THE FEASIBILITY OF COGNITIVE-MOTOR INTEGRATION TRAINING IN DEMENTIA

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ABSTRACT

Living our daily lives often requires us to think and move at the same time, especially when we are not directly interacting with an object of interest and require cognitive-motor integration (CMI). These CMI tasks require us to utilize various brain regions and networks. Alzheimer's disease is the most common form of dementia, and is often categorized with a progressive decline in memory and hippocampal neuropathology. Previous studies have shown that these CMI tasks are impaired in AD, mild cognitive impairment and in asymptomatic adults at high risk of developing dementia. Our group has also shown that these individuals also have an impaired frontoparietal network through behavioral and neuroimaging studies. The present study tests the feasibility and preliminary utility of a CMI-based training intervention in adults with mild to moderate cognitive impairment, and neurologically healthy older adults. We observed that adults in the early stages of dementia partaking in the CMI training regime improved their performance, unlike purely cognitive or purely visuomotor tasks alone. While their overall improvement was not to the same extent as the healthy controls, it nevertheless demonstrates that this approach is promising for future research. In addition, these data support and expand previous research on the manner of CMI performance impairment in mild and moderate AD participants and its relationship to standard neuropsychological measures of cognitive function. We suggest that the improvements or stabilization of measures we observed during our program may be due to an enhanced frontoparietal network, and connected memory-related structures. Our findings provide a basis for future studies to assess CMI training as a tool for functional decline prevention in various neuropathological conditions.

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P.S. Thank you, espresso machine for allowing me to complete this whole process!

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Glossary of terms:

Aβ – Beta amyloid

AD – Alzheimer's disease

ADL – Activities of Daily Measure

AE – Absolute Error

APOE4 – Apolipoprotein E epsilon 4

BBB – Blood brain barrier

CHT – Centre hold time

CMA – Cingulate motor area

CMI – Cognitive motor integration

CMT – Corrective Movement Time

CVD – Cardiovascular disease

CT – Cognitive training

DLPFC – Dorsal lateral pre-frontal cortex

DTI – Diffusion Tensor Imaging

DR – Direction Reversal

eAD – Early stage Alzheimer's disease

FA – Fractional Anisotropy

FR – Feedback reversal

GM – Grey Matter

HR – Heart rate

MCI – Mild cognitive impairment

MFG – Middle frontal gyrus

MRI – Magnetic Resonance Imaging

MOCA – Montreal Cognitive Assessment

MMSE – Mini-mental state exam

MT – Movement Time (ballistic)

NFT – Neurofibrillary tangles

PA – Physical activity

PCC – Posterior Cingulate Cortex

PD – Plane dissociated

PET – Position Emission Tomography

PMC – Pre Motor Cortex

PMd- Pre motor dorsal

- ➔ PMdc – Pre motor dorsal caudal
- ➔ PMdr – Pre motor dorsal rostral

RCT – Randomized Controlled Trials

RT – Reaction Time

S – Standard condition

SFG – Superior frontal gyrus

SMA – Supplementary motor area

SPL – Superior parietal lobule

T2DM – Type 2 diabetes mellitus

THT – Target hold time

TMT – Total Movement Time

VE – Variable Error

WM – White Matter

WMH – White matter hyperintensities

Introduction

Alzheimer's disease (AD) is the most common form of dementia affecting about 15% of Canadians 65 years or older. It is estimated that the number of AD patients can rise affecting 1.4 million people by 2031 if nothing changes in the detection and treatment of AD (Alzheimer's Society, 2012). The AD phenotype is typically characterized by progressively declining cognition and hippocampal atrophies (Hawkins & Sergio, 2014; Buchman & Bennett, 2011). It is well established that AD is accompanied by neurofibrillary tangles and senile plaques. These plaques are extracellular deposits that are formed with a dense core of amyloid containing hyperphosphorylated tau proteins and microglia. Research has consistently shown that many patients will exhibit no symptoms while AD develops over the course of years. Traditional clinical diagnostic techniques of dementia are often insufficient to diagnose dementia patients in the early stages of their disease. Our study aims to substantiate cognitive-motor integration as a sensitive means to assess functional ability in early dementia. Importantly, we also wish to determine if cognitive-motor integration training is feasible in a dementia population, in order to support future research into functional decline prevention or even improvements in this group.

It is well accepted that motor deficits exist in the latter stages of AD. Recent research suggests that these motor deficits may exist even in the early AD or mild cognitive impairment stages prior to clinically diagnosed AD. Motor function is not a simple process, it requires the coordination of multiple motor systems to initiate, plan and execute the movement. Multiple interconnected cortical and subcortical structures as well as visuospatial feedback is required for accurate movements. Increasing the complexity or presenting a novel motor task increases the cognitive and sensory processing loads to accurately perform the movements (Buchman & Bennett, 2011; Gorbet, et al., 2004). Previous studies have shown that patients with mild

cognitive impairments, AD, or those at risk for AD had abnormal performances on fine or complex motor tasks. Their results showed that motor tasks were able to identify the cognitive status of a subject as normal, MCI or eAD as accurately as traditional cognitive tests (Kluger, et al., 1997). It is important to understand that typical or standard tasks do not seem to be impaired in eAD or MCI patients. Stereotyped actions such as direct interactions have been shown to be not impaired in eAD (Tippett & Sergio, 2006). These deficits are evident when the movements are "nonstandard", in that one must integrate cognitive information which require an effector to move to a spatial location not directly aligned with a visual target (Hawkins & Sergio, 2014). During reaching movements, vision provides key information about the position and status of a target prior to any motor commands being generated, and visual information can be used to monitor the movement to adjust the trajectory if necessary (Ghilardi, et al., 2000). In one of the earliest studies to look at nonstandard visually-guided movements in AD, Ghilardi, et al., 1999 showed that when subjects were asked to move a hand-held cursor towards a target viewed on a computer monitor accurately and quickly as possible, AD patients had greater movement times with visual guidance. They also showed that without visual guidance accuracy decreased for AD patients. These findings suggest that AD patients rely heavily on continuous sensory monitoring of their hands. Slower movements in AD subjects may be due to impaired feedforward (planning) mechanisms, thus these patients depend more on feedback mechanisms, using external cues such as vision (Hawkins & Sergio, 2014). These data suggest that detecting visuomotor deficts may be an efficient way to identify patients in the early stages of AD (Verheij, et al., 2012; Buchman & Bennett, 2011). Visuomotor performance in nonstandard motor tasks have been negatively corrleated with MOCA scores, suggesting that older adults with lower scores on cognitive tests exhibit greater visuomotor deficits during nonstandard conditions (Hawkins & Sergio, 2014).

Patient's with advanced AD often display upper limb apraxia, however Crutch, et al., 2007 have demonstrated that even MCI or eAD patients exhibit apraxia in sensitive tests. MCI patients with upper limb apraxia were significantly more likely to be diagnosed with AD in the future (Crutch, et al., 2007). Further, it has been shown that MCI patients took significantly longer to plan movements requiring intermediate or greater levels of nonstandard mapping. Thus movements requiring rule integrations seem to be affected at the very early stages of cognitive decline (Salek, et al., 2011).

Anatomical/network changes in Alzheimer's disease

AD is generally associated with hippocampal atrophies and memory loss. However, it has been demonstrated that the frontoparietal network is also impaired, and has been implicated in the functional decline in AD patients (Braak & Braak,1991). In this section we will examine the various frontal and parietal regions that have been shown to be involved in cognitive-motor integration, as well as the networks connecting these regions. We will further attempt to understand the brain-behavior relationships and how these alterations are affecting performance in CMI tasks.

Grey matter and white matter changes in Alzheimer's disease

Several imaging studies have shown significant GM and WM changes in AD risk, MCI, eAD and AD patients. Kinematic measures from a cognitively demanding nonstandard task has been shown to be associated with identifiable brain alterations in eAD and individuals at risk for AD (Hawkins, et al., 2015). WM changes in eAD and MCI patients appear to be occurring in posterior regions while in normal aging anterior regions are affected, no GM changes were observed in high or low AD risk groups. The high AD risk groups presented lower WM integrity and these disruptions were more widespread compared to control groups. In addition, WM

integrity has been negatively correlated with performance on cognitively demanding visuomotor tasks (Hawkins, et al., 2015). DTI studies can be a good tool for detecting AD before the onset of symptoms, however due to its impracticality it is unfavorable as a clinically feasible assessment tool. Since cognitively demanding visuomotor tests are strongly correlated with DTI findings of WM disruptions, such tests represent a promising alternative to detecting pre-symptomatic AD.

WM lesions are caused by demyelination or microvascular ischemic events, and are associated with declining cognition and alteration of cognitive networks. WM lesions are responsible for a reduced resting state connectivity and these lesions are increased in subjects with T2DM (Tchistiakova, et al., 2015). Such lesions may thus underlie the recent demonstration that resting-state connectivity declines are correlated with poor cognitive-motor integration performance in asymptomatic adults at risk for AD (Hawkins and Sergio, 2016).

DTI studies in MCI and eAD have suggested altered parietal-frontal-temporal connections and disruptions from the hippocampus to the inferior parietal regions (Gold, et al., 2010; Villain, et al., 2008). WM integrity disruptions are evident when comparing low AD risk subjects to high AD risk subjects (Bosch, et al., 2012; Bai, et al., 2009). Imaging data suggests that WM disruptions, GM hypometabolism and GM atrophies are interconnected. The hypometabolism of the PCC does not result only from local pathologies but most likely due to distant effects of neuronal damage. The rostral part of the cingulum bundle, a WM tract connecting the hippocampus to the PCC, is disrupted in AD. There is also a significant correlation between the PCC hypometabolism and hippocampal atrophy via the cingulum bundle disruption (Villain, et al., 2008). Thus it is possible that the cingulum bundle disruption is inducing a temporo-parietal hypometabolism via an indirect connection with the ventral PCC. Imaging studies have shown that atrophy of the precuneus and parahippocampal gyrus occurs

prior to the onset of clinical AD symptoms (Honea, et al., 2011). Although impossible to determine causation, it is likely that these atrophies are caused by or causing the PCC and cingulum bundle disruptions.

Genetics and having a maternal history of dementia are well-established risk factors for the development of AD (Smith, et al., 2010; Hawkins & Sergio, 2014; Buchman & Bennett, 2011). DTI studies have shown that WM pathways affecting the frontal-temporal-parietal areas are disrupted in healthy women with increased risk for AD. The decrease in FA in the inferior temporal lobe bilaterally suggests WM disruptions in the hippocampal anterior region and the ventral visual association areas posteriorly (Smith, et al., 2010).

Functional imaging (fMRI) studies also support altered corticomotor connections in eAD. Participants with eAD who performed a simple visually directed motor tasks had lower PMC and SMA activations, suggesting that their motor system had issues with motor planning or generating alternative strategies (Vidoni, et al., 2012), skills needed for nonstandard visuomotor tasks. These findings suggest that functional networks needed for goal-oriented movements are altered by AD. Alternatively, it is possible that visuomotor deficits in eAD and AD risk groups are due to impaired visual-spatial recalibrations and strategic control due to WM integrity disruptions. High AD risk subjects seem to rely more heavily on sensory feedback mechanisms, have disrupted attentional control networks and impaired hippocampal-parietal processing systems.

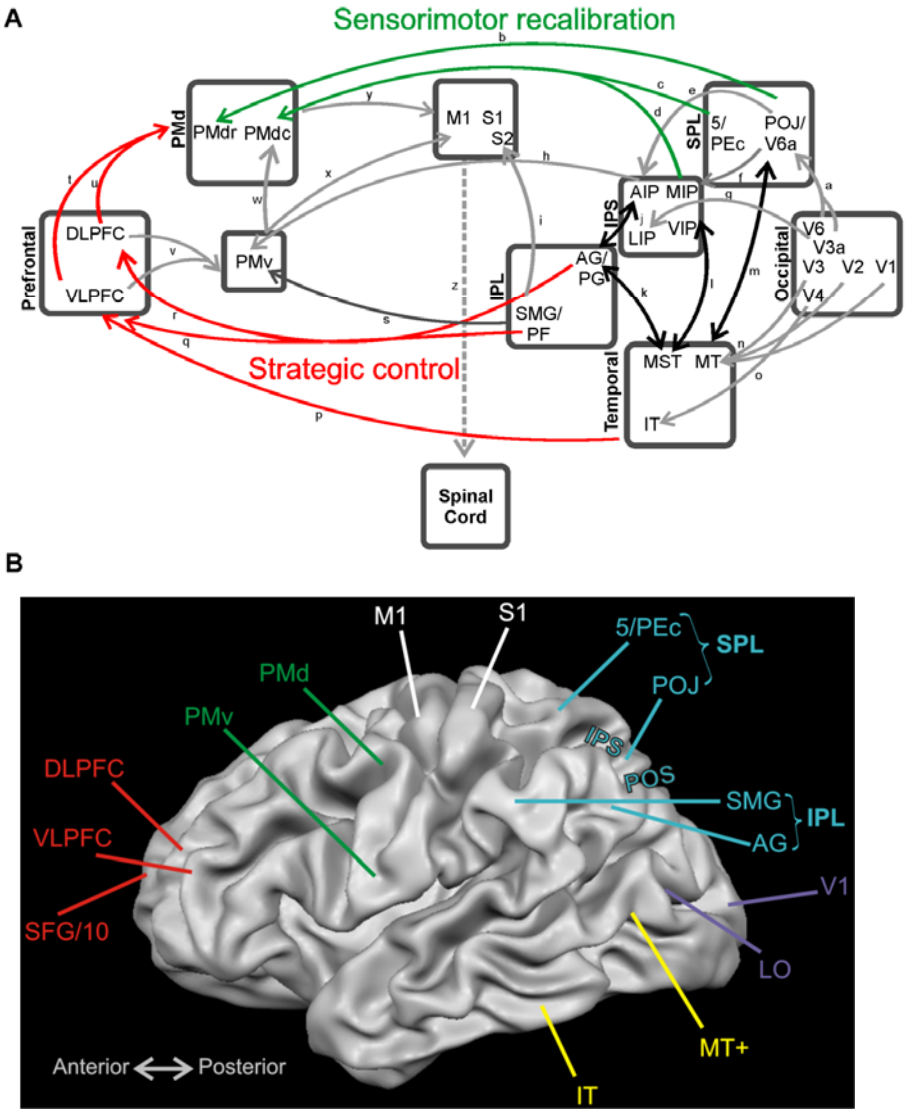

Figure 1. A schematic of the human brain networks for movement control viewed from a lateral perspective. (A) Schematic of the possible cortical connections based on a consolidation of human and macaque connectivity experiments involved in explicit (red) and implicit (green) motor control, cross-talk between networks (black double arrows), and other intermediate connections (grey). Note that although most connections are drawn with arrows pointing in one direction, most connections are reciprocal. (B) Inflated human brain schematic. The prefrontal cortex (red) is comprised of SFG (superior frontal gyrus), VLPFC, and DLPFC (ventrolateral and dorsolateral prefrontal cortex). The lateral premotor cortex (represented in green) is comprised of PMv and PMd (ventral and dorsal premotor area). The primary motor and sensory cortices (white) are comprised of M1 and S1, respectively. The posterior parietal cortex (blue) is comprised of SPL (superior parietal lobule) which includes the parieto-occipital junction; POJ and area 5; monkey area PEc), and IPL (inferior parietal lobule) which includes the supramarginal gyrus (SMG) and the angular gyrus (AG). The occipital cortex includes V1 (primary visual) and LO (lateral occipital) cortices. The temporal cortex includes IT (inferior temporal cortex) and MT+ (middle temporal complex). Adapted from J. Granek, 2013.

Networks and regions involved in AD risk, eAD, and AD

The premotor cortical regions PMdc (caudal portion) and PMdr (rostral portion) have been shown to be highly active during nonstandard motor tasks where the spatial locations of the eye and the hand are decoupled (Figure 1), thus not directly interacting with the viewed object (Sayegh et al. 2013, 2014). The PMdr is more involved in the integration of rule-based visually guided reach while PMdc is more involved in the online updating of decoupled reach via feedback mechanisms. There are changes that occur within PMd during coupled or decoupled movements, and lesions in this cortical region have been shown to impair performance in conditional sensorimotor tasks (Sayegh, et al., 2013). In addition, as previously discussed there is also a significant reduction in glucose metabolism as measured by PET scans in the DLPFC of eAD subjects. This is highly relevant to rule-based motor control, given that DLPFC is highly connected to the PMd and parietal regions (Reiman, et al., 1996; Small, et al., 1995; Small, et al., 2000). It is important to note that the DLPFC is related to the learning of association rules between stimuli and responses (Miller & Cummings, 2013). Given these findings it is possible that the ability to perform decoupled movements likely requires communication between prefrontal and premotor areas. It is possible that the decrease in glucose metabolism of DLPFC in APOE4 allele carriers is affecting the PMd and causing poor performances on nonstandard decoupled tasks prior to clinical diagnosis of AD.

In the parietal lobe, the superior parietal lobule (SPL, Figure 1) is involved in integrating eye and hand signals so one can successfully calculate the reach vector under visual guidance (Sayegh, et al., 2014). Hawkins, et al., 2013 observed that the neural activity of the deep SPL cells were higher during standard tasks while the activity of superficial SPL cells were firing preferentially to plane dissociated conditions. The anterior parts of the SPL are closely connected

to the PMdc an area involved with online updating of decoupled reaching movements (Sayegh, et al., 2014; Sayegh, et al., 2013; Hawkins, et al., 2013). It is possible that the glucose metabolism disruptions in the DLPFC is compromising the connections to the PMdc and the anterior region of the SPL. This disruption of the anterior SPL may account for a part of the decrease in metabolism of the parietal lobe in high AD risk subjects. Perceptual motor informations from the parietal areas are needed to integrate with the cognitive informations from the frontal areas to successfully execute a dissociated movement (Hawkins, et al., 2013). We speculate this frontoparietal network is defective in eAD or high AD risk subjects.

Family history and genetics as AD risk factors

It is well established that carriers of the APOE4 allele and history of maternal dementia increase the risk of developing AD. Studies have shown that healthy adults with a maternal or paternal history of AD have altered GM and WM changes. Subjects with family history of AD had greater whole brain atrophy, but those with maternal history had greater GM atrophy compared to subjects with paternal history or no familial history (Honea, et al., 2011). Carrying the APOE4 allele has been shown to significantly increase the risk of developing AD (Buchman & Bennett, 2011; Hawkins & Sergio, 2014). PET scan studies have shown that healthy homozygous APOE4 carriers have decreased glucose metabolism in parietal, temporal and frontal areas when compared to non-carriers. These metabolic reductions are consistent with clinically diagnosed AD patients' PET scans. It appears that there is a significant difference in the DLPFC region when compared to non-carrier controls; this area is highly connected to the PMd which was previously described (Reiman, et al., 1996; Small, et al., 1995; Small, et al., 2000). These metabolic disruptions to the parietal, frontal and temporal regions are consistent with DTI studies showing WM disruptions in these areas (Smith, et al., 2010). These DTI and

PET results suggest that there is a correlation between poor performance on cognitively demanding motor tasks and myelin degradation of areas associated with visuomotor association in eAD (Hawkins, et al., 2015). Lastly, it is possible that the relationship between hippocampal atrophy, WM integrity loss (Smith, et al., 2010), and altered GM metabolism (Reiman, et al., 1996; Small, et al., 1995; Small, et al., 2000) in eAD are due to the cingulum bundle disruptions causing hypometabolism of the PCC, middle cingulate gyrus, parahippocampal gyrus and right temporoparietal association cortex. These frontoparietal networks are needed for visuomotor transformations (Hawkins, et al., 2015).

Training programs to prevent progressive functional impairments with aging

Cognitive Training (CT) in older adults, eAD, and AD

Cognitive impairments are the most commonly associated symptoms in MCI, eAD, or AD. Even in eAD the cognitive deficits can produce significant functional impairments. Although memory impairments are the most pronounced, impairments in attention, visuospatial functioning, language and reasoning are all affected along with personality or behavioural changes (Buchman & Bennett 2011). Due to a tradition of cognition-focused interventions within dementia care, cognitive interventions have been extensively studied in various populations. Interventions are often composed of cognitive stimulation (global mental stimulation) and CT (guided practice on a set of standard tasks designed to target specific cognitive functions) (Clare & Woods 2004). CT programs are able to act as an alternative or supplemental treatment to pharmacological interventions. CT can be divided into subcategories based on their goals as either compensatory or restorative. (Sitzer et al. 2006).

Compensatory strategies can utilize internal abilities such as organizing information via categorization, visualizing information or encoding through multiple senses. They are also able

to utilize external strategies such as environmental cues or procedural training to teach higher-order cognitively mediated tasks often involved in ADLs. Restorative strategies attempt to improve functioning in a specific cognitive domain in hopes to improve functions to premorbid levels, such as reality orientation therapy to assist patients with date, location and other orientation measures (Sitzer et al. 2006).

Since CT is widely available through commercial distributors or research studies targeting cognition, Sitzer et al. 2006 conducted a meta-analysis of various CT programs and analyzed the effects of CT on multiple functional domains to calculate an overall effect size. The results of the analysis found that CT has varied effects, and those that show a positive effect are often with small samples, case-studies or non-controlled studies. A modest mean effect was determined for all CT programs analyzed, they further determined that restorative methodologies in individual session formats were the most effective and that general stimulation techniques saw the greatest benefits supporting the notion that maintaining higher levels of mental activity is beneficial (Sitzer et al. 2006). Other studies saw similar findings that reality orientation may assist cognitive or behavioural difficulties (Spector et al. 2000) and that CTs that were RCTs modestly improved some domains of function but unable to find a strong support for use in eAD or AD participants (Clare & Woods 2003). Since small sample sizes are a common critique for CT programs, Ball et al. 2002 used a large sample of MCI to cognitively healthy participants and observed similar results as others. Each intervention improved the targeted cognitive domain but there were no effects on everyday functioning (Ball et al. 2002). In contrast, it has been observed that stimulating procedural memory produces greater improvements in ADL measures compared to training of partially spared cognitive functions. This finding may be partially due to that

everyday tasks have greater reliance on procedural memories rather than other cognitive domains (Farina et al. 2002).

Hence, several limitations exist in cognitive training programs. Firstly, person centred models should be adapted since participants are often afraid of possible negative outcomes of participating due to insufficient sensitivity to the patients needs and responses. Secondly, the participants may find common cognitive interventions not motivating. Finally, participants may fear that their deficits will be highlighted and refuse to participate to avoid embarrassment or failures (Clare & Woods 2004).

Physical Activity (PA) Training in older adults, eAD and AD

Physical activity has been shown to promote various health benefits via prevention, maintenance and rehabilitation. PA is accessible to nearly everyone at low costs and skills therefore is a feasible solution for interventional therapies. Given the feasibility of PA it is possible to promote widespread adoption among communities. (Kramer & Erickson 2007). Increasing theories suggest that PA may have a protective effect on brain functioning in older adults or that it may slowdown the progression of cognitive impairments such as in AD (Rolland et al. 2008).

Systemic reviews of epidemiological, short-term RCTs, and molecular research studies suggest that PA improves cognitive abilities in healthy older adults. However, no RCT studies show that regular PA can prevent any form of dementia (Rolland et al. 2008). For example, healthy older adults that were subjected to a PA intervention in a RCT study demonstrated that exercise can improve cognition in those with possible MCI. These results should be accepted with caution since only a small improvement in cognitive function was determined, and its application to real-life situations can be limited (Lautenschlager et al. 2015). In order to assess

real-life applications Rolland et al. 2007 assessed the effectiveness of PA training on ADL measures on mild to severe AD patients in nursing homes. Their findings suggest that PA can slow the decline in ADL related functions in AD patients (Rolland et al. 2007). It may be possible that PA may serve as a method of protection for individuals with greater genetic predisposition for dementia. Engaging in PA at midlife was associated with a reduced risk of developing dementia, these associations were more pronounced in APOE4 allele carriers (Rovio et al. 2005). It is possible that individuals with the APOE4 genotype may have less neuronal protection mechanisms (Hawkins & Sergio 2014; Buchman & Bennett 2011), and abnormal molecular interactions (Cole et al. 2007; Dallongeville et al. 1992) therefore more reliant on lifestyle mediated factors such as exercise (Rolland et al. 2008).

To date very few studies have shown that exercise training influences human brain structures and/or functions (Kramer & Erickson 2007). Completing an aerobic PA intervention in humans have been associated with greater blood perfusions in the brain at the SFG, MFG and SPL (Colcombe et al. 2004) as well as increased grey matter volumes in the frontal and temporal cortex's and anterior white matter volumes (Colcombe et al. 2006). It is possible that PA may be essential in prevention and management of AD complications rather than direct AD pathology. It is very unlikely that PA can reverse the progressiveness of AD pathology especially within the short time period of these interventions (Rolland et al. 2008). However, given the rather sedentary lifestyles of elders especially in assisted-care facilities even a modest amount of PA may have great effects. Since there is high variability among PA training studies it is necessary to determine the efficacy of PA training programs on cognitively impaired older adults. There remain questions around the optimal age, cognitive status, exercise intensity and frequency

ranges to target interventions (Rolland et al. 2008; Lautenschlager et al. 2015) as well as determine molecular factors affected by PA interventions (Kramer & Erickson 2007).

Cognitive-Motor Integration (CMI) Training in older adults, eAD and AD

Researchers have traditionally studied cognition-focused interventions for dementia care (Clare & Woods 2004) and increasing recent theories suggested the possible use of PA interventions for dementia care (Rolland et al. 2008). Although these studies often focused cognitive and motor skills separately, they require integration for real-life situations often measured by ADL indexes. Very few studies have assessed CMI training as a tool to improve or prevent decline in function for cognitively impaired older adults. The few studies that do acknowledge cognitive and motor integrations define CMI interventions as stimulation programs designed to primarily target cognition via various cognitive activities followed by training of ADL skills and psychomotor exercises (Olazarán et al. 2004; Muniz et al. 2015). In theory, a comprehensive stimulation program in AD patients can enhance neuroplasticity to reduce cognitive loss and to prolong their functional independence. AD patients who have undergone CMI interventions have shown to retain cognitive statuses up to 6 months (Olazarán et al. 2004; Yokoyama et al. 2015) and ADL measures up to 2-3 years (Muniz et al. 2015). Further, CMI interventions have not yet been shown to induce molecular changes in Aβ metabolism (Yokoyama et al. 2015). However, in a more directly related recent study, Tippett and Rizkalla (2014) observed that six older adults with progressive cognitive decline either remained stable or improved in daily living measures following 14 weeks of visuomotor/visuospatial training. The task in this study (the popular game Pac-Man™) required visual navigation control in a complex environment where the hand motion was decoupled from the video monitor. Thus, the introduction of nonstandard mapping elements may be crucial to the success of brain-network

integrity preservation in these types of training programs. A limitation to this exploratory study, however, was the lack of healthy controls for comparison.

Major limitations exist in current CMI training programs for cognitively impaired older adults. Since the mild-moderate stages of AD can last 3-4 years, it is essential to assess long-term CMI interventions (Muniz et al. 2015). The current CMI training programs do not incorporate the ability to assess cognitive loads, in essence they fail to determine if the participant has the ability to adapt to new cognitively challenging situations. They also appear to assess cognition and motor skills in separate domains, since their interventions comprise conducting cognitive training then separately completing motor skills such as rule-based exercises.

Current study rationale and hypothesis

In real-life we require the ability to think and move at the same time. Our daily life often includes more implicit rule-integration to perform movements successfully (such as using a computer mouse on a horizontal surface to direct a cursor on a vertical monitor). To successfully execute these movements, we require CMI especially in challenging conditions where cognitive load may be greater. Currently, only one other group has attempted CMI training in dementia patients addressing the issue of cognitive load and rule-based visuospatial transformations required for everyday life, with limitations (Tippett and Rizkalla, 2014). Here we wish to extend the very limited research on combined cognitive-motor training, something not yet done.

It has been previously shown that CMI is impaired in older adults with MCI, eAD and those with family history of AD (Crutch et al. 2007; Salek et al. 2011; Hawkins & Sergio 2014). This study attempts to explore if having dementia patients undergo a repeated CMI training program can improve or stabilize movement and/or neuropsychological measures. Such a change

may contribute to improved functional abilities and prevention of functional decline in this population.

Hypothesis:

1. Older adults with dementia will show greater impairments in CMI performance compared to healthy controls in accordance with previous findings.
2. CMI training will be feasible in a cognitively impaired/healthy older adult population. Dementia participants will improve in CMI performance measures or not show progressive deterioration in CMI performance measures throughout our intervention.

Methods

Participants

Patients (AD Group) – Dementia participants were recruited from November 2015 to March 2016 from Memory and Company (Markham, Ontario), an assisted day-facility for cognitively impaired older adults. Participants had to fulfill the following criteria: symptomatic/clinically verified dementia, a MOCA score of <26, patient and caregiver/power of attorney's willingness and capability to receive a CMI intervention. Exclusion criteria were illiteracy, any neurological diagnoses except dementia, any psychiatric disorders, upper-limb disability, moderate-severe hearing or vision deficits, and any non-controlled systemic illness that can preclude their full participation in the CMI training i.e. arthritis.

Healthy Controls (CTL Group) – Healthy controls were recruited from March 2016 to June 2016 from York University and its affiliated networks. Participants had to fulfill the following criteria: a MOCA score of ≥26, participant's willingness and capability to receive CMI intervention. Exclusion criteria were illiteracy, any neurological diagnoses including AD or dementia, any

psychiatric disorders, upper-limb disability, moderate-severe hearing or vision deficits, and any non-controlled systemic illness that can preclude their full participation in the CMI training.

Consent was obtained from all participants and/or caregivers. The study protocol was approved by the Human Participants Review Sub-Committee from York University's Ethics Review Board.

Neuropsychological assessment/Questionnaire

All participants completed the education adjusted Montreal Cognitive Assessment Version 7.1 during baseline and final assessments. All participants were asked to complete a questionnaire during their baseline assessment to determine any exclusion factors, sex, age, dominant hand, family history of dementia, smoking and diabetes status.

Experimental task

All participants were asked to complete four visuomotor transformation tasks (Brain Dysfunction Indicator BrDI^{TM} Figure 2) every 5-10 days for a total of 7 sessions. These tasks were presented on an Asus Transformer Book T100 2in1 tablet connected to a standard 15-inch Dell desktop monitor.

In all conditions, participants were instructed to move as quickly and accurately as possible. In the standard (S) condition, participants were asked to slide the index figure of their dominant hand directly to the targets on the horizontal tablet (i.e., the cursor was under their finger). In the feedback reversal (FR) condition, the cursor moved in the opposite direction of the participant's finger movements, requiring them to slide their finger away from the visual target in order to direct the cursor towards it. In the plane dissociated (PD) condition, participants slid their finger along the horizontal tablet in order to direct the cursor displayed on the vertical

computer monitor towards visual targets in the vertical plane. And finally, during FR+PD condition, movements in the opposite direction of the visual targets, as well as in a different spatial plane from the guiding visual information, were required (Figure 2). In all conditions participants were instructed to look at the location of the presented target, regardless of whether their finger was sliding to that target or in a different direction/spatial plane. Thus, in all but the standard condition the final spatial locations of gaze and hand were decoupled.

To summarize:

1. Direct Interaction Task **(Condition S)** – Target location and movement aligned. Movement not decoupled
2. Feedback Reversal Task **(Condition FR)** – Visual feedback reversed. Movement not decoupled.
3. Plane Dissociation Task **(Condition PD)** – Target location and cursor movement aligned. Vision and action decoupled.
4. Feedback Reversal and Plane Dissociation Task **(Condition FR+PD)** – Visual feedback reversed. Vision and action decoupled.

Four different peripheral targets (10mm diameter) were presented at the top, right, bottom and left of the screen center, for a total of 20 trials (5 to each peripheral target direction), thus 80 trials per participant at one given session excluding practice or failed/missed trials. Distance between the middle of a peripheral target and middle of the centre "home" target was 55mm for conditions S/FR and 68mm for conditions PD/FR+PD. Trial timing: After touching the center target for 1000 ms, its disappearance and peripheral target appearance, served as "go-signal" to initiate movement to peripheral target. Target hold time was 250ms.

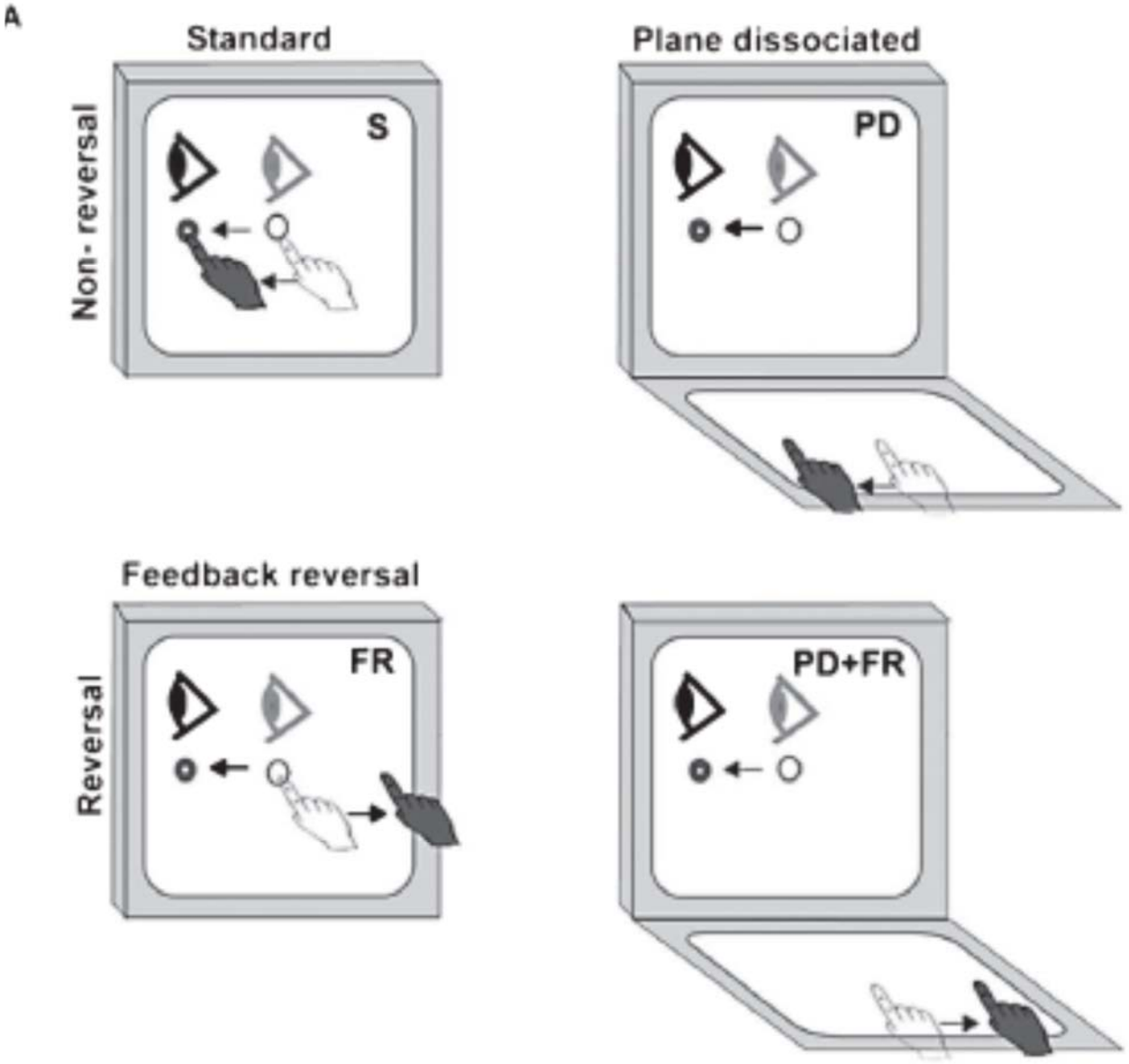

Figure 2. Schematic drawing of experimental conditions S, FR, PD and PD+FR: Visual stimuli were presented on the tablet for S and FR conditions and on a vertical external monitor for PD and PD+FR trials. Light grey cursor, eye, and hand symbols denote the starting position for each trial (center target). Dark grey eye and hand symbols denote the instructed eye and hand movements for each task. Dark circles denote the peripheral (reach) target, presented randomly in one of four locations (left, up, right, down). The dark crosshair denotes the cursor feedback provided during each condition.

Dependent Kinematic Measures – Reaction time; ballistic, total and corrected movement time; ballistic, full and corrected pathlength; direction reversal error; and number of failed trials. At target: absolute error, variable error, absolute distance constant error, absolute direction constant error. These measures are described in detail below.

Dependent Neuropsychological Measure – Difference in MOCA scores between final and baseline session.

Data processing

All dependent kinematic measures were recorded for each trial and converted into a MATLAB readable format using a custom C++ written application. Errors were determined on a trial by trial cases with the assistance of the custom application. Trials considered errors were analyzed, if the participant was able to complete the movement from the home target to the peripheral target. These "successful" error trials were recorded

Types of errors that were not included in the kinematic analysis (Failed trials):

- RT was too short (<150ms) or too long (>8000ms)
- Pre-entry timed out (>10000ms) – participant failed to hold the home target completely
- MT was too long (>20000ms)
- Finger was removed from the tablet during the trial

Types of errors that were included in the analysis (Successful trials):

- Direction reversals were continuous movements
- Left home target too early (<250ms) but the onset of peripheral target had occurred

Endpoint analysis

Absolute error, AE, was defined as the accuracy of the endpoints, and was calculated by determining the mean X, Y coordinates for all endpoints for the target ($\sum x/n$, $\sum y/n$). This distance between this point and the actual target location was calculated to determine AE. Variable error (VE), i.e. the endpoint precision, was determined as the distance between the endpoints of the individual movements ($\sigma 2$) from their mean movements. For both measures the grand mean for all targets and trials were used as the measure. Previously we have not found a target effect on these measures with the populations under study here (Hawkins & Sergio, 2014).

Movement trajectories/pathlengths

Custom software was used to generate a velocity profile of each participant's movement from each trial. Movement onset and completion of the first ballistic movement was recorded as the point at which the finger moved beyond 10% peak velocity. Corrective movement pathlengths were manually calculated subtracting ballistic movement pathlengths from total movement pathlengths. If the participant performed a direction reversal and the trial was not subject to manual deletion as described above, the total movement including all corrective paths were calculated into the total movement pathlengths.

A handpath was defined as the distance moved by the participant's finger/hand from start location (central target) to end location (peripheral target). This distance from start to end location was measured, and any curves or deviations from the straight line that connects these locations were deemed altered pathlengths.

Measurements of pathlengths were recorded for each target and calculated as a percentage of the length of the straight line connecting the two targets. This allowed us to

accurately compare from the plane dissociated (condition PD, PD+FR) and direct tablet interaction (condition S, FR) tasks. All pathlength measures were converted into a percentage by dividing the pathlength (mm) by the distance from the center of the central "home" target to the center of the peripheral target at $0^{o,}$ 90^{o}, 180^{o}, 270^{o}.

%Pathlength = (x/55mm) for conditions S, FR and %Pathlength = (x/68mm) for conditions PD and FR+PD.

Absolute on-axis error (distance error) was determined using deviations of path from the straight line that connects the central target to the displayed peripheral target on the Y-axis for 0^{o} and 180^{o} targets, and perpendicular deviations of path from the straight line that connects the central target to the displayed peripheral target on the X-axis for 90^{o} and 270^{o} targets. Absolute off-axis error (direction error) was determined using deviations from the straight line that connects the central target to the displayed peripheral target on the X-axis for 90^{o} and 270^{o} targets, and perpendicular deviations of path from the straight line that connects the central target to the displayed peripheral target on the Y-axis for 0^{o} and 180^{o} targets.

Performance Timing Analysis

Reaction time, RT, was calculated from the moment of central target disappearance to the beginning of movement (determined by the finger velocity exceeding 10% peak velocity). After the onset of 10% peak velocity, Movement time, MT, was calculated from time of movement onset to end of first ballistic movement (thus, this was the movement time resulting from the participant's initial feedforward motor plan, without feedback correction). Total movement time, TMT, was calculated from time of movement onset to total completion of movement (at end of trial). Corrective movement time, CMT, was manually calculated subtracting MT from TMT, thus represented the amount of time a participant spent using feedback to correct a movement.

Direction Reversal Errors

Direction reversal errors were considered successful trials if the participant was able to successfully reach the correct peripheral target by the given maximum movement time (20000ms) and no other trial failure criterion were met. A movement that deviated $\geq 45^{o}$ from the straight line that connected the central home target and the peripheral target were considered direction reversal errors. DRs were only counted for trials FR and FR+PD. DRs that occurred for conditions S and PD that did not meet a trial failed criterion were considered successful. All direction reversal errors were converted into a percentage ($\sum x/n*100\%$), where the total number of direction reversals were divided by the total number of trials per condition at a given session.

Failed Trials Analysis

We manually calculated the number of trials that the participants could not successfully reach the peripheral targets for all trials. This data was further categorized into non-plane dissociated and plane dissociated conditions. The following errors as detected by our scoring program and manual verification were considered failed trials:

- Errors 2, 4, 5, 7
    - 2 – Fail to remain in central target
    - 4 – Leaving central target late
    - 5 – Exceeding maximum movement time
    - 7 – Manually deleted (cannot be scored/categorized or finger was taken off the tablet surface during movement)

Statistical Analysis

All statistical analyses were performed using SPSS Statistics 23 (IBM Inc.). After consulting with a statistician we analyzed using nonparametric methods and generalized linear models on all kinematic measures due to small sample sizes. All kinematic measures were initially assessed using a descriptive statistics function to determine the distribution of the data.

Only normative and positively skewed data (skewness value >2) were present in our data sets. Statistical significance levels were set to 0.05.

Outliers – Outliers were determined separately for the dementia patients and healthy controls to preserve the clinically significant measures expected from our AD group.

For AE, VE, Absolute On-Axis and Absolute Off-Axis measures upper limit outliers were calculated using Q3+(IQR*2.5) and lower limit outliers via Q1-(IQR*2.5). Our study used a standard deviation factor of 2.5 compared to the common 1.5 to allow our data to show the true range of values from our AD participants.

For RT, MT, TMT and CMT the maximum and minimum allocated times during participant's trials were used as upper and lower limits respectively. The maximum limit was set at 8000ms and minimum limit at 150ms for RT. The maximum limit was set at 20000ms and minimum limit at >150ms for MT, TMT and CMT.

No outlier values were set for ballistic, full or corrective pathlengths because extremely high or low numbers could represent clinical significance and since all scored trials were subject to a criterion that the participant reaches the peripheral target successfully.

Within-subject analysis

To assess the effects of 7 sessions on all kinematic measures we used a Wald Chi-square analysis to determine the effect of session on dependent measures (generalized estimating equations function). The difference in MOCA score between the final and baselines sessions were utilized as a covariate to determine if there was an interaction. Least significant difference was used as a post-hoc analysis.

Normative distribution data sets were analyzed via linear scale response. If a data set displayed Gamma distribution, the scalar response was modified to reflect this distribution on the generalized estimating equations.

MOCA score interactions

All participants' data were categorized into a MOCA score group (No Change, Decreased, or Increased), based on the differences between the final and baseline MOCA scores.

If an interaction was found significant or likely we conducted a Kruskal-Wallis analysis to determine if the dependent measures had differences between the MOCA score groups. If the Kruskal-Wallis test yielded significance, we conducted a series of Mann-Whitney U as a post-hoc analysis.

- We did not conduct a Kruskal-Wallis analysis for control data because these participants only had 2 MOCA score groups (No Change or Decreased). Thus, we conducted a Mann-Whitney U test to determine the differences between these 2 groups.

Experimental group comparisons

We conducted a Mann-Whitney U analysis in all dependent measures between the AD and control participants. These analyses were conducted with data sets from the overall training program, only session 1 measures and only session 7 measures.

Crawford and Howell comparisons

To assess individual AD patient performance with normative healthy control measures we conducted a Crawford and Howell modified t-test analysis. The analysis was conducted on a custom software provided by the authors on an open source website. The Crawford and Howell

model allowed us conservatively analyze individual scores compared against our small control group without overestimating the rarity of an individual's score (Crawford & Garthwaite, 2002; Crawford & Howell, 1998).

We assessed 3 CMI performance measures RT, CMT and corrective pathlength. All 3 measures were normally distributed. Other CMI measures were not analyzed because we did not observe a significant pattern from our other statistical analysis or an extreme difference between the two experimental groups existed.

The Crawford and Howell analysis was conducted for measures from the baseline or final recorded sessions during our most challenging condition (FR+PD).

Results

Statistical results for AD and control groups are reported on Table 2 at the end of the results section. Table 1 presents demographic information for the two study groups.

Table 1. Detailed demographics of all dementia patients and healthy older adults. Dementia patients n=5, control participants n=4. Highest level of education attained C=College, B=Bachelor, M=Masters, D=Doctorate degrees; all participants had ≥ 12 years of formal education. Family history of dementia Ma=Maternal, Pa=Paternal.

	Subject #:	Age	Sex	MOCA Baseline	MOCA Final	Family History	Training Duration (weeks)	Highest Edu. Attained
Dementia Patients	1	86	F	12	15	Ma.	10	B
	2	80	F	20	18	Pa.	10	M
	3	61	M	0	0	NO	7	B
	4	76	M	6	10	Pa.	9	B
	5	60	M	8	7	Pa.	10	B
	Average	**72.6 ± 11.6**	**-**	**9.2 ± 7.4**	**10.0 ± 7.0**	**-**	**9.2**	**-**
Control	2	75	F	28	26	Pa.	7	B
	3	60	M	30	28	NO	7	C
	4	72	M	27	26	NO	5.6	D
	5	58	M	26	26	NO	5	C
	Average	**66.2 ± 7.7**	**-**	**27.8 ± 1.9**	**26.5 ± 1.5**	**-**	**6.15**	**-**

Endpoint Analysis

We analyzed both accuracy (absolute error) and precision (variable error) and their changes as affected by sessions. We observed a learning effect from our AD group in accuracy measures during our easiest direct condition, S ($X^2(4) = 223.8$, $p<0.05$) as well as during our most cognitively demanding condition, FR+PD ($X^2(4) = 10.9$, $p<0.05$). However, AE increased during our FR and PD conditions. Accuracy measures from our control groups saw a learning

effect during non-plane dissociated tasks, S ($X^2(3) = 20.5$, $p<0.05$), FR ($X^2(3) = 1121.2$, $p<0.05$), and increased or did not change for our plane dissociated tasks. Accuracy was not found to have a significant interaction with MOCA scores in both groups.

We observed an increase in precision in our dementia patients, reflected as a decrease in Variable Error, in the most challenging condition FR+PD ($X^2(4) = 290.0$, $p<0.05$). We did not see a change in precision in this group in any other condition (Figure 3). In addition, we found that precision was affected by MOCA scores in 2 of our conditions; FR ($X^2(2) = 10.9$, $p<0.05$), PD ($X^2(2) = 6.1$, $p<0.05$) (Table 3). Our results indicate that dementia patients who had an increasing

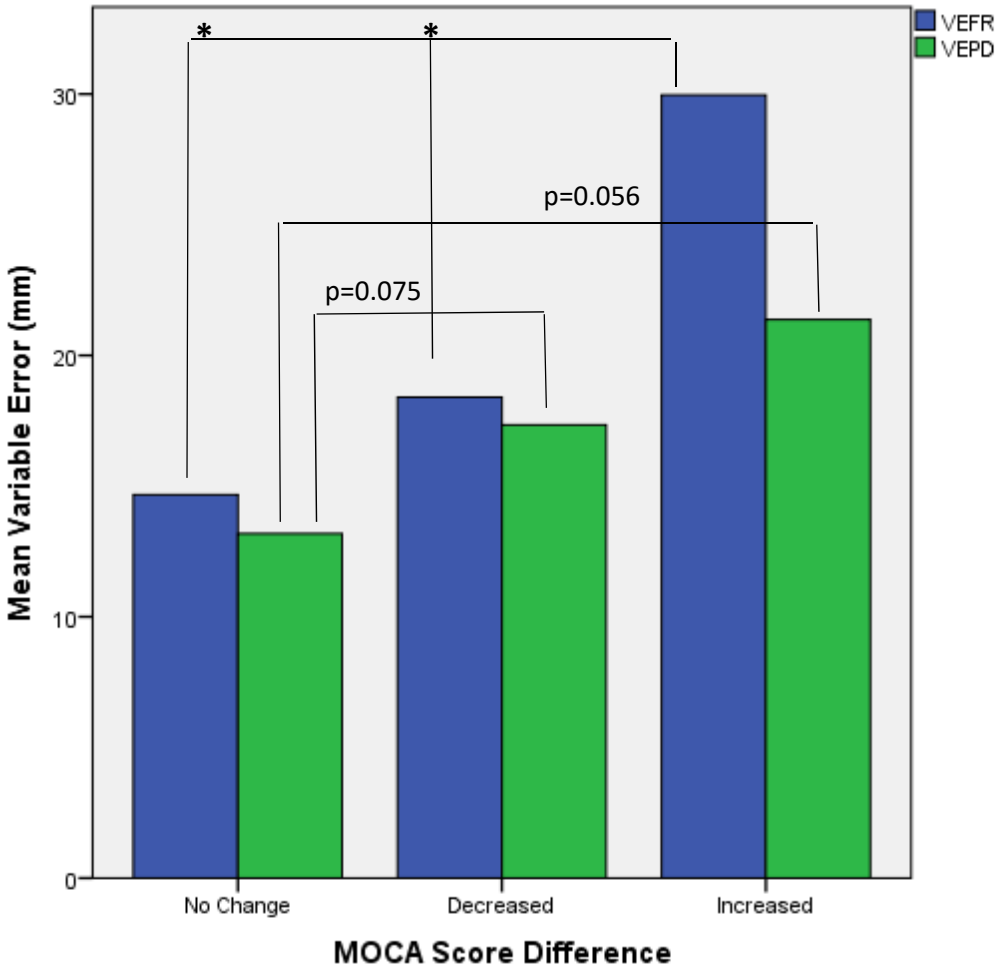

Figure 3. Overall mean VE (mm) during FR and PD conditions for AD patients in different groups categorized by the difference in MOCA scores from final and baseline session. Statistical significance only shown for $p<0.05$ between groups. *Condition FR* – AD participants in the increased score group had significantly higher VE than those in decreased and no change groups. *Condition PD* – Strong trend suggesting that AD participants in the increased and decreased score group had higher VE scores than those in the no change groups.

change in MOCA scores had a higher overall mean VE compared to others (Figure 3). Precision measures did not change over time from our control groups for any conditions. However, we did determine that participants that had no change in their MOCA scores had less precision during our most challenging condition compared to the other conditions (Table 3).

Trajectory and Pathlength Analysis

The deviations in trajectory from the straight line connecting the CHT and peripheral target were determined by the absolute-on axis and absolute-off axis errors. Absolute-on axis errors from dementia patients were decreasing in our simplest (S) ($X^2(4) = 83.3$, $p<0.05$) and our most challenging (FR+PD) ($X^2(4) = 99.1$, $p<0.05$) conditions. They failed to improve during our FR condition and increased during our PD condition. Off-axis errors from dementia patients did not change except during our FR condition ($X^2(4) = 236.2$, $p<0.05$), where we observed that their on-axis errors were greater over time. On-axis errors from control groups decreased over time for our non-plane dissociated tasks (S $X^2(3) = 18.2$, $p<0.05$), (FR $X^2(3) = 25.3$, $p<0.05$) and they increased or did not change in the PD and FR+PD conditions respectively. Off-axis errors did not change for our control groups except during our least challenging condition ($X^2(3) = 350.7$, $p<0.05$), where we observed that our control participants were able to improve their off-axis errors.

Ballistic pathlength during conditions S ($X^2(4) = 71.8$, $p<0.05$), FR ($X^2(4) = 39.8$, $p<0.05$) and PD ($X^2(4) = 19.1$, $p<0.05$) were improving over time suggesting that dementia patients were utilizing less corrective movements to reach their targets. However, ballistic pathlengths for our most challenging condition (FR+PD) were decreasing ($X^2(4) = 50823.4$, $p<0.05$) over time. Ballistic pathlengths from our control groups did not show any changes during non-plane dissociated tasks, while we observed an improvement over time for plane dissociated conditions

(PD $X^2(3) = 106.0$, $p<0.05$), (FR $X^2(3) = 57.5$, $p<0.05$). Full pathlengths from our dementia patients did not change when their movements were aligned with the cursor's feedbacks (S/PD). However, full pathlength was observed to be increasing over time during the FR condition ($X^2(4) = 87.6$, $p<0.05$), and decreasing during the FR+PD condition ($X^2(5) = 2.6$, $p<0.05$). Full pathlengths from our control groups did not change over time in our nonstandard conditions. However, we did observe an improvement in full pathlength over time for our standard condition.

Corrective pathlengths from our dementia patients did improve over time for our standard ($X^2(4) = 26.2$, $p<0.05$), and most challenging condition FR+PD ($X^2(4) = 23.2$, $p<0.05$). However, these corrective movements were increasing during our FR condition, and did not change during our PD condition. Unlike our dementia patients, the control group was able to reduce their corrective pathlengths for all conditions (Table 2, Figure 4).

Performance Timing Analysis

Performance timing measures were analyzed separately for reaction time, movement time (ballistic), total movement time and corrective movement time. Reaction time was defined as a period of time prior to onset of movement, thus is an indicator of movement planning. Our dementia patients all were able to reduce their RT measures in all conditions (Table 2, Figure 5), therefore plan their movements quicker throughout the sessions. RT did have a significant interaction with the MOCA scores in our most complex condition FR+PD (Table 3) ($X^2(2) = 23.0$, $p<0.05$). We were able to determine that dementia patients that did not have a change in their MOCA scores had the greatest overall RT ($U=11.0$, $p<0.05$), followed by the increased ($U=4.0$, $p<0.05$) and decreased groups ($U=0$, $p<0.05$) respectively (Figure 5). Movement planning was unaffected in our control groups except in our most complex condition FR+PD

($X^2(3) = 33.1$, $p<0.05$), where we observed a decrease in amount of time required to plan their movements. A strong trend indicating an interaction between RT and MOCA scores were observed for condition S in control groups, suggesting that those with a stable MOCA score had the greatest RT (U=39.0, $p<0.05$) (Table 3).

Ballistic movement time was determined by calculating the onset of movement until the completion of the initial movement. Dementia patients did not change the amount of time making ballistic movements, except in the PD condition where we observed an improvement over sessions. We also observed that dementia patients with a stable or improved MOCA scores had a greater overall MT measure in condition PD (Table 3). Control participants did not have any changes in MT measures throughout the sessions.

Total movement time was calculated from the onset of movement until the completion of the whole movement. Dementia patients had no changes in TMT measures for conditions where the movement and visual feedback were aligned. However, we observed an increase in TMT during the FR condition ($X^2(4) = 25.6$, $p<0.05$), as well as a decrease in TMT during the FR+PD condition ($X^2(4) = 51.6$, $p<0.05$). TMT did have an interaction with MOCA scores for the PD condition in dementia patients, we observed that those with a stable or increased MOCA scores had a higher TMT compared to the decreased MOCA group (Table 3). Our control groups did not have any changes in TMT during the non-plane dissociated tasks, however we observed a decrease in TMT for our plane dissociated tasks (PD $X^2(3) = 74.5$, $p<0.05$), (FR+PD $X^2(3) = 25.6$, $p<0.05$).

Corrective movement time was manually calculated by subtracting the ballistic movement time from the total movement time, thus represented the amount of time required to

perform corrective movements after the initial movement to successfully reach the peripheral targets. Our dementia patients did not have any changes in CMT over sessions during plane

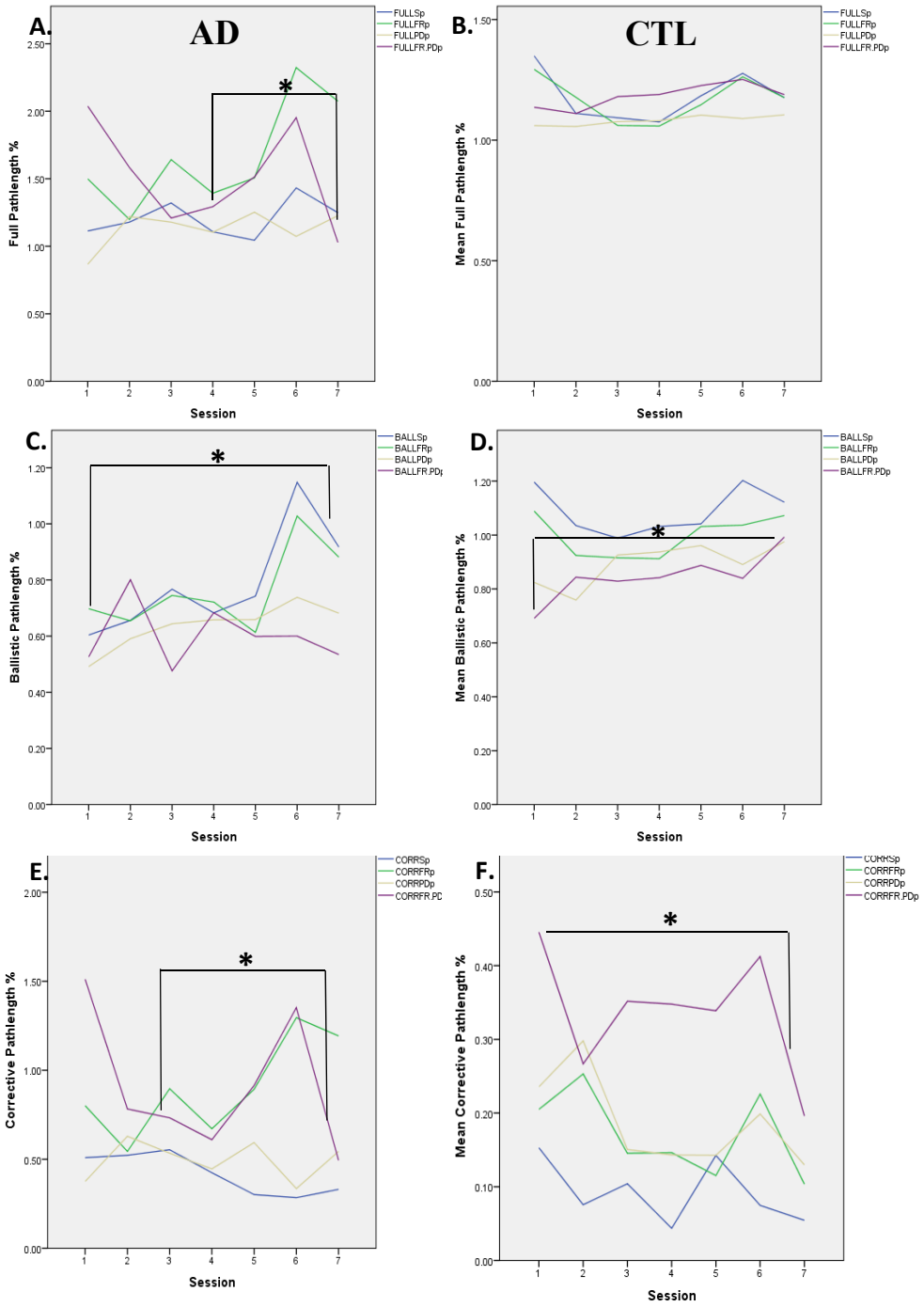

Figure 4. Pathlength % shown across from session 1 through to 7 in all conditions. Statistical significance only shown for longest sessional difference, unless otherwise indicated. No significant interactions with MOCA score differences and pathlength % in all AD analysis. **A.** Full pathlength % (AD) post-hoc for condition FR+PD showed significance between sessions 4 and 7 (p=0.018) **B.** Full pathlength % (CTL) no significances shown. **C.** Ballistic pathlength % (AD) post-hoc for condition S and FR showed significance between sessions 1 and 7 (p=0.000, p=0.008). **D.** Ballistic pathlength % (CTL) post-hoc for condition FR+PD showed significance between session 1 through to 7. **E.** Corrective pathlength % (AD) post-hoc for condition FR+PD showed significance between sessions 3 and 7 (p=0.001). **F.** Corrective pathlength % (CTL) post-hoc for condition FR+PD showed significance between sessions 1 and 7.

dissociated conditions, however we observed a decrease and increase in CMT for our standard or feedback reversal conditions respectively. CMT measures from all conditions were decreasing across sessions for our control participants (Table 2, Figure 5). No interactions between CMT and MOCA scores were observed in dementia participants. We observed that control participants that had a decreased MOCA score spent greater amounts of time making corrective movements (Table 3) (U=28.0, $p<0.05$).

Direction Reversal Errors

Direction reversal errors were considered successful trials if the participant was able to successfully reach the correct peripheral target by the given maximum movement time and no other trial failure criterion were met. The number of DR errors were not affected by sessions in both the AD or control groups for the FR condition. However, during our most cognitively demanding condition (FR+PD) both AD ($X^2(4) = 10.3$, $p<0.05$) and control groups ($X^2(3) = 10.6$, $p<0.05$) decreased their number of DR errors by session 7 (Figure 6). For session 1 we observed that the AD group had a greater amount of DR errors compared to controls only in the FR+PD condition. However, in session 7 the AD group had a significantly greater amount of DR errors in both FR and FR+PD conditions.

Failed Trials Analysis

Participants in both AD ($X^2(3) = 412.0$, $p<0.05$) and control ($X^2(3) = 12.0$, $p<0.05$) groups were able to significantly reduce the total number of failed trials overall. However, when we further categorized this data into non-plane dissociated and plane dissociated conditions, we observed that only dementia patients were decreasing the number of failed trials for non-PD conditions ($X^2(3) = 8.9$, $p<0.05$). Both groups were able to reduce the number of failed trials during the PD

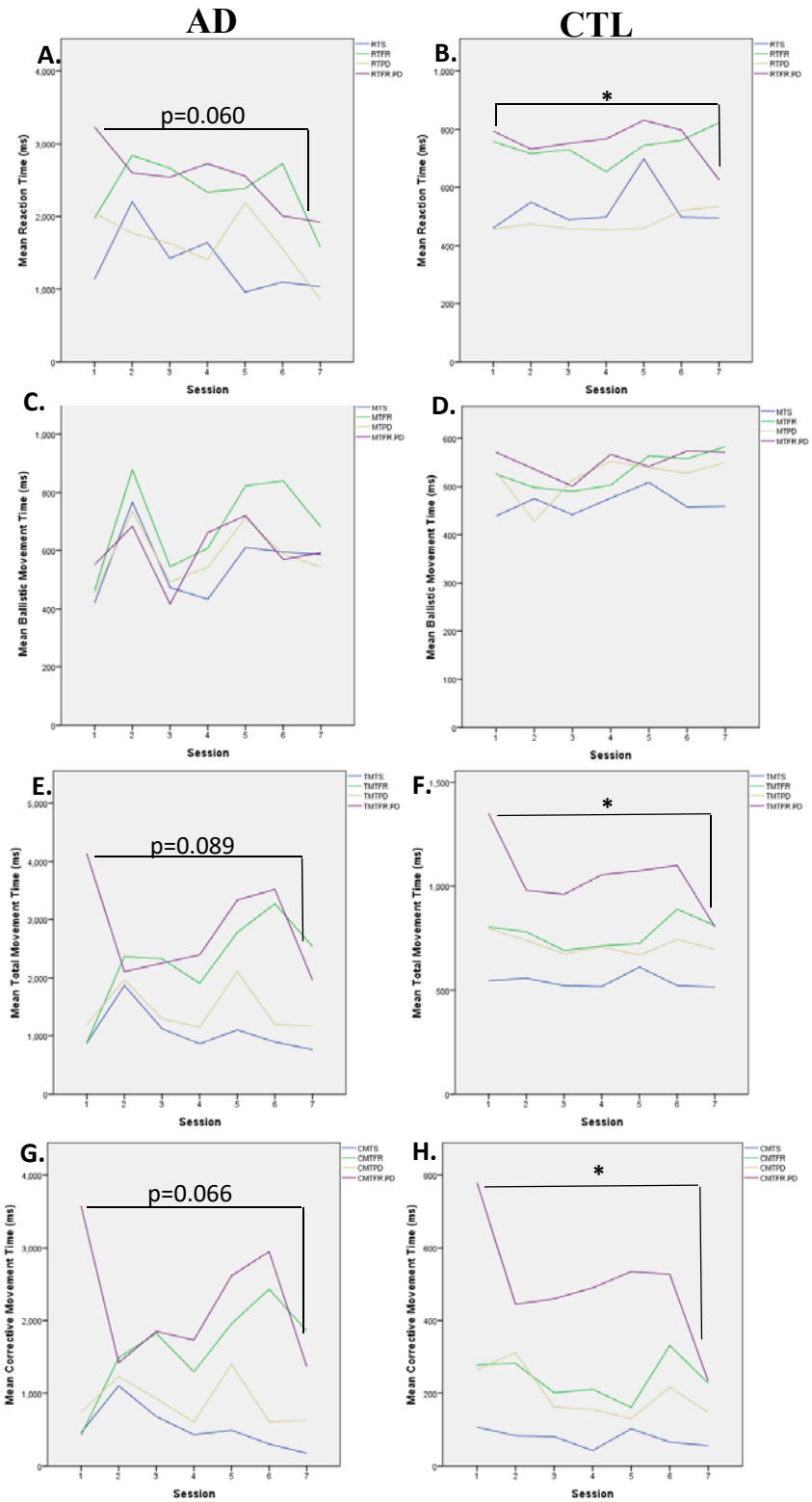

Figure 5. Performance timing measures shown across from session 1 through to 7 in all conditions. Statistical significance or strong trends only shown for longest sessional difference in the FR+PD condition, unless otherwise indicated. **A.** Reaction time (AD) session 1 and 7 (p=0.060). **B.** Reaction time (CTL) session 1 and 7 (p=0.002). **C.** Movement time (AD) no change. **D.** Movement time (CTL) no change. **E.** Total movement time (AD) session 1 and 7 (p=0.089). **F.** Total movement time (CTL) session 1 and 7 (p=0.000). **G.** Corrective movement time (AD) session 1 and 7 (p=0.066). **H.** Corrective movement time (CTL) session 1 and 7 (p=0.011).

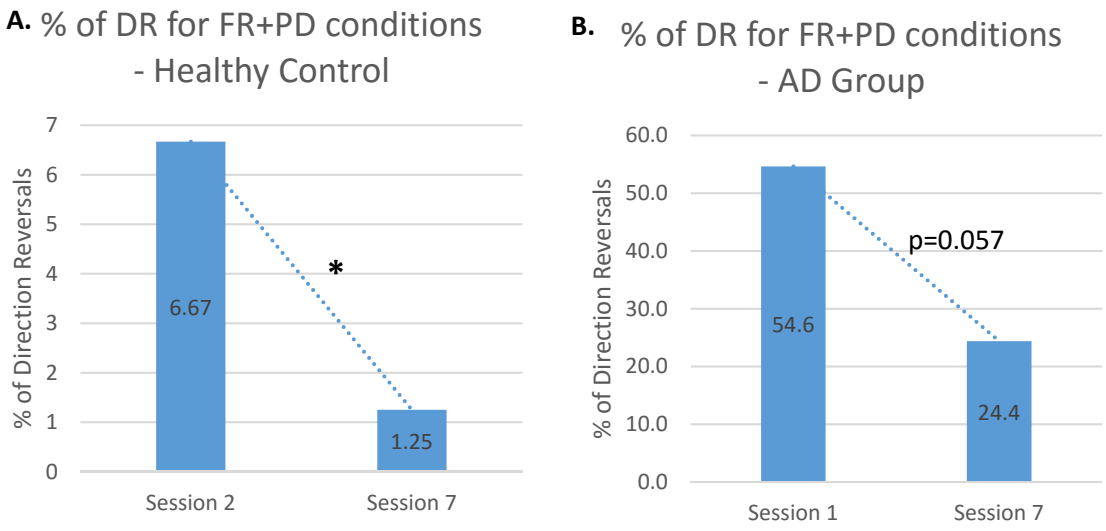

Figure 6. % DR errors, significance or strong trend only shown between the longest sessional difference. **A.** CTL between session 2 and 7 (p=0.003). **B.** AD between sessions 1 and 7 (p=0.057).

conditions over the 7 sessions (AD $X^2(3) = 273.2$, $p<0.05$), (CTL $X^2(3) = 12.0$, $P<0.05$). We observed that there were no significant differences in the number of errors for the non-PD conditions between the AD and control groups during session 1 or 7. However, during 1 and 7 we observed a strong trend indicating differences for PD conditions (Figure 7).

AD and Control Groups Comparisons

No statistical differences in age were observed between the two experimental groups ($U=4.5$, $p\geq0.05$). We observed that when comparing overall between AD and control groups, a majority of our measures with the exception of few (Table 4) had statistically significant differences. In general dementia patients had greater accuracy and precision errors, greater trajectory deviations, longer pathlengths except ballistic, slower movements and greater number of direction reversal and failed trials errors. To further examine our findings, we conducted a comparisons test between these groups using measures from just session 1 and 7. At session 1, both groups had very few statistically significant (or strong trend) differences in most measures, except during our most cognitively demanding conditions for accuracy and precision errors (Figure 8) as well as total and corrective timing measures (Figure 9). Reaction time had a strong trend suggesting differences between the groups for all conditions (Figure 10). Pathlengths were generally not significantly different between the two groups at session 1. At session 7, we had a less number of significant (or strong trend) differences between the two groups during our most demanding conditions in AE, on-axis error, TMT and CMT. Accuracy and precision measures were different during our FR conditions (Figure 8), and no trajectory deviation were observed to have any differences. Reaction time had differences between the two groups for all conditions. We did observe few differences in timing (Figure 9, 10) and pathlength measures however, with

the exception of ballistic pathlength, none of these differences were in our most challenging condition.

We also compared our individual dementia patients to the mean measures from control groups for RT, CMT and corrective pathlength using the Crawford and Howell modified t-test. Overall, we observed that individual dementia patient performances were greatly impaired when compared to the healthy control groups. Our most impaired patient, displayed a significant difference in both movement planning and execution during his first and last recorded sessions in our most challenging condition (FR+PD). On the contrary, our least impaired patient displayed significant differences in movement planning and execution only during her baseline sessions. She was able to improve her movement execution performance to the level of healthy controls by her final session. We did observe one patient with a moderate level of cognitive impairment improve their corrective pathlength performance to the level of healthy controls by session 7, however he was unable to improve his CMT suggesting that he was more accurately executing his movements but was unable to complete the task faster. The remaining participants were not able to perform at a level of healthy controls either during baseline or final sessions, with the exception of a few isolated measures (Table 5).

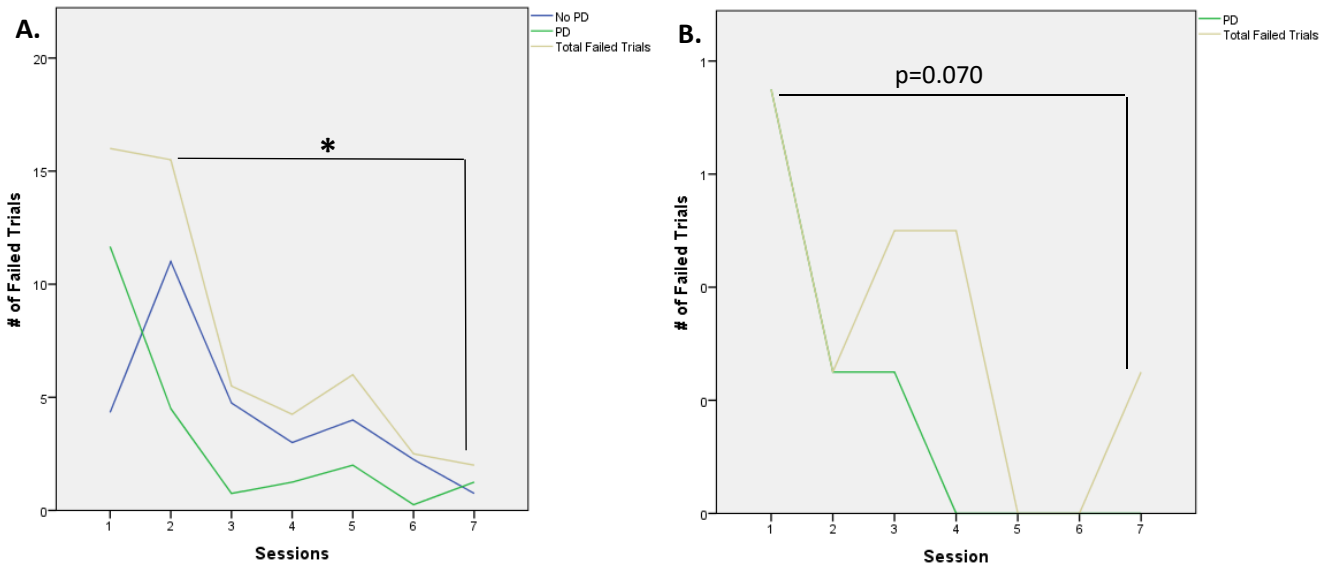

Figure 7. Number of failed trials significance or strong trend only shown for the longest sessional differences. **A.** AD group total between sessions 2 through to 7 (p=0.000). **B.** CTL group total between sessions 1 and 7 (p=0.070)

To determine the differences in learning rates between the two groups we conducted a generalized linear model repeated measures analysis with the cognitive group status as a between-subjects factor (AD or Control). Precision and variable errors did differ in the rate of change between the two groups only for our most complex condition (FR+PD, Figure 8). Trajectory deviations as measured by on and off-axis errors were only different between the two groups for the standard condition. Pathlength comparisons did not yield consistent results, full pathlength rates of change were only different during the reversed conditions (FR, FR+PD,). Ballistic and corrective pathlengths rates of changes were only different during the standard conditions. Performance timing measure comparisons also did not yield consistent results, reaction time and total movement time only had a different rate of change during the FR conditions (Figure 10). Ballistic movement time did not yield any significant differences between the two groups in rates of change. Lastly, corrective movement time was only different between the two groups in rates of change during our non-plane dissociated conditions.

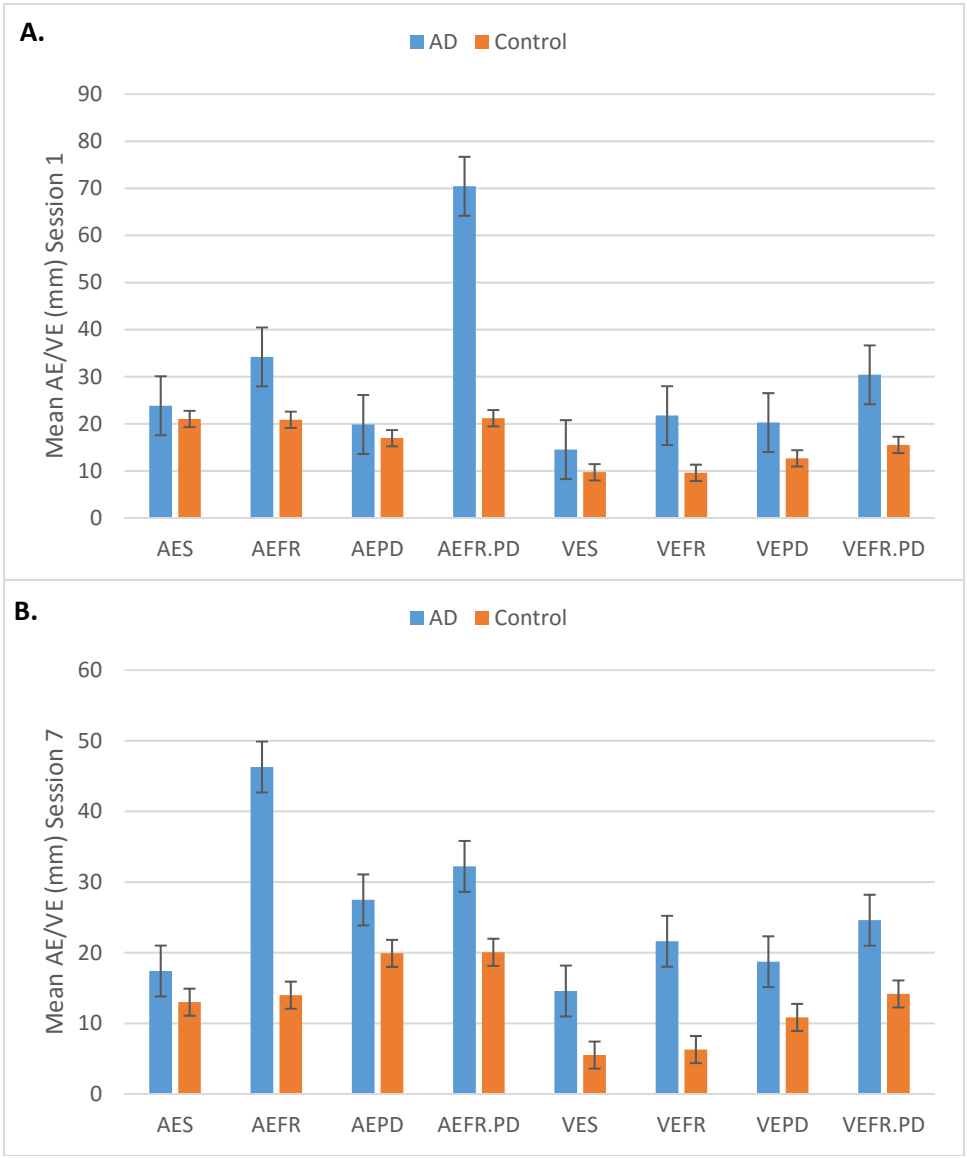

Figure 8. Mean AE and VE shown from AD and control groups. For statistical significance see Table 4. **A.** Measures from session 1. **B.** Measures from session 7.

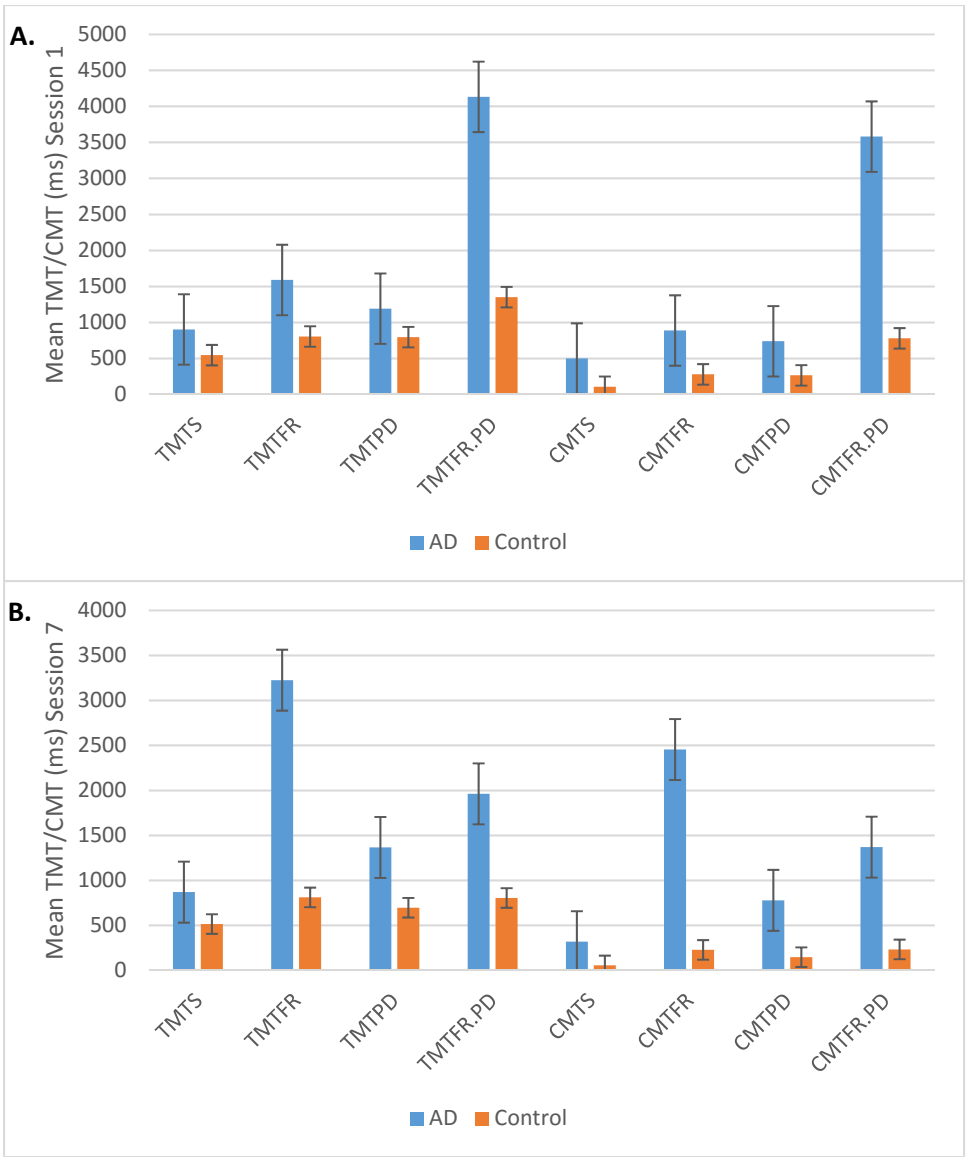

Figure 9. Mean TMT and CMT shown from AD and control groups. For statistical significances see Table 4. **A.** Measures from session 1. **B.** Measures from session 7.

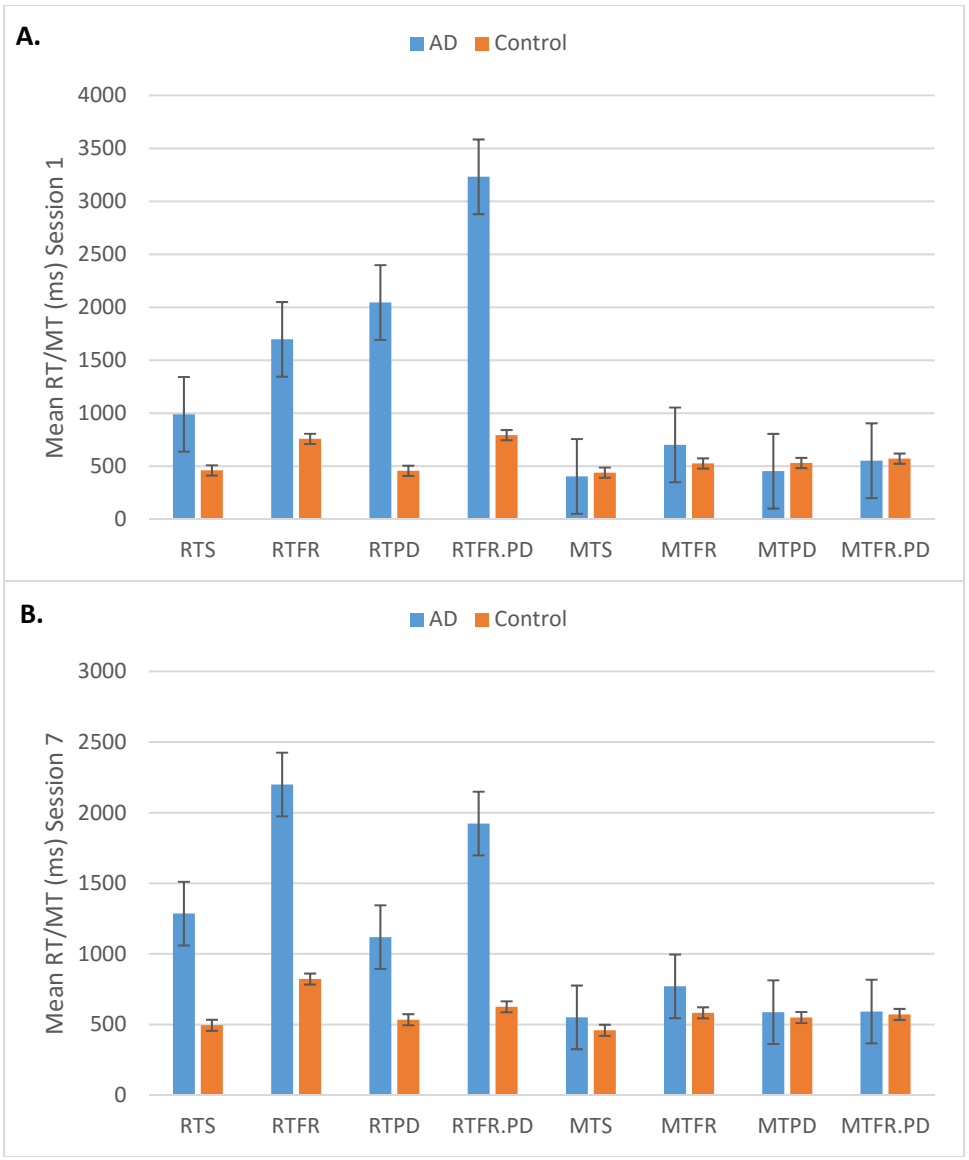

Figure 10. Mean RT and MT shown from AD and control groups. For statistical significance see Table 4. **A.** Measures from session 1. **B.** Measures from session 7.

Table 2. AD and control groups all measures – means across sessions, and Wald Chi-square p-values. NC = no change. AE, VE Abs. On and Abs. Off axis measures (mm); performance timing measures (ms); pathlengths and direction reversals (%); variability (std. dev.)

Statistical Report AD and Control											
			Sessions							p	Trend
Parameter	Cond.	Group	1	2	3	4	5	6	7		
Absolute Error	S	AD	23.93	26.09	26.10	24.94	16.20	19.42	17.40	0.00	↓
Variability	-	-	3.17	4.12	3.39	2.96	4.30	2.04	3.86	-	-
Absolute Error	S	CTL	21.02	8.59	8.82	6.61	12.39	16.99	13.00	0.00	↓
Variability	-	-	2.62	1.62	3.09	3.29	2.79	3.28	2.96	-	-
Absolute Error	FR	AD	34.42	29.82	38.10	31.68	34.34	44.15	46.27	0.00	↑
Variability	-	-	5.56	3.26	2.47	3.24	1.61	2.18	10.71	-	-
Absolute Error	FR	CTL	20.86	14.03	10.89	9.51	11.95	16.00	13.99	0.00	↓
Variability	-	-	2.46	3.04	1.93	2.25	1.99	2.56	2.92	-	-
Absolute Error	PD	AD	19.56	24.10	27.31	18.72	26.01	22.87	27.51	0.00	↑
Variability	-	-	1.09	2.87	1.86	2.80	0.97	2.20	5.62	-	-
Absolute Error	PD	CTL	16.95	14.31	15.38	14.15	17.37	18.44	19.91	0.00	↑
Variability	-	-	1.51	1.70	1.30	1.35	2.54	2.36	1.25	-	-
Absolute Error	FR+PD	AD	70.13	31.58	36.28	27.27	36.62	46.38	32.19	0.03	↓
Variability	-	-	17.52	6.93	4.68	4.19	5.08	7.03	3.12	-	-
Absolute Error	FR+PD	CTL	21.19	19.66	18.20	20.29	20.81	23.85	20.06	0.87	NC
Variability	-	-	3.46	0.83	2.34	1.18	1.96	1.79	3.68	-	-
Variable Error	S	AD	14.49	19.98	18.05	17.35	6.57	13.24	14.58	0.00	NC
Variability	-	-	1.37	2.50	1.88	0.65	2.29	2.46	2.97	-	-
Variable Error	S	CTL	9.64	5.66	7.94	4.71	7.39	5.57	5.43	0.00	↓
Variability	-	-	4.16	3.35	3.03	3.10	2.13	3.60	3.39	-	-
Variable Error	FR	AD	21.30	16.56	26.67	15.66	21.90	34.84	21.68	0.00	NC
Variability	-	-	1.90	1.44	1.99	3.83	4.00	4.07	3.23	-	-
Variable Error	FR	CTL	9.59	8.19	8.70	7.75	9.50	13.66	6.29	0.00	NC
Variability	-	-	3.03	2.71	3.48	1.70	2.85	2.91	1.79	-	-
Variable Error	PD	AD	19.66	18.35	24.82	16.42	16.88	14.69	19.08	0.00	NC
Variability	-	-	1.25	2.09	5.16	1.29	3.58	1.42	2.50	-	-
Variable Error	PD	CTL	12.67	12.63	10.82	10.02	12.17	13.31	10.84	0.86	NC
Variability	-	-	1.55	1.96	2.58	2.67	2.84	3.36	3.58	-	-
Variable Error	FR+PD	AD	29.92	28.90	17.47	19.60	23.64	25.61	24.54	0.00	↓
Variability	-	-	3.37	7.21	3.00	2.39	7.67	6.51	3.23	-	-
Variable Error	FR+PD	CTL	15.51	16.30	19.22	18.51	17.09	20.15	14.17	0.10	NC
Variability	-	-	2.79	3.83	4.26	4.32	5.03	3.36	4.12	-	-
Abs. On Axis Error	S	AD	22.07	23.27	21.33	22.46	18.63	13.37	12.43	0.00	↓
Variability	-	-	2.99	4.09	4.69	3.49	7.48	3.70	2.79	-	-

Abs. On Axis Error	S	CTL	17.80	5.70	5.70	4.90	8.30	15.45	12.49	0.00	↓
Variability	-	-	3.89	3.57	1.71	1.56	2.73	3.61	4.12	-	-
Abs. On Axis Error	FR	AD	31.43	28.65	31.38	31.27	33.66	35.95	40.14	0.29	NC
Variability	-	-	5.63	2.62	4.19	3.94	3.67	2.95	11.25	-	-
Abs. On Axis Error	FR	CTL	19.47	12.20	7.23	8.05	8.48	9.23	12.25	0.00	↓
Variability	-	-	2.66	2.66	2.99	3.00	3.78	1.89	3.65	-	-
Abs. On Axis Error	PD	AD	9.83	16.50	20.30	13.77	21.75	16.63	20.88	0.06	↑
Variability	-	-	1.27	4.53	3.42	2.59	3.27	4.74	5.92	-	-
Abs. On Axis Error	PD	CTL	11.21	9.20	11.20	9.38	11.87	12.41	15.85	0.00	↑
Variability	-	-	1.29	1.82	2.05	3.04	2.58	3.66	2.42	-	-
Abs. On Axis Error	FR+PD	AD	65.88	21.58	31.10	26.87	33.13	45.36	21.29	0.00	↓
Variability	-	-	18.12	5.41	6.99	1.60	3.41	8.03	6.97	-	-
Abs. On Axis Error	FR+PD	CTL	15.55	14.86	8.39	11.62	11.67	15.17	13.41	0.00	NC
Variability	-	-	2.80	1.58	0.89	2.41	2.61	2.63	3.22	-	-
Abs. Off Axis Error	S	AD	1.50	3.47	2.47	1.72	1.14	1.78	1.82	0.00	NC
Variability	-	-	0.39	1.23	0.88	0.12	0.28	0.56	0.48	-	-
Abs. Off Axis Error	S	CTL	2.25	1.40	0.91	0.88	1.66	1.54	1.32	0.00	↓
Variability	-	-	0.15	0.12	0.23	0.05	0.28	0.10	0.19	-	-
Abs. Off Axis Error	FR	AD	1.98	1.27	2.34	2.70	2.30	3.74	2.28	0.00	↑
Variability	-	-	0.68	0.21	0.20	0.68	0.22	0.72	0.31	-	-
Abs. Off Axis Error	FR	CTL	2.36	2.55	2.06	1.78	1.95	3.05	2.69	0.75	NC
Variability	-	-	0.41	0.45	0.63	0.36	0.23	0.48	0.52	-	-
Abs. Off Axis Error	PD	AD	2.93	3.37	5.54	3.06	4.88	3.24	3.58	0.07	NC
Variability	-	-	0.32	0.58	2.20	0.42	0.86	0.38	0.94	-	-
Abs. Off Axis Error	PD	CTL	2.17	2.11	1.59	2.07	1.94	1.43	2.15	0.13	NC
Variability	-	-	0.31	0.14	0.39	0.07	0.19	0.13	0.27	-	-
Abs. Off Axis Error	FR+PD	AD	4.11	3.74	3.33	5.02	5.16	4.94	3.36	0.00	NC
Variability	-	-	0.57	1.23	0.52	0.50	0.73	1.30	0.47	-	-
Abs. Off Axis Error	FR+PD	CTL	3.83	3.10	3.04	3.69	3.54	3.48	3.98	0.61	NC
Variability	-	-	0.90	0.48	0.92	1.05	1.48	1.59	1.75	-	-
Ballistic Pathlength	S	AD	0.60	0.66	0.77	0.68	0.74	1.15	0.92	0.00	↑
Variability	-	-	0.05	0.05	0.10	0.10	0.15	0.05	0.08	-	-

Ballistic Pathlength	S	CTL	1.20	1.04	0.99	1.03	1.04	1.20	1.12	0.00	NC
Variability	-	-	0.09	0.10	0.02	0.05	0.10	0.10	0.13	-	-
Ballistic Pathlength	FR	AD	0.69	0.66	0.75	0.72	0.61	1.03	0.88	0.00	↑
Variability	-	-	0.02	0.02	0.10	0.11	0.09	0.06	0.07	-	-
Ballistic Pathlength	FR	CTL	1.09	0.92	0.92	0.91	1.03	1.04	1.07	0.00	NC
Variability	-	-	0.17	0.17	0.01	0.01	0.14	0.11	0.16	-	-
Ballistic Pathlength	PD	AD	0.49	0.59	0.64	0.66	0.66	0.74	0.68	0.00	↑
Variability	-	-	0.13	0.11	0.13	0.11	0.15	0.11	0.09	-	-
Ballistic Pathlength	PD	CTL	0.82	0.76	0.93	0.94	0.96	0.89	0.98	0.00	↑
Variability	-	-	0.13	0.13	0.08	0.09	0.10	0.12	0.11	-	-
Ballistic Pathlength	FR+PD	AD	0.53	0.80	0.48	0.68	0.60	0.60	0.53	0.00	↓
Variability	-	-	0.18	0.11	0.17	0.17	0.16	0.11	0.19	-	-
Ballistic Pathlength	FR+PD	CTL	0.69	0.84	0.83	0.84	0.89	0.84	0.99	0.00	↑
Variability	-	-	0.18	0.16	0.11	0.14	0.13	0.16	0.09	-	-
Full Pathlength	S	AD	1.11	1.18	1.32	1.11	1.04	1.43	1.25	0.00	NC
Variability	-	-	0.12	0.11	0.10	0.07	0.04	0.08	0.12	-	-
Full Pathlength	S	CTL	1.35	1.11	1.09	1.08	1.18	1.28	1.18	0.00	↓
Variability	-	-	0.04	0.07	0.06	0.07	0.11	0.07	0.09	-	-
Full Pathlength	FR	AD	1.50	1.20	1.64	1.39	1.51	2.32	2.07	0.00	↑
Variability	-	-	0.16	0.09	0.07	0.09	0.05	0.27	0.35	-	-
Full Pathlength	FR	CTL	1.29	1.18	1.06	1.06	1.15	1.26	1.18	0.03	NC
Variability	-	-	0.08	0.12	0.06	0.05	0.09	0.06	0.11	-	-
Full Pathlength	PD	AD	0.86	1.22	1.18	1.10	1.25	1.07	1.23	0.00	NC
Variability	-	-	0.21	0.06	0.07	0.04	0.11	0.04	0.15	-	-
Full Pathlength	PD	CTL	1.06	1.06	1.08	1.08	1.10	1.09	1.11	0.61	NC
Variability	-	-	0.07	0.06	0.03	0.03	0.05	0.05	0.02	-	-
Full Pathlength	FR+PD	AD	2.03	1.59	1.21	1.29	1.51	1.95	1.03	0.00	↓
Variability	-	-	0.68	0.29	0.15	0.12	0.21	0.39	0.23	-	-
Full Pathlength	FR+PD	CTL	1.14	1.11	1.18	1.19	1.23	1.25	1.19	0.00	NC
Variability	-	-	0.03	0.03	0.06	0.07	0.07	0.09	0.06	-	-
Corr. Pathlength	S	AD	0.51	0.52	0.55	0.42	0.30	0.28	0.33	0.00	↓
Variability	-	-	0.11	0.11	0.11	0.07	0.14	0.08	0.14	-	-
Corr. Pathlength	S	CTL	0.15	0.08	0.10	0.04	0.14	0.07	0.05	0.09	↓
Variability	-	-	0.07	0.04	0.06	0.04	0.04	0.07	0.05	-	-
Corr. Pathlength	FR	AD	0.81	0.54	0.90	0.67	0.89	1.29	1.19	0.00	↑
Variability	-	-	0.16	0.11	0.09	0.13	0.11	0.31	0.35	-	-
Corr. Pathlength	FR	CTL	0.21	0.25	0.15	0.15	0.12	0.23	0.10	0.05	↓

Variability	-	-	0.11	0.09	0.05	0.04	0.06	0.08	0.05	-	-
Corr. Pathlength	PD	AD	0.37	0.63	0.53	0.45	0.59	0.34	0.54	0.00	NC
Variability	-	-	0.11	0.14	0.07	0.12	0.04	0.10	0.15	-	-
Corr. Pathlength	PD	CTL	0.24	0.30	0.15	0.14	0.14	0.20	0.13	0.00	↓
Variability	-	-	0.07	0.07	0.06	0.06	0.05	0.07	0.09	-	-
Corr. Pathlength	FR+PD	AD	1.50	0.78	0.73	0.61	0.92	1.35	0.50	0.00	↓
Variability	-	-	0.54	0.20	0.18	0.15	0.12	0.34	0.17	-	-
Corr. Pathlength	FR+PD	CTL	0.45	0.27	0.35	0.35	0.34	0.41	0.20	0.00	↓
Variability	-	-	0.20	0.15	0.17	0.20	0.20	0.21	0.11	-	-
Reaction Time	S	AD	959	2140	1483	1560	957	1075	1271	0.03	↓
Variability	-	-	139	201	457	327	174	254	245	-	-
Reaction Time	S	CTL	465	547	490	496	678	499	494	0.00	NC
Variability	-	-	72	41	35	42	120	47	35	-	-
Reaction Time	FR	AD	1664	2842	2668	2338	2389	2728	2204	0.00	↓
Variability	-	-	295	205	400	330	319	729	505	-	-
Reaction Time	FR	CTL	758	715	730	654	745	762	822	0.00	NC
Variability	-	-	139	82	90	98	117	92	131	-	-
Reaction Time	PD	AD	1959	1778	1641	1410	2199	1565	1127	0.00	↓
Variability	-	-	535	403	317	414	578	598	273	-	-
Reaction Time	PD	CTL	456	474	458	453	460	520	534	0.60	NC
Variability	-	-	53	46	48	61	58	67	108	-	-
Reaction Time	FR+PD	AD	3017	2629	2569	2755	2585	2037	1896	0.01	↓
Variability	-	-	539	617	868	396	344	367	195	-	-
Reaction Time	FR+PD	CTL	794	732	752	767	831	797	626	0.00	↓
Variability	-	-	119	91	82	114	97	75	120	-	-
Movement Time	S	AD	400	767	444	433	611	595	551	0.00	NC
Variability	-	-	62	209	55	63	100	63	61	-	-
Movement Time	S	CTL	440	475	442	476	508	458	459	0.00	NC
Variability	-	-	36	22	25	23	48	2	17	-	-
Movement Time	FR	AD	702	878	502	608	823	840	770	0.00	NC
Variability	-	-	191	149	68	39	112	60	83	-	-
Movement Time	FR	CTL	526	498	490	503	564	558	583	0.00	NC
Variability	-	-	66	53	27	29	30	20	55	-	-
Movement Time	PD	AD	426	738	488	547	715	591	591	0.00	↑
Variability	-	-	53	115	42	33	94	20	52	-	-
Movement Time	PD	CTL	531	428	514	552	539	528	550	0.03	NC
Variability	-	-	52	52	58	42	20	29	31	-	-
Movement Time	FR+PD	AD	524	687	405	666	724	573	589	0.00	NC
Variability	-	-	79	150	23	111	173	58	61	-	-
Movement Time	FR+PD	CTL	572	536	501	567	541	574	572	0.02	NC
Variability	-	-	83	51	53	50	38	13	61	-	-

TMT	S	AD	900	1869	1123	864	1102	896	870	0.00	NC
Variability	-	-	61	372	212	50	188	92	119	-	-
TMT	S	CTL	546	558	523	518	611	523	515	0.00	NC
Variability	-	-	49	19	17	21	47	32	28	-	-
TMT	FR	AD	1628	2360	2321	1899	2773	3266	3219	0.00	↑
Variability	-	-	210	341	419	278	128	345	677	-	-
TMT	FR	CTL	805	780	691	714	725	890	811	0.02	NC
Variability	-	-	163	45	50	78	101	146	191	-	-
TMT	PD	AD	1079	1977	1305	1157	2122	1206	1378	0.01	NC
Variability	-	-	364	513	218	306	542	344	298	-	-
TMT	PD	CTL	796	740	675	708	669	744	697	0.00	↓
Variability	-	-	68	57	76	82	70	78	117	-	-
TMT	FR+PD	AD	3990	2125	2272	2414	3354	3537	1944	0.00	↓
Variability	-	-	1091	505	634	626	491	593	682	-	-
TMT	FR+PD	CTL	1351	981	961	1057	1076	1101	805	0.00	↓
Variability	-	-	303	208	208	295	254	268	238	-	-
CMT	S	AD	500	1102	679	431	491	300	319	0.02	↓
Variability	-	-	58	262	211	62	246	89	120	-	-
CMT	S	CTL	107	83	81	42	102	66	56	0.00	↓
Variability	-	-	32	11	20	24	13	30	26	-	-
CMT	FR	AD	925	1483	1820	1291	1950	2426	2449	0.00	↑
Variability	-	-	99	214	420	284	131	373	641	-	-
CMT	FR	CTL	279	282	201	210	161	332	228	0.00	↓
Variability	-	-	154	92	30	52	84	135	145	-	-
CMT	PD	AD	656	1240	931	611	1408	616	787	0.03	NC
Variability	-	-	332	463	295	318	462	361	283	-	-
CMT	PD	CTL	265	312	162	155	130	216	147	0.00	↓
Variability	-	-	81	83	67	64	69	88	100	-	-
CMT	FR+PD	AD	3466	1437	1867	1748	2630	2964	1356	0.00	NC
Variability	-	-	1025	370	620	538	507	621	622	-	-
CMT	FR+PD	CTL	779	445	460	490	535	527	233	0.07	↓
Variability	-	-	313	207	191	275	263	265	192	-	-
DR	FR	AD	37.23	37.98	30.51	30.81	45.45	36.62	38.93	0.05	NC
Variability	-	-	10.05	4.23	5.87	8.52	9.08	6.02	12.90	-	-
DR	FR	CTL	0.00	3.75	1.25	1.39	0.00	3.75	0.00	0.00	NC
Variability	-	-	0.19	1.89	1.22	1.34	0.19	1.23	0.19	-	-
DR	FR+PD	AD	53.13	28.79	29.59	42.14	40.26	54.49	24.19	0.04	↓
Variability	-	-	12.63	8.48	10.42	8.67	9.40	10.72	8.34	-	-
DR	FR+PD	CTL	7.50	7.50	9.01	7.32	4.94	8.96	1.25	0.01	↓
Variability	-	-	9.09	2.79	6.58	5.08	3.70	6.54	2.42	-	-

Table 3. All overall measures with a significant interaction with MOCA score differences. AD group: Kruskal-Wallis to determine a difference between the 3 MOCA score groups, and Mann-Whitney U used as post-hoc analysis. Control group: Mann-Whitney U to determine difference between the 2 MOCA score groups.

MOCA score interactions						
			Kruskal-Wallis	No Change &↑	No Change & ↓	↑&↓
Parameter	Group	Condition	p	p	p	p
Variable Errror (mm)	AD	FR	0.004	0.033	0.274	0.001
Variable Errror (mm)	AD	PD	0.047	0.056	0.075	0.116
Corrective Pathlength (%)	CTL	S	-	-	0.055	-
Corrective Pathlength (%)	CTL	FR	-	-	0.071	-
Reaction Time (ms)	AD	FR+PD	0.000	0.026	0.001	0.000
Reaction Time (ms)	CTL	S	-	-	0.071	-
Movement Time (ms)	AD	PD	0.015	1.000	0.055	0.007
Total Movement Time (ms)	AD	PD	0.002	0.741	0.009	0.002
Corrective Movement Time (ms)	CTL	S	-	-	0.016	-

Table 4. Comparison between AD and control groups in all accuracy, precision, trajectory/pathlength, and timing performance measures overall, at session 1 and session 7. p-values displayed for overall, only session 1 and only session 7 measures.

AD and Control Comparisons Chart																
	AES	AEFR	AEPD	AEFR.PD	VES	VEFR	VEPD	VEFR.PD	ONS	ONFR	ONPD	ONFR.PD				
Overall	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.007	0.002	0.000	0.010	0.000				
Session 1	0.773	0.386	0.157	0.034	0.564	0.083	0.034	0.034	0.386	0.386	0.480	0.034				
Session 7	0.462	0.027	0.327	0.083	0.050	0.014	0.050	0.083	1.000	0.086	0.806	0.386				
	OFFS	OFFFR	OFFPD	OFFFR.PD	RTS	RTFR	RTPD	RTFR.PD	MTS	MTFR	MTPD	MTFR.PD				
Overall	0.276	0.766	0.000	0.159	0.000	0.000	0.000	0.000	0.329	0.002	0.192	0.906				
Session 1	0.083	0.386	0.157	0.724	0.043	0.043	0.034	0.034	0.773	0.773	0.289	0.480				
Session 7	0.462	0.624	0.462	0.773	0.027	0.050	0.050	0.021	0.327	0.327	0.806	0.773				
	TMTS	TMTFR	TMTPD	TMTFR.PD	CMTS	CMTFR	CMTPD	CMTFR.PD	FULLS%	FULLFR%	FULLPD%	FULLFR.PD%				
Overall	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.854	0.000	0.130	0.003				
Session 1	0.021	0.564	0.157	0.034	0.021	0.248	0.157	0.034	0.248	0.773	0.564	0.248				
Session 7	0.027	0.014	0.086	0.248	0.086	0.027	0.027	0.248	1.000	0.050	0.624	1.000				
	BALLS%	BALLFR%	BALLPD%	BALLFR.PD%	CORRS%	CORRFR%	CORRPD%	CORRFR.PD %								
Overall	0.000	0.005	0.000	0.004	0.000	0.000	0.000	0.000								
Session 1	0.021	0.149	0.043	0.564	0.043	0.083	0.248	0.248								
Session 7	0.221	0.462	0.027	0.027	0.050	0.014	0.050	0.327								

Table 5. Crawford and Howell modified t-test comparing individual dementia patients with normative control data during our most cognitively demanding condition (FR+PD). Significance accepted at $p<0.05$. For detailed demographics of all dementia patients please see Table 1.

Subject	Session	Measure	p
1	1	RT	0.000
	7		0.000
	1	CMT	0.001
	7		0.028
	1	Corrective Pathlength	0.120
	7		0.003
2	1	RT	0.080
	7		0.025
	1	CMT	0.004
	7		0.332
	1	Corrective Pathlength	0.003
	7		0.661
3	1	RT	0.001
	7		0.000
	1	CMT	0.049
	7		0.068
	1	Corrective Pathlength	0.012
	7		0.223
4	2	RT	0.003
	7		0.193
	2	CMT	0.049
	7		0.068
	2	Corrective Pathlength	0.042
	7		0.020
5	2	RT	0.000
	6		0.000
	2	CMT	0.038
	6		0.001
	2	Corrective Pathlength	0.034
	6		0.014

Discussion

Our overall aim was to conduct a pilot study in order to determine the feasibility of CMI training in older adults with cognitive impairments. Our findings support our hypothesis that CMI training can improve and stabilize kinematic measures in a cognitively impaired or healthy geriatric population. As well, our findings confirm that CMI performance is indeed impaired in dementia patients compared to both healthy adults and to their own standard movement control. However, we should interpret our results with caution since we did experience a high level of variability in the measures especially for our dementia patients, thus accept our findings as preliminary although promising for future research. We established that a training program utilizing cognitive-motor integration can allow us to quantitatively measure the ability to integrate cognitive information into a motor action in dementia patients with severe to mild impairments. Strategic control and/or visual-spatial recalibration tasks allowed us to indirectly measure our participants' abilities to effectively plan, perform and integrate visuospatial transformations. Compared to traditional cognitive-alone or motor training programs, we believe our CMI protocol will have greater relevance to functional activities of daily living and may assist in functional decline prevention. Importantly, we have now established a feasible method for studying the effects of cognitive-motor training on maintaining functional brain health in adults in the early stages of dementia.

Our results support previous findings that visuomotor networks involved in CMI performances are compromised in individuals with dementia (Hawkins & Sergio, 2014). We observed impairments in nonstandard movements, those requiring explicit cognitive strategic control, those requiring implicit visual-spatial (proprioceptive) recalibration, as well as conditions that require the integration of the latter two for dementia patients compared to healthy

controls. We also observed a significant impairment in dementia patients displaying direction reversal errors in the feedback reversal conditions, suggesting a highly impaired inhibition of desired responses. Further, we noted an overall slowing of movement planning and movement execution across tasks, when compared to healthy controls. These above mentioned findings support previous studies examining those with AD, MCI or elevated AD risk (Tippett & Sergio, 2006; Hawkins & Sergio, 2014; Hawkins, et al., 2015; Salek et al. 2011).

We suggest that CMI training programs may strengthen networks or regions associated with visuomotor transformations identified by imaging and neurophysiological studies (Reiman, et al., 1996; Small, et al., 1995; Small, et al., 2000; Miller & Cummings, 2013). Incorporating a memory aspect to our training protocol was not considered since disruptions in the DLPFC and this regions association with visual working memory can impair rule-based integrations by placing too much cognitive demand (Curtis, 2006; Luck & Vogel, 2013). Imaging studies have also showed atrophy of the precuneus (Honea, et al., 2010), an area associated with memory-guided anti-reaching movements (Fernandez-Ruiz, et al., 2007), prior to the onset of symptoms in AD. Therefore, it is likely that the addition of a memory component would yield greater deficits, but may result in a ceiling effect in the current paradigm (Tippett, et al., 2007)

In terms of the different types of cognitive-motor integration that we examined with our task, we found that dementia patients had a greater impairment with strategic control compared to visual-spatial recalibration. Our analysis revealed that not only is strategic control the second highest impairment in many measures, it was also the only measure to continually deteriorate during our training program.

Deterioration of strategic control

We observed that our AD group displayed a deterioration of measures in the FR condition selectively, except for MT and ballistic pathlength. Comparatively, our control group had very few measures indicating poorer performances. We suggest that impairments in the SPL may be the driving factor behind this deterioration of strategic control. Given the SPL's role in strategic control and its inhibition during plane dissociation we believe that disruptions in the frontoparietal network may result in SPL impairments. However, since the deep SPL has been associated with increased neural activity during reach planning and early movement execution (Hawkins, et al., 2013) we must accept our interpretations with caution since ballistic measures were not changing or deteriorating in the AD group. SPL lesion cases have shown to produce similar results to our findings (Granek, et al., 2012), where strategic control (FR) conditions were shown to have greater impairments than visual-spatial recalibration tasks in patients with optic ataxia.

Accuracy and precision

Overall, we observed a greater deficit in dementia patients for accuracy and precision measures compared to control groups, as well as between sessions 1 and 7. We observed that dementia patients were able to improve their precision and accuracy errors in our most challenging condition, unlike our control group. Accuracy and variability have been shown to have diminished performance in older adults compared to young adults, however several studies have shown that fine motor learning rates are not generally different between age groups (Voelcker-Rehage, 2008; Anshel, 1978; Smith, et al., 2005). Previous studies have shown accuracy measures to be diminished when visual feedback was unavailable (Ghilardi, et al., 1999), therefore it is possible that our dementia patients are learning to improve their accuracy

without visual feedback of their hand positions across sessions. This finding suggests that brain network connectivity between movement planning regions and proprioceptive sense regions may be improving in this group.

Our results indirectly support previous studies that suggest motor learning abilities differentiate between young and older adults with greater difficulty in tasks (Breitenstein, et al., 1996) since our precision and accuracy measures only had a different rate of change between the two experimental groups during our most complex condition.

Timing performance

Overall we observed greater deficits in dementia patients in all timing measures compared to control groups. However, further analysis revealed that these differences between groups were not as pronounced during sessions 1 and 7, with the exception of movement planning and ballistic movement timing. Reaction time was of particular importance to our findings, since it was able to decrease across sessions for our AD group in all conditions. We detected a noteworthy trend in the non-plane dissociated conditions, where dementia patients increased their RT's at session 2 compared to their session 1 and only observed an improving trend after session 2. We propose that these measures may not be due to coincidence, but rather a compensatory mechanism in which the dementia patients learn to significantly plan their movements longer to successfully execute it. Previous research has shown that older adults displayed slower movement speeds compared to those younger (Smith, et al., 2005). Our findings also support that older adults with, or at risk for, cognitive impairments with an altered frontoparietal network display slower movements (Hawkins & Sergio, 2014). It was also noteworthy that we detected a significant interaction between the differences in MOCA scores and movement planning during our most cognitively challenging condition. We observed that

dementia patients with either no change or an increased MOCA score at the end of our training program had greater RT measures compared to those in the decreased group. It is possible that participants with a stable or improved cognitive abilities still have enough plasticity to learn that greater movement planning can allow a higher chance of successful trials. Although not directly supported by our findings, several studies have observed possible plasticity in the AD brain especially if subject to a stimulating environment such as physical activity (Erickson, et al., 2012). As well, imaging studies have observed hyperactivities in task-positive regions, suggesting a compensatory mechanism (Elman, et al., 2014). Given the severity of cognitive decline in our AD group and since compensatory mechanisms in CMI performances have not been assessed, we cannot infer if these findings from previous studies are applicable, since our dementia patients may have a high level of neural inefficiencies where compensatory mechanisms cannot assist their performances. We suggest that these decreases in timing measures for our most demanding condition may be a result of an improving speed-accuracy trade off since our endpoints measures improve during these conditions as well.

Our control groups only showed an improvement in movement planning during the most complex conditions, suggesting that the other three less demanding conditions did not provide a great enough challenge to change RT across sessions (ceiling effect). Ballistic movement time was not affected by sessions, and TMT was able to improve in the plane dissociated conditions. Such a ceiling effect in healthy adults in comparison to our dementia group illustrates the sensitivity of measures that combine domains, in this case cognition and action, for assessing brain network integrity.

Compared to our dementia patient group, our control participants were able to reduce their CMT measures, reflecting on-line feedback processing, in all conditions. We also observed

that CMT had a different rate of change in non-plane dissociated conditions, suggesting that dementia patients were not able to learn at the same rate as healthy adults in conditions involving plane dissociation. These results suggest that AD groups may have impaired superficial SPL and PMdc networks or regions (Sayegh, et al., 2013; Sayegh, et al., 2014). Given previous work showing that dementia participants display an impaired DLPFC metabolism, it is possible that disruptions in this specific frontoparietal network is not allowing the AD group to learn to reduce their corrective measures like the healthy controls.

Pathlengths

Overall, we observed greater deficits in full and corrective pathlength measures in the dementia patient group compared to healthy controls. However, further analysis revealed that at session 1 only the corrective movements during our non-plane dissociated conditions were different. Session 7 revealed greater differences between the two groups, most notably with the additional differences in corrective movements for condition PD.

We were able to observe an increase in ballistic pathlengths in all conditions except our most difficult task in dementia patients. This could suggest that the dorsomedial pathway associated with arm reaching and online corrections are strengthening through our training program (Gallivan & Culham, 2015). We believe that the SPOC/SPL→PMd→M1 pathway is being targeted at the PMd either directly due to the areas involvement with sensorimotor tasks or indirectly through the areas association with DLPFC. In support of our theory lesions at the PMd have been shown to impair visuomotor transformation tasks (Sayegh, et al., 2013).

Control groups most notably differed from the AD group since they were able to decrease their corrective movements in all conditions, and ballistic movements were able to increase for our plane dissociated conditions. Ballistic pathlengths were not affected by sessions in non-plane

dissociated conditions, since they were able to reach their targets with a ballistic movement nearly 100% of the time from baseline. We believe that our control group was able to train the same dorsomedial pathway discussed earlier, however given that disruptions in the frontoparietal network does not exist to the same extent of dementia patients, they were able to utilize neural plasticity to train this network with greater effects over our training period. Note however that our inferences about brain network alterations are of course indirect, given the psychophysical nature of our research method. These data however, will assist in targeting regions of interest for imaging studies planned by our group using this approach in the near future.

We did observe that the rate of change between groups was different for full movements during our reversed conditions, suggesting that healthy controls were able to learn to reduce their full movements hand path distance across sessions. These results are supported by our findings from the direction reversal errors, since the dementia patient group had significantly greater DRs overall compared to controls.

Trajectory

Results from our trajectory measures did not yield consistent findings across conditions. Indeed, we did not find any statistical differences between the two experimental groups in our comparisons analysis at sessions 1 or 7. We suggest the improvement of on-axis errors (reflecting planned movement distance) in the AD group during our most cognitively demanding task is due to an improved ability to utilize online updating involving the cerebellum. Studies have suggested that various forms of dementia including AD can alter cerebellum connectivity and volume (Caminiti, et al., 2016; Lamer, 1997; Wegiel, et al., 1999). At the molecular level, the lack of cell adhesion molecules has been attributed to impaired cell-cell interactions as well as plasticity (Murray, et al., 2016). Importantly, cerebellar disruptions have been observed in

healthy older adults as well AD patients' post-mortem, and may explain why we did not see any differences during our comparisons analysis. The cerebellum, in its role coordinating muscle timing – important for planning movement distance – may be affected by aging across groups.

Direction reversals and failed trials

Our findings have shown that the AD group was able to reduce the number of DR errors and failed trials in FR and FR+PD conditions. Thus, they were able to improve our performances in strategic control and tasks requiring the integration with visual-spatial recalibrations. These results are supportive of our earlier interpretations of our CMI performance measures. We believe the strengthening of the dorsomedial pathway, as well as the connectivity between SPL and associated regions (Figure 1) are allowing our dementia patients to decrease their DR errors. Since these networks described, have connections with the DLPFC, we suggest the increased ability to form short-term memories as well as enhanced attention is improving their abilities to perform and remember rule-based integration tasks. However, healthy controls were only able to display improvements during the most challenging condition. Therefore, we suggest that healthy older adults were training the same networks described above, however with a greater emphasis of training DLPFC, SPL and PMd connectivity to successfully execute visuomotor transformations.

Individual dementia patient analysis

Our findings from our Crawford and Howell analysis confirm our findings that overall all dementia patients exhibited a greater level of CMI performance impairment when compared to healthy controls. We also believe that our findings can infer a possible target range of cognitive impairment, for CMI training to be effective in this population. We found that the greater the level of cognitive impairment as measured by the MOCA, the greater the likelihood that CMI

performance measures will be significantly more impaired when compared with healthy older adults in baseline or final training sessions. However, given that our least cognitively impaired dementia patient was able to improve her movement execution measures by the end of CMI training, these findings suggest CMI training as a promising method of intervention to prevent decline or improve functional performance. It is important to note that given our limited sample, our findings may not represent the possible link between cognitive impairment and performance as indicated above. Our findings may be due to other external factors later discussed in this paper.

Allocentric and egocentric coding in CMI

Our visuomotor experimental tasks as previously described requires the coordination of various brain regions and networks as well as the ability to integrate allocentric and egocentric regions to successfully execute our nonstandard tasks. We suggest our plane dissociated conditions (PD & FR+PD) utilize egocentric coding mechanisms, since these conditions rely heavily on continuous monitoring of proprioception. In contrast, our non-plane dissociated conditions (S & FR) may be utilizing allocentric coding mechanisms i.e. tablet/visual field borders. Our results suggest that dementia participants were able to increase their inhibition of desired responses to show promising changes in endpoint accuracy measures during our most demanding condition. Given these positive changes in endpoint accuracy, we suggest that our dementia patients were able to better operate egocentric coding mechanisms with training compared to initial sessions. The improved ability to utilize egocentric coding may be responsible for the decreases in corrective measures we observed. Increased network connectivity from the medial temporal lobe to the inferior parietal regions via the cingulum bundle may be allowing a greater egocentric representation in dementia patients with CMI training. Given the PPC's involvement with egocentric representations, as well as the MTL's

involvement with allocentric/egocentric representations one would expect both egocentric and allocentric coding impairments in individuals with dementia.

Study limitations

Our study did have several limitations. We believe our greatest limitation was the small sample size of dementia and control participants, as well as the large range of cognitive impairment for our patient group. Due to this small sample size we had extremely high variability within the data especially for our dementia patient group. This variability caused statistical significances during our Wald Chi-square analysis due to the large differences between sessions in some measures. We attempted to control this limitation by visually inspecting the post-hoc analysis to determine if a clinically significant pattern or trend could be determined. We also examined variability as a dependent measure on its own, since such performance variability reflects biological noise in the movement planning system. With this sample size however we did not observe significant reductions in variability in our AD group, despite such a reduction being typical of motor learning paradigms. Future work will require greater sample sizes so that variability itself can be studied as a source of neural network plasticity during multi-domain tasks. Given the large variability in measures from dementia participants, we must accept all our interpretations with extreme caution. Any improvements, stabilizations or deterioration of any measures may be due to the high level of variability itself and not a true reflection of participant's performances across sessions. Another limitation was that during our PD and FR+PD conditions, our experimental setup also displayed visual feedback from the direct plane (horizontal tablet). We controlled this limitation by verbally reminding the participants to keep their eyes on the vertical external monitor during PD trials. However, the capability to track eye movements of the participants would have allowed us to better control this limitation. Third, a

significant barrier especially with the AD group was the participants' attention and willingness to participate. All subjects had periods of decreased attention due to external distractions, which we attempted to minimize inattentiveness by setting up our experimental setups in a quiet room with no other sounds or persons. A few participants from both the AD and control groups expressed their concerns about their release of information; therefore, we must develop techniques to provide a more comforting environment for participants. Finally, our AD group was recruited from a care facility for geriatric populations with cognitive impairments. Therefore, our participants were subjected to a variety of other recreational programs that have been shown to assist those with cognitive impairments such as physical activity, music therapy, socialization and cognitive training (activities/puzzles). This final limitation is of high importance, since we cannot conclusively determine that any changes in measures we observed were due to CMI training alone. One would hope, however, that our control participants experienced a similarly enriched daily life in between sessions, although this is something that perhaps should be measured explicitly in follow-up research.

Circadian rhythm influences on CMI performance

During our CMI training program we did attempt to control the time of day our participants were assessed since it is well established that cognitive performances can fluctuate significantly throughout the day, especially when interacting with different prescription medications. Unfortunately, due to researcher and participants' schedules we were unable to always control our assessment times. During our analysis we observed that several measures during session 6 for our AD group were higher than the expected values (determined by pattern/trend). Upon detailed investigations of the data and collection methods, we determined that the increases in several measures at session 6 were due to an increase in measures from our

two most cognitively impaired patients. We observed that these measures were taken immediately post-meal. Given findings from several studies that linked diabetes, CVD and hypertension with impaired executive functioning it may be possible that these participants had diminished attention or cognitive functions associated with poor glucose or sodium regulations. It is important to note that both participants did not have a diagnosis of diabetes. However, since this is an isolated incident, and our interpretations are not based on controlled factors (diet, exercise, metabolic regulation) we will need to supplement our limited findings with further studies.

Conclusions and implications

Our findings support the concept that CMI training is feasible for dementia patients with severe, moderate, and mild cognitive impairments. Based on our results we suggest that kinematic measures may improve even in severely impaired dementia patients. We have also replicated previous studies from our lab, showing that dementia patients during CMI training display similar findings to SPL lesion patients. Furthermore, we believe that CMI training can provide functional decline prevention as measured by ADL or independence living assessments in healthy, MCI, eAD and dementia participants. Importantly, our results provide evidence that the integration of cognitive and motor training can yield valuable, and clinically-relevant outcomes.

In the future we would like to incorporate a more intensive and longer CMI training program to determine if our findings can be replicated. It is possible that healthy older adults did not experience the same level of cognitive demand compared to our dementia participants, given the vast difference in neural inefficiencies. Therefore, we suggest a ceiling effect may have occurred for our control participants. In future studies we would like to assess this ceiling effect

and provide healthy older adults with a task that matches in difficulty experienced by our dementia population. We believe CMI training may provide changes in brain structures or networks that can be detected via imaging techniques. However, it would be important to determine at what level of cognitive impairment are these improvements applicable to real life scenarios, and if we can target an optimal range of cognitive abilities as detected by common neuropsychological assessments. Finally, we believe CMI training may have uses outside of AD or dementia, such as individuals with CVD, diabetes, family history of dementia or those with acquired brain injury, to maintain functionally relevant abilities.

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