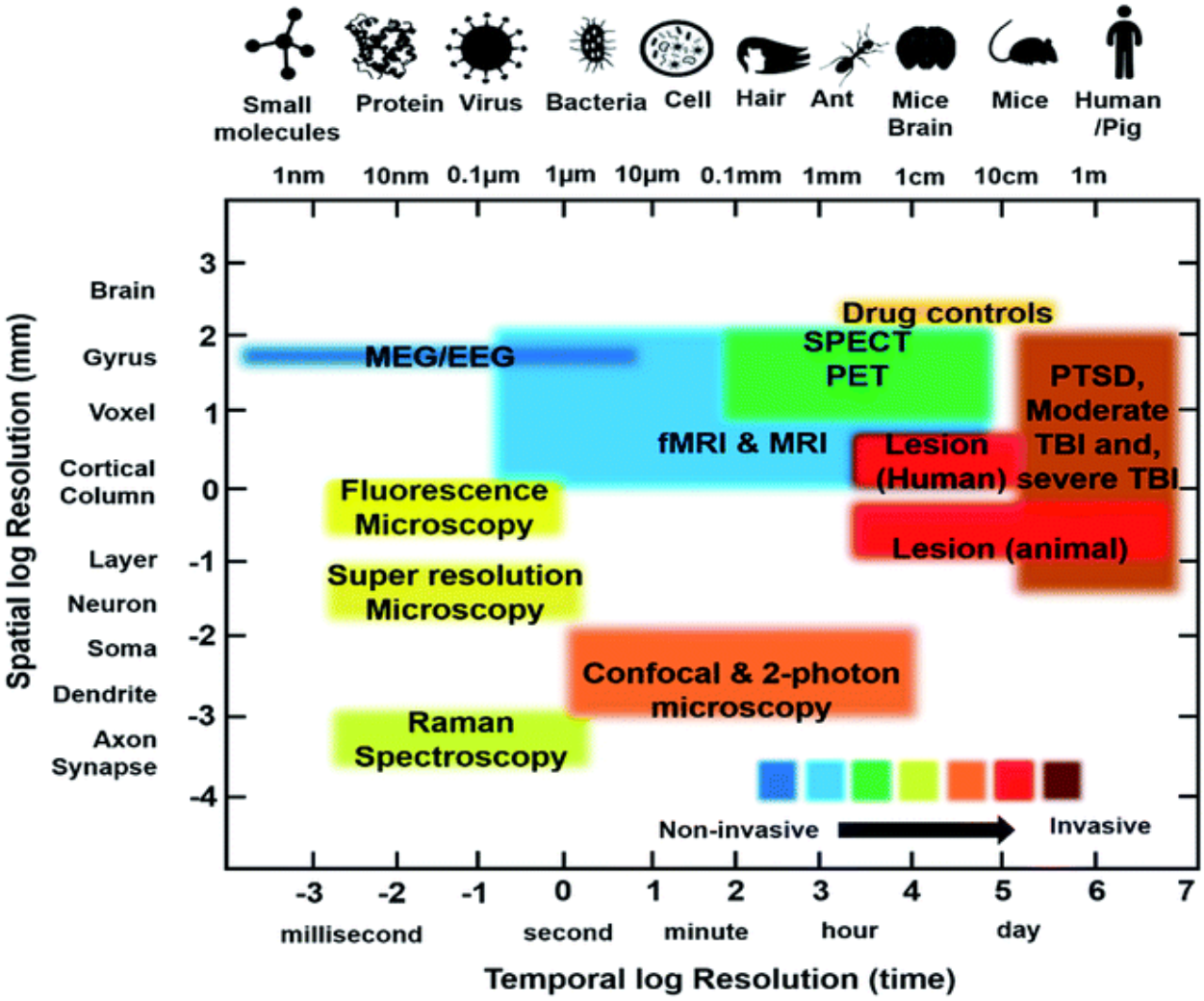

Figure 1.4 Neuroscience techniques differ in temporal (x-axis) and spatial resolution (y-axis). fMRI, functional magnetic resonance imaging; ERPs, event-related potentials; MEG, magnetoencephalography; TMS, transcranial magnetic stimulation; EEG, electroencephalography; PET, positron emission tomography (203).

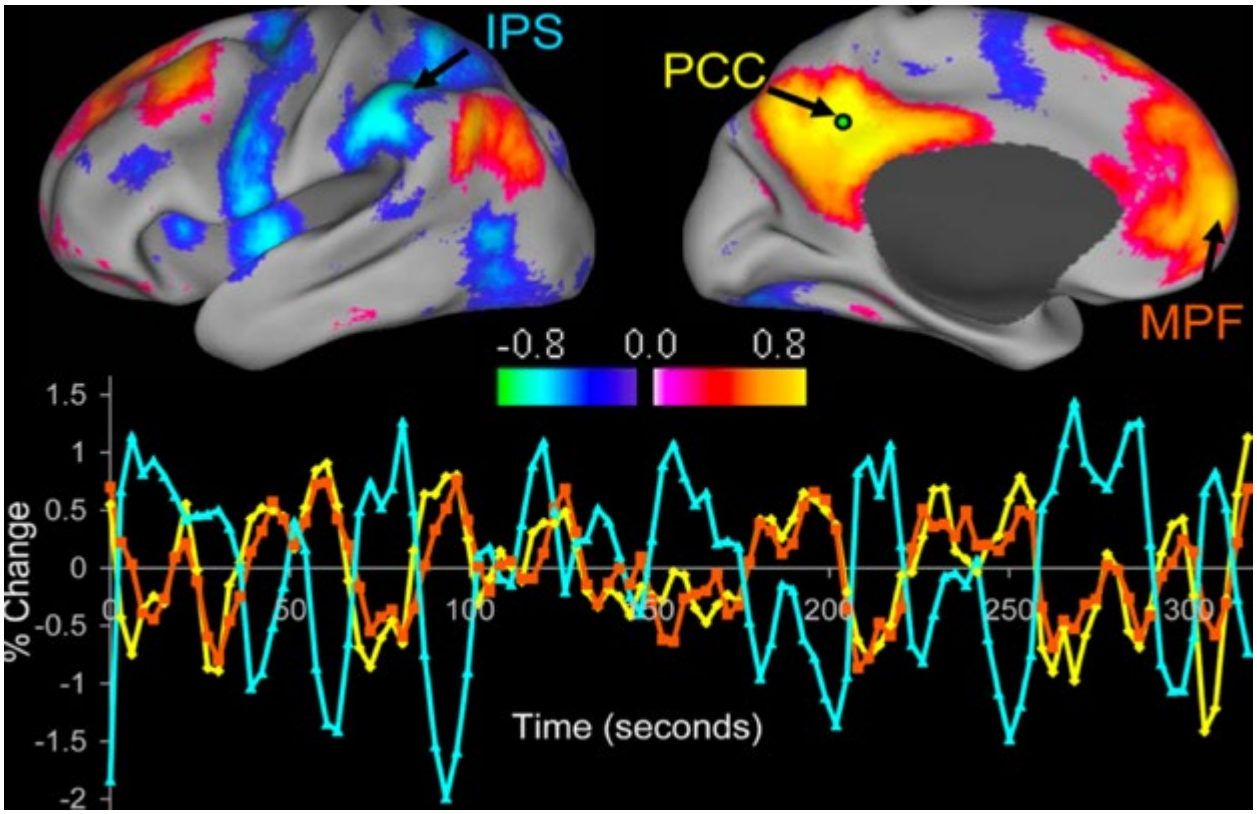

Figure 1.5 Schematic of functional brain network connectivity (FBNC). Despite being anatomically separate, BOLD signals are temporally similar in the posterior cingulate cortex (PCC – yellow line) and medial prefrontal cortex (MPF – orange line). Therefore, the PCC is functionally correlated or connected with the MPF. The PCC and MPF are common regions of interest in the Default-mode Network (DMN). Conversely, the BOLD signal of the Intraparietal Sulcus (IPS – light blue line) is almost entirely opposite, and so, it is anti-correlated with both the PCC and MPF (204).

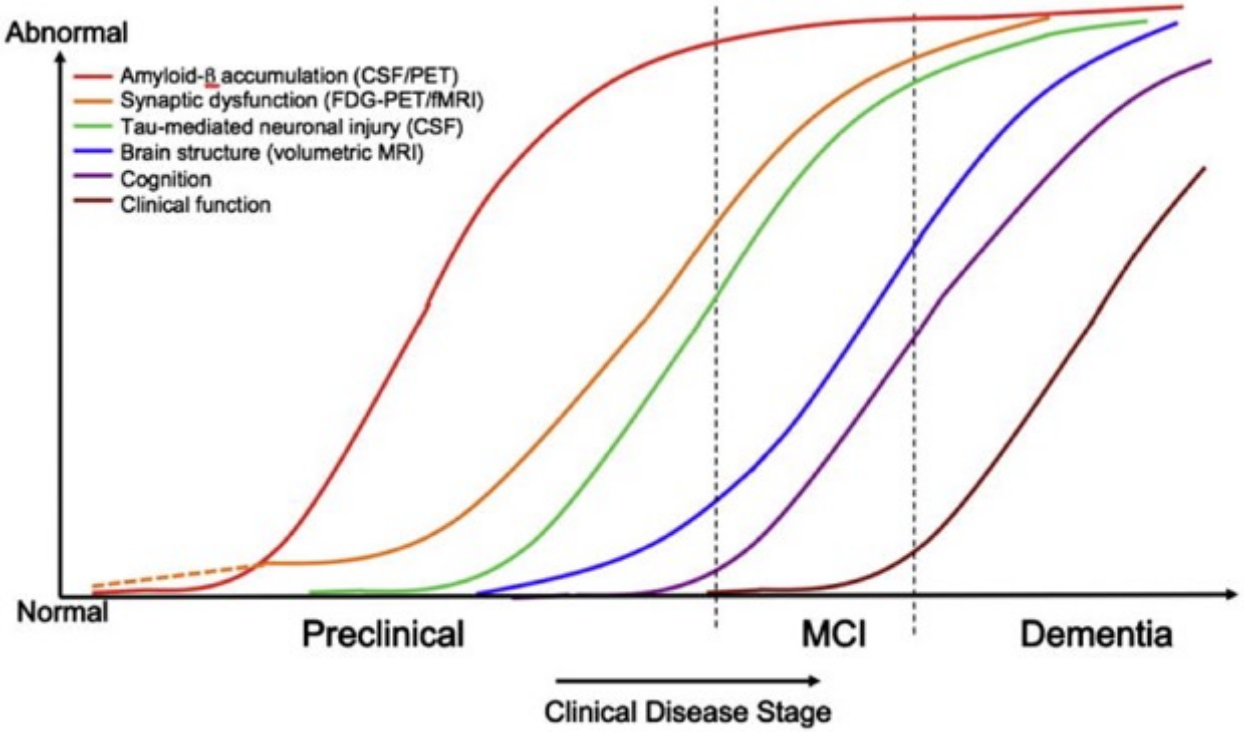

Figure 1.6 Biomarkers in those at risk of progressing to dementia. Changes in fMRI (orange line) measures, such as functional brain network connectivity (FBNC), represent some of the earliest changes in those at risk for dementia. Preceding changes in brain structure (blue line) and the onset of symptoms (dashed lines) (170).

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1.7 Supplementary Material

Supplemental Material A: Required proof of copyright for figures 1,2 and 6.

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CHAPTER 2: THE EFFECT OF PHYSICAL EXERCISE ON FUNCTIONAL BRAIN NETWORK CONNECTIVITY IN OLDER ADULTS WITH AND WITHOUT COGNITIVE IMPAIRMENT. A SYSTEMATIC REVIEW.

Abstract: *Introduction:* Neurodegeneration is a biproduct of aging that results in concomitant cognitive decline. Physical exercise is an emerging intervention to improve brain health. The underlying neural mechanisms linking exercise to neurodegeneration, however, are unclear. Functional brain network connectivity (FBNC) refers to neural regions that are anatomically separate but temporally synched in functional signalling. FBNC can be measured using functional Magnetic Resonance Imaging (fMRI) and is affected by neurodegeneration. *Methods:* We conducted a systematic review using PubMed and EMBASE to assess the effect of physical exercise on FBNC in older adults with and without cognitive impairment. *Results:* Our search yielded 1474 articles; after exclusion, 13 were included in the final review, 8 of which focused on cognitively healthy older adults. 10 studies demonstrated an increase in FBNC post-exercise intervention, while 11 studies showed improvements in secondary outcomes (cognitive and/or physical performance). One study showed significant correlations between FBNC and cognitive performance measures that significantly improved post-intervention. *Discussion:* We found evidence that physical exercise increases FBNC. When assessing the association between FBNC with physical and cognitive functioning, careful consideration must be given to variability in exercise parameters, neural regions of interest and networks examined, and heterogeneity in methodological approaches.

2.1 INTRODUCTION

Physical exercise is an emerging intervention to improve cognition and neurodegeneration in older adults. The birth of exercise as an interventional strategy can be attributed to cross-sectional studies demonstrating that older adults with poor physical fitness show altered brain structure and function, as well as decreased cognitive performance (1–3). There is also evidence of a relationship between physical and cognitive performance, with changes in brain function potentially mediating their simultaneous decline (4,5). Importantly, current pharmacological treatments for dementia syndromes have failed to decrease or reverse cognitive impairments, and as such, there has been an important shift to prevention via non-pharmacological strategies (6).

In recent years, an abundance of systematic reviews and meta-analyses have emerged, examining the effect of exercise interventions on cognitive function in older adults (7–15). Generally, these

studies provide evidence of exercise improving cognitive outcomes, however, the underlying mechanism by which exercise may improve cognition remains elusive. Cognitive performance is well correlated with changes in cerebral blood flow during cognitive tasks (16), therefore, one could expect functional brain changes to mediate cognitive improvements observed post-exercise intervention. A potential approach to improve our understanding of this relationship is to analyze cerebral function changes induced by exercise interventions.

fMRI provides an opportunity to measure brain activity via the blood oxygen level dependent signal (17,18). Subsequently, this permits the measurement of functional brain network connectivity (FBNC), which refers to areas of the brain that are spatially distinct but temporally linked in their signalling (19). Brain function is altered in even normal aging (20–22), but the specificity of these changes appears to be dependent on the region of interest (23–25). Functional alterations are further complicated by the onset of dementia-related syndromes due to the accelerated but variable rates of neurodegeneration (26–29). Exercise may capitalize on the plasticity of the human brain and re-establish typical FBNC by increasing circulating neurotrophic factors that promote neurogenesis, synaptogenesis, angiogenesis, and gliogenesis (30–33).

We are aware of only three reviews that have examined brain function via fMRI post-exercise intervention. One review found that aerobic exercise may increase functional activation or connectivity within the Default-Mode Network, but it included both young and older populations and concluded that the variability of included studies limited the robustness of the findings (34). Another review was critical in examining the influence of non-pharmacological interventions on brain networks, but it included only five studies that utilized exercise interventions (35). And

finally, a recent review showed that dancing, an unconventional form of exercise, improved connectivity between hemispheres (36). No study has reviewed the effect of exercise on FBNC in both cognitively healthy and cognitively impaired older adults.

The purpose of this systematic review was to assess the effect of exercise with and without other interventions on FBNC (as assessed by fMRI) in older adults with and without cognitive impairment. Given the established relationships between exercise and physical performance, as well as cognition and brain function, we also reviewed the effect of the proposed interventions on secondary outcomes of physical and cognitive function. Additionally, we reviewed the correlations between changes in FBNC and secondary outcomes in order to determine the clinical impact of altered FBNC. We hypothesized that exercise would simply lead to changes in FBNC, that would be correlated with exercise-improved secondary outcomes.

2.2 METHODS

2.2.1 Study Design & Search Strategy

This systematic review was registered with the International Prospective Register of Systematic Reviews – PROSPERO (CRD42018115015 – Supplemental Material A), and reporting follows the PRISMA statement (37). A literature search, without date or language restrictions, was conducted via PubMed and EMBASE for all relevant literature published prior to 07/2018 and then updated in 12/2020. The search utilized subject headings in PubMed and EMBASE related to exercise, fMRI, and the brain (Table 1 and 2). Additional records were identified through reverse citation searching from included articles.

2.2.2 Screening

The screening process incorporated: 1) removal of duplicates; 2) title and abstract screening; and 3) full-text screening. Studies were included if they met the following criteria: 1) published as a randomized controlled trial; 2) measured FBNC via fMRI, before and after an intervention that focused on or included exercise; and 3) sample with a mean age of 60+ years with or without cognitive impairment and absence of other neurological conditions (i.e., Parkinson's, stroke, etc.). Exercise was defined as:

> *Physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective. Physical fitness can be divided into two components with specific sub-categories: 1) Health-related (cardiorespiratory capacity, muscular endurance, muscular strength, body composition, and flexibility); and 2) Skill-related (agility, balance, coordination, speed, power, reaction time)* (38).

We selected Caspersen's definition (38) because of its emphasis on the periodization training principle (i.e., plan, structured, repetitive, and purposeful), as this permitted the selection of only studies that designed interventions with planned increments in volume and intensity of exercise.

Two authors (NWB and FPF) independently reviewed and screened all retrieved studies. Post-individual screening, reviewers met to resolve inconsistencies regarding inclusion decision. If a resolution was not found, a third reviewer (MMO) was consulted to make a final decision. Using Kappa Statistics, we assessed interrater reliability after completion of the title and abstract, as well as full-text screening.

2.2.3 Bias Assessment

Bias assessment followed the same process detailed in section 2.2.2. The Cochrane Collaboration Tool was utilized to assess bias (39,40) because of its recommendation for systematic reviews examining randomized controlled trials (41) and its usage in other reviews examining brain function and exercise (34,35). Briefly, the Cochrane Collaboration Tool includes seven domains for assessing bias, each of which can be ranked as low, high, unclear, or not applicable: 1) Random sequence generation; 2) Allocation concealment; 3) Blinding of participants and personnel; 4) Blinding of outcome assessment; 5) Incomplete outcome data; 6) Selective Reporting; 7) Other

Reviewers agreed, beforehand, to be conservative (i.e., towards high or unclear risk) when rendering a final decision between two options. The "Other" domain was not utilized within the present review. The creators of the Cochrane Collaboration Tool advise against an overall bias score, and as such, no studies were excluded because of their bias ranking.

2.2.4 Outcome measures

The primary outcome measure was the direction of change in FBNC, as measured by fMRI. Secondary outcomes included measures of cognition and physical function. We also reviewed the existence of significant correlations between significant changes in FBNC and secondary outcomes in the included articles.

2.2.5 Data Extraction

The following information was extracted from the articles selected for final analysis; study ID (author, publication year, study design); sample characteristics (age, sample size, and cognitive status); type of exercise and from of delivery; change in outcome measures (FBNC, cognitive performance, and physical performance). To enhance the clinical relevance of our study, we also retrieved effect sizes for all correlation analyses conducted in both the intervention and control groups. Included studies were stratified based upon those that focused on participants with and without cognitive impairment.

The reporting of brain networks within the present review was relative to each individual study; networks refer to widespread regions showing functional connectivity, which are believed to enable efficient information processing and completion of complex functions (42). Therefore, it was possible for an area to be identified as belonging to a different neural network from one study to the next. We also report “no change” of FBNC for a fraction of the studies based on how results are presented by the authors. Although not reported by the original authors, most studies likely had "no change" in at least one brain area or neural network given that a seed-voxel whole-brain analysis, the most commonly used FBNC analytical method of the included studies, examines connectivity throughout the entire brain.

2.3 Results

2.3.1 Search Results, Inter-Rater Reliability, and Bias Assessment

A total of 1474 articles were initially identified by the electronic search (Figure 1). All articles were published after 2010, highlighting the ability of our search terms to capture relatively recent literature. Upon completion of title and abstract screening, 54 articles remained for full-text

screening, and 43 articles were removed because they did not meet the inclusion criteria. Of note, studies inclusive of those with (43–45) and without cognitive impairment populations (3,46–54) satisfied all inclusion criteria for this systematic review, with the exception that they measured brain activation and not functional connectivity. We also excluded studies that did not directly measure the strength and direction of functional connectivity (55), but rather the similarities between brain-regions (i.e., low-frequency fluctuations) (56), local connections (i.e., regional homogeneity) (57), and/or the integration of information (i.e., node-based) (58). Another study was excluded from our final analysis because, although a randomized controlled trial, imaging was not conducted in their control group and therefore prevented interpretation of between-group differences (59). Finally, one study was excluded because results (60) were previously reported (61). Two articles were added after the reverse citation search (61,62).

Kappa Statistics score was >0.8 after completing both screens, reflecting a high degree of interrater agreement and suggesting a clear *a priori* study inclusion/exclusion criteria (Supplemental Material B).

Bias assessment was completed in all 13 studies (Figure 2 and 3). Studies were mostly ranked as "unclear" for the first four domains because they failed to describe the randomization procedure or allocation concealment and if exercise training personnel or fMRI assessors were blinded. The majority of studies were ranked as "unclear" for "selective reporting" because the trial was not pre-registered to a national database. Finally, studies were often ranked as "high-risk" for "incomplete outcome data" due to the amount of and/or rationale for participant dropout. The Cochrane Collaboration Tool does not recommend excluding studies based upon bias

assessment, but given the number of studies with the majority of their rankings as "high-risk" or "unclear," the reader should interpret the proceeding results with caution.

2.3.2 Cognitively Impaired Older Adults

Five studies focused on cognitively impaired older adults, inclusive of subjective and mild cognitive impairment, as well as mild subcortical ischemic vascular cognitive impairment (62–66) (Table 3). In total, the studies included 203 participants with a mean age ranging from 64-75 years and sample size ranging from 5 to 22 participants per group. Two studies included more females than males, while the number of females in one study was unclear. Aerobic exercise and multi-domain interventions were the most popular intervention strategies. Interventions were as short as eight weeks and as long as six months (Table 4). Maintaining usual care was the most common interventional strategy for the control groups. Therefore, 3/5 studies failed to account for social engagement by not requiring their control group to take part in a control or placebo intervention (62,64,66). Specific brain networks included but were not limited to neural regions associated with language, superior-parietal regions, and frontoparietal regions. The Default-Mode Network, however, was the most commonly cited.

2.3.2.1 FBNC

All studies included or focused solely on resting-state fMRI. One study did not present how FBNC independently changed post-intervention or rather only reported how changes in FBNC correlated with cognitive performance (65). Three of the remaining four studies showed an increase or bidirectional (increase and decrease) change in FBNC in one or more of their intervention groups. The study that showed no change in their intervention group reported an

increase in FBNC in their control group but only during one of their task-based imaging sequences (64).

2.3.2.2 Secondary outcomes

There was a variety of cognitive and physical performance outcomes measured, with only the Alzheimer's Disease Assessment Scale-Cognitive (67) scale being included in more than one study. Only one study assessed physical performance measures, showing no change after the intervention (64). The remaining four studies focused on cognitive outcomes, with all but one study (62) showing an improvement in their intervention group. One study also showed a decrease in a cognitive performance measure for the intervention group (63). All studies also demonstrated no change in at least one secondary outcome for both an intervention and control group.

Results for both the primary and secondary outcomes are summarized in Table 3. More detailed results can be found in Supplemental Material C and D, inclusive of between and within-group differences, brain areas/networks examined, and specific tests of physical and cognitive performance.

2.3.3 Cognitively Healthy Older Adults

Eight studies focused exclusively on cognitively healthy older adults, with an inclusive total of 480 participants ranging in mean age from 60-73 years; one study did not provide a mean age but only a range (Table 5) (61,68–74). Sample size per group ranged from 11 to 53. Four studies included more females than males in their sample, while two studies were equally balanced. Aerobic training was the most popular interventional strategy, and intervention length ranged

from six-weeks to one-year (Table 4). Unlike studies of cognitively impaired adults, some form of balance, toning, and/or stretching was the most common interventional strategy for control groups; such an interventional strategy is not considered exercise as they are not programmed with enough intensity or progression to have beneficial effects on muscle strength or endurance. Only one study failed to account for social interaction by not requiring their control group to take part in a control or placebo intervention (i.e., control participants simply maintained their usual care for the duration of the experiment) (71). There was an abundance of different networks imaged, including but not limited to the executive-control, salience, and sensorimotor neural networks, but similar to studies of cognitively impaired older adults, the Default-Mode Network was the most commonly cited.

2.3.3.1 FBNC

Seven (68–74) of the eight studies conducted imaging while participants were at rest (61). Five (69–71,73,74) of the eight studies showed an increase in FBNC in their intervention groups, while two studies, one being the task-based fMRI (61,72), demonstrated bidirectional (increase and decrease) changes. Interestingly, this study was also the only one that appeared to look at connectivity between different neural networks (61). The control group from separate studies showed an increase (61), decrease (72), and bidirectional (72) change, respectively.

2.3.3.2 Secondary outcomes

Similar to studies of cognitively impaired older adults, there was an abundance of secondary measures in physical and cognitive performance. The most common measures of cognition and physical performance were the trail making tests (75) and tests of cardiovascular fitness. Seven

(61,69–74) of the eight studies included measures of cognitive performance, five (69–72,74) of which showed both an improvement and no change. Two control groups had a decrease in a cognitive performance outcome (70,72). Five (61,68,71,72,74) of the eight included studies measured physical performance, with three (61,68,74) showing an improvement in an intervention group. Two studies (68) had an improvement in physical performance in their control group, one of which did not show a similar change in their intervention group (72). Except for one (73) and similar to the cognitively impaired sample, all studies demonstrated no change in at least one secondary outcome for both an intervention and control group.

Results for both the primary and secondary outcomes are summarized in Table 5. More detailed results can be found in Supplemental Material E and F, inclusive of between and within-group differences, brain areas/networks examined, and specific tests of physical and cognitive performance.

2.3.4 Relationship between changes in FBNC, physical performance, and cognition.

We restricted our review of correlations to only measures of FBNC, cognition, and physical performance that independently demonstrated a significant change post-intervention and did not collapse for all subjects. As such, only four studies met this criteria (64,69–71), and only one showed significant (negative) correlations between connectivity of the precuneus and tests of delayed recall and processing skills, as well as between the angular gyrus and processing skills (71). In this study, there was also a significant positive correlation between posterior cingulate connectivity and delayed recall. Meaning, increases in connectivity were associated with an improvement and decrease in cognitive performance. Importantly, all FBNC measures within

this study did not survive correction for false discovery rate, and therefore, the authors believed that their findings should be interpreted with caution.

Studies that conducted a correlation analysis consistently reported, albeit different measures of effect size (61,64,65,69–71). Given the clinical implications, effect sizes are reported in Supplementary Materials G and H. In brief and as expected, given the variety of tests conducted, authors reported various effect sizes. Similar to our review of significant correlations, we excluded or could not report effect sizes from studies that collapsed intervention and control groups (63,68,73) or did not conduct any correlation analyses (62,66,72,74).

2.4 Discussion

This systematic review investigated the effect of physical exercise on FBNC (as assessed by fMRI) in older adults with and without cognitive impairment. In support of our hypothesis, we found evidence that physical exercise provokes changes in FBNC in older adults with and without cognitive impairments. Specifically, the interventions within 10 studies led to an increase in FBNC. Conversely, only two control groups showed an increase in connectivity, while another showed a decrease and bidirectional change. Interestingly, two of the studies showing an increase in FBNC in control groups performed task-based fMRI. Increases in FBNC during a task may reflect increases in activation and, thus, a lack of neural efficiency or compensation for task completion (76).

Also in support of our hypothesis, we found studies demonstrating an improvement in measures of physical (n = 3/6) or cognitive (n = 9/11) performance post-exercise intervention. For cognitive performance, however, this should be interpreted with caution as 7/9 studies showed an

improvement in addition to no change. With respect to the relationship between changes in FBNC and cognitive/physical performance, contrary to our hypothesis, only one study showed a significant correlation, and the connections within this particular study did not correct for false discovery rate.

Lack of more specific findings is similar to those of other recent reviews on the effects of interventions on brain function (34,77). In addition to the typical issues of variance in age and sex, the heterogeneity of the findings in the present review can likely be attributed to the inter-study variability in exercise parameters, brain areas examined, and methodological approaches, which are discussed in greater detail below.

2.4.1 Exercise-induced Changes in Brain Function

In reviewing the exercise parameters (Frequency, Intensity, Time, Type, Volume, and Progression) of included studies, it is evident that there are meaningful inter-study differences. For example, interventions ranged in length from 6-weeks to 1-year, with 6-months being the most common length. There were also variations in minutes per week, days per week, and of course, the type of exercise intervention across studies. All exercise parameters are critical elements to the development of any exercise program and must be carefully considered in context of the overall goal(s), as highlighted by their inclusion in the American College of Sports Medicine's Exercise Prescription guidelines (78). Future studies exploring the effect of exercise on any outcome must report all exercise parameters, as this will aid understanding and replication. In particular, progression and intensity should be given critical consideration, as they were unclearly defined in several studies included within the present review.

2.4.2 Common Neural Networks

The most common neural network explored through the included studies was the Default-Mode Network (79). Overall, studies retrieved by our search strategy included over 15 different networks, in addition to several other areas that were not identified as belonging to any one individual network. The inclusion of different areas/networks undoubtedly contributed to the variability in findings. Previous research has demonstrated that some networks show a consistent change in connectivity, while others depend on the specific area within the network (80,81), inter-network relationships (82,83), or are simply inconsistent (84,85). Our understanding of brain function is further complicated by emotional (86) and arousal (87) states during imaging and nomenclature (88). Finally, variations in the different dementia-related pathologies likely cause inconsistencies in FBNC (29); this particular review included older adults that were classified as "normal," as well as those with subjective cognitive impairment, mild cognitive impairment, and mild subcortical ischemic vascular cognitive impairment.

2.4.3 Methodological (In)Consistencies

Sample sizes ranged from 14-189 participants, thus studies near the lower end of that range should be interpreted with caution. In reviewing just some of the analytical approaches, we noted differences in neuroimaging pre-processing and denoising strategies, as well as the programs or toolboxes used to conduct the neuroimaging analyses, such as the FMRIB Software Library (89) and the CONN Functional Connectivity Toolbox (90). Finally, resting-state scans were performed with eyes both opened and closed, which is another important consideration given that visual state alters neural function (91). The only true consistency among all included studies was

the usage of a 3.0 Tesla scanner, which simply ensures that imaging quality and spatial resolution are consistent across studies.

Variability exists among even recent studies, but it is extrapolated when comparing studies published over a decade's span of time, given the rapid technological and scientific advancements in the field of neuroimaging. The identification of a gold-standard method of analysis is likely not recommended, as some variability is required depending on the specific research question and subsequent analyses being conducted. Regardless, there has been a shift towards the standardization of some stages of the neuroimaging process, including the actual imaging sequence (92), structuring of imaging file folders (93), quality control (94), and the pre-processing (95). Furthermore, in an effort to promote open science and reproducibility, pre-registration is growing in popularity, thereby providing details of the methodology employed in each study for the reference of researchers and neuroscientists alike.

2.4.4 Cognitive/Physical Performance and Brain Function

We also examined the effect of the interventions on physical and cognitive performance outcomes, as well as their correlation with changes in FBNC. Overall, the exercise intervention strategies led to an improvement in these secondary outcomes in 11/13 studies. All but one study (73) demonstrated no change in at least one secondary (i.e., cognitive and/or physical performance) outcome for both an intervention and control group. Lack of change in either group, particularly those with neurodegeneration due to their accelerated rate of decline (26–29, 96), may be regarded as positive as even normal aging is associated with worsening brain health (97,98) and physical function (99,100). As previously highlighted, most interventions were $\leq$ 6-months and, therefore, represent a generally short time frame in the overall scheme of aging,

particularly for those with participants classified as cognitively normal. Meaningful decline may seem unlikely over such timeframes, but previous work has demonstrated worsening in similar outcomes for control groups of vulnerable older adults over shorter periods (101). Ultimately, the rate of decline is an ongoing area of research, impacted by the interaction of several factors, including genetics, lifestyle, and socioeconomic status (102).

Surprisingly, only one included study found a significant correlation between measures of FBNC and cognitive/physical performance that independently demonstrated a significant change post-intervention. Importantly, the lack of relationship may be attributed to the restrictions we placed upon our review. We only considered studies that did not collapse their intervention and control groups. There were studies that demonstrated a correlation between changes in brain function, cognition, and/or physical performance, but the groups were collapsed. Secondly, we restricted our review of the correlation measures to only those that demonstrated a significant change. There were studies that demonstrated a correlation between changes in FBNC and cognition/physical performance, but the included measures did not independently show a significant change after the intervention. FBNC may still be responsible for changes in clinical outcomes, as lack of a correlation does not negate its role as a mediator (103). At the very least, further investigation may be warranted for the correlations demonstrating a large effect size. Individual differences, such as baseline physical fitness/sedentary behaviour, may also play an important role in the impact of exercise on FBNC.

2.4.5 Future Studies

This review reveals the promising effect of physical exercise on brain function in older adults with and without cognitive impairment. Furthermore, it supports other recent reviews on the

topic, such that physical exercise appears to increase connectivity (34,36). This review also creates a starting point for research accumulation while indicating important solvable limitations. Critically, and given the lack of studies in our review that failed to do so, future studies must be adequately powered to detect a post-exercise intervention difference in FBNC (104). Another avenue is to assess the relationship between FBNC and cognitive/physical performance post-intervention. Examining these secondary outcomes within the context of frailty may provide further insights, as frailty alone has been linked to both physical and cognitive decline (105–108), it is considered a prime target for exercise interventions (101,109,110), and it may help to explain the relationship between Alzheimer's pathology and its symptoms (111). Finally, continuing to associate changes (increase/decrease) in FBNC with well-established biological, physical, and cognitive outcomes will help to delineate their implications.

2.4.6 Limitations

To our knowledge, this is the first systematic review to comprehensively examine the effect of exercise on FBNC in older adults both with and without cognitive impairment, but it is not without limitation. We excluded studies that measured activation but not connectivity as they did not satisfy our pre-registration criteria and could have contributed to the heterogeneous findings. Previous reviews have included results of both neural activation and connectivity (34). Unlike our recent review on exercise and biomarkers (33), we conducted no formal synthesis or dose-response relationship due to the inter-study variability. Another important limitation is the number of included studies, particularly those in cognitive impairment, that failed to account for social (participant-participant or participant-exerciser trainer) engagement. Social engagement is an essential consideration as previous research indicates that it alone can positively impact brain

health (112). The reader should cautiously interpret the results of studies (n = 4) that failed to account for social engagement as it is not possible to determine if altered FBNC is entirely due to physical exercise (62,64,66,71). Importantly, studies (n = 6) that did account for social interaction showed altered FBNC (61,63,69,70,73,74) while their control group did not or showed divergent alterations. Finally, the number of included studies with bias assessment categories ranked as "high-risk" or "unclear" is another limitation. Findings from such studies should also be interpreted with caution as the degree of bias and not the actual intervention may be responsible for the observed changes in outcomes.

2.5 Conclusion

We found evidence that physical exercise, in general, increases FBNC in both healthy and cognitively impaired older adults. Interestingly, evidence for correlations between changes in measures of FBNC following physical exercise interventions and secondary outcomes that significantly improved post-intervention are weak. Methodological inconsistencies, including exercise protocols, brain regions of interest and neural networks examined, and methodological approaches are likely responsible for the variability in findings across these randomized controlled trials. Our results provide evidence that variation in patterns of neural functioning is one mechanism underlying the link between physical exercise and neurodegeneration. Moreover, the findings of this review indicate that across studies, functional neural connectivity increases post-exercise intervention in older adults both with and without cognitive impairment. These findings provide unique insights into the understanding of *how* physical exercise may improve cognitive functioning in the aging brain.

2.6 GRAPHICS

2.6.1 Figures

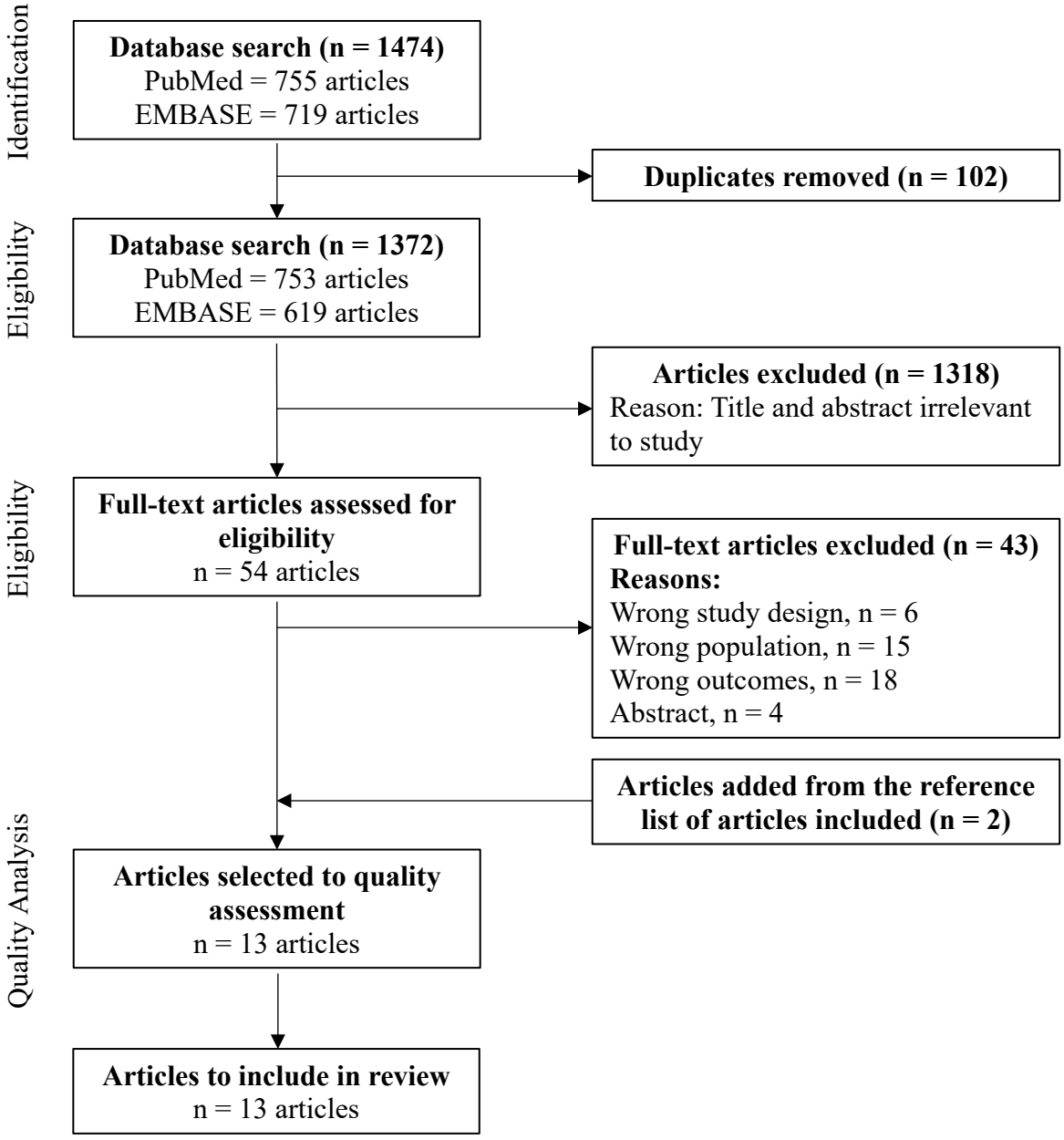

Figure 2.1 Flow diagram of the study selection process.

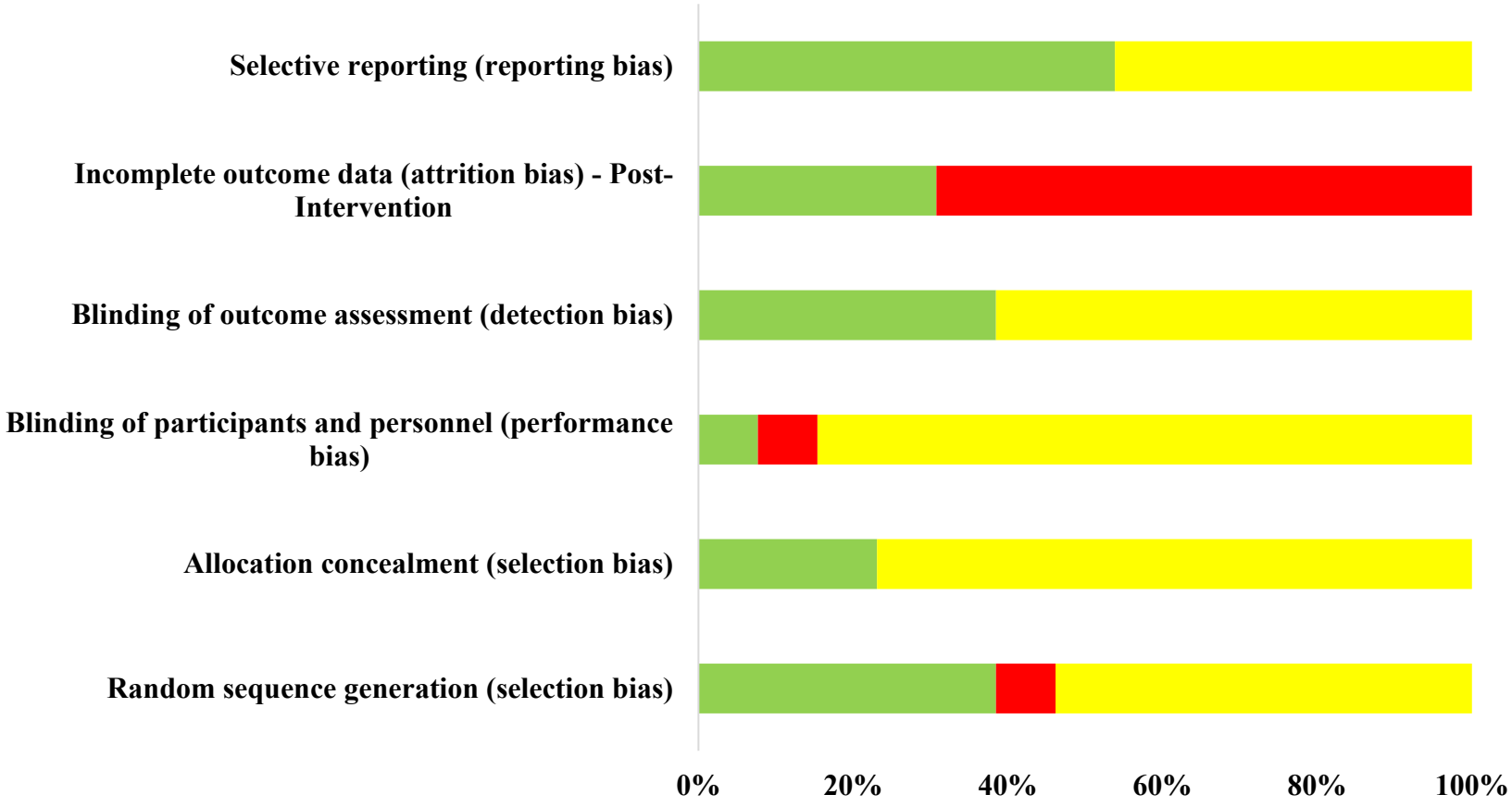

Figure 2.2 Risk of bias summary. Green (+), low risk; red (-), high risk; yellow (?), unclear.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias) - Post-Intervention	Selective reporting (reporting bias)
Wells et al, 2013	+	?	?	+	+	+
Eyre et al, 2016	+	+	+	+	-	?
Suo et al, 2016	+	?	?	+	+	+
Tao et al, 2019	+	+	-	+	-	+
Hsu et al, 2017	+	+	?	+	-	+
Pieramico et al, 2012	?	?	?	?	+	?
Li et al, 2014	-	?	?	?	-	+
Tao et al, 2016	?	?	?	?	-	+
Flodin et al, 2017	?	?	?	?	-	?
Ji et al, 2017	?	?	?	?	-	?
Prehn et al, 2017	?	?	?	?	-	?
Voss et al, 2019	?	?	?	?	-	+
Voss et al, 2010	?	?	?	?	+	?

Figure 2.3 Risk of bias detailed. Green (+), low risk; red (-), high risk; yellow (?), unclear.

2.6.2 Tables

Table 2.1 Search terms.

Main Concepts	PubMed MeSH Term	EMBASE Subject Heading
Exercise	Exercise OR Exercise Therapy	exp Exercise OR exp Kinesiotherapy
fMRI	Functional Neuroimaging OR Magnetic Resonance Imaging	exp Functional Connectivity OR exp Functional Magnetic Resonance Imaging
Brain	Brain	exp Brain

Note: fMRI, functional magnetic resonance imaging; exp, explode.

Table 2.2 Search strategy for PubMed and EMBASE.

USING PUBMED DATABASE
Exercise/ OR Exercise Therapy/
Functional Neuroimaging/ OR Magnetic Resonance Imaging/
Brain/
Strategy 1 AND 2 AND 3

USING EMBASE DATABASE
exp Exercise/
exp Kinesiotherapy/
1 OR 2
exp Functional Connectivity/
exp Functional Magnetic Resonance Imaging/
4 OR 5
exp Brain/
3 AND 6 AND 7

Note: exp, explode.

Table 2.3 Characteristics and results for studies that focused on a cognitively impaired sample.

Study ID (Author, year, and type of study)	Sample Characteristics		Exercise		Change in Outcome Measures		
	Cognitive Status	Age; Sample Size (female)	Type	Delivery	FBNC	Cognitive Performance	Physical Performance
Wells et al. 2013 *Pilot, single-blind, block RCT*	MCI	I: 73.0 ± 8.0; n = 9 (6)	MDI	Group & Individual	↑	↔	NM
		C: 75.0 ± 7.0; n = 5 (2)	UC	Not applicable	↔	↔	
Eyre et al. 2016 *Double-blind, cluster RCT*	SCI & MCI	I: 67.1 ± 9.5; n = 14 (6)	Yoga	Group & Individual	NRI	✚ ↔	NM
		C: 67.8 ± 9.7; n = 11 (6)	CT	Group & Individual	NRI	↔	
Suo et al. 2016 *Double-blind, factorial RCT*	MCI	I1: 70.1 ± 6.7‡; n = 22 (NR)	MDI	Group	↑ ↓	✚ ↔	NM
		I2: 70.1 ± 6.7‡; n = 19 (NR)	RT + Sham CT	Group	↑ ↓	✚ ━ ↔	
		I3: 70.1 ± 6.7‡; n = 21 (NR)	Sham RT + CT	Group	↑ ↓	↔	
		C: 70.1 ± 6.7‡; n = 24 (NR)	Sham RT& CT	Group	↔	━ ↔	
Tao et al. 2019 *RCT (blinding unclear)*	MCI	I1: 66.17 ± 4.17; n = 20 (15)	Baduanjin*	Unclear but appears to be in groups	↑ ↔	✚	NM
		I2: 64.32 ± 2.60; n = 17 (10)	Brisk Walking*	Unclear but appears to be in groups	↔	↔	
		C: 65.97 ± 5.66; n = 20 (14)	UC*	Not applicable	↔	↔	
			* All groups also received health education				
Hsu et al. 2017 *Single-blind RCT*	mSCIVCI	I: 72.0 ± 8.6; n = 12 (4)	Aerobic	Group	↔	NM	↔
		C: 69.9 ± 9.2; n = 9 (4)	UC	Not applicable	↑		↔

Note: Reading table from left to right indicates results for each group i.e., Intervention group in Wells et al., 2013 performed MDI in a group and individual setting and showed an ↑ in FBNC, and ↔ & NM in cognitive and physical performance. Given the breadth of brain areas examined and cognitive/physical performance outcomes, a study can show more than one result, i.e., ↑ ↔, ✚ 0, etc. Except for Hsu et al. 2017 (task & rest), all studies performed only resting-state fMRI. Studies with multiple intervention groups are

numbered i.e., I1, I2, etc. Age (years) is mean ± standard deviation. C, control; CT, cognitive training; I, intervention; MCI, mild cognitive impairment; MDI, multi-domain intervention; mSCIVCI, mild subcortical ischemic vascular cognitive impairment; NM, not measured; NRI, not reported independently; RCT, randomized controlled trial; RT, resistance training; SCI, subjective cognitive impairment; UC, usual care; ↑, significantly increased; ↓, significantly decreased; +, significantly improved; −, significantly declined; ↔, unchanged. ‡, age based on pooled parent sample.

Table 2.4 Exercise parameters applied to each study included in this review.

Study ID (Author and year)	FITT-VP					
	Frequency	**Intensity**	**Time (min/session)**	**Type**	**Volume (min/week)**	**Progression**
Wells et al. 2013	I: 1x/week for 8-weeks (home workout also encouraged)	I: Unclear	I: 120	I: MDI (Yoga) C: UC	I: 120	I: Unclear
Eyre et al. 2016	I: 1x/week for 12-weeks	I: Unclear	I: 60	I: Yoga C: CT	I: 60	I: Standard protocol for the KY practice; content and structure of the class did not differ from one week to another
Suo et al. 2016	I1-2: 2x/week for 26-weeks	I1-2: 15-18 on the Borg RPE scale; and 80 to 92% of current 1RM	I1-2: 45	I1: MDI (RT) I2: RT + Sham CT I3: Sham RT + CT C: Sham RT& CT	I1-2: 90; 3 sets of 8 per session	I1-2: Re-tested 1RM's every 3 weeks and alternated exercises
Tao et al. 2019	I1-2: 3x/week for 24-weeks	I1: Unclear I2: 55-75% of HRR	I1-2: 60	I1: Baduanjin I2: Brisk Walking C: Usual care * All groups received health education	I1-2: 180	I1: Unclear but included 10-postures I2: Unclear
Hsu et al. 2017	I: 3x/week for 6-months	I: 40-70% of HRR; 14-15 on Borg RPE scale; and talk test	I: 60	I: Aerobic C: UC	I: 180	I: Progressed over the first 12 weeks to 60–70% of HRR, which was sustained for remainder
Pieramico et al, 2012	I: 3x/week for 6-months	I: Unclear	I: 60	I: MDI (Aerobic - dance, walking, and ADL) C: UC	I: 180	I: Unclear
Li et al, 2014	I: 3x/week for 6-weeks	I: Unclear	I: 60		I: 180	

				I: MDI (Tai Chi) C: Lectures on health & aging		I: Learning of all postures/the entire sequence
Tao et al, 2016	I1-2: 5x/week for 12-weeks	I1-2: Unclear	I1-2: 60	I1: Tai-Chi Chuan I2: Baduanjin C: Health education	I1-2: 300	I1: Unclear but based on Yang-style 24-form I2: Unclear but based on Health Qigong – Baduanjin
Flodin et al, 2017	I: 3x/week for 6-months	I: 40-80% of estimated max HR	I: 30-60	I: Aerobic C: S&T	I: 90-180	I: HR load of each session was increased incrementally
Ji et al, 2017[†]	I: Every day for 6 weeks	I: Unclear	I: 30	I: MME (Nintendo Wii - aerobic, balance, weightlifting, and yoga) C: UC	I: 210	I: Unclear
Prehn et al, 2017	I: 2x/week for 6-months	I: 80% of anaerobic threshold	I: 45	I: Aerobic C: S&T	I: 90	I: Starting at 20-minutes, increased duration at target intensity
Voss et al, 2019	I1-3: 3x/week for 6-months	I1: Unclear but HR and RPE were measured I2-3: 50-75% of max HR	I1-3: 60	I1: Dance I2: Aerobic (Walk) I3: MDI (Walk) C: Strength, stretching, and stability	I1-3: 180	I1: Learn complex social dance sequences, and choreographed dance combinations that became progressively more challenging I2-3: 5-min increments from week 1-7 and then remained at 40-minutes for remainder; and 50-60% for the first 6-weeks and 60-75% for the last 18
Voss et al, 2010	I: 3x/week for 1-year	I: 50–75% of max HRR	I: 20-50	I: Aerobic C: S&T	I: 60-150	I: 5-min increments from week 1-7 and then remained at 40-minutes for remainder; and 50-60% for the first 6-weeks and 60-75% for the remainder

Note: Studies with multiple intervention groups are numbered i.e., I1, I2, etc. Empty row divided cognitively impaired studies (top) from cognitively healthy (bottom). 1RM, 1 repetition maximum; C, control; CT, cognitive training; HR, heart rate; HRR, heart rate reserve; I, intervention; MDI, multi-domain intervention; min, minute; MME, Multi-modal exercise; NA, not applicable; RPE, rating of perceived exertion; RT, resistance training; S&T, stretching and toning; UC, usual care.

Table 2.5 Characteristics and results for studies that focused on a cognitively healthy sample.

Study ID (Author, year, and type of study)	Age; Sample Size (female)	Exercise		Change in Outcome Measures					
		Type	Delivery	FBNC		Cognitive Performance		Physical Performance	
Pieramico et al., 2012 *RCT (blinding unclear)*	I1: 60-75; n = 15 (8)	MDI	Group & Individual	↑		+	↔	↔	
	C: 60-75; n = 15 (7)	UC	Not applicable	↔		↔		↔	
Li et al., 2014 *Double-blind, cluster RCT*	I: 68.6 ± 5.7; n = 17 (8)	MDI	Group & Individual	↑	↔	+	↔	NM	
	C: 71.7 ± 4.0; n = 17 (6)	Lectures on health & aging	Unclear but appears to be in groups	↓	↔	−	↔		
Tao et al., 2016 *Single-blind RCT*	I1: 62.4 ± 4.6; n = 21 (13)	Tai-Chi Chuan	Unclear but appears to be in groups	↑		+		NM	
	I2: 62.2 ± 3.8; n = 16 (10)	Baduanjin	Unclear but appears to be in groups	↑		+			
	C: 59.8 ± 4.8; n = 25 (19)	Health education	Unclear but appears to be in groups	↔		↔			
Flodin et al., 2017 *RCT (blinding unclear)*	I: 68.4 ± 2.6; n = 22 (13)	Aerobic	Unclear but appears to be in groups	↔		NM		+	
	C: 69.2 ± 3.0; n = 25 (14)	Stretching and Toning	Unclear but appears to be in groups	↔				+	
Ji et al., 2017† *Quasi-RCT (blinding unclear)*	I: 67.0 ± 6.4; n = 12 (5)	MME	Individual	↑		+	↔	NM	
	C: 73.0 ± 8.0; n = 12 (7)	UC	Not applicable	↔		↔			
Prehn et al., 2017 *Single-blind RCT*	I: 69.0 ± 4.5; n = 11 (4)	Aerobic	Unclear but appears to be individually	↑	↓	+	↔	↔	
	C: 65.0 ± 5.8; n = 18 (10)	Stretching and Toning	Unclear but appears to be individually	↑	↓	−	↔	+	
Voss et al., 2019 *RCT (blinding unclear)*	I1: 65.66 ± 4.62; n = 53 (36)	Dance	Group	↔		−	↔	↔	
	I2: 65.49 ± 4.67; n = 39 (28)	Aerobic (Walk)	Group	↔		↔		+	

	I3: 64.62 ± 4.10; n = 45 (31)	MDI (Walk+)	Group	↑		+	↔	+
	C: 65.85 ± 4.29; n = 52 (34)	Strength, stretching, and stability	Group	↔		↔		↔
Voss et al., 2010 *RCT (blinding unclear)*	I: 67.3 ± 5.8; n = 30 (22)	Aerobic	Group	↑	↓	↔		+
	C: 65.4 ± 5.2; n = 35 (25)	Stretching and Toning	Group	↑		↔		↔

Note: Reading table from left to right indicates results for each group i.e., Intervention group in Pieramico et al., 2012 performed MDI in a group and individual setting and showed an ↑ in FBNC, and + ↔ & ↔ in cognitive and physical performance. Given the breadth of brain areas examined and cognitive/physical performance outcomes, a study can show more than one result, i.e. ↑ ↔, + 0, etc. Except for Voss et al. 2010 (task), all studies performed only resting-state fMRI. Studies with multiple intervention groups are numbered i.e., I1, I2, etc. Age (years) is mean ± standard deviation. C, control; I, intervention; MDI, multi-domain intervention; MME, multi-modal exercise; NM, not measured; RCT, randomized controlled trial; UC, usual care ↑, significantly increased; ↓, significantly decreased; +, significantly improved; −, significantly declined; ↔, unchanged. †, includes left-handed participants, and control group did not complete cognitive testing post-intervention.

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2.8 SUPPLEMENTARY MATERIAL

Supplemental Material A: PROSPERO Registration

The effect of exercise on functional brain network connectivity (FBNC) in older adults with and without cognitive impairment

Nick Bray, Frederico Pieruccini-Faria, Manuel Montero-Odasso

Citation

Nick Bray, Frederico Pieruccini-Faria, Manuel Montero-Odasso. The effect of exercise on functional brain network connectivity (FBNC) in older adults with and without cognitive impairment. PROSPERO 2018 CRD42018115015 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018115015

Review question

1) To identify the effect of exercise on FBNC, as measured by functional magnetic resonance imaging (fMRI), in older adults (60+ years of age) that are:

A) cognitively healthy/normal.

B) cognitively impaired; which will be divided further into those that are diagnosed with:

I) mild cognitive impairment (MCI).

II) all other dementia-related syndromes (i.e. Alzheimer's, Lewy body, vascular, etc.).

Searches

Sources include Embase and PubMed. There were no restrictions on country, language or publication period. Search date was 07/2018. Upon completion of full-text screening, the reference list of all included studies will be 'hand-searched' for additional articles that meet the inclusion criteria.

Types of study to be included

Inclusion criteria:

1) Type of study to be included:

A) Randomized Controlled Trials (RCT).

B) Quasi-RCT.

2) Studies with exercise, as previously defined, as the sole intervention or combined with other interventions, inclusive of:

A) Multi-modal - Exercise, as previously defined, plus other modalities (i.e. nutrition/diet advice, cognitive training, etc.).

B) Motor-cognitive - i.e. virtual reality games that combine exercise with cognitively demanding tasks; motor component will be considered exercise if it meets the previously identified definition.

3) Studies that measure FBNC using fMRI.

Exclusion criteria:

1) Type of study to be excluded:

A) Meta-Analysis.

Supplemental Material B: Kappa Statistics.

Formula:

		Reviewer 2			Total
		Include	**Exclude**	**Unsure**	
Reviewer 1	**Include**	a	b	c	I_1
	Exclude	d	e	f	E_1
	Unsure	g	h	i	U_1
Total		I_2	E_2	U_2	K

$P_O = a + e + i / K$
$P_E = I_1 \times I_2 + E_1 \times E_2 + U_1 \times U_2 / K^2$
Kappa Score = $P_O - P_E / 1 - P_E$

Note: P_O, observed agreement; P_E, chance-expected agreement; letters in formula represent a specific cell within the table

Title and Abstract Screening Results:

		Reviewer FPF			Total
		Include	**Exclude**	**Unsure**	
Reviewer NB	**Include**	172	9	7	188
	Exclude	4	1123	13	1140
	Unsure	8	28	8	44
Total		184	1160	28	1372
Kappa Score		0.82			

Full-Text Screening Results:

		Reviewer FPF			Total
		Include	**Exclude**	**Unsure**	
Reviewer NB	**Include**	13	0	0	13
	Exclude	3	38	0	41
	Unsure	0	0	0	0
Total		16	38	0	54
Kappa Score		0.80			

Supplemental Material C: Connectivity changes for studies that focused on a cognitively impaired sample

Author & Date	Analysis	Type of Exercise	Brain Area/Network	Post-intervention Change
Wells et al, 2013	1. Seed-based analysis of DMN	I: MDI C: UC	I > C: Posterior Cingulate Cortex → Medial Prefrontal Cortex.B. (DMN) I > C: Posterior Cingulate Cortex → Hippocampus.L. (DMN)	↑
Eyre et al, 2016	1. Correlations between voxel-wise changes in network connectivity	I: Yoga C: CT	I & C: DMN I & C: Posterior DMN I & C: Language Network I & C: Superior Parietal Network	NRI
Suo et al, 2016	1. Seed-wise of the whole brain	I1: MDI I2: RT + Sham CT I3: Sham RT + CT C: Sham RT& CT	I1 > I2, I3 & C: Hippocampus.B. → Superior Frontal Gyrus.R. I1 > I2, I3 & C: Hippocampus.B. → Anterior Cingulate Cortex* I1 & I2 > I3 & C: Hippocampus.B. → Middle Frontal Cortex* I1 & I3 > I2 & C: Hippocampus.B. → Inferior Temporal Lobe.R. I1 & I3 > I2 & C: Hippocampus.B. → Superior Frontal Gyrus.L. *	↑
			I1 > I2, I3 & C: Posterior Cingulate → Anterior Cingulate Cortex (DMN) I1 > I2, I3 & C: Posterior Cingulate → Posterior Cingulate (DMN) I1 & I2 > I3 & C: Posterior Cingulate → Inferior Temporal Lobe.L. (DMN)* I1 & I2 > I3 & C: Posterior Cingulate → Anterior Cingulate Cortex (DMN) I1 & I2 > I3 & C: Hippocampus.B. → Inferior Temporal Lobe.R. I1 & I3 > I2 & C: Posterior Cingulate → Anterior Cingulate Cortex.R. (DMN) I1 & I3 > I2 & C: Posterior Cingulate → Superior Frontal Lobe.L. (DMN) * Did not survive correction for baseline connectivity	↓
Tao et al, 2019	1. Seed-to-Voxel whole brain	I1: Baduanjin I2: Brisk Walking C: Usual care * All groups received health education	I1 > C: Hippocampus.R. → Angular Gyrus.R. I1 > C: Hippocampus.R. → Medial Prefrontal Cortex.L.* * At a less conservative threshold	↑
			I1,I2 & C: Anterior Cingulate Cortex.B. → Central Operculum.L. I1,I2 & C: Anterior Cingulate Cortex.B. → Cerebellum.B.	↔
Hsu et al, 2017	1. Seed-based analysis of the FPN	I: Aerobic C: UC	C > I : FPN → FPN *lost significance with an ITT analysis	↑
			I: FPN → FPN	↔

Note: Studies with multiple intervention groups are numbered i.e. I1, I2, etc. Network of specific brain area(s), relative to particular study, is enclosed in brackets i.e. Hippocampus.B. → Posterior Cingulate (DMN). → identifies specific connections identified by original authors. I, intervention; C, control; DMN, Default Mode Network; FPN, Frontoparietal Network; L, left; R, right; B, bilateral; NRI, not reported independently; ↑, significantly increased; ↓, significantly decreased; ↔, no change.

Supplemental Material D: Secondary outcomes of cognition and physical performance for studies that focused on a cognitively impaired sample.

Author & Date	Type of Exercise	Cognition and/or Physical Performance Outcome	Post-intervention Change
Wells et al, 2013	I: MDI C: UC	I & C: Alzheimer's Disease Assessment Scale-Cognitive	↔
Eyre et al, 2016	I: Yoga C: CT	I: Rey-Osterrieth Complex Figure Test Delayed Recall	+
		I & C: Hopkins Verbal Learning Test–Revised	↔
Suo et al, 2016	I1: MDI I2: RT + Sham CT I3: Sham RT + CT C: Sham RT& CT	I1 & I2 > I3 & C: Alzheimer's Disease Assessment Scale-Cognitive	+
		I2 & C > I1 & I3: Composite memory domain score	-
		I1-3 & C: Executive domain I1-3 & C: Attention-speed domain I1-3 & C: Subjective memory expectations I1-3 & C: Memory concerns	↔
Tao et al, 2019	I1: Baduanjin I2: Brisk Walking C: Usual care * All groups received health education	I1 > I2 & C: Montreal Cognitive Assessment	+
Hsu et al, 2017	I: Aerobic C: UC	I & C: Timed-Up-and-Go Test I & C: Short Physical Performance Battery Protocol I & C: Cardiovascular fitness (Six-Minute Walk Test) I & C: Physical Activities Scale for the Elderly	↔

Studies with multiple intervention groups are numbered i.e. I1, I2, etc. I, Intervention; C, Control; +, significantly improved; -, significantly decreased; ↔, no change.

Supplemental Material E: Connectivity changes for studies that focused on a cognitively healthy sample

Author & Date	Analysis	Type of Exercise	Brain Area/Network	Post-intervention Change
Pieramico et al, 2012	1. Resting state networks via independent component analysis	I: MDI C: UC	I: Precuneus (DMN)* I: Angular Gyrus.R. (DMN)* I: Posterior Ciingulate Cortex (DMN)* I: Frontal Eye Field.L. (DAN)* * Did not survive correction for false discovery rate	↑
			I & C: Other resting state networks	↔
Li et al, 2014	1. Region-to-region functional connectivity within the DMN 2. Seed-based whole-brain analysis	I: MDI C: Lectures on health & aging	I > C: Medial Prefrontal Cortex → Parahippocampal Cortex.L. (DMN) I > C: Medial Prefrontal Cortex → Parahippocampal Gyrus.L. (DMN)	↑
			C > I: Medial Prefrontal Cortex → Medial Frontal Gyrus (DMN)	↓
			I & C: Medial Prefrontal Cortex → Parahippocampal Cortex.R. (DMN) I & C: Medial Prefrontal Cortex → Hippocampal Formation.B. (DMN) I & C: Medial Prefrontal Cortex → Posterior Cingulate/Retrosplenial Cortex (DMN) I & C: Medial Prefrontal Cortex → Lateral Parietal Cortex.B. (DMN) I & C: Posterior Cingulate/Retrosplenial Cortex → Lateral Parietal Cortex.B. (DMN) I & C: Posterior Cingulate/Retrosplenial Cortex → Hippocampal Formation.B. (DMN) I & C: Posterior Cingulate/Retrosplenial Cortex → Parahippocampal Cortex.B. (DMN) I & C: Lateral Parietal Cortex.L. → Lateral Parietal Cortex.R. (DMN) I & C: Lateral Parietal Cortex.B. → Hippocampal Formation.B. (DMN) I & C: Lateral Parietal Cortex.B. → Parahippocampal Cortex.B. (DMN) I & C: Hippocampal Formation.L. → Hippocampal Formation.R. (DMN) I & C: Hippocampal Formation.B. → Parahippocampal Cortex.B. (DMN) I & C: Parahippocampal Cortex.L. → Parahippocampal Cortex.R. (DMN)	↔

Tao et al, 2016	1. Seed-to-voxel whole brain analysis, focusing on medial prefrontal cortex	I1: Tai-Chi Chuan I2: Baduanjin C: Health education	I1 > C: Hippocampus.B. → Medial Prefrontal Cortex.B. I2 > C: Hippocampus.B. → Medial Prefrontal Cortex.B.* * At a less conservative threshold	↑
Flodin et al, 2017	1. Seed-based correlation 2. Independent component analyses 3. Whole brain pattern via multivariate pattern analysis + others	I: Aerobic C: S&T	I & C: DMN I & C: Frontoparietal Network I & C: Cingulo-opercular Network I & C: Dorsal Attention Network I & C: Visual Network I & C: Somatosensory Network I & C: Ventral Attention Network I & C: Salience Network I & C: Auditory Network I & C: Subcortical Network I & C: Somato-motor Network I & C: Sensorimotor Network I & C: Non-identified Network Areas	↔
Ji et al, 2017[†]	1. ROI-to-ROI + others	I: MME C: UC	I > C: Putamen.R. → Superior Frontal Gyrus, Dorsolateral.R. I > C: Putamen.R. → Supplementary Motor Area.L. I > C: Putamen.R. → Median Cingulate (and Paracingulate Gyri).R. I > C: Putamen.R. → Amygdala.L. I > C: Putamen.R. → Cuneus.B. I > C: Putamen.R. → Superior Occipital Gyrus.B. I > C: Putamen.R. → Middle Occipital Gyrus.B. I > C: Putamen.R. → Inferior Occipital Gyrus.L. I > C: Putamen.R. → Fusiform.R. I > C: Putamen.R. → Inferior Parietal Gyrus.R. I > C: Putamen.R. → Supramarginal Gyrus.L. I > C: Putamen.R. → Angular Gyrus.R. I > C: Putamen.R. → Precuneus.B. I > C: Putamen.R. → Paracentral Lobule.L. I > C: Putamen.R. → Lenticular Nucleus, Putamen.R. I > C: Putamen.R. → Thalamus.R. I > C: Putamen.R. → Middle Temporal Gyrus.R. I > C: Putamen.R. → Temporal Pole (middle temporal gyrus).R. I > C: Globus Pallidus.R. → Posterior Cingulate Gyrus.L. I > C: Globus Pallidus.R. → Cuneus.L. I > C: Globus Pallidus.R. → Superior Occipital Gyrus.B.	↑

			I > C: Globus Pallidus.R. → Middle Occipital Gyrus.B. I > C: Globus Pallidus.R. → Fusiform.R. I > C: Globus Pallidus.R. → Inferior Parietal Gyrus.R. I > C: Globus Pallidus.R. → Supramarginal Gyrus.L. I > C: Globus Pallidus.R. → Angular.R. I > C: Globus Pallidus.R. → Precuneus.B. I > C: Globus Pallidus.R. → Lenticular Nucleus, Pallidum.R. I > C: Globus Pallidus.R. → Middle Temporal Gyrus.R. I > C: Globus Pallidus.R. → Temporal Pole (middle temporal gyrus).B. I > C: Globus Pallidus.R. → Cerebellum.R.	
Prehn et al, 2017	1. Seed-based whole brain analysis, focusing on ECN	I: Aerobic C: S&T	I > C: Dorsolateral Prefrontal Cortex.L. → Superior Parietal Gyrus/Precuneus.R. (ECN) I: Dorsolateral Prefrontal Cortex.L. → Middle Frontal Gyrus.R. (ECN) I: Dorsolateral Prefrontal Cortex.L. → Cerebellum.L. I > C: Dorsolateral Prefrontal Cortex.R. → Precuneus.L. (ECN) C > I: Dorsolateral Prefrontal Cortex.L. → Medial Superior Frontal Gyrus.L. (ECN)	↑
			I: Dorsolateral Prefrontal Cortex.L. → Cerebellum.L. C: Dorsolateral Prefrontal Cortex.B. → Precuneus.L. (ECN)	↓
Voss et al, 2019	ROI-ROI in networks listed	I1: Dance I2: Aerobic (Walk) I3: MDI (Walk+) C: Strength, stretching, and stability	I3 > C: SAL* * Additional interaction with those on anti-anxiety/depression medication	↑
			I1, I2, I3 & C: DMN, DAN, ECN	↔
Voss et al, 2010	1. Seeding connectivity of the DMN, FEN, and FPN, as well as the right primary motor and right auditory cortex	I: Aerobic C: S&T	I > C: Middle Temporal Gyrus.B. → Parahippocampal Gyrus.B. (DMN) I > C: Parahippocampal Gyrus.B. → Lateral Occipital/Parietal Cortex.B. (DMN) I > C: Middle Frontal Gyrus.L. → Middle Temporal Gyrus.B. (DMN) I > C: Anterior Lateral Prefrontal Cortex.R → Prefrontal Cortex.B. (FEN/CON) C > I: Frontal Operculum/Insula Cortex.R. → Lateral Occipital/Parietal Cortex.R. (FEN/CON/FPN)	↑
			I > C: Anterior Lateral Prefrontal Cortex.R. → Hippocampus.L./Anterior Parahippocampal Gyrus (DMN/FEN/CON)	↓

Note: Studies with multiple intervention groups are numbered i.e. I1, I2, etc. Network of specific brain area(s), relative to particular study, is enclosed in brackets i.e. Dorsolateral prefrontal cortex.R. → Precuneus.L. (ECN). → identifies specific connections identified

by original authors. I, Intervention; C, Control; DMN, Default Mode Network; ECN, Executive control Network; L, left; R, right; B, bilateral; ↑, significantly increased; ↓, significantly decreased; ↔, unchanged; †, includes left-handed participants, and control group did not complete cognitive testing post-intervention.

Supplemental Material F: Secondary outcomes of cognition and physical performance for studies that focused on a cognitively healthy sample.

Author & Date	Type of Exercise	Cognition and/or Physical Performance Outcome	Post-intervention Change
Pieramico et al, 2012	I: MDI C: UC	I: Babcock Story Recall Test Delayed Recall Test I > C: Occupational Therapy Evaluation: Process Skills	+
		I & C: Mini Mental State Examination I & C: Trail Making Tests A, B, and B-A I & C: Babcock Story Overall (Global Prose Memory) I & C: Babcock Story Immediate Recall Test I & C: Frontal Assessment Battery I & C: Phonemic fluency test (FAS form) I & C: Occupational Therapy Evaluation: Motor & Time Skills	↔
Li et al, 2014	I: MDI C: Lectures on health & aging	I > C: Paired Associative Learning Test	+
		C: Trail Making Tests	-
		I & C: Digit Span Forward and Backward Tests I & C: Stroop Test I & C: Category Fluency Test	↔
Tao et al, 2016	I1: Tai-Chi Chuan I2: Baduanjin C: Health education	I1 & I2 > C: Wechsler Memory Scale Test-Chinese Revision Memory Quotient	+
Flodin et al, 2017	I: Aerobic C: S&T	I & C: Cardiovascular fitness (cycle ergometer test) I > C: Cardiovascular fitness (cycle ergometer test)	+
Ji et al, 2017[†]	I: MME C: UC	I: WAIS-III Digit-Symbol Substitution Modality Test I > C: Discrimination rate for task performed during MRI	+

		I: Rivermead Behavioral Memory Test - immediate and delayed story recall I: Hopkins Verbal Learning Test-Revised - immediate, delayed, and recognition recall I: Trail Making Tests I: Stroop Color and Word Test I: WAIS-III Digit Span Test I & C: Performance accuracy for task performed during MRI	↔
Prehn et al, 2017	I: Aerobic C: S&T	I > C: Trail Making Tests change score I > C: Trail Making Test B C: Cardiovascular fitness (cycle ergometer test)	+
		C: Trail Making Test A C: Trail Making Test B C: Selective Attention Test	-
		I & C: Digit Span Backwards Test I & C: Stroop Color Word Interference Test I & C: Test of verbal fluency I & C: Test of verbal flexibility I & C: Verbal Learning and Memory Test: learning, delayed recall, consolidation, and recognition subsets	↔
Voss et al, 2019	I1: Dance I2: Aerobic (Walk) I3: MDI (Walk+) C: Strength, stretching, and stability	I2 & I3 > C: Cardiovascular fitness (treadmill test) I3 > C: Composite score of perceptual speed *	+
		I1 > C: Composite score of fluid abilities I1 > C: Composite score of perceptual speed*	-
		I1-3 & C: Composite score of memory I1-3 & C: Composite score of vocabulary *For those on anti-anxiety/depression medication)	↔
Voss et al, 2010	I: Aerobic C: S&T	I: Cardiovascular fitness (treadmill test)	+
		I & C: Forward and Backward Digit Span Test I & C: Spatial working memory task I & C: Test of task-switching I & C: Wisconsin Card Sort Task (all cognitive tests combined into composite measures)	↔

Note: Studies with multiple intervention groups are numbered i.e. I1, I2, etc. I, Intervention; C = Control; +, significantly improved; -, significantly decreased; ↔, no change. †, includes left-handed participants, and control group did not complete cognitive testing post-intervention.

Supplemental Material G: Correlation results of change scores (Post – pre) for studies that focused on a cognitively impaired sample.

Study ID (Author and year)	Type of Exercise	Variables Correlated		Correlation Results	
		Brain Area/Network	Cognition and/or Physical Performance Outcome	Intervention	Control
Wells et al., 2013			Not Completed		
Eyre et al., 2016	I: Yoga	Anterior cingulate cortex (DMN)	Hopkins Verbal Learning Test Delayed Recall	R_{14} = 0.84, p < 0.001	R_{11} = 0.73, p = 0.011
	C: CT	Frontal medial cortex (DMN)	Hopkins Verbal Learning Test Delayed Recall	R_{14} = 0.91, p < 0.001	R_{11} = 0.64, p = 0.035
		Posterior cingulate cortex (DMN)	Hopkins Verbal Learning Test Delayed Recall	R_{14} = 0.78, p = 0.001*	R_{11} = 0.68, p = 0.02
		Left lateral occipital cortex (DMN)	Hopkins Verbal Learning Test Delayed Recall	R_{14} = 0.81, p < 0.001*	R_{11} = 0.77, p = 0.005
		Dorsolateral pre-frontal cortex (DMN)	Hopkins Verbal Learning Test Delayed Recall	R_{14} = 0.87, p < 0.001	R_{11} = 0.68, p = 0.02
		Inferior frontal gyrus.L. (Language Network)	Hopkins Verbal Learning Test Delayed Recall	R_{14} = 0.82, p < 0.001*	R_{11} = 0.55, p = 0.079
		Near precentral and postcentral gyri (SPN)	Rey-Osterrieth Complex Figure Test Delayed Recall	R_{14} = –0.59, p = 0.028	R_{11} = –0.73, p = 0.011
				* Correlation was not significant after removal of an outlier	
Suo et al., 2016			Collapsed Groups		
Tao et al., 2019			Not Completed		
Hsu et al., 2017	I: Aerobic	FPN during right finger tapping	Timed-Up-and-Go Test	r = 0.67, p = 0.02	
	C: UC	FPN during right finger tapping	Short Physical Performance Battery Protocol	r = 0.14, p > 0.05	Not Reported
		FPN during right finger tapping	Cardiovascular fitness (Six-Minute Walk Test)	r = -0.37, p > 0.05	

Note. Correlations are based upon change (post-pre) for brain area/network and change (post-pre) for cognitive or physical performance outcomes. CT, cognitive training; UC, usual care; L, left; DMN, Default-Mode Network; SPN, superior parietal network; FPN, Frontoparietal Network.

Supplemental Material H: Correlation results of change scores (Post – pre) for studies that focused on a cognitively healthy sample.

Study ID (Author and year)	Type of Exercise	Variables Correlated		Correlation Results	
		Brain Area/Network	Cognition and/or Physical Performance Outcome	Intervention	Control
Pieramico et al., 2012	I: MDI	Precuneus (DMN)	Mini Mental State Examination	R = 0.11, p = 0.608	R = 0.238, p = 0.263
	C: UC	Precuneus (DMN)	Trail Making Tests A	R = 0.089, p = 0.68	R = 0.007, p = 0.975
		Precuneus (DMN)	Trail Making Tests B	R = 0.211, p = 0.322	R = -0.297, p = 0.159
		Precuneus (DMN)	Trail Making Tests B-A	R = 0.183, p = 0.393	R = 0.006, p = 0.977
		Precuneus (DMN)	Babcock Story Overall (Global Prose Memory)	R = -0.313, p = 0.136	R = -0.171, p = 0.424
		Precuneus (DMN)	Babcock Story Immediate Recall Test	R = -0.277, p = 0.189	R = -0.126, p = 0.556
		Precuneus (DMN)	Babcock Story Delayed Recall Test	R = -0.43, p = 0.036	R = -0.163, p = 0.448
		Precuneus (DMN)	Phonemic fluency test (FAS form)	R = -0.176, p = 0.411	R = -0.123, p = 0.568
		Precuneus (DMN)	Frontal Assessment Battery	R = -0.273, p = 0.196	R = -0.291, p = 0.167
		Precuneus (DMN)	Occupational Therapy Evaluation: Motor Skills	R = -0.199, p = 0.35	R = -0.355, p = 0.088
		Precuneus (DMN)	Occupational Therapy Evaluation: Process Skills	R = -0.547, p = 0.006	R = -0.176, p = 0.412
		Precuneus (DMN)	Occupational Therapy Evaluation: Time Skills	R = 0.275, p = 0.193	R = 0.393, p = 0.057
		Angular Gyrus.R. (DMN)	Mini Mental State Examination	R = 0.052, p = 0.81	R = 0.173, p = 0.42
		Angular Gyrus.R. (DMN)	Trail Making Tests A	R = -0.037, p = 0.862	R = 0.109, p = 0.613
		Angular Gyrus.R. (DMN)	Trail Making Tests B	R = -0.039, p = 0.857	R = -0.095, p = 0.658
		Angular Gyrus.R. (DMN)	Trail Making Tests B-A	R = -0.054, p = 0.802	R = 0.154, p = 0.472
		Angular Gyrus.R. (DMN)	Babcock Story Overall (Global Prose Memory)	R = -0.381, p = 0.067	R = -0.282, p = 0.182
		Angular Gyrus.R. (DMN)	Babcock Story Immediate Recall Test	R = -0.404, p = 0.05	R = -0.199, p = 0.352
		Angular Gyrus.R. (DMN)	Babcock Story Delayed Recall Test	R = -0.479, p = 0.018	R = -0.344, p = 0.099
		Angular Gyrus.R. (DMN)	Phonemic fluency test (FAS form)	R = -0.104, p = 0.629	R = -0.226, p = 0.288
		Angular Gyrus.R. (DMN)	Frontal Assessment Battery	R = -0.202, p = 0.345	R = -0.281, p = 0.184
		Angular Gyrus.R. (DMN)	Occupational Therapy Evaluation: Motor Skills	R = -0.293, p = 0.164	R = -0.275, p = 0.194
		Angular Gyrus.R. (DMN)	Occupational Therapy Evaluation: Process Skills	R = -0.517, p = 0.01	R = -0.276, p = 0.191
		Angular Gyrus.R. (DMN)	Occupational Therapy Evaluation: Time Skills	R = 0.162, p = 0.449	R = 0.379, p = 0.068

		Posterior Ciingulate Cortex (DMN)	Mini Mental State Examination	R = -0.192, p = 0.368	R = 0.168, p = 0.433
		Posterior Ciingulate Cortex (DMN)	Trail Making Tests A	R = -0.34, p = 0.104	R = 0.211, p = 0.323
		Posterior Ciingulate Cortex (DMN)	Trail Making Tests B	R = -0.328, p = 0.118	R = 0.291, p = 0.167
		Posterior Ciingulate Cortex (DMN)	Trail Making Tests B-A	R = -0.267, p = 0.207	R = 0.161, p = 0.451
		Posterior Ciingulate Cortex (DMN)	Babcock Story Overall (Global Prose Memory)	R = 0.498, p = 0.013	R = -0.038, p = 0.861
		Posterior Ciingulate Cortex (DMN)	Babcock Story Immediate Recall Test	R = 0.407, p = 0.049	R = -0.027, p = 0.899
		Posterior Ciingulate Cortex (DMN)	Babcock Story Delayed Recall Test	R = 0.408, p = 0.048	R = -0.017, p = 0.936
		Posterior Ciingulate Cortex (DMN)	Phonemic fluency test (FAS form)	R = 0.075, p = 0.727	R = -0.431, p = 0.035
		Posterior Ciingulate Cortex (DMN)	Frontal Assessment Battery	R = 0.007, p = 0.976	R = -0.052, p = 0.809
		Posterior Ciingulate Cortex (DMN)	Occupational Therapy Evaluation: Motor Skills	R = 0.109, p = 0.612	R = -0.038, p = 0.861
		Posterior Ciingulate Cortex (DMN)	Occupational Therapy Evaluation: Process Skills	R = 0.378, p = 0.069	R = -0.275, p = 0.193
		Posterior Ciingulate Cortex (DMN)	Occupational Therapy Evaluation: Time Skills	R = 0.184, p = 0.39	R = 0.305, p = 0.148
		Frontal Eye Field.L. (DAN)	Mini Mental State Examination	R = 0.074, p = 0.73	R = 0.358, p = 0.086
		Frontal Eye Field.L. (DAN)	Trail Making Tests A	R = -0.215, p = 0.313	R = 0.074, p = 0.732
		Frontal Eye Field.L. (DAN)	Trail Making Tests B	R = -0.354, p = 0.09	R = -0.181, p = 0.397
		Frontal Eye Field.L. (DAN)	Trail Making Tests B-A	R = -0.423, p = 0.04	R = 0.011, p = 0.958
		Frontal Eye Field.L. (DAN)	Babcock Story Overall (Global Prose Memory)	R = 0.478, p = 0.018	R = 0.009, p = 0.966
		Frontal Eye Field.L. (DAN)	Babcock Story Immediate Recall Test	R = 0.384, p = 0.064	R = 0.02, p = 0.926
		Frontal Eye Field.L. (DAN)	Babcock Story Delayed Recall Test	R = 0.306, p = 0.146	R = -0.055, p = 0.8
		Frontal Eye Field.L. (DAN)	Phonemic fluency test (FAS form)	R = -0.051, p = 0.812	R = 0.039, p = 0.857
		Frontal Eye Field.L. (DAN)	Frontal Assessment Battery	R = -0.132, p = 0.538	R = -0.039, p = 0.855
		Frontal Eye Field.L. (DAN)	Occupational Therapy Evaluation: Motor Skills	R = 0.198, p = 0.353	R = -0.355, p = 0.088
		Frontal Eye Field.L. (DAN)	Occupational Therapy Evaluation: Process Skills	R = 0.297, p = 0.159	R = -0.189, p = 0.376
		Frontal Eye Field.L. (DAN)	Occupational Therapy Evaluation: Time Skills	R = 0.034, p = 0.876	R = 0.15, p = 0.485
Li et al., 2014	I: MDI C: Lectures on health & aging	Medial Prefrontal Cortex → Parahippocampal Gyrus (DMN)	Category Fluency Test	r = 0.669, p = 0.003	Not Reported
		Medial Prefrontal Cortex → Parahippocampal Gyrus (DMN)	Trail Making Tests	r = -0.268, p = 0.298*	r = -0.397, p = 0.114*
		Medial Prefrontal Cortex → Parahippocampal Cortex.L. (DMN)	Trail Making Tests	r = -0.159, p = 0.541*	r = -0.529, p = 0.03*
		Medial Prefrontal Cortex → Medial Frontal Gyrus (DMN)	Trail Making Tests	r = -0.485, p = 0.049*	r = -0.237, p = 0.359*
		Medial Prefrontal Cortex → Medial Frontal Gyrus (DMN)	Category Fluency Test	r = 0.535, p = 0.027*	r = 0.522, p = 0.032*

				* Correlation of post-intervention scores, not change scores	
Tao et al., 2016			Collapsed Groups		
Flodin et al., 2017			Collapsed Groups		
Ji et al., 2017†	I: MME C: UC	Putamen.R. → Thalamus.R.	Changes of executive function (Inclusive of Trails B and Stroop Color & Word)	r = 0.7071, p = 0.015	Not Reported
Prehn et al., 2017			Not Completed		
Voss et al., 2019			Not Completed		
Voss et al., 2010	I: Aerobic C: S&T	Parahippocampal Gyrus.B. → Lateral Occipital/Parietal Cortex.B. (DMN) Middle Frontal Gyrus.L. → Middle Temporal Gyrus.B. (DMN)	Component score of executive function Component score of executive function	pr (44) = 0.39, p = 0.003 pr(44) = 0.27, p = 0.03	Not Reported

Note. Correlations are based upon change (post-pre) for brain area/network and change (post-pre) for cognitive or physical performance outcomes. MDI, multi-domain intervention; S&T, stretching and toning; MME, Multi-modal exercise; UC, usual care; L, left; R, right; B, bilateral; DMN, Default-Mode Network; DAN, Dorsal Attention Network. †, includes left-handed participants, and control group did not complete cognitive testing post-intervention.

CHAPTER 3: THE EFFECT OF HIGH DOSE VITAMIN D_3 ON PHYSICAL PERFORMANCE IN FRAIL OLDER ADULTS. A FEASIBILITY STUDY

Abstract: *Background:* Vitamin D deficiency is ubiquitous in frailty but the effectiveness of vitamin D supplementation to improve outcomes in frail individuals is unclear. It has been postulated that higher than the current recommended doses (800 IU/day) may be needed to achieve a neuromuscular effect in frail individuals. *Objectives:* 1) determine if 4000 IU per day of vitamin D_3 is safe for frail older adults; and 2) establish the efficacy of this dose to improve physical performance outcomes in this population. *Design:* Open-label, feasibility study. *Setting:* Community retirement centre. *Participants:* 40 older adults with frail or pre-frail characteristics. *Intervention:* 4000 IU of vitamin D_3 and 1200 mcg of calcium carbonate daily for four months. *Measurements:* Physical performance (grip strength, gait speed and short physical performance battery score), cognitive health and vitamin D and iPTH serum levels before and after the intervention. *Results:* Frail individuals improved short physical performance battery score (1.19, $p = 0.005$), fast gait speed (4.65, $p = 0.066$) and vitamin D levels (7.81, $p = 0.011$). Only frail females made a significant improvement in grip strength (1.92, $p = 0.003$). Stratifying the sample by baseline vitamin D levels revealed that participants with vitamin D insufficiency (≤ 75 nmol/L) significantly improved short physical performance battery score (1.06, $p = 0.04$), fast gait speed (6.28, $p = 0.004$) and vitamin D levels (25.73, $p = <0.0001$). Pre-frail individuals, as well as those with sufficient vitamin D levels (> 75 nmol/L) made no significant improvement in any outcome. *Conclusions:* Vitamin D supplementation using 4000 IU/daily is safe and has a modest beneficial effect on physical performance for frail individuals and those with insufficient vitamin D levels. Participants with vitamin D insufficiency (≤ 75 nmol/L) showed greater benefits. Our feasibility study provides results to help calculate effect size for a future RCT.

3.1 INTRODUCTION

Frailty is recognized as a state of mild to severe vulnerability caused by a reduction across various physiological systems which places the individual at increased risk for disease and disability (1). The expected growth of the aging population will result in a rapid increase in the absolute prevalence of this geriatric syndrome over the next 30 years (2), placing a significant financial burden upon healthcare systems. Frailty is an independent predictor of hospitalization, institutionalization, falls, worsening health status, and even mortality but it does not mark the end of life (3,4). Frailty exists on a spectrum (non- frail, pre-frail, and frail) and there is even heterogeneity in pure frail individuals (5). However, transitions between states are not unidirectional.

Physical exercise (6,7) and nutritional supplementation (8) are the only interventions to consistently delay or reverse frailty. Sarcopenia and osteoporosis are two of several potential modifiable factors that may indirectly improve frailty status, although treatments remain inconclusive (9).

Vitamin D deficiency is ubiquitous in frailty (10), and it has been associated with slowing gait (11,12), higher comorbidities (13), falls (14), brain health (15) and mortality (16). However, the efficacy of vitamin D supplementation to improve neuromuscular outcomes in frail individuals is unclear. A meta-analysis conducted by our group concluded that at least 800-1000 IU in daily doses demonstrates beneficial effects on balance and muscle strength in healthy and clinical populations (17), showing more benefits with higher doses. This meta-analysis suggested that doses higher than the minimum current recommendations (400 to 800 IU/day; 18) for bone health, may be needed to achieve a neuromuscular effect in frail individuals due to their higher risk of vitamin D deficiency.

Only one study has performed a vitamin D intervention utilizing a daily dosing strategy (1000-2000 IU/day) greater than the current recommended amount for participants classified according to a frailty identification tool (19). However, participants were exclusively pre-frail, doses varied based upon baseline vitamin D levels, and the intervention was completed as an 8-week run-in phase to a resistance training program.

Therefore, the purpose of our study was: 1) to determine if an even greater dose (4000 IU/day) of vitamin D was safe and feasible for frail and pre-frail older adults; and 2) to establish the efficacy of this dose to improve neuromuscular physical performance outcomes in this population. We hypothesized that 4000 IU/day of vitamin D would: 1) be feasible and safe for

frail and pre-frail older adults; and 2) lead to an improvement in gait, strength and short physical performance battery (SPPB) scores, as well as cognition.

3.2 METHODS

3.2.1 Design & Participants

This was an open-label, interventional study, that included 40 older adults with frailty characteristics. Sample size was estimated to detect a significant increase in gait speed, 10 cm/s after intervention, assuming a power of 80%, α of 5% and dropout rate of 10%. Participants were recruited from the Cherryhill naturally occurring retirement centre, a 13-building apartment complex in London, Ontario housing 2,500 older adults (mean age = 79.53 ± 9.53 years).

In addition to being frail or pre-frail, inclusion criteria were the following: 75 years of age or more; male or female; able to ambulate 10 meters with or without a mobility aid; and proficiency in English. Individuals were excluded if they: were taking vitamin D doses >1000 IU/day within the last six months; had a hip or knee fracture/replacement in the preceding six months; were diagnosed with dementia; had a history of severe bone disease (osteomalacia); had overactive parathyroid glands (hyperparathyroidism) or severe kidney problems that require dialysis (renal insufficiency); and were suffering from any neurological disorder (i.e. stroke) with residual motor deficits affecting gait.

Ethics approval was obtained from the Western University's Ethics Board for Health Sciences Research involving Human Subjects (Review Number: 15663). All participants read and signed a letter of informed consent during enrollment.

3.2.2 Frailty Status Ascertainment

Frailty status was ascertained using a modified (4) Frailty Phenotype (20), which has been previously validated (21, 22). In brief, slow gait speed was met if the participant walked below one meter per second (1m/sec) at a usual and comfortable pace. Previous research suggests gait speed below 1m/sec indicates risk of adverse health outcomes (23, 24). Low physical activity criterion was operationalized using the Physical Activity Scale for the Elderly (PASE). PASE scores less than 64/52 for men/women indicated a positive response of low physical activity. The muscle weakness criterion was met when grip strength in the dominant hand was less than or equal to cut-off points used in the original Frailty Phenotype (20). The exhaustion criterion was evaluated using two questions from the Center for Epidemiologic Studies Depression Scale; participants that confirmed everything they did was an effort or that they felt they could not get going in the previous two months, indicated a positive response. Participants met the weight criteria if they had unintentionally lost more than five kilos in the previous 12 months. A total score for frailty status was then calculated as the sum of positive findings. Individuals were then categorized into one of three frailty categories based on the total frail score, as follows: frail, score ≥3; pre-frail, score of 1–2; and non-frail, score of 0.

3.2.3 Intervention

Participants consumed 4000 IU of vitamin D_3 (cholecalciferol) and 1200 micrograms (mcg) of calcium carbonate upon waking, every day for four months. Tablets were provided in a monthly blister package prepared by our research pharmacist. At the end of every month of enrollment, a research assistant completed a check-in with each participant. During check-ins, tablets from "missed" days were collected and tabulated, and the next month supply was delivered. These

procedures helped to promote adherence and compliance. Information about falls, adverse events related to the intervention and general well-being were also collected during check-ins. For the duration of the intervention, participants were asked to maintain their normal diet and routine, and not consume any additional vitamin D and/or calcium.

3.2.4 Assessment Timeline

Assessments were completed at baseline (T0) and post- intervention (T4) during the four months of follow-up.

3.2.5 Medical & Cognitive Assessments

Information pertaining to sociodemographic characteristics, previous falls, fractures, prescribed medications, comorbidities and anthropometrics were recorded and confirmed using electronic medical records. A disability scale developed for community-based cohorts evaluated functional capacity in basic activities of daily living. Summed disability scores ranged from 0-16, with higher scores equating to greater disability.

Cognition was assessed via the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) questionnaire. Alternate MoCA versions were utilized during follow-up assessments to prevent a learning effect.

3.2.6 Physical Performance Assessments

Grip strength was assessed using a hand-held dynamometer (Jamar, Sammons Preston, Bolingbrook, IL), in a seated position, with the shoulder neutrally rotated and elbow flexed to 90˚ so that the lower part of the contracting arm rested upon the arm of the chair. Participants were

instructed to not lift their arm from the arm of the chair while contracting or the repetition would be repeated. The result of this test was used in the grip strength criteria for frailty ascertainment. Knee extension strength was evaluated using a Biodex System 3 Dynamometer (Biodex Medical Systems Inc., Shirley, NY) via a standardized protocol by Bassey and Short (1990). Participants performed three contractions on the dominant hand and leg, and the average was used for data analysis.

Gait performance was assessed using the six-meter GAITRite Portable Walkway System (CIR Systems Inc., Franklin, NJ). The GAITRite software collects and analyzes the imprint of each foot fall in real-time to calculate the participant's gait speed. Participants performed one untimed practice trial before completing three trials at both a usual and fast pace; these walking conditions have been previously described elsewhere (22). Participants started/finished each walk one meter before/after either walkway end to avoid recording acceleration/deceleration phases.

General physical performance was assessed via the SPPB, a standardized performance test applied in research and geriatric settings, which characterizes older adults across a broad spectrum of lower extremity function (26). The SPPB requires individuals to complete a: 1) hierarchy of balance tasks; 2) repeated five-time sit-to-stand task; and 3) a 2.4 meter walking course at their "normal speed". Individuals are assigned a score of 0-4 for all tasks, for a total possible score ranging from 0-12; higher scores indicate greater physical performance and thus, functional independence.

3.2.7 Vitamin D, iPTH & Calcium Serum Levels

Venous blood samples were collected for the measurement of 25(OH) vitamin D, intact parathyroid hormone (iPTH) and calcium serum levels. Specimens were stored at -82° C as aliquots, immediately after centrifugation. Serum 25(OH) vitamin D was measured using a specific RIA (Diasorin Inc., Sallugia, Italy). Serum levels of iPTH were determined by a two-site chemiluminescent ELISA (Alpco Ltd., Salem, NH; range:10-55pg/ml, sensitivity:1.57 pg/ml). Serum ionized calcium levels were evaluated via the Kodak method® (Kodak, USA).

3.2.8 Primary Outcome Measure

The primary outcome measures were gait speed, muscle strength, and SPPB score. The secondary outcome was the effect of the intervention upon cognitive status.

3.2.9 Statistical Analysis

Demographics and clinical characteristics are summarized using either means and standard deviations or frequencies and percentages, as appropriate. A one-way analysis of variance or Pearson chi-square analysis compared baseline characteristics. A one-way analysis of covariance assessed primary and secondary outcome measures, stratified by frailty status (pre-frail or frail) and baseline vitamin D levels (> or ≤ 75 nmol/L), and adjusted for relevant confounders, including age, sex, baseline vitamin D levels and number of comorbidities and medications. All statistical tests were two-tailed and a p-value ≤ 0.05 indicated significance. Analyses were made using SPSS version 23.0 (SPSS Inc., IBM Corporation, Chicago, IL).

3.3 RESULTS

Forty older adults were included in this study. Participants were mostly female (78%), and had an average age, body mass index and years of education of 84.20 (±4.88), 25.64 (±3.70) and 12.38 (±3.07), respectively. Baseline vitamin D levels were insufficient (≤ 75 nmol/L) or sufficient (> 75 nmol/L) in 16 and 24 participants, respectively. Coincidently, sixteen participants were pre-frail (1-2 indicators) and 24 were frail (≥ 3 indicators). Slow gait was the most common indicator of frailty, followed by weakness, exhaustion, low activity and weight loss. Baseline participant characteristics, stratified by vitamin D levels, were statistically similar (Table 1).

Outcome variables post-intervention, stratified by frailty status and baseline vitamin D levels, are displayed in Table 2 and 3, respectively. Frail individuals showed significant improvement in SPPB score, PASE score and vitamin D levels (Figure 1). Additionally, fast gait speed was trending ($p = 0.066$) towards significance (Table 2). Only frail females made a significant improvement in grip strength ($p = 0.003$; not shown in table). Pre-frail individuals exhibited no significant improvement in any outcome variable. Individuals with insufficient vitamin D levels showed significant improvement in SPPB score, fast gait speed and vitamin D levels (Figure 1). Individuals with sufficient vitamin D levels demonstrated no significant improvement in any outcome variable (Table 3). The dosing strategy did not lead to an adverse event, nor to the development of hypercalcemia.

3.4 Discussion

Vitamin D_3 supplementation in a daily dose of 4000 IU for four months results in significant improvement in SPPB and PASE score in frail individuals. Grip strength and fast gait speed also improved in frail individuals but only the former is significant, and only in females. When

stratifying the sample by baseline vitamin D levels, we found that SPPB score and fast gait speed significantly improve for those with insufficiency. No participant, regardless of baseline vitamin D or frailty status, experienced an adverse outcome.

These results suggest improvement in lower extremity function for those with greater deficits i.e. frail and insufficient vitamin D levels. These groups experienced a clinical (27) and statistically significant improvement in SPBB score. These changes have meaningful implications as SPPB score has been associated with disability, institutionalization and falls (27). Improvement in lower extremity function is further supported by the observed increases in knee strength for those with insufficient vitamin D levels, albeit not significant.

Our results also suggest improvement in physical reserve. Although all participants were instructed to maintain their normal routine during the intervention, frail individuals made a significant improvement in PASE score. Vitamin D supplementation may have helped to partially alleviate the significant deficits that are commonly associated with frailty. Previous research has highlighted that vitamin D supplementation may be a restorative hormone given its positive impact upon postural sway, falls risk, and bone fractures (9). Thus, the intervention may have led to greater functional capacity, ability to perform activities of daily living and possibly even exercise, creating a positive feedback loop leading to enhanced overall fitness.

Improvement in physical reserve is supported further by the observed change in fast gait speed. Fast gait speed significantly improved in those with insufficient vitamin D levels and was trending towards a statistically significant improvement in frail participants. The ability to alter walking speed from a usual to fast pace has been termed walking speed reserve (28). A greater

difference between these walking conditions demonstrates greater reserve and may indicate better physiological and cognitive abilities (28).

The significant improvement observed in grip strength for only frail females post-intervention is likely attributed to the male-female health-survival paradox; a phenomenon where females become frail earlier, yet live longer than males (29). It has been shown that females have higher frailty scores when compared to men across seven different frailty scales (30). Thus, onset and progression of the syndrome follow sex-specific pathways and ultimately, further complicate this geriatric syndrome.

Previous research in vitamin D supplementation and pre- frail older adults demonstrated a significant and non-significant improvement in sit-to-stand power and SPPB score following an eight week intervention, respectively (19). Discrepancies in SPPB results between our study and the previous research provide further support for the possibility that those with greater deficits may benefit the most from a high dose vitamin D intervention. Our study did not measure power and thus, cannot draw conclusions with the only other measure of lower extremity function from this previous research. However, in consideration with the other findings of our study, these studies synergistically suggest that interventions ≥ 1000 IU/day for 8+ weeks may improve lower extremity function.

Important limitations include the limited sample size that may have affected our ability to find additional significant associations, and the risk of type I error for multiple testing. The open-label design precludes us from ascertaining a significant effect compared with placebo. However, our results provide effect sizes that can guide future trials. Given that our stratification reveals that those with greater deficits can benefit from this intervention, we suggest that future studies focus

on frail individuals with insufficient vitamin D levels. Ultimately, high dose (4000 IU/day) vitamin D may be a simple and cost-effective intervention to improve and maintain physical performance in older adults with frailty.

Vitamin D supplementation, in a daily high dose (4000 IU) is safe, feasible, and may have a beneficial effect on physical performance in older adults with frailty and those with insufficient vitamin D levels. A larger randomized controlled trial is required to confirm our preliminary findings.

3.5 GRAPHICS

3.5.1 Figures

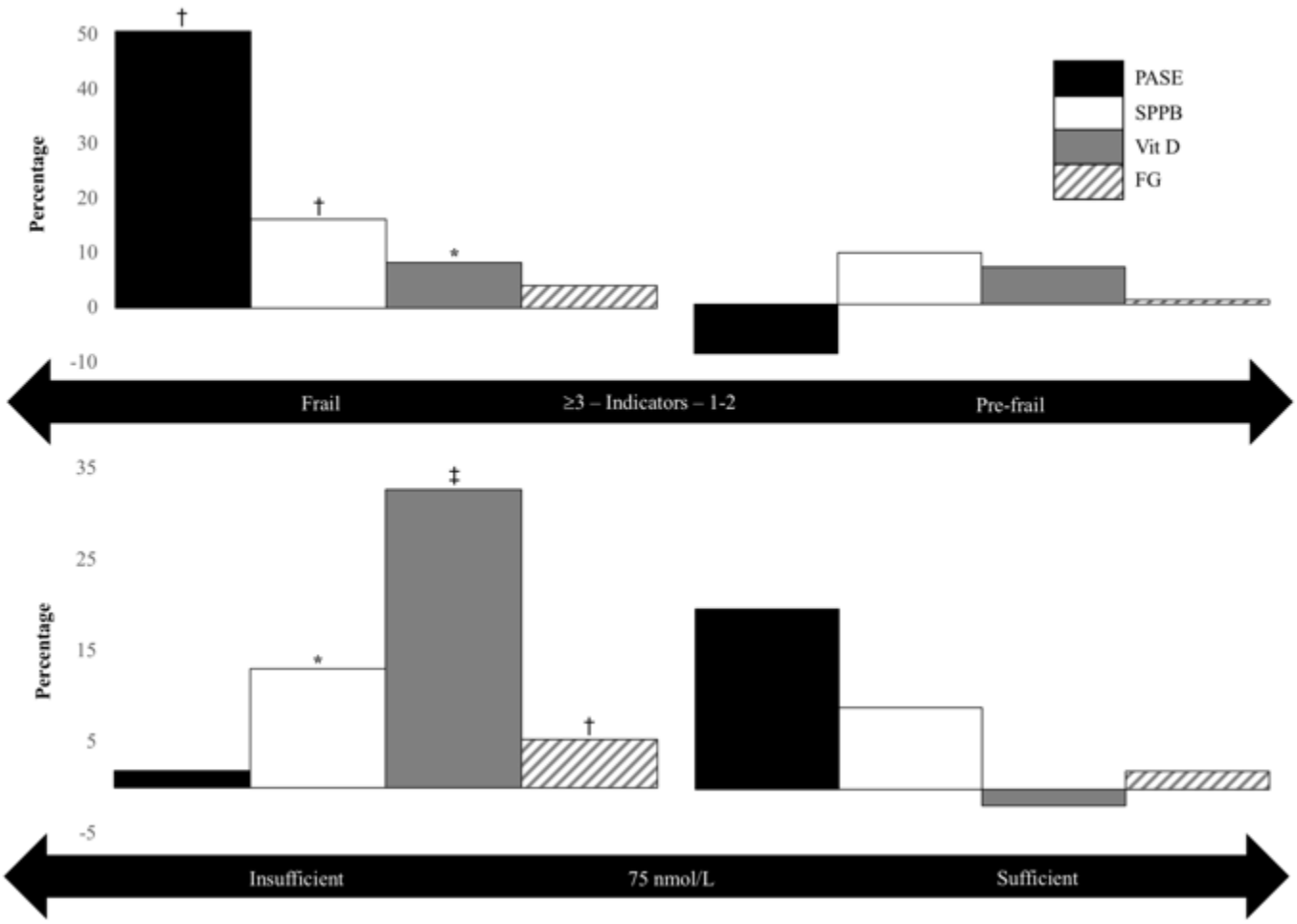

Figure 3.1 Percentage change in measures with significant change, stratified by frailty and vitamin D status. PASE = Physical Activity Scale for the Elderly; SPPB = Short Physical Performance Battery; Vit D = vitamin D levels; FG = fast gait speed; nmol/L = nanomoles per litre; * = p-value <0.05; † = p-value <0.01; ‡ = p-value <0.0001.

3.5.2 Tables

Table 3.1 Baseline characteristics (n=40) stratified by baseline vitamin D levels (Insufficient and Normal).

Characteristic	Total (n=40)	Vitamin D Levels		*p*-value
		Insufficient (n=16) ≤75 nmol/L	Sufficient (n=24) >75 nmol/L	
Age (Mean, SD)	84.20 (4.88)	83.38 (4.60)	84.75 (5.08)	0.39
Female (n, %)	31 (78%)	14 (88%)	17 (71%)	0.272
Years of Education (Mean, SD)	12.38 (3.07)	11.94 (2.70)	12.67 (3.32)	0.469
Body Mass Index (Mean, SD)	25.64 (3.70)	25.11 (3.55)	26.00 (3.83)	0.464
No. Comorbidities (Mean, SD)	4.30 (1.80)	4.75 (1.39)	4.00 (2.00)	0.201
No. Prescription Medications (Mean, SD)	7.10 (4.70)	5.44 (4.03)	8.26 (4.85)[a]	0.064
Disability Score (Mean, SD)	3.23 (3.66)	2.88 (3.07)	3.46 (4.05)	0.628
No. Falls (Mean, SD)	0.55 (2.15)	0.31 (0.60)	0.71 (2.74)	0.575
Self-report memory problems (n,%)	17 (44%)	4 (25%)	13 (57%)[a]	0.051
Frail (n, %)	24 (62%)	10 (67%)	14 (58%)	0.603

Note: ANOVA, Pearson chi-square analysis as appropriate. a, n=22.

Table 3.2 Changes in outcome measures after intervention (T4), stratified by baseline (T0) frailty status.

Outcome	Frail (≥ 3)				Pre-frail (1-2)			
	T0	T4	Change at T4	*p*-value	T0	T4	Change at T4	*p*-value
MMSE	27.05 (3.02)	27.30 (2.56)	+0.25 (1.77)	0.555	27.57 (2.79)	28.14 (1.29)	+0.57 (2.68)	0.439
MoCA	22.50 (4.25)	22.85 (3.79)	+0.35 (2.57)	0.557	22.29 (3.65)	23.00 (4.10)	+0.71 (3.27)	0.428
PASE	**22.75 (12.25)**	**46.19 (25.71)**	**+23.44 (26.21)**	**0.004**	90.46 (45.95)	83.55 (31.17)	-6.91 (33.78)	0.475
SPPB	**6.14 (1.93)**	**7.33 (2.58)**	**+1.19 (1.72)**	**0.005**	7.65 (1.91)	8.36 (1.95)	+0.71 (2.02)	0.208
Disability scale	4.24 (3.92)	3.86 (4.34)	-0.38 (2.52)	0.479	1.07 (1.69)	0.57 (1.22)	-0.50 (2.10)	0.390
Grip Strength (N)	19.72 (8.12)	20.44 (6.92)	+0.72 (2.47)	0.212	19.76 (5.17)	17.83 (3.92)	-1.93 (4.11)	0.103
Knee Strength (N)	53.24 (20.69)	54.98 (23.32)	+1.74 (17.13)	0.672	50.56 (16.12)	51.82 (11.59)	+1.26 (8.07)	0.568
Vitamin D (nmol/L)	**85.95 (27.15)**	**93.76 (23.46)**	**+7.81 (14.54)**	**0.011**	98.25 (37.72)	104.75 (24.45)	+6.50 (29.18)	0.457
iPTH (pg/ml)	50.05 (30.07)	61.27 (39.83)	+11.22 (22.64)	0.071	73.70 (68.70)	76.70 (106.31)	+3.00 (44.19)	0.857
Calcium (mmol/L)	2.13 (0.41)	2.32 (0.12)	+0.19 (0.42)	0.064	2.33 (0.11)	2.38 (0.12)	+0.05 (0.12)	0.134
UG Speed (cm/sec)	78.73 (23.47)	79.27 (21.54)	+0.54 (10.86)	0.825	98.89 (13.08)	100.94 (13.73)	+2.05 (6.69)	0.27
FG Speed (cm/sec)	109.45 (27.80)	114.10 (26.10)	+4.65 (10.58)	0.066	125.34 (17.65)	126.23 (15.98)	+0.89 (9.78)	0.738

Note: iPTH = intact parathyroid hormone; UG = usual gait; FG = fast gait; N = newton; nmol/L = nanomoles per litre; pg/ml = pictograms per millilitre; mmol/L = millimoles per litre; cm/sec = centimeters per second.

Table 3.3 Changes in outcome measures after intervention (T4), stratified by baseline (T0) vitamin D levels.

Outcome	Insufficient (≤75 nmol/L)				Sufficient (>75 nmol/L)			
	T0	**T4**	**Change at T4**	***p*-value**	**T0**	**T4**	**Change at T4**	***p*-value**
MMSE	27.88 (1.87)	27.65 (2.29)	-0.23 (1.22)	0.431	26.91 (3.39)	27.77 (2.11)	+0.86 (2.45)	0.117
MoCA	23.06 (3.65)	23.82 (3.81)	+0.76 (2.84)	0.269	22.23 (4.21)	22.36 (3.79)	+0.13 (2.89)	0.83
PASE	74.53 (39.14)	75.93 (34.59)	+1.40 (26.75)	0.862	47.90 (47.84)	59.66 (31.80)	+11.76 (34.30)	0.169
SPPB	**7.06 (1.98)**	**8.12 (2.42)**	**+1.06 (1.78)**	**0.04**	6.61 (2.27)	7.26 (2.36)	+0.65 (1.83)	0.105
Disability scale	2.71 (3.06)	1.94 (1.85)	-0.77 (2.34)	0.185	3.61 (4.08)	3.22 (4.52)	-0.39 (2.28)	0.429
Grip Strength (N)	18.69 (7.63)	18.25 (7.19)	-0.44 (2.58)	0.523	20.20 (5.97)	19.77 (4.47)	-0.43 (3.74)	0.58
Knee Strength (N)	55.91 (21.78)	60.01 (22.94)	+4.10 (22.77)	0.452	49.68 (18.22)	50.87 (16.54)	+1.19 (9.48)	0.559
Vitamin D (nmol/L)	**53.00 (14.50)**	**78.73 (17.17)**	**+25.73 (18.22)**	**<0.0001**	107.70 (18.84)	105.83 (20.97)	-1.87 (12.43)	0.478
iPTH (pg/ml)	61.35 (29.19)	57.51 (31.50)	-3.84 (31.94)	0.633	51.82 (47.14)	63.62 (71.04)	+11.80 (31.01)	0.07
Calcium (mmol/L)	2.22 (0.30)	2.31 (0.11)	+0.09 (0.31)	0.249	2.22 (0.34)	2.36 (0.12)	+0.14 (0.36)	0.079
UG Speed (cm/sec)	88.80 (22.01)	91.27 (20.47)	+2.47 (6.27)	0.125	84.52 (22.15)	85.56 (21.64)	+1.04 (10.85)	0.654
FG Speed (cm/sec)	**112.79 (26.32)**	**119.07 (23.97)**	**+6.28 (7.77)**	**0.004**	117.99 (23.27)	120.39 (21.01)	+2.40 (11.52)	0.363

Note: iPTH = intact parathyroid hormone; UG = usual gait; FG = fast gait; N = newton; nmol/L = nanomoles per litre; pg/ml = pictograms per millilitre; mmol/L = millimoles per litre; cm/sec = centimeters per second.

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CHAPTER 4: A MULTIMODAL INTERVENTION TO INCREASE FUNCTIONAL BRAIN NETWORK CONNECTIVITY IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT. RESULTS FROM SYNERGIC, A DOUBLE-BLIND, MULTI-SITE RCT.

Abstract: *Introduction:* Functional brain network connectivity (FBNC) identifies areas that are spatially separate but temporally similar in their neural signaling, but it is altered in those with mild cognitive impairment (MCI), a pre-dementia state. Lifestyle modification is a promising interventional strategy to lower dementia risk. *Methods:* Double-blind, multi-site RCT assigned participants with MCI to one of five study arms. 3x/week for 20-weeks, participants performed 30-minutes of cognitive or controlled cognitive training, followed by 60-minutes of physical or control physical exercise. Vitamin D (10,000 IU/pill) or control were ingested 3x/week for 20-weeks. Pre and post-intervention, participants underwent 3-Tesla resting-state fMRI and a battery of physical and cognitive tests. Using the CONN toolbox, we measured FBNC change (Post – (minus) Pre) across four statistical models that collapsed for and/or included some or all study arms. Pearson's investigated correlations between FBNC change and secondary outcome change. *Results:* Our study included 120 participants (mean age: 73.89±6.50). Compared to the pure control, physical exercise (model 1) with cognitive training (model 2) and all three interventions combined (model 4) demonstrated a between-arm increase (Post - Pre) in FBNC between the Hippocampus and Angular Gyrus. After controlling for false discovery rate, there was no significant correlation between FBNC change and cognitive or physical performance change, but effect sizes ranged from small to large. *Conclusion:* Physical exercise appears to be as efficacious as combined interventions to restore FBNC in regions (Hippocampus to Angular Gyrus) of the Default-mode, one of the initial networks compromised in MCI. Implications for behavioral outcomes remain unclear.

4.1 INTRODUCTION

Brain health deteriorates in normal aging (1–4), but it occurs much more rapidly in those with MCI (5,6), an intermediate state between normal cognitive aging and dementia syndromes, including Alzheimer's disease (7,8). Changes in brain function represent one of the earliest biomarkers in those at risk for dementia syndromes as they precede structural atrophy and occur years before clinical manifestation (9). fMRI provides one avenue to measure brain function via the blood oxygen level dependent signal (10,11). Subsequently, this permits the measurement of FBNC or areas of the brain that are spatially separated but temporally linked in their neural signaling (12), enabling efficient information processing and completion of complex functions (13). Indeed, individuals with MCI show alterations in FBNC (14–16).

The rising aging population and subsequent increase in absolute cases (17), as well as the ineffectiveness of pharmacological interventions, have created a fundamental shift to early identification and prevention of those at risk of dementia syndromes (18). Lifestyle modification involves altering long-term routines and might delay or prevent up to 40% of all dementias (19). As a result, there has been a significant uptick in the number of intervention trials evaluating efficacy in dementia-related outcomes. In August 2020 (20), nine manuscripts were published covering just the efficacy of physical exercise (21–23), cognitive training (24–27), adequate nutrition intake (28), or some combination (29).

Our recent systematic review found that within-network FBNC increased following an intervention that focused on or included physical exercise in older adults, regardless of cognitive status (30). Two other similar and recent reviews found that exercise may increase functional activation or connectivity within a specific network (31) and strengthen connectivity between hemispheres (32). A meta-analysis on the effects of cognitive training in aging also found an increase in within-network connectivity (33). No previous intervention has examined the effectiveness of vitamin D supplementation on an fMRI-related outcome. However, vitamin D deficiency is associated with reduced Hippocampal volume and altered structural connectivity (34), as well as cortical thinning (35) and a higher risk of Alzheimer's disease (36).

The purpose of this study was to evaluate the effect of combined physical exercise (PE) modalities (aerobic and resistance training) separately and synergistically with cognitive training (CT) and/or vitamin D (VD) supplementation (multimodal intervention) on FBNC in older adults with MCI. Given the known impact of PE on physical performance, and the relationship between FBNC and cognitive performance, we also determined if a change in FBNC correlated with a

change in physical and cognitive performance outcomes. We hypothesized that: 1) compared to the control arm, the combined exercise and multimodal intervention would show significant increases in within-network FBNC; and 2) changes in FBNC would be significantly correlated with changes in physical and cognitive performance.

4.2 METHODS

4.2.1 Design & Participants

The SYNchronizing Exercises, Remedies in GaIt and Cognition (SYNERGIC or SYN) trial (37) (NCT02808676) was a multi-site, randomized, phase II, quasi-factorial, double-blind controlled study evaluating the effect of combined PE separately and synergistically with CT and/or VD supplementation in older adults (60 to 85 years) with MCI. All SYNERGIC sites resided in Canada and included Western University (London, ON; lead site), University of Waterloo (Waterloo, ON), Wilfrid Laurier University (Waterloo, ON), University of Montreal (Montreal, QC), and University of British Columbia (Vancouver, BC). Potential participants were diagnosed with MCI as per existing guidelines (38). SYNERGIC recruited potential participants from the community and clinics serving MCI populations and based the sample size on change in Alzheimer's Disease Assessment Scale (ADAS)-Cog and Cog 13 (39).

In addition to a clinical screening, SYNERGIC participants completed three in-person assessments, including pre-intervention (T0), post-intervention (T6), and follow-up (T12). T0 and T6 occurred immediately before and after a 20-week intervention, while T12 occurred 6-months after T6. All in-person assessments included the collection of demographic information and a battery of neuropsychological tests, as well as physical and metabolic tests. SYNERGIC

only conducted imaging at T0 and T6, and therefore, these are the only time points of interest for the present study (Figure 1). The present study's inclusion and exclusion criteria were identical to SYNERGIC, except the following two additions to the exclusion criteria: 1) Did not complete an MRI assessment at both T0 and T6; and 2) Participants consider their left hand to be dominant.

Randomization for SYNERGIC was generated centrally by a research pharmacist using a web-based randomization service (www.randomizer.org) for each study site. Block randomization by five was applied to ensure an appropriate balance of participant characteristics. Permuted blocks were employed to ensure balance over time. After the T0 assessment, research personnel not involved in measuring outcomes or administering the intervention accessed the randomization list to determine arm allocation. Research personnel were blinded to arm allocation while performing and analyzing all assessments. Participants were blind to the "active" intervention and study hypotheses. Intervention personnel (i.e., trainers) were aware of arm allocation but were not directly informed of the study hypotheses. All institutions received approval from their local ethics board.

4.2.2 Intervention

Overview – Regardless of the intervention arm, all participants completed group-training sessions 3x/week for 20-weeks. Each training session included 30-minutes of CT or cognitive training control (CTc), followed by 60-minutes of combined PE or physical exercise control (PEc). We removed participants from the study if they could not maintain adherence (i.e., 80% of sessions attended). To ensure a 1(trainer):4 ratio, no more than eight individuals participated in a single exercise session. Trainers were undergraduate students from health and exercise

science fields (i.e., Kinesiology, Human Kinetics, etc.), supervised by graduate students from a similar field.

Active & Control Cognitive Training – Participants performed CT and CTc on a tablet (iPad®). CT included two different visuomotor tasks that targeted working memory and attention. The CT program was custom-written, previously utilized for neuro-rehabilitation (40,41), and individually tailored to the participant. CTc alternated between performing a pre-defined touristic search of a foreign city and watching a National Geographic video. Each session included a new city or video. The pre-defined touristic search required participants to find three hotels, tourist attractions, and restaurants. After watching the National Geographic video, the participant answered three questions (Supplemental Material A).

Combined & Control Physical Exercise – PE began with a 10-minute warm-up on either a treadmill, stationary bike, or elliptical at a self-selected pace that would increase heart rate. Resistance training incorporated two lower (leg press and hamstring curl) and three upper body (chest press, seated row, and latissimus dorsi pull) exercises. Participants began with an upper-body exercise of their choosing for each session and then alternated between a lower and upper body exercise. Resistance training followed a pre-determined, standardized intensity, volume, and progression. Within each session, trainers prescribed resistance training so that participants reached exhaustion at or near the last prescribed repetition of the final set for every exercise. Therefore, trainers increased the resistance training weight when it became too easy, as per a rating of perceived exertion of 8 or less (42,43). Following resistance training, participants performed 2x10-minutes of aerobic training on the same ergometers used to warm-up. Like resistance training, aerobic training intensity systematically increased throughout the program

(Supplemental Material B). PEc included stretching, balance, and toning exercises that did not improve muscle strength or endurance nor progress in volume, intensity, and rest periods. To keep participants engaged, PEc exercises alternated every three weeks according to a pre-determined schedule.

Combined & Control Vitamin D – The VD intervention required participants to ingest one tablet of 10,000IU of vitamin D_3 3x/week for 20-weeks. Our previous work demonstrating safety and efficacy provided the rationale for the dosing strategy (44). Vitamin D control (VDc) participants followed the same dosing timeline but ingested a placebo pill identical to the VD capsule.

Overall, PE, CT, and VD interventions were combined within arm 1 and represented the SYN group. Conversely, PEc, CTc, and VDc were combined within arm 5 and represented the pure control (PC) group. In addition to PE, arms 2, 3, and 4 included CT and VDc, CTc and VD, and CTc and VDc, respectively.

4.2.3 MRIs

Acquisition – We conducted imaging for Ontario, Montreal, and British Columbia sites at Robarts Research Institute, Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, and UBC MRI Research Centre. Both Ontario and Montreal sites utilized a Siemens Magnetom Prisma Fit 3 Tesla MRI scanner (Siemens AG, Munich, Germany). The British Columbia site conducted imaging on a Philips Achieva 3 Tesla MRI Scanner (Koninklijke Philips N.V., Amsterdam, The Netherlands). MRIs followed version 3.8 of the Canadian Dementia Imaging Protocol (45). Imaging included a variety of modalities with a total scan time of 1.3 hours, but for the present study, we utilized only T1W (Siemens: 20-channel head coil;

sequence: MPRAGE; acceleration factor: 2; TR/TE: 2300/2.98 ms; flip angle: 9°; slice thickness: 1.0mm without gap; acquisition matrix: 256x256 mm; resolution: 1.0 x 1.0 mm; bandwidth: 240 Hz. Phillips: 8-channel Sense head coil; sequence: MPRAGE; acceleration factor: 2; TR/TE: 7.3/3.3 ms; flip angle: 9°; slice thickness: 1.0mm without gap; acquisition matrix: 248(AP) x 256 (FH) mm; resolution: 1.0 x 1.0 mm; bandwidth: 228.6 Hz) and resting state-fMRI (Siemens: 20-channel head coil; sequence: EPI BOLD; acceleration factor: 2; TR/TE: 2130/30 ms; flip angle: 70°; slice thickness: 3.5 mm without gap; acquisition matrix: 64x64 mm; volumes: 250; resolution: 3.5 x 3.5 mm; bandwidth: 2442 Hz; eyes: open. Phillips:8-channel Sense head coil; EPI (Fast Field Echo); acceleration factor: 2; TR/TE: 2110/30 ms; flip angle: 70°; slice thickness: 3.5 mm without gap; acquisition matrix: 64x64 mm; volumes: 250; resolution: 3.5 x 3.5 mm; bandwidth: 2371.7 Hz; eyes: open).

Preprocessing – We visually inspected all raw data before using in-house tools (46–48) to organize files according to the brain imaging data structure (49) and then preprocess them using fMRIPrep (version 20.2.0) (50) (Supplemental Material C). Post-fMRIPrep, the data was skull-stripped using FMRIB Software Library (version 6.0.4) (51) Brain Extraction Tool (52) and then uploaded to the CONN Functional Connectivity Toolbox (version 20.b) (53). CONN is an open-source MATLAB (version R2020b) and Statistical Parametric Mapping (version SPM12) based cross-platform software. As per recommendations (54) and as a final preprocessing step, an 8mm FWHM Gaussian kernel smoothed the functional volumes. Similar to previous publications using CONN (55), denoising regressed out signal contributions of white matter (5 parameters) and cerebrospinal fluid (5 parameters), as well as motion realignment parameters and their first-order derivatives (12 parameters). Intermediate (0.5 mm, 3 sd) ART-based scrubbing detected

and removed outlier volumes. Additional denoising steps included linear detrending and band-pass filtering (0.008 Hz to 0.09 Hz) after regression (RegBP).

ROI-ROI Analysis – A bivariate correlations coefficient (Fisher's transformed) with a hemodynamic response function weighting calculated a functional connectivity map between each region of interest (ROI). We included the following networks and their ROIs: Default-Mode (56), Dorsal Attention (57), Salience (58), Frontoparietal (59), and Sensorimotor (60), because of their inclusion in a prior publication (61), susceptibility to aging (62,63), and relation to secondary outcomes (64–67) (Supplemental Material D). The CONN Toolbox automatically includes the selected networks and their ROIs, based upon a CONN Independent Component Analysis of 497 subjects from the Human Connectome Project (68) (Supplemental Material E).

S-V Analysis – Given the present study's exploratory nature and that previous researchers have conducted multiple analyses within the same study (69,70), we also completed a seed-to-voxel (S-V) analysis. We selected the left and right Hippocampus as seeds because of their susceptibility to dementia-related syndromes, usage in similar studies (71,72), and because most participants were classified as amnestic MCI. The S-V analysis was identical to the ROI-ROI, except a functional connectivity map was generated for the seed(s) and every other voxel in the brain (Supplemental Material E).

4.2.4 Secondary Outcomes

We selected seven secondary outcomes because they represented a broad range of functions. Alzheimer's Disease Assessment Scale-Cog 13 (39), a global measure of cognition, was the SYNERGIC trial's primary outcome. We used the number of items missed on delayed recall of

the Alzheimer's Disease Assessment Scale-Cog 13 (39) and trail-making test normalized ((B-A)/A) (73) to evaluate memory and executive function, respectively. The trail-making test was also the most common cognitive outcome in our systematic review (30).

The physical performance outcomes included grip strength because of its popularity (74), as well as average usual gait speed and sit-to-stand time (muscle power) because of their sensitivity to aging (75,76). Furthermore, we decided to include muscle strength and power measures because no previous study has examined their relationship with fMRI data, despite a call to do so (77). Cardiovascular fitness (i.e., six-minute walk distance) was the most common physical performance outcome in our systematic review (30).

All cognitive assessments and the six-minute walk test followed standardized instructions (78). As previously described in another publication (44), we assessed maximum grip strength and usual gait speed via three attempts with the average used for data analysis. Sit-to-stand testing followed instructions from the short physical performance battery protocol (79).

4.2.5 Statistical Analysis

Pre-intervention (T0) Characteristics: Except for sex reported as sample size, demographics and clinical characteristics for each study arm are summarized using means and standard deviations. Notably, SYNERGIC was a double-blind, randomized controlled trial, and as such, any between-arm differences at T0 would be strictly due to chance. To identify differences in characteristics regarding MRI status and thus, provide insight into who or why specific individuals chose to forgo MRIs, we also compared T0 characteristics of participants that completed: 1) both T0 and T6 imaging; 2) only T0 imaging; and 3) no imaging. A one-way analysis of variance (ANOVA)

or Pearson chi-square assessed differences between arms/groups for all participant characteristics.

Models of Analyses: Within the present study, we conducted four separate models of analyses using the five study arms. In brief:

- Model 1 investigated the effects of PE: PE (arm 1+2+3+4) versus PC (arm 5)
- Model 2 investigated the synergistic effect of CT and PE: PE & CT (arm 1+2) versus PE & CTc (arm 3+4) versus PC (arm 5)
- Model 3 investigated the synergistic effect of VD and PE: PE & VD (arm 1+3) versus PE & VDc (arm 2+4) versus PC (arm 5)
- Model 4 investigated the full synergistic effect: PE & CT & VD (SYN; arm 1) versus PC (arm 5)

See Figure 2 for an aerial view of the statistical model.

FBNC: To determine between-arm differences at T0 (main effect), we conducted a t-test in models 1 and 4 and a one-way ANOVA in models 2 and 3. For the primary outcome, we analyzed average change (T6 - (minus) T0) in FBNC using a 2x2 mixed ANOVA in models 1 and 4; and a 3x2 mixed ANOVA in models 2 and 3. If model 2 or 3 identified a significant difference between the three study arms, we conducted post-hoc testing via a 2x2 mixed ANOVA (54).

Covariates & False Discovery Rate: We adjusted all FBNC analyses for the covariates of age, sex, self-reported years of education, and self-reported number of comorbidities. Change in FBNC was considered statistically significant based upon standard settings for cluster-based

inferences of ROI-ROI (cluster threshold: $p < 0.05$ cluster-level p-false discovery rate (FDR) corrected; connection threshold: $p < 0.05$ p-uncorrected) (80), and S-V analyses (cluster threshold: $p < 0.05$ cluster-size p-FDR corrected; voxel threshold: $p < 0.001$ p-uncorrected) (81).

Secondary Outcomes: Using Statistical Package for the Social Sciences (SPSS version 27; IBM Canada Ltd. Markham, Ontario), change score (T6-T0) was calculated for all secondary outcomes and then converted to a z-score of standardized residuals via linear regression to control for the same covariates used in the FBNC analysis (age, sex, number of comorbidities, and years of education).

Correlation: In SPSS, we assessed all change (T6-T0) scores for linearity, outliers, and normality. Pearson's correlation is considered robust to deviations from normality but is susceptible to outliers. Therefore, extreme outliers, identified as those with a standardized residual change score three times the interquartile range, were removed. For the present study, correlation analyses aimed to determine the relationship between FBNC change (T6-T0) and physical and cognitive performance change (T6-T0) in each model's intervention and control arms. In alignment with our previous systematic review (30), we restricted correlation to only connections that survived the most conservative standards (correcting for FDR and adjusting for all covariates). Correlations were two-tailed, and a p-value ≤ 0.05 controlling for FDR (Supplemental Material F) indicated statistical significance.

4.3 Results

Demographic Information – 183 participants were randomized into the five study arms. 90 participants completed both T0 and T6 MRI, but eight were excluded (left-handedness, n = 6;

and image artifacts, n =2) (Figure 3) from the following arms: arm 1 (SYN), n = 1; arm 2 (PE&CT&VDc), n = 1; arm 3 (PE&CTc&VD), n = 1; arm 4 (PE&CTc&VDc), n = 2; and arm 5 (PC), n = 3. Therefore, our final analysis included 82 participants. Participants abstained from T0 MRI for various reasons (i.e., not interested, claustrophobia, etc.), and most participants missed their T6 MRI due to restrictions surrounding the COVID-19 pandemic. The average number of days between T0 MRI and start of the intervention, and end of the intervention and T6 MRI were 27 and 22, respectively.

There was a significant between-arm difference in sex distribution and height (cm) at T0 (Table 1). As previously highlighted, SYNERGIC was a double-blind RCT. As such, any differences are strictly due to chance. There were no significant between-group differences for those that completed imaging versus those that completed only T0 imaging or no imaging (Supplemental Material G).

FBNC ROI-ROI – There was a significant between-arm difference in T0 Salience network connectivity in model 4 (SYN vs. PC). However, this difference no longer existed at T6 (Supplemental Material H). There were no significant between-arm changes (T6-T0) in FBNC in models 1 (PE vs. PC), 2 (PE&CT vs. PE&CTc vs. PC), or 3 (PE&VD vs. PE&VDc vs. PC). The intervention arm demonstrated a significant between-arm increase (T6-T0) in connectivity for a single cluster in model 4 (SYN vs. PC), ($F(2,27) = 6.57$; $p\text{-}FDR < 0.05$; Supplemental Material I). However, the cluster only survived controlling for years of education and sex.

FBNC S-V (Seed = Right Hippocampus) – There were no between-arm differences at T0. Intervention arms demonstrated a significant between-arm increase (T6-T0) in model 1 (PE vs. PC; Cluster: size = 376 & 215 p-FDR < 0.01 & < 0.05), 2 (PE&CT vs. PE&CTc vs. PC; Cluster:

size = 535 *p*-FDR = < 0.001), and 4 (SYN vs. PC; Cluster: size = 381 *p*-FDR = < 0.01). In all models, the cluster included the left superior division of the Lateral Occipital Cortex and left Angular Gyrus. For model 2, post-hoc tests showed that the significant between-arm increases (T6-T0) were for both intervention arms relative to the PC (PE&CT; Cluster: size = 265 *p*-FDR < 0.05 / PE&CTc; Cluster: size = 334 *p*-FDR < 0.01). All connections maintained significance after controlling for all covariates (Table 2).

FBNC S-V (Seed = Left Hippocampus) – There was a significant between-arm difference in connectivity with the left inferior frontal and precentral gyrus at T0 in model 4 (SYN vs. PC). However, this difference no longer existed at T6 (Supplemental Material H). The intervention arm demonstrated a significant between-arm increase (T6-T0) in only model 4 (SYN vs. PC; Cluster: size = 297 *p*-FDR < 0.01). The cluster included only the left superior division of the Lateral Occipital Cortex. The connection maintained significance after controlling for all covariates (Table 2).

Despite slight differences in the coordinates of clusters that demonstrated significant change in connectivity, they displayed general overlap when reviewed in Multi-image Analysis GUI (MANGO; version 4.1) (82) (Figure 4). Given the inconsistency in the brain's anatomical labeling (83) and because our S-V clusters included two different anatomical regions, we used xjView (version 9.7) (84) to review anatomical labelling. In brief, only the left Angular Gyrus had a high number (~40-70%) of active voxels across all models.

Correlation – We restricted our Pearson's correlation of change (T6-T0) scores to only the S-V analysis because it survived controlling for all covariates. Specific to sit-to-stand time, we removed four participants from the analysis who could not perform the task at either T0 or T6.

We also removed outliers from the Alzheimer's Disease Assessment Scale-Cog overall (n = 1), grip strength (n = 1), six-minute walk distance (n = 4), and connectivity score in model 2 (n = 1). Supplemental Material J includes mean scores for all secondary outcomes at T0, T6, and T6-T0.

Only connectivity change (T6-T0) in model 2 (PE&CT x PE&CTc x PC) demonstrated statistically significant correlations at a *p*-value <0.05. PE&CTc cluster connectivity change showed a moderate negative correlation with usual gait speed change ($r(30) = -0.365$, $p = 0.04$). Meaning, an increase in connectivity correlated with a decrease (decline) in gait speed (centimeters per second; cm/sec). Other correlations across multiple models were trending towards but ultimately failed to reach a *p*-value <0.05 (Table 3). Notably, sit-to-stand time change for PE of model 1 (PE vs. PC) showed a small-moderate negative correlation with cluster connectivity change ($r(59) = -0.226$ $p = 0.08$). Meaning, an increase in connectivity correlated with a decrease (improvement) in sit-to-stand time (sec). Notably, no correlations survived correction for FDR.

4.4 Discussion

We investigated the effect of a multimodal intervention on FBNC, as assessed by fMRI, in older adults with MCI. In support of our hypothesis, we found significant increases in within-network FBNC in interventions that included PE (model 1) with CT (model 2) and VD (model 4). Contrary to our hypothesis, there was no correlation between FBNC change (T6-T0) and change in secondary outcomes of physical and cognitive performance after controlling for FDR.

Our results suggest that CT with and without VD may provide some additional increases in FBNC, but based upon its involvement in all models, PE appears to be primarily responsible for

the observed changes; this is supported further by the S-V clusters that, despite being from different models, displayed general overlap. The lack of significant change in FBNC when we added just VD to PE (model 3) inevitably brings into question its effectiveness. Vitamin D is an essential nutrient and work by our group (44), as well as another (85), has suggested that high-doses provide benefits to physical but not cognitive performance in those with the most significant deficits (i.e., physically frail and/or insufficient vitamin D serum levels). Therefore, the lack of findings in model 3 may reflect our failure to account for these variables.

Research has previously suggested a linkage between the Hippocampus and Angular Gyrus (86,87). Although not included in CONN's ROIs, previous research indicates that both the Hippocampus and Angular Gyrus are part of the Default-Mode Network (88,89), albeit with some evidence of lateralization (90,91). The Hippocampus and Angular Gyrus also play a role in the "core" (91) and "core recollection network" (92), which overlap but are different from the Default-Mode Network (93). The Default-Mode Network is one of the first networks to demonstrate alterations (decrease in connectivity) for those at risk of Alzheimer's disease (94). Anatomically, the Default-Mode Network overlaps with regions that accumulate the highest amount of Alzheimer's pathology (95,96). Therefore, our intervention-induced increases in Hippocampus to Angular Gyrus connectivity may help offset the initial changes in FBNC for those at risk of dementia syndromes and, in doing so, reflect a return to brain function that may be considered more typical of normal aging.

As part of the Default-Mode Network, the Hippocampus and Angular Gyrus play a role in self-referential thought, such as remembering the past and planning for the future (97). Hippocampus to Angular Gyrus connectivity may also be crucial to spatial navigation or knowing where you

are and how to get to places (98,99). Despite not reaching significance once corrected for FDR, our findings showed that change in usual gait speed and sit-to-stand time had moderate to large effect sizes with change in Hippocampus to Angular Gyrus connectivity. Therefore, such changes in connectivity may influence the completion of physical performance or everyday functional tasks like walking and sitting. Research must continue to examine the relationship between FBNC and behavioral outcomes as it will help delineate increases and decreases in connectivity. Relative to sit-to-stand time, future research should address if increases in Hippocampus to Angular Gyrus connectivity reflect alterations in spatial navigation or ability to exert muscle power, for which sit-to-stand time is considered a proxy measure. Such information could have important implications for interventional strategies.

The present study supports our recent systematic review and others (31,33) showing that RCTs increase within-network FBNC, regardless of older adults' cognitive status (30). Our systematic review included five studies on older adults with MCI, three (71,72,100) of which included the Hippocampus as a seed. Except for one, the Hippocampus demonstrated an increase in connectivity with all clusters, including but not limited to the posterior cingulate cortex, middle frontal cortex, and like the present study, Angular Gyrus; two of these three studies also identified their anatomical areas as belonging to the Default-Mode Network. The remaining two studies on MCI did not conduct an independent statistical analysis of FBNC (101) or focused on the Frontoparietal Network (102). Similar to our findings, no previous studies demonstrated a significant correlation between FBNC change and change in physical or cognitive performance in just the intervention group after controlling for covariates and/or correcting for FDR. Therefore, implications for behavioral outcomes at this current time are unclear. Correlations

with moderate to large effect sizes are encouraging and, at the very least, warrant further examination in future work.

Changes in FBNC are believed to reflect a cascade of biological and cellular changes (103). Potential downstream effects on behavioral outcomes are likely to be moderated by various genetic and lifestyle factors. For example, individuals with higher (worse) frailty status demonstrate more significant clinical impairment despite lower Alzheimer's pathology (104). Ultimately, how exactly interventions alter FBNC and the resulting change, if any, in behavioral outcomes is complex given the variety of biological, cellular, genetic, and lifestyle factors involved, further complicated by their interaction with neurodegeneration.

The current study is the first to examine the effect of PE, CT, and high dose VD supplementation in older adults with MCI, but it is not without limitation. Only our S-V analysis showed a significant change in connectivity and none of our seven secondary outcomes correlated with a change in connectivity after correcting for FDR. Therefore, most of our analyses demonstrated no significant results. Furthermore, the present study includes just two (ROI-ROI and S-V) of the many analysis options available, and as shown previously, researchers can take a different approach to the same question (105). We did not include site, scanner, body mass index, etc., as covariates, but similar to the selection of MRI preprocessing methods (106), covariate use in neuroimaging is an active area of research (107). Although a multi-site trial, we only included participants from central and western Canada. The Atlantic provinces of Canada hold some of the highest obesity rates (108), likely reflecting an alternative lifestyle. As such, our sample should not be considered indicative of all Canadians. As with all exercise interventions and despite excluding individuals that participated in a structured exercise program for the six

months before their T0 assessment, we cannot rule out that our current sample reflects those with a high affinity for exercise. Given the low rates of physical activity within Canada, our participants should be considered atypical (109). Finally, and given the already small (≤20) number of participants per study arm, we did not conduct a separate analysis for each sex.

In addition to the previous suggestions already put forth, future research in FBNC must be adequately powered to detect true post-exercise intervention differences, despite MRI being described as the least enjoyable component of tested outcomes (110). Researchers should also examine factors that moderate the impact of PE on FBNC. Given recent work, frailty status (104,111) and vascular properties (i.e., flow, reserve, etc.) (112,113) represent just some of the potential avenues. PE represents a therapeutic intervention with a multitude of benefits (114,115). Still, detailed reporting of exercise parameters (i.e., frequency, intensity, time, type, etc.) (116) is sometimes inadequate (30,117) despite being critical to replication and clinical uptake. Similarly, future work must compare different exercise parameters if we are to identify an optimal approach. For example, machine versus free-weight resistance training, specific exercise selection, and different intensity ranges; high-intensity aerobic interventions may be more beneficial (118,119) and equally or more enjoyable than continuous training (120,121).

4.5 Conclusion

The present study examined the impact of PE separately and synergistically with CT and/or VD on FBNC, assessed via fMRI, in older adults with MCI. In support of our hypothesis, we demonstrated that PE increased FBNC between the Hippocampus and the Angular Gyrus, representing regions of the Default-Mode Network. CT with and without VD created some additional changes to PE-induced FBNC. No intervention or control arms demonstrated a

significant correlation between FBNC change and change in secondary outcomes of physical and cognitive performance after controlling for FDR, but some effect sizes were in the moderate to large range. These findings support previous research that PE with and without other interventional strategies is efficacious in restoring connectivity to the Default-Mode Network, one of the initial networks compromised in MCI. However, the behavioral implications for change in FBNC require further investigation.

4.6 GRAPHICS

4.6.1 Figures

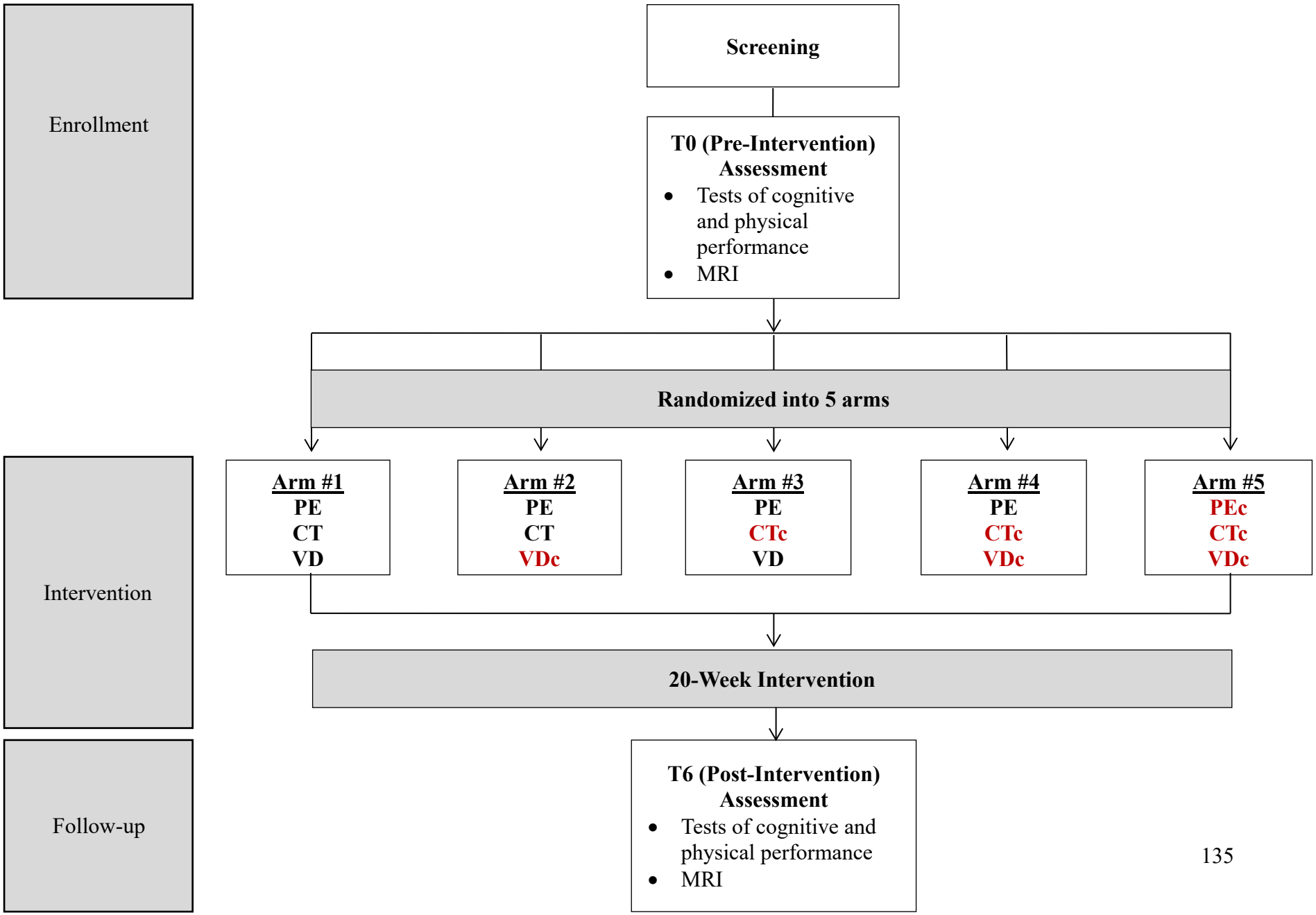

Figure 4.1 Overview of the timeline, assessment periods, and study arms. Red font identifies control arms. c, control; CT, cognitive training; MRI, magnetic resonance imaging; PC, pure control; PE, physical exercise; SYN, synergic; VD, vitamin D.

1) Model 1: PE vs. PC

Arm #1 (n = 18)	Arm #2 (n = 15)	Arm #3 (n = 20)	Arm #4 (n = 15)	Arm 5 (n = 14)
PE	PE	PE	PE	PEc
CT	CT	CTc	CTc	CTc
VD	VDc	VD	VDc	VDc

2) Model 2: PE&CT vs. PE&CTc vs. PC

Arm #1 (n = 18)	Arm #2 (n = 15)	Arm #3 (n = 20)	Arm #4 (n = 15)	Arm 5 (n = 14)
PE	PE	PE	PE	PEc
CT	CT	CTc	CTc	CTc
VD	VDc	VD	VDc	VDc

3) Model 3: PE&VD vs. PE&VDc vs. PC

Arm #1 (n = 18)	Arm #2 (n = 15)	Arm #3 (n = 20)	Arm #4 (n = 15)	Arm 5 (n = 14)
PE	PE	PE	PE	PEc
CT	CT	CTc	CTc	CTc
VD	VDc	VD	VDc	VDc

4) Model 4: SYN vs. PC

Arm #1 (n = 18)	Arm 5 (n = 14)
PE	PEc
CT	CTc
VD	VDc

Figure 4.2 Overview of the four models used for statistical analyses. Shading (white, grey, and black) identifies arms that are collapsed within each model. Red font identifies control arms. c, control; CT, cognitive training; PC, pure control; PE, physical exercise; SYN, synergic; VD, vitamin D. Post-hoc testing in model 2:

A: Collapsed Arms 3-4 vs Arm 5;
B: Collapsed Arms 1-2 vs Arm 5;
C: Collapsed Arms 1-2 vs Collapsed Arms 3-4.

No post-hoc test in model 3 as comparison of all three groups identified no significant differences.

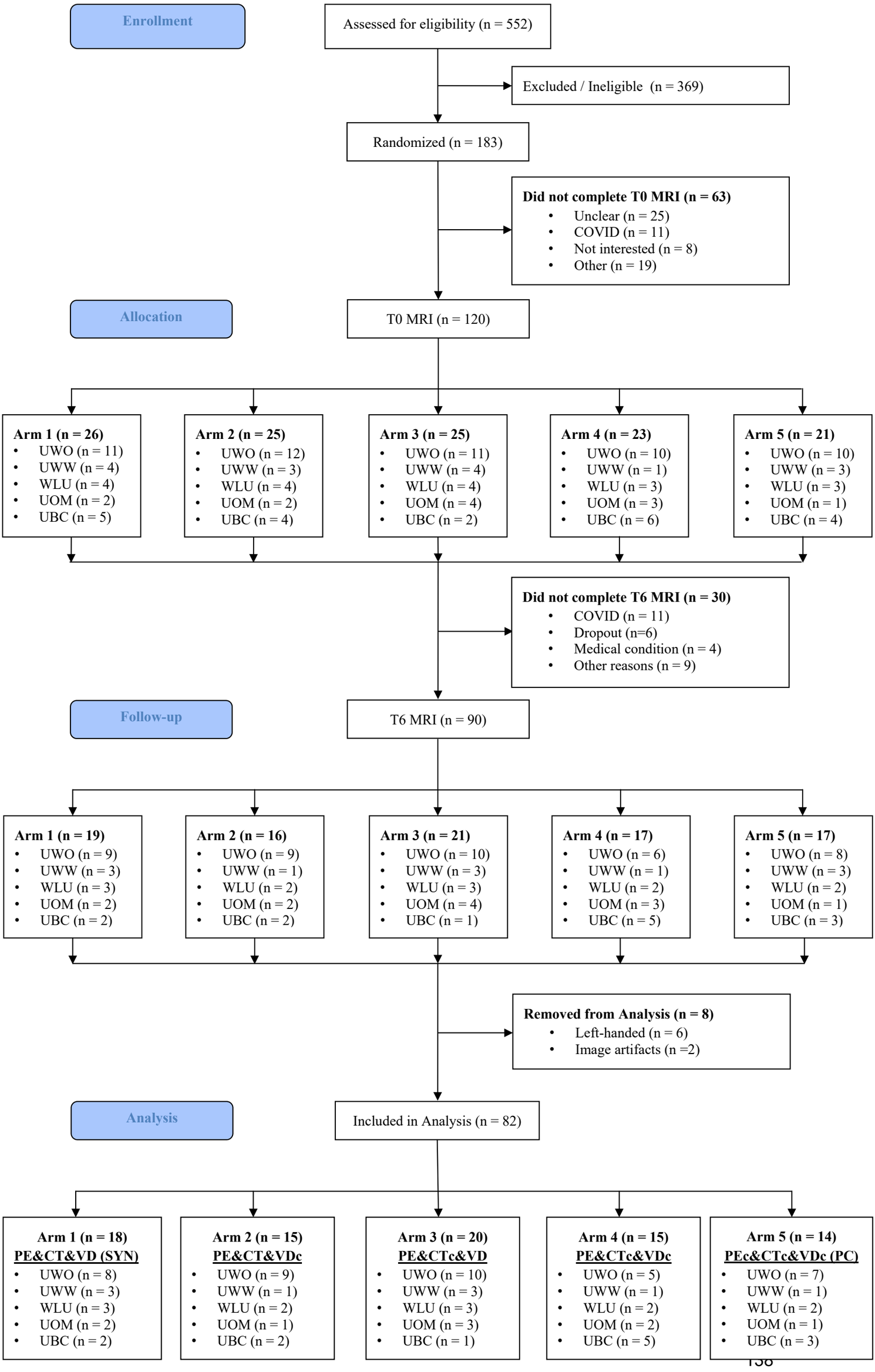
Enrollment
Assessed for eligibility (n = 552)
Excluded / Ineligible (n = 369)
Randomized (n = 183)
Did not complete T0 MRI (n = 63)
Unclear (n = 25)
COVID (n = 11)
Not interested (n = 8)
Other (n = 19)
Allocation
T0 MRI (n = 120)
Arm 1 (n = 26)
UWO (n = 11)
UWW (n = 4)
WLU (n = 4)
UOM (n = 2)
UBC (n = 5)
Arm 2 (n = 25)
UWO (n = 12)
UWW (n = 3)
WLU (n = 4)
UOM (n = 2)
UBC (n = 4)
Arm 3 (n = 25)
UWO (n = 11)
UWW (n = 4)
WLU (n = 4)
UOM (n = 4)
UBC (n = 2)
Arm 4 (n = 23)
UWO (n = 10)
UWW (n = 1)
WLU (n = 3)
UOM (n = 3)
UBC (n = 6)
Arm 5 (n = 21)
UWO (n = 10)
UWW (n = 3)
WLU (n = 3)
UOM (n = 1)
UBC (n = 4)
Did not complete T6 MRI (n = 30)
COVID (n = 11)
Dropout (n=6)
Medical condition (n = 4)
Other reasons (n = 9)
Follow-up
T6 MRI (n = 90)
Arm 1 (n = 19)
UWO (n = 9)
UWW (n = 3)
WLU (n = 3)
UOM (n = 2)
UBC (n = 2)
Arm 2 (n = 16)
UWO (n = 9)
UWW (n = 1)
WLU (n = 2)
UOM (n = 2)
UBC (n = 2)
Arm 3 (n = 21)
UWO (n = 10)
UWW (n = 3)
WLU (n = 3)
UOM (n = 4)
UBC (n = 1)
Arm 4 (n = 17)
UWO (n = 6)
UWW (n = 1)
WLU (n = 2)
UOM (n = 3)
UBC (n = 5)
Arm 5 (n = 17)
UWO (n = 8)
UWW (n = 3)
WLU (n = 2)
UOM (n = 1)
UBC (n = 3)
Removed from Analysis (n = 8)
Left-handed (n = 6)
Image artifacts (n =2)
Analysis
Included in Analysis (n = 82)
Arm 1 (n = 18)
PE&CT&VD (SYN)
UWO (n = 8)
UWW (n = 3)
WLU (n = 3)
UOM (n = 2)
UBC (n = 2)
Arm 2 (n = 15)
PE&CT&VDc
UWO (n = 9)
UWW (n = 1)
WLU (n = 2)
UOM (n = 1)
UBC (n = 2)
Arm 3 (n = 20)
PE&CTc&VD
UWO (n = 10)
UWW (n = 3)
WLU (n = 3)
UOM (n = 3)
UBC (n = 1)
Arm 4 (n = 15)
PE&CTc&VDc
UWO (n = 5)
UWW (n = 1)
WLU (n = 2)
UOM (n = 2)
UBC (n = 5)
Arm 5 (n = 14)
PEc&CTc&VDc (PC)
UWO (n = 7)
UWW (n = 1)
WLU (n = 2)
UOM (n = 1)
UBC (n = 3)

Figure 4.3 Study flowchart for participants included in imaging analysis, stratified by SYNERGIC arms. c, control; CT, cognitive training; MRI, magnetic resonance imaging; PC, pure control; PE, physical exercise; SYN, synergic; VD, vitamin D. UWO, University of Western Ontario; UWW, University of Waterloo; WLU, Wilfrid Laurier University; UOM, University of Montreal; UBC, University of British Columbia.

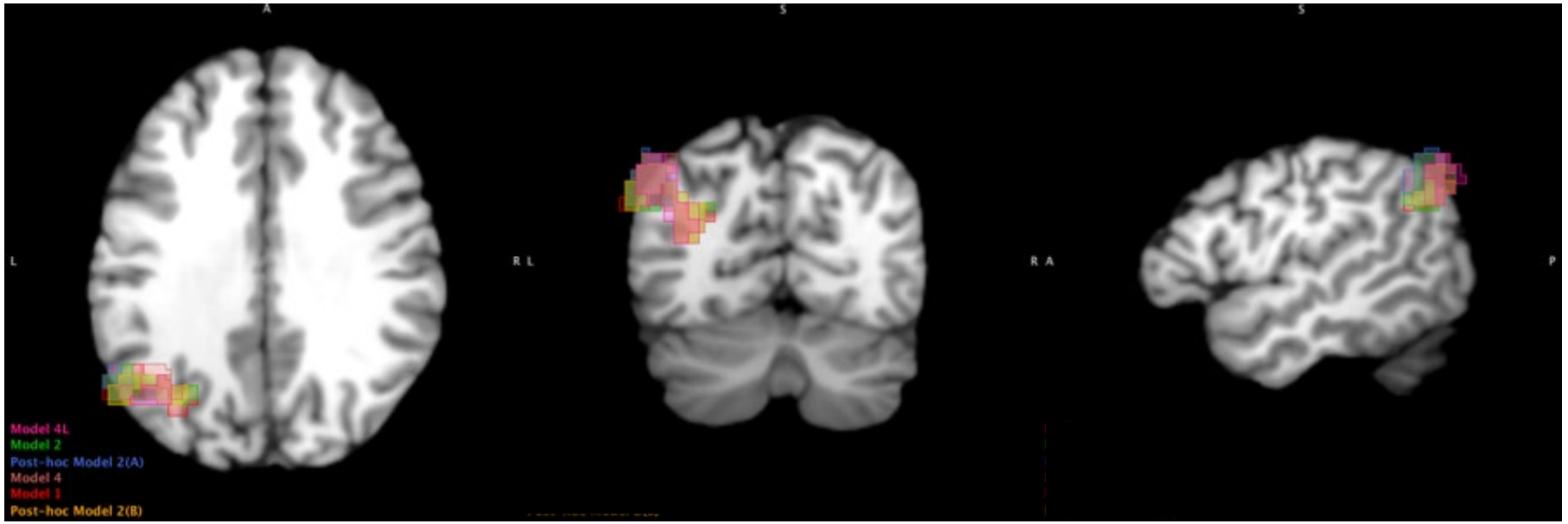

Figure 4.4 Overlay of all clusters (see Table 2) that showed a significant increase (T6-T0) with the Hippocampus. Clusters are from the seed-voxel analysis. Created using Multi-image Analysis GUI (MANGO) version 4.1. Left to right = axial, coronal, and sagittal view. Coordinates (x, y, z) = -49, -65, 31. A, anterior; L, left; P, posterior; R, right; S, superior.

4.6.2 Tables

Table 4.1 T0 (Pre-intervention) characteristics for participants included in imaging analysis, stratified by SYNERGIC arms.

Characteristic	**Total (n = 90)**	**Arm 1** PE&CT&VD (SYN) **(n = 19)**	**Arm 2** PE&CT&VDc **(n = 16)**	**Arm 3** PE&CTc&VD **(n = 21)**	**Arm 4** PE&CTc&VDc **(n = 17)**	**Arm 5** PEc&CTc&VDc (PC) **(n = 17)**	**p-value**
Age	73.89 ± 6.50	73.68 ± 6.86	73.25 ± 7.39	75.90 ± 7.55	72.12 ± 4.15	74.00 ± 5.77	0.491
# of Males (Females)	47 (43)	9 (10)	11 (5)	11 (10)	12 (5)	4 (13)	0.043*
# of Comorbidities	4.77 ± 2.46	5.21 ± 2.62	5.00 ± 2.10	4.90 ± 3.03	4.18 ± 2.51	4.47 ± 1.84	0.735
Years of Education	15.35 ± 3.66	14.21 ± 2.76	15.75 ± 3.28	14.81 ± 2.98	15.38 ± 2.98	16.88 ± 5.60	0.244
Height (cm)	167.61 ± 10.03	169.33 ± 10.04	168.13 ± 10.68	168.68 ± 7.73	170.74 ± 10.84	160.74 ± 9.02	0.029*
Weight (kg)	76.39 ± 14.61	76.79 ± 16.55	77.89 ± 12.52	77.08 ± 12.67	79.77 ± 15.78	70.31 ± 15.11	0.401
Body Mass Index	27.13 ± 4.39	26.66 ± 4.59	27.62 ± 4.11	27.04 ± 3.75	27.29 ± 4.58	27.17 ± 5.33	0.979
MoCA	22.94 ± 2.96	23.68 ± 4.03	23.13 ± 2.45	22.90 ± 3.05	22.82 ± 1.81	22.12 ± 2.91	0.634

Note: All values are mean ± standard deviation, except sex shows the sample size. ANOVA or Pearson chi-square analysis as appropriate. MoCA, Montreal Cognitive Assessment; *, *p*-value ≤ 0.05; #, number; cm, centimeters; kg, kilograms. c, control; CT, cognitive training; PC, pure control; PE, physical exercise; SYN, synergic; VD, vitamin D.

Table 4.2 Clusters with a significant increase (T6-T0) in connectivity with the Hippocampus.

Model	Cluster		size *p*-FDR	peak *p*-unc.	Anatomical Area	Covering	
	x, y, z	Size				%	Voxels
1 (PE vs. PC)	-50, -64, 36	376	0.008716	0.000004	Lateral Occipital Cortex, superior division Left	60	225
					Angular Gyrus Left	38	141
					Not Labelled	3	10
	-30, -70, 22	215	0.046003	0.000003	Lateral Occipital Cortex, superior division Left	33	71
					Angular Gyrus Left	4	8
					Not Labelled	63	136
2 (PE&CT vs. PE&CTc vs. PC)	-50, -64, 32	535	0.0003	0.000008	Lateral Occipital Cortex, superior division Left	57	303
					Angular Gyrus Left	16	87
					Not Labelled	27	145
Post-hoc for 2 (PE&CTc vs. PC)	-50, -64, 44	265	0.035973	0.000023	Lateral Occipital Cortex, superior division Left	60	158
					Angular Gyrus Left	37	98
					Not Labelled	3	9
Post-hoc for 2 (PE&CT vs. PC)	-30, -72, 20	334	0.003614	0.000002	Lateral Occipital Cortex, superior division Left	53	177
					Angular Gyrus Left	7	25
					Not Labelled	40	132
4 (SYN vs. PC)	-38, -60, 32	381	0.001073	0.000007	Lateral Occipital Cortex, superior division Left	51	194
					Angular Gyrus Left	10	38
					Not Labelled	39	149
4L (SYN vs. PC)	-46, -66, 42	297	0.00562	0.000012	Lateral Occipital Cortex, superior division Left	84	248
					Not Labelled	16	49

Note: All from the seed-voxel analysis. With the exception of model 4L, the significant clusters within each model demonstrated increased connectivity with the right Hippocampus. c, control; CT, cognitive training; PC, pure control; PE, physical exercise; SYN, synergic; VD, vitamin D; vs., versus.

Table 4.3 Pearson correlation between change (T6-T0) in connectivity and change in secondary outcomes.

Model	Arms	Change in Connectivity		Standardized Residual						
				Change in Adas-Cog13	Change in ADAS-Cog 13 Delayed Recall	Change in Trail Making Test Normalized	Change in Grip strength (kg)	Change in Usual Gait (cm/sec)	Change in 6-Minute Walk Distance (m)	Change in Sit-to-stand (sec)
1 (PE vs. PC)	1-4 (PE)	Hippocampus. R → -50, -64, 36	Pearson Correlation	-0.196	-0.064	-0.036	0.075	-0.173	0.159	*-0.226*
			Sig. (2-tailed)	0.109	0.605	0.777	0.543	0.173	0.217	*0.08*
			n	68	68	66	68	64	62	*61*
	5 (PC)		Pearson Correlation	0.391	0.403	*0.476*	-0.084	0.118	0.504	-0.259
			Sig. (2-tailed)	0.167	0.153	*0.085*	0.774	0.687	0.166	0.372
			n	14	14	*14*	14	14	9	14
	1-4 (PE)	Hippocampus. R → -30, -70, 22	Pearson Correlation	-0.075	-0.134	0.15	0.036	*-0.234*	-0.129	*0.231*
			Sig. (2-tailed)	0.545	0.276	0.23	0.768	*0.062*	0.317	*0.073*
			n	68	68	66	68	*64*	62	*61*
	5 (PC)		Pearson Correlation	-0.159	*-0.46*	0.246	0.233	-0.004	-0.233	0.333
			Sig. (2-tailed)	0.587	*0.098*	0.397	0.422	0.99	0.547	0.245
			n	14	*14*	14	14	14	9	14
2 (PE&CT vs. PE&CTc vs. PC)	1-2 (PE&CT)	Hippocampus. R → -50, -64, 32	Pearson Correlation	0.092	0.045	0.196	-0.153	-0.022	0.121	*0.332*
			Sig. (2-tailed)	0.622	0.808	0.292	0.402	0.907	0.533	*0.073*
			n	31	32	31	32	31	29	*30*
	3-4 (PE&CTc)		Pearson Correlation	-0.152	-0.11	-0.118	0.235	**-.444***	-0.035	-0.163
			Sig. (2-tailed)	0.383	0.528	0.507	0.175	**0.011**	0.847	0.388
			n	35	35	34	35	**32**	32	30
	5 (PC)		Pearson Correlation	0.243	0.262	**.555***	-0.155	0.132	0.353	-0.052
			Sig. (2-tailed)	0.402	0.365	**0.04**	0.597	0.652	0.351	0.859
			n	14	14	**14**	14	14	9	14

Post-hoc for 2 (PE&CTc vs. PC)	3-4 (PE&CT)	Hippocampus. R → -50, -64, 44	Pearson Correlation	-0.132	0.006	-0.202	0.23	**-.365***	-0.088	-0.125
			Sig. (2-tailed)	0.451	0.973	0.253	0.184	**0.04**	0.628	0.48
			n	35	35	34	35	**32**	33	34
	5 (PC)		Pearson Correlation	0.403	0.356	0.435	-0.05	0.125	-0.277	-0.235
			Sig. (2-tailed)	0.154	0.212	0.12	0.865	0.669	0.384	0.418
			n	14	14	14	14	14	12	14
Post-hoc for 2 (PE&CT vs. PC)	1-2 (PE&CT)	Hippocampus. R → -30, -72, 20	Pearson Correlation	0.01	0.04	0.185	-0.08	-0.019	0.113	0.096
			Sig. (2-tailed)	0.957	0.825	0.31	0.658	0.917	0.553	0.609
			n	33	33	32	33	32	30	31
	5 (PC)		Pearson Correlation	0.087	0.01	**.633***	0.09	0.173	-0.095	0.076
			Sig. (2-tailed)	0.767	0.974	**0.015**	0.76	0.555	0.768	0.797
			n	14	14	**14**	14	14	12	14
4 (SYN vs. PC)	1 (SYN)	Hippocampus. R → -38, -60, 32	Pearson Correlation	-0.286	-0.052	0.121	0.049	0.17	0.413	-0.177
			Sig. (2-tailed)	0.25	0.839	0.644	0.852	0.514	0.112	0.497
			n	18	18	17	17	17	16	17
	5 (PC)		Pearson Correlation	0.276	0.383	*0.506*	-0.26	0.121	-0.179	-0.017
			Sig. (2-tailed)	0.339	0.177	*0.065*	0.369	0.68	0.578	0.953
			n	14	14	*14*	14	14	12	14
4L (SYN vs. PC)	1 (SYN)	Hippocampus. L → -46, -66, 42	Pearson Correlation	0.01	-0.132	-0.073	-0.193	0.396	0.334	-0.247
			Sig. (2-tailed)	0.968	0.603	0.782	0.457	0.115	0.207	0.339
			n	18	18	17	17	17	16	17
	5 (PC)		Pearson Correlation	0.403	0.185	0.067	-0.4	0.132	0.106	-0.102
			Sig. (2-tailed)	0.153	0.527	0.821	0.157	0.652	0.743	0.73
			n	14	14	14	14	14	12	14

Note: All connections are from S-V analysis. **Bold** values, *p*-value <0.05. *Italicized* values are those trending towards significance at a *p*-value <0.05. Notably, no correlation survived correction for false discovery rate. c, control; cm/sec, centimeters per second; CT, cognitive training; m, meters; L, left; PC, pure control; PE, physical exercise; R, right; SYN, synergic; VD, vitamin D; vs., versus.

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4.8 SUPPLEMENTARY MATERIAL

Supplemental Material A: Cognitive training control.

Cognitive Training Task 1 Log Sheet – Touristic Searching

Find <u>three hotels</u> of your preference to stay in Brussels Belgium:

Hotel #1: _____; Price: _____; Distance from city centre: _____
Hotel #2: _____; Price: _____; Distance from city centre: _____
Hotel #3: _____; Price: _____; Distance from city centre: _____

Find <u>three tourist attractions</u> of your preference in the pre-specified city above:

Attraction #1: _____; Address: _____
Attraction #2: _____; Address: _____
Attraction #3: _____; Address: _____

Find <u>three restaurants</u> of your preference in the pre-specified city above:

Restaurant #1:_____; Address: _____
Restaurant #2:_____; Address: _____
Restaurant #3:_____; Address: _____

Cognitive Training Task 2 Log Sheet – Video Watching

Watch the following National Geographic video for 20 minutes and then answer the questions below:

Video: Secrets of Body Language (1:30:30)

1. What is this video about?

Answer: _____
_____

2. What is the most important information in your opinion?

Answer: _____
_____

3. Create a question based on the watched video and answer your own question.

Question: _____

Answer: _____
_____

Note: Task 1) Pre-defined touristic search in a sample city. Task 2) Three questions to complete after watching a (sample) National Geographic video.

Supplemental Material B: Training program.

A)

Weeks	Sets			Repetitions			Rest between sets (sec)
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	
1-4	2	2	2	15-18	15-18	15-18	30
5-8	3	2	3	12-15	12-15	12-15	30
9-12	3	2	3	10	10	10	60
13-16	2	3	2	8	12	8	60
17-20	3	2	3	6	8	6	60

B)

Weeks	Sets	Duration (min)	Intensity (Borg 0-10)	Rest between sets (min)
1-4	2	10	5-6	1
5-8	2	10	5-6	1
9-12	2	10	6-7	1
13-16	2	10	6-7	1
17-20	2	10	7-8	1

Note: A) Resistance training program. Sets indicate the number of times the participant should repeat the repetitions of the exercise. Repetitions indicate the number of times the participant should execute the exercise. From one session to the next, and in order to stay within the identified repetition range, weight for a resistance exercise was increased when the participants self-selected rating of perceived exertion (RPE) (Borg 1982) was 8 or less. sec, seconds; B) Aerobic exercise program. Sets indicate the number of times the participant should repeat the duration of the exercise. min, minutes.

Supplemental Material C: Preprocessing through fMRIPrep

Results included in this manuscript come from preprocessing performed using *fMRIPrep* 20.2.0 (Esteban, Markiewicz, et al. (2018); Esteban, Blair, et al. (2018); RRID:SCR_016216), which is based on *Nipype* 1.5.1 (Gorgolewski et al. 2011; Gorgolewski et al. 2018); RRID:SCR_002502).

Anatomical data preprocessing – A total of 2 T1-weighted (T1w) images were found within the input BIDS dataset. All of them were corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al. 2010), distributed with ANTs 2.3.3 (Avants et al. 2008, RRID:SCR_004757). The T1w-reference was then skull-stripped with a *Nipype* implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 5.0.9, RRID:SCR_002823, Zhang, Brady, and Smith 2001). A T1w-reference map was computed after registration of 2 T1w images (after INU-correction) using mri_robust_template (FreeSurfer 6.0.1, Reuter, Rosas, and Fischl 2010). Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with antsRegistration (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following template was selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym],

Functional data preprocessing – For each of the 2 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. A deformation

field to correct for susceptibility distortions was estimated based on *fMRIPrep's fieldmap-less* approach. The deformation field is that resulting from co-registering the BOLD reference to the same-subject T1w-reference with its intensity inverted (Wang et al. 2017; Huntenburg 2014). Registration is performed with antsRegistration (ANTs 2.3.3), and the process regularized by constraining deformation to be nonzero only along the phase-encoding direction, and modulated with an average fieldmap template (Treiber et al. 2016). Based on the estimated susceptibility distortion, a corrected EPI (echo-planar imaging) reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using flirt (FSL 5.0.9, Jenkinson and Smith 2001) with the boundary-based registration (Greve and Fischl 2009) cost-function. Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9, Jenkinson et al. 2002). BOLD runs were slice-time corrected using 3dTshift from bold 20160207 (Cox and Hyde 1997, RRID:SCR_005927). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as *preprocessed BOLD in original space*, or just *preprocessed BOLD*. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two

formulations following Power (absolute sum of relative motions, Power et al. (2014)) and Jenkinson (relative root mean square displacement between affines, Jenkinson et al. (2002)). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al. 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*, Behzadi et al. 2007). Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by thresholding the corresponding partial volume map at 0.05, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the *k* components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion

of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. All resamplings can be performed with *a single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos 1964). Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer).

Many internal operations of *fMRIPrep* use *Nilearn* 0.6.2 (Abraham et al. 2014, RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep's* documentation.

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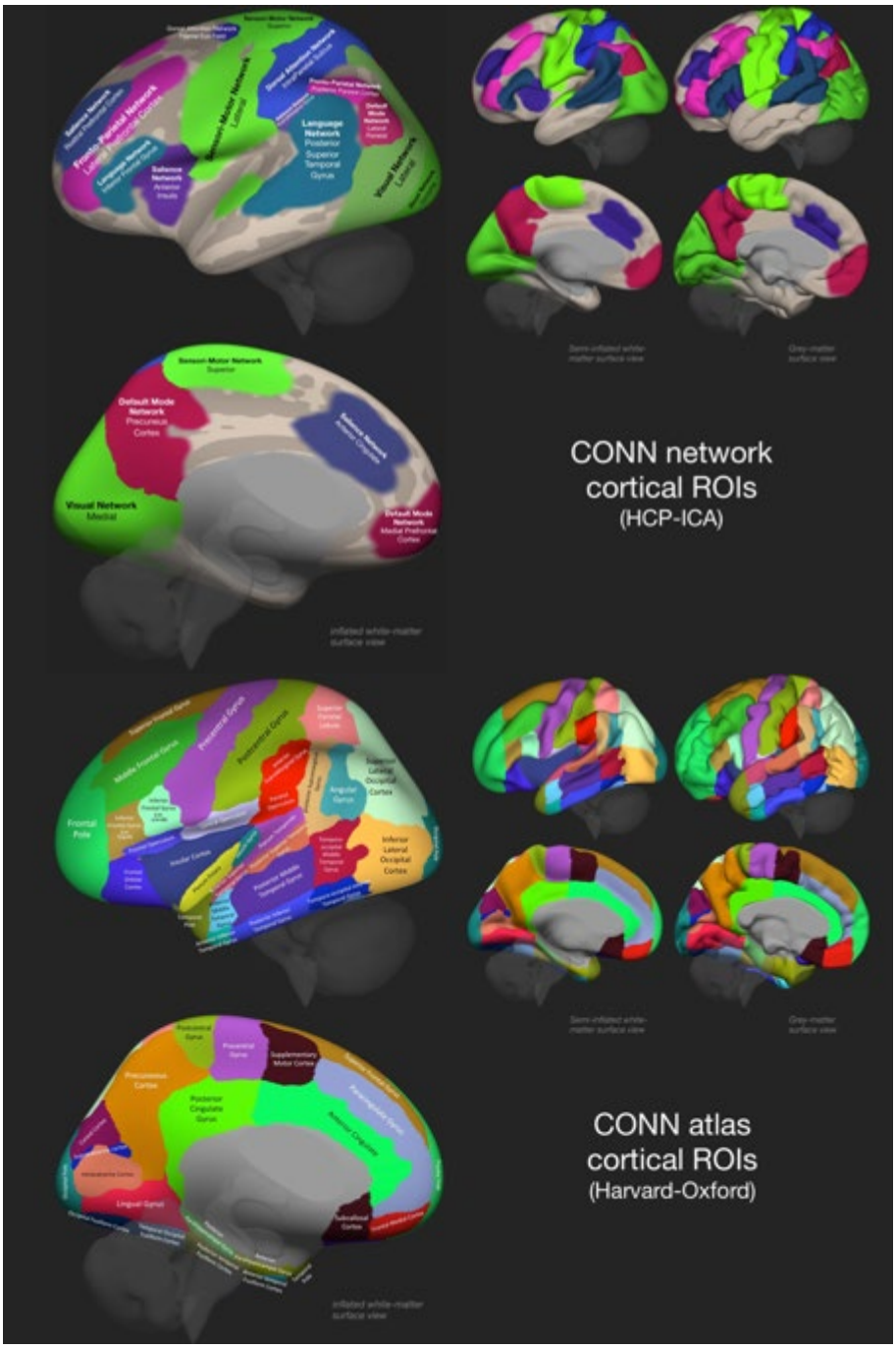
Supplementary Material D: List of included networks and their Regions of Interest (ROIs) with MNI coordinates.

Network	Region of interest with MNI coordinates
Default Mode Network (DMN)	Medial Prefrontal Cortex (MPFC; 1, 55, -3) Lateral Parietal Cortex (LP) L (-39, -77, 33) Lateral Parietal Cortex (LP) R (47, -67, 29) Posterior Cingulate Cortex (PCC; 1, -61, 38)
Sensorimotor Network (SMN)	Lateral L (-55, -12, 29) Lateral R (56, -10, 29) Superior (0, -31, 67)
Salience Network (SAN)	Anterior Cingulate Cortex (ACC; 0, 22, 35) Anterior Insula (Ainsula) L (-44, 13, 1) Anterior Insula (Ainsula) R (47, 14, 0) Rostral Prefrontal Cortex (RPFC) L (-32, 45, 27) Rostral Prefrontal Cortex (RPFC) R (32, 46, 27) Supramarginal Gyrus (SMG) L (-60, -39, 31) Supramarginal Gyrus (SMG) R (62, -35, 32)
Dorsal Attention Network (DAN)	Frontal Eye Fields (FEF) L (-27, -9, 64) Frontal Eye Fields (FEF) R (30, -6, 64) Intraparietal Sulcus (IPS) L (-39, -43, 52) Intraparietal Sulcus (IPS) R (39, -42, 54)
Frontoparietal Network (FPN)	Lateral Prefrontal Cortex (LPFC) L (-43, 33, 28) Posterior Parietal Cortex (PPC) L (-46, -58, 49) Lateral Prefrontal Cortex (LPFC) R (41, 38, 30) Posterior Parietal Cortex (PPC) R (52, -52, 45)

Note: L, left; R, right.

Supplementary Material E: CONN networks (top) and atlas (bottom) with their cortical Regions of Interest (ROIs).



Note: Networks in the ROI-ROI analysis are the Default-Mode (DMN), Sensorimotor (SMN), Salience (SAN), Dorsal-Attention (DAN), and Frontoparietal (FPN). Seeds for the seed-to-voxel analysis are the left and right Hippocampus. Networks are based upon CONN Independent Component Analysis (ICA) analysis of 497 subjects from the Human Connectome Project (HCP), and atlas is the Harvard-Oxford.

Supplementary Material F: Syntax code inputted into SPSS to correct for false discovery rate (FDR).

```
DATA LIST free / p (F5.3).
BEGIN DATA
.152 .093 .055 .035 .044 .017 .001
END DATA.
SORT CASES by p (a).
COMPUTE i=$casenum.
SORT CASES by i (d).
COMPUTE q=.05.
COMPUTE m=max(i,lag(m)).
COMPUTE crit=q*i/m.
COMPUTE test=(p le crit).
COMPUTE test=max(test,lag(test)).
FORMATS i m test(f8.0) q (f8.2) crit(f8.6).
VALUE LABELS test 1 'Significant' 0 'Not Significant'.
LIST.
```

Note: Significant results have variable test = 1. *p*-values (**bolded**) listed are just an example. Syntax executed individually for each model, therefore, 28 p-values listed for model 1, 21 for model 2, etc. Code uses Benjamini & Hochberg (1995) approach, and is discussed here: Weaver, 2015.

Supplementary Material G: T0 characteristics stratified by MRI completion status, i.e., participants that completed both pre-(T0) and post-intervention (T6) imaging, versus participants that only completed pre-intervention (T0) imaging, versus participants that completed neither pre-(T0) nor post-intervention (T6) imaging.

Characteristic	Completed imaging at T0 & T6 (n = 90)	Only Completed Imaging @ T0 (n = 30)	Completed No Imaging (n = 55)	p-value
Age	73.89 ± 6.5	72.9 ± 5.39	71.54 ± 6.80[b]	0.107
# of Males (Females)	47 (43)	13 (17)	30 (27)	0.664
# of Comorbidities	4.77 ± 2.46	4.23 ± 2.57	4.33 ± 2.28[b]	0.439
Years of Education	15.35 ± 3.66	14.88 ± 3.50[a]	15.51 ± 3.92[b]	0.759
Height (cm)	167.61 ± 10.03	166.39 ± 11.19	166.12 ± 10.73	0.674
Weight (kg)	76.39 ± 14.61	76.02 ± 17.24	78.50 ± 22.36	0.746
Body Mass Index	27.13 ± 4.39	27.35 ± 5.21	28.18 ± 6.74	0.514
MoCA	22.94 ± 2.96	22.86 ± 3.19 [a]	22.17 ± 3.19 [b]	0.322

Note: Analysis was conducted to determine if there were any characteristic differences at T0, between those that completed imaging, versus those that completed only part of or no imaging. Result may have provided insight into what or why individuals chose to not complete imaging at T0 and/or T6. All values are mean ± standard deviation, except sex shows the sample size. ANOVA or Pearson chi-square analysis as appropriate. No significant differences between-groups for any characteristic. MoCA, Montreal Cognitive Assessment; #, number; cm, centimeters; kg, kilograms; a, n=29; b, n=54.

Supplementary Material H: Comparison of group connectivity at T0 for all models in both the ROI-ROI and S-V analysis.

A)

Model	Timepoint	Connection	Statistics
1 (PE vs. PC)	T0	No Significant Differences	
	T6	No Significant Differences	
2 (PE&CT vs. PE&CTc vs. PC)	T0	No Significant Differences	
	T6	No Significant Differences	
3 (PE&VD vs. PE&VDc vs. PC)	T0	No Significant Differences	
	T6	No Significant Differences	
4 (SYN vs. PC)	T0	SAN - Rostral Prefrontal Cortex L → SAN - Supramarginal Gyrus R	T(26) = -2.70; p-unc = 0.012057
		SAN - Rostral Prefrontal Cortex L → SAN - Anterior Insula L	T(26) = -2.44; p-unc = 0.021629
		SAN - Rostral Prefrontal Cortex L → SAN - Supramarginal Gyrus L	T(26) = -2.18; p-unc = 0.038111
		SAN - Rostral Prefrontal Cortex L → SAN - Anterior Insula R	T(26) = -2.07; p-unc = 0.048360
	T6	No Significant Differences	

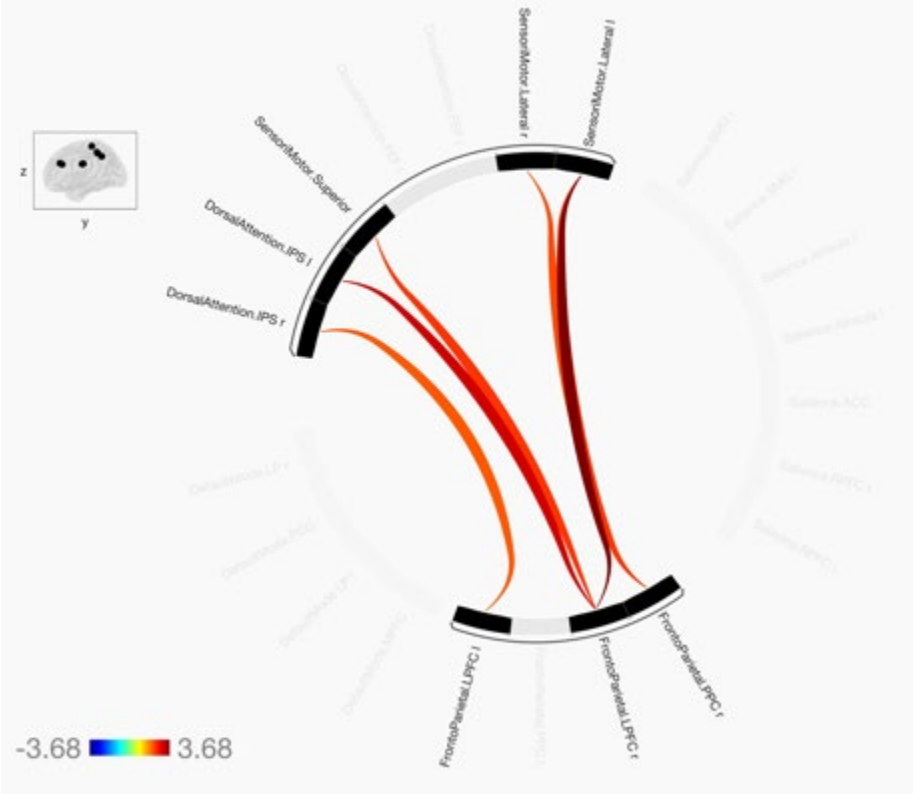
B)

Model	Time	Cluster		size *p*-FDR	peak *p*-unc.	Anatomical Area	Covering	
		x, y, z	Size				%	Voxels
1 (PE vs. PC)	T0	No Significant Differences						
	T6	No Significant Differences						
2 (PE&CT vs. PE&CTc vs. PC)	T0	No Significant Differences						
	T6	No Significant Differences						
3 (PE&VD vs. PE&VDc vs. PC)	T0	No Significant Differences						
	T6	No Significant Differences						
4 (SYN vs. PC)	T0	No Significant Differences						
	T6	No Significant Differences						
4L (SYN vs. PC)	T0	-56, 18, 16	168	0.029316	0.000296	Inferior Frontal Gyrus, Left	61	103
						Precentral Gyrus Left	36	60
						NL	3	5
	T6	No Significant Differences						

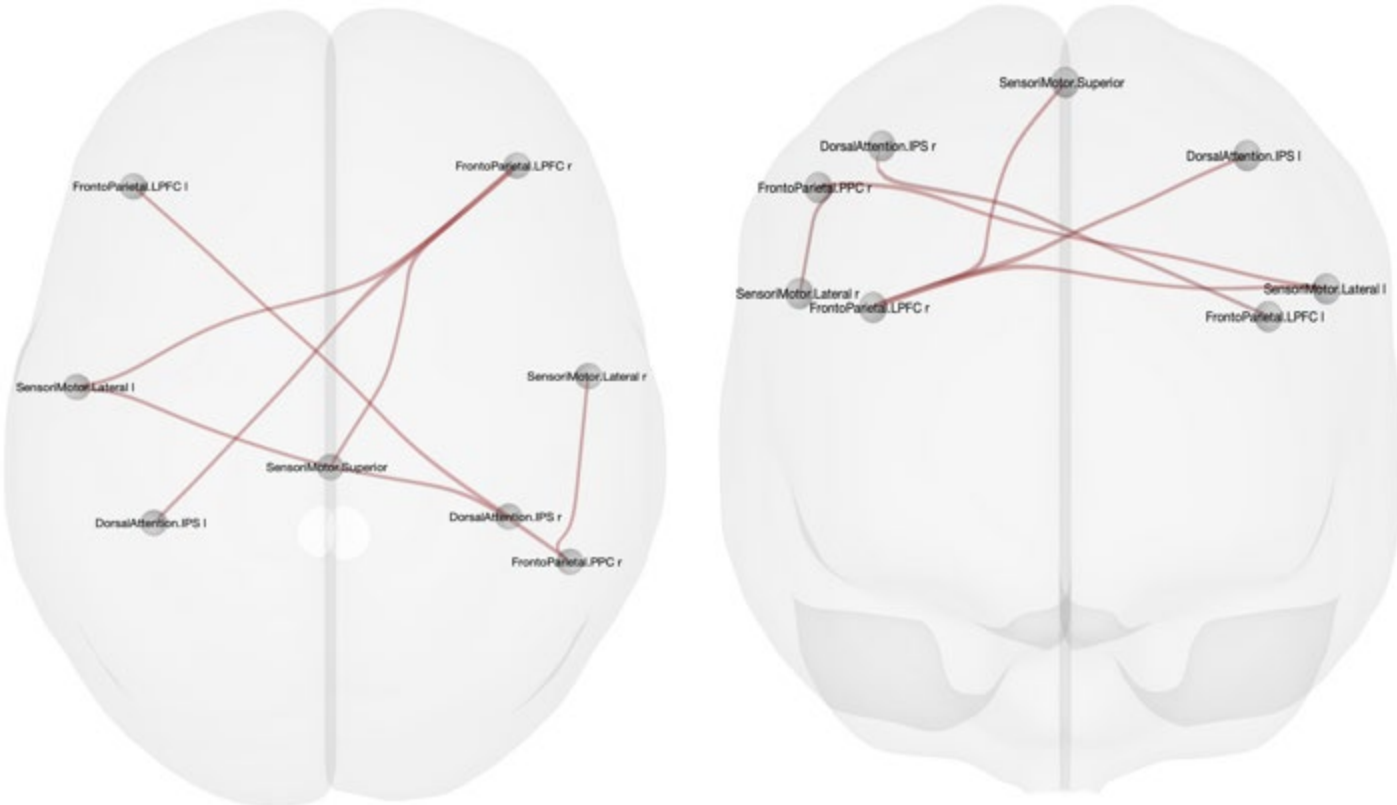
Note: A) ROI-ROI analysis. B) S-V Analysis. Models 1-4 of S-V analysis represent results of both seeds (left and right Hippocampus). Results in model 4L are based upon connectivity with only the left Hippocampus. FPN, Frontoparietal Network; SMN, Sensorimotor Network; DAN, Dorsal Attention Network; R, right; L, left; PE, physical exercise; CT, cognitive training; VD, vitamin D; c, control; SYN, synergic; PC, pure control; vs., versus.

Supplementary Material I: Results of ROI-ROI analysis in model 4.

A)



B) A S



C)

Connection	Statistics
FPN - Lateral Prefrontal Cortex R → **SMN** - Lateral L	T(28) = 3.68; p-unc = 0.000975
FPN - Lateral Prefrontal Cortex R → **DAN** - Intraparietal Sulcus L	T(28) = 3.07; p-unc = 0.004777
FPN - Posterior Parietal Cortex R → **SMN** - Lateral L	T(28) = 2.39; p-unc = 0.023656
FPN - Posterior Parietal Cortex R → **SMN** - Lateral R	T(28) = 2.24; p-unc = 0.033021
FPN - Lateral Prefrontal Cortex R → **SMN** - Superior	T(28) = 2.40; p-unc = 0.023177
FPN - Lateral Prefrontal Cortex L → **DAN** - Intraparietal Sulcus R	T(28) = 2.12; p-unc = 0.043296

Note: A) ROI – ROI connectome ring: significant increase (T6-T0) in connectivity in the intervention group when compared to the control in model 4 (SYN vs. PC) after controlling for false discovery rate and covariates of years of education and sex. Cluster lost significance once the covariates of number of comorbidities and age were added to the model. FPN, Frontoparietal Network; SMN, Sensorimotor Network; DAN, Dorsal Attention Network; R, right; L, left. B) Same connections of the connectome ring but displayed within a glass brain in axial and coronal view. R, right; L, left; A, anterior; S, superior. C) Statistics for the significant connections displayed in connectome ring and glass brain.

Supplemental Material J. Original (i.e., non-standardized residual) scores of all secondary outcomes.

Variable	T0 (Pre-intervention)	T6 (Post-intervention)	Change
ADAS-Cog 13 Overall	14.44 ± 6.19	13.60 ± 6.33	-0.84 ± 3.18
ADAS-Cog 13 Delayed Recall	4.99 ± 2.35	4.67 ± 2.58	-0.32 ± 1.62
Normalized Trail Making Test	1.97 ± 1.3[a]	2.09 ± 1.42	0.13 ± 1.69[a]
Grip (kg)	26.78 ± 10.37	27.67 ± 10.67	0.89 ± 3.94
Usual Gait (cm/sec)	119.98 ± 19.67[a]	124.85 ± 20.72[a]	4.26 ± 14.88[b]
Six Minute Walk Distance (m)	466.58 ± 91.34[a]	467.47 ± 87.65[c]	4.71 ± 55.44[d]
Sit-to-Stand Time (sec)	13.75 ± 4.53[c]	13.42 ± 4.31[e]	-0.29 ± 3.73[d]

Note: All values are mean ± standard deviation. Only the four participants that chose not to complete sit-to-stand at either T0 or T6 have been removed. Therefore, statistical outliers are included. Any other missing data (i.e., $n \neq 82$) due to data not being collected/missed. a, n = 80; b, n = 78; c, n = 77; d, n = 75; e, n = 76. kg, kilograms; cm/sec, centimeters per second; m, meters; sec, seconds.

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CHAPTER 5: FRAILTY AND FUNCTIONAL BRAIN NETWORK CONNECTIVITY (FBNC) IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT (MCI): RESULTS FROM THE SYNERGIC TRIAL.

Abstract: *Introduction:* Frailty, a state of decreased physiological reserve, confounds the relationship between Alzheimer's disease pathology and clinical symptoms. Functional brain network connectivity (FBNC) represents a sensitive biomarker for monitoring the progression of Dementia syndromes. However, only one study has examined the relationship between FBNC and frailty, and researchers focused on physical measures of frailty and FBNC of motor areas. *Methods:* In our cross-sectional study, we measured frailty according to a frailty index encompassing various domains (i.e., physical, functional, neuropsychiatric, etc.). Using the CONN toolbox, we measured FBNC of multiple networks. Pearson's investigated correlations between FBNC and frailty index in the full sample and by sex. We also divided the full sample and each sex into tertiles based upon index score and then assessed tertile differences in FBNC. *Results:* The full sample and males demonstrated increasing connectivity was correlated with increasing (worse) frailty. Connectivity increased between the right Hippocampus and clusters that were broadly labelled. We believe the changes reflect an increase in between-network connectivity. Males also demonstrated between-tertile differences in right Hippocampus connectivity to another broadly labelled cluster. Specifically, the low (non-frail) tertile demonstrated less connectivity than intermediate (pre-frail) but more than high (frail). *Discussion:* Our results suggest that frailty status is an important consideration when measuring FBNC. Furthermore, the relationship between the two variables appears to differ by sex. Our results may help elucidate why certain individuals progress to a dementia syndrome while others remain stable in pre-dementia states.

5.1 INTRODUCTION

Mild cognitive impairment (MCI) represents an intermediary stage between normal cognitive decline and dementia, but more than half of those classified remain stable or even revert to "normal" cognition (1–3). Identifying which individuals will eventually progress to a dementia syndrome (i.e., Alzheimer's disease) is a "major goal of current research" (4). Frailty is highly prevalent in older adults with Alzheimer's disease (5), and it moderates the relationship between Alzheimer's disease pathology and clinical symptoms (6); meaning, people with a low amount of frailty are better able to tolerate Alzheimer's pathology. Ultimately, frailty may help to partially explain the progression or lack thereof amongst individuals with MCI.

Conceptually, frailty is a state of decreased physiological reserve that gives rise to vulnerability to adverse health outcomes or stressors (7), such as the novel COVID-19 virus (8). Frailty is a distinct entity (9) that is multidimensional (10), often including deficits in both cognitive (11) and physical function (12), as well as social and emotional domains (13). Similar to cognitive decline, frailty exists on a spectrum, typically beginning with non-frail, followed by a transitional or intermediary state commonly referred to as pre-frail, and then frail (14). Notably, transitions between states are not unidirectional as pre-frail or frail individuals can revert to non-frail (15,16). Changes in frailty status may occur concurrently with changes in neural substrates underlying dementia syndromes as frailty predicts dementia (17). Recently, there has been a call for investigation into their common etiology (18).

Researchers have shown frailty to be negatively associated with global brain volume (19), as well as the microstructure of gray and white matter (20). However, functional neural aspects have garnered less attention. Functional brain network connectivity (FBNC) refers to brain areas that are spatially separated but temporally linked in their neural signaling (21); it is believed to enable efficient information processing and completion of complex functions (22). FBNC can be measured using functional magnetic resonance imaging (fMRI) and is considered a sensitive biomarker in those at risk of progression to dementia as changes precede structural atrophy and occur years before clinical manifestation (23). To date, only two studies have examined FBNC relative to frailty status, using magnetoencephalography (24) and fMRI (25). Both studies classified their "healthy" sample (i.e., cognitively normal individuals) using the Cardiovascular Health Study – Frailty Phenotype, which is considered to focus on the physical domain of frailty (26). Additionally, researchers restricted their investigation of FBNC to motor areas (24,25). Currently, no studies have examined the relationship between frailty and FBNC in individuals

with cognitive impairment or how a more multidimensional measure of frailty status, such as the Frailty Index (FI) (27), is associated with FBNC in motor areas and beyond.

The purpose of this cross-sectional study was to examine the relationship between frailty status, assessed using the FI, and FBNC in individuals clinically classified with MCI. We hypothesized that frailty would be associated with FBNC in individuals with MCI. Notably, males and females demonstrate differences in cerebral function (28) and blood flow (29). Males are at a greater risk of developing MCI (30), but frailty is more common in females (31). Therefore, we also conducted a sub-analysis based upon the hypothesis that males and females would differ in their association between frailty and FBNC.

5.2 METHODS

5.2.1 Design & Participants

Chapter 4 previously discussed the SYNchronizing Exercises, Remedies in GaIt and Cognition (SYNERGIC or SYN) trial (32) (NCT02808676). In brief, SYNERGIC was a multi-site, randomized, phase II, quasi-factorial, double-blind controlled study evaluating the effect of combined physical exercise separately and synergistically with cognitive training and/or high-dose vitamin D supplementation in older adults (60 to 85 years) with MCI. All institutions (University of Western Ontario, University of Waterloo, Wilfrid Laurier, University of Montreal, and the University of British Columbia) received approval from their local ethics board.

In addition to a clinical screening, SYNERGIC participants completed three in-person assessments, including baseline or pre-intervention (T0), post-intervention (T6), and follow-up (T12). T0 and T6 occurred immediately before and after a 20-week intervention, while T12

occurred 6-months after T6. Given the cross-sectional nature of the present study, baseline is the only time point of interest (Supplemental Material A). The present study's inclusion and exclusion criteria were identical to SYNERGIC, except for the following additions to the exclusion criteria: 1) Did not complete an MRI assessment at baseline; and 2) Participants consider their left hand to be dominant.

5.2.2 Frailty

All in-person assessments included collecting demographic information and a battery of tests (Supplemental Material B). Therefore, it permitted a secondary, retroactive analysis of participant's frailty status via the FI. The FI is considered a health state measure that reflects vulnerability to adverse health outcomes or, put more simply, a cumulative deficit model where 'the more individuals have wrong with them, the more likely they are to be frail (33).' The FI is calculated as:

$$\text{FI} = \frac{\text{number of health deficits present}}{\text{number of health deficits measured}}$$

A person with 9 of 30 potential deficits has an FI of (9/30) 0.30 and is considered 'more frail' than an individual with 4 of 30 potential deficits (4/30 = 0.13). Compared to other tools, the FI is unidimensional and has been suggested to have high predictive value in community settings and for adverse outcomes (7). All variables in the present study's FI have been previously utilized in other FIs (34,35) (Supplemental Material C). Given the demographic, we excluded measures of cognitive function from our FI as such variables were expected to be impaired; previous research has done the same for cardiovascular outcomes in a cardiac rehabilitation demographic (34).

Notably, the total number of variables included in the FI is inconsequential as long as there are 30 (36).

5.2.3 MRIs

Image acquisition, preprocessing, and type of analyses was similar to those in Chapter 4. In short, we collected MRIs according to version 3.8 of the Canadian Dementia Imaging Protocol (37), but only T1W and resting-state fMRI scans were used in the present study. We visually inspected data for overall quality and then organized according to the brain imaging data structure (38), preprocessed via fMRIPrep (version 20.2.0) (39) (Supplemental Material D), skull-stripped using FMRIB Software Library (version 6.0.4) (40) Brain Extraction Tool (41), and then uploaded it to the CONN Functional Connectivity Toolbox (version 20.b) (42). Once in CONN, we denoised and analyzed data using both a region-of-interest (ROI)-to-ROI (ROI-ROI) and seed-to-voxel (S-V) approach. ROIs included the Default-Mode (43), Dorsal Attention (44), Salience (45), Frontoparietal (46), and Sensorimotor (47) Networks. We used both the left and right Hippocampus as seeds (Supplemental Material E-F). Finally, and similar to Chapter 4, we exported significant clusters into both Multi-image Analysis GUI (MANGO; version 4.1) (48) and xjView (version 9.7) (49) to review the overlap of cluster coordinates and consistency in anatomical labeling, respectively.

Notably, CONN's quality assurance plots, including variables related to motion, global signal change, and valid scans, should score $\geq$ 95% (50). After completing the original denoising, the quality assurance plots did not achieve the 95% goal. Therefore, we extracted voxel-wise standardization (DVARS) and mean framewise displacement values, which reflect signal change and motion, from MRIQC (51); similar to fMRIPrep, MRIQC is another app (52) available to

datasets organized according to the brain imaging data structure. Subsequently, DVARS and framewise displacement values were imported into the Statical Package for Social Sciences (SPSS version 27; IBM Canada Ltd. Markham, Ontario) to identify and remove participants classified as extreme (±3 times the interquartile range) outliers. Quality assurance plots then achieved the recommended 95% goal (Supplemental Material G).

5.2.4 Statistical Analysis

Demographic Information: Except for sex reported as sample size, we summarized demographic characteristics using means and standard deviations. Similar to Chapter 4, to identify who or potentially why specific individuals chose to forgo MRIs, we also compared characteristics of participants that completed baseline imagining versus those that did not. In SPSS, an independent samples t-test assessed between-group (i.e., sex and MRI completion status) differences in participant characteristics.

FBNC and Frailty in ROI-ROI: Unlike chapter 4, we applied no cluster or connection threshold to the ROI-ROI analysis as we aimed to ascertain the average connectivity score for every within-network connection for every participant after controlling for age, sex, and years of education. Therefore, we imported covariates into CONN. We then calculated the average within-network connectivity for each participant by averaging the individual connectivity scores. For example, the Default-Mode Network includes four ROIs (Medial Prefrontal Cortex, Posterior Cingulate Cortex, and Lateral Parietal Cortex Left and Right). We calculated the connectivity of the six possible connections for each participant and then averaged the six connections for a Default-Mode connectivity score. We then imported each participant's average within-network connectivity score into SPSS, where we completed a Pearson correlation with FI

z-score. We converted FI to a z-score via standardized residuals of linear regression to control for the same covariates used in CONN (age, sex, and years of education).

FBNC and Frailty in S-V: Unlike ROI-ROI, we imported raw FI values into CONN to test the existence of significant associations between connectivity and FI after controlling for the same covariates (age, sex, and years of education). As such, we utilized standard S-V thresholds (cluster threshold: $p < 0.05$ cluster-size p-FDR corrected; voxel threshold: $p < 0.001$ p-uncorrected) (53). We did not follow the same procedure for the ROI-ROI analysis due to: 1) no interest in a particular connection with the seed; and 2) the likely overwhelming number of results produced from eliminating cluster and voxel thresholds.

Sex: The above analyses were repeated in males and females separately, keeping age and years of education as covariates.

Tertiles: We divided our entire sample and each sex into FI tertiles (cut-points = 0.16 and 0.23) like other research in frailty and brain health (18). Tertiles permit the grouping and, thus, comparison of the sample across a relative frailty spectrum, i.e., low or non-frail, intermediate or pre-frail, and high or frail. We then aimed to determine if the average connectivity differed between the three tertiles after controlling for sex, age, and self-reported years of education; sex was removed as a covariate when conducting tertile analyses in males and females. We assessed baseline characteristics between tertiles to determine if any differences other than mean FI value existed; tertile characteristics were compared in SPSS using a one-way analysis of variance (ANOVA).

5.3 Results

Demographic Information: SYNERGIC randomized 183 participants. 120 completed a baseline MRI, but we removed 20 from the present study's analysis (Figure 1). The rationale for exclusion included: Left-handedness, n=8; MRI artifacts, n=2; FI data inaccessible due to COVID, n=4; Did not fully complete baseline (T0) MRI, n=1; Identified as an outlier based upon DVARS and/or framewise displacement values, n=5. Therefore, the final analysis included 100 participants, inclusive of 52 males and 48 females.

There was a significant difference in age for those that completed an MRI versus those that did not (Supplemental Material H). The baseline characteristics of the participants included in the present study's analysis (n=100) were reflective of the original (n=120) sample (Supplemental Material I), with a significant sex difference in height, weight, and years of education (Table 1). The average FI score for the full sample (n=100) was 0.19. It did not reach statistical significance, but females were more frail than males. However, females demonstrated statistically higher Default-Mode connectivity.

Finally, tertiles for the full sample (Table 2), as well as female (Table 3) and male (Table 4) tertiles, all demonstrated a significant between-tertile difference in the average number of comorbidities and, as expected, FI value. The full sample also showed a significant difference in body mass index when comparing the low and intermediary tertiles.

ROI-ROI - FBNC and FI: There was no significant correlation between connectivity of our networks (Default-Mode, Sensorimotor, Salience, Dorsal Attention, and Frontoparietal) and FI values for the full sample (continuous or tertiles). All effect sizes were considered insignificant to small ($|r| < 0.3$). Similarly, neither males nor females demonstrated a significant correlation

between network connectivity and FI values (continuous or tertiles). Effect sizes were also in the insignificant to small range (Table 5 and Supplemental Material J-K).

S-V - FBNC and FI: After controlling for covariates, the right Hippocampus of the full sample demonstrated increased connectivity *to the* left inferior and middle Temporal Gyrus (Figure 2). Meaning, an increasing (worse) FI value was correlated with an increase in connectivity. Females showed no significant association between FI and FBNC. Conversely, male's right Hippocampus increased connectivity *to* bilateral regions of the inferior and middle Temporal Gyrus (Figure 3) even after controlling for covariates; one cluster demonstrated overlap with the cluster from the full sample (Supplemental Material L). Meaning, an increasing (worse) FI value was correlated with an increase in connectivity.

Only males demonstrated a significant between-tertile difference in connectivity of the right Hippocampus to one cluster. Specifically, non-frail (low) demonstrated less connectivity than the intermediate (pre-frail) tertile, but more than the high (frail) tertile (Figure 4); the significant difference for low (non-frail) versus intermediate (pre-frail) was at a more liberal (p <0.05) voxel threshold.

Statistics for all S-V connections that survived correction for covariates are included in Table 6. Additionally, anatomical labeling of significant connections according to both CONN and xjVIEW are available in Supplemental Material M.

5.4 Discussion

In this cross-sectional study of older adults with MCI, we examined the relationship between frailty status, assessed using the FI, and FBNC throughout the brain. In support of our

hypothesis, we found significant associations between FI values and FBNC in the full sample. Also supporting our hypothesis, we found significant sex-specific associations between FI and FBNC.

The ROI-ROI analysis included five networks (Default-Mode, Sensorimotor, Salience, Dorsal Attention, and Frontoparietal) with a total of 42 different connections. The main finding from the ROI-ROI analysis was that females possess greater connectivity within the Default-Mode Network. Notably, no ROI-ROI networks demonstrated a significant association between connectivity and FI values for any other analysis (continuous or tertiles in the full sample and/or by sex). The S-V analysis used the right and left Hippocampus as a seed, but only the right demonstrated connections significantly associated with FI values. When analyzing the full sample and males continuously, the right Hippocampus increased connectivity to the left and bilateral regions of the inferior and middle Temporal Gyrus. Such results suggest that males are likely driving the significant connection to the left inferior/middle Temporal Gyrus in the full sample. Only males demonstrated a significant between-tertile difference, specifically for one connection of the right Hippocampus; low (non-frail) tertile possessed greater connectivity than high (frail) but less than intermediate (pre-frail).

The connectivity coefficients that were significantly associated with FI demonstrated a positive relationship. Meaning, an increasing (worse) FI value was correlated with an increase in connectivity. These significant connections appear to be between regions not typically linked or belonging to a single network. Admittedly, this is hard to confirm given the broad (Temporal Lobe) anatomically labelling applied to the cluster, which contrasts the more specific labelling observed in Chapter 4. As such, we believe this connection may reflect compensation or an

attempt to maintain homeostasis by increasing between-network connectivity via alternative circuits. Such adjustments reflect the "scaffolding" theory (54) and have been previously demonstrated with the Default-Mode (55). Further support for this compensatory behaviour comes from the present study demonstrating no significant associations between FI and within-network connectivity. Additionally, our male intermediate tertile possessed greater connectivity than our low tertile, despite being more frail. Combined with the high (frail) tertile showing the lowest connectivity, a possible explanation is that pre-frail reflects a compensation stage where new connections form to maintain homeostasis before becoming more frail and/or cognitively impaired and beginning a downward anti-correlation trajectory. Accordingly, the high (frail) male tertile may be at the greatest risk of progression to Alzheimer's disease, despite receiving an identical cognitive classification.

Our findings both support and refute previous research. Only two studies have previously examined the relationship between FBNC and frailty status (24,25). Both used the Cardiovascular Health Study – Frailty Phenotype (26), only included "cognitively healthy" older adults, and restricted their analysis to motor regions. Only Lammers and colleagues used fMRI and performed scans with eyes closed (25). They found a significant negative relationship with the Supplementary Motor Area, but not the pre-SMA (25). Conversely, we found no significant associations between the Sensorimotor Network and FI, nor any of our other networks. The discrepancy between studies may reflect methodological differences as we utilized a FI that included variables from various domains, focused on clinically impaired older adults, and performed fMRI scans with eyes open; visual status is an essential consideration for neural function (56). Network-specific associations to the same health outcome are further supported by

previous work examining the relationship between FBNC and gait parameters (57). Evidently, more research is needed on FBNC and its relationship with frailty.

Our results suggest that sex is an essential consideration in understanding the association between frailty and FBNC. Lammer and colleagues did not conduct a separate analysis by sex, but other researchers have demonstrated sex-specific differences in both brain function (28) and brain blood flow (29). Furthermore, sex-specific differences in frailty are well established as females become frail earlier, and at any given age are more frail than their male counterparts but manage to live longer; such a phenomenon is "the male-female health survival paradox" (31,58) and is an active area of research (59). Females' greater within-network Default-Mode connectivity and lack of what we identified as increases in between-network connectivity for males may reflect "better" brain function and further support female's frailty resilience. It is likely that sex hormones play a role, but a 2017 review highlighted two biological theories for the frailty-sex discrepancy: 1) males possess less physiological reserve so, at the same FI score, they are at a greater risk of mortality; and 2) females tend to accumulate less severe deficits or deficits associated with lower risk of mortality, which highlights the issue of collecting the number, but not the nature of the deficits (60). Notably, sex differences may be responsible for the lack of more meaningful findings in the present study's full sample, and more research is needed into its relationship with FBNC.

Given the present findings, future studies should consider frailty scores and sex when conducting FBNC analyses in clinical groups. Lack of more meaningful findings in Chapters 2 and 4 may reflect not including frailty as a covariate or performing a sub-analysis by frailty status. Similar to research in frailty and exercise interventions (15,16), future research should analyze frailty

status using both the Frailty Phenotype and FI to determine if they produce divergent findings. Furthermore, such analysis should be simultaneously conducted in cognitively healthy and impaired older adults to help elucidate how dementia-related neurodegeneration alters the FBNC-frailty relationship. Along the dementia spectrum, researchers may even want to consider the stage or classification of mild cognitive impairment (i.e., amnestic vs. non-amnestic (61,62), early vs. late (63), and single vs. multi-domain (64,65)) as this is potentially another factor confounding relationships. Researchers should not restrict their analysis to a single region as some networks are more susceptible than others to neurodegeneration, which subsequently impacts connectivity (66). Moreover, the "neural context" hypothesis suggests that the functional relevance of a brain area depends on the "status" of other connected areas (67). Therefore, alterations in one region do not necessarily have the same implications as alterations in another. Only by examining the entire connectome will we better understand global and local alterations and their potential downstream effects for behavioural outcomes. Ultimately, tracking the longitudinal relationship between FBNC and frailty will provide the greatest insight to many of the suggestions offered above while providing an opportunity for early intervention.

We conducted the first study to cross-sectionally analyze the relationship between FBNC and frailty status using the FI in individuals with MCI, but it is not without limitation. The benefit of the FI is that it can be created retroactively and is not restricted to any one variable (36). Unfortunately, this means no two FIs are identical. The inclusion of more, less, or different variables than the 59 included in the present study may have produced a different result. We classified most but not all of our participants with amnestic mild cognitive impairment. As previously discussed, different sub-types may be convoluting our findings. As is typical with FBNC, the present study merely reflects two analyses available to researchers. Our previous

systematic review (68,69) and other works (70) have demonstrated that researchers can take different approaches to answer the same question. Our sample may be considered less frail than other work in frailty and brain health as our maximum value was the equivalent of another study's upper tertile cut-point (18). Similarly, our sex tertile results should be interpreted cautiously given their small sample size (<20). No "cognitively healthy" comparator makes it difficult to draw interpretations for biological aging. Finally, cross-sectional studies inherently create several limitations, including the inability to make causal inferences, the "snapshot" nature, and the risk of Neyman Bias (71).

5.5 Conclusion

The present study examined the cross-sectional association between FBNC throughout the brain, and frailty status, as per a FI. Individuals with worse frailty scores had increasing positive connectivity of the right Hippocampus to a broadly labelled cluster. We believe such changes reflect compensation via an increase in between-network connectivity. Frailty and FBNC associations differ by sex, as only males demonstrated significant associations between frailty and FBNC, but females showed greater within-network Default-Mode connectivity than males. Overall, our findings add to the growing literature on how frailty impacts males and females differently and suggest why some individuals may progress to a dementia syndrome while others classified with MCI remain stable.

5.6 Graphics

5.6.1 Figures

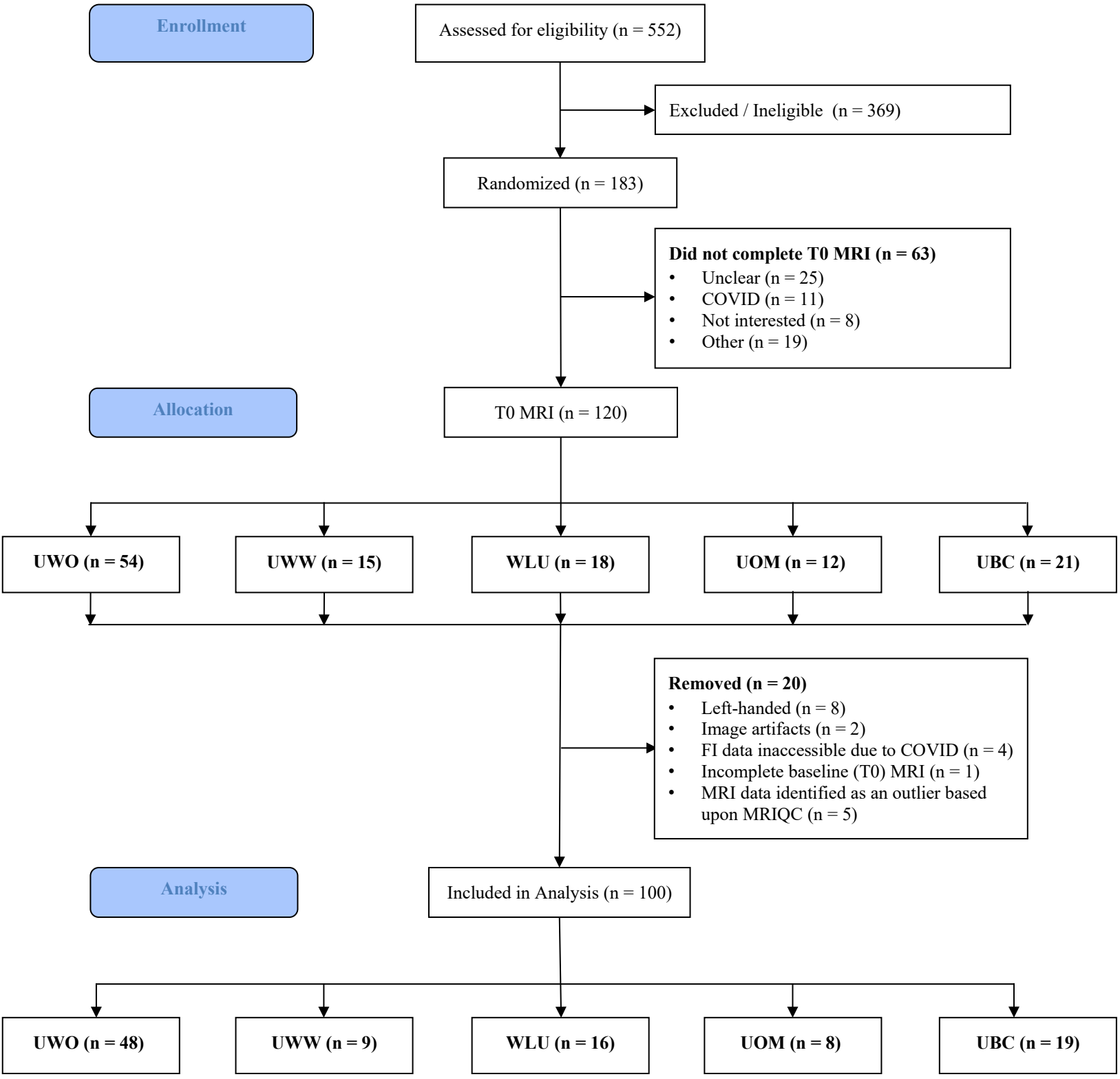


Figure 5.1 Study flowchart for participants included in imaging analysis, stratified by study site. UWO, University of Western Ontario; UWW, University of Waterloo; WLU, Wilfrid Laurier University; UOM, University of Montreal; UBC, University of British Columbia.

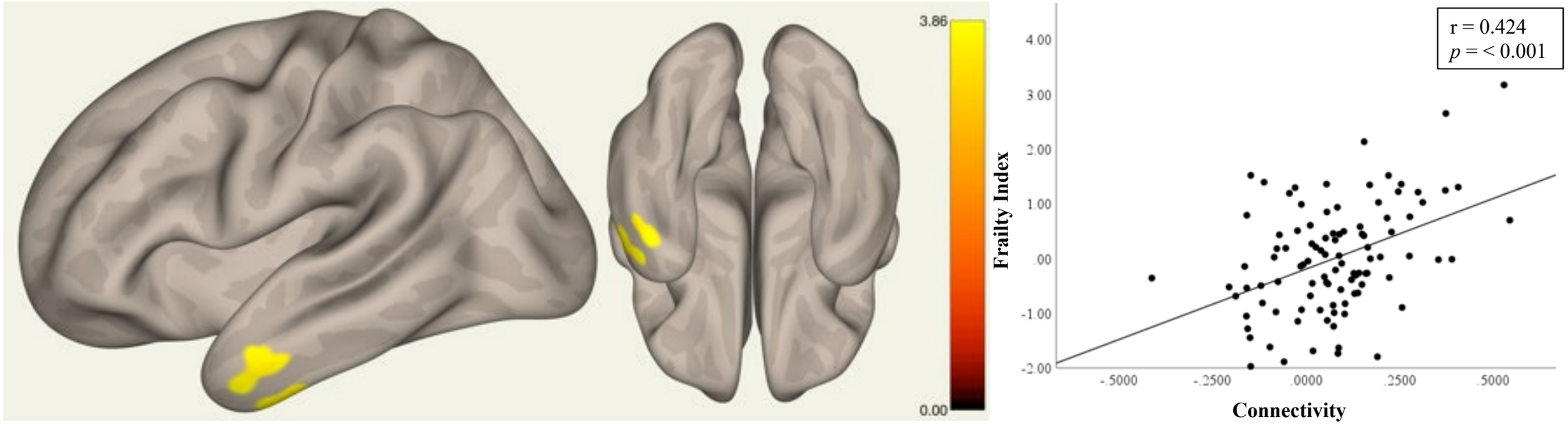
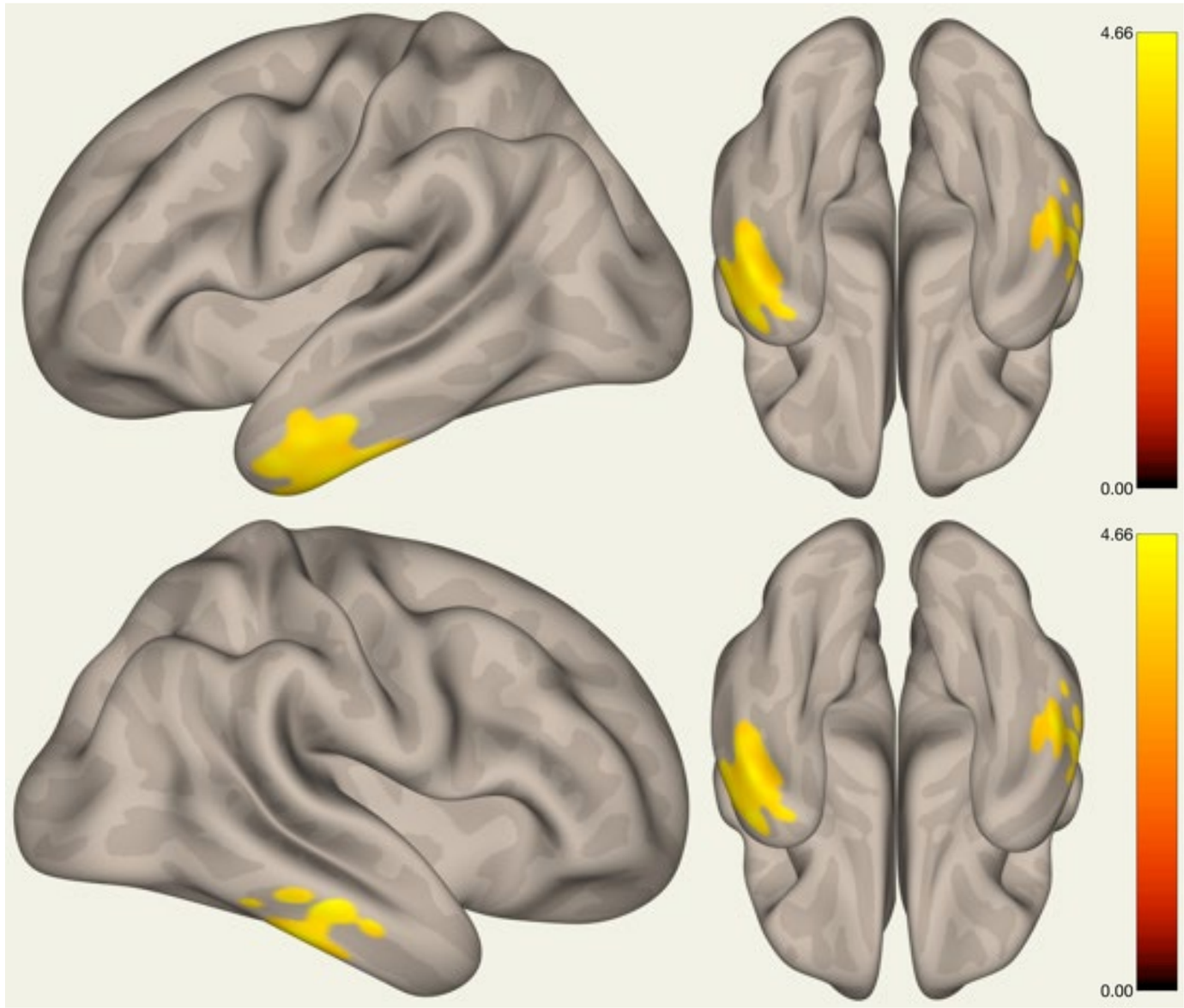


Figure 5.2 Full sample result (n =100); increasing frailty associated with increasing connectivity from right Hippocampus *to the* cluster shown. Left and inferior view for brain images. Frailty Index value is a z-score via standardized residuals of linear regression. Connectivity value is a Fisher-transformed correlation coefficient. See Table 5.6 for more details about cluster.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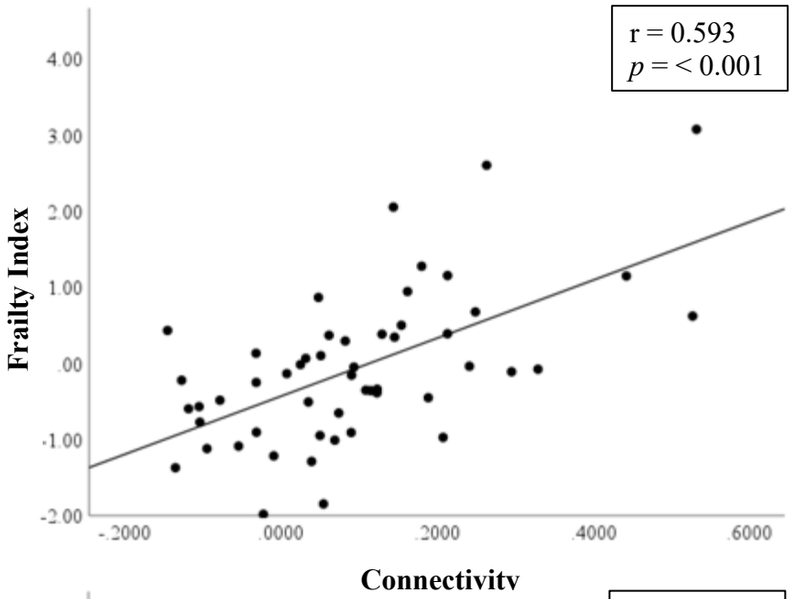
0.00


r = 0.593
p = < 0.001
Frailty Index
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2.00
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-1.00
-2.00
-.2000
.0000
.2000
.4000
.6000
Connectivitv

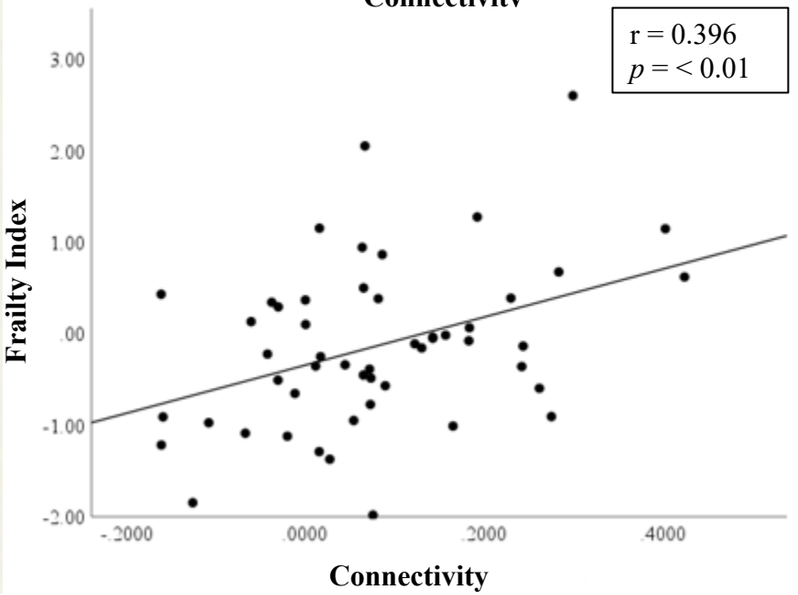
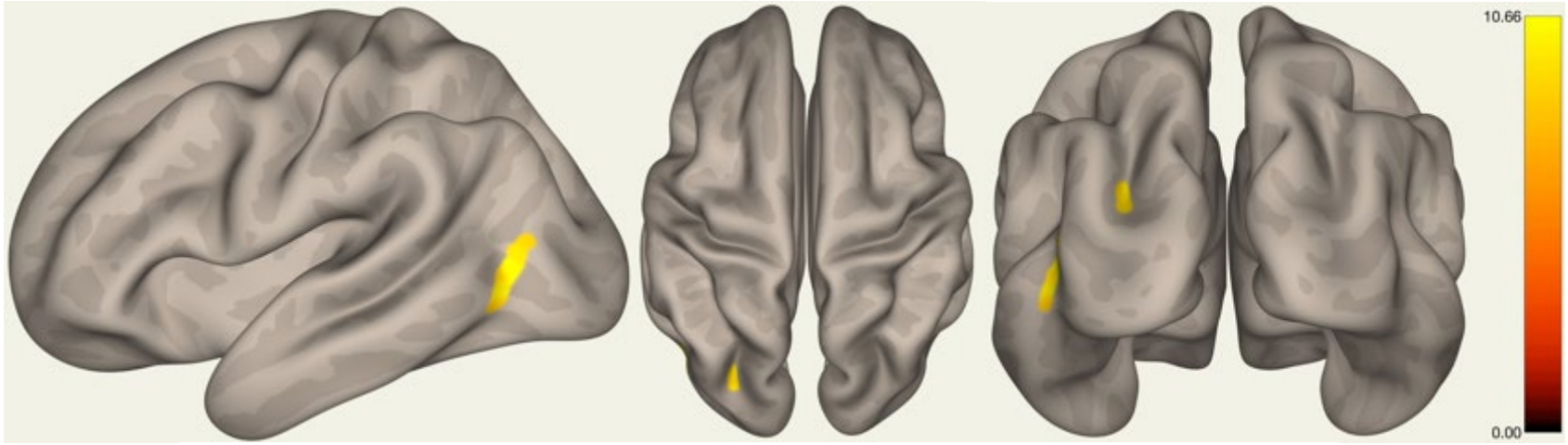

r = 0.396
p = < 0.01
Frailty Index
3.00
2.00
1.00
.00
-1.00
-2.00
-.2000
.0000
.2000
.4000
Connectivity

Figure 5.3 Male sample result (n=52, top and n=51, bottom); increasing frailty associated with increasing connectivity from right Hippocampus *to the* clusters shown. Right, left, and inferior view for brain images. Frailty Index value is a z-score via standardized residuals of linear regression. Connectivity value is a Fisher-transformed correlation coefficient. See Table 5.6 for more details about cluster.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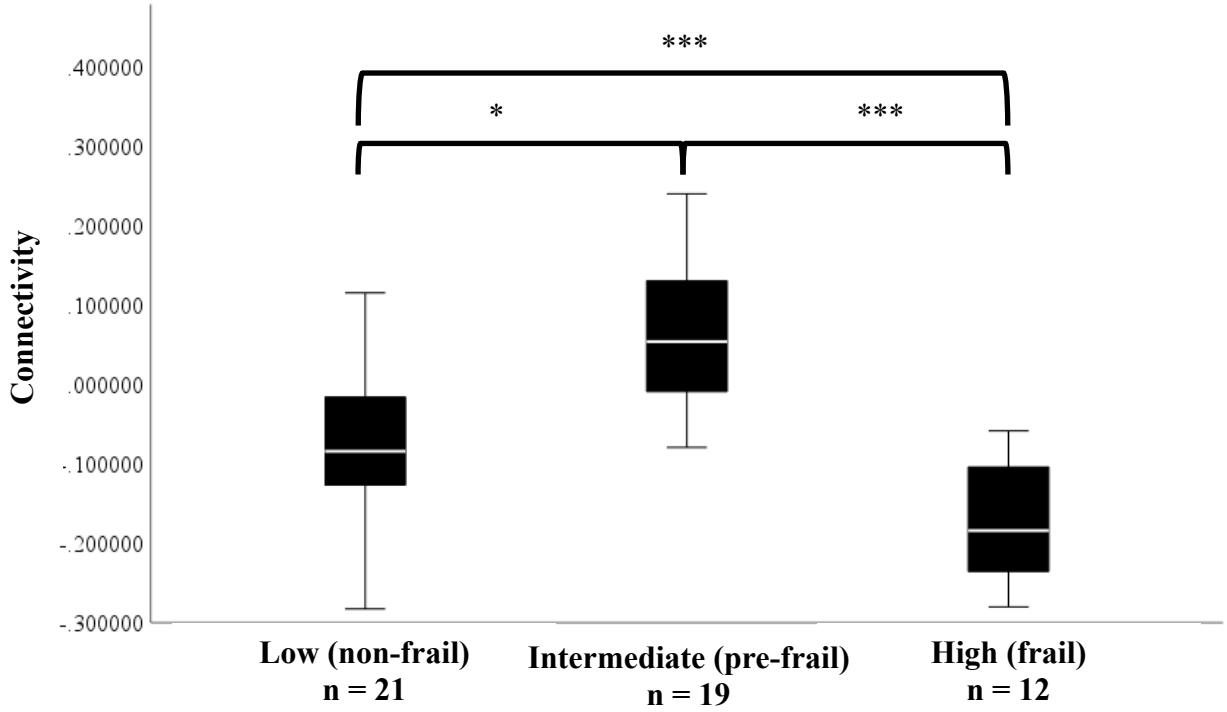
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.100000
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-.200000
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Connectivity
Low (non-frail)
n = 21
Intermediate (pre-frail)
n = 19
High (frail)
n = 12

Figure 5.4 Male tertiles result (n = 52) between low (non-frail), intermediate (pre-frail), and high (frail) tertile. Left, superior, and posterior for brain images. Connectivity value is a Fisher-transformed correlation coefficients (53). See Table 5.6 for more details about cluster. *** standard cluster and connections thresholds; * connection threshold at a more liberal voxel threshold of *p*-value = 0.05.

5.6.2 Tables

Table 5.1 Characteristics of full sample (n=100).

Characteristic	Total (n = 100)	Males (n = 52)	Females (n = 48)	*p-value*
Age	73.79 ± 6.24	74.27 ± 6.19	73.27 ± 6.31	0.426
# of Comorbidities	4.73 ± 2.54	4.65 ± 2.57	4.81 ± 2.53	0.757
Years of Education	15.10 ± 3.67	15.79 ± 4.08	14.33 ± 3.04	***0.047***
Height (cm)	167.33 ± 10.05	173.81 ± 7.21	160.31 ± 7.70	***< 0.001***
Weight (kg)	74.94 ± 14.89	82.56 ± 13.40	66.69 ± 11.77	***< 0.001***
Body Mass Index	26.65 ± 4.20	27.29 ± 3.94	25.96 ± 4.41	0.114
MoCA	22.88 ± 3.06[a]	22.94 ± 2.89	22.81 ± 3.27[b]	0.829
Frailty Index Value	0.19 ± 0.07	0.19 ± 0.07	0.20 ± 0.07	0.594
Default-Mode Connectivity	0.5283 ± 0.1712	0.4915 ± 0.1659	0.5682 ± 0.1696	***0.024***
Sensorimotor Connectivity	0.5784 ± 0.2462	0.6085 ± 0.2405	0.5458 ± 0.2505	0.205
Salience Connectivity	0.3974 ± 0.1490	0.3785 ± 0.1497	0.4179 ± 0.1470	0.188
Dorsal Attention Connectivity	0.4458 ± 0.1674	0.4695 ± 0.1836	0.4201 ± 0.1456	0.141
Frontoparietal Connectivity	0.4875 ± 0.1730	0.4693 ± 0.1834	0.5072 ± 0.1605	0.275

Note: All values are mean ± standard deviation. Independent samples t-test used for analysis. MoCA, Montreal Cognitive Assessment; #, number; cm, centimeters; kg, kilograms; R, right; a, n = 99; b, n = 47. *p*-values compare males and females.

Table 5.2 Characteristics of full sample divided into tertiles based upon frailty index value.

Characteristic	Low (n = 39)	Intermediate (n = 31)	High (n = 30)	*p-value*
Age	72.62 ± 6.39	74.16 ± 7.04	74.93 ± 4.97	0.289
# of Comorbidities	2.56 ± 1.47	4.97 ± 1.47	7.30 ± 1.93	***< 0.001*** *
Years of Education	14.94 ± 3.02	15.73 ± 4.86	14.63 ± 3.00	0.486
Height (cm)	169.11 ± 10.71	168.68 ± 9.37	163.62 ± 9.11	0.052
Weight (kg)	72.59 ± 14.06	79.03 ± 15.45	73.79 ± 14.97	0.175
Body Mass Index	25.22 ± 3.39	27.69 ± 4.59	27.44 ± 4.36	***0.023*** ***
MoCA	22.69 ± 3.33	23.19 ± 2.96	22.79 ± 2.87[a]	0.784
Frailty Index Value	0.13 ± 0.03	0.20 ± 0.02	0.27 ± 0.05	***< 0.001*** *
Default-Mode Connectivity	0.5340 ± 0.1818	0.5418 ± 0.1518	0.5070 ± 0.1796	0.710
Sensorimotor Connectivity	0.5580 ± 0.2777	0.6420 ± 0.2232	0.5394 ± 0.2186	0.215
Salience Connectivity	0.4034 ± 0.166	0.3957 ± 0.1354	0.3914 ± 0.1436	0.945
Dorsal Attention Connectivity	0.4240 ± 0.1970	0.4609 ± 0.1256	0.4585 ± 0.1658	0.587
Frontoparietal Connectivity	0.4750 ± 0.1899	0.5081 ± 0.1791	0.4825 ± 0.1450	0.719

Note: All values are mean ± standard deviation. One-way ANOVA used for analysis. MoCA, Montreal Cognitive Assessment; #, number; cm, centimeters; kg, kilograms; a, n = 29; *, all three groups significantly different from one another; *** low significantly different than intermediate.

Table 5.3 Characteristics of female sample divided into tertiles based upon frailty index value.

Characteristic	Low (n = 18)	Intermediate (n = 12)	High (n = 18)	*p-value*
Age	71.44 ± 5.88	74.17 ± 9.05	74.5 ± 4.09	0.302
# of Comorbidities	2.39 ± 1.58	5.17 ± 1.34	7.00 ± 1.65	***< 0.001*** *
Years of Education	14.81 ± 3.11	14.79 ± 3.58	13.56 ± 2.55	0.397
Height (cm)	160.99 ± 8.56	162.67 ± 8.56	158.06 ± 5.8	0.25
Weight (kg)	63.53 ± 11.22	70.52 ± 15.14	67.31 ± 9.36	0.275
Body Mass Index	24.43 ± 3.43	26.67 ± 5.67	27.02 ± 4.15	0.174
MoCA	22.61 ± 3.57	22.92 ± 3.85	22.94 ± 2.63[a]	0.95
Frailty Index Value	0.12 ± 0.04	0.20 ± 0.02	0.27 ± 0.03	***< 0.001*** *
Default-Mode Connectivity	0.6134 ± 0.1411	0.5520 ± 0.1588	0.5338 ± 0.1993	0.353
Sensorimotor Connectivity	0.5586 ± 0.3090	0.5399 ± 0.2661	0.5370 ± 0.1788	0.968
Salience Connectivity	0.4093 ± 0.1435	0.4122 ± 0.1720	0.4303 ± 0.1405	0.905
Dorsal Attention Connectivity	0.3988 ± 0.1619	0.4338 ± 0.0919	0.4323 ± 0.1617	0.741
Frontoparietal Connectivity	0.4892 ± 0.1843	0.5322 ± 0.1879	0.5086 ± 0.1167	0.778

Note: All values are mean ± standard deviation. One-way ANOVA used for analysis. MoCA, Montreal Cognitive Assessment; #, number; cm, centimeters; kg, kilograms; a, n = 17; *, all three groups significantly different from one another.

Table 5.4 Characteristics of male sample divided into tertiles based upon frailty index value.

Characteristic	Low (n = 21)	Intermediate (n = 19)	High (n = 12)	*p-value*
Age	73.62 ± 6.76	74.16 ± 5.70	75.58 ± 6.20	0.686
# of Comorbidities	2.71 ± 1.38	4.84 ± 1.57	7.75 ± 2.30	***< 0.001*** *
Years of Education	15.05 ± 3.01	16.32 ± 5.54	16.25 ± 2.99	0.569
Height (cm)	176.07 ± 6.73	172.47 ± 7.91	171.98 ± 6.31	0.176
Weight (kg)	80.35 ± 11.47	84.40 ± 13.38	83.52 ± 16.84	0.618
Body Mass Index	25.91 ± 3.28	28.33 ± 3.79	28.08 ± 4.77	0.11
MoCA	22.76 ± 3.19	23.37 ± 2.34	22.58 ± 3.29	0.72
Frailty Index Value	0.13 ± 0.03	0.20 ± 0.02	0.28 ± 0.07	***< 0.001*** *
Default-Mode Connectivity	0.4659 ± 0.188	0.5353 ± 0.1513	0.4668 ± 0.144	0.359
Sensorimotor Connectivity	0.5574 ± 0.2556	0.7065 ± 0.1686	0.5429 ± 0.2768	0.080
Salience Connectivity	0.3984 ± 0.1865	0.3853 ± 0.1104	0.3331 ± 0.1328	0.478
Dorsal Attention Connectivity	0.4457 ± 0.2244	0.4780 ± 0.1426	0.4977 ± 0.1713	0.721
Frontoparietal Connectivity	0.4628 ± 0.1982	0.4929 ± 0.1768	0.4433 ± 0.1778	0.755

Note: All values are mean ± standard deviation. One-way ANOVA used for analysis. MoCA, Montreal Cognitive Assessment; #, number; cm, centimeters; kg, kilograms; *, all three groups significantly different from one another.

Table 5.5 Pearson correlation results for ROI-ROI analysis in full sample, males and females.

Group		Variables	Pearson Correlation (r)	Sig. (2-tailed; *p*)
All Subjects (n=100)	**Standardized Residual FI**	**Default-Mode Connectivity**	-0.098	0.334
		Sensorimotor Connectivity	0.040	0.692
		Salience Connectivity	-0.014	0.892
		Dorsal Attention Connectivity	0.178	0.076
		Frontoparietal Connectivity	-0.035	0.727
Females (n=48)	**Standardized Residual FI**	**Default-Mode Connectivity**	-0.210	0.153
		Sensorimotor Connectivity	0.000	0.998
		Salience Connectivity	0.129	0.382
		Dorsal Attention Connectivity	0.155	0.294
		Frontoparietal Connectivity	0.029	0.845
Males (n=52)	**Standardized Residual FI**	**Default-Mode Connectivity**	0.007	0.963
		Sensorimotor Connectivity	0.076	0.590
		Salience Connectivity	-0.146	0.302
		Dorsal Attention Connectivity	0.200	0.156
		Frontoparietal Connectivity	-0.095	0.504

Table 5.6 All connections from seed-to-voxel analysis that were associated with frailty index score after controlling for covariates.

Demographic	Seed	Direction of Connectivity	Cluster						
			x, y, z	Size	size *p*-FDR	peak *p*-unc.	Anatomical Area	%	Voxels
Full (n=100)	Right Hippocampus	↑	-48 +2 -44	291	0.029812	0.000107	Inferior Temporal Gyrus, anterior division Left	44	127
							Temporal Pole Left	13	37
							Middle Temporal Gyrus, anterior division Left	11	31
							Not-labeled	33	96
Male (n=52)	Right Hippocampus	↑	-44 +4 -46	993	0.000021	0.000004	Inferior Temporal Gyrus, anterior division Left	26	262
							Inferior Temporal Gyrus, posterior division Left	18	174
							Temporal Pole Left	11	105
							Middle Temporal Gyrus, anterior division Left	9	91
							Middle Temporal Gyrus, posterior division Left	2	15
							Temporal Fusiform Cortex, anterior division Left	0	2
							Temporal Fusiform Cortex, posterior division Left	0	1
							Not-labeled	35	343
		↑	66 -28 -26	451	0.00351	< 0.000001	Inferior Temporal Gyrus, posterior division Right	49	219
							Middle Temporal Gyrus, posterior division Right	20	88
							Inferior Temporal Gyrus, temporooccipital part Right	0	2
							Not-labeled	31	142
Male Tertiles (n = 52)	Right Hippocampus	↑	-26 -70 +16	289	0.015491	0.000006	Lateral Occipital Cortex, inferior division Left	6	18
							Lateral Occipital Cortex, superior division Left	2	5
							Not-labeled	92	266
Intermediate > Low and High									

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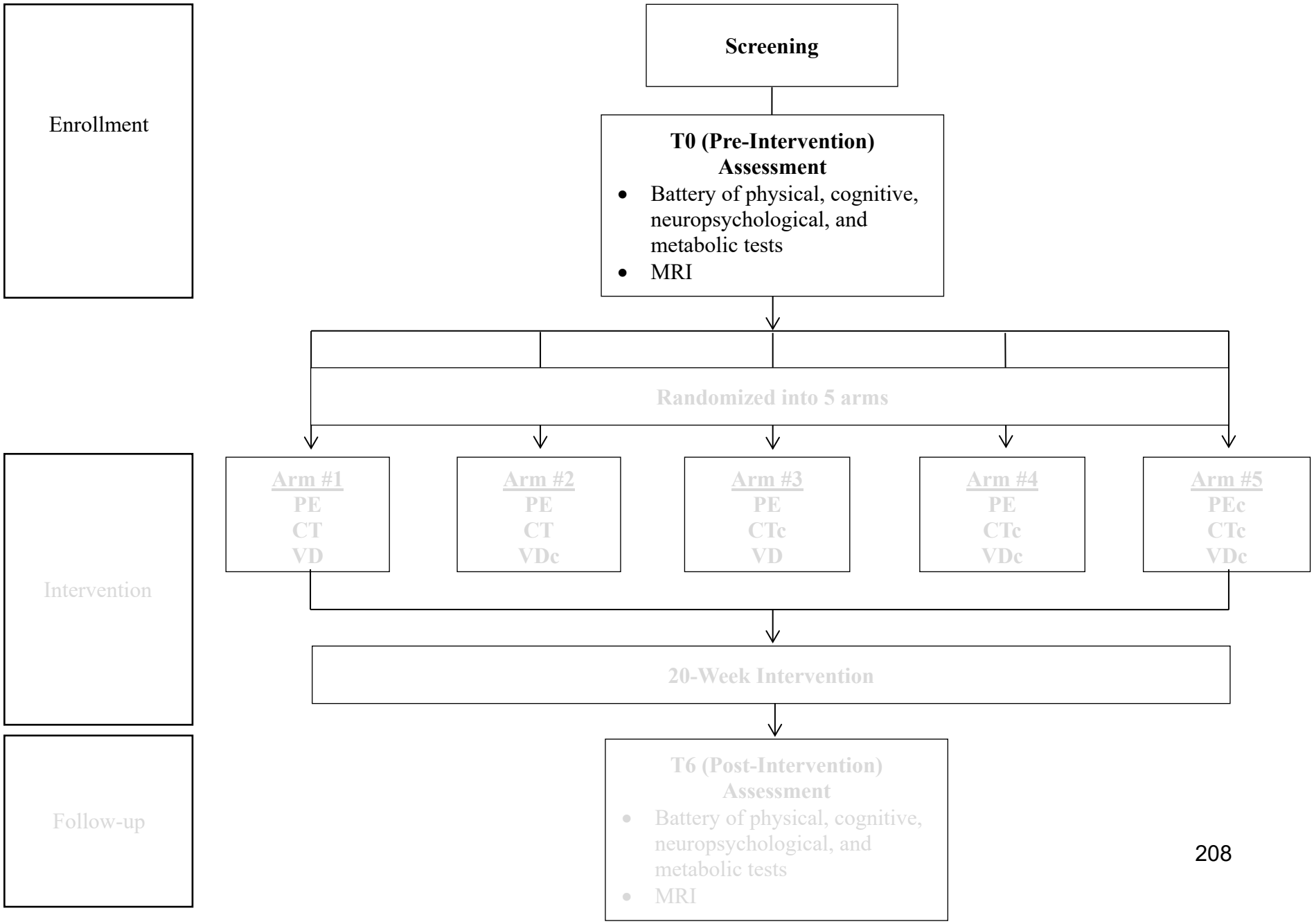
5.8 SUPPLEMENTARY MATERIAL

Supplementary Material A: Overview of the SYNERGIC trial.



Note: Only screening and baseline or pre-intervention (T0) assessments were relevant to the present study. MRI, magnetic resonance imaging.

Supplementary Material B: Assessments across study visits for SYNERGIC Trial.

Procedure	**Visit 1** Screening	**Visit 2** Baseline (T0)	**Visit 3** 6-month (T6)	**Telephone** 9-month	**Visit 4** 12-month (T12)
Written Informed Consent	X				
Demographic Information	X				
Mini Mental State Examination (MMSE)	X				
Physical Activity Readiness Questionnaire Plus (PARQ +)	X				
Logical Memory 1 & 2	X				
CERAD Word List Recall	X				
PASE Questionnaire	X				
Montreal Cognitive Assessment (MoCA)	X		X		X
Generalized Anxiety Disorder 7 (GAD-7)	X		X		X
Geriatric Depression Scale (GDS-30)	X		X		X
Clinical Dementia Rating (CDR)	X		X		X
Activities of Daily Living (ADCS-ADL and IADL)	X		X		X
Clinical Medical Questionnaire		X	X		X
Dual Task Control Assessment		X	X		X
ADAS-Cog 13 (+ tests *)		X	X		X
Trail Making Test A & B *		X	X		X
Digit Symbol Test *		X	X		X
Digit Span Forward and Backward WAIS-III *		X	X		X
Boston Naming Test *		X	X		X
Verbal Fluency Test *		X	X		X
Color Word Interference Test		X	X		X
Quality of Life Questionnaire (SF-36)		X	X		X
Short Physical Performance Battery (SPPB)		X	X		X
Gait Assessment using Gait Mat and accelerometers		X	X		X
Six Minute Walk Test (6MWT) ^		X	X		X
Neuroimaging (MRI)		X	X		
Blood Draw		X	X		
Falls Calendar ^^		X	X	X	X

* Testing included in the ADAS-Cog plus.
^ This test may be completed at the gym facility on the first day of intervention.
^^ Calendar will be given to participant to complete and will be submitted to Research Staff at exercise training.

Supplemental Material C: Frailty Index.

DOMAIN	VARIABLE	TOOL USED TO MEASURE	CUT-OFF POINT	COUNT
Physical	Repeated chair stand	Short Physical Performance Battery (SPPB) (Guralnik et al., 1994)	1: Unable 0.75: >16.7 seconds (sec) 0.5: 13.7 - 16.6 sec 0.25: 11.2 - 13.6 sec 0: <11.1 sec	1
	Balance	Short Physical Performance Battery (SPPB)	1: Side by side for 0-9 sec or unable 0.75: Side by side 10 sec, semi-tandem <10 sec 0.5: Semi-tandem 10 sec, tandem 0-2 sec 0.25: Semi-tandem 10 sec, tandem 3-9 sec 0: Tandem 10 sec	2
	Gait-speed			
	Usual	8 meters (m) (1m acceleration/deceleration) on electronic walkway (Montero-Odasso et al., 2016)	<1.0 m/sec	3
	Fast	8m (1m acceleration & deceleration) on electronic walkway	<1.2 m/sec	4
	Physical activity level	Physical Activity Scale for the Elderly (PASE) (Washburn et al., 1993)	Males Females 1: <64 1: <52 0: ≥ 64 0: >52	5
	Grip strength	Handheld dynamometer & Fried's Frailty Phenotype (Fried et al., 2001)	Males 1: ≤29 kilograms (kg) or 0: >29 kg (Body mass index; BMI <24) 1: ≤30 kg or 0: >30 kg (BMI 24.1-26) 1: ≤30 kg or 0: >30 kg (BMI 26.1-28) 1: ≤32 kg or 0: >32 kg (BMI >28) Females 1: <17 kg or 0: >17 kg (BMI <23) 1: <17.3 kg or 0: >17.3 kg (BMI 23.1-26) 1: <18 kg or 0: >18 kg (BMI 26.1-29) 1: <21 kg or 0: >21 kg (BMI >29)	6
	Peak metabolic equivalent (METs) calculated via Ross et al., 2010	6-minute walk test (Crapo et al., 2002)	1: <5 METs 0: ≥5 METs	7

Functional	Telephone	Instrumental Activities of Daily Living (IADL) Scale (Lawton et al., 1969)	1: Does not use telephone 0.67: Answers telephone but does not dial 0.33: Dials a few well-known numbers 0: Operates telephone on own initiative	8
	Shopping	Instrumental Activities of Daily Living (IADL) Scale	1: Completely unable to shop 0.67: Accompanied on any shopping trip 0.33: Shops independently for small purchases 0: Takes care of all shopping needs independently	9
	Food preparation	Instrumental Activities of Daily Living (IADL) Scale	1: Needs to have meals prepared and served 0.67: Heats, serves and prepares meals, or prepares meals but does not maintain adequate diet 0.33: Prepares adequate meals if supplied with ingredients 0: Plans, prepares and serves adequate meals independently	10
	Housekeeping	Instrumental Activities of Daily Living (IADL) Scale	1: Does not participate in any housekeeping tasks 0.75: Needs help with all home maintenance tasks 0.5: Performs light daily tasks but cannot maintain acceptable level of cleanliness 0.25: Performs light daily tasks such as dish washing, bed making 0: Maintains house alone or with occasional assistance	11
	Laundry	Instrumental Activities of Daily Living (IADL) Scale	1: All laundry must be done by others 0.5: Launders small items - rinses stockings, etc. 0: Does personal laundry completely	12
	Transportation	Instrumental Activities of Daily Living (IADL) Scale	1: Does not travel at all 0.75: Travel limited to taxi or automobile with assistance of another 0.5: Travels on public transportation when accompanied by another 0.25: Arranges own travel via taxi, but does not otherwise use public transportation 0: Travels independently on public transportation or drives own car	13

Functional (cont'd)	Medications	Instrumental Activities of Daily Living (IADL) Scale	1: Is not capable of dispensing own medication 0.5: Takes responsibility if medication is prepared in advance in separate dosage 0: Is responsible for taking medication in correct dosages at correct time	14
	Handling finances	Instrumental Activities of Daily Living (IADL) Scale	1: Incapable of handling money 0.5: Manages day-to-day purchases, but needs help with banking, major purchases, etc. 0: Manages financial matters independently	15
Exhaustion	Typical level of energy	Modified Fried's Frailty Phenotype (Islam et al., 2014)	1: Low 0.5: Moderate 0: High	16
	A lot of energy during the past 4 weeks	Modified Fried's Frailty Phenotype	1: All of the time 0.5: Half of the time 0: Little/none of the time	17
	Felt everything was an effort	Modified Fried's Frailty Phenotype	1: Yes 0: No	18
	Felt they could not get going	Modified Fried's Frailty Phenotype	1: Yes 0: No	19
Nutrition	Unintentional weight loss	Modified Fried's Frailty Phenotype	1: >10 lbs 0.67: 5-10 lbs 0.33: 1-5 lbs 0: None	20
	Body Mass Index (BMI)	General data collection form	1: <18.5 or >30 0.5: 25.1-29.9 0: 18.5-25	21
Neuropsychiatric	Self-rating of health	SF-36 (Brazier et al., 1992)	1: Poor 0.75: Fair 0.5: Good 0.25: Very good 0: Excellent	22

Neuropsychiatric (cont'd)	How health has changed in last year	SF-36	1: Much worse 0.75: Somewhat worse 0.5: Same 0.25: Somewhat better 0: Much better	23
	Depression	Geriatric Depression Scale (GDS) (Yesavage et al., 1982)	1: 20-30 0.5: 10-19 0: 0-9	24
	Anxiety	Generalized Anxiety Disorder 7-Item Scale (GAD-7) (Spitzer et al., 2006)	1: 14-21 0.5: 7-13 0: 0-6	25
Falling	Fall within the past 6 months	Data Collection Form	1: Yes 0: No	26
Comorbidities	Hypertension	Data Collection Form	1: Yes 0: No	27
	Congestive heart failure	Data Collection Form	1: Yes 0: No	28
	Diabetes	Data Collection Form	1: Yes 0: No	29
	Parkinson's disease	Data Collection Form	1: Yes 0: No	30
	Anemia	Data Collection Form	1: Yes 0: No	31
	Osteoporosis	Data Collection Form	1: Yes 0: No	32
	Lung disease	Data Collection Form	1: Yes 0: No	33
	Osteoarthritis	Data Collection Form	1: Yes 0: No	34
	Cancer	Data Collection Form	1: Yes 0: No	35

Comorbidities (cont'd)	Hearing problem	Data Collection Form	1: Yes 0: No	36
	Dyslipidemia	Data Collection Form	1: Yes 0: No	37
	Major joint replaced	Data Collection Form	1: Yes 0: No	38
	Depression	Data Collection Form	1: Yes 0: No	39
	Smoker	Data Collection Form	1: Yes 0: No	40
	Stroke	Data Collection Form	1: Yes 0: No	41
	Transient ischemic attack	Data Collection Form	1: Yes 0: No	42
	Glasses	Data Collection Form	1: Yes 0: No	43
	Cataract surgery	Data Collection Form	1: Yes 0: No	44
	Macular degeneration	Data Collection Form	1: Yes 0: No	45
	Cataracts	Data Collection Form	1: Yes 0: No	46
	Glaucoma	Data Collection Form	1: Yes 0: No	47
	Legally blind	Data Collection Form	1: Yes 0: No	48
	Myocardial infarction	Data Collection Form	1: Yes 0: No	49
	Atrial fibrillation	Data Collection Form	1: Yes 0: No	50

Comorbidities (cont'd)	Angioplasty	Data Collection Form	1: Yes 0: No	51
	Pacemaker	Data Collection Form	1: Yes 0: No	52
	Bypass	Data Collection Form	1: Yes 0: No	53
	Angina	Data Collection Form	1: Yes 0: No	54
	"Other"	Data Collection Form	1: Yes 0: No	55
Vital Signs	Seated Heart Rate	Data Collection Form	1: <60 beats per minute (bpm) or >99 bpm 0: 60-99 bpm	56
	Seated Systolic Blood Pressure	Data Collection Form	1: <90 mmHg or >140 mmHg 0: 90-140 mmHg	57
	Seated Diastolic Blood Pressure	Data Collection Form	1: <60 millimetre of mercury (mmHg) or >90 mmHg 0: 60-90 mmHg	58
Medications	Total number of medications	Patient Provided Medication List	5: 20-22 4: 17-19 3: 14-16 2: 11-13 1: 8-10 0.5: 6-7 0: 0-5	59

Supplementary Material D: Preprocessing with fMRIPrep.

Results included in this manuscript come from preprocessing performed using ***fMRIPrep*** 20.2.0 (Esteban, Markiewicz, et al. (2018); Esteban, Blair, et al. (2018); RRID:SCR_016216), which is based on ***Nipype*** 1.5.1 (Gorgolewski et al. (2011); Gorgolewski et al. (2018); RRID:SCR_002502).

Anatomical data preprocessing

A total of 1 T1-weighted (T1w) images were found within the input BIDS dataset. The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al. 2010), distributed with ANTs 2.3.3 (Avants et al. 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a ***Nipype*** implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 5.0.9, RRID:SCR_002823, Zhang, Brady, and Smith 2001). Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with antsRegistration (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following template was selected for spatial normalization: ***ICBM 152 Nonlinear Asymmetrical template version 2009c*** [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym],

Functional data preprocessing

For each of the 1 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of ***fMRIPrep***. A deformation field to correct for susceptibility distortions was estimated based on ***fMRIPrep's fieldmap-less*** approach. The deformation field is that resulting from co-registering the BOLD reference to the same-subject T1w-reference with its intensity inverted (Wang et al. 2017; Huntenburg 2014). Registration is performed with antsRegistration (ANTs 2.3.3), and the process regularized by constraining deformation to be nonzero only along the phase-encoding direction, and modulated with an average fieldmap template (Treiber et al. 2016). Based on the estimated susceptibility distortion, a corrected EPI (echo-planar imaging) reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using flirt (FSL 5.0.9, Jenkinson and Smith 2001) with the boundary-based registration (Greve and Fischl 2009) cost-function. Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9, Jenkinson et al. 2002). BOLD runs were slice-time corrected using 3dTshift from AFNI 20160207 (Cox and Hyde 1997, RRID:SCR_005927). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as ***preprocessed BOLD in original space***, or just ***preprocessed BOLD***. The BOLD time-series were resampled into standard space, generating a ***preprocessed BOLD run in MNI152NLin2009cAsym space***. First, a reference volume and its skull-stripped version were

generated using a custom methodology of ***fMRIPrep***. Several confounding time-series were calculated based on the ***preprocessed BOLD***: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, Power et al. (2014)) and Jenkinson (relative root mean square displacement between affines, Jenkinson et al. (2002)). FD and DVARS are calculated for each functional run, both using their implementations in ***Nipype*** (following the definitions by Power et al. 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (***CompCor***, Behzadi et al. 2007). Principal components are estimated after high-pass filtering the ***preprocessed BOLD*** time-series (using a discrete cosine filter with 128s cut-off) for the two ***CompCor*** variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by thresholding the corresponding partial volume map at 0.05, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the ***k*** components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in

the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. All resamplings can be performed with ***a single interpolation step*** by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos 1964). Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer).

Many internal operations of ***fMRIPrep*** use ***Nilearn*** 0.6.2 (Abraham et al. 2014, RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in ***fMRIPrep's*** documentation.

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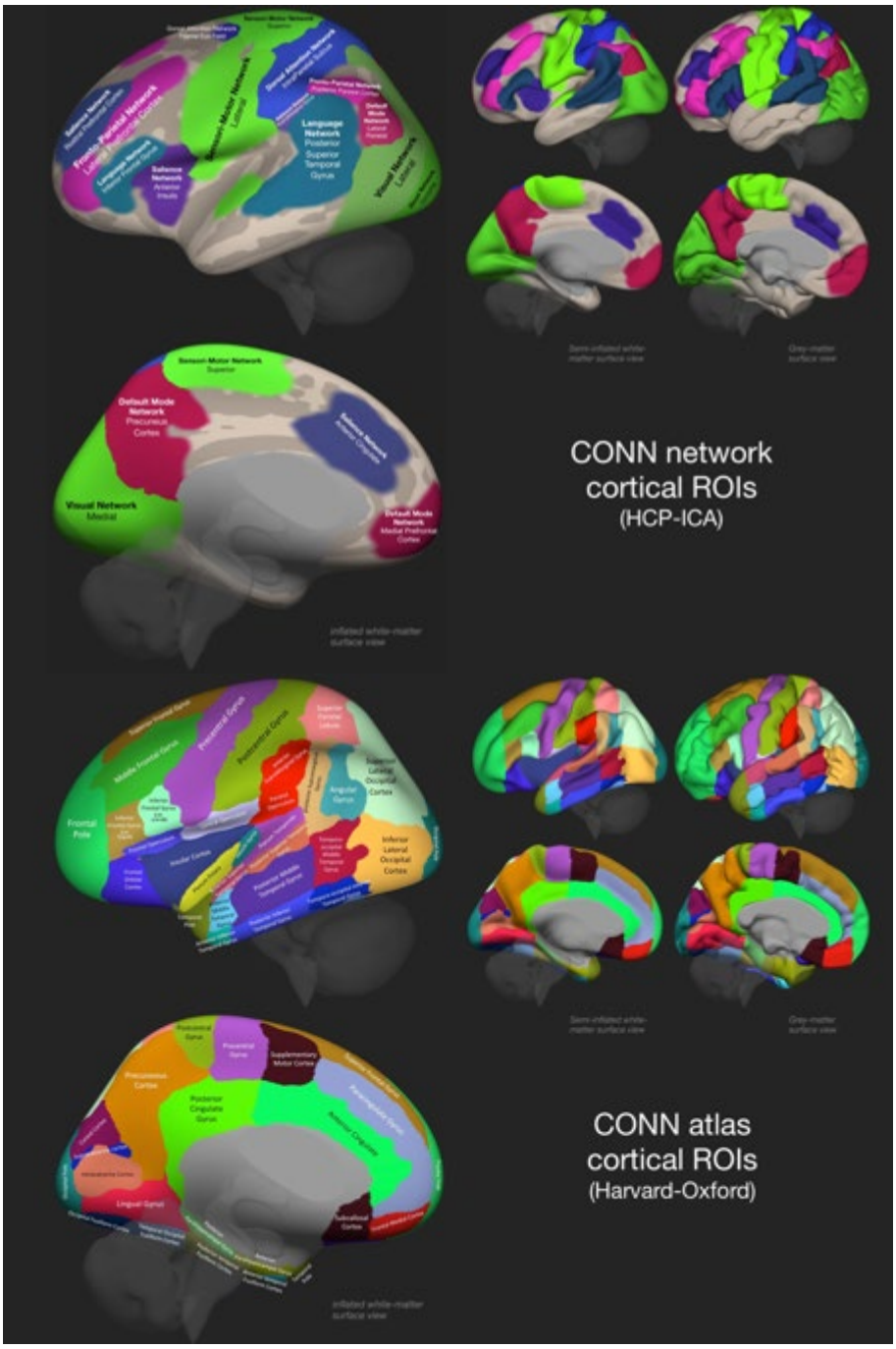
Supplementary Material E: List of included networks and their Regions of Interest (ROIs) with MNI coordinates.

Network	Region of interest with MNI coordinates
Default Mode Network	Medial Prefrontal Cortex (MPFC; 1, 55, -3) Lateral Parietal Cortex (LP) L (-39, -77, 33) Lateral Parietal Cortex (LP) R (47, -67, 29) Posterior Cingulate Cortex (PCC; 1, -61, 38)
Sensorimotor Network	Lateral L (-55, -12, 29) Lateral R (56, -10, 29) Superior (0, -31, 67)
Salience Network	Anterior Cingulate Cortex (ACC; 0, 22, 35) Anterior Insula (Ainsula) L (-44, 13, 1) Anterior Insula (Ainsula) R (47, 14, 0) Rostral Prefrontal Cortex (RPFC) L (-32, 45, 27) Rostral Prefrontal Cortex (RPFC) R (32, 46, 27) Supramarginal Gyrus (SMG) L (-60, -39, 31) Supramarginal Gyrus (SMG) R (62, -35, 32)
Dorsal Attention Network	Frontal Eye Fields (FEF) L (-27, -9, 64) Frontal Eye Fields (FEF) R (30, -6, 64) Intraparietal Sulcus (IPS) L (-39, -43, 52) Intraparietal Sulcus (IPS) R (39, -42, 54)
Frontoparietal Network	Lateral Prefrontal Cortex (LPFC) L (-43, 33, 28) Posterior Parietal Cortex (PPC) L (-46, -58, 49) Lateral Prefrontal Cortex (LPFC) R (41, 38, 30) Posterior Parietal Cortex (PPC) R (52, -52, 45)

Note: L, left; R, right.

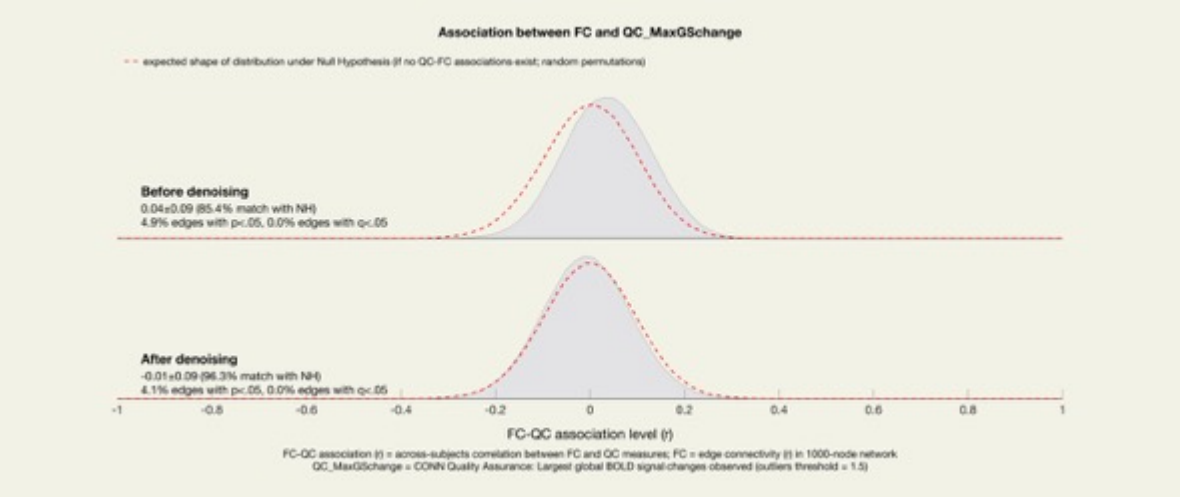
Supplementary Material F: CONN networks (top) and atlas (bottom) with their cortical Regions of Interest (ROIs).



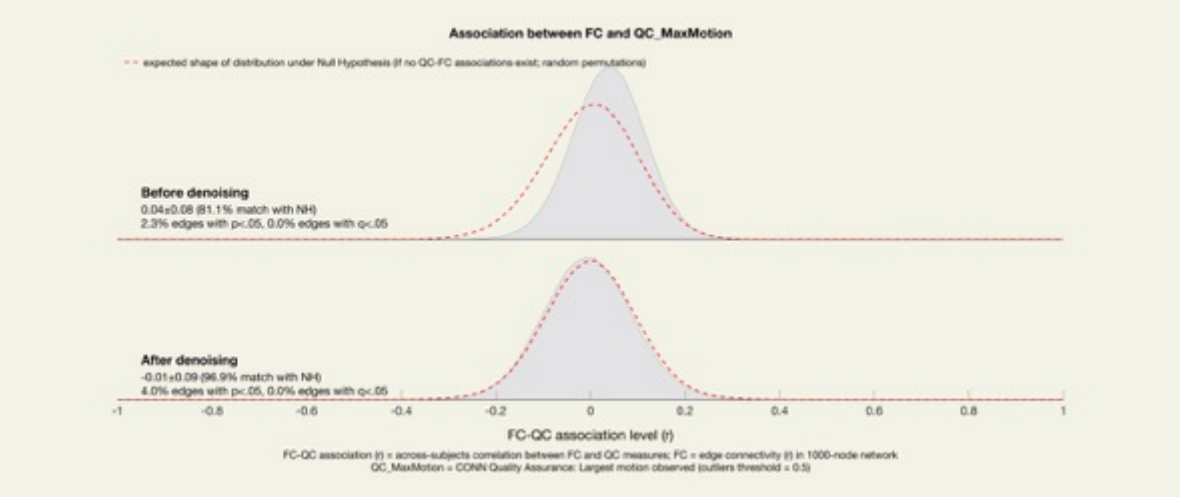
Note: Networks in the ROI-ROI analysis are the Default Mode Network (DMN), Sensorimotor Network (SMN), Salience Network (SAN), Dorsal Attention Network (DAN), Frontoparietal Network (FPN). Seeds for the seed-to-voxel analysis were the left and right Hippocampus. Networks are based upon CONN Independent Component Analysis (ICA) analyses of 497 subjects from the Human Connectome Project (HCP), and atlas is the Harvard-Oxford.

Supplementary Material G: CONN quality assurance plots.

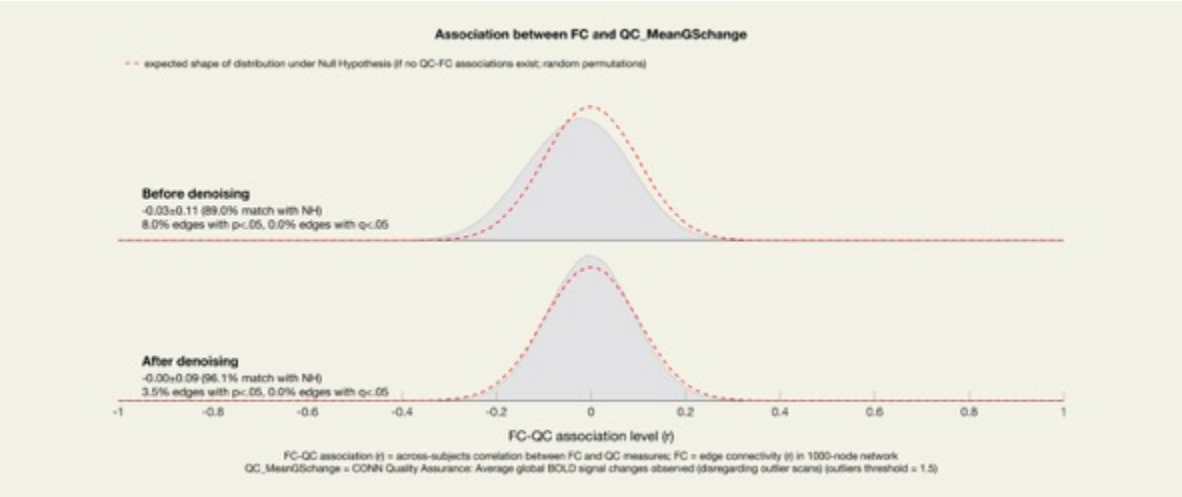
A)



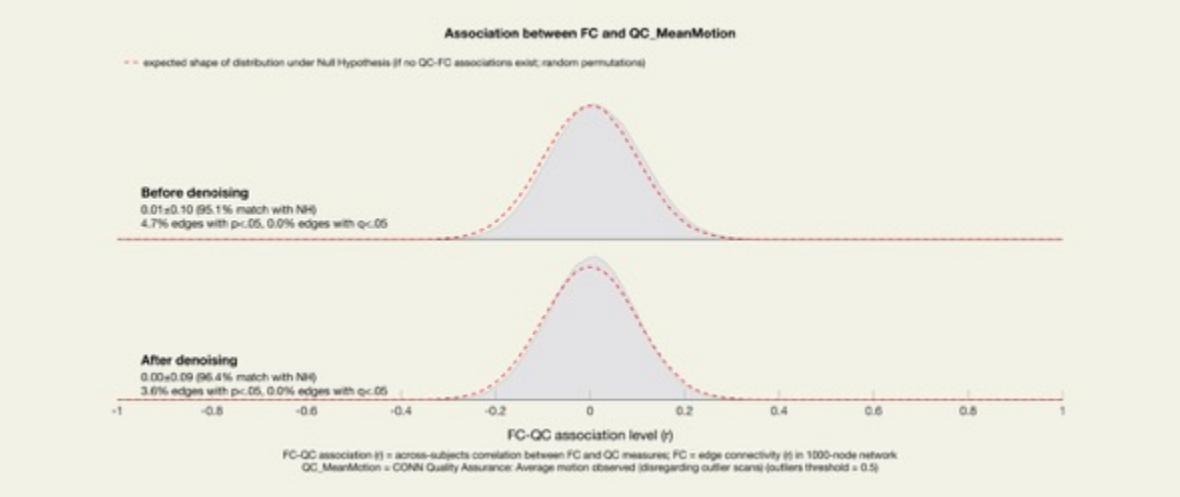
B)



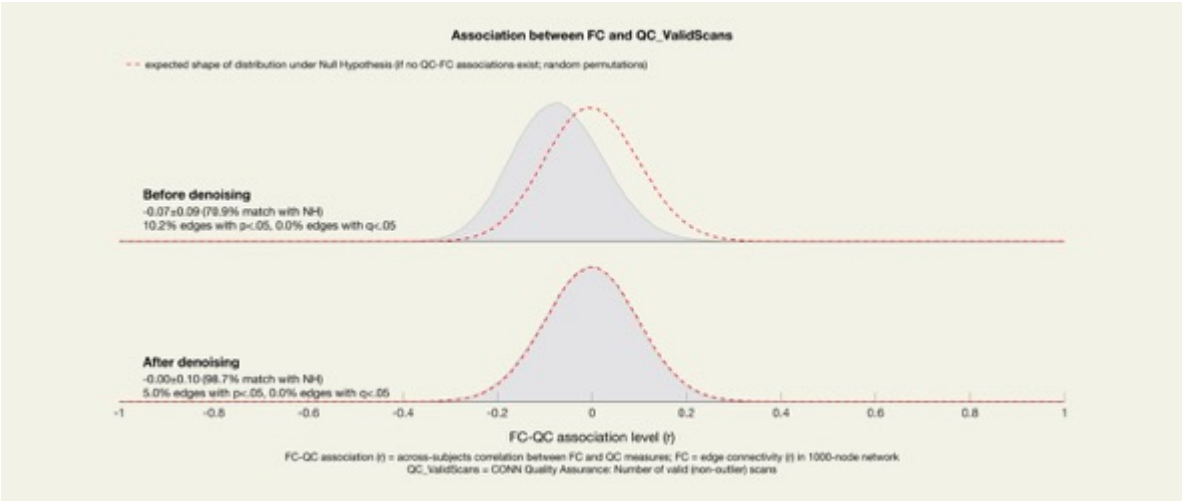
C)



D)



E)



Note: A) max global signal change, b) max motion, c) mean global signal change, d) mean motion, and e) valid scans. "After denoising results" are for the sample sized used in the analysis (i.e., n=100). As per CONN instructional manual, goal is for plots to score >95% after denoising (Nieto-Castanon, 2020).

Supplementary Material H: Baseline characteristics stratified by MRI completion status.

Characteristic	Completed imaging at T0 (n = 120)	Completed No Imaging (n = 55)	p-value
Age	73.64 ± 6.23	71.54 ± 6.80[b]	***0.047***
# of Males (Females)	60 (60)	30 (27)	0.743
# of Comorbidities	4.63 ± 2.49	4.33 ± 2.28[b]	0.452
Years of Education	15.24 ± 3.61[a]	15.51 ± 3.92[b]	0.653
Height (cm)	167.30 ± 10.30	166.12 ± 10.73	0.487
Weight (kg)	76.30 ± 15.24	78.50 ± 22.36	0.509
Body Mass Index	27.19 ± 4.58	28.18 ± 6.74	0.323
MoCA	22.92 ± 3.00[a]	22.17 ± 3.19[b]	0.133

Note: Analysis was conducted to determine if there were any characteristic differences at baseline (T0) between those that completed imaging, versus those that did not. Result provide insight into what or why individuals chose to not complete imaging. All values are mean ± standard deviation, except sex shows the sample size. Independent samples t-test or Pearson chi-square analysis as appropriate. MoCA, Montreal Cognitive Assessment; #, number; cm, centimeters; kg, kilograms; a, n=119; b, n=54. n = 55 and not 63 (original number randomized) for "Completed No Imaging" based upon available data.

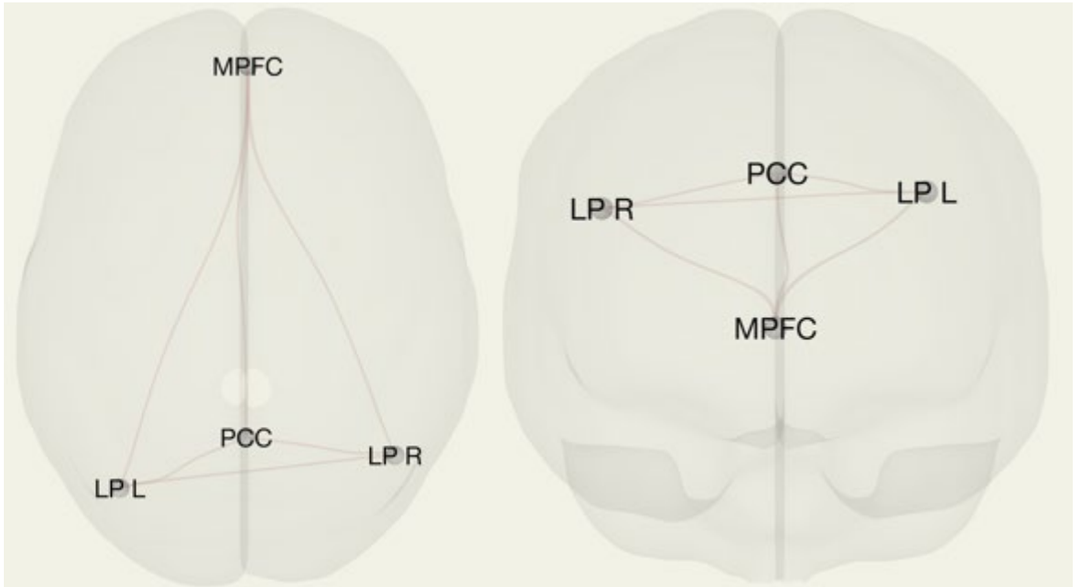
Supplementary Material I: Characteristics for participants that completed imaging at baseline.

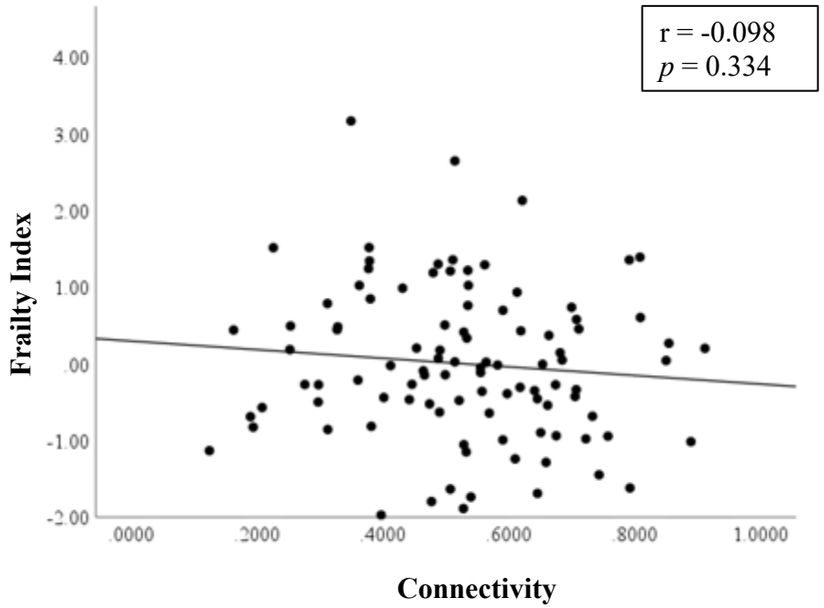
Characteristic	Total (n = 120)	Males (n = 60)	Females (n = 60)	p-value
Age	73.64 ± 6.23	74.00 ± 6.30	73.28 ± 6.20	0.531
# of Comorbidities	4.63 ± 2.49	4.48 ± 2.55	4.78 ± 2.44	0.512
Years of Education	15.24 ± 3.61[a]	15.83 ± 4.05	14.63 ± 3.02[b]	0.068
Height (cm)	167.30 ± 10.30	174.21 ± 7.24	160.4 ± 8.02	***<0.001***
Weight (kg)	76.30 ± 15.24	83.38 ± 14.04	69.22 ± 13.01	***<0.001***
Body Mass Index	27.19 ± 4.58	27.46 ± 4.31	26.92 ± 4.86	0.523
MoCA	22.92 ± 3.00 [a]	22.88 ± 2.91	22.97 ± 3.12 [b]	0.881

Note: All values are mean ± standard deviation. Independent samples t-test used to compare sex. MoCA, Montreal Cognitive Assessment; #, number; cm, centimeters; kg, kilograms.

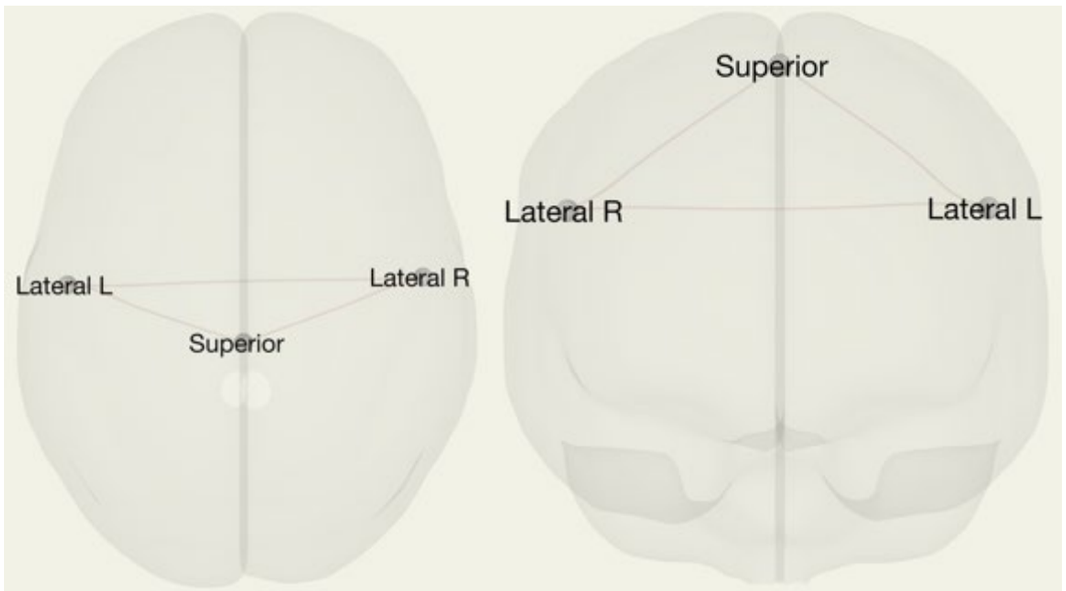
Supplemental Material J: CONN networks displayed on a glass brain and Pearson correlation results for the full sample (n=100).

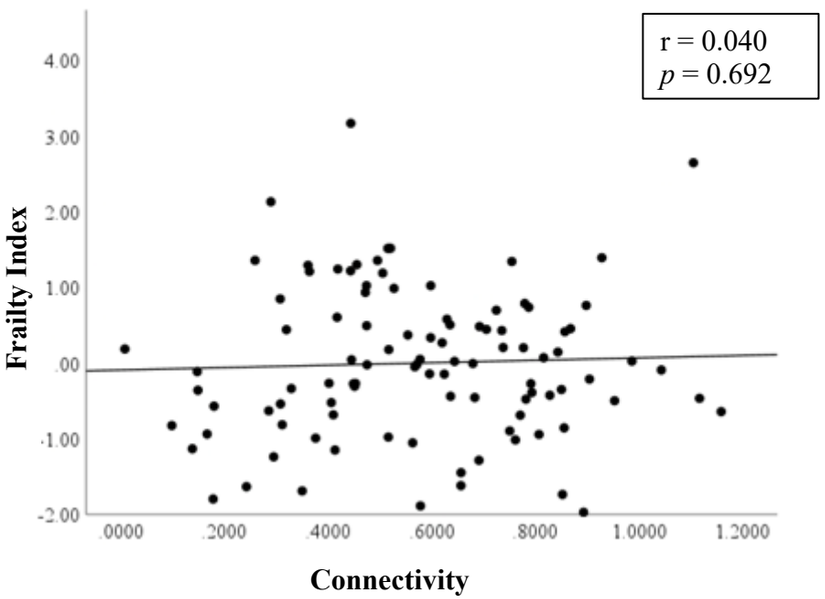
A)



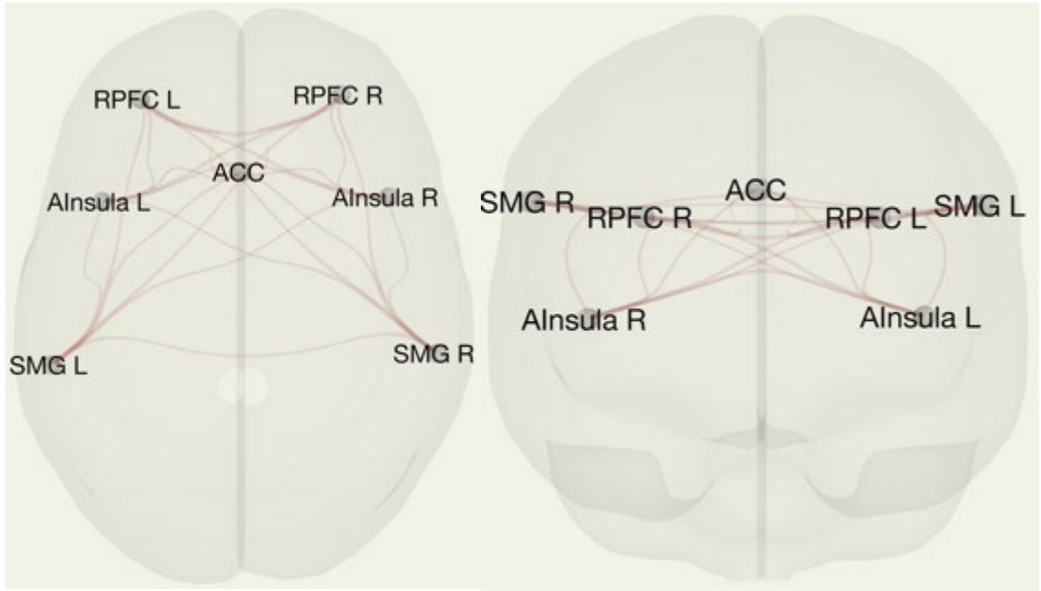


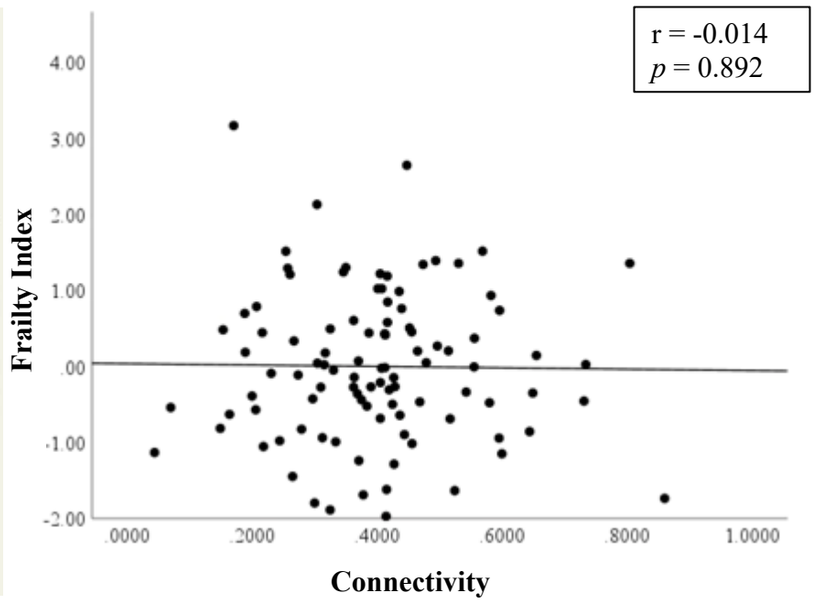
B)



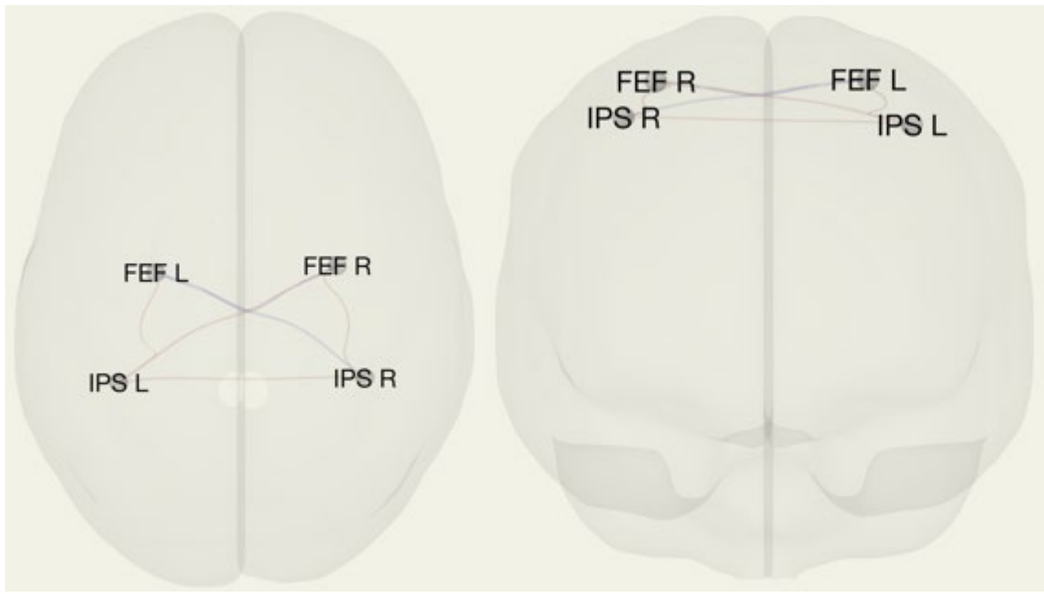


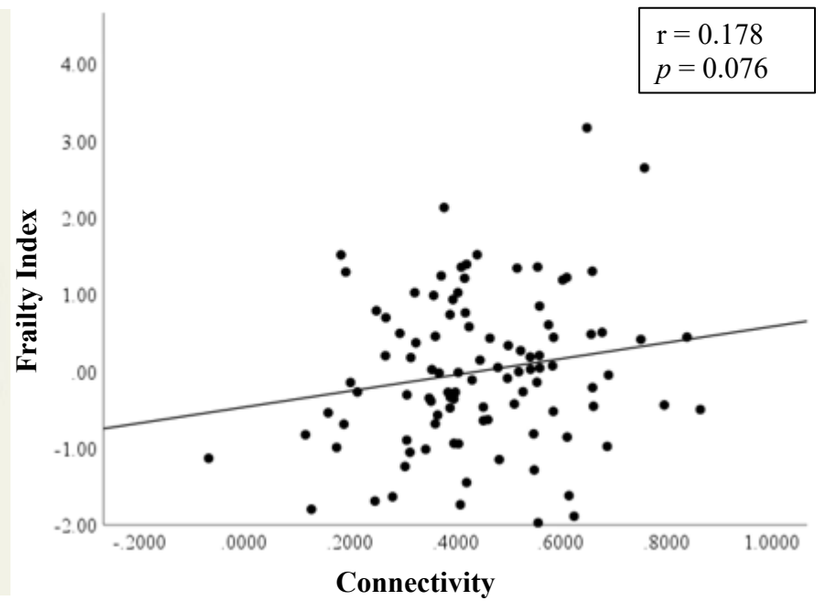
C)


RPFC L
RPFC R
ACC
AInsula L
AInsula R
SMG L
SMG R
SMG R
RPFC R
ACC
RPFC L
SMG L
AInsula R
AInsula L

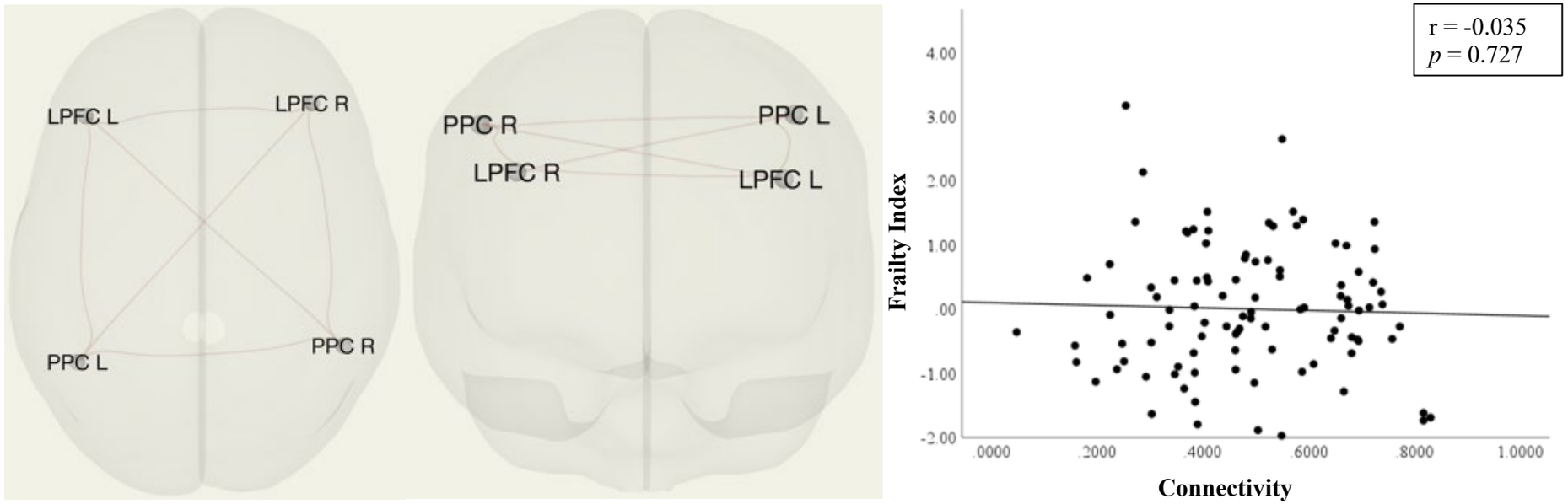

r = -0.014
p = 0.892
Frailty Index
4.00
3.00
2.00
1.00
.00
-1.00
-2.00
.0000
.2000
.4000
.6000
.8000
1.0000
Connectivity

D)


FEF L
FEF R
IPS L
IPS R
FEF R
FEF L
IPS R
IPS L


r = 0.178
p = 0.076
Frailty Index
4.00
3.00
2.00
1.00
.00
-1.00
-2.00
-.2000
.0000
.2000
.4000
.6000
.8000
1.0000
Connectivity

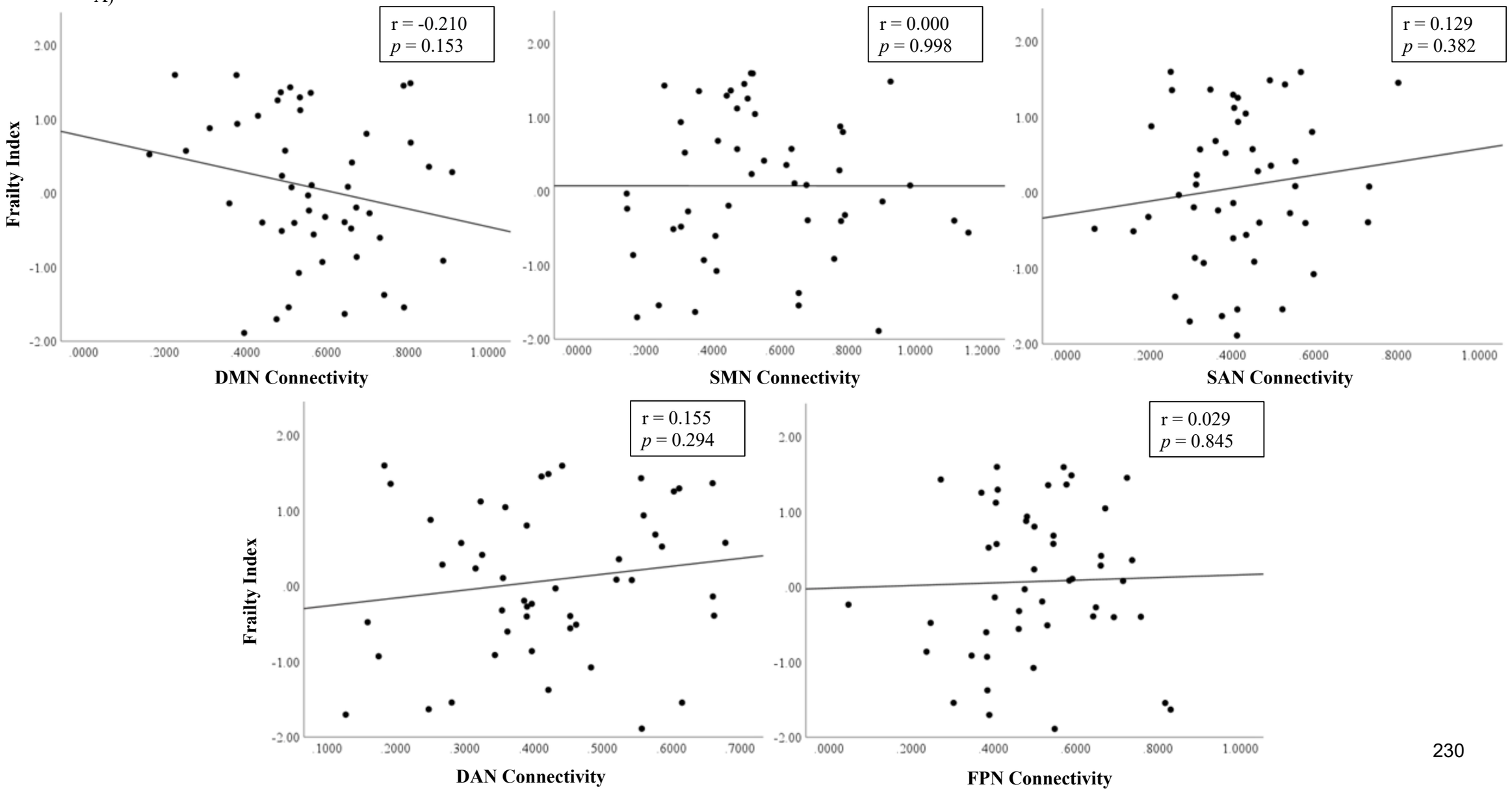
E)



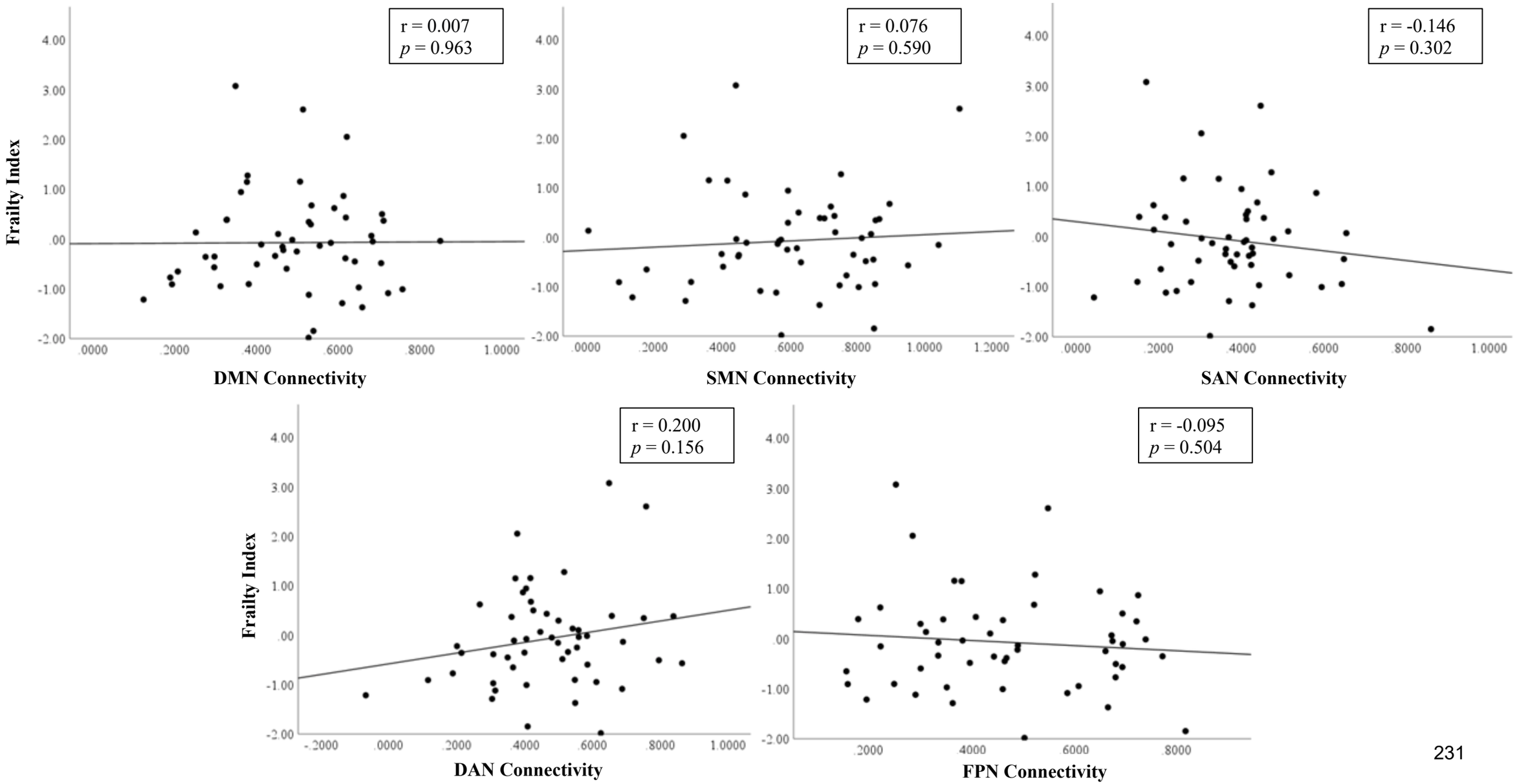
Note: Frailty Index value is a z-score via standardized residuals of linear regression. Connectivity value is a Fisher-transformed correlation coefficients. A, Default-Mode Network; B, Sensorimotor Network; C, Salience Network; D, Dorsal Attention Network; E, Frontoparietal Network. See Supplementary Material E for clarification regarding ROI abbreviations.

Supplemental Material K: Pearson correlation results by sex.

A)

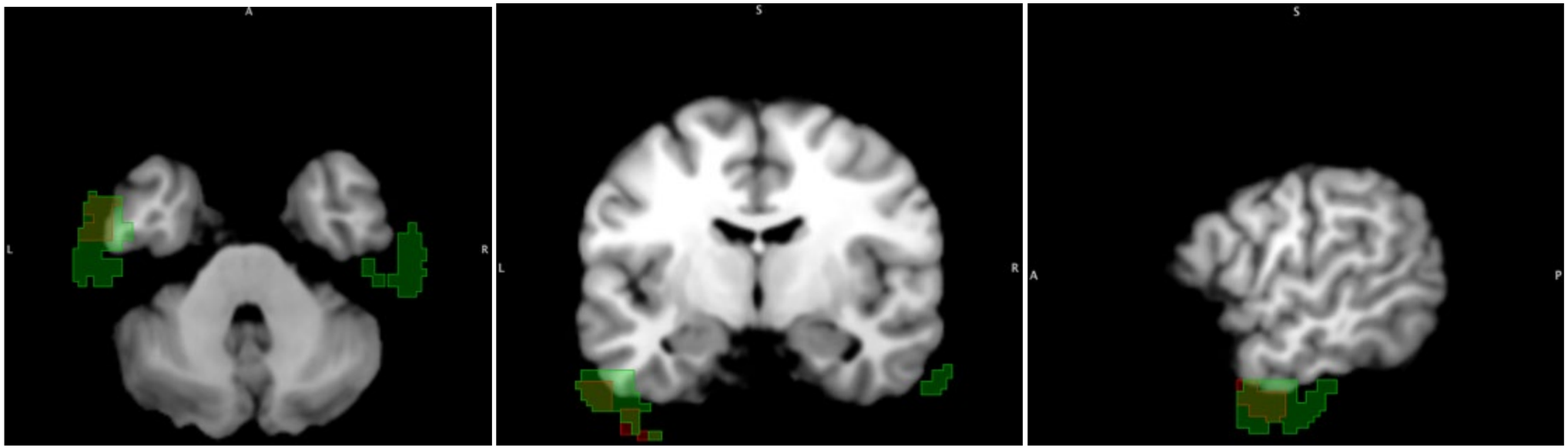


B)


r = 0.007
p = 0.963
r = 0.076
p = 0.590
r = -0.146
p = 0.302
r = 0.200
p = 0.156
r = -0.095
p = 0.504
Frailty Index
DMN Connectivity
SMN Connectivity
SAN Connectivity
DAN Connectivity
FPN Connectivity

Note: Frailty Index value is a z-score via standardized residuals of linear regression. Connectivity value is a Fisher-transformed correlation coefficients. A, Females; B, Males; DMN, Default-Mode Network; SMN, Sensorimotor Network; SAN, Salience Network; DAN, Dorsal Attention Network; FPN, Frontoparietal Network.

Supplemental Material L: Overlay of clusters from a continuous sample that showed a significant (increase) in connectivity with the right Hippocampus.



Note: Red, full sample (n = 100); green, male sample (n = 52). Created using Multi-image Analysis GUI (MANGO) version 4.1. Left to right = axial, coronal, and sagittal view. Coordinates (x, y, z) = -55, -9, -31. L, left; A, anterior; R, right; S, superior; P, posterior.

Supplemental Material M: Anatomical Labelling in CONN versus xjView for S-V significant clusters.

Demographic	Seed	Direction of Connectivity	Cluster								
			x, y, z	Size	size *p*-FDR	peak *p*-unc.	CONN			xjView	
							Anatomical Area	%	Voxels	Anatomical Area	Voxels
Full (n=100)	Right Hippocampus	↑	-48 +2 -44	291	0.029812	0.000107	Inferior Temporal Gyrus, anterior division Left	44	127	--TOTAL # VOXELS--	291
							Temporal Pole Left	13	37	Temporal_Inf_ Left (aal)	108
							Middle Temporal Gyrus, anterior division Left	11	31	Left Cerebrum	99
							Not-labeled	33	96	Temporal Lobe	99
										Inferior Temporal Gyrus	64
										Gray Matter	50
										brodmann area 20	37
										Temporal_Mid_ Left (aal)	36
										Middle Temporal Gyrus	31
										White Matter	19
										brodmann area 21	13
Male (n=52)	Right Hippocampus	↑	-44 +4 -46	993	0.000021	0.000004	Inferior Temporal Gyrus, anterior division Left	26	262	--TOTAL # VOXELS--	993
							Inferior Temporal Gyrus, posterior division Left	18	174	Temporal Lobe	434
							Temporal Pole Left	11	105	Temporal_Inf_ Left (aal)	433
							Middle Temporal Gyrus, anterior division Left	9	91	Left Cerebrum	432
							Middle Temporal Gyrus, posterior division Left	2	15	Inferior Temporal Gyrus	236
							Temporal Fusiform Cortex, anterior division Left	0	2	Gray Matter	230
							Temporal Fusiform Cortex, posterior division Left	0	1	brodmann area 20	196
							Not-labeled	35	343	Fusiform Gyrus	119
										White Matter	116
										Middle Temporal Gyrus	78
										Temporal_Mid_ Left (aal)	53
										brodmann area 21	30
										brodmann area 38	4
										Temporal_Pole_Mid_ Left (aal)	2
		↑	66 -28 -26	451	0.00351	< 0.000001	Inferior Temporal Gyrus, posterior division Right	49	219	--TOTAL # VOXELS--	451
							Middle Temporal Gyrus, posterior division Right	20	88	Temporal_Inf_Right (aal)	360
							Inferior Temporal Gyrus, temporooccipital part Right	0	2	Right Cerebrum	183
							Not-labeled	31	142	Temporal Lobe	183
										Inferior Temporal Gyrus	134
										Gray Matter	111
										brodmann area 20	100
										White Matter	48
										Temporal_Mid_Right (aal)	42

										Fusiform Gyrus 33 Middle Temporal Gyrus 14 brodmann area 21 11 Sub-Gyral 2 Fusiform_R (aal) 2
Male Tertiles (n = 52) Intermediate > Low and High	Right Hippocampus	↑	-26 -70 +16	289	0.015491	0.000006	Lateral Occipital Cortex, inferior division Left Lateral Occipital Cortex, superior division Left Not-labeled	6 2 92	18 5 266	--TOTAL # VOXELS-- 289 Left Cerebrum 289 White Matter 262 Sub-Gyral 139 Temporal Lobe 136 Occipital Lobe 119 Middle Temporal Gyrus 40 Cuneus 39 Occipital_Mid_ Left (aal) 30 Middle Occipital Gyrus 24 Gray Matter 24 Sub-lobar 19 Extra-Nuclear 16 Posterior Cingulate 15 Limbic Lobe 15 Precuneus 13 brodmann area 30 10 Calcarine_ Left (aal) 10 brodmann area 31 9 Temporal_Mid_ Left (aal) 7 brodmann area 18 5 Lateral Ventricle 3 Cerebro-Spinal Fluid 3

Note: AAL, automated anatomical labelling.

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CHAPTER 6: CHAPTER SUMMARY AND GENERAL DISCUSSION

6.1 SUMMARY OF FINDINGS

The present dissertation provides an overview and unique experimental evidence in vulnerable (mild cognitive impairment and frail) older adults, describing: 1) how FBNC is altered following a lifestyle intervention; 2) what these changes mean for physical and cognitive function; and 3) how FBNC and its relationship with behavioural outcomes may be implicated by initial health status and sex. First, I will provide a summary of our findings, followed by a discussion relative to the central themes, and conclude with limitations and suggestions for future work.

In **Chapter 2**, I conducted a systematic review on the effect of physical exercise with and without other interventional strategies in older adults (60+ years of age) that are cognitively healthy and impaired (1). The rationale for the review was: 1) a desire to better understand the underlying physiology of exercise-induced changes in cognitive and physical performance; 2) a lack of consensus on the effect of physical exercise on FBNC; and 3) hypothesis formulation for **Chapter 4**, our randomized controlled trial. The majority (10/12) of studies showed an *increase* in intervention-induced FBNC, particularly within-network. All included studies demonstrated an improvement in a measure of physical and/or cognitive function. However, only one demonstrated a significant correlation with a behavioral outcome (cognitive performance), and they did not control for multiple comparisons. Despite a lack of correlation with behavioural outcomes, and in conjunction with other systematic reviews (2–5), I concluded that *increasing* within-network FBNC reflects "better" brain function. The rationale for our conclusion is discussed in the following sections.

In **Chapter 3,** I conducted an open-label, high-dose vitamin D feasibility intervention in older adults (6), motivated by: 1) a previous review from our group suggesting that older adults with more deficits may require doses greater than the currently recommended amounts; and 2) a desire to test the feasibility and efficacy of high-dose vitamin D independently (7), given its inclusion in **Chapter 4's** randomized controlled trial. No participants experienced an adverse event, and physical but not cognitive performance measures improved post-intervention, but only in those that were frail and/or possessed insufficient ($\leq$ 75 nmol/L) vitamin D serum levels; there was also evidence of sex-specific findings. In conjunction with previous work (8), I concluded that high-dose vitamin D may be safe and efficacious, particularly for lower extremity function, and only in those with the greatest deficits. Why I showed changes in physical but not cognitive performance is unclear but supports the mixed results from both fields (9). It may also reflect test selection for cognitive performance, which has previously altered interpretation (10). Importantly, a recent randomized controlled trial demonstrated negative consequences for high-dose vitamin D supplementation in falls-risk. As such, **Chapter 3** results should be interpreted cautiously.

In **Chapter 4**, I conducted a multi-site, double-blind, phase II randomized controlled trial, motivated by a desire to understand: 1) the combined effect of aerobic and resistance training on health outcomes in older adults with MCI as no previous intervention had included both modalities; and 2) the added benefits of cognitive training and/or high-dose vitamin D supplementation. Relative to the pure control arm, physical exercise demonstrated a between-arm *increase* (Post – pre) in FBNC between the Hippocampus and the left Angular Gyrus; these regions are believed to represent areas of the Default-Mode Network (11,12), thus, reflecting *increasing* within-network connectivity. Adding cognitive training with and without high-dose

vitamin D created some additional changes to the exercise-induced FBNC alterations. After controlling for multiple comparisons, there was no evidence of correlation with behavioural outcomes. Similar to **Chapter 2**, I suggested that *increasing* within-network FBNC may reflect "better" brain function, but implications for behavioural outcomes remain unclear.

In **Chapter 5**, I conducted a cross-sectional study exploring the relationship between frailty status and FBNC, motivated by 1) a desire to understand if frailty confounds FBNC; 2) lack of research previously investigating the two variables (13–15); 3) previous work demonstrating that frailty implicates other brain health outcomes (16); and 4) a call to explore the common etiology of both frailty and dementia syndromes (17). I found evidence of *increasing* FBNC between regions not believed to belong to a single network. Furthermore, these increases in connectivity were associated with increasing (worse) frailty. I also added support for a sex-specific experience of frailty (18–20) by demonstrating that males and females show differences in their association with FBNC. I concluded that *increasing* between-network connectivity is associated with increasing (worse) frailty. Furthermore, researchers should consider frailty and sex when examining FBNC, and that failing to do so may partially explain the lack of significant correlations between FBNC and behavioral outcomes in **Chapters 2** and **4**

6.2 General Discussion

The reoccurring theme throughout this dissertation is that FBNC, as well as behavioural outcomes, are altered following lifestyle interventions, but alterations depend on original or baseline clinical status and sex. Broadly, aging and neurodegenerative disorders appear to be characterized by a *decrease* in within-network FBNC. For example, the Default-Mode loses connectivity between its anterior and posterior divisions (21) and shows activation when it is

supposed to be suppressed (22). In an initial attempt to maintain homeostasis, the "plastic" human brain scaffolds new connections with alternate neural circuits or, stated differently, *increases* between-network connectivity (23). As a result, networks or regions that may have been anti-correlated or had no correlation now display more positive connections, potentially reflecting their cohesive work. In addition to other systematic reviews on the topic (2–5), **Chapters 2** and **4** provided support for lifestyle interventions *increasing* within-network connectivity. *Increasing* within-network connectivity produces FBNC that more closely reflects "healthy" or young brains. Therefore, a broad and simplistic view is that *increasing* between and within-network connectivity reflects "bad" and "good" reorganization, respectively. But is this really true?

Chapters 2 and **4** demonstrated little support for FBNC alterations impacting behavioural outcomes. As such, *increasing* within-network connectivity may not be "good" or rather, whether reorganization is classified as "bad" and "good" may simply depend on the criterion. For example, if *increasing* between-network connectivity negatively impacts a health-related outcome (i.e., gait, falls, etc.) but is later shown to be associated with slower progression to a dementia syndrome, then how should it be classified? Initial clinical status and sex and their implications for such outcome measurements are another important consideration. **Chapter 3** suggests that both frailty status, serum vitamin D levels, and to a lesser extent, sex should be considered when examining physical performance outcomes. Similarly, **Chapter 5** suggests frailty and sex should be considered when examining FBNC. Failure to account for these variables may result in misclassification of reorganized FBNC as "good" or "bad" or failure to find any relationship at all. Finally, the classification of reorganization may also depend on the network or region. The functional hubs hypothesis suggests that certain regions of networks are

more critical to communication and neuronal integration (24,25). Similarly, the neural context hypothesis suggests that the functional relevance of a brain area depends on the "status" of other connected areas (26). Together, such hypotheses imply that not all regions and their connections are equal. Accordingly, if the reorganization of one network or area comes at the expense of another, how should it be classified, especially when failing to identify clinical significance? As will be discussed in the future studies section, understanding "bad" and "good" reorganization will likely only be afforded through longitudinal, detailed investigation of the entire connectome.

Discussion of the present dissertation's findings would be incomplete without considering how within-network connectivity is *increased*? Work by previous groups suggests a model encompassing a cascade of multi-layered physiological changes (27–30).

At the molecular level, long-term exercise upregulates neurotrophic factors and downregulates chronic low-grade inflammation and pro-inflammatory cytokines (31) to create a cellular environment conducive to neurogenesis, gliogenesis, synaptogenesis, and angiogenesis (32–34). As a result, the plastic brain now contains more neurons and/or connections, as well as supporting glia and an increased blood supply, in addition to the cardiorespiratory benefits that impact oxygen delivery. Notably, these working models, particularly at the molecular and cellular level, are largely based upon animal subjects. Furthermore, and based upon the previously discussed functional hubs hypothesis, it is unlikely that these cellular and molecular changes are homogenous throughout the cortex. Cognitive training appears to provoke changes in brain health via the same mechanisms of physical exercise (i.e., neurogenesis, gliogenesis, synaptogenesis, and angiogenesis) (35), but vitamin D may work differently.

Vitamin D may directly influence cognitive and physical function as vitamin D receptors are located throughout the body, including muscle cells and brain regions critical to function (36). The physiological results of vitamin D binding are complex, but in short, it leads to proper gene expression and the transport of minerals, such as calcium (37). Indirectly, vitamin D is believed to improve systemic health by positively impacting immunity (38,39), oxidative stress (40), endothelial function (41,42), and inflammation (43). Taken together, all of the physiological changes mentioned above serve to promote "better" health and create an environment conducive to "good" reorganization. Failure to execute these simple but effective lifestyle strategies as we age may mean that the brain is left to defend itself via "bad" reorganization or *increasing* between-network connectivity.

One final note regarding the previously highlighted multi-layered model describing physiological changes induced by physical and cognitive training (27–30). Given the complexity, the process can "fail" at any one level and not result in the desired effect, as suggested by the lack of correlations observed in **Chapters 2** and **4,** as well as the numerous behavioural outcomes that showed no improvement in **Chapter 2**. Furthermore, and within the context of FBNC, this model may be considered somewhat incomplete without considering changes in the remaining nervous system. Remodeling via denervation and reinnervation occurs throughout aging (44). Other alterations in the peripheral nervous system include shifts in fiber type (45,46), a destabilized neuromuscular junction (47), and muscle loss (i.e., sarcopenia) (48). Depending on the interventional strategy, these changes in the peripheral nervous system may make it difficult for "good" reorganization of FBNC to exert its influence on behavioural outcomes, particularly those of physical performance.

6.3 LIMITATIONS

Subjective cognitive impairment, mild cognitive impairment, mild subcortical ischemic vascular cognitive impairment, insufficient vitamin D serum levels, and (pre)frail older adults were all of the characterized demographics included within this dissertation, and at times compared to "normal" or "healthy" older adults. As a result, this dissertation contains an extensive view of the two issues that plague older adults and impact quality of life in the remaining years: cognitive and physical decline. Importantly, researchers have postulated that such issues may share similar pathophysiology (49–58), which is an active area of research, in addition to experiencing the same indirect intervention-induced benefits (i.e., anti-inflammatory) (31,59,60). However, such an approach also comes with limitations. Variation between and within (i.e., amnestic versus non-amnestic MCI) a demographic creates a degree of heterogeneity that may be responsible for the lack of more meaningful or specific trends in describing FBNC's role to improve cognitive and physical function.

Another limitation is that study participants for **Chapters 2, 4,** and **5** were interested in participating in exercise interventions. Physical inactivity is currently considered a global epidemic due to the number of individuals not meeting the recommended 150-minutes of moderate to vigorous physical activity per week (61,62). Therefore, given these participants' general interest in participating in exercise, they should not be considered reflective of the overall population. Another issue with participants from **Chapters 2-5** is that they resided in countries generally classified as having a higher socioeconomic status. A recent update to a Lancet report highlights that countries of lower socioeconomic status are likely to suffer the greatest increase of dementia cases in the near future (63). Therefore, there is a need for

adequately-powered trials within these countries to determine if results differ from regions with a higher socioeconomic status.

Finally, the positives of fMRI also create several drawbacks. fMRI provides an excellent balance between temporal and spatial resolution, but it may be necessary to heighten one resolution at another's expense depending on the research question. For example, if researchers desire increased temporal resolution, it may make more sense to employ Magnetoencephalography or Electroencephalography (64). fMRI is a surrogate measure of neuronal activity that reflects changes in cerebral blood flow, cerebral blood volume, and oxygen metabolism (65). As a result, a cascade of physiological factors could alter the HDR, further complicated by the uncertainty in what represents "baseline," as well as the exercise-induced physiological changes previously discussed. Choice of parameters also impacts the final images, even before researchers decide from the myriad of preprocessing and analysis options available (66,67). Other more general drawbacks include the cost and lack of portability of MRI scanners. ~30% of individuals cannot complete an MRI due to a medical condition such as claustrophobia (68). Individuals who have completed an MRI feel that it is the least enjoyable research component (69), which is problematic and costly (70) to longitudinal or interventional studies. Overall, fMRI and FBNC represent one of many techniques available to examine brain health. There is no "one size fits all," and a complement of techniques will likely provide the most insight.

6.4 Future Directions

Despite a decrease in the prevalence (71) and incidence (72) of dementia, the aging population's estimated growth will result in an absolute increase in the number of older adults suffering from cognitive and/or physical impairments. In the United States, the number of Alzheimer's disease

cases will double over the next 30 years (73). Current estimates show the total payments for all dementia syndromes in the United States is $305 billion (74), not including the ~244 billion of unpaid, informal caregiving (75). The number of geriatric healthcare professionals is already too low, and the discrepancy will only increase with the aging workforce (76). Unfortunately, these estimates have the likelihood to grow exponentially in light of the novel COVID-19 virus (77,78).

Given the field's infancy, future work must continue to discern how both aging and neurodegenerative disorders impact individual networks of FBNC and the connectome as a whole. To provide a deeper understanding, and as discussed throughout the present dissertation, researchers must correlate FBNC with well-understood cognitive and physical performance outcomes. Future analyses should also look beyond correlation and examine FBNC's role as a mediator and what factors may moderate FBNC changes. Recent work has demonstrated that vascular health may play a role in FBNC (79), as well as all dementias (80,81); researchers are calling for "V" (vascular) to be added to the A (β-amyloid) T (tau) N (neurodegeneration) Alzheimer's biomarker system (82).

Cross-sectional studies will help, but longitudinal studies will provide greater insight into the FBNC timeline and implications. Examining FBNC within the simultaneous existence of multiple diseases and geriatric syndromes is another important consideration for understanding systematic aging. As previously highlighted, sex (biological) differences must also be acknowledged (83,84). Other considerations for researchers include gender (socio-economical) (85), race (86), and determine if a sweeping demographic view (i.e., MCI or frailty) provides

more or less insight than focusing on a sub-type (i.e., amnestic vs. non-amnestic MCI or pre-frail vs. frail).

Ultimately, such research will further our understanding of pathophysiology while enhancing our ability to intervene sooner and deliver more effective interventions. Allowing those at risk to delay progression and reduce the number of quality years lost to a physical or cognitive impairment, and in doing so, help decrease the future economic and social challenges posed by the "grey wave."

6.5 Significance

Physical and cognitive decline are synonymous with aging but accelerate in vulnerable older adults suffering from frailty or cognitive impairment. Lifestyle modification, including altering physical activity and obtaining adequate nutrition, represents small and achievable changes that, when accumulated over time, can positively alter long-term health. fMRI-related outcomes, such as FBNC, represent a sensitive biomarker in understanding the underlying physiology. The present dissertation represents an amalgamated collection of reviews and novel experiments in understanding FBNC's relationship with frailty and sex and its role in lifestyle interventions to improve cognitive and physical function. First, I provide evidence that physical exercise with and without other interventional strategies *increases* within-network FBNC. Second, I demonstrated that high-dose vitamin D supplementation positively influences physical performance outcomes and is safe, but further investigation is needed given the feasibility nature of the study. The findings of my RCT supported our systematic review while testing the role of novel interventional strategies. Finally, I added to the novel but growing body of knowledge surrounding the relationship between brain health and frailty and how it differs by sex.

Hopefully, this dissertation directs future experiments including FBNC, behavioural outcomes, frailty, sex, and lifestyle interventions.

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Curriculum Vitae

Nick W. Bray, PhD (c), CSEP-CEP

Date prepared: 12 July 2021

Table of Contents

Identification

Name	Nick Bray (he/him/his)
Nationality	Canadian
Current Positions	PhD Candidate Faculty of Health Sciences, School of Kinesiology University of Western Ontario, London, Canada Teaching Assistant Faculty of Health Sciences, School of Kinesiology University of Western Ontario, London, Canada
Languages	English (oral and written)

Education

Sept 2017 – July 2021	Doctor of Philosophy Faculty of Health Sciences, School of Kinesiology University of Western Ontario, London, Canada Dissertation: Describing functional brain connectivity's role in the relationship of multi-domain interventions to improve cognitive and physical function in vulnerable (frailty & mild cognitive impairment) older adults Supervisor: Dr. Manuel Montero-Odasso
Sept 2015 – Aug 2017	Master of Science Faculty of Health and Social Development, School of Health and Exercise Sciences UBC Okanagan, Kelowna, Canada Thesis topic: Multi-component exercise to reverse frailty in pre-frail older females. Supervisors: Dr. Jennifer Jakobi and Dr. Gareth Jones
Jan 2013 – April 2015	Bachelor of Kinesiology Faculty of Professional Studies, Department of Kinesiology Acadia University, Wolfville, Canada

Work Experience

Sept 2020 – Dec 2020	Teaching Assistant/Guest Lecturer* Faculty of Health Sciences, School of Kinesiology University of Western Ontario, London, Canada
Sept 2017 – Aug 2020	Research Assistant Lawson Health Research Institute London, Canada
Sept 2018 – April 2019	Teaching Assistant/Guest Lecturer* Faculty of Health Sciences, School of Kinesiology University of Western Ontario, London, Canada
Sept 2017 – April 2018	Teaching Assistant/Guest Lecturer* Faculty of Health Sciences, School of Kinesiology University of Western Ontario, London, Canada
Sept 2016 – April 2017	Teaching Assistant/Lab Instructor* Faculty of Health and Social Development, School of Health and Exercise Sciences UBC Okanagan, Kelowna, Canada
Sept 2015 – Aug 2016	Knowledge Broker HealtheSteps (Public Health Agency of Canada, UBC Okanagan, and University of Western Ontario) Kelowna, Canada
Sept 2015 – April 2016	Teaching Assistant* Faculty of Health and Social Development, School of Health and Exercise Sciences UBC Okanagan, Kelowna, Canada
April – June 2015	Assistant Strength & Conditioning Coach Acadia University, Wolfville, Canada
Sept – Dec 2014	Teaching Assistant* Faculty of Professional Studies, Department of Kinesiology Acadia University, Wolfville, Canada
Jan – April 2014	Teaching Assistant/Lab Instructor* Faculty of Professional Studies, Department of Kinesiology Acadia University, Wolfville, Canada

* For more details, see Teaching Dossier.

Research Funding & Academic Awards

Sept 2021 – Aug 2023	Eyes High Postdoctoral Fellowship University of Calgary Funded: $50,000.00 CAD/year
Sept 2021 – Aug 2023	Harley Hotchkiss – Samuel Weiss Postdoctoral Fellowship University of Calgary Funded: $50,000.00 CAD/year *Declined award in favour of Eyes High Postdoctoral Fellowship*
Sept 2020 – Aug 2021	Western Graduate Research Scholarship University of Western Ontario Funded: $9,999.99 CAD/year
April 2021	First Prize – (Virtual) Poster Category: Cognitive Vitality and Brain Health Parkwood Institute Research Day
May 2020 – April 2021	Ontario Graduate Scholarship University of Western Ontario and Province of Ontario Funded: $15,000.00 CAD/year
Sept 2019 – Aug 2020	Western Graduate Research Scholarship University of Western Ontario Funded: $11,213.79 CAD/year
May 2019 – April 2020	Ontario Graduate Scholarship University of Western Ontario and Province of Ontario Funded: $15,000.00 CAD/year
Jan 2020	Society of Graduate Studies Travel Subsidy University of Western Ontario Funded: $500.00
Dec 2019	Faculty of Health Sciences Conference Travel Award University of Western Ontario Funded: $210.00 CAD
Sept 2018 – Aug 2019	Western Graduate Research Scholarship University of Western Ontario Funded: $6,663.69 CAD/year
Aug 2019	School of Kinesiology Conference Travel Award University of Western Ontario Funded: $334.00 CAD

May 2018 – April 2019	Ontario Graduate Scholarship University of Western Ontario and Province of Ontario Funded: $15,000.00 CAD/year
Jan 2019	Society of Graduate Students Travel Subsidy University of Western Ontario Funded: $263.17
Nov 2018	Faculty of Health Sciences Conference Travel Award University of Western Ontario Funded: $125.00 CAD
Sept 2018	Student Scholarship Program – Canadian Powerlifting Union Funded: $250.00 CAD Awarded to a registered member who demonstrates a high level of academic achievement and commitment to the sport of powerlifting.
Sept 2017 – Aug 2018	Western Graduate Research Scholarship University of Western Ontario Funded: $13,641.38 CAD/year
June 2018	School of Kinesiology Conference Travel Award University of Western Ontario Funded: $500.00 CAD
May 2018	First Prize – Poster Category: Prevention of Diseases and Health Conditions and Promotion of Well-being London Health Research Day Conference
Sept 2016 – Aug 2017	University Graduate Fellowship Award University of British Columbia Okanagan Funded: $6,000.00 CAD/year
Sept 2015 – Aug 2016	University Graduate Fellowship Award University of British Columbia Okanagan Funded: $6,000.00 CAD/year
May 2015	Canadian Council of University Physical Education and Kinesiology Administrators Leadership Award Acadia University In recognition of an exceptional graduating student who will make a difference in their chosen field.

Academic Contributions

A. Manuscripts

Submitted

1. Pieruccini-Faria F, Hassan SM, **Bray NW**, et al. Brain Cortical And Subcortical Correlates Of Adaptive Gait In Older Persons. *Journal of Gerontology: Medical Sciences.* In-Review. JGMS-2021-RES-0547.

2. O'Brien MW, Wong MYS, Sui Y, Voss ML, **Bray NW**, et al. Education and Collaboration as Strategies to Promote Physical Activity by Primary Care Providers During and Beyond the COVID-19 Pandemic. *Journal of Medical Education Research*. In-Press. Submission Number: 1894.

3. Furlano JA, Morava A, Wong MYS, **Bray NW**, et al. Exercise behaviors, perceived barriers and motivators to exercise, and use of on- and off-campus exercise resources among graduate students at a Canadian university: A cross-sectional study. *Journal of American College Health.* In-Press. JACH-2020-11-0735

4. **Bray NW**, et al. The effect of physical exercise on functional brain network connectivity in older adults with and without cognitive impairment. A systematic review. *Mechanisms of Ageing and Development.* 2021 Apr 19;111493. https://doi.org/10.1016/j.mad.2021.111493

5. O'Brien MW, **Bray NW**, et al. A Scoping Review of Exercise Referral Schemes Involving Qualified Exercise Professionals in Primary Health Care. *Applied Physiology, Nutrition, and Metabolism*. 2021 Apr 19. https://doi.org/10.1139/apnm-2020-1070

6. Titus J, **Bray NW**, et al. The Role of Physical Exercise in Modulating Peripheral Inflammatory and Neurotrophic Biomarkers in Older Adults. A Systematic Review & Meta-Analysis. *Mechanisms of Ageing and Development*. 2021 Mar 1;194:111431. https://doi.org/10.1016/J.MAD.2021.111431

7. Montero-Odasso M, Sarquis-Adamson Y, Nellie K, Pieruccini-Faria F, **Bray NW**, et al. Dual-task gait speed assessments with an electronic walkway and a stopwatch in older adults. A reliability study. *Experimental Gerontology.* 142 (2020) 111102. https://doi.org/10.1016/j.exger.2020.111102

8. Montero-Odasso M, Speechley M, Muir-Hunter SW, Pieruccini-Faria F, Sarquis-Adamson Y, Hachinski V, Bherer L, Borrie M, Wells J, Garg AX, Tian Q, Ferrucci L, **Bray NW**, et al. Dual Decline in Gait Speed and Cognition is associated with future dementia: evidence for a Phenotype. *Age and Ageing*. 2020;49(6):995-1002. https://doi.org/10.1093/ageing/afaa106

9. **Bray NW**, et al. Multi-component Exercise with High-intensity, Free-weight, Functional Resistance-training in Pre-frail Females: A Quasi-experimental, Pilot Study. *Journal of Frailty & Aging.* 2020;9(2):111-117. https://doi.org/10.14283/jfa.2020.13

10. **Bray NW**, et al. Practical Implications for Strength and Conditioning of Older Pre-Frail Females. *Journal of Frailty & Aging.* 2020;9(2):118-121. https://doi.org/10.14283/jfa.2020.15

11. Pieruccini-Faria F, Sarquis-Adamson Y, Anton I, Nogueron-Garcia A, **Bray NW**, et al. Mapping Associations between Gait Decline and Falls Risk in Mild Cognitive Impairment. *Journal of the American Geriatrics Society.* 2020 Mar;68(3):576-584. https://doi.org/10.1111/jgs.16265

12. Montero-Odasso M, Sarquis-Adamson Y, Song HY, **Bray NW**, et al. Polypharmacy, Gait Performance, and Falls in Community-Dwelling Older Adults. Results from the Gait and Brain Study. *Journal of the American Geriatrics Society*. 2019 Jun;67(6):1182-1188. https://doi.org/10.1111/jgs.15774

13. **Bray NW**, et al. The Effect of High Dose Vitamin D_3 on Physical Performance in Frail Older Adults. A Feasibility Study. *The Journal of Frailty & Aging*. 2018 Jul 1;7(3):155-61. https://doi.org/10.14283/jfa.2018.18

14. **Bray NW**, et al. Exercise Prescription to Reverse Frailty. *Applied Physiology, Nutrition, and Metabolism*. 2016 Sep 21;41(10):1112-6. https://doi.org/10.1139/apnm-2016-0226

In-Progress

1. **Bray NW**, et al. Effect of a multi-domain intervention on functional cerebral network connectivity: Results from the SYNERGIC Trial.

2. **Bray NW**, et al. Chronic static stretch training increases electromechanical delay and decreases the rate of torque development during maximal voluntary contraction of the plantar flexors.

B. Abstracts & Presentations

1. ***Bray NW**, et al. The effect of a multi-domain intervention on functional cerebral network connectivity in older adults with mild cognitive impairment (MCI): Results from the SYNERGIC Trial. Canadian Geriatrics Society (CGS) Annual Scientific Meeting. Virtual, May 2021
   Presentation Format: Virtual Poster.

2. ***Bray NW**, et al. The effect of a multi-domain intervention on functional cerebral network connectivity in older adults with mild cognitive impairment (MCI): Results from the SYNERGIC Trial. Parkwood Institute Research Day. Virtual, April 2021
   Presentation Format: Virtual Poster.

3. ***Bray NW**, et al. The Effect of Physical Exercise on Brain Function of Older Adults. *Canadian Consortium on Neurodegeneration in Aging Partners Forum and Science Days.* Virtual, Oct 2020.
   Presentation Format: Virtual - Poster

4. Montero Odasso M, Speechley MR, Camicioli R, Kamkar N, Tian Q, Ferrucci L, **Bray NW**, et al. Dual-Decline in Gait and Cognition is associated with future Dementia. Evidence for a Phenotype. *Gerontological Society of America.* Philadelphia, USA, Nov 2020. https://doi.org/10.1093/geroni/igaa057
   Presentation Format: Virtual.

5. Pieruccini-Faria F, Seyyed Mohammad H, **Bray NW**, et al. Walking Adaptability is Associated with Grey Matter Volume in "Navigation Areas" in MCI. *London Health Research Day*. London, Canada, May 2020.
   Presentation Format: Cancelled due to COVID-19.

6. Montero-Odasso M, Kamkar N, Sarquis-Adamson Y, Pieruccini-Faria F, **Bray NW**, et al. Falls Risk Stratification: When is 'Low Risk' not Low Risk? *American Geriatrics Society Annual General Meeting.* Long Beach, USA, May 2020. https://doi.org/10.1111/jgs.16431
   Presentation Format: Poster

7. ***Bray NW**, et al. The Effect of Exercise Interventions on Functional Brain Connectivity (FBC) of Older Adults with and without Cognitive Impairment: A Systematic Review. *Canadian Society for Exercise Physiology Annual General Meeting*. Kelowna, Canada, Nov 2019. https://doi.org/10.1139/apnm-2019-0569
   Presentation Format: Poster

8. ***Bray NW**, et al. The Effect of Physical Exercise on Functional Brain Network Connectivity in Older Adults with and without Cognitive Impairment: A Systematic Review. *Kinesiology Graduate Student Association Symposium*. London, Canada, May 2019.
   Presentation Format: Podium

9. Pieruccini-Faria F, **Bray NW**, et al. Frailty Impairs Obstacle Negotiation While Walking. Results from the Gait and Brain Study. *Canadian Geriatrics Society Annual General Meeting*. Halifax, Canada, May 2019. http://doi.org/10.5770/cgj.22.385
   Presentation Format: Podium

10. Montero-Odasso M, Sakurai R, **Bray NW**, et al. Dynapenia is Associated with Executive Dysfunction. Results from the Gait and Brain Study. *International Conference on Frailty and Sarcopenia Research*. Miami, USA, Feb 2019. https://doi.org/10.14283/jfa.2019.1
    Presentation Format: Podium

11. ***Bray NW**, et al. The Effect of High Dose Vitamin D on Physical Performance in Frail Older Adults: A Feasibility Study. *Canadian Society for Exercise Physiology Annual General Meeting*. Niagara Falls, Canada, Oct 2018. https://doi.org/10.1139/apnm-2018-0499
    Presentation Format: Podium

12. ***Bray NW**, et al. The Effect of High Dose Vitamin D on Physical Performance in Frail Older Adults: A Feasibility Study. *London Health Research Day*. London, Canada, May 2018.
    Presentation Format: Poster

13. ***Bray NW**, et al. Can a Multi-domain Intervention Improve Brain Health in Older Adults with Mild Cognitive Impairment? *Kinesiology Graduate Student Association Symposium*. London, Canada, May 2018.
    Presentation Format: Podium

14. ***Bray NW**, et al. Exercise to Reverse Frailty in Older Females. *Canadian Society for Exercise Physiology Annual General Meeting*. Winnipeg, Canada, Oct 2017. https://doi.org/10.1139/apnm-2017-0432
    Presentation Format: Poster

15. ***Bray NW,** et al. Implementation of the BC HealtheSteps Program: Family Medicine Clinic Versus Community Exercise Centre. *Interdisciplinary Student Health Conference*. Kelowna, Canada, April 2017.
    Presentation Format: Poster

16. ***Bray NW**, et al. The Impact of Delivery Site on Participant Adherence to the BC HealtheSteps Program. *Canadian Society for Exercise Physiology Annual General Meeting*. Victoria, Canada, Oct 2016. https://doi.org/10.1139/apnm-2016-0366
    Presentation Format: Poster

17. ***Bray NW**, et al. Electromechanical Delay and Rate of Force Development are Negatively Impacted by 6 weeks of Stretch Training. *European College of Sport Science Congress*. Vienna, Austria, July 2016. Available from: http://wp1191596.server-he.de/DATA/CONGRESSES/VIENNA_2016/DOCUMENTS/VIENNA_BoA.pdf
    Presentation Format: Podium

* I presented all abstracts for which I am the first author.

C. Reviewer

Apr 2020	Journal of Aging and Physical Activity
Nov 2019	Applied Physiology, Nutrition, and Metabolism
May 2019	Journal of Alzheimer's Disease
Mar 2019	Journal of Alzheimer's Disease
Dec 2018	Journal of Alzheimer's Disease
Oct 2018	Journal of Alzheimer's Disease

Memberships & Committees

Oct 2019 – Present	Clinical Exercise Physiologist (CEP) Canadian Society for Exercise Physiology
Aug 2019 – Present	Communications Coordinator Exercise is Medicine: Canada Offered position as a result of the work completed with the University of Western Ontario committee. Duties similar to that of role with the University of Western Ontario committee but at the national level.
Aug 2018 – Present	Communications Coordinator Exercise is Medicine: University of Western Ontario London, Canada Committee aimed at helping individuals live a healthier lifestyle via exercise. Responsible for creating and posting social media content. Fostered community partnerships and recruited program donors.
Sept 2016 – Aug 2017	Student Representative Embrace Aging Committee (UBC Okanagan, Institute for Healthy Living & Chronic Disease Prevention, and Interior Health Authority) Kelowna, Canada Committee aimed at creating a month full of events that would help older adults "age in place." Topics of events included but were not limited to pickleball, staying physically healthy, and age-related financial decisions.

Training

Ongoing	Western Certificate in University Teaching and Learning University of Western Ontario Description: Enhance teaching quality by graduate students and postdoctoral scholars and prepare them for a future faculty or professional career.
July 2020	Neurohackademy University of Washington eScience Institute but conducted virtually Seattle, USA Description: 5-day workshop devoted to hands-on lectures and participant-directed activities focusing on technologies used to make human neuroscience data shareable and reproducible.

May 2019	CONN Toolbox for Functional Connectivity Analysis of the Human Brain Athinoula A. Martinos Center for Biomedical Imaging Boston, USA Description: 5-days of highly interactive courses that covered all aspects of functional connectivity analyses in the CONN toolbox.
Sept 2015 – Aug 2017	Biodex Dynamometer System 4 Pro (Biodex Medical Systems Incorporated) Kelowna, Canada Description: A multi-mode computerized robotic instrument designed to measure muscle strength; used to assess primary outcome of MSc research.

Knowledge Translation

April 2020	CSEP Communique Strength Training to Fight Pre-frailty in Older Females. Link: https://www.csep.ca/KnowledgeTranslations.asp?a=view&id=50&pageToView=1
April 2018 & 2019	Presenter Talks on Fridays, Lawson Health Research Institute London, Canada Presentation to disseminate current research findings to community members, clinicians, and other researchers.
Jan 2018	Presenter @ the Barre - Her First Community Event London, Canada A one-day workshop aimed at promoting women's physical and mental health. Included interactive presentations from experts in mental health, diet, and exercise.
March 2017	Interviewee, Okanagan Seniors Urged to Get Active Global News Okanagan, Global TV Kelowna, Canada Link: https://globalnews.ca/video/3297654/okanagan-seniors-urged-to-exercise-daily-to-ensure-healthy-aging
Sept 2016	Interviewee, Using Exercise to Fight Frailty UBC Okanagan News, UBC Studios Okanagan Kelowna, Canada

Link: https://www.youtube.com/watch?v=v2dgRWU9kL0

April 2016

Presenter
Seniors Learning Retreat
Kelowna, Canada
Informative presentation about how exercise can help keep older adults physically strong and maintain their functional independence. Presentation was based upon current findings from our research lab, as well as other groups.

Feb 2016

Presenter
Exercise is Medicine: Seniors Health and Exercise Fair
Kelowna, Canada
Promotional event where older adults received informative presentations, engaged in exercise, and socialized with researchers, community activists, exercise professionals, and other older adults.

Volunteerism

May 2018 & 2019

Facilitator
Discovery Day: Canadian Medical Hall of Fame
London, Canada
A one-day event that allows secondary school students to explore various career options in medicine and health science. Led an interactive workshop that provided insight into life as a graduate student and the research conducted within our lab.

Oct 2015 – Aug 2017

Facilitator
Youth Outreach Program: UBC Okanagan
Kelowna, Canada
Program aimed at promoting the fields of science, technology, engineering, and mathematics (STEM) to youth ranging from elementary to secondary school. Presented research from the field of Kinesiology. Facilitated the interactive use of lab technology.