Assessment of a Cognitive-Motor Training Program in Adults at Increased Risk for Developing Dementia

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A thesis submitted to the Faculty of Graduate Studies in partial fulfillment
of the requirements for the degree of
Master of Science

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Toronto, Ontario
July 2018

Abstract

With the prevalence of dementia increasing each year, preclinically implemented therapeutic interventions are critically needed. It has been suggested that cascading neural network failures may bring on behavioural deficits associated with Alzheimer's disease. Previously we have shown that cognitive-motor integration (CMI) training in adults with mild cognitive impairments generalized to improved global cognitive and activities of daily living scores. Here we employ a novel movement-control based training approach involving CMI rather than traditional cognition-only brain training. We hypothesized that such training would stimulate widespread neural networks and enhance rule-based visuomotor ability in at-risk individuals. We observed a significant improvement in bimanual coordination in the at-risk training group. We also observed significant decreases in movement variability for the most complex CMI condition in the at-risk and healthy training groups. These data suggest that integrating cognition into action in a training intervention may be effective at strengthening vulnerable brain networks in asymptomatic adults at risk for developing dementia.

Acknowledgments

I'd like to thank my family, starting with my grandmother (Jean Echlin) and uncle (Ken Echlin) for encouraging me and supporting me the whole way through; my aunt and uncle (Suzanne and Bob Echlin) for guiding my pursuit for a higher education from a young age; and my aunt (Donna Echlin) for inspiring me to choose this field to work in. Finally, I'd like to thank Dan Gheorghiu for being with me every step of the way, and for the endless love and support.

I'd also like to thank my wonderful lab-mates (past and present) and research scientist for being so supportive, for editing my work and for the helpful advice along the way as well as Dr. Lauren Sergio for being an excellent and supportive supervisor and for making this process an enjoyable one for me. I'd also like to give a special thanks to Mirka Ondrack for her statistical guidance during my analyses. Thank you to all of you and to all other friends and loved ones that have offered continuous support to me during this process.

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Glossary of Abbreviations

Aβ – Beta Amyloid
AD – Alzheimer's disease
ADL – Activities of Daily Living
AE – Absolute Error
ApoE ε4 – Apolipoprotein E Epsilon 4
CMI – Cognitive Motor Integration
CVD – Cardiovascular Disease
CT – Cognitive Training
DLPFC – Dorsal Lateral Prefrontal Cortex
DTI – Diffusion Tensor Imaging
DR – Direction Reversal
eAD – Early Stage Alzheimer's disease
FA – Fractional Anisotropy
GM – Gray Matter
ILF – Inferior Longitudinal Fasciculus
IPL – Inferior Parietal Lobule
MCI – Mild Cognitive Impairment
MLF – Middle Longitudinal Fasciculus
MRI – Magnetic Resonance Imaging
MOCA – Montreal Cognitive Assessment
MMSE – Mini-Mental State Exam
MST – Medial Superior Temporal Area
MT – Movement Time
M1 – Primary Motor Area
PCC – Posterior Cingulate Cortex
PFC – Prefrontal Cortex
PM – Premotor Cortex
PMd- Dorsal Premotor Area
PMdc – Premotor Dorsal Caudal
PMdr – Premotor Dorsal Rostral
PMv – Ventral Premotor Area
RD – Radial Diffusivity
RT – Reaction Time
SLF – Superior Longitudinal Fasciculus
SMA – Supplementary Motor Area
SPL – Superior Parietal Lobule
SPOC – Superior Parieto-Occipital Cortex
TMS – Transcranial Magnetic Stimulation
TSP – Trans-Saccadic Perception
VE – Variable Error
VSM – Visuospatial Memory
V1 – Primary Visual Area
WM – White Matter

Introduction

In recent years, a consensus has emerged that research on non-pharmaceutical intervention strategies to prevent functional decline in dementia should focus on preclinical disease stages (Sperling et al., 2011). Dementia is an umbrella term for a broad range of heterogeneous brain diseases which often manifest as progressively worsening motor, affective and cognitive processes. The most common cause of the pathological decline which leads to dementia is Alzheimer's disease (AD; Jorm, & Jolley, 1998). Presently there is no curative treatment for dementia, and early diagnosis is still elusive. With such a large portion of the population over the age of 60, the prevalence of dementia is increasing drastically, leaving a larger number of patients and caregivers in overwhelming duress (Prince et al., 2013). There is a heavy demand for research that focuses on low-cost, non-invasive therapeutic intervention strategies to offset this increasing healthcare burden. Thus, research is shifting focus towards the preclinical stages of dementia for clues about the timeline of pathological decline in the brain, symptom development, and prevention.

The ability to make a resolute early diagnosis of dementia is still in its infancy. At present a diagnosis generally relies on an interview with a caregiver, neuropsychological tests, painful cerebrospinal fluid biomarker procedures, and/or expensive neuroimaging. A probable diagnosis of AD can be made only after clinical symptoms appear and significant damage to the brain has already occurred (Ewers, Sperling, Klunk, Weiner, & Hampel, 2011). With current clinical diagnostic techniques, it is especially difficult to detect when an individual may be in the preclinical stages because behavioural symptoms are mostly absent, despite the fact that the pathophysiological processes of AD begin years to decades before clinical symptoms would appear (Morris, 2005; Sperling et al., 2011). It is becoming evident that treatment should be targeted towards individuals before symptoms develop, as is commonly done for other chronic illnesses like cardiovascular disease (CVD) or diabetes.

A general shift in strategy is taking place from traditional, single aspect strategies, e.g., cognitive training (CT) or improvement of cardiovascular health, to strategies that focus on integrated approaches and more generalizable improvements to brain health. Two recent insights drive this shift: 1) the pathological changes associated with dementia start years or decades before the onset of clinical symptoms (Prince et al., 2013), and 2) the earliest changes in the dementia brain appear to be an altered functionality of large brain-wide neural networks rather than atrophy, in specific regions such as the medial-temporal area (Hawkins, Goyal, & Sergio, 2015; Jones et al., 2016). Here these concepts will be incorporated into a decline-prevention strategy by examining the efficacy of a tablet based, behavioral intervention program in older adults at an increased risk of developing dementia.

Neural Correlates of Movement Control

Properly coordinating smooth movements for regular daily activity requires many areas of the brain for even the most basic movements. Movements often begin with visual input to the retina about an object of interest. This visual information is processed in the primary visual cortex (V1; see Figure 1) and can be sent dorsally to the parieto-occipital extrastriate cortex to facilitate action based on vision (Kandel, Schwartz, & Jessell, 2000, p. 396-399; Mishkin & Ungerleider, 1982; Mishkin, Ungerleider, & Macko, 1983). Input is received by the posterior parietal cortex (PPC), which is an area that has an essential role in encoding spatial information in relation to motor output by transforming visual cues into a motor plan that will properly align movement effectors with a target (i.e., by computing the effector position in fixation-centred coordinates). This function is mainly computed in the superior parietal lobule (SPL; John F Kalaska, Scott, Cisek, & Sergio, 1997). With information from the PPC about placement of the body in peripersonal space, connections to the frontal lobes carry this information to the premotor cortex (PM; Wise, Boussaoud, Johnson, & Caminiti, 1997). This input is continually updated in the PM via feedback from the PPC, which allows the desired trajectory to be planned based on the displacement of the hand during movement in relation to the target position.

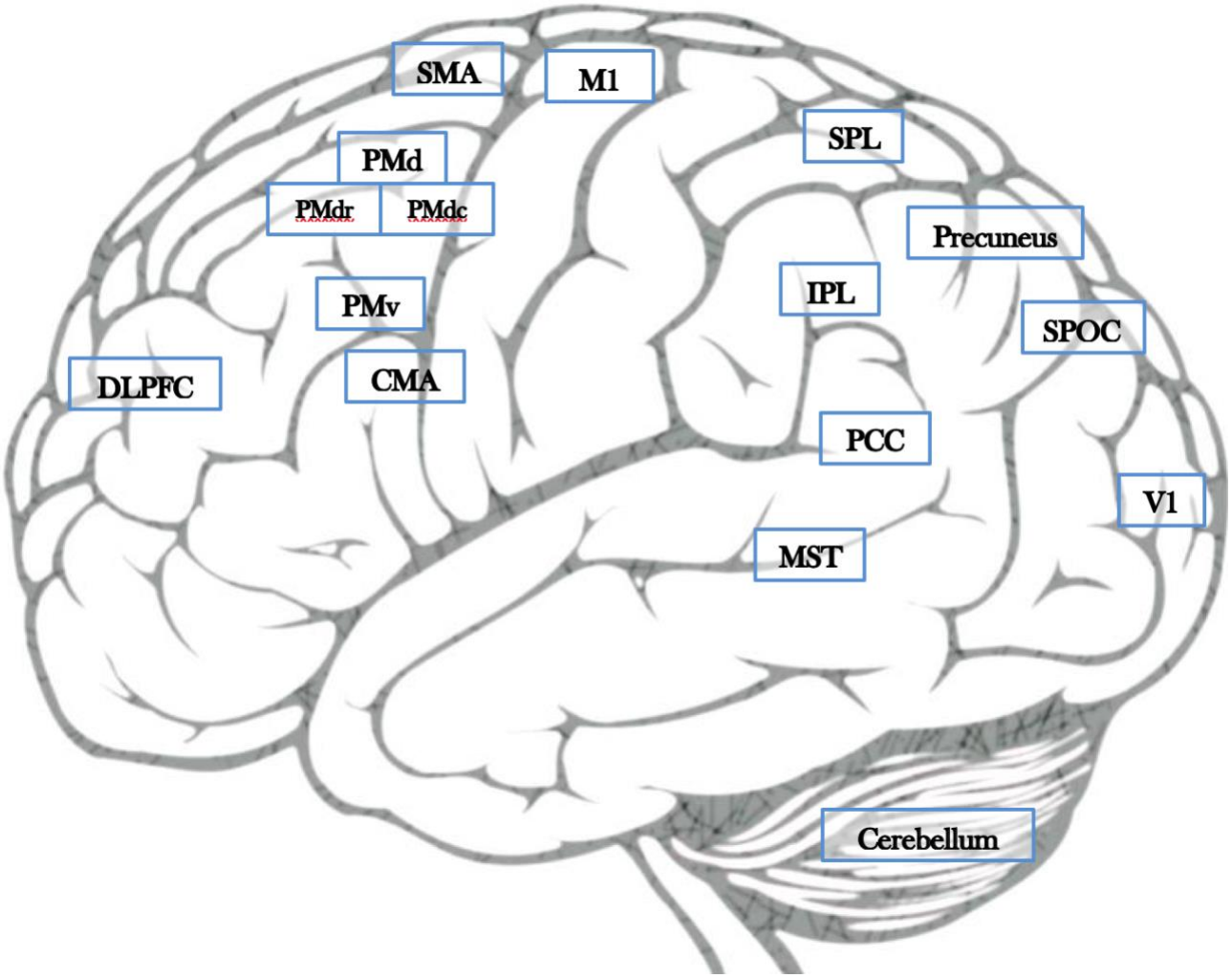

Figure 1. Simplified overview of brain regions involved in both standard and non-standard visuomotor transformations. Primary visual cortex (V1), superior parieto-occipital extrastriate cortex (SPOC), superior parietal lobule (SPL) inferior parietal lobule (IPL), dorsal premotor cortex (PMd), dorsal premotor rostral (PMdr), dorsal premotor caudal (PMdc), ventral premotor cortex (PMv), supplementary motor area (SMA), cingulate motor area (CMA), primary motor area (M1), dorsolateral prefrontal cortex (DLPFC), medial superior temporal area (MST), posterior cingulate cortex (PCC).

The PM functions in planning, spatial/sensory guidance, rule-integration and in some cases, direct control of movement (having direct connections to motor neurons driving proximal musculature). PM neurons organize and gather information to assist with selecting the most effective primary motor cortex (M1) neurons to carry-out the desired task (Kandel, Schwartz, & Jessell, 2000, p. 412-415). Specifically, the dorsal premotor cortex (PMd) seems to be intricately involved in the process of creating motor plans for reaching and pointing by identifying the target and selecting an effector (Hoshi & Tanji, 2006). Neurons in the caudal area of the dorsal, caudal area (PMdc) appear to fire rapidly for specific target positions in relation to the hand during the planning phase and execution of the reaching movement (Cisek & Kalaska, 2005; Sayegh, Hawkins, Hoffman, & Sergio, 2013). Additionally, cells in the rostral area of the dorsal premotor cortex (PMdr) are selective for arbitrary associations and rule integration in planning movements (Muhammad, Wallis, & Miller, 2006; Sayegh et al., 2013). Additional areas outside of the PM, like the precuneus region, contribute to this program by updating visuospatial information, specifically by creating spatial representations of the environment in relation to the self (Cavanna & Trimble, 2006). The cerebellum also offers pertinent contributions regarding coordination of the movement, corrective motor learning, state estimation and possibly combining predicted and perceived sensory consequences of movement (Hart & Henriques, 2016; Miall, Reckess, & Imamizu, 2001), and thus becomes more activated as movement tasks become more complex (Gorbet & Sergio, 2016). After such extensive processing, the necessary forces to enact a planned movement are encoded by M1 and this information is transformed into a command to the spinal cord to coordinate the desired muscle activity patterns (Kandel et al., 2000, p. 344).

The control of movement to perform regular activities in daily life involves intricate processing and communication in the brain. This action requires multiple brain areas to work together to process and then integrate information with assistance from white matter (WM) tracts that connect these areas and allow for communication between cortical areas. For example, vision guides most goal-directed movements and requires a transformation from input to the retina into a command for motor neurons to

move limbs to the desired location; this is referred to as a visuomotor transformation. The frontoparietal network appears to be important for transforming extrinsic visuospatial information into intrinsic motor activity (Corbetta, 1998). This network has many association fibres that mainly consist of reciprocal connections between the parietal lobe and the frontal lobe, among others. Overall, these fibres include the superior longitudinal fasciculus (SLF) and to a lesser extent, other subdivisions including, the middle longitudinal fasciculus (MLF), the inferior longitudinal fasciculus (ILF), the cingulum bundle and the fronto-occipital fasciculus (Schmahmann & Pandya, 2009). Specifically, the frontoparietal network is involved in assisting with the integration of cognitive processing and motor planning via frontal and parietal lobes for computation of visuomotor tasks (Hawkins et al., 2015).

Different movements recruit distinct brain areas and WM tracts for precise timing and smooth motor output. Simple movements typically involve a direct/standard interaction with an object whereby vision and movements are aligned with a target. Visuomotor brain networks are responsible for coordinating these types of movements by incorporating input from M1, SPL, and PMd during the planning stages and initiation of the movement (Gorbet, Staines, & Sergio, 2004). When movements become more complicated, they require resources from additional brain networks to create an algorithm that will assist with creating and following cognitive rules to help align the effector with the desired target location when this location is not consistent with guiding visual stimuli (Wise, di Pellegrino, & Boussaoud, 1996; Redding & Wallace, 1996). The frontoparietal network is particularly helpful in transferring information between brain areas to create the algorithm for this type of movement. An example of such a nonstandard interaction occurs when using a desktop computer: in this case, gaze remains fixed on the screen in the vertical plane while hand movements over a mouse or touchpad are performed in the horizontal plane (Wise, di Pellegrino, & Boussaoud, 1996). The horizontally placed mouse controls a cursor in the vertical plane, but the two are spatially dissociated. The ability to perform more complex rule-based visuomotor tasks by integrating information from multiple brain areas is called cognitive-motor integration (CMI). It appears that for nonstandard CMI tasks, the

anterior SPL, PFC and the PMdc, which are connected by the frontoparietal network, integrate information about planned movement direction with updates from current limb and target position to produce movement based on cognitive decisions (Hawkins, Sayegh, Yan, Crawford, & Sergio, 2013; Sayegh et al., 2013).

The decoupling of visual and spatial target information can be differentially processed based on either spatial or strategic recalibrations. When learning to work in a separate plane, like when using a desktop computer as described above, implicit recalibration based on internal recognition of movement error causes corrective feedback for the movement without conscious awareness (Clower & Boussaoud, 2000). Alternatively, the premise of strategic control is that an explicit rule will be adapted to properly perform a selected movement (Clower & Boussaoud, 2000). In this case, working with reversed visual feedback, like when getting used to using a mouse to scroll up and down on a new laptop, may require rule-integration until the motor behaviour is learned (i.e. remembering a rule like to scroll down to move up a webpage and vice versa). This type of movement learning relies on external feedback of errors and uses explicit rules to incorporate the new appropriate movement pattern. Therefore, tasks that require spatial or strategic recalibration offer insights into an individual's CMI ability by demonstrating how well their brain can perform thinking-while-moving tasks.

It appears that in performing movements where planes are spatially dissociated, most of the same brain areas are activated as in non-dissociated movements; however, patterns of activity within these regions differ substantially. This indicates that cells throughout visuomotor brain regions, like PMd cells, have a preferred direction for firing that matches both targets, are co-activated to fire in alignment to movement toward either target (Gorbet & Sergio, 2017; Klaes, Westendorff, Chakrabarti, & Gail, 2011). When the movement path is selected, the path to the unchosen target is simply inhibited. Thus, when complicated movements are required, it appears that the brain plans accordingly for any relevant potential movement, but upon execution of the motor plan, the unselected movements are inhibited, and the chosen path is implemented. Proper movements in the correct direction while

receiving reversed visual feedback require areas of the brain (i.e. cuneus and medial premotor cortex) to transform motor output to overcome the default tendency to move eyes and hands to the same spatial location (Gorbet & Sergio, 2016). The movement itself relies on a number of areas, but with altered visual feedback, there is additional reliance on the left superior posterior cerebellum and right inferior parietal lobule (IPL) to organize and produce the nonstandard movement (Gorbet & Sergio, 2016). Additionally, both the PMdc and PMdr tend to be activated during nonstandard tasks (Sayegh et al., 2013).

Another important factor for effective motor control that is used in day-to-day living is bimanual coordination. Bimanual coordination engages communication through interhemispheric WM tracts of the corpus callosum (CC) which joins left and right parietal regions posteriorly and the left and right frontal lobes anteriorly. According to previous research, damage to the CC in participants with traumatic brain injury was related to decreased fractional anisotropy (FA) and increased radial diffusivity (RD) in sub-regional callosal fibers in parietal and prefrontal areas. These WM changes were associated with decreased movement times (MT), reaction times (RT) and performance during bimanual coordination tasks (Caeyenberghs et al., 2011). Many of the brain areas and even brain cells involved in unimanual movements, are the same as those used for bimanual coordination, although they have differing patterns of activity (Walsh, Small, Chen, & Solodkin, 2008). More often than not, unimanual movements are used to enact a visuomotor transformation, but more research is needed to understand how stimulation to this network during a unimanual task may affect (i.e., produce behavioural change) in the overlapping bimanual areas. Since bimanual coordination and nonstandard visuomotor tasks seem to be functionally related (Hawkins et al., 2015), more research will be needed to understand whether bimanual coordination tasks may also be an early indicator of brain network pathology.

Cortical Control of Video-game Playing

Playing video-games often involves nonstandard visuomotor brain mapping, which requires CMI; video-gamers with extensive experience have altered cortical activation of the frontoparietal network, cerebellar and visual areas during nonstandard tasks (Gorbet & Sergio, 2018; Granek, Gorbet, & Sergio, 2010) . One of the biggest differences between standard and nonstandard brain networks is the functional involvement of the PMd. This is highlighted by a study in which non-human primates were injected with muscimol, a localized depressant, to their PMd area and separately given both standard and nonstandard tasks to perform. Performance was not altered in direct interactions, but the primates became unable to learn the motor skills required for the nonstandard interaction task (Kurata & Hoffman, 1994). When playing a video-game, there is often a physical external device that is used to manipulate a virtual in-game character. When an action requires the use of a tool to indirectly act upon another stimulus, the brain must incorporate the tool as an additional property of its own effector (i.e., the hand). For example, adding a controller or computer mouse as an extension of the hand in this way involves incorporation of a representation of the updated effector in the ventral premotor area (PMv) as well as an adaptation for the updated movement for using the controller; performed by the IPL (Obayashi et al., 2001). Neural load is increased during movements that incorporate the addition of a controller to the end effector along with spatial dissociation between movements and guiding visual stimuli on screen in the video-game. According to previous research, in cases of increased neural load, additional brain networks are recruited for task performance (Gorbet, Staines, & Sergio, 2004). This study found that overall, in nonstandard tasks like these, less brain areas were activated during performance; it was hypothesized that this was due to silencing of the standard motor plan (i.e. the natural movement tendency) to enact the nonstandard motor plan only.

When playing a video-game, movement goals may be inferred from supplementary information, as they might not always be based on permanently present or static stimuli. In allocentric coding, a target location can be inferred relative to other reference points, even without sight of the target

location (Chen et al., 2014). Gaze-centred and allocentric mechanisms also assist with goal-oriented movement extrapolation to pre-emptively avoid an incoming projectile (Byrne & Crawford, 2010) or to remap gaze-centred signals based on self-motion during a video-game (Crawford et al., 2011). Movement goals can be inferred using a combination of position and velocity information (i.e., about moving targets). This type of goal extrapolation is especially useful when playing a video-game because success often depends on the brain's ability to incorporate current position with velocities of other nearby objects to determine an end goal for movement location. According to a study that used repetitive transcranial magnetic stimulation (TMS) to assess the spatial and temporal aspects of movement when the hand intercepts an object, the superior parieto-occipital cortex (SPOC) appears to be active during position coding, whereas the medial superior temporal (MST) region and areas for visual processing of motion appear to account for the timing of when the target will reach the hand (Dessing, Vesia, & Crawford, 2013). The final movement time is calculated as a combination of information about the position and change in time relative to object motion (Dessing et al., 2013). The mid-posterior intraparietal sulcus is activated when calculating the distance of the reach and how far/close the hand should go by calculating these vectors in visual coordinates. This assists in mapping where a target is in visual space based on its depth (Yu, Farley, Jin, & Sur, 2005).

Once the task commences, various stimuli generally appear, and the eyes move rapidly between them while the fingers/hands respond accordingly. The location of stimuli in a video-game must be remapped for perception and appropriate action. Trans-saccadic perception (TSP) enables the additional storage of information about the stimulus between eye and limb movements (Melcher & Colby, 2008). For this to occur, information must be retained in visuospatial memory (VSM), followed by spatial updating that accounts for changes in the position of the retina with changes in the visual stimuli on screen. To retain information about stimuli between saccades, previously retained information from a point of earlier fixation must be integrated with the updated information from the current fixation point; to do so, it seems that VSM and mechanisms for egocentric spatial updating must be combined

(Melcher & Colby, 2008)**.** Evidence suggests that this organization takes place around visually attended points in space, without explicit remapping of the features (Cavanaugh et al., 2010).

For such complicated, nonstandard video-game tasks several brain areas take on specialized roles in processing information and executing an appropriate movement. The precuneus area as previously described seems to assist with processing visuospatial information. It also appears to have a central role in cognitive control of task performance while task complexity is continually increasing (Wenderoth, Debaere, Sunaert, & Swinnen, 2005). This area also seems to have a specialized function in working with the tracking of moving stimuli/objects seen on a screen (Culham et al., 1998), as is often the case in video-game playing.

Cascading Decline in Large-Scale Networks in Neurodegenerative Diseases

Motor deficits exist in later stages of AD, early AD (eAD) and possibly preclinical AD. Proper execution of motor skills in everyday living is a complicated process which requires input from many brain areas throughout sensorimotor networks. Movements require planning, initiating, executing and sometimes correcting the movement with sensory feedback. Accurate movements rely on visuospatial ability, especially when processing burden occurs after the introduction of a new or complex task (Buchman & Bennett, 2011; Gorbet, Staines, & Sergio, 2004). One study was able to differentiate/detect pathology in cognition based on complex fine-motor tasks in groups at-risk for developing dementia with some mild cognitive impairments (MCI), diagnosed AD and healthy controls (Kluger, Gianutsos, Golomb, Ferris, & Reisberg, 1997). Additionally, another study found that individuals in eAD or those with MCI do not yet have difficulty with tasks that require standard/direct interactions (Yashar Salek, Anderson, & Sergio, 2011). However, when individuals who were only at-risk of developing dementia were required to perform nonstandard tasks, performance deficits were evident when compared to controls (Hawkins & Sergio, 2014). The performance decrements that were observed during nonstandard tasks in the at-risk group were also associated with lower scores of

cognitive statuses on the Montreal Cognitive Assessment (MOCA), which suggests that visuomotor impairment may be related to cognitive decline. Importantly, even when MOCA scores were normal in at-risk groups, there were still evident deficits in CMI ability. Visuomotor skill is relevant to daily life functioning in that many tasks carried out each day like driving, walking or climbing stairs require adequate visuomotor ability (Elble & Leffler, 2000). Current research in the field has demonstrated that gray matter (GM) atrophy and hypometabolism, and WM compromise occur in eAD and that before clinical manifestation of symptoms, WM disruptions are particularly characteristic of preclinical stages (Fischer, Wolf, Scheurich, & Fellgiebel, 2015; Honea, Swerdlow, Vidoni, & Burns, 2011; Mosconi et al., 2007). Thus, tasks which rely on the functional connectivity of large-scale networks to integrate information from many brain areas would unsurprisingly result in depreciated performance in these groups.

The brain is highly interconnected by WM tracts that tie together cortical areas; damage to these WM tracts, as in the disruptions that are expected with the progression of AD, result in decreased overall brain processing capability which reduces general performance ability for complex tasks (Voineskos et al., 2012). Diffusion tensor imaging (DTI) can be helpful for detecting alterations in WM tracts before behavioural symptoms are evident. To further investigate this brain-behaviour relationship Hawkins and colleagues (2015) assessed structural/functional brain images of participants in relation to their difficulty with performing CMI tasks. They found that large frontopartietal networks which are required for task performance also appeared to be compromised in individuals at-risk of developing dementia. This is consistent with previous research which has shown that patients with AD have compromised WM tracts in frontoparietal networks that is associated with decline in functional abilities (Braak & Braak, 1991). Imaging techniques including DTI and resting state functional magnetic resonance imaging (rs-fMRI) are effective for diagnosing AD but unfortunately are also costly and not accessible to most patients. Since nonstandard cognitive-motor tasks have been strongly correlated with DTI of WM compromise, implementing these tasks may be a more feasible substitute for early

detection of pathology in asymptomatic individuals who are at-risk of developing dementia.

Risk factors for developing dementia mainly include age (i.e., typically age 65 and over) and genetic factors like carrying one or two copies of the Apolipoprotein E Epsilon 4 (ApoE ε4) allele, or having multiple family members with diagnoses of dementia or AD (Duara et al., 1996; Fratiglioni, Ahlbom, Viitanen, & Winblad, 1993; Green, 2002; Mosconi et al., 2007; Reitz & Mayeux, 2014). The ApoE gene is a lipid-binding protein with important functions in maintaining myelin and neuronal cell membrane integrity. The ApoE ε4 allele particularly, is associated with reduced efficiency of beta amyloid (Aβ) clearance in the brain along with tau accumulation; the main biomarkers of AD pathology (Mattsson et al., 2009). In North America, Alzheimer's patients that also carried an ApoE ε4 allele made up 58% of the total population of diagnosed patients, the rest may have been attributable to other genetic or environmental factors (Crean et al., 2011). Again, in patients with AD, 58% had a family history of dementia; these two factors independently increase risk of developing dementia, but together can also increase risk additively (Duara et al., 1996). Having a first-degree relative with AD doubles the lifetime risk of developing late-onset AD (Reitz & Mayeux, 2014). The prevalence of AD is also higher in females and maternal history of AD is more indicative of risk for development than paternal history of AD (Honea et al., 2011; Lisa Mosconi et al., 2010; Schmidt et al., 2008). There are other factors that independently increase risk of developing dementia including psychiatric illness, chronic depression, substantial alcohol consumption, diabetes or hypertension (Yoshitake et al., 1995). According to Dubois and colleagues (2016), there are no discrete clinical events that characterize the preclinical stages. The genetic risk factors distinguish work with this variable type of risk group as a primary prevention intervention which involves intervening in those with no outward symptoms – the general population.

Dementia is more commonly being recognized as a disconnection or 'network failure syndrome' (Agosta et al., 2012; Jones et al., 2016; Liu et al., 2014; Villain et al., 2008). According to this framework, disruptions in white matter tracts of the posterior cingulum bundle are associated with

hippocampal atrophy (Villain et al., 2008); it seems that these disconnections may augment the cascading failure that implicate posterior regions. Aside from the typical GM atrophy associated with dementia, one of the first pathological changes that can be detected through behavioural measures is a reduced efficiency of communication in WM networks, including between frontal and parietal areas (Bonnì et al., 2013). As a form of treatment, stimulating networks that are most vulnerable in early stages of decline seems to be a promising way to enhance overall brain health. Previous studies and as well as a recent pilot study in our lab demonstrated that cognitive-motor training improved global cognitive scores in populations with MCI (de Boer, Echlin, Rogojin, Baltaretu, & Sergio, 2018; Tippett & Rizkalla, 2014). The results were encouraging because participants' cognitive status improved after 16-weeks of video-game training; the improvement according to multiple cognitive tests was not related to the tasks that participants were trained on during the intervention. These findings suggest that behavioural intervention strategies which incorporate large neural networks like the frontoparietal network in this case, may enhance brain-wide connectivity by stimulating communication between areas of the brain that are needed to perform these tasks. It appears that enhancing network connectivity through longitudinal CMI training may be an effective method of preventing decline in functional independence in individuals with cognitive deficits.

Studies have indicated that no symptoms exist in individuals in the preclinical stage, but recent research has demonstrated that individuals who may be at-risk do indeed have compromised performance, specifically in nonstandard visuomotor tasks; along with altered functional networks (Hawkins et al., 2015; Hawkins & Sergio, 2016). The behavioural deficits may stem from the neural load caused by the required recalibration. When decoupling of visual and spatial target information occurs during a task, healthy populations tend to perform with decreased accuracy and increased RT and MT (Gorbet & Sergio, 2009). The increased difficulty during nonstandard tasks in populations with cognitive impairments is less understood. Research that is specifically targeted toward better understanding why CMI ability falters in preclinical disease stages and this link to functional ability is

of the utmost importance for finding preventative and rehabilitative measures for those with cognitive impairments or those who are at-risk for developing dementia.

Contrary to the commonly held belief that disease-related decline begins with Aβ accumulation and hippocampal atrophy, recent evidence suggests instead that in the early stages of cognitive decline, decreased WM integrity is associated with reduced resting state connectivity, with origins in the PPC. According to Jones et al. (2016), in AD, this decreased connectivity begins in the posterior parietal node, which shifts processing burden to adjacent nodes and results in increased connectivity in these areas; with Aβ build-up in the brain, interactions with pre-existing vulnerable substrates in the medial temporal lobes leads to a tau-associated neurodegenerative process. Additionally, in another study cognitively healthy older adults with two copies of the ApoE ε4 allele (which is associated with the highest risk of developing AD) underwent PET scans and they found that preclinically there was reduced glucose metabolism in posterior cingulate, parietal, temporal and prefrontal regions which was in alignment with findings from patients with probable AD (Reiman et al., 1996). Issues with simple eye-hand coordination tasks or complex movements, typical of older adults with MCI or AD/dementia, seem to arise due to this altered brain connectivity, especially in the posterior parietal area.

The early stages of degradation in structure and function of the posterior parietal area and/or compromised frontoparietal WM tracts seem to be the initial factors that impinge on visuomotor ability; effective visuomotor performance relies on both frontoparietal networks and posterior parietal areas (Caminiti, Ferraina, & Battaglia Mayer, 1998). Nonstandard tasks that are specifically targeted to stimulate frontoparietal networks in those at-risk of developing dementia would use eye-hand coordination tasks with movements that involve increasing levels of complexity and cognitive demand. This sort of nonstandard movement requires rule-integration and altered visuomotor mapping into a motor plan. From this, localizing issues in frontoparietal WM tracts (i.e., based on the ability to integrate information) or in cerebral regions responsible for the processing of a single domain may be possible. Research indicates that the former is more likely, since large-scale WM tracts appear to be

disrupted and show symptoms of decline before the connected cerebral areas demonstrate deficits in any single domain (Bartzokis, 2004; Gold, Powell, Andersen, & Smith, 2010; Smith et al., 2010). To this end, simple motor deficits (i.e., deficits in standard visuomotor mappings) alone typically do not appear until clinical symptoms are quite advanced (Parakh, Roy, Koo, & Black, 2004). The networks involved in these praxic functions appear to undergo degradation in early or preclinical stages of dementia and could therefore be useful as an early identifying feature and target for intervention (Buchman & Bennett, 2011; Verheij et al., 2012).

With such vast interconnectivity between brain areas, there are plenty of routes for pathology to interfere with proper brain function or cause disconnection. For example, the rostral cingulum bundle which connects the hippocampus to the posterior cingulate cortex (PCC), appears to be disrupted in those with AD which may be associated with PCC hypometabolism and hippocampal atrophy (Villain et al., 2008). Additionally, areas in the prefrontal cortex (PFC), mainly the energy-demanding dorsal lateral prefrontal cortex (DLPFC), tend to experience hypometabolism in eAD. The DLPFC is highly connected to the PMd and has reciprocal connections particularly in the SPL (Tomassini et al., 2007); once this area experiences initial stages of decline it may negatively impact the ability to perform decoupled movements.

Failures and Successes of Current Treatments for Symptoms of Dementia

Generally, symptoms of dementia are initially recognized by an apparent decline in memory, cognitive functions, and independence/functionality in daily living. With the prevalence of dementia expected to double every 20 years (Prince et al., 2013), commercially available prevention strategies have become popular. Unfortunately, the merit behind these programs is often lacking and they are regularly debunked for not having a generalizable effect on overall cognitive status (Kable et al., 2017; Owen et al., 2010). Intervention strategies usually target the preservation or compensation of these functions after symptom onset; however, it has been with limited success. Research has indicated that

instead, restorative therapeutic interventions appear more fruitful for improving cognitive functions (Sitzer, Twamley, & Jeste, 2006). Restorative strategies are targeted towards improving performance in the specific cognitive domain that a patient is experiencing decline in. When visuomotor activities are incorporated in restorative interventions, more beneficial and generalizable effects are found (Acevedo & Loewenstein, 2007; Basak, Boot, Voss, & Kramer, 2008; Lee et al., 2012). A meta-analysis of restorative strategies that were implemented in CT programs to elderly with cognitive deficits found that this type of intervention is most effective when given in individual sessions using more generalized stimulation (Sitzer et al., 2006). To observe if these effects exist in an appropriately larger sample, Ball and colleagues offered this type of training program to individuals with minor cognitive impairments and healthy individuals; verifying that these findings remained stable, with the caveat of not finding any generalizable effects to functional abilities (Ball et al., 2002). Notably, it appears that intervention programs that train procedural memory are more successful in generalizing to improvements in functional ability to perform activities of daily living (ADL; Farina et al., 2002).

Lately, it appears that research is disproving the efficacy of many commercially-accepted methods of preventing pathological decline using diet supplementation (Mecocci, Tinarelli, Schulz, & Polidori, 2014). There are many possible targets for intervention with regards to supplementation but, it appears that most nutraceuticals and even some pharmaceuticals have shown miniscule or sometimes no effects on cognition after years of rigorous testing (Amenta, Parnetti, Gallai, & Wallin, 2001; Mecocci et al., 2014). Some non-product related alternatives appear to produce more benefits for preventing cognitive decline than their marketed counterparts. For example, it is estimated that about one third of all dementia cases can be attributed to modifiable risk factors related to lifestyle habits involving obesity, smoking, depression, lack of exercise, lack of mental stimulation, diet, diabetes and low levels of education (Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). Modifying diet in particular, has demonstrated positive effects on cognitive status in older adults with no cognitive impairment according to randomized clinical trials (Valls-Pedret et al., 2015). Diet appears to be a

common theme among many of the modifiable risk factors mentioned and might be an important target for therapeutic intervention.

Since the pathological decline that leads to dementia is not well understood, more research is needed about the efficacy of non-pharmaceutical, early-targeted intervention programs that aim to stimulate large-scale brain networks. Since cognitive symptoms are often the earliest indicator of decline, many studies have attempted to use CT to increase brain connectivity and improve brain health globally. Most CT programs have difficulty in obtaining this generalizability (Owen et al., 2010; Roberts et al., 2016). CT alone does not typically produce the desired generalizability in global cognitive status or functional ability in populations with eAD (Clare & Woods, 2004); but CT can still result in positive effects in the same areas that an individual is trained in, especially in unimpaired adults (Valenzuela, Hons, & Sachdev, 2009; Willis et al., 2013). Although, there are many caveats like these to using interventions that train cognitive domains only, this evidence may still be helpful for individuals in preclinical stages, as they perform at healthy control levels on cognitive tests and thus may still experience benefits from this type of training (Gates & Sachdev, 2014). Since cognitive symptoms may indicate a pathological decline leading to dementia, it's also possible that participants may feel too ashamed or embarrassed to participate in CT programs alone due to a fear of having their deficits exposed (Clare & Woods, 2004). It appears that CT can be helpful for treating symptoms of decline but combining other types of training to this type of program would likely aid in producing larger and more generalizable effects.

Similarly, physical aerobic training has become a popular treatment method, but has also shown only modest effects on cognitive functioning, which usually do not have lasting results. Many studies have highlighted the potential benefit of physical activity on cognitive status when working with healthy older adults (Kramer & Erickson, 2007; Yaffe et al., 2009). Aerobic training is useful for enhancing brain oxygenation and for increasing levels of some neurotransmitters (González-Alonso et al., 2004; Patrick & Ames, 2015), like serotonin which can have beneficial effects on hippocampal cells

that subserve memory function (Haider, Khaliq, Ahmed, & Haleem, 2006). Some studies indicate that aerobic training may have a beneficial impact on the timing of symptom development by delaying symptom onset; still, physical activity does not appear to have much influence in terms of curative treatment for the underlying pathology (Rolland, Abellan van Kan, & Vellas, 2008). Other studies have shown beneficial effects from aerobic exercise, including increased frontal and parietal GM densities that may result from increased blood supply and synaptic connections; this may act as a form of brain reserve that can be recruited when in conditions of higher cognitive load (Colcombe et al., 2006; Fratiglioni & Wang, 2007; Stern, 2009). Lack of physical exercise causes decreased mobility in elderly and this is associated with ratings of lower quality of life as well as higher instances of falls and hospitalizations (Cesari et al., 2009; Oh et al., 2014). These studies highlight the indirect benefits of living an active lifestyle. Physical activity is a necessity for maintaining general brain health and quality of life, especially when combined with other types of training; it appears that physical training can produce substantial benefits to overall health.

Motor and cognitive processes are performed in the brain simultaneously, which suggests that it would be more advantageous to test them simultaneously as well. This would assist with getting a better understanding of how an individual's brain is functioning overall. Research indicates that AD-vulnerable large-scale networks tend to interact with one another when learning different training strategies and this has beneficial network-wide effects. (Voss et al., 2012) Previous studies have attempted interventions with separate cognitive and motor components since both types of training might be expected to contribute incrementally to global cognitive status (Maffei et al., 2017); but this has not necessarily been the case for most studies. For example, separate cognitive and motor training was administered to patients with primary degenerative dementia, but deterioration of cognitive function and activities of daily living was still evident by 10-months follow-up (Luttenberger, Hofner, & Graessel, 2012). This study design still does not address the issue of having cognitive and motor skills performed in conjunction. The brain operates in an integrative way to receive and send signals

simultaneously for optimal functioning; this is how training and test measures should also train/assess performance ability. Many strategies have been attempted in recent decades to stave off symptoms of decline in elderly populations, but success rates in these domains are negligible. With this, it seems that assessment measures should invoke efforts from different areas of the brain so that integration is required in a way that stimulates large-scale networks.

To avoid reliance on prescription medications to improve cognitive symptoms, more research is needed about interventions involving social interactions and/or puzzles that require strategic planning and engagement of brain networks in ways that may otherwise be left unstimulated**.** Using these strategies but with an added component (i.e., CMI) would highly diversify future studies from previous research by incorporating an analysis of the brain's ability to integrate information; an indirect method of testing the integrity of WM pathways in addition to relevant cortical areas. As previously described, large WM tracts like the frontoparietal WM pathways in the brain are some of the first to show behavioural symptoms of decline in preclinical dementia; the weakening of these tracts reduces the communication between movement control and cognitive processing areas of the brain resulting in greater visuomotor deficits on CMI tasks. In preclinical dementia, individuals appear healthy and perform at normal levels on cognitive and other standard tests. Aside from accumulation of proteins in the brain, some structural/functional changes, and possible gait disturbances (Ramakers et al., 2007), visuomotor deficits are the only other behavioural identifiers in this group at present. These changes may be slight and potentially difficult to detect; therefore, focusing on fine motor, eye-hand coordination-based visuomotor tasks would enable a more detailed assessment, sensitive enough to detect minute changes as compared to gross motor movements. The transparent discrepancy is that more strategies for preventing decline should incorporate large neural networks to produce generalizable effects on other brain areas and domains. If this type of intervention were introduced preclinically, it would enable vulnerable brain networks to be strengthened before decline could begin. This in turn would offer important insights about decline prevention in populations without a diagnosis

but with an increased risk of developing dementia.

Purpose & Hypotheses

Maintaining functional independence in the face of dementia is a major health concern for a growing number of Canadians. Unfortunately, individuals with dementia are unable to preserve this ability in their daily lives. The focus of the present study is to characterize how a movement control-based 16-week behavioural intervention program may influence cognitive, motor and visuomotor skill performance in those who are at risk of developing dementia. One of the apparent downfalls of most training and assessment measures that are used in dementia research is that they separately target cognitive processing and motor control, even though the brain performs these actions in unison. The current study will address this issue by including a cognitive measure, a motor measure, and a cognitive-motor measure before and after a 16-week intervention so that these relationships can be observed in depth by comparing these domains to each other. Accordingly, instead of studying the affected cognitive and motor processes independently, this study will introduce a task that requires the performance of both cognitive and motor functions in conjunction. The experimental setup for this assessment uses a touchscreen tablet to track finger-sliding movements in response to a dynamically changing task. This study uses CMI tasks to assess performance differences in those at risk of developing dementia based on maternal family history or having multiple family members with a diagnosis (Hawkins & Sergio, 2014).

The design of the study employs a novel approach to indirectly assess WM integrity through tasks that require the brain to integrate processes from different domains (i.e. cognitive processing in frontal areas and sensory-integrated motor planning in visuomotor areas). According to a recent neuroimaging study, these WM tracts which are engaged during this task while information is integrated, have shown an early vulnerability to pathology in preclinical and early dementia (Hawkins et al., 2015). More specifically, reductions in hippocampal, frontal and parietal neural networks were

implicated in rule-integration and goal-directed movement (Hawkins et al., 2013; Sayegh et al., 2014, 2013). With this apparent early faltering, it seems plausible that engaging in CMI tasks may be useful for stimulating communication between relevant brain areas. The present study will require participants to perform CMI on visuomotor tasks with increasing levels of complexity to detect and improve on possible impairment in at-risk groups. The preclinical stages of dementia are not typically accompanied by any behavioural deficits that are detectable with current clinical assessment practises nor are there tools available for this type of behavioural assessment, aside from visuomotor impairment and the proposed CMI technology. Use of CMI tools for the assessment of subtle visuomotor deficits offers an objective way of better understanding the relationship between altered kinematics and the associated pathological decline. Based on the generalizability of CMI training to increased global cognitive status in previous research, we expect that this training will result in a strengthening of the large neural networks involved in the task as detected by measures of visuomotor ability in a healthy population with increased risk for developing dementia (de Boer et al., 2018).

The intervention protocol relies on similar principles as the assessment tool in that it involves playing a video-game using nonstandard interactions that require CMI. Since research has shown that optimal functioning of large-scale WM tracts, particularly frontoparietal networks, are required to perform CMI tasks and that individuals with cognitive impairment show deficits when performing these tasks, then introducing a task which requires communication between relevant brain areas may promote neuroplasticity, strengthen connections in these brain networks and improve performance on said tasks. This repeated stimulation during training is expected to engage these large-scale networks in a way that will enhance visuomotor performance ability thereby strengthening these networks which may potentially serve as a protective factor for potential symptom progression in asymptomatic individuals who are at risk of developing dementia. In previous research, improvements from this training setup generalized over time to improved cognitive status (de Boer et al., 2018), but since the population for the current study is still cognitively healthy it would only be reflected by improved

cognitive-motor ability and likely a healthy boost in connectivity in large-scale brain networks which is important for avoiding pathological decline. These findings will add to the current research on functional decline prevention in individuals facing neurodegenerative disease and may also provide indirect insight about the brain networks that are used for CMI and how training may relate to improved global cognition.

Previous studies have shown that similarly designed video-games with added CMI components have demonstrated beneficial effects in populations with cognitive impairment (de Boer et al., 2017; Tippett & Rizkalla, 2014). According to de Boer and colleagues, this improved global cognition may stem from a strengthening of brain networks in a large-scale manner that translates from stimulation with CMI into improvements in other domains in groups with MCI (de Boer et al., 2018). This evidence supports our hypothesis that behavioural intervention strategies may preserve and enhance the connections in large-scale networks that are stimulated by CMI tasks. Using this portable equipment and simple video-game design, the objective is to assess whether longitudinal CMI training can strengthen the targeted brain networks preclinically, as measured by improved visuomotor ability, before cognitive symptoms begin to appear to prolong healthy cognitive status. If training in at-risk groups enables participants to improve CMI ability close to healthy control levels compared to those at-risk who do not receive training, then we hope that this simple to administer, non-invasive, low-cost, and self-motivational method will be adapted to disrupt symptom progression in populations at-risk of developing dementia. This study will indirectly offer a better understanding of the relationship between functionality in daily living and brain network integrity and how it can be preserved or enhanced through CMI training. The focus is to address the issue of finding an evidence-based intervention for preventing decline in functionality and promoting stabilization of cognitive status among those at increased risk of developing dementia. The specific hypotheses of the study are as follows:

1. The at-risk groups will perform worse than both healthy control groups on the CMI and motor measures at initial assessment.

2. All training groups will show an improvement over time on the nonstandard intervention task.
3. The at-risk training group will demonstrate greater improvement over time on the CMI and motor assessments compared to the at-risk control group.

Methods

Participants

For this study, 23 participants between the ages of 50-71 were recruited from the community via a senior's home called Unionville Home Society and through a volunteer-based program from York University. These participants were placed into an at-risk or healthy training group based on having reported a maternal history of dementia/multiple family members with a diagnosis or reported no family history of dementia. Both groups of participants were age/sex-matched with control groups who did not partake in the intervention but completed the pre- and post-tests five months apart. The at-risk training group was matched with another at-risk group that did not receive training and the healthy training group was matched with a healthy group that also did not receive training. In total there were 10 participants with dementia risk, and 13 without. Participants did not have any cognitive complaints or deficits including a diagnosis of a neurological disorder, severe head injury or the presence of a motor disability which may hinder performance on the tasks that are used for this study. Cognitive status was assessed at baseline and post-intervention to ascertain that a healthy sample was used. This study was approved by the Human Participants Review Sub-Committee of York University's Ethics Review Board.

Measures

Demographic questionnaire.

Participants were given a demographic questionnaire to obtain information about family history of dementia as well as age, sex, ethnicity, level of education, activity level and video-game/tablet

experience (see appendix A). This questionnaire was used to ascertain that participants were eligible to participate based on inclusion/exclusion criteria. Exclusion criteria included health-related factors that could interfere with the study design such as a diagnosis of a neurological disorder, severe head injury or vision/upper limb impairment. Participants also self-reported their experience with a tablet, video-games, puzzles and computers on a likert-type scale ranging from *1 = almost never* to *5 = almost always*. Another survey of self-reported activity levels was included as an assessment of participants' activeness regarding things like "labour work" or "walking for more than 25 minutes" whereby participants indicated on a likert-type scale how often they engage in these activities in a typical week (*0 = never, 5 = 5-7 days per week*)

Dementia Rating Scale-2 (DRS-2; Jurica, Leitten, & Mattis, 2001).

The Dementia Rating Scale-2 is used to assess mental status in those with suspected dementia. The test has five subscales: attention, initiation/perseveration, construction, conceptualization and memory. The entire test is out of 144 and a higher score is indicative of better cognitive health and lack of symptoms of dementia, the overall score is representative of estimated dementia symptom severity. Points are allotted based on whether participants can successfully complete mildly cognitively demanding tasks like repeating back a string of numbers to the experimenter backwards, copying hand movements or drawing simple shapes. The test-retest reliability of the DRS has been established in several studies, in one study, this test was administered twice within one week to 30 participants with Alzheimer's type dementia; the correlation coefficient for the DRS total score was .97. The subscales ranged from .61 to .94 (Coblentz, J. M., Mattis, S., Zingesser, L. H., Kasoff S.S., & Wiśniewski, H.M., 1973). The DRS has demonstrated construct validity with many other cognitive health-based measures. The Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) is a widely used, brief measure of cognitive status. The DRS was compared with the MMSE over a three-year period in a group of patients who were diagnosed with probable AD. These two tests afforded a significant correlation (r = .82), with the DRS showing greater sensitivity to more severe cases of dementia and to

change over time. Further, in a group of 20 patients with organic brain syndromes between the ages of 58-71, high construct validity (r = .75) was demonstrated between the Wechsler Adult Intelligence Scale Full Scale IQ (WAIS; Wechsler, 1944, 1955) test and the DRS (Coblentz et al., 1973). The DRS has also demonstrated internal consistency; the split-half reliability of the DRS was observed with a group of 25 patients who were diagnosed with either senile dementia or organic brain syndrome (Gardner, Oliver-Munoz, Fisher, & Empting, 1981). The split-half reliability coefficient indicated that the test had high internal consistency ($\alpha = .90$), an additional t-test indicated that there were no significant differences between the two halves of the test.

Brain Dysfunction Indicator (BrDI™).

The BrDI™ measure is an indicator of CMI ability that is sensitive to brain network dysfunction. Four conditions of the task were used in total for each participant including direct, feedback reversal (FR), plane change and plane change reversal conditions (see Figure 2). The BrDI™ task was done using a 10.1-inch tablet (ASUS Transformer Book T100 2 in 1 tablet, sampling rate: 60 Hz) situated for use in the vertical plane, with an external Keytec™ touchpad (Keytec Magic Screen: Model KTMT-1315, sampling rate: 100 Hz; Keytec™, Garland, TX, USA; 18 inch) placed directly below, in the horizontal plane. A calibration was done during setup so that the functional area of the Keytec™ matched the dimensions of the tablet. The Keytec™ was only used for conditions that involved a plane dissociation (PD). Participants sat at a table in front of this setup, where they could comfortably reach both apparatuses and were given instructions to move straight to the target as quickly and accurately as possible on all trials.

The standard condition involved a direct interaction with targets on the tablet touchscreen, using the dominant hand. Participants were instructed to keep their finger on the touchscreen for the duration of the task and to move their finger to the centre of the screen. Once the task commenced, a yellow target circle in the centre of the screen appeared (7.5mm in diameter) and participants moved their finger to this location by directly touching the vertical screen. When the software detected the presence

of a finger in the central target, it turned green. After 2000ms a red peripheral target appeared 55mm away from the central target in one of four directions (90° to the top, bottom, left or right of the centre target), eye movements were directed toward the presented target to guide the finger sliding movement on the same screen. This red circle was a cue for participants to begin their finger-sliding movement toward the peripheral target. Once the participant reached the peripheral target and remained there for 500ms, the peripheral target disappeared. Then, after an inter-trial interval of 2000ms, the yellow central home target reappeared, signaling the beginning of the next trial (see Figure 3). Participants completed five trials per target for a total of 20 trials per condition in random order; 80 in total.

During nonstandard conditions, all timing, presentation order and sizes/measurements were unchanged. In the feedback reversal condition, a 180° visual feedback reversal is incorporated into the task meaning that participants were required to move in the opposite direction of the intended target to successfully complete the trial; this introduces a strategic control requirement. The plane change condition involves a plane dissociation between guiding visual stimuli and hand movements. Participants were instructed to look at the targets on the vertical tablet screen, rather than look at their hand moving on the horizontal Keytec™ touchpad below the tablet screen (i.e., gaze and hand movements were spatially dissociated from each other). The plane change reversal condition incorporates both the spatially dissociated planes between eye and hand movements, but also a 180° feedback as well. Each condition was presented in random order between participants. All nonstandard conditions required participants to keep their gaze on the vertical tablet screen throughout the task; these nonstandard conditions require CMI for effective task performance.

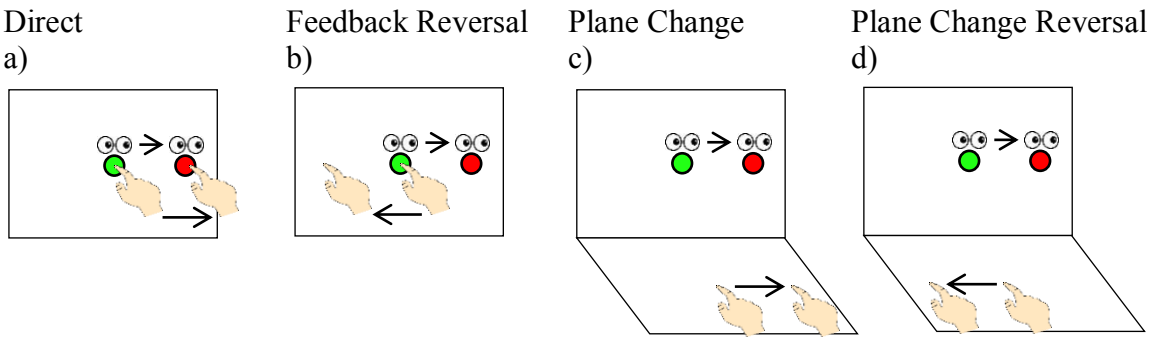

Figure 2. Graphic of the computer-based visuomotor conditions in the BrDI task. The task requires finger-sliding movements on a touchscreen from a central target to one of four peripheral targets. The green circle denotes the center, or home, target in which all movements begin, and the lighter eye and hand symbols denote the starting position for each trial. The red circle represents the peripheral target (which appears randomly to either 90º to top, bottom, left, or right of centre) and the peripheral eye and hand symbols represent the instructed eye/hand movements for the task. a) Direct (standard interaction) condition involves simple finger-sliding movements to peripheral targets with hand and eye movements on the same screen. b) Feedback Reversal (nonstandard interaction) condition incorporates a 180° feedback reversal into the task. c) Plane Change (nonstandard interaction) condition involves a plane dissociation between guiding visual stimuli and hand movements. d) Plane Change Reversal (nonstandard) condition incorporates both the spatially dissociated planes between eye and hand movements, with a 180° feedback reversal as well. All nonstandard tasks described here also require CMI.

Figure 3. Sequence of events during one trial of the BrDI task. The green circle in the centre of box 1 denotes the home target, where all movements begin. This target changes from yellow to green to signify that the software can detect the presence of a participant's finger. After 2000ms a red peripheral target appears in one of four directions (90° to the top, bottom, left or right of the centre target) which signifies the cue for participants to begin their finger-sliding movement toward the peripheral target. Once the participant has reached the peripheral target and remained there for an inter-trial interval of 2000ms, the yellow centre home target reappears, signaling the end of the previous trial and initiation of the following trial.

Each trial was scored using a normalized measure of velocity; with absolute velocity data available as well. The movement was considered initiated once a participant's velocity surpassed 10% of their normalized peak velocity. In the same way, the movement was considered complete once velocity decelerated to lower than 10% of peak velocity within the peripheral target. An image of the entire reach trajectory was available for additional inspection and when necessary, revision of movement onset and offset timing along with the velocity profile data which is analyzed in MATLAB by a program made using custom software. The data are presented on a Cartesian plot which depicts the trajectory of a single finger movement from the centre home target to the peripheral target. Several outcome measures are produced based on the scored data. These measures summarize the profile of the movement based on timing, errors, and execution. After scoring is completed, the data is processed once more to remove outliers beyond two standard deviations from the participant's mean for each outcome measure.

If trials are considered unsuccessful by the data collection software, then they are terminated during the active trial and scored based on the type of error that resulted in termination. Kinematic outcome measures are not computed from these data aside from the type of error that caused trial termination. Trials are terminated if a participant made any of the following mistakes: if the finger does not enter or leaves the home target before the peripheral target appears; if RT is less than 150ms or beyond 8000ms; if total MT exceeds 10,000ms; if participants do not hold their finger in the peripheral target for 500ms. The exception to these error trials are direction reversals (DR) because these data are removed from the correct trials but are still analyzed. A DR occurs when a participant moves more than 90° away from the cued peripheral target upon initiating movement out of the central target.

The kinematic outcome variables used for this study were: MT for the full movement (MTf), RT, absolute error (AE), variable error (VE), peak velocity (PV), and percentage of DR's (%DR). The MTf refers to the time in milliseconds between initial movement acceleration beyond 10% of peak velocity to final deceleration of the full movement going below the 10% threshold of peak velocity

once more in the peripheral target (i.e., after any movement corrections). The RT is scored as the time in milliseconds for movement onset in response to the appearance of a peripheral target. The AE is a measure of the distance of finger end-point position in relation to target location in millimeters, while VE represents the variability of individual finger end-point locations from the average end-point location in millimeters. The PV is the maximum velocity of each finger-sliding movement per trial. Finally, the %DR is calculated as the percentage of trials that begin with a movement from the central target at least 90° in the wrong direction of the desired peripheral target.

This task has been used in asymptomatic adults who were at-risk of developing dementia based on their family history. Discriminant analyses were able to differentiate between those who were at high-risk and those who were not, using this task (FH+: Wilks' Lambda=0.474, $p<0.001$, canonical correlation=0.73; MCI: Wilks' Lambda=0.344, $p<0.001$, canonical correlation=0.81. The grouping of cases also resulted in an overall classification accuracy of 86.4%, with a sensitivity of 81.8% and specificity of 90.9%. Poor CMI performance on BrDI™ has correlated with decreased scores on other measures of cognitive status (i.e., MOCA scores), and as well as with positive family history of dementia (Hawkins & Sergio, 2014). Each condition of the task (i.e., using timing variables) has been able to demonstrate medium-large effect sizes between healthy control and AD groups: $d = 0.74$ for the direct condition, $d = 0.75$ for the feedback reversal condition, $d = 1.2$ for the plane change condition and $d = 0.94$ for the plane change reversal condition (Tippett et al., 2012). These studies suggest that this tool could be helpful for distinguishing between behavioural signs of healthy and pathological aging. At present, this measure is lacking statistical analysis of validation, but recent neuroimaging has supported our hypotheses that the brain areas and networks activated during CMI tasks are reliant on the frontoparietal network in addition to cerebellar and visual areas (Gorbet & Sergio, 2018).

Bimanual Coordination Tasks.

The Bimanual Coordination Tasks (Albines, Granek, Gorbet, & Sergio, 2016) are timed tasks that involve switching between left and right hands to either pick up a lever or move a washer/press a

button in serial order according to the rules of the board used (i.e., washers or buttons; see Figure 4). First, the task was explained and demonstrated until participants indicated that they understood the procedure. The order of the two bimanual coordination tasks was randomized to counterbalance any learning effects. The boards were placed in front of the participants on a table at approximately hip height.

For the Precision board which used washers, there were six equally spaced pegs along the bottom edge of the board closest to the participants where all 12 washers were evenly stacked in pairs (see Figure 4; the brown board on the left). A small washer of 22mm was placed beneath a larger washer of 25mm on each peg before the task began. Towards the middle of the board were two more pegs, both covered by spring-loaded, hinged metal levers. The lever closer to the participant was 18cm from the bottom edge; this lever was lifted by the participant's left hand. The second lever was further from participants, 32cm from the bottom edge of the board and was lifted by the participant's right hand. Start and stop buttons were placed to the left of the pegs for recording participants' task completion time. To begin, participants pressed the start button and lifted the closest lever with their left hand to reveal a peg; next, their right hand quickly moved a washer from the bottom of the board to the peg they just revealed. The next step is to repeat the following step using the opposite hand and alternating positions/movement locations (i.e., participants then lift the furthest lever with their right hand and place a washer on that peg with their left hand). This switching continued until all 12 washers were on the two pegs in the centre of the board and then the participant pressed the stop button.

Similarly, for the whole-hand/Button version of the Bimanual Coordination Task, a board was placed in front of participants on a table at approximately hip height (see Figure 4; the grey board on the right). Much like the washer version of the task, participants were given a start button to track the time to completion but instead of washers there were four buttons. Two buttons were located at the bottom edge of the board closest to the participant, one is red, and one is green. In the centre of the board, with the same distance measurements as the previous task are two hinged metal levers with one

button underneath. The closer lever on the left covered a green button and the more distant lever on the right covered a red button. Once participants pressed the start button, their left hand lifted the lever on the left and then the participant pressed the green button at the bottom of the board and sequentially pressed the corresponding green button that was under the lever. The next step was to lift the farther lever on the right with the right hand and use the left hand to press the red button at the bottom of the board and then the red button under the lever. These alternating movements would continue for a total of 12 repetitions. The dependent variable was the total time to complete the task on the first attempt.

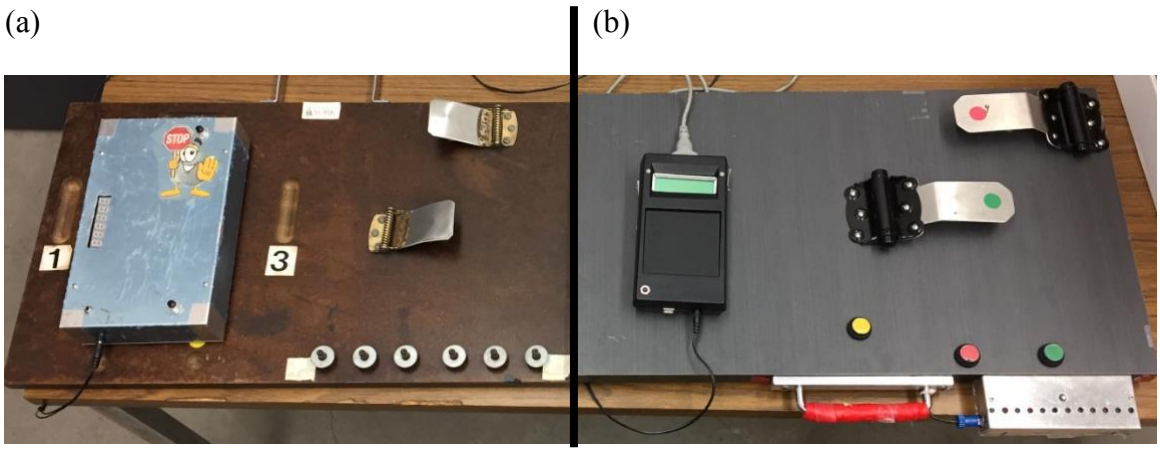

Figure 4. Two Bimanual Coordination Tasks. (a) The Precision Bimanual Task. Participants must move the washers from the pegs at the bottom of the board to the pegs beneath the levers, one at a time and while switching between left and right hands. (b) The Whole-Hand Bimanual Task. Participants must press the yellow start button to begin and then press the green button at the bottom of the board, lift the corresponding lever with the matching green circle using their left hand and press the green button that is underneath with their right hand. Immediately after, the red button at the bottom of the board will be pressed, the corresponding lever marked with a red circle will be lifted by the participants right hand, and the red button underneath will be pressed by the participants left hand. These movement patterns will repeat in this exact order for 12 repetitions.

Fruit Ninja® intervention.

The intervention protocol used a proxy video-game called Fruit Ninja® which was modified to require CMI (see Figure 5). The intervention task has adapted similar CMI principles as per the BrDI assessment task, but the intervention task allows for less structured movements and more cognitive processing/flexibility than BrDI in that there are more dynamic and variable exercises presented. Approximately two weeks after baseline data collection, participants began playing this video-game twice a week for 30 minutes each time, for 16 weeks in total. This visuomotor training game required basic eye-hand coordination to swipe at fruit that appear quickly on the screen; this game was chosen because invoking these types of actions requires the use of frontopartietal networks. This task was done in three different conditions, the first being the direct condition in which participants simply played the game on a tablet placed on the horizontal plane in front of them. The Plane Change condition required participants to cast their screen to a TV or external monitor so that they could look up at the screen in the vertical plane while their hand still moved on the tablet in the horizontal plane, which spatially dissociated their gaze and reach. The third condition required participants to physically turn their tablet upside down while it was casting to incorporate both the plane dissociation and a visual feedback rotation of 180 degrees.

The game also has 2 modes, in the "Zen" version of the game which is used as practice; participants are given 90 seconds to swipe as many moving fruits on their screen as possible. The total number of fruit that are intercepted by the participant's finger is saved and presented at the end of the trial. In the "Classic" mode there is a no-go bomb task which requires additional cognitive processing for inhibiting action, i.e., not touching the bomb while still accurately slicing the fruit. No more than three fruits can be missed or else the game will end, with usually fewer total numbers of fruit intercepted.

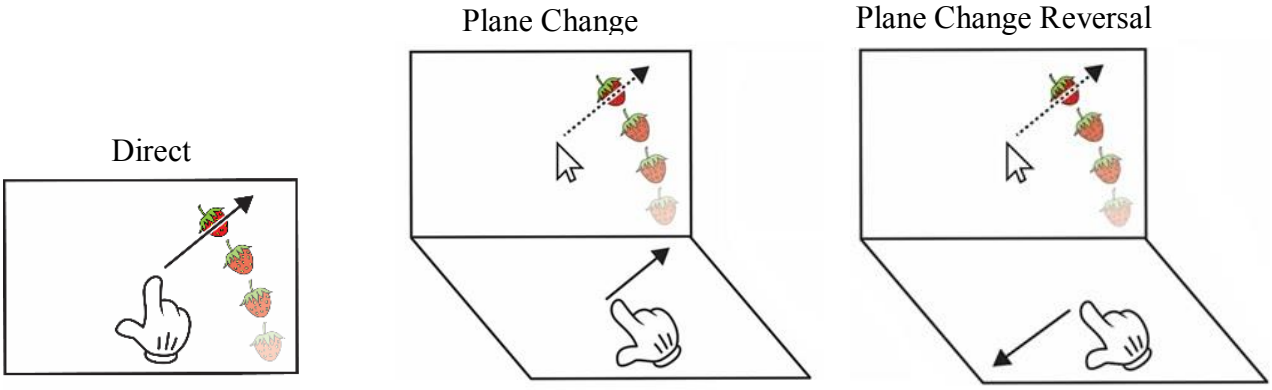

Figure 5. Schematic drawing of the tablet-based video-game intervention. All participants played a practice mode and a no-go inhibition mode across three settings: (1) Direct setting: viewing and movement plane are the same, (2) Plane Change setting: viewing and movement planes are dissociated (i.e. the player watches a vertical monitor while moving their finger on a horizontal screen), and (3) Plane Change Reversal setting: viewing and moving planes are dissociated, and the movement plane is reversed (left=right, up=down).

Procedure

All participants were asked to give written informed consent (see Appendix B) before commencing with the study. The training groups did a 16-week training program in which they played a video-game that required CMI (described above). The video-game assessed participants' ability to quickly slide their finger across a tablet screen toward moving targets with altered visual feedback and/or a dissociated spatial plane between guiding visual stimuli and motor movements. This training was performed for 30 minutes, twice a week, for four months, for a total of 32 sessions. The no-training groups simply did one hour of crosswords/puzzles from home each week. The study was designed as an intervention and thus involved a pre-test battery made up of the aforementioned cognitive, motor, and visuomotor measures followed in one to two weeks by the intervention period and then finished with a post-test battery of all the same measures as the pre-test battery. The test batteries consisted of a neuropsychological test called the Dementia Rating Scale-2 (DRS-2), a CMI touchscreen task called the Brain Dysfunction Indicator (BrDI), two fine-motor Bimanual Coordination tasks, and a questionnaire quantifying relevant variables like activity levels, history of concussion or dementia, and tablet/video-game experience. The pre- and post-test battery was used to assess cognitive processing, motor control and visuomotor ability. Performance in these domains was used to make inferences about whether impairments exist in CMI or in the processing of a single domain.

During training, participants played the Zen version in Direct, Plane Change and Plane Change Reversal conditions, as well as the Classic version in Direct, Plane Change and Plane Change Reversal conditions of the game, three times each per condition. The video-game was played from home, twice a week, by repeating all the previous steps fully. The participants were responsible for writing down their scores on a scoring sheet after each game and emailing them to the experimenter each week. The experimental setup required participants to have access to a tablet, as well as an adapter which connects to an external monitor to project live visuals from the game for the plane change conditions. Participants were instructed how to set up the experiment from home, sent home with the appropriate

equipment and instructions and were also given a demonstration in person about how to setup the equipment. As a proof of principle study, we were interested in seeing if participants could perform the intervention independently from home to provide further evidence for the feasibility and efficacy of this intervention. This method would offer an alternate method for at-home care as an easy to access tool for a busy working-class population.

Design and analyses.

To assess whether there is a difference in CMI ability, fine motor skill and cognitive status from baseline to post-intervention sessions, in at-risk groups compared to healthy groups without training or with training, paired and independent nonparametric tests as well as repeated measures analysis of variance were conducted. The intervention was given to half of the at-risk participants and half of the healthy participants to observe changes over time in any of the previously mentioned domains due to the intervention as compared to the healthy controls and those who did not receive training.

Due to the low sample size, non-parametric tests were computed to assess most dependent variables; however, a large amount of the data did not violate tests of equal variances or normality. In cases where the majority of the data, or data of interest did not violate normality or equality of variance tests, repeated measures ANOVAs were performed to follow-up in assessing any preliminary trends. If all dependent variables for a particular measure passed tests of normality and equality of variances, then repeated measures ANOVAs were performed on each dependent variable as stand-alone tests. Since the omnibus tests were not the main interest based on the hypotheses, post-hoc comparisons were assessed for all outcomes variables even if omnibus tests were not significant. The pairwise comparisons of particular interest were between the at-risk training participants and their no-training counterparts at baseline and post-intervention. To assess video-game score changes in Fruit Ninja® during training, data were grouped into 4 blocks corresponding to the average scores of each month of training and a repeated measures ANOVA was used to assess the progression of scores over time. The within-subject variable was the training month, while group was used as the between-subject variable.

The statistical analysis of data was done using SPSS statistical software (SPSS 24, IBM). The rejection level for all analyses were set at $p = 0.05$.

Overall Timing and End Point Error composite variables were created based on their respective outcome variables obtained during the CMI task. To create the timing composite variable, z-scores based on the mean of both healthy control groups were used; these combined reaction time, full movement time and peak velocity. The value for peak velocity was inversed so that all negative values on each timing variable corresponded to better performance. The same procedure was used to make an end point error score that was based on absolute error and variable error z-scores for the CMI task.

Internal consistency was assessed using Cronbach's alphas for the z-scores that comprised the timing and end point error composites to ascertain that the appropriate kinematic outcome measures were effectively combined to create a score that was similarly as meaningful as measuring each variable separately (see Table 1). The Cronbach's alpha for the totaled average timing and end point error composites of 0.724 and 0.789 respectively, indicates an acceptable level of internal consistency for both composites.

Table 1 *Cronbach's alphas for each condition of the BrDI task at baseline and post-intervention.*

	Direct condition	Feedback Reversal condition	Plane Change condition	Plane Change Reversal condition
Timing composite: Baseline	0.805	0.746	0.708	0.713
Timing composite: Post-Intervention	0.761	0.607	0.757	0.702
End Point Error composite: Baseline	0.762	0.671	0.928	0.904
End Point Error composite: Post-Intervention	0.836	0.563	0.773	0.877

Results

Demographic Characteristics

Participants were mostly female (female: 18, male: 5), and Caucasian (74%), with an average age of 62.2 years (SD = 6.6) and with an average of 16.4 years of formal education (SD = 1.8); see Table 1. Generally, outcome measure performance was the same between males and females. However, sex differences could not be tested in all groups due to a lack of power (i.e., sample size was small, and some groups had no males). A one-way ANOVA with group as the factor and age as the dependent variable, indicated that there was no significant differences in age in each group ($F(3, 21) = 1.234$, $p = 0.326$). There were no effects of group on baseline cognitive test scores ($F(3, 21) = 0.603$, $p = 0.621$) or on the bimanual coordination washers ($F(3, 17) = 0.652$, $p = 0.595$ or buttons ($F(3, 17) = 0.384$, $p = 0.766$) tasks.

Table 2 *Demographic characteristics for all groups.*

Variable	At-Risk Training (n = 5)	Healthy Training (n = 6)	Healthy No - Training (n = 7)	At-Risk No - Training (n = 5)	Overall (n = 23)
Sex: *Female n* (%)	4 (80%)	6 (100%)	6 (86%)	2 (40%)	18 (78%)
Ethnicity: *Caucasian n* (%)	5 (100%)	6 (100%)	3 (43%)	3 (60%)	17 (74%)
Age *mean (SD)*	62.4 (5.1)	64 (7.8)	65.9 (6.0)	59.8 (7.3)	62.9 (6.6)
Years of Education *mean (SD)*	17 (1.6)	14 (1.5)	15.8 (1.8)	19.2 (2.3)	16.4 (1.8)

Where appropriate, data is expressed as means and standard deviations.

Progression During the Intervention Program

After affirmation of normality in all conditions, multivariate repeated-measures ANOVAs were used to assess the progression of training scores across the four months of training for at-risk and healthy training groups, according to each training condition. The within-subject variable was the training month, while group was used as the between-subject variable. The repeated-measures ANOVA indicated that there was no main effect of group, meaning that both groups had a similar pattern of training score progression overall. In the Zen mode of the training game, there was a significant effect for training month ($F(3, 27) = 4.623$, $p = 0.010$, $\eta_p^2 = 0.339$) but no significant month by group interaction ($F(3, 27) = 0.279$, $p = 0.840$, $\eta_p^2 = 0.030$), and a trend for a significant effect for group in the Direct condition ($F(1,9) = 4.789$, $p = 0.056$, $\eta_p^2 = 0.348$; see Figure 6). Sidak post-hoc comparisons of training month progression indicated that there were no significant differences in training scores in the Direct Zen condition. There were no significant changes in training scores in the Plane Change Zen condition (See Figure 7). There was, however, a significant effect for training month ($F(3, 27) = 4.135$, $p = 0.016$. $\eta_p^2 = 0.315$) in the Plane Change Reversal condition (See Figure 8). Post-hoc comparisons of training month progression in the Plane Change Reversal Zen condition indicated that there were no significant differences in any months of training.

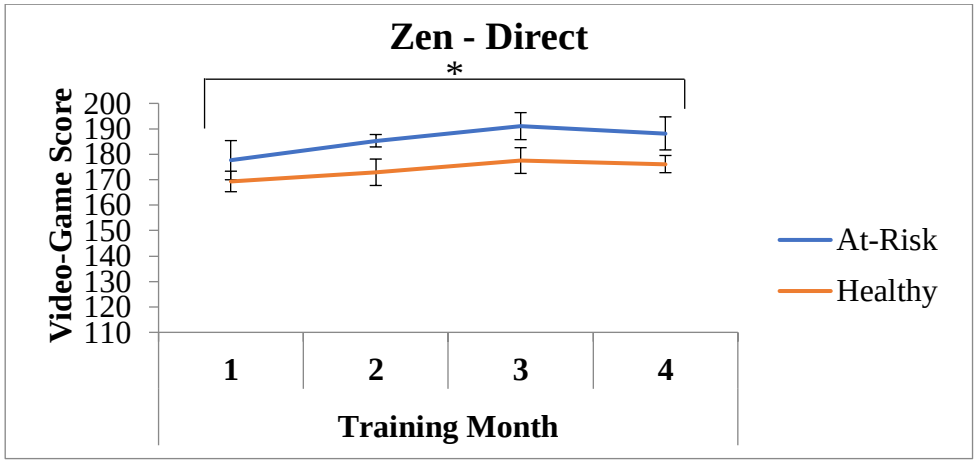

Figure 6. Average monthly performance on the video-game training program for both groups in the Direct Zen condition. Error bars represent the standard error of the mean (SEM), * = < 0.05.

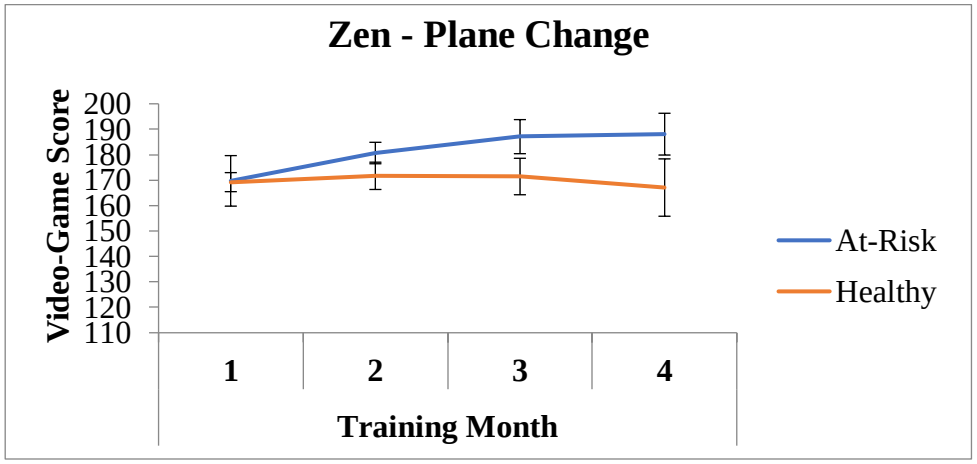

Figure 7. Average monthly performance on the video-game training program for both groups in the Plane Change Zen condition. Error bars represent standard error of the mean (SEM), * = < 0.05.

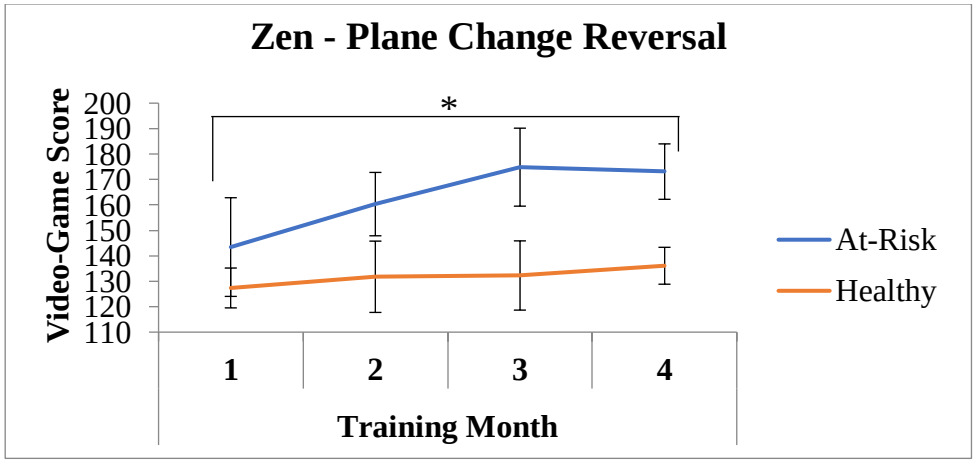

Figure 8. Average monthly performance on the video-game training program for both groups in the Plane Change Reversal Zen condition. Error bars represent standard error of the mean (SEM), * = < 0.05.

In the Classic mode of the training game (requiring inhibition of responses at random times), there was a significant effect of training month ($F(3, 27)$, = 13.742, $p < 0.001$, $\eta_p^2 = 0.604$) and a significant month by group interaction ($F(3, 27) = 6.789$, $p = 0.005$, $\eta_p^2 = 0.430$), but no main effect for group in the Direct condition (See Figure 9). Sidak post-hoc comparisons of training month progression in the Direct Classic condition indicated that there was a significant improvement in training scores from month one ($M = 66.3$, $SEM = 8.6$) to two ($M = 81.6$, $SEM = 10.1$; $p = 0.014$), from month one to three ($M = 95$, $SEM = 10$; $p = 0.004$), and from month one to four ($M = 97.7$, $SEM = 11.3$; $p = 0.007$). The post-hoc comparison of month by group interactions indicated that there were significant differences between month one ($M = 77.7$, $SEM = 11.6$) to two ($M = 96.4$, $SEM = 13.6$; $p = 0.026$) for the healthy training group and between month one ($M = 54.8$, $SEM = 12.7$) to three ($M = 88$, $SEM = 14.8$; $p = 0.021$), one to four ($M = 105.8$, $SEM = 16.7$; $p = 0.004$) and month two to four ($p = 0.002$) in the at-risk group on the Direct Classic condition. In the Plane Change condition (See Figure 10), there was only a significant effect of training month ($F(3, 27) = 4.454$, $p = 0.011$, $\eta_p^2 = 0.331$). Post-hoc comparisons of training month progression in the Plane Change Classic condition indicated that there were no significant differences in training scores in any month of training. In the Plane Change Reversal condition (See Figure 11), there was also only an effect of training month ($F(3, 27) = 7.559$, $p = 0.001$). Post-hoc comparisons of training month progression in the Plane Change Reversal Classic condition indicated that there were no significant differences in any specific months of training. Overall, both groups showed a significant improvement across the four months of training in five of the six conditions, with a relatively similar progression pattern.

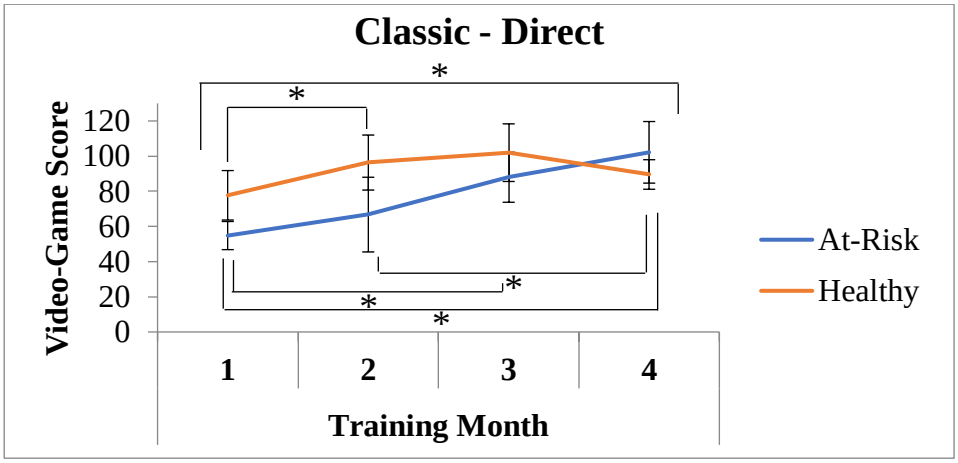

Figure 9. Average monthly performance on the video-game training program for both groups in the Direct Classic condition. Error bars represent standard error of the mean (SEM), * = < 0.05.

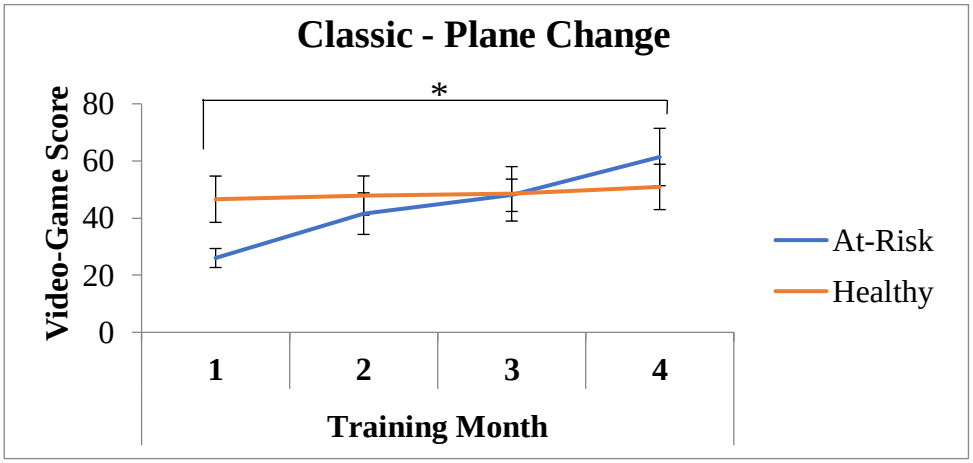

Figure 10. Average monthly performance on the video-game training program for both groups in the Plane Change Classic condition. Error bars represent standard error of the mean (SEM), * = < 0.05.

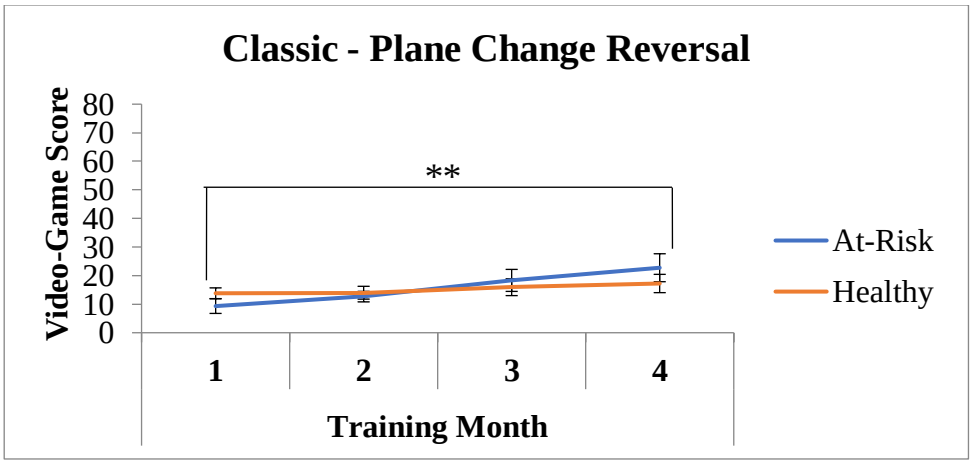

Figure 11. Average monthly performance on the video-game training program for both groups in the Plane Change Reversal Classic condition. Error bars represent standard error of the mean (SEM), * = < 0.05, ** = < 0.01.

Effects of the Intervention on Neurocognitive Test Scores

Since the distribution of neurocognitive test scores violated the assumptions of normality according to the Shapiro-Wilk test of normality at baseline ($W(17) = 0.744$, $p < 0.001$) and post-intervention ($W(17) = 0.600$, $p < 0.001$), related-samples non-parametric tests were used. A Related-Samples Wilcoxon Signed Rank Test indicated that there were no significant differences from baseline to post-intervention in neurocognitive scores in the at-risk training group ($Z = -1.000$, $p = 0.317$), in the healthy training group ($Z = -1.841$, $p = 0.066$), the healthy no-training group ($Z = -1.342$, $p = 0.180$) or the at-risk no-training group ($Z = -1.000$, $p = 0.317$, see Fig. 12). Given that all participants were cognitively healthy to begin with, this finding was not unexpected.

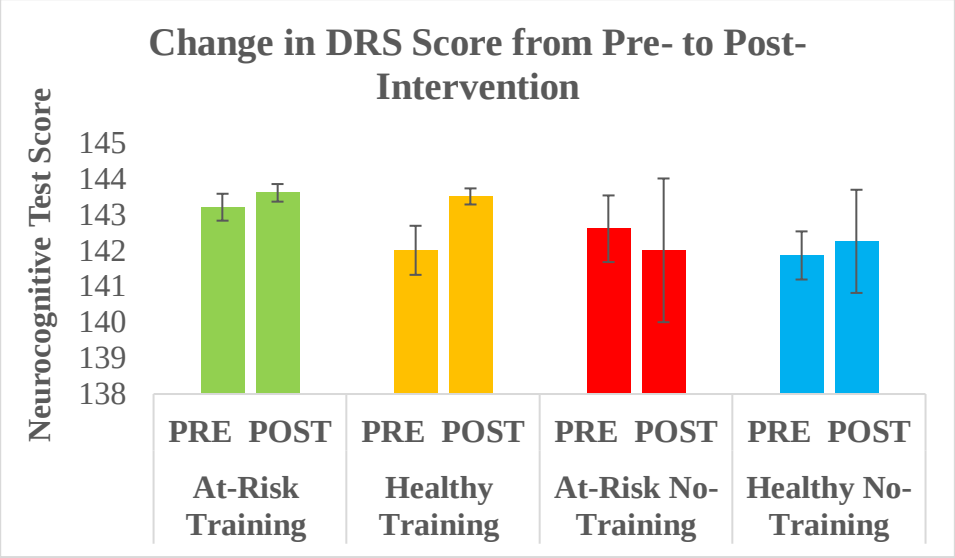

Figure 12. Change in neurocognitive test scores on the Dementia Rating Scale II from baseline to the post-intervention period across each group. Error bars represent standard error of the mean (SEM).

Effects of the Intervention on Fine-Motor Bimanual Tasks

Shapiro-Wilk tests of normality indicated that the sample distribution was normal for the Bimanual Washers task both at baseline ($W(13) = 0.911$, $p = 0.191$) and post-intervention ($W(13) = 0.984$, $p = 0.993$) after exclusion of one outlier; see Figure 13. These were confirmed by the Box's test ($p = 0.990$) and Levene's Tests Equality of Error Variances was also checked for Bimanual Washers at baseline ($F(3, 9) = 0.398$, $p = 0.758$) and post-intervention ($F(3, 9) = 0.209$, $p = 0.888$). Despite the small sample sizes at baseline and post-intervention, ANOVAs were used since no tests of normality nor equality of error variances were violated. A univariate repeated measures ANOVA indicated that there was a significant effect of time point on the Bimanual Coordination Washers task ($F(1, 9) = 13.451$, $p = 0.005$, $\eta_p^2 = 0.599$; Fig. 13). There was no time point by group interaction ($F(3, 9) = 0.668$, $p = 0.593$, $\eta_p^2 = 0.182$) and no significant effect of group on this task ($F(3, 9) = 1.212$, $p = 0.360$, $\eta_p^2 = 0.288$). LSD post-hoc tests indicated that there was a significant improvement overall ($p = 0.005$) from baseline ($M = 25.65$ s, SEM = 1.018) to post-intervention ($M = 23.65$ s, SEM = 0.679). Despite the lack of a significant group by timepoint interaction, LSD post-hoc tests indicated that the at-risk training group significantly improved ($p = 0.006$) from baseline ($M = 27.6$ s, SEM = 1.558) to post-intervention ($M = 24.6$ s, SEM = 1.039). Notably we observed no change in performance across time in untrained groups which suggests that the lack of significant group differences may be due to the lack of power.

A Shapiro-Wilk test of normality indicated that the sample distribution was normal for the Bimanual Coordination Buttons task both at baseline ($W(12) = 0.9112$, $p = 0.228$) and post-intervention ($W(12) = 0.885$, $p = 0.103$) after exclusion of two outliers; see Figure 14. These were confirmed by the Box's test ($p = 0.158$); Levene's Test for Equality of Error Variance was nonsignificant for Bimanual Buttons at baseline ($F(3, 8) = 1.736$, $p = 0.237$) and post-intervention ($F(3, 8) = 1.641$, $p = 0.256$). Additionally, based on a univariate repeated measures ANOVA, there were no significant effects of time point ($F(1, 8) = 0.340$, $p = 0.576$), or group ($F(3, 8) = 0.355$, $p = 0.787$), and no time point by group interaction ($F(3, 8) = 1.847$, $p = 0.217$) for the bimanual button task.

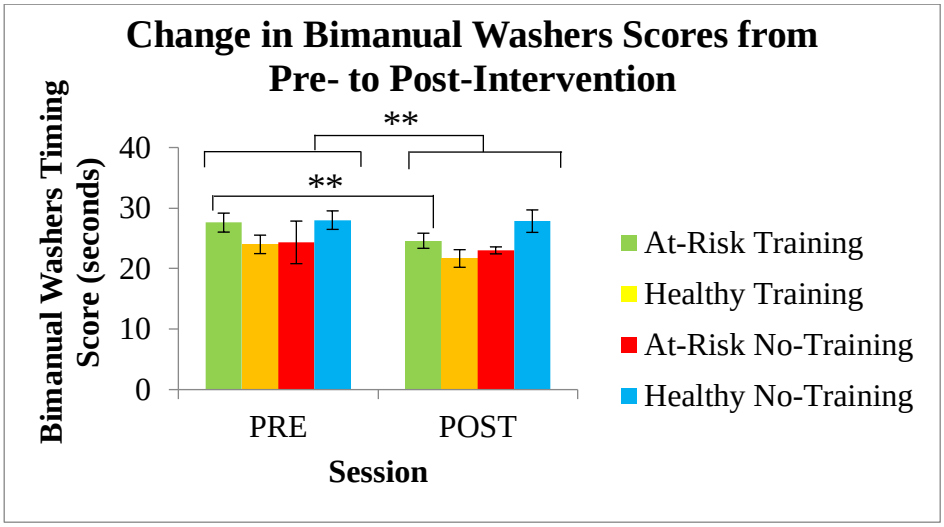

Figure 13. Change in Bimanual Coordination Timing scores on the Washers task from baseline to the post-intervention period across each group. Error bars represent standard error of the mean (SEM), * = < 0.05, ** = < 0.01.

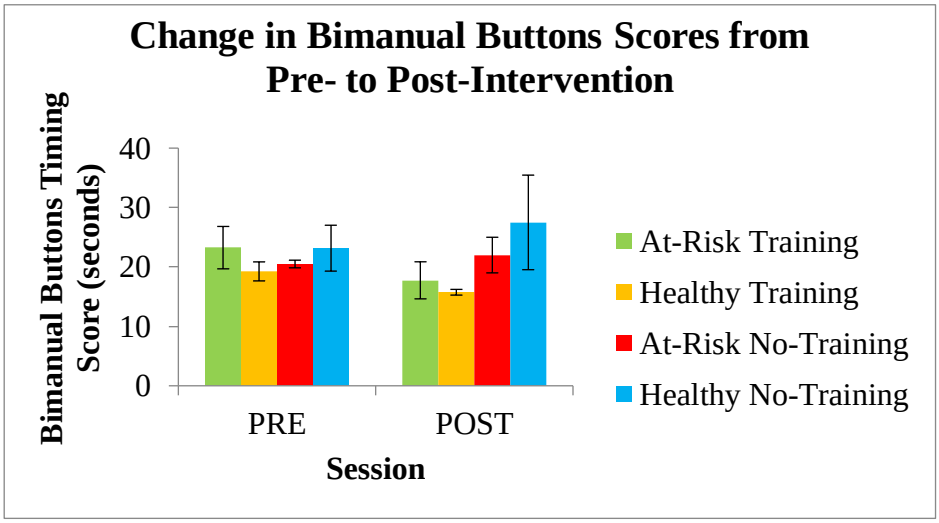

Figure 14. Change in Bimanual Coordination Timing scores on the Buttons task from baseline to the post-intervention period across each group. Error bars represent standard error of the mean (SEM).

Effects of the Intervention on outcome measures of the Cognitive-Motor Integration Task

Generally, we observed some behavioural changes across groups in their ability to follow cognitive rules while executing movements after 16-weeks of rule-based visuomotor training. Figure 15 demonstrates examples of both healthy and at-risk sample trajectories after the intervention period. A noticeable difference in overall trajectory can be seen across groups, especially in the at-risk no-training group; this participant had quite large trajectory deviations compared to the other healthy or trained groups, after an equivalent passing of time. The at-risk participant that received training appears to be performing at a similar level of ability as the healthy participants. Specific indicators of performance ability based on the percentage of direction reversals, overall timing composites, and end point error composites will be discussed further below.

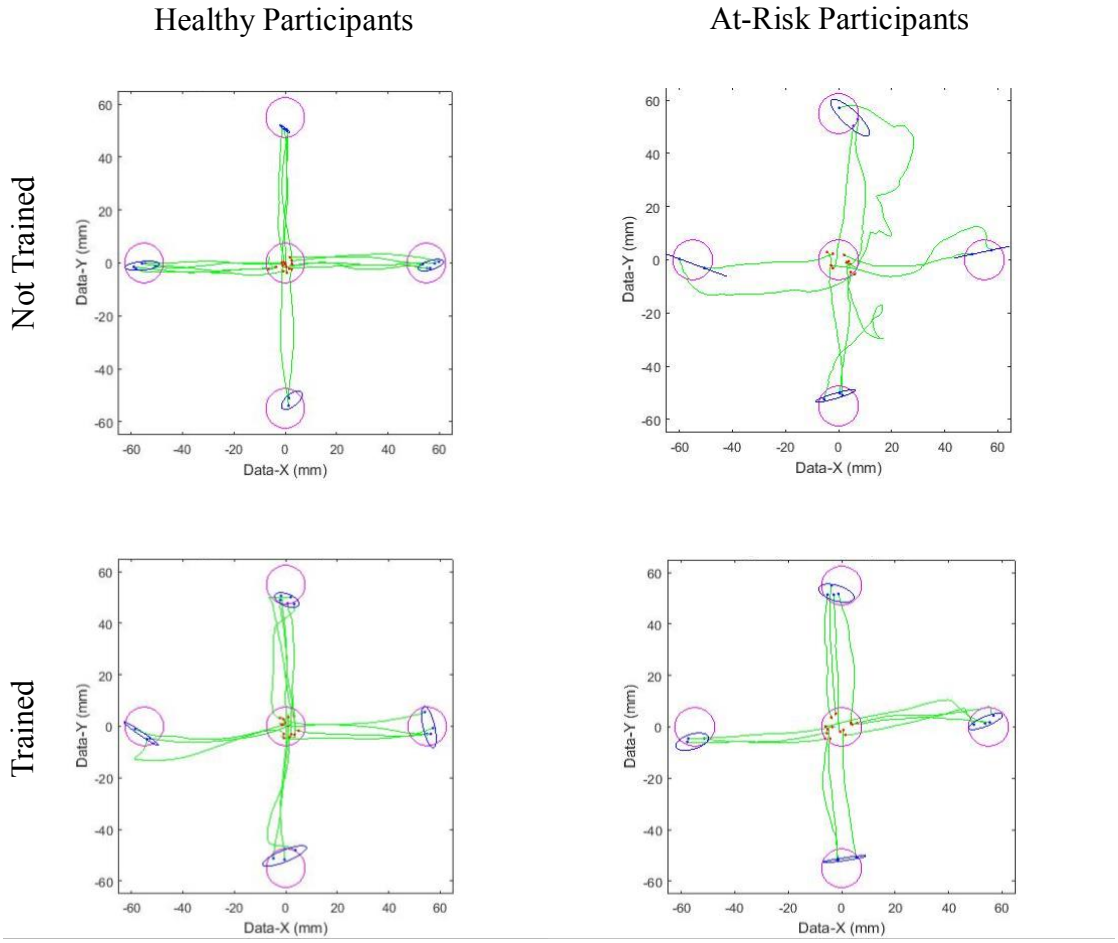

Figure 15. Sample hand movement trajectories from a participant in each group at post-intervention, as measured by the Plane Change Reversal condition of the BrDI task. This is the most challenging condition which involves two levels of dissociation at once. Hand trajectories began at the central target (the red dots in the central circle) and move towards one of the four peripheral targets. Each green line represents a single movement trajectory; the blue ellipses denote the 95% confidence interval for the final end point of the finger movements (the blue dots in the peripheral circles). These data provide an indication of overall cognitive-motor integration performance.

Change in direction reversals based on training.

The longitudinal effects of training or no-training on direction reversals were analyzed with related-samples non-parametric tests since the sample distribution violated assumptions of normality according to Shapiro-Wilk's test of normality, across most conditions; see Figure 16. The Related-Samples Wilcoxon Signed Rank Test indicated that there was no change in the percentage of direction reversals from baseline to post-intervention on the Direct condition in at-risk training ($Z < 0.001$, $p = 1.000$), healthy training ($Z = -1.000$, p = 0.317), healthy no-training ($Z < 0.001$, $p = 1.000$), or at-risk no-training ($Z < 0.001$, $p = 1.000$); in the Feedback Reversal condition in at-risk training ($Z = -1.342$, $p = 0.180$), healthy training ($Z = -1.483$, $p = 0.138$), healthy no-training ($Z = -1.604$, $p = 0.109$, or at-risk no-training ($Z < 0.001$, $p = 1.000$); on the Plane Change condition in at-risk training ($Z = -0.447$, $p = 0.665$), healthy training ($Z = -1.069$, $p = 0.285$), healthy no-training ($Z = -1.000$, $p = 0.317$), or at-risk no-training ($Z = -1.000$, $p = 0.317$); nor on the Plane Change Reversal condition in at-risk training ($Z = -0.730$, $p = 0.465$), healthy training ($Z = -0.338$, $p = 0.735$), healthy no-training ($Z = -0.365$, $p = 0.715$), or at-risk no-training ($Z = -0.447$, $p = 0.655$).

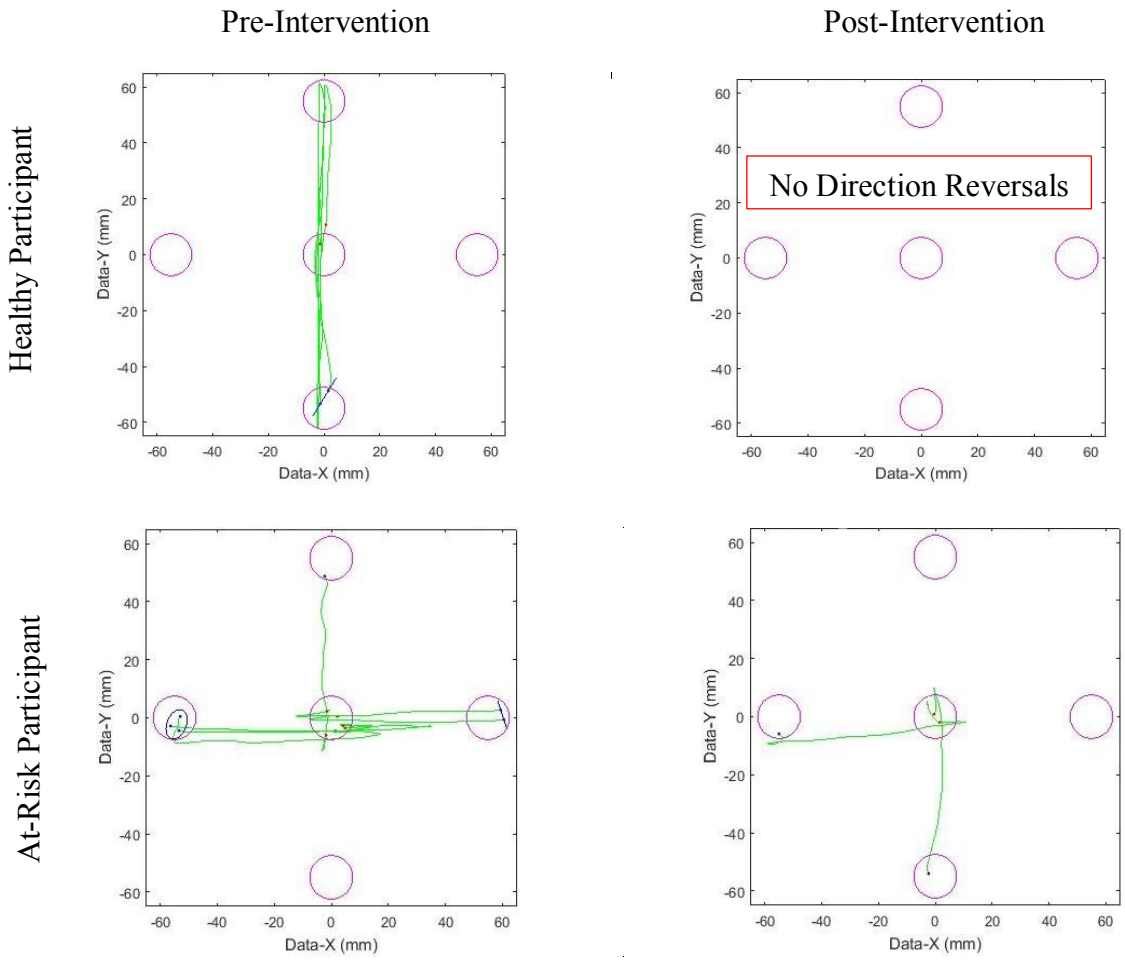

Figure 16. Sample trajectories of direction reversals from a participant in the at-risk training group and a healthy control participant. These images indicate improvement/reduction in the number of direction reversal errors from baseline (left images: 6 errors for the at-risk participant and 2 for the healthy participant) to post-intervention (right images: 2 direction reversal errors for the at-risk participant and 0 for the healthy participant) during the BrDI task in the Plane Change Reversal condition. This condition involves two levels of dissociation; and since it is performed upside down and backwards, participants may be more likely to make a directional error upon movement execution in this condition.

Change in timing composite scores based on training.

Since most individuals with MCI or dementia are still able to perform tasks with only one level of dissociation and the present study recruited healthy adults, we did not expect differences in performance on conditions with less than two levels of dissociation. Therefore, we only examined variability analyses and post-hoc comparisons if significance was found in the Plane Change Reversal condition. According to the Shapiro-Wilk tests of normality, seven of the eight timing composite score variables had a normal distribution: Direct condition at baseline ($W(17) = 0.968$, $p = 0.786$) and post-intervention ($W(17) = 0.949$, $p = 0.446$); Feedback Reversal condition at baseline ($W(17) = 0.981$, $p = 0.969$) and post-intervention ($W(17) = 0.912$, $p = 0.106$); Plane Change condition at baseline ($W(17) = 0.936$, $p = 0.277$) and post-intervention ($W(17) = 0.963$, $p = 0.683$); Plane Change Reversal condition at baseline ($W(17) = 0.964$, $p = 0.699$) and post-intervention ($W(17) = 0.852$, $p = 0.012$).

Additionally, according to Levene's Test of Equality of Error Variance, six of the eight dependent variables had equal error variances: Direct condition at baseline ($F(3, 13) = 10.797$, $p = 0.001$) and post-intervention ($F(3, 13) = 2.444$, $p = 0.111$); the Feedback Reversal condition at baseline ($F(3, 13) = 0.656$, $p = 0.594$) and post-intervention ($F(3, 13) = 3.653$, $p = 0.042$); the Plane Change condition at baseline ($F(3, 13) = 0.521$, $p = 0.675$) and post-intervention ($F(3, 13) = 2.752$, $p = 0.085$); the Plane Change Reversal condition at baseline ($F(3, 13) = 1.078$, $p = 0.393$) and post-intervention ($F(3, 13) = 2.316$, $p = 0.124$). With a lack of significance from the Levene's test on the Plane Change Reversal condition, more in-depth analyses of pre- to post-test variability were not performed on composite timing scores.

Since this pilot study was lacking in sample size, the longitudinal effects of training or not on timing and error composites across all groups were analyzed first with non-parametric tests and then were followed-up with multivariate repeated measures ANOVAs to investigate patterns further. Time point was the within-subject factor, and group was the between-subject factor. A Related-Samples Wilcoxon Signed Rank Test was performed to observe each group on all 4 conditions for any change in

timing composites from pre- to post-intervention; none of which were significant. An independent samples Kruskal-Wallis H Test was used to assess median differences between groups over time on each condition of this task. There were no significant differences in performance between any groups at baseline or post-intervention for any condition (see Figure 17).

According to the multivariate repeated measures ANOVA, there were no significant differences in timing composites from pre- to post-intervention in the Direct condition ($F(1, 13) = 1.174$, $p = 0.298$, $\eta_p^2 = 0.083$), the Feedback Reversal condition ($F(1, 13) = 0.401$, $p = 0.538$, $\eta_p^2 = 0.030$), the Plane Change condition ($F(1, 13) = 0.069$, $p = 0.798$, $\eta_p^2 = 0.005$) or the Plane Change Reversal condition ($F(1, 13) = 0.450$, $p = 0.514$, $\eta_p^2 = 0.033$). There were also no time point by group interactions from pre- to post-intervention in the Direct condition ($F(3, 13) = 1.911$, $p = 0.178$, $\eta_p^2 = 0.306$), the Feedback Reversal condition ($F(3, 13) = 1.329$, $p = 0.308$, $\eta_p^2 = 0.235$), the Plane Change condition ($F(3, 13) = 0.829$, $p = 0.501$, $\eta_p^2 = 0.161$), or the Plane Change Reversal condition ($F(3, 13) = 0.994$, $p = 0.426$, $\eta_p^2 = 0.187$). Finally, there were no effects of group in the Direct condition ($F(3, 13) = 0.262$, $p = 0.852$, $\eta_p^2 = 0.057$), the Feedback Reversal condition ($F(3, 13) = 1.599$, $p = 0.238$, $\eta_p^2 = 0.270$), the Plane Change condition ($F(3, 13) = 0.908$, $p = 0.464$, $\eta_p^2 = 0.173$), or the Plane Change Reversal condition ($F(3, 13) = 2.094$, $p = 0.150$, $\eta_p^2 = 0.326$).

Although there was no significant time point by group interactions in any condition, LSD post-hoc comparisons suggest that there was a significant difference in timing composites on the Plane Change Reversal condition at post-intervention between the at-risk training group ($M = -4.401$, $SEM = 1.480$) and the at-risk no-training group ($M = 1.775$, $SEM = 2.340$; $p = 0.044$); and also, between the at-risk training group and the healthy no-training group ($M = 0.591$ $SEM = 1.655$; $p = 0.043$); the at-risk training group was significantly fastest. These significant post-hoc tests suggest an underlying time point by group interaction for timing composites; however, power was lacking for statistical demonstration of effects.

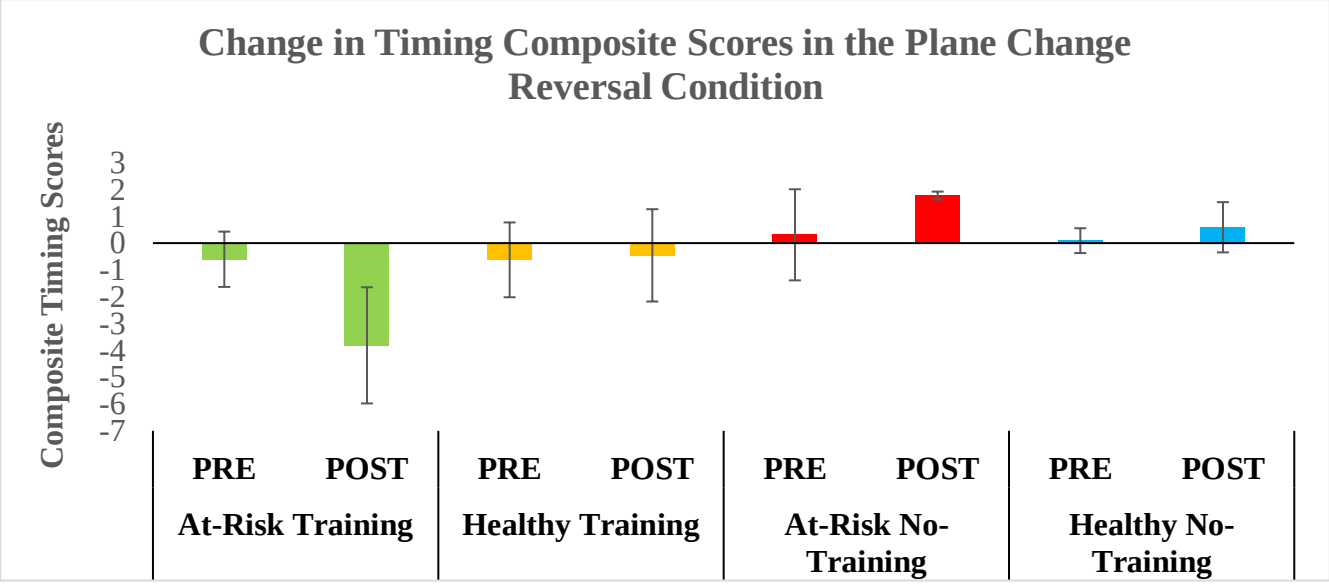

Figure 17. Change in the timing composite scores during the BrDI task on the Plane Change Reversal condition from baseline to the post-intervention period across each group. A negative composite score indicates better (i.e., faster) performance. Error bars represent standard error of the mean (SEM).

Change in end point error composite scores based on training.

According to the Shapiro-Wilk tests of normality, six of the eight end point error composite score variables had a normal distribution: Direct condition at baseline ($W(17) = 0.901$, $p = 0.072$) and post-intervention ($W(17) = 0.951$, $p = 0.481$); the Feedback Reversal condition at baseline ($W(17) = 0.911$, $p = 0.104$) and post-intervention ($W(17) = 0.947$, $p = 0.434$); the Plane Change condition at baseline ($W(17) = 0.923$, $p = 0.166$) and post-intervention ($W(17) = 0.946$, $p = 0.398$); the Plane Change Reversal condition at baseline ($W(17) = 0.799$, $p = 0.002$) and post-intervention ($W(17) = 0.672$, $p < 0.001$).

Additionally, according to Levene's Test of Equality of Error Variance, five of the eight dependent variables had equal error variances: Direct condition at baseline ($F(3, 13) = 1.211$, $p = 0.345$) and post-intervention ($F(3, 13) = 1.077$, $p = 0.393$); the Feedback Reversal condition at baseline ($F(3, 13) = 4.437$, $p = 0.023$) and post-intervention ($F(3, 13) = 2.331$, $p = 0.122$); the Plane Change condition at baseline ($F(3, 13) = 6.450$, $p = 0.007$) and post-intervention ($F(3, 13) = 0.967$, $p = 0.438$); the Plane Change Reversal condition at baseline ($F(3, 13) = 3.241$, $p = 0.057$) and post-intervention ($F(3, 13) = 5.966$, $p = 0.009$).

Since there was a significant difference on the condition of interest (i.e., Plane Change Reversal) variance at post-intervention between groups, this condition was explored further with additional Levene's tests. A univariate ANOVA with performance on the Plane Change Reversal condition among all groups as the dependent variable and pre- and post- combined with group as the between subjects factor was conducted, output from the Levene's test indicated that there was a significant difference in variance between baseline and post-intervention overall ($F(8, 34) = 3.448$, $p = 0.007$). To explore this further, additional univariate ANOVAs were conducted for each group to assess change in variability from pre- to post-intervention. The resulting Levene's tests indicated that the at-risk training group had a significant reduction in variability ($F(1, 8) = 6.371$, $p = 0.036$) from pre- ($SD = 1.56$) to post-intervention ($SD = 0.48$) while that at-risk no-training group had a significant increase

in variability ($F(1, 5) = 9.218$, $p = 0.029$) from pre- ($SD = 0.62$) to post-intervention ($SD = 2.75$). Variance did not significantly change from pre- to post-intervention in either of the healthy control groups.

A Related-Samples Wilcoxon Signed Rank Test was performed to observe each group on all 4 conditions for any change in median end point error composites from pre- to post-intervention; none of which were significant. An independent samples Kruskal-Wallis H Test was used to assess median differences between groups over time on each condition of this task. There were no significant differences in performance between any groups at baseline or post-intervention for any condition.

According to the multivariate repeated measures ANOVA with end point error composites in each condition as the dependent variable, time point as within-subject variable and group as the between-subject variable, there were no significant differences in end point error composites from pre- to post-intervention in the direct condition ($F(1, 13) = 0.003$, $p = 0.958$, $\eta_p^2 = 0.005$), in the Feedback Reversal condition ($F(1, 13) = 0.219$, $p = 0.648$, $\eta_p^2 = 0.001$), in the Plane Change condition ($F(1, 13) = 0.156$, $p = 0.699$, $\eta_p^2 = 0.016$) or in the Plane Change Reversal condition ($F(1, 13) = 0.368$, $p = 0.554$, $\eta_p^2 = 0.025$). There were also no significant time point by group interactions from pre- to post-intervention in the Direct condition ($F(3, 13) = 2.287$, $p = 0.127$, $\eta_p^2 = 0.347$); the Feedback Reversal condition ($F(3, 13) = 0.135$, $p = 0.937$, $\eta_p^2 = 0.041$); the Plane Change condition ($F(3, 13) = 0.752$, $p = 0.540$, $\eta_p^2 = 0.148$); the Plane Change Reversal condition ($F(3, 13) = 0.510$, $p = 0.682$, $\eta_p^2 = 0.103$). Finally, there were no significant effects of group from pre- to post-intervention in the Direct condition ($F(3, 13) = 0.709$, $p = 0.563$, $\eta_p^2 = 0.142$), in the Feedback Reversal condition ($F(3, 13) = 1.380$ $p = 0.293$, $\eta_p^2 = 0.238$), in the Plane Change condition ($F(3, 13) = 0.720$, $p = 0.558$, $\eta_p^2 = 0.142$), or in the Plane Change Reversal condition ($F(3, 13) = 2.844$, $p = 0.079$, $\eta_p^2 = 0.395$).

Despite non-significant group by time point interactions, LSD post-hoc comparisons indicated a significant difference in end point error scores on the Plane Change Reversal condition at post-intervention, the at-risk training group ($M = -0.621$, $SEM = 0.807$) significantly outperformed the at-

risk no-training group (M = 2.709, SEM = 1.276; p = 0.046); and the healthy training group (M = -0.721, SEM = 0.736) also significantly outperformed the at-risk no-training group (p = 0.037), which actually got worse. Again, these patterns of significance among post-hoc comparisons suggest that with a larger sample size, effects may have been present but with the current sample size, it was not possible to detect these patterns. See Figure 18.

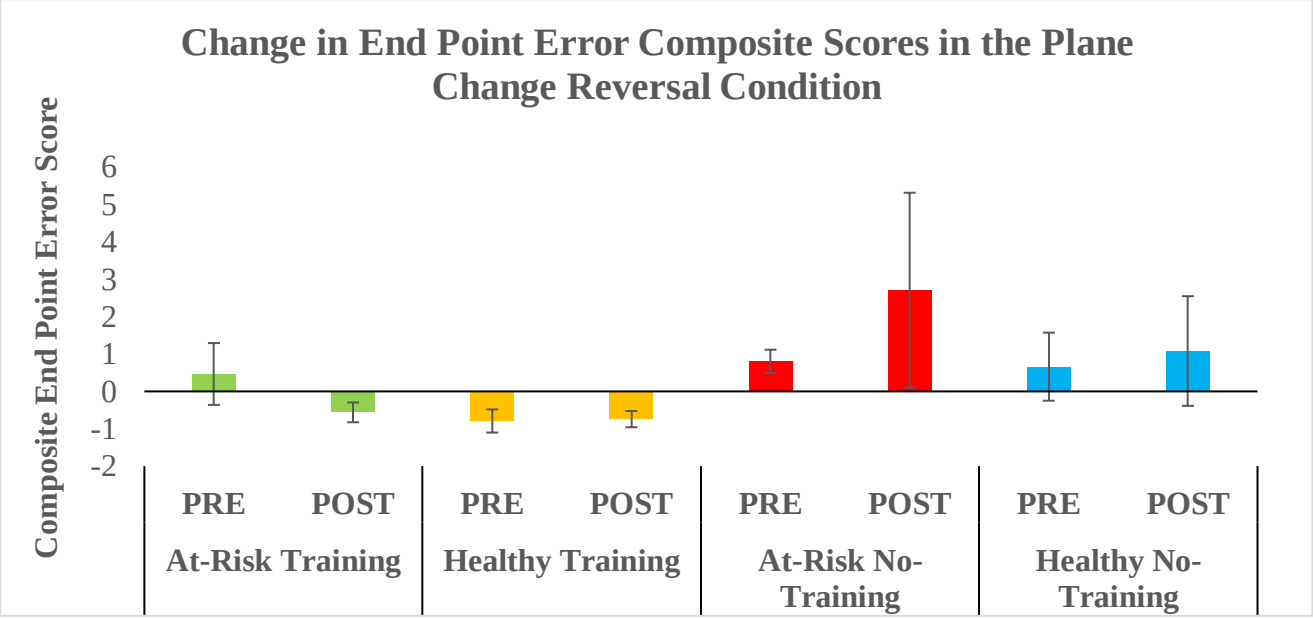

Figure 18. Change in the end point error composite scores during the BrDI task on the Plane Change Reversal condition from baseline to the post-intervention period across each group. A negative composite score indicates better (i.e., more accurate and precise) performance. Error bars represent standard error of the mean (SEM).

Discussion

The goal of this study was to incorporate the study design used by de Boer and colleagues (2018), but in an asymptomatic population with increased risk for developing dementia to strengthen neural processes prior to any potential symptom onset. To this effect, we made minor adjustments to the study design by asking participants to perform the training twice a week instead of once and by adding a measure of motor ability since we showed previously that cognitive status is affected by CMI training and we did not expect to find similar changes in cognitive status in healthy groups; instead we hoped to see some generalizability of the training to motor skill along with improved CMI ability. As a quickly expanding field of literature, objective measures of health status (i.e., like measures of motor skill) are in higher demand since previously, changes in cognition have been the central focus. Cognition can be difficult to assess, especially in at-risk, asymptomatic adults since status may deteriorate after only advanced disease progression and testing of it may be accompanied by biases or error not related to cognitive status (e.g., language barriers, hearing difficulties or poor instructions), and for this reason objective measures are desired. We were particularly interested in knowing if visuomotor training could translate to improved motor skill, as it did to cognitive status in groups with sub-average cognition/MCI in previous work from our lab. Based on the current findings, this study was able to find a translation effect of visuomotor training to improved motor ability on a skill requiring communication between hemispheres.

The specific motor skill of interest was bimanual coordination since performance of this task also incorporates large-scale neural networks (i.e., similar in scale to the associative fibres in the frontoparietal network). This task requires interhemispheric communication reliant on callosal fibres that transmit signals from one side of the brain to the other. We postulate that the findings of generalizability (e.g., visuomotor training translating to improved functional independence and global cognition) from the previous study are attributed to the use of tasks that stimulate large neural networks that are deeply interconnected with various domains and require altered patterns of

neuronal firing. For example, recent neuroimaging research has found that during nonstandard, feedback reversal tasks (i.e., as in the training program) there is greater activation in the right IPL and left superior posterior cerebellum; additionally, based on their roles, activation in the cuneus and medial premotor area suggest that these regions were involved in detecting/differentiating between standard and nonstandard tasks (Gorbet & Sergio, 2016). According to another recent fMRI study and some animal neurophysiology research, most of the same brain areas are activated during plane dissociation tasks as in movements without a plane dissociation (Cisek, 2006; Gorbet & Sergio, 2018). However, PMd cells which have a preferred direction for firing that matches both plane dissociated and non-dissociated targets, are co-activated to fire in alignment to movement toward either target. The non-selected target pathway is then inhibited for the desired movement to occur in these nonstandard interactions (Cisek, 2006). Therefore, with information from these studies combined, the brain areas involved in performing the plane change condition and reversed visual feedback conditions (i.e., tasks that require CMI) have been mapped along the frontoparietal network as expected (in addition to cerebellar and visual areas). Without neuroimaging in the present study, these studies assisted with providing a framework for our hypothesis that the CMI task is engaging large-scale integrative networks and relevant cortical areas for task performance; many of which overlap with AD-vulnerable networks (Jones et al., 2016).

In a similar way, the bimanual coordination tasks involved inhibitory control processes in order to properly sequence the correct movement, and this also involves following cognitive rules via frontal and parietal connections. Previous research has shown that poor CMI ability in at-risk individuals is correlated with WM disruptions in areas that overlap with those involved in bimanually coordinated movements (Hawkins et al., 2015). This overlapping network-based generalizability idea has support from the literature which indicates that brain regions within the frontoparietal network that are also involved with bimanual coordination, show altered activation with more experience and skill acquisition (Haslinger et al., 2004; Jäncke, Shah, & Peters, 2000; Sun, Miller, Rao, & D'Esposito,

2007). This is consistent with the effect that visuomotor training has on this network (Granek, Gorbet, & Sergio, 2010); which has translated to improved functioning in cognitive areas as well (de Boer et al., 2018). Therefore, the present data provide further evidence for the benefits of performing tasks that stimulate large neural networks, particularly the frontoparietal network, for generalizable effects from one domain to another in older/middle-aged adults.

Baseline Motor and CMI Performance in Participants At-Risk for Dementia

The hypothesis that the at-risk groups would perform significantly worse on measures of CMI and motor ability than the healthy groups at baseline, was not supported. None of the groups were significantly different from one another on any measures at baseline testing. The lack of baseline differences between at-risk and not at-risk groups in the present study is contradictory to what we have seen previously in our group's research using a CMI task. In previous work, we have found that females who are at-risk for developing dementia based on their family history, have worse CMI ability that is associated with WM disruption and reduced resting state functional connectivity (Hawkins et al., 2015; Hawkins & Sergio, 2016). One possible reason for this lack of group differences in the present study is that in both at-risk groups combined, the sample was made up of 50 percent males. In more recent, not yet published work, it has been noted that males tend not to express these visuomotor deficits as much as females, or perhaps not as early (Rogojin, Gorbet, Hawkins, & Sergio, n.d.). The combination of males and females together in a small sample may have washed-out this sex-related difference effect (i.e., as opposed to using a sample of only women that may be more likely to show early visuomotor deficits with an at-risk status).

Alternatively, all groups were considered healthy and were not exhibiting any symptoms. They were a normal sample of middle-aged/older adults and perhaps they did not differ across tasks at baseline because they were too young to experience any such symptoms (i.e., if at-risk participants were to express any such early symptoms, perhaps they would still manifest later on, with an even later

expression of MCI). This notion is supported by previous work which suggests that impaired CMI ability is associated with the earliest stages of damage to the brain which starts with decreased connectivity in the posterior node (Hawkins & Sergio, 2016; Jones et al., 2016). The current findings suggest that the participants in this group were not at that level of impairment, but this cross-sectional data does not tell us if they will develop this impairment later, since the CMI task is only sensitive to network dysfunction that is already present. Finally, it is also possible that the at-risk training group was particularly keen, and this may have been a protective factor or performance bias against evidence of decline in this group; or perhaps with a more aware and prevention-tailored lifestyle, these individuals may have had more cognitive reserve. Cognitive reserve would have benefitted participants on each task, since all training and outcome measures incorporated an aspect of cognitive ability. When individuals were contacted via the York University research participant pool, there may have been a bias in that those who were worried about their health based on their family history may also have been more likely to respond. Also, many of the control group members were obtained in a more random fashion; some were workers at a facility for seniors who may have been motivated to participate based on genuine interest in contributing to the scientific literature and to support ongoing research at their facility and with their senior community in the future (i.e., with less reason for concern about their health, the healthy controls may not have been as keen as the at-risk group).

Progression in Video-Game Scores During the Intervention Program

The hypothesis that all groups would show an improvement over time on the intervention task was supported. Mainly, the biggest improvement was seen as a function of time, consistent across groups, rather than any specific differences among groups. Therefore, all groups showed a fairly consistent progression of motor learning across the 16-week training period based on their video-game scores. The literature is supportive of this finding in many regards, since impaired ability to show any motor learning over time would be indicative of a more severe form of impairment, which would have

met the exclusion criteria for the present study. Among the distributed neural networks that are first affected by neurodegenerative disease, those involved in basic motor learning and functional ability tend not to be affected until later stages of the disease (Eslinger & Damasio, 1986; Salek, Anderson, & Sergio, 2011). This study was comprised of healthy older adults with no cognitive or motor symptoms, and thus finding that scores of visuomotor skill on the training task improved significantly over time in all groups was highly anticipated.

Many of the adults in this study indicated that they had little to no previous video-gaming experience; since these training exercises incorporated adaptations to altered motor skills (i.e., changing the plane of movement or moving upside-down to reach the target), we would expect a steeper learning curve earlier on in the program (i.e., faster processes for learning earlier on, and slower processes later for better retention along with skill plateau; Karni et al., 1998; Ruttle, Cressman, 'T Hart, & Henriques, 2016). A similar finding, although less rapid, was noted in the present study when comparing performance from later months back to performance in month one of the program, especially in the at-risk group. Despite the low sample size and lack of significant group differences, some patterns can be noted in our findings. Specifically, the at-risk group tends to show a steeper (i.e., increased) rate of learning as suggested by the video-game scores. With more potential network vulnerability in this group, they would be more likely to have subthreshold visuomotor deficits and thus steeper learning earlier on in their training. Stimulating training early on that leads to enhanced skill may have protective effects against network decline. In a longitudinal motor skill acquisition study, it was shown that at a five year follow up, older adults declined in their ability to perform a motor task that was done at baseline; however, adults that performed similarly to younger cohorts at baseline, showed no such decline in performance at the five-year follow-up (Rodrigue, Kennedy, & Raz, 2005). This prevention of functional decline has similar implications for the type of visuomotor training that was performed in the present study. If training can stave-off symptoms of decline, then perhaps the stimulation of these same networks will have a similar protective effect globally.

Effects of the Intervention Program on CMI and Motor Performance

The hypothesis that the at-risk group would demonstrate greater improvement over time on the measures of CMI and motor ability compared to the at-risk no-training group was partially supported. While all groups seemed to improve slightly over time (i.e., possible practice effects), the at-risk training group was the only group to significantly improve performance from baseline to post-intervention on the Bimanual Washers task. Interestingly, this effect was only found in the Bimanual Washers task and not the Bimanual Buttons task. It is possible that the lack of significant findings for the Buttons task is simply due to the small sample size, but it is also possible that since the Washers task required more complex, fine-motor precision, that higher demand on neural resources and involvement of more brain areas needed to produce such intricate movement, ultimately lead to the division in performance across tasks. Gross motor tasks can distinguish groups with eAD from healthy controls, but typically movements with fine-motor components are required to differentiate individuals with MCI from healthy controls (Kluger, Gianutsos, Golomb, Ferris, George, et al., 1997). This increases the complexity of the task as well as the likelihood for connections with other brain areas that may be affected by visuomotor training. Thus, we speculate that the Bimanual Washers task required more precision and had a more demanding cross-hemispheric motor control component than the Bimanual Buttons task, which in contrast, may have been too simple and resulted in a ceiling effect.

Additionally, there were trends for differences between the at-risk training and at-risk no-training groups on both main outcome measures of CMI. In regard to the timing composite score in the Plane Change Reversal condition, although significance was not present in the omnibus tests, post-hoc comparisons indicated a trend for a significant difference at post-intervention between the at-risk training and at-risk no-training groups and between the at-risk training and healthy no-training groups. The at-risk training group had a faster average speed in both comparisons. Similarly, post-hoc comparisons indicated trends for differences between both training groups and the at-risk no-training group at post-intervention for the end point error scores as well. In this case the at-risk no-training

group demonstrated a lower average end point error score in both comparisons (i.e., poorer accuracy and precision). There were no significant differences between any other groups. There were also no improvements over time, nor differences between groups in their ability to inhibit movements that would result in a direction reversal. Variability in this outcome measure was quite large, and thus a larger sample would have assisted in clarifying these findings. Also, since all groups were healthy, they were not necessarily at the point of demonstrating significant impairment in these domains.

Additionally, the two groups that received training showed a significant reduction in movement variability from pre- to post-intervention on the CMI task while the groups that did not receive training had greater movement variability at post-intervention compared to their baseline. While biological noise is an innate and normal aspect of cellular functioning that promotes heterogeneity and makes each human unique, sometimes having cells in a particular system (i.e., motor systems) fire with less cohesivity may indicate a less optimal and concise conduction of signals that may result in poorer motor performance (Matthews, 1996). With training, cells can adapt by sending signals with improved timing and muscle recruitment. Considering that all groups in the present study were asymptomatic, we may not expect evident behavioural differences to appear on the measures tested, but reduced movement variability instead may be indicative of a reduction in noisy signals (Müller & Sternad, 2004). Therefore, the reduced movement variability across time in the end point error composites for the training groups were positive findings since these suggests that the training program may have improved the efficiency of the coordination of motor planning/execution as a result of less noisy signals.

Together, these findings suggest that there was a difference in the way that the visuomotor training affected the at-risk training group compared to the other control groups. When observing test performance in each domain, it seems that the at-risk group showed the greatest improvement based on the longitudinal training, even though findings did not always reach significance. Some of the adults sampled may be at higher risk than others for developing dementia, but currently symptoms are not

evident; although, they showed some benefit from receiving training which suggests that the vulnerable brain networks that were targeted may have been strengthened with this stimulation. With these optimistic results based on the rule-based visuomotor training, it seems likely that the targeted vulnerable brain networks were stimulated in a beneficial way; future brain imaging studies with pre- and post-training will be needed in order to assess this thoroughly. With the present patterns, it seems likely that these findings would be supported further with a larger sample size. It is also quite possible that with a larger sample, or more females, underlying differences in performance at baseline may become evident. This would be consistent with the literature which indicates that being at-risk alone may predispose individuals to poorer/earlier decline in motor/CMI performance (Buchman & Bennett, 2011; Hawkins et al., 2015).

Limitations and Future Directions

Overall, behavioural evidence from this proof-of-principle study supports previous research which has indicated that cognitive-motor training may be beneficial for generalized improvement of functional ability via increased frontoparietal network integrity. Although the present study was limited by the small sample size and a lack of pre- to post-test neuroimaging, patterns of improvement after 16-weeks of visuomotor training in the at-risk group suggest that we may have indeed stimulated these targeted neural networks in a beneficial way. Thus, future research with this form of intervention should also include structural and functional neuroimaging both before and after the intervention as well as baseline genotyping to assess dementia risk in more depth along with network changes associated with the program. In addition, future studies could improve upon this design by recruiting a larger sample with a balanced age and gender ratio. One important limitation of the current study was that participants were not allocated to their respective groups in randomized order. Participants were assigned to groups based on their family history of AD/dementia, as well as their willingness to complete the training program or not. This may have been confounding to some degree since

participants with a family history of dementia who volunteered for this study may have been particularly keen and more interested in maintaining their overall health and therefore not necessarily representative of the general population. Also, if participants were not fully equipped with the technology at home beyond what the study could provide, then they were placed in the control no-training group; they were still able to receive training if they chose, but only after a delay and with alternative hardware involved.

Conclusions

The findings of this study have numerous therapeutic implications. Firstly, these findings lend support to the literature about the effectiveness and simplicity of using video games as a tool to improve motor functioning. Importantly, this visuomotor training had a generalizable effect on performance for motor skills that were not directly involved in the training program itself. That is, the training program was a unimanual task, but bimanual coordination improved, a skill that required brain network communication via the corpus callosum. Previously, in adults with MCI, training with these video-games translated to improved visuomotor and global cognition as well (de Boer et al., 2018). Since the sample for the current study was healthy and had a healthier cognitive status overall, the present study was only able to extend these results to improved motor ability with the additional finding of reduced movement variability in groups that were trained. This finding is consistent with previous literature suggesting that certain visuomotor abilities may be a more sensitive measure of early decline (i.e., a target for therapeutic intervention) than measures of cognitive status (Buchman & Bennett, 2011; Hawkins et al., 2015). Second, the importance of using tasks that incorporate large-scale neural networks are highlighted by our findings. The interconnectedness of the networks involved in the training task may contribute to the generalizability of effects that we have seen across tasks. Third, motor areas of the brain can offer objective information about brain health given that the process of degradation is a whole-brain process. Some areas are affected earlier than others, but ultimately,

evaluating cognitive status is an important indicator of pathological processes that have already taken place in the brain and evaluating motor ability also has functional relevance. Requiring combined output from both domains at once places more demand on brain resources and may be a more sensitive measure of early indication of decline. The novelty and benefit of a performance-based task like the one used for this study, is that it is quick to administer (i.e., about 15 minutes), portable, computerized, and a biased-reduced assessment tool. Participants did not report any difficulty setting up or using this training task from home for 16-weeks. Hence the feasibility of remotely administering a technology-based solution for maintenance of brain health and potentially the prevention of functional decline is supported by this approach. Overall, the findings of this study contribute to present knowledge about functional decline prevention in individuals facing a neurodegenerative disease.

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APPENDIX A

Questionnaire

Pretest Intake Questionnaire - BrDI Flight study

(The information received will remain confidential)

ID: _____ **Age**: _____ **DOB:** _____

Dominant Hand: LEFT or RIGHT or BOTH **Sex**: Male or Female

Level of Education: _____ **Work Full Time / Part Time / Neither**:_____

Ethnicity: _____ **Occupation**: _____

Sport(s) Played (recreational or competitive):_____

How long did you play your sport(s):_____

1. Do you **currently** have a concussion? (an impact to the head which MAY have resulted in: headaches, loss of consciousness, confusion, amnesia, dizziness, nausea, etc.)

   YES or NO

   a) Date of concussion: _____

   b) Did you lose consciousness? _____ For how long? _____

   c) Please list any current signs and symptoms:

_____

_____

2. Have you **previously** had any concussions (an impact to the head which MAY have resulted in: headaches, loss of consciousness, confusion, amnesia, dizziness, nausea, etc)?

   YES or NO

   a) How many? _____

   b) Did you lose consciousness? _____ For how long? _____

   c) Date(s) and time out before returning to play:

_____

_____

3. Do you smoke? YES or NO

a) Do you smoke: Cigarettes, Cannabis, Both or Other: _____

b) How often do you smoke the above-mentioned substance(s) per day, week or month?

_____

4. Do you **currently** have a non-head related injury? YES or NO

a) Has it kept you from play for longer than 48 hours? YES or NO

b) Has it kept you from play for longer than 3 weeks? YES or NO

5. Have you been diagnosed with any neurological disorders? YES or NO

What disorder? _____

6. Do you have a computer (YES or NO) or a tablet (YES or NO) at home?

How often do you use your computer? (all the time / often / sometimes / rarely / never)

How often do you use your tablet? (all the time / often / sometimes / rarely / never)

7. Do you do puzzles? YES or NO (all the time / often / sometimes / rarely / never)

8. Do you play video games? YES or NO (all the time / often / sometimes / rarely / never)

a) What type of games do you typically play? ACTION (time pressure) or NON-ACTION

b) How would you rate your skill compared to your peers? (Low / Intermediate / High)

9. To your knowledge, does anyone in your family have any form of dementia? YES or NO

a) What is their relationship to you (e.g., mother, father, brother, sister, **maternal** aunt, uncle, grandmother, grandfather, cousin, **paternal** aunt, uncle, grandmother, grandfather, cousin). List all if more than one relative.

_____

_____

THE FOLLOWING IS A LIST OF ACTIVITIES THAT PEOPLE MAY PARTICIPATE IN. PLEASE INDICATE THE FREQUENCY (IN DAYS PER WEEK) THAT YOU TYPICALLY PARTICIPATE IN THESE ACTIVITES.
FOR EACH ITEM CHOOSE FROM ONE OF THE FOLLOWING ALTERNATIVES:

	NEVER	RARELY (1 DAY/ WEEK)	SOMETIMES (2 DAYS/ WEEK)	FAIRLY OFTEN (3-4 DAYS/ WEEK)	VERY OFTEN (5-7 DAYS/ WEEK)
	0	1	2	3	4
1. WATCHING TV OR MOVIES	0	1	2	3	4
2. READING	0	1	2	3	4
3. SOCIALIZING (E.G. PLAYING CARDS, TALKING TO FRIENDS, ETC.)	0	1	2	3	4
4. PLAYING REC SPORTS	0	1	2	3	4
5. PLAYING COMPETITIVE SPORTS	0	1	2	3	4
6. PLAYING VIDEO/ COMPUTER GAMES	0	1	2	3	4
7. WALKING (AT LEAST 25 MINUTES)	0	1	2	3	4
8. LISTENING TO MUSIC	0	1	2	3	4
9. EXERCISING AT A GYM	0	1	2	3	4
10. DOING NON-LABOUR WORK (PAID OR VOLUNTEER)	0	1	2	3	4
11. DOING LABOUR WORK (E.G. LANDSCAPING SHOVELING, PAINTING, ETC. PAID OR VOLUNTEER)	0	1	2	3	4
12. RUNNING/JOGGING	0	1	2	3	4
13. PUZZLES, ARTS & CRAFTS (E.G. KNITTING, CROSSWORDS, ETC.)	0	1	2	3	4

APPENDIX B

INFORMED CONSENT

School of Kinesiology and Health Science, Faculty of Graduate Studies
York University, Toronto, ON Canada

"Cognitive-motor integration training for functional decline prevention in early dementia"

Investigators: Dr. Lauren E. Sergio (Associate Professor), Dr. Diana Gorbet (Research Scientist), Dr. Marc Dalecki, Dr. Casper de Boer, Holly Echlin, Sarah Zaidl (research trainees)

Our research team is working to understand the control processes employed by the brain when interacting with one's environment. The data from this study will benefit you indirectly, by providing us with information about your ability to interact with your environment when the guiding visual stimulus and the required motor action are dissociated from one another. This information will be used to devise an assessment tool of functional eye-hand coordination ability in neurologically healthy adults and neurological patient populations. The research team is headed by Dr. L. Sergio, and the York University Human Participants Review Committee has approved the study. There are no risks involved in the study, which will involve the following procedures:

You will be asked to make simple point-to-point hand movements in order to move a cursor to a target displayed on a computer monitor. We will be recording the position of your finger as you displace the cursor. To obtain these measures, we will ask you to move your finger along a touch sensitive screen. There should be no discomfort or fatigue associated with these procedures.

Your participation in the study is completely voluntary and you may choose to stop participating at any time. If you do not volunteer for the study, this decision will not influence any treatment that you may be receiving, the nature of the ongoing relationship you may have with the researchers or study staff, or the nature of your relationship with York University either now, or in the future.

Your estimated participation time will be between 5 to 20 minutes total for the tasks. You will be given breaks between tasks if you wish. You can stop participating in the study at any time, for any reason. If you decide to stop participating, all associated data collected will be immediately destroyed wherever possible. Your decision to stop participating, or to refuse to answer particular questions, will not affect your relationship with the researchers, York University, or any other group associated with this project.

All information you supply during the research will be held in confidence and unless you specifically indicate your consent, your name will not appear in any report or publication of the research. Your data will be safely stored in a locked facility and only research staff will have access to this information. Confidentiality will be provided to the fullest extent possible by law. The data will be stored securely for 10 years and then destroyed.

If you have questions about the research in general or about your role in the study, please feel free to contact Dr. Sergio either by telephone at [redacted]. This research has been reviewed by the Human Participants in Research Committee, York University's Ethics Review Board and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines. If you have any questions about this process or about your rights as a participant in the study, please contact the Sr. Manager & Policy Advisor for the Office of Research Ethics, 5th Floor, York Research Tower, York University (telephone [redacted] or e-mail [redacted].

INFORMED CONSENT

School of Kinesiology and Health Science, Faculty of Graduate Studies
York University, Toronto, ON Canada

"Cognitive-motor integration training for functional decline prevention in early dementia"

I, _____, consent to participate in "**Cognitive-motor integration training for functional decline prevention in early dementia**" conducted by Dr. Lauren E. Sergio. I understand the nature of this project and wish to participate. I am not waiving any of my legal rights by signing this form. My signature below indicates my consent.

Signature_____ **Date**_____

Signature_____ **Date**_____
Principal Investigator