SEX-DIFFERENCES IN THE EARLY DETECTION OF DEMENTIA RISK USING A COGNITIVE-MOTOR INTEGRATION TASK

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ABSTRACT

Cognitive-motor integration (CMI) involves concurrent thought and action which requires the interaction of large brain networks. Our research objectives were to examine the effect that dementia risk has on the ability to integrate rules into action and to investigate sex-related differences in this rule-based motor performance. Given that early-stage dementia involves neural network dysfunction, problems with CMI may prove useful for early dementia detection. Males and females at high- and low-dementia risk were tested on increasingly spatially-dissociated visuomotor tasks. We observed significantly greater endpoint error scores and corrective path lengths in females compared to males in the most complex CMI condition. These data suggest that underlying brain networks controlling simultaneous thought and action differ between the sexes, and that dementia risk may affect female CMI performance to a greater extent. Thus, sex-related differences must be taken into account when assessing CMI performance as a means to examine dementia risk-related functional abilities.

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LIST OF ABBREVIATIONS

#SubMvt – Number of sub-movements
%SubMvt – Percentage of sub-movements
Aβ – Amyloid beta
AD – Alzheimer's disease
AE – Absolute error
APOE – Apolipoprotein E
    e2, e3, e4 - APOE epsilon alleles
APP – Amyloid precursor protein
BIN1 – Bridging indicator 1
BOLD – Blood oxygen level dependent
CLU – Clusterin
CMA – Cingulate motor area
CMI – Cognitive-motor integration
CMRGlc – Cerebral metabolic rate for glucose
CNS – Central nervous system
CPL – Corrective path length
CR1 – Complement receptor 1
CSF – Cerebrospinal fluid
DMN – Default mode network
DR – Direction reversal
DSM-5 – Diagnostic and Statistical Manual of Mental Disorders V
DTI – Diffusion tensor imaging
EOAD – Early-onset Alzheimer's disease
FA – Fractional anisotropy
FD – Frame displacement
FR – Feedback reversal
GM – Grey matter
GWAS – Genome-wide association studies
HRT – Hormone replacement therapy
IPL – Inferior parietal lobule
IPS – Intraparietal sulcus
    AIP – Anterior IPS
    MIP – Medial IPS
    LIP – Lateral IPS
    VIP – Ventral IPS
KMO – Kaiser-Meyer-Olkin test
LOAD – Late-onset Alzheimer's disease
M1 – Primary motor cortex
MCI – Mild cognitive impairment

MoCA – Montreal Cognitive Assessment
MRI – Magnetic resonance imaging
    fMRI – functional MRI
    rsfMRI – resting-state fMRI
MT – Movement time
    MTb – movement time ballistic
    MTf – movement time full
NIA/AA – National Institute on Aging and the Alzheimer's Association
NINCDS-ADRDA – Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PC – Plane-change
PCA – Principle components analysis
PET – Positron emission tomography
PICALM – Phosphatidylinositol binding clathrin assembly protein
PL – Path length
    PLb – path length ballistic
    PLf – path length full
PMC – premotor cortex
    SMA - Supplementary motor area
    CMA – Cingulate motor area
    PMd – Lateral dorsal premotor area
    PMv – Lateral ventral premotor areas
PO – Parieto-occipital region
PPC – Posterior parietal cortex
PSEN – Presenilin protein
PV – Peak velocity
R – Observed correlation matrix
r – Effect size
RT – Reaction time
S – Standard mapping task
SCP – Slow cortical potentials
SMA – Supplementary motor area
SNP – Single nucleotide polymorphism
SPL – Superior parietal lobule
TMS – Transcranial magnetic stimulation
V1 – Primary visual cortex
VE – Variable error
WM – White matter

INTRODUCTION

Dementia

Prevalence and costs

Dementia is a syndrome characterized by 1) cognitive impairments in a variety of domains (memory declines, language problems, psychiatric changes), and 2) disruption of activities in daily living (Burns and Illife, 2009). Alzheimer's disease (AD) is the most common cause of dementia (Reitz and Mayeux, 2014). According to the 2015 World Alzheimer Report, approximately 46.8 million people worldwide are living with dementia - this is greater than the current population of Canada (Prince et al., 2015). By the year 2030, this number is expected to increase to more than 74 million worldwide, with 886 000 in Canada. In addition to being a global health issue, dementia also has a considerable economic impact. The Public Health Agency of Canada (2014) projects the cost of dementia to be over 16 billion CAD, while the 2015 World Alzheimer Report (Prince et al., 2015) estimates global costs to rise to 2 trillion USD.

Pathophysiology of Alzheimer's disease

AD is characterized by three brain abnormalities 1) atrophy (narrowed gyri, widened sulci, reduced brain weight, enlarged ventricles), 2) extracellular amyloid plaques, and 3) cytoskeletal abnormalities from intracellular accumulation of neurofibrillary tangles (hyperphosphorylated tau protein) (Schwartz et al., 2012). It has been proposed that the neurodegeneration in AD may be due to abnormal deposition of amyloid beta (Aβ) protein in plaques in brain tissue (Hardy and Selkoe, 2002). The amyloid hypothesis states that the primary driving force of AD pathology is the accumulation of Aβ in the brain, and that the rest of disease pathology (such as formation of neurofibrillary tangles) is a direct result of an imbalance in Aβ deposition and Aβ clearance.

However, recent studies have proposed that it is equally plausible that alterations in tau are not downstream of Aβ accumulation, but rather that tau and Aβ act in parallel pathways to enhance one another's toxic effects and cause AD pathology (Small and Duff, 2008).

Genetic epidemiology of Alzheimer's disease

Genetic factors play a large role in determining an individual's risk for AD. AD can be classified based on its age of onset into early-onset AD (EOAD) and late-onset AD (LOAD) (Reitz and Mayeux, 2014). EOAD is the less common of the two, affecting approximately 1-5% of all cases with a typical onset of <65 years old. It exhibits a Mendelian pattern of autosomal dominant inheritance and genetic heterogeneity, where three genes (*APP*, *PSEN1*, and *PSEN2*) are associated with EOAD pathophysiology (Martin et al., 1991; Campion et al., 1995). AD-linked mutations in these genes and their protein products lead to Aβ generation and aggregation (Martin et al., 1991).

LOAD is more common, accounting for >95% of all cases with an onset of >65 years old and it is not associated with a Mendelian pattern of inheritance (Reitz and Mayeux, 2014). Instead, first-degree cognitively normal relatives of people with LOAD are at twice the risk of developing AD compared to those who do not have a first-degree relative with LOAD. This, in combination with the increased frequency of LOAD in monozygotic compared to dizygotic twins, indicates a 60-80% contribution of genetic factors. One study looked at parental family history of AD and any potential parent gender effects on AD risk (Mosconi et al., 2007). They found reductions in the cerebral metabolic rate for glucose (CMRGlc) corresponding to AD pathology in individuals with a maternal family history of AD after having accounted for other possible risk factors for AD (age, gender, *APOE*, education level, and reported memory complaints).

One of many genes that predisposes the carrier to AD is an isoform of the apolipoprotein E (*APOE*) gene, the *APOE* e4 allele (Mahley et al., 2009). *APOE* expressed as one of three isoforms, which are coded for by the three alleles, *APOE* e2, e3, and e4 (Reitz and Mayeux, 2014). *APOE* is a lipid-binding protein that transports cholesterol between cells in multiple tissues (including the brain), and regulates the redistribution of cholesterol within cell membranes (Puglielli et al., 2003). These functions are essential for the nervous system, since cholesterol is needed for maintaining myelin and neuronal membrane integrity (Leduc et al., 2010). While *APOE* works in conjunction with other cholesterol transporters, it is more abundant in the brain and thus makes the CNS particularly dependent on *APOE* for cholesterol transport. Studies comparing properties of the three *APOE* isoforms found structural differences that lead to varying physiological effects. Specifically looking at the brain, the e4 isoform has been shown to cause a reduced ability for *APOE*-dependent Aβ clearance, and increased tau accumulation, resulting in an overall increased risk for Alzheimer's (Andersson et al., 2006; Mattsson et al., 2009; Strittmatter et al., 1994).

APOE has been identified as a susceptibility gene for the development of both EOAD and LOAD, with the proportion of the *APOE* e4 allele in LOAD being greater than in EOAD (Panegyres and Chen, 2013). Interestingly, findings show that the *APOE* e2 allele is seen more with EOAD, suggesting a genetic difference between LOAD and EOAD. As a result, *APOE* e4 has been identified as a major genetic risk factor for development of LOAD (Panegyres et al., 2000). It is important to note, however, that although it increases the risk of LOAD, not everyone with the allele will develop AD and not everyone with AD has the allele. Genome-wide association studies (GWAS) have identified polymorphisms in other genes (e.g. *CLU*, *PICALM*,

CR1, *BIN1*, etc.) as additional susceptibility loci for AD, however they provide less of a risk when compared with *APOE* (Seshadri et al., 2010).

A meta-analysis looked at the association between *APOE* e4 and AD in men and women aged 40 to 90 years across a variety of ethnic groups (Farrer et al., 1997). The study confirmed the *APOE* e4 allele as a major risk factor for AD across all studied ethnic groups, however the extent of the risk *APOE* e4 poses in African Americans is diminished. Another study found that there is increased risk for heterozygous *APOE* e4 in Caucasians and Hispanics, but not in African-Americans (Tang et al., 1996). However, when looking at homozygous *APOE* e4 individuals, the relative risk for AD associated with the e4 allele was similar across the three ethnic groups. Additionally, the risk of AD given a specific *APOE* genotype varies depending not only on ethnicity, but also on sex. Just one copy of the *APOE* e4 allele in women is equivalent to the increased AD risk associated with having two copies of the e4 allele in men (Farrer et al., 1997; Parami et al., 1994).

Neural correlates of preclinical and prodromal Alzheimer's disease

The past several years have seen a shift in methods used to study AD. Specifically, there has been an increase in studies using brain imaging techniques to explore different brain measures to investigate the neural underpinnings of AD.

Grey matter integrity. Imaging and histopathological studies together have shown that AD affects limbic structures early on in the disease (Blennow et al., 2006; Braak and Braak, 1991a,b; Braak et al., 1996; Grieve et al., 2005). Interestingly, it is not amyloid deposits but rather neurofibrillary tangles beginning in the transentorhinal cortex and then spreading into the entorhinal region and hippocampus that are highly correlated with neuropsychological impairments and severity of dementia (Arriagada et al., 1992; Bierer et al., 1995; Braak and

Braak, 1991b; Braak and Braak, 1995; Braak et al., 1996; Hyman et al., 1984; Guillozet et al., 2003). A meta-analysis study supported the idea that alterations in the transentorhinal region, hippocampus, inferior parietal lobules (IPL), and precuneus may predict progression from mild cognitive impairment (MCI) to AD (Schroeter et al., 2009). The parietal impairments seen in the IPL and precuneus may be a result of Aβ protein deposits (Braak and Braak, 1991b; Jack et al., 2008; Kemppainen et al., 2007), and the diaschisis hypothesis (disruption of the cingulum bundle causing disconnection from the hippocampus) (Villain et al., 2008). Imaging studies have demonstrated that disruption of the precuneus is involved in deficits in visually-guided behaviour (Cavanna & Trimble, 2006), and thus may underlie the early visuomotor impairments seen in AD. Alterations in the IPL have been suggested as the most reliable indicators for transition from MCI to AD (Schroeter et al., 2009). Furthermore, MRI studies have found that individuals with a maternal family history of AD have lower grey matter volumes in AD-vulnerable brain areas, with progressive grey matter atrophy in the parahippocampal gyrus and precuneus (Honea et al., 2010).

White matter integrity. Neuroimaging studies employ diffusion tensor imaging (DTI) to map out and examine white matter (WM) integrity of tracts connecting various regions of the brain. The accumulation of Aβ and tau proteins leads to inflammation and eventual neuronal atrophy and cell death (Braak and Braak, 1991b; Braak and Braak, 1995). With the loss of neurons, WM volume in the brain also decreases both as a result of myelin degeneration and loss of axons in neural fibre tracts (Braak and Braak, 1996; Braskie et al., 2011; Hua et al., 2013). DTI studies have shown that WM integrity declines as early as in the preclinical stages of AD (Fischer et al., 2015; Kantarci et al., 2014; Prescott et al., 2014). With disease progression, WM alterations spread from association tracts within the limbic system to temporal and parietal areas

(Kantarci et al., 2010; Nowrangi et al., 2013). Alterations in WM appear to follow typical grey matter neurodegeneration patterns seen in AD, suggesting that disruptions in WM are associated particularly with tau pathology of AD (Kuczynski et al., 2010; Villain et al., 2008). Young adults that are carriers for certain AD risk genes show differences in DTI measures years before typical age onset of AD (Braskie et al., 2011). Several studies on patients with AD and MCI have found associations between cognitive impairment and reduced fractional anisotropy (a measure of tract integrity) in the corpus callosum, fornix, cingulum, and superior and inferior longitudinal fasciculi (Liu et al., 2009; Stricker et al., 2009). Furthermore, lower fractional anisotropy (FA) is seen in AD and MCI patients across the whole brain when compared to healthy controls, and more specifically in the medial temporal lobe, which is the first to show AD pathology (Braak and Braak, 1991b; Braak and Braak, 1995). Lower FA in the parahippocampal gyrus white matter is also associated with presence of *APOE* e4 (Nierenberg et al., 2005). While more work needs to be done, some studies suggest that DTI changes may precede volume loss, making it a potential detection tool of early neurodegeneration (Hugenschmidt et al., 2008; Nir et al., 2012).

Default mode network functional connectivity. Recent studies have demonstrated the importance of studying resting state conditions in disease. Specifically, the clinical diagnosis of AD has shown a correlation with changes in default mode network (DMN) activity (Greicius et al., 2004; Lustig et al., 2003; Rombouts et al., 2005; Wang et al., 2006). Molecular imaging using positron emission tomography (PET) showing where amyloid plaques form in early AD show similar patterns to areas of DMN activity in young adults (Buckner et al., 2005). Longitudinal MRI studies have shown that these regions are affected by AD pathology, and show atrophy with disease progression (Buckner et al., 2005; Scahill et al., 2002). It has been proposed that DMN activity across the lifetime may increase a metabolism-dependent cascade of

events that leads to AD pathology and later symptoms of dementia (Buckner et al., 2005; Cirrito et al., 2005; Selkoe, 2006). Lower connectivity within the DMN was found in healthy older *APOE* e4 carriers, with a sex interaction in the precuneus (a major region of the DMN) (Riedel et al., 2016). This region is connected to the medial temporal lobe, one of the first regions of the brain to exhibit AD tau pathology and reduced glucose metabolism in early AD (Reiman et al., 1996).

Clinical symptoms and diagnosis of Alzheimer's disease

Dementia due to AD is often associated with decrements in cognitive function and short-term memory, and with disease progression these are accompanied by deficits in the ability to perform complex movements (Hebert et al., 2010). The antemortem diagnosis of AD was based on criteria established in 1984 by the National Institude of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). These criteria focused exclusively on clinical symptoms to assign diagnoses of "unlikely", "possible", "probable", and "definite" AD, and were mainly a diagnosis of exclusion. The Diagnostic and Statistical Manual of Mental Disorders V (DSM-5) lists similar criteria for major neurocognitive disorder (previously called dementia), as well as impairments in activities of daily living (American Psychiatric Association, 2013). These impairments present as cognitive deficits that begin to interfere with independence in everyday activities, where assistance is required with complex instrumental activities, such as paying bills.

With recent advances made in knowledge regarding AD biomarkers, the 1984 NINCDS-ADRDA criteria have become outdated and biomarkers were proposed in scientific literature to be included in future diagnostic criteria (Dubois et al., 2007; Hyman, 2007; Reisberg, 2006). The National Institute on Aging and the Alzheimer's Association (NIA/AA) tasked a workgroup with

the revision of the 1984 NINCDS-ADRDA criteria for AD dementia to account for biomarkers. While the new NIA/AA guidelines do focus on future research directions, the DSM-5 focuses exclusively on a clinical diagnosis. The workgroup tasked by the NIA/AA incorporated biomarkers from neuroimaging and laboratory assessments (cerebrospinal fluid assays) to create new criteria for AD dementia (McKhann et al., 2011). The new diagnostic categories are "dementia unlikely due to AD", "possible AD dementia", and "probable AD dementia" - all diagnoses can be made based on solely clinical criteria, or may further include evidence of the AD pathophysiological process. The new workgroup proposed (1) core criteria for all-cause dementia, and (2) criteria for dementia caused by AD. Probable AD dementia is diagnosed when the person meets all the core clinical criteria. Possible AD is diagnosed when there is an atypical or mixed presentation of the disease. Finally, probable or possible AD dementia can be diagnosed with evidence of the AD pathological process when there is biomarker evidence that increases the certainty of the dementia being caused by AD.

Clinical symptoms of dementia appear only after there has already been significant damage to the brain. Patients that presented with cognitive complaints but did not meet criteria for dementia (at-risk for AD) and patients with very mild AD both differed from healthy adults in entorhinal volume, but not from one another (Dickerson et al., 2001). Furthermore, the two patient groups differed from controls, as well as from each other, in hippocampal volume where the AD patients had the greatest atrophy. Another study reported approximately 20% volume loss in the entorhinal cortex and hippocampus in patients with mild AD (Karow et al., 2010). These findings indicate that atrophy in select brain areas occurs before the onset of dementia. Converging evidence further suggests that the pathophysiological process of AD precedes the diagnosis of clinical dementia by years, if not decades (Morris, 2005). This means that early

detection is not only essential, but it is also possible. Although there have been advances in the early detection of AD, including neuroimaging or invasive procedures (taking blood or CSF samples), both are costly and not easily accessible to the public. Insights into the dysfunction of neural networks underlying visuomotor transformations in early-stage AD provide a novel behavioural target for its detection.

Cognitive-motor Integration (CMI)

Sensorimotor transformations in visually-guided movements

In everyday life we perform daily activities that require interaction with objects in our environment. The current study is guided by the theory that various skilled movements requiring visuomotor transformations are processed in separate, but overlapping, frontoparietal networks; these networks are differentially affected by healthy aging versus neurological disorders.

Standard mapping. Most reaching movements are referred to as standard visuomotor transformations. Imagine a cup of coffee being placed on the table in front of you. When you reach towards the cup, it involves first looking at the object before initiating the reaching movement. Your brain then automatically transforms any relevant visuospatial information into a motor output for you to successfully get to the target (in this case, the coffee cup). This process is automatic because the brain's default visuomotor mapping is thought to have the gaze and hand spatially aligned (Gielen et al., 1984; Helsen et al., 1998). This action involves the spatially congruent guidance of the eyes, limbs, and body directly towards a visual target of a reach (Wise et al., 1996). In other words, the eyes are directed towards the object and the hand moves to the same spatial location that object is in. However, with the advent of tool-use, many learned movements have an element of dissociation between the targets of gaze, attention, and reaching.

There is an integration of some form of cognitive information into the visuomotor transformation. This form of visuomotor guidance depends on non-standard mapping, and involves thinking and moving at the same time (cognitive-motor integration).

Non-standard mapping. For cognitive-motor integration (CMI), the mapping between the visual stimulus and response must be learned and calibrated. Non-standard mapping is used in situations when there is some level of dissociation between the target of a reach and the motor output. There are two categories of non-standard visuomotor mapping: 1) *arbitrary*, and 2) *transformational*. Non-standard arbitrary mapping involves, as the name suggests, selection of motor behaviour based on arbitrary sensory stimuli (Murray et al., 2000). Nonspatial properties of a visual stimulus, such as colour, provide information about the target for the motor output. For instance, when driving a car, a red traffic light means the person driving must step on the brake pedal to stop the car. The stimulus (red light) is arbitrary in the sense that the action it leads to has no relationship to the stimulus itself other than an associative link formed through learning to drive. Non-standard transformational mapping also involves dissociated visual cues and motor outputs; however unlike arbitrary mapping, it uses spatial information to relate the position of the visual target to the direction of an action. Non-standard transformational mapping is itself further broken down into two forms: 1) *sensorimotor recalibration*, and 2) *strategic control* (Wise et al., 1996).

Sensorimotor recalibration is used when the spatial location of a visual target and the required movement are in different planes. When using a laptop trackpad, the visual target (cursor on the computer monitor) is in a different plane from the required movement (trackpad on a horizontal surface). This type of non-standard mapping is also used for laparoscopic surgeries. There needs to be a coordinated remapping of the visual target and hand representation

in one plane, onto the target representation and true location of the hand in another plane (Bedford, 1993; Clower and Boussaoud, 2000; Lackner and Dizio, 1994). For the movement to be successful, there also needs to be constant feedback and updating of the hand relative to the target location.

Strategic control is used in movements where an explicit rule needs to be applied in order to move correctly (Redding and Wallace, 1996; Redding et al., 2005). Going back to the laptop trackpad example, this is seen in certain laptops where in order to scroll down, you need to slide your fingers up. There is a 180^{o} rotation, where your motor output (hand moving up) needs to go in the opposite direction of the target (page scrolling down) to successfully complete the task. Sensorimotor recalibration is implicit, whereas strategic control uses explicit rules. In my research, I study non-standard transformational mapping as it requires cognitive-motor integration which has been shown to differ between healthy and clinical populations, such as in those with AD.

Brain networks involved in CMI

Accurate movements towards a target represent the ability to coordinate the perception of our surroundings with action of the body. This coordination requires a transformation of sensory information about body and target positions into appropriate motor outputs - in other words, sensorimotor transformation. While the underlying neurological computations are not fully understood, a visually guided movement involves a transformation from extrinsic (using external cues) to intrinsic (the required joint and muscle activations) reference frames (Kakei et al., 2003; Kalaska et al., 1997; Kalaska and Crammond, 1992). Specifically, an eye-centered coordinate frame (i.e., internal representation of a target in space using its position on the retina) needs to be transformed to an effector-centered motor coordinate frame (i.e., position of muscles and joints

performing the movement) (Anderson et al., 1985; Flanders et al., 1992; Ghilardi et al., 1995; Kalaska and Crammond, 1992; Soechting and Flanders, 1989a,b). In a visually-guided reaching task, this is known as visuomotor integration. The activation of neurons encoding eye-centered target positions and initial limb positions are influenced by different combinations of visual input, eye position, arm position, and arm movement (Galletti et al., 1999; Snyder, 2000). Specifically, interconnected neuronal populations from parietal, premotor, and primary motor areas forming the frontoparietal network have been established as brain areas necessary for visuomotor integration (Sabes, 2000; Wise et al., 1997). For a standard reaching movement to occur, there needs to be a transformation from extrinsic visuospatial information to intrinsic muscle and joint representations (Battaglia-Mayer et al., 2000; Crawford et al., 2011; Kalaska et al., 1997; Kalaska et al., 1998; Sergio and Kalaska, 2003). The following is a simplified flow of information necessary for visuomotor transformations in the frontoparietal network; in reality, this processing involves local connections and large reciprocal cortico-cortical projections that act both serially and in parallel to one another (Alexander and Crutcher, 1990; Kalaska and Crammond, 1992; Kalaska et al., 1997; Sabes, 2000) (**Figure 1**).

Processing of visual stimuli. Visual information comes in through the primary visual cortex (V1) in the occipital lobe, and is further processed through the parieto-occipital region (PO). From there, information flows to the posterior parietal cortex (PPC), containing the superior parietal lobule (SPL) and areas of the intraparietal sulcus (IPS). These areas are called the anterior (AIP), medial (MIP), lateral (LIP), and ventral (VIP) intraparietal areas.

Planning and executing a motor output. From the PPC, information is sent to the premotor cortex (PMC), which includes areas responsible for motor planning. These areas are the medial supplementary motor area (SMA), cingulate motor area (CMA), lateral dorsal (PMd) and ventral

(PMv) premotor areas. The motor plan is then executed when these areas output information to the primary motor cortex (M1).

Looking further into the particulars of the frontoparietal reach network, neurons in the PPC are important for visuomotor transformations as they discharge in response to both sensation and movement (Blangero et al., 2009; Kalaska, 1996). Neurophysiological studies done by our laboratory in rhesus macaque monkeys showed differences between brain areas involved in standard versus non-standard visuomotor transformation tasks. Specifically, differences in neuronal activity were found in the parietal and premotor areas (Hawkins et al., 2013; Sayegh et al., 2013; Sayegh et al., 2014; Sayegh et al., 2017). Standard reaches showed enhanced activity within SPL regions surrounding the MIP, and the caudal PMd. In contrast, caudal SPL and rostral PMd showed enhanced activity during non-standard reaches where there was a decoupling of the eyes and hand. These results demonstrate a separation by region in the SPL and PMd during standard versus non-standard visuomotor tasks.

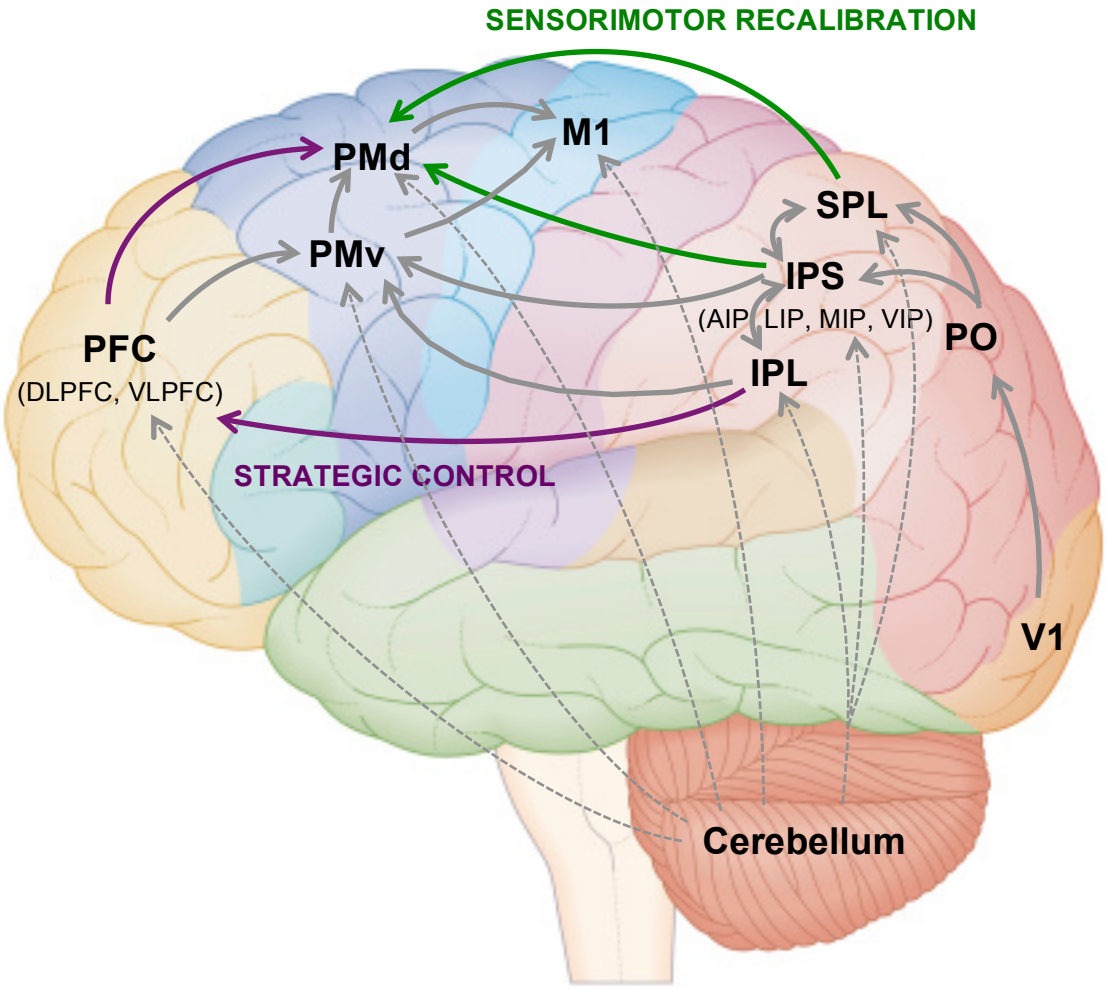


Figure 1. Putative cortical networks required for cognitive-motor integration (CMI). The simplified schematic diagram depicts the possible cortical connections involved in strategic control (purple arrows) and sensorimotor recalibration (green arrows). Other intermediate connections in the networks are indicated with grey double arrows, and connections to the cerebellum are shown with dashed grey lines. Although most cortico-cortical connections are shown with one-way arrows, most connections are reciprocal. The prefrontal cortex (PFC) consists of the ventrolateral (VLPFC) and dorsolateral (DLPFC) prefrontal cortices. The posterior parietal cortex includes the superior parietal lobule (SPL) and inferior parietal lobule (IPL). The SPL and IPL are separated by the intraparietal sulcus (IPS), which contains anterior (AIP), lateral (LIP), medial (MIP), and ventral (VIP) subdivisions. The occipital cortex includes the primary visual cortex (V1). Dorsal premotor cortex (PMd), ventral premotor cortex (PMv), parieto-occipital region (PO), and primary motor cortex (M1) are shown as well.

Figure adapted from Granek and Sergio (2015), brain template obtained from Getty Images.

Another study by our laboratory was conducted on humans, using neuroimaging (event-related BOLD fMRI) to characterize the brain areas required for standard versus non-standard mapping (Gorbet et al., 2004). They found that common for all tasks, there was activity in the contralateral primary, premotor, and medial motor regions, as well as the postcentral gyrus. As tasks required motor outputs that were increasingly dissociated from the visual input, there were regions in addition to the basic pattern of activity that were required for visuomotor transformations. These regions included increased activity in the left precuneus, the right superior frontal and middle temporal gyri, and bilaterally in the angular gyri and inferior parietal lobule (IPL). IPL activity has been associated with tool-use in humans, which requires increasingly dissociated sensorimotor transformations (Inoue et al., 2001).

Sex-based differences in performance of skilled movements

Performance differences on eye-hand coordination tasks have been reported between males and females (Roalf et al., 2006). Typically, women excel in tasks requiring accuracy and bimanual coordination, while men outperform women in tasks requiring speed (Albines et al., 2016; Fozard et al., 1994; Kimura, 1993; Kimura and Harshman, 1984). Not only has task performance differed between males and females, the underlying brain activity required for these tasks differs between the sexes, too. Functional neuroimaging studies in humans showed sex-related differences in processed required for normal motor control (Gron et al., 2000; Jordan et al., 2002; Sadato et al., 2000; Seurinck et al., 2004; Weiss et al., 2003). Our lab looked at event-related BOLD fMRI in both sexes for tasks requiring movements that are increasingly dissociated from visual stimuli (Gorbet and Sergio, 2007). While there were no sex-related differences in behavioural performance of the tasks, there were sex-differences in the underlying brain activity. In general, the right dorsal premotor cortex, right superior parietal lobule, and left

sensorimotor cortex were more active in women compared to men in tasks where the movement was dissociated from vision. In contrast, the superior temporal gyri were bilaterally more active in men. There were also sex differences in the laterality of brain activity in the frontoparietal network during the preparation of movements for visually-guided reaching tasks. While both sexes showed activity in the PMd and SPL contralateral to arm movements, women also showed greater ipsilateral activity in these regions. This suggests a more bilateral activation in women during visually-guided reaching tasks. Another study done by our laboratory used electroencephalography (EEG) to look at hemispheric laterality of event-related slow cortical potentials (SCPs) during visually-guided arm movement preparation (Gorbet et al., 2010). Activity during the preparatory period for movement was mainly contralateral to reaching in men, and bilateral in women. Furthermore, ipsilateral PMd activity in females may not be functionally necessary during reaching movements – rather, it may provide a redundancy to compensate for any decreased activity in the contralateral PMd (Gorbet and Staines, 2011). Meanwhile, men may be more dependent on the contralateral PMd for movement planning.

Effects of healthy aging versus Alzheimer's disease on visuomotor integration

There are reductions in movement speed and accuracy, as well as difficulties in processing complex visual scenes, that come with healthy aging (Darling et al., 1989; Ketcham et al., 2002; Munoz et al., 1998; Sekuler et al., 2000; Stelmach et al., 1987). Our laboratory looked specifically at how these changes may contribute to a deterioration of motor function in increasingly dissociated reaching tasks. Healthy younger and older adults showed declines in performance of visuomotor transformation tasks requiring non-standard mapping (Hawkins and Sergio, 2014). Reaction times and movement times were both significantly longer in the older adults when compared to younger adults in the non-standard conditions.

Looking to the clinical population, patients in the early stages of AD may not yet exhibit significant memory deficits typically associated with the disease. However, there are structural changes that occur in the brain. Brain autopsies of demented patients showed widespread Aβ deposits and characteristic distribution patterns of neurofibrillary tangles in parietal and frontal lobes (Braak and Braak, 1991). Behavioural studies looking at AD patients found performance declines of eye-hand coordination tasks requiring non-standard mapping (Ghilardi et al., 1999, Ghilardi et al., 2000). One might expect early-stage AD patients without cognitive deficits to show difficulties in movements requiring the integration of cognitive information (CMI tasks) due to 1) structural degradation in parietal areas (essential in frontoparietal networks for visuomotor control), and 2) declines seen in performance of non-standard mapping tasks. This was shown in studies done by our laboratory in individuals with mild cognitive impairment (MCI) and in Alzheimer's patients (Salek et al., 2011; Tippett and Sergio, 2006; Tippett et al., 2007; Tippett et al., 2012). Both clinical populations performed the same as healthy age-matched controls on a standard mapping task, but had difficulty once an element of decoupling was introduced between gaze and movement, thus requiring CMI. However, it is not only clinical populations that show significant declines in performance of non-standard CMI tasks. Indeed, our laboratory found that when compared to healthy age-matched controls, women at an increased risk for AD revealed significant performance disruptions as task demands increased and required CMI (Hawkins and Sergio, 2014). Furthermore, these behavioural deficits in the dementia-risk group were associated with declines in white matter integrity and lower resting-state functional connectivity within the default mode network (DMN) in the brain (Hawkins et al., 2015; Hawkins and Sergio, 2016).

CURRENT STUDY

PURPOSE

Research investigating the biological basis of disease has predominantly focused solely on males; findings from males were then applied to the entire species. One literature review found that male bias in animal species was evident in 8 of 10 disciplines; notably, it was most prominent in neuroscience, where studies solely focusing on males outnumbered those solely focusing on females 5.5 to 1 (Beery and Zucker, 2011). In humans, women are underrepresented in clinical trials. Geller et al. (2007) reported that of 46 clinical studies enrolling both men and women, women made up only 37% of the sample and only a quarter of the sample in drug trials specifically. In cardiovascular-related clinical trials between 1997 and 2006, the mean enrollment of women was 27% ranging from 10% to 47% (Kim et al., 2008). Recently, there has been an increase in research collecting data from both sexes. However, studies often combine male and female data and neglect to look at sex-differences explicitly (Cahill, 2006; Geller et al., 2007). We know that there are sex-related differences in dementia prevalence, progression, and genetic profiles. Furthermore, there are differences between men and women in how the brain controls movements and CMI, which could provide clinically relevant information. It's important to expand on current combined-sex data, and look at data from males and females separately to better understand the aging brain. As mentioned previously, preliminary research findings from a female population did show deficits in performance of the CMI task with alterations in structural and functional connectivity typically seen in individuals with AD (Hawkins and Sergio, 2014). In the current study, I will look at the same behavioural measures in the male population. If the findings for males also show this association between CMI deficits and dementia-risk, then

kinematic measures can potentially be used as an easily accessible assessment tool for detection of dementia risk, applicable to both halves of the human species.

HYPOTHESIS

In accordance with findings from the female population, I expect to see cognitive-motor impairments for increasingly dissociated visually-guided movement tasks in older male adults at increased Alzheimer's disease risk when compared to healthy controls. Furthermore, previous studies from our laboratory have shown that there are no sex-related differences in behavioural performance of CMI tasks (Gorbet and Sergio, 2009; Gorbet and Sergio, 2007). As such, I do not expect to see behavioural differences between the control male and female groups nor the dementia-risk male and female groups in their performance of the CMI tasks.

MATERIALS AND METHODS

Participants

The present study collected data from the male population, and compared findings to the 20 previously collected female datasets which were reanalyzed for the current study (Hawkins et al., 2015; Hawkins and Sergio, 2016). There were four additional female participants recruited for this study to increase the sample size in female groups. This study recruited 29 right-handed participants aged 49 to 69: 13 males at high-dementia risk (at-risk), 2 females are high-dementia risk (at-risk), 12 male at low-dementia risk (control), and 2 females are low-demetia risk (control) (see **Table 1** for demographic statistics). At-risk participants were recruited from Memory and Company (Alzheimer's health club), the Alzheimer Society of Canada, a Metro newspaper advertisement, and the York Research Participant Pool (YRPP). Control participants were recruited through YRPP and advertisements posted on Kijiji. Individuals were classified as high-dementia risk if they had a self-reported maternal or multiple family history of AD or

probable AD, but no cognitive impairment. Cognitive function was measured with the Montreal Cognitive Assessment (MoCA), where no cognitive impairment is indicated by scoring at or above education-adjusted norms. The choice of maternal history over paternal history is based on the higher risk for AD associated with a maternal history (Honea et al., 2011). Low-dementia risk participants were age-balanced with high- dementia risk participants. Individuals were classified as low-dementia risk if they had no family history of AD or any other type of dementia, did not demonstrate memory impairments outside of their age range norm, and scored at or above age-average on the MoCA. Exclusion criteria included vision impairments, upper-limb impairments, medical conditions that would hinder motor task performance (e.g. severe arthritis or dystonia), any neurological illnesses (e.g. Parkinson's disease, depression, schizophrenia, alcoholism, epilepsy), any history of head injury (e.g. mild, severe), stroke, and any medical diagnoses that would impact white matter integrity and brain connectivity (e.g. hypertension or diabetes). Signed informed consent was obtained from all participants prior to the start of the study. The study protocol was approved by the Human Participants Review Sub-Committee in the York University's Ethics Review Board.

Questionnaire

All subjects completed an entrance questionnaire to determine eligibility for the study. The questionnaire collected information about age, ethnicity, years of education, occupation, vision, computer and touchscreen experience, and video game use (**Appendix A**). Additionally, it covered health related questions about any diagnosed neurological disorders, family history of dementia or other neurological disorders, type I or II diabetes, smoking history, acquired brain injury (such as stroke or traumatic brain injury), and any medications that the individual was prescribed.

Table 1

Summary of participant information

	Control Male	At-risk Male	Control Female	At-risk Female
n	12	13	12	12
Age years (SD)	59 (5.5)	58 (6.0)	58 (5.3)	59 (6.5)
Range	49 - 66	51 - 69	50 - 67	51 - 68
MoCA score (SD)	28.1 (1.56)	27.2 (1.36)	27.9 (1.62)	28.5 (1.45)
Range	26 - 30	26 - 30	26 - 30	26 - 30
Computer experience years (SD)	2.8 (0.45)	2.6 (0.51)	2.6 (0.67)	2.9 (0.29)
Touchscreen experience years (SD)	1.8 (0.75)	1.6 (0.87)	1.8 (0.71)	2.1 (0.93)

AD: Alzheimer's disease; SD: standard deviation; MoCA score: Montreal Cognitive Assessment score.

Behavioural Data

All subjects completed four visuomotor transformation tasks, similar to those previously used by our laboratory (Hawkins and Sergio, 2014; Hawkins et al., 2015; Hawkins and Sergio, 2016; Salek et al., 2011; Tippett et al., 2006; Tippett et al., 2007; Tippett et al., 2012). This task has been found to discriminate between women at high- and low-AD risk with a classification accuracy of 86.4% (sensitivity: 81.8%, specificity: 90.9%) (Hawkins and Sergio, 2014). The tasks involved making simple sliding finger movements between targets displayed on an Acer Iconia 6120 dual-touchscreen tablet. These tasks were divided into one standard mapping condition (gaze and movement were coupled) and three different non-standard mapping conditions (gaze and movement were decoupled). In all four conditions, participants were instructed to slide the index finger of their right hand along the touch screen (either the vertical or horizontal screen depending on the condition) in order to displace the cursor from a central target to one of four peripheral targets (up, down, left, right) as quickly and as accurately as possible. The standard mapping task (S) involved the spatial location of the visual target and the required movement being the same. The non-standard mapping tasks involved the finger movements being made either on a different plane (plane-change, PC), in the opposite direction (feedback reversal, FR), or both (PC+FR), from the spatial target location (see **Figure 2** for depictions of all four visuomotor transformation task conditions). Eye movements were the same across all conditions (ie. always to the guiding visual target on the vertical screen).

The four conditions were presented in randomized blocks, each consisting of five pseudo-randomly presented trials to each of the four peripheral targets. Peripheral targets were located 75 mm from the central target, with target diameters set to 20 mm. The tasks were displayed on a 170 x 170 mm black square and a surrounding grey background. There was a total of 20 trials

per condition, and thus each participant completed a total of 80 trials across the four conditions. To ensure task comprehension, each participant was given two practice trials per peripheral target prior to each of the four conditions. The trial timings and participant movements consisted of the following steps: 1) a yellow central (home) target was presented on the vertical tablet, 2) participants moved a white cursor to the central target, changing its colour to green once they reached it, 3) after holding the central target for 4000 ms, one of four red peripheral targets appeared and the central target disappeared, serving as the 'Go' signal for initiation of a movement, 4) participants were told to look towards the visual target and slide their finger along the touchscreen to direct the cursor towards the target, 5) once the peripheral target was reached and the participant held it for 500 ms, it disappeared, signalling the end of the trial, 5) the next trial began with the presentation of the central target after an inter-trial interval of 2000 ms (see **Figure 3** for visual representations of a single trial completion).

In the standard condition, participants were asked to slide their finger directly to the target on the vertical screen (the cursor was directly under their finger). In the PC condition (non-standard), participants needed to move on the horizontal screen while looking at the vertical screen in order to direct the cursor towards the visual target displayed on the vertical screen. In the FR condition (non-standard), the cursor moved in the opposite direction of the participant's finger movements, requiring them to slide their finger on the vertical screen away from the visual target in order to move the cursor towards it. Finally, in the PC+FR condition (non-standard), movements needed be made in the opposite direction and on a different plane from the visual target in order to direct the cursor towards it.

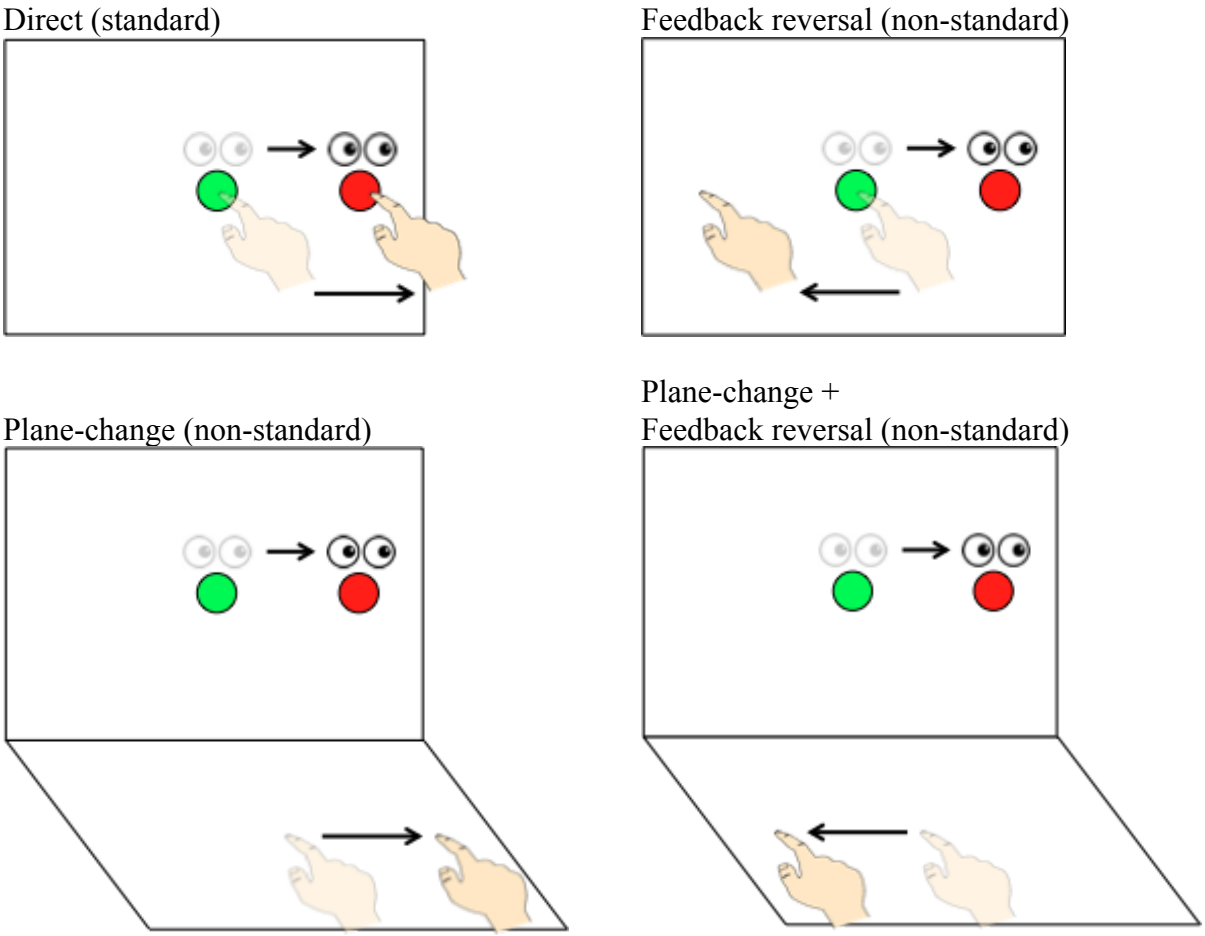


Figure 2. Schematic drawing of the visuomotor transformation tasks. Lighter eye and hand symbols denote the starting position for each trial (green central target). Darker eye and hand symbols denote the instructed eye and hand movements for each task. Red circles denote the peripheral (reach) target, presented randomly in one of four locations (left, up, right, or down relative to the central target). The direct interaction tasks requires standard mapping, where participants slide their finger on a touch screen to move a cursor from a central target to one of four peripheral targets. The other three are non-standard conditions that are cognitive-motor integration (CMI) tasks, where targets are either spatially dissociated from the plane of hand motion (plane-change), have a 180° feedback reversal (feedback reversal), or both (plane-change + feedback reversal).

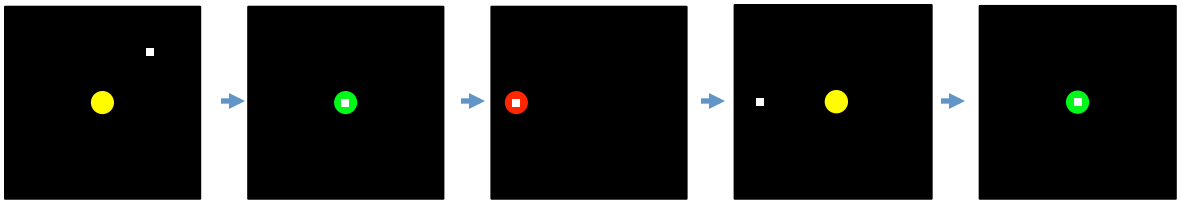


Figure 3. Sequence of events during one trial of the visuomotor task. The central (home) target is where all trials begin. Once the participant moves the cursor (white square) into the central target, the target changes from yellow to green to signify a movement preparation period. After 4000 ms, a red peripheral target appears in one of four directions (up, down, left or right of the centre) and serves as the 'Go' signal. Once the peripheral target is acquired and held for 500 ms it disappears, signaling the end of the trial. After an inter-trial interval of 2000 ms, the central yellow target reappears and the participant moves back to the central target to start the next trial.

Data processing

Kinematic measures, including timing, finger position (x, y coordinates; 50 Hz sampling rate), and error data were recorded for each trial and converted into a MATLAB readable format using a custom written (C++) application. Custom analysis software (Matlab, Mathworks Inc.) was used to process individuals' finger trajectories with a fourth-order (dual pass) low-pass Butterworth filter at 10 Hz. Finger trajectories were generated from these filtered paths for each successful trial, and were displayed on a Cartesian plot illustrating finger location data superimposed on central and peripheral target locations. Movement onsets and ballistic movement offsets (the initial movement prior to any corrective movements) were scored at 10% peak velocity. Total movement offsets were scored as the final 10% peak velocity point once the finger position was within the correct peripheral target. If the initial movement successfully resulted in the finger reaching the peripheral target, then ballistic and total movement offsets were the same. These movement profiles were then verified by visual inspection, and manually corrected when necessary. The number of sub-movements, or corrective movements, was also verified by visual inspection. Sub-movements were defined as a decelerated movement followed by an accelerated movement throughout the movement trajectory. Sub-movements were counted for every trial in each condition.

Unsuccessful trials (error data) were detected by the data collection software by meeting the following criteria: finger left the home target too early (<4000 ms), reaction time (RT) was <150 ms or >8000 ms, or total movement time was >10 000 ms. Trials in which the first ballistic movement exited the boundaries of the central target in the wrong direction (>90^{o} in either direction from a straight line to the target) were coded as direction reversals (DR), and weren't included in metrics from correct trials but were analyzed as a separate variable. All scored data

were then processed to compute 11 different timing, accuracy, and precision measures described below. Any trials exceeding 2 standard deviations from the participant's mean for any of the outcome measures were eliminated from final outcome calculations.

Dependent measures

The kinematic measures of interest in this study were reaction time (RT), movement time full (MTf), movement time ballistic (MTb), peak velocity (PV), path length full (PLf), path length ballistic (PLb), absolute error (AE), variable error (VE), and direction reversal errors (DR). RT (in ms) is the time interval between the central target disappearance and movement onset. MT (in ms) is the time between movement onset and offset, divided into MTf (full movement offset) and MTb (initial movement offset). MTb is the initial movement prior to any potential subsequent movement corrections. If this first movement does not end in the peripheral target, MTf is time of the first ballistic movements plus the time taken to make corrections and end in the target. AE (in mm) is a measure of end-point accuracy, and is the average distance from the individual ballistic movement endpoints ($\sum x/n$, $\sum y/n$) to the actual target location. VE (in mm) is a measure of end-point precision, and is the distance between the individual ballistic movement endpoints (σ) from their mean movement. PL (in mm) is the total distance (calculated from the x and y trajectories) travelled between movement onset and offset. It is calculated as both PLf (full movement offset) as well as PLb (initial movement offset). Corrective path length (CPL) represents corrective movements, and was quantified by subtracting the PLb from the PLf. PV is the maximum velocity obtained during the ballistic movement, and is used to calculate the 10% threshold used for determining movement onsets and offsets. Direction reversals were recorded as a percentage of total completed trials. All kinematic measures were averaged across the four peripheral targets for each condition. Number of sub-movements (#SubMvt) was

calculated as the average number of sub-movements per each correct trial, and the percentage of sub-movements (%SubMvt) were calculated as the percent of correct trials in which sub-movements were present.

Establishing composite scores

With the large number of outcome metrics derived from data scoring, certain measures would need to be combined into composite scores to decrease the number of comparisons in data analysis. A principal component analysis (PCA) is a method used to identify interrelationships between the variables to create clusters or groups of variables that are highly correlated - these clusters, or components, are the output from the analysis. A PCA reduces the number of variables while still keeping the original variance by establishing a set of linear components and then determining how each measured variable might contribute to each component (Conway and Huffcutt, 2003). A rotated component matrix, also known as the loadings, is the main output of PCA and reports the estimated correlations between each of the measured variables (in our case, the kinematic measures) and the estimated components. PCA produces multiple components but not all are retained from the analysis - typically, eigenvalues are calculated for the components and these indicate the relative importance of each component. Kaiser (1960) recommends preserving factors with eigenvalues greater than 1, stating that components with scores less than 1 will have negative reliability. The resultant components retained following analysis are used as the composite scores for analysis to allow for the control of Type I error rates when testing multiple comparisons, and for the organization of highly correlated variables into meaningful information regarding motor control. PCA may be helpful in exploratory analyses for identifying hidden dimensions (a structure that categorizes measures) in the data (Song et al., 2013).

It is convention to standardize the outcome variables to be used in a PCA; my kinematic measures were standardized using z-scores. Z-scores were calculated for the males and females based on the combined male and female control groups' means to allow us to assess how the at-risk individuals compared to all of the healthy controls. The means and standard deviations of RT, MTf, PV, AE, VE, and PLf were first calculated for all control participants. Taking RT as an example, z-scores for each participant were calculated by subtracting the control group mean from each participant's individual score, followed by dividing the resultant difference by the standard deviation of the control group. This process was repeated for the other five kinematic measures. A z-score is a measure of the number of standard deviations that a raw score is from the population mean - in my analysis, it is the number of standard deviations that a raw score is from the control group mean. The mean z-scores for the at-risk groups will be either positive, negative, or equal to 0. A positive value indicates the score is above the control mean, a negative value indicates the score is below the control mean, and a value of 0 indicates the score is identical to the control mean. The z-score for PV was multiplied by -1 to match the other two timing measures RT and MT (where a lower value indicates better performance). Therefore, a lower PV will have a higher z-score and indicate worse performance, while a higher PV will have a lower z-score and indicate better performance. All analyses discussed in the results section were also run on the data when male and female controls were not combined for z-score calculation. Instead, z-scores for male participants were calculated based on means from male controls, and z-scores for the female participants were calculated based on means from female controls. Combining the male and female control groups for z-score calculation did not give different results compared to when the sexes were kept separate. Thereofre, male and female

controls were combined for the means in order to prevent any sex-bias being introduced into the data.

There are several ways to create composite scores that reflect the components found through the PCA, with simple averaging being the most commonly used approach when the original variables are continuous (Song et al., 2013). This approach was used for my data and involves the addition of the z-scores, resulting in equal contributions of each of the original raw scores to the composite score. The composite timing score was calculated by adding the z-scores of the highly correlated outcome variables from component 1 of the PCA which were the RT, MTf, and PV. The composite endpoint error score was calculated by addition of the z-scores that were highly correlated from component 2 of the PCA which consisted of the AE and VE. The Kaiser-Meyer-Olkin (KMO) measure was used to verify the sampling adequacy for the PCA. It indicates the proportion of variance among variables that might be caused by common underlying factors. High KMO values indicate a PCA will be useful, while lower KMO values (less than 0.5) suggest it will not be. Bartlett's test of sphericity is a further measure used to determine if a PCA is appropriate for the data. It compares the observed correlation matrix to the identity matrix, where an identity matrix is a square matrix in which all elements of the main diagonal are ones and all other elements are zeroes. If all variables in a correlation matrix are perfectly correlated, a single factor can be used to summarize them. If they are orthogonal, then their correlations are zero and the same number of factors is needed as there are variables - in this case, the correlation matrix is the same as the identity matrix. If the absolute values are high outside the main diagonal, some variables are correlated and a PCA may be useful. If they are close to zero, a PCA would not be useful as there would be little to no correlation between any of the variables. Bartlett's test is used to check if the observed correlation matrix R is significantly

different from the identity matrix (matrix under the null hypothesis that variables are orthogonal). If the null hypothesis is rejected with a significance value of $p < 0.05$, then the R matrix is not an identity matrix and PCA can be used. Cronbach's alpha was used to test for reliability, or internal consistency, of the composite scores.

Statistical Analysis

All statistical analyses were carried out using SPSS statistical software (SPSS 24, IBM). A PCA was conducted with orthogonal rotation (varimax) on the standardized z-values of each kinematic variable separately across the four conditions for the males and females together. Eigenvalues were obtained, with two components having eigenvalues over Kaiser's criterion of 1. These were the two components retained for analysis. The rotated component matrix from the PCA showed factor loadings of each variable for the two components - these are the correlation coefficients between the variables and the factors. Factor loadings with an absolute value greater than .3 are considered moderate-to-strong. Factor loadings across the four conditions and for both sexes suggested that component 1 is represented by RT, MTf, and PV while component 2 is represented by the AE and the VE. As PLf did not show high correlation with either component, it will be used in combination with the PLb to calculate and analyse the CPL separately from the composite scores.

A Shapiro-Wilk test was used to test for normality of each kinematic measure for both the male and female groups across the four conditions. While the majority of the dependent variables for the standard and feedback reversal conditions were normally distributed across the sexes, both the PC and FR + PC condition kinematic outcomes were significantly non-normal. Consequently, all statistical testing was carried out using nonparametric analysis techniques.

Diagnostic and sex-differences

A Kruskal-Wallis test was used to test for differences between several independent groups. This test is the non-parametric equivalent of the one-way independent ANOVA, and is based on ranked data. Ignoring the group to which the dependent variable belongs to, the scores are ordered from lowest to highest with the lowest assigned a rank of one, the next highest a rank of two, and so on until all scores have been ranked. Ranked scores are added based on the group they belong to, and the test statistic for the data is then calculated. This test statistic has a chi-square distribution. If there is no difference between the groups, the expected result would be similar ranks within each group and the total summed ranks would be about the same. If the groups differ, then the summed ranks of the groups would be higher in some groups and lower in others. The lowest of the group sums is taken as the test statistic, and significance is determined at $p < 0.05$.

The groups analyzed for differences using the Kruskal-Wallis test were the at-risk males, control males, at-risk females, and control females on timing scores, endpoint error scores, corrective path lengths, percentage of direction reversals, number of sub-movements, and percentage of sub-movements. Mann-Whitney tests were used for post hoc analysis to follow up on statistically significant findings, with comparison between i) at-risk and control males, ii) at-risk and control females, iii) at-risk females and males, and iv) control females and males. A Bonferroni correction was applied so all effects are reported at a .0125 level of significance. Results from the Mann-Whitney tests can be interpreted in different ways. If the distributions for all groups have a similar shape, the medians of the dependent variables can be compared. If the distributions are not the same shape, the Mann-Whitney test can only be used to compare mean ranks. The distributions for all groups were visually inspected and compared across all four

conditions, and were found to be different shapes. All results were therefore interpreted using means. Calculating effect size (r) for the Kruskal-Wallis test is not very useful as it summarizes a general effect, and so all effect sizes were calculated for post hocs. Descriptive statistics and statistical outcomes of the non-parametric Kruskal-Wallis and post hocs for all dependent variables for group are summarized in **Table 2**.

All groups were age-balanced, with no statistically significant differences in age observed between the four experimental groups ($H = .408$, $p>0.05$). There were also no statistically significant differences observed between groups on MoCA scores ($H = 4.622$, $p>0.05$), computer experience ($H = 3.268$, $p>0.05$), and touchscreen experience ($H = 1.995$, $p>0.05$).

RESULTS

CMI behaviour

There is a deterioration in movement control as cognitive demands of the task increase observed in at-risk participants compared to age-matched controls. The full movement trajectories plotted in **Figure 4** show a disruption in performance of hand movements, evident as increased deviations from a straight trajectory between the central target to the four peripheral targets in the non-standard conditions. For comparison, the standard condition illustrates minimal deviations from a straight trajectory across all four participant groups.

Composite scores

All Kaiser-Meyer-Olkin (KMO) values were greater than the acceptable limit established by Field (2009) of .5, with the exception of the FR condition with a KMO = .467. As this value is close to the acceptable limit, and all other values were above it, the sample was taken to be adequate for a PCA. Bartlett's test of sphericity had a $p < 0.001$ for all variables in both sexes,

indicating that correlations between items are sufficiently large for a PCA. The timing and endpoint error scores for both the males and females across all conditions both have high reliabilities, Cronbach's $\alpha = .879$ and .772, respectively. As mentioned previously, the means of the composite z-scores demonstrate how the groups performed compared to the combined male and female control group.

Timing scores. Timing scores were not significantly affected by group (**Table 2**). At-risk females had faster timing scores on the standard, FR, and PC conditions, but were slower on the PC + FR condition compared to controls (**Figure 5**). Conversely, at-risk males had slower timing scores on all three non-standard conditions, but were faster on the standard condition compared to controls.

Endpoint error scores. Endpoint error scores were significantly affected by group for all three non-standard conditions (**Table 2**). Post hoc analysis revealed that performance by at-risk males did not differ from control males, and control females did not differ from control males, for any of the conditions (**Figure 6**). However, at-risk females had greater endpoint errors (lower accuracy and precision) compared to control females on all three non-standard conditions ($U_{FR} = 27.00$, $r_{FR} = -.53$; $U_{PC} = 27.00$, $r_{PC} = -.53$; $U_{PCFR} = 22.00$, $r_{PCFR} = -.59$) as well as compared to at-risk males on the PC + FR condition ($U_{PCFR} = 31.00$, $r_{PCFR} = -.51$). At-risk males do have greater endpoint error scores on the standard and FR condition compared to controls, but they perform better on the two non-standard conditions involving a plane-change.

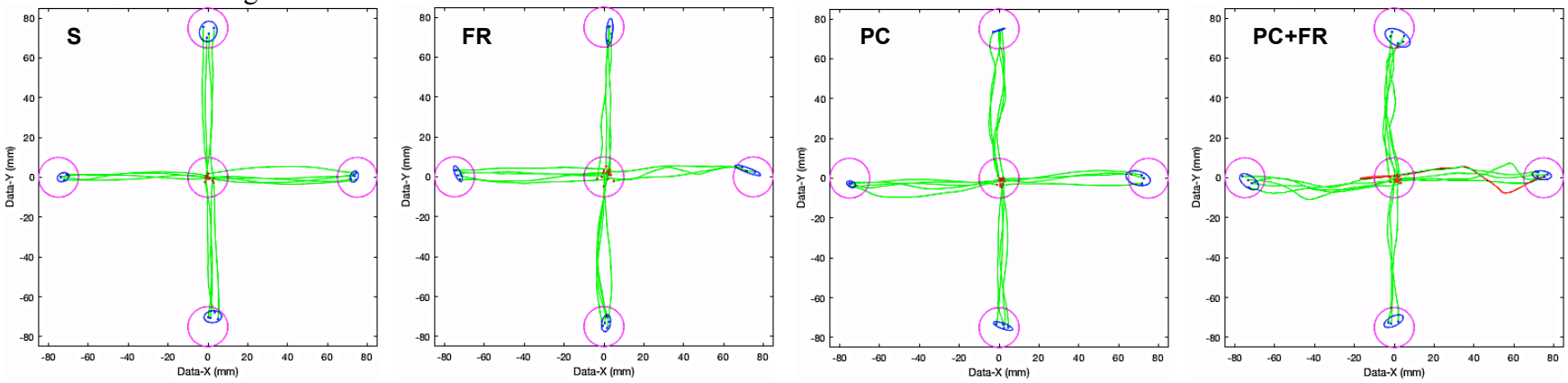
Corrective path lengths. Corrective path lengths were significantly affected by group in the plane-change + feedback reversal condition (**Table 2**). Post hoc analysis revealed that performance by at-risk males did not differ from control males, and control females did not differ from control males, in any of the conditions. However, at-risk females had greater corrective

path lengths (higher trajectory deviation) compared to control females on the PC + FR condition (U_{PCFR} = 21.00, r_{PCFR} = -.60) as well as compared to at-risk males on the PC + FR condition (U_{PCFR} = 26.00, r_{PCFR} = -.57). The three non-standard tasks show greater corrective path lengths compared to the standard, and the at-risk participants show more corrective path lengths than the controls (**Figure 7**). The magnitude of the corrective path lengths is also similar across the two non-standard conditions with one level of dissociation (FR and PC). The PC + FR condition, involving two levels of dissociation, has the greatest corrective path lengths across all groups, especially in the at-risk females. This is reflected in the post-hoc analyses mentioned previously.

Percentage of direction reversals. The percentage of direction reversals was not significantly affected by group (**Table 2**). The two non-standard conditions requiring strategic control, FR and PC + FR, both have a substantially larger number of direction reversals compared to the standard and plane-change conditions (**Figure 8**). For the most part, males have more direction reversals than females and the at-risk participants have more direction reversals compared to controls.

Corrective sub-movements. The number of corrective sub-movements and percentage of corrective sub-movements were only significantly affected by group in the standard condition (**Table 2**). Results for #SubMvt and %SubMvt are shown in **Figure 9** and **Figure 10**, respectively. Both corrective sub-movement measures show similar effects across the conditions, with the standard having the least corrective sub-movements, followed by the FR and PC conditions with roughly equal corrective sub-movements, and finally the PC + FR condition with the greatest number and percentage of corrective sub-movements.

A. Control male – aged 62



B. At-risk male – aged 61

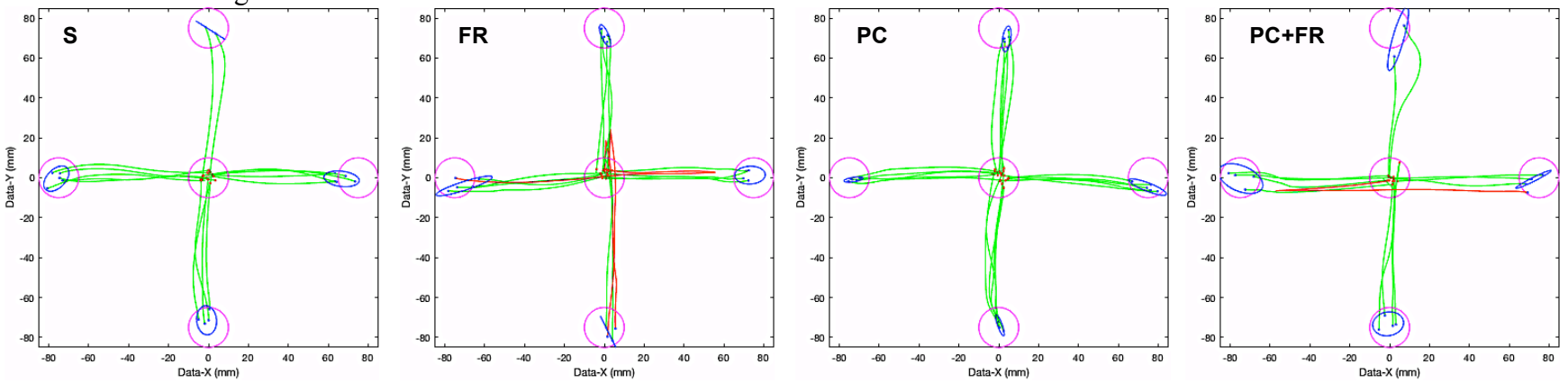
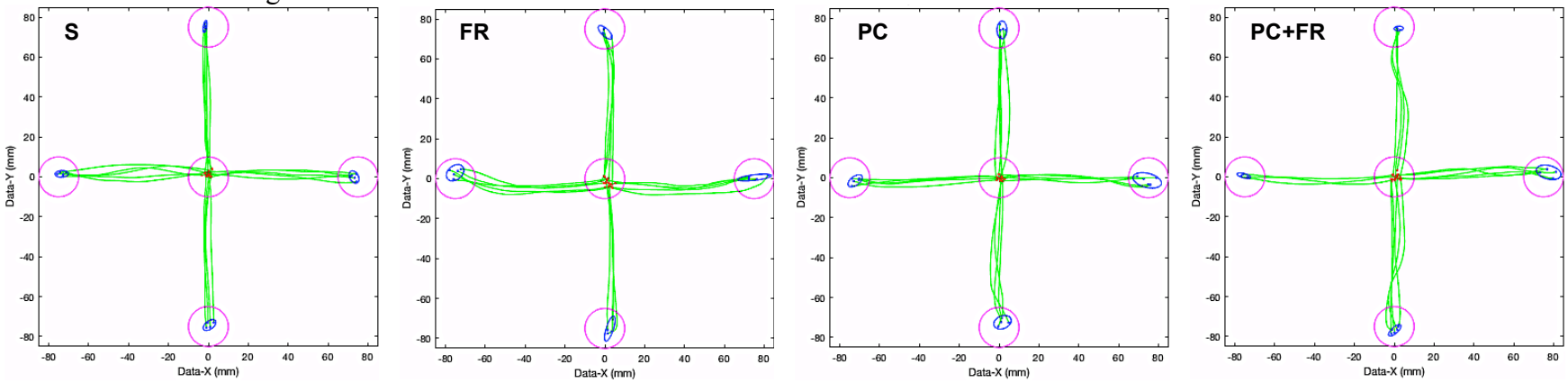


Figure 4a. Examples of typical full hand movement trajectories for males in the: A. Control group, and B. At-risk group. Hand trajectories begin at the central target (red dots) and move towards one of four peripheral targets, where each green line represents a single movement trajectory. Blue ellipses denote the 95% C.I. for the final end point of the finger movements (blue dots). Only correct trials (green lines) and direction reversals (red lines) are shown. Any peripheral target with less than 5 trajectories indicates error trials, which are not shown. S: Standard; FR: Feedback reversal; PC: Plane-change; PC+FR: Plane-change feedback reversal.

C. Control female – aged 62



D. At-risk female – aged 62

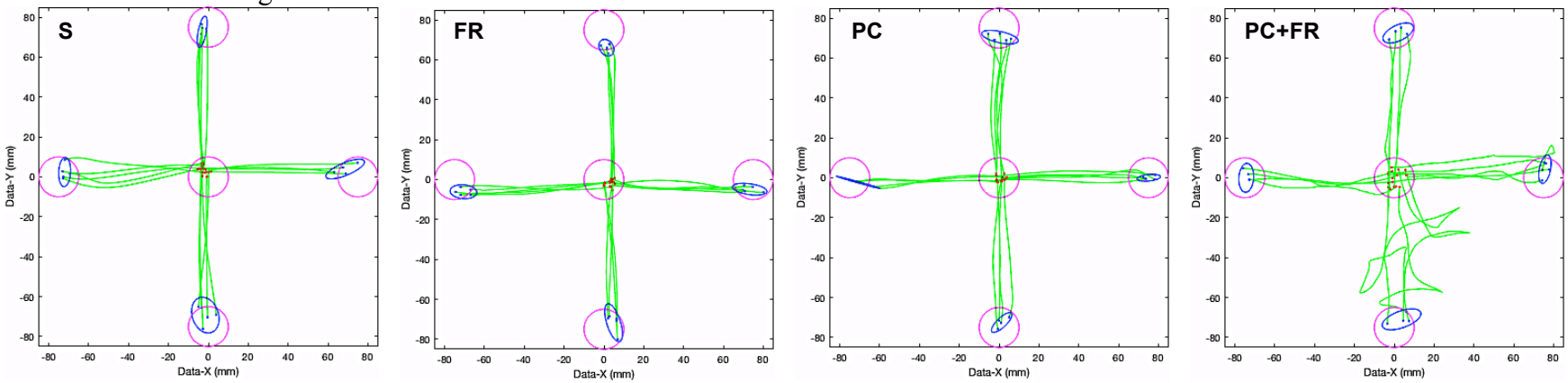


Figure 4b. Examples of typical full hand movement trajectories for females in the: **C.** Control group, and **D.** At-risk group. Hand trajectories begin at the central target (red dots) and move towards one of four peripheral targets, where each green line represents a single movement trajectory. Blue ellipses denote the 95% C.I. for the final end point of the finger movements (blue dots). Only correct trials (green lines) and direction reversals (red lines) are shown. Any peripheral target with less than 5 trajectories indicates error trials, which are not shown. S: Standard; FR: Feedback reversal; PC: Plane-change; PC+FR: Plane-change feedback reversal.

Table 2

Descriptive statistics of participant groups and statistical outcomes of the Kruskal-Wallis H and Mann-Whitney U tests

	Control Male	**At-risk Male**	**Control Female**	**At-risk Female**	**KW test**	**Mann-Whitney post-hoc**			
Kinematic measure	*Mean (SEM)*	*Mean (SEM)*	*Mean (SEM)*	*Mean (SEM)*	*H-statistic*	*At-risk vs control females*	*At-risk vs control males*	*Females vs males at-risk*	*Female vs male controls*
Timing score									
S	0.446 (0.7402)	-0.093 (0.7477)	-0.446 (0.8385)	-2.359 (0.8411)	4.890^{NS}	-	-	-	-
FR	-1.097 (0.5935)	0.967 (1.4111)	1.006 (0.7234)	-0.680 (0.7976)	5.229^{NS}	-	-	-	-
PC	-0.369 (0.8505)	0.787 (0.9492)	0.338 (0.7124)	-1.522 (1.1091)	5.012^{NS}	-	-	-	-
PC+FR	-0.999 (0.6597)	-0.619 (0.6467)	0.999 (0.6321)	2.089 (1.6806)	5.115^{NS}	-	-	-	-
Endpoint error score									
S	0.091 (0.5314)	0.337 (0.6289)	-0.091 (0.4193)	0.874 (0.5759)	1.116^{NS}	-	-	-	-
FR	0.787 (0.6069)	2.812 (1.1043)	-0.722 (0.3699)	1.431 (0.5977)	10.330*	27.00**	34.00^{NS}	47.00^{NS}	34.00^{NS}
PC	0.467 (0.6304)	-0.031 (0.6628)	-0.429 (0.4558)	2.921 (0.9664)	9.526*	27.00**	46.00^{NS}	26.00^{NS}	51.00^{NS}
PC+FR	0.423 (0.5085)	-0.016 (0.7263)	-0.423 (0.5513)	3.870 (1.2484)	11.357**	22.00**	56.00 ^{NS}	31.00**	50.00^{NS}
Corrective path length									
S	0.041 (0.0298)	0.053 (0.0286)	0.000 (0.0000)	0.306 (0.3057)	3.180^{NS}	-	-	-	-
FR	0.691 (0.1886)	1.980 (0.6852)	0.382 (0.2126)	0.865 (0.3441)	6.669^{NS}	-	-	-	-
PC	0.755 (0.4381)	0.667 (0.4512)	0.448 (0.2203)	1.584 (0.6429)	3.200^{NS}	-	-	-	-
PC+FR	4.310 (1.2667)	3.591 (1.6316)	2.317 (0.9085)	13.450 (3.2946)	11.895**	21.00**	64.00^{NS}	26.00**	54.00^{NS}
% Direction reversals									
S	0.490 (0.4902)	0.481 (0.4808)	0.463 (0.4630)	0.000 (0.0000)	1.016^{NS}	-	-	-	-
FR	3.624 (1.7891)	7.163 (3.2811)	1.046 (0.7067)	3.288 (1.6321)	2.301^{NS}	-	-	-	-
PC	0.000 (0.0000)	0.000 (0.0000)	0.000 (0.0000)	0.439 (0.4386)	2.750^{NS}	-	-	-	-
PC+FR	8.119 (3.5078)	7.392 (2.2257)	7.298 (3.4000)	7.498 (2.4127)	0.789^{NS}	-	-	-	-

# Corrective sub-movements									
S	0.253 (0.0469)	0.247 (0.0481)	0.165 (0.0456)	0.099 (0.0309)	8.648*	50.00^{NS}	75.00^{NS}	32.50*	43.00^{NS}
FR	0.696 (0.2034)	0.830 (0.1727)	0.780 (0.1746)	0.392 (0.0582)	5.086^{NS}	-	-	-	-
PC	0.715 (0.0838)	0.794 (0.1318)	0.830 (0.1096)	0.512 (0.0824)	4.641^{NS}	-	-	-	-
PC+FR	1.383 (0.1888)	1.212 (0.1630)	1.349 (0.1758)	1.671 (0.2243)	2.730^{NS}	-	-	-	-
% Corrective sub-movements									
S	23.97 (4.569)	21.85 (3.933)	15.61 (4.099)	9.94 (3.095)	8.172*	50.00^{NS}	70.50^{NS}	32.50*	45.50^{NS}
FR	47.51 (8.153)	58.78 (8.96)	51.14 (8.186)	37.98 (7.157)	3.200^{NS}	-	-	-	-
PC	52.26 (4.727)	57.27 (7.897)	58.16 (6.609)	45.36 (6.753)	1.993^{NS}	-	-	-	-
PC+FR	74.41 (5.812)	2.01 (5.430)	73.53 (4.525)	76.67 (4.615)	0.252^{NS}	-	-	-	-

*p<0.05; **p<Bonferroni criterion = 0.0125

S: Standard; FR: Feedback reversal; PC: Plane-change; PC+FR: Plane-change feedback reversal; NS: No significance; SD: standard deviation; KW test: Kruskal-Wallis test

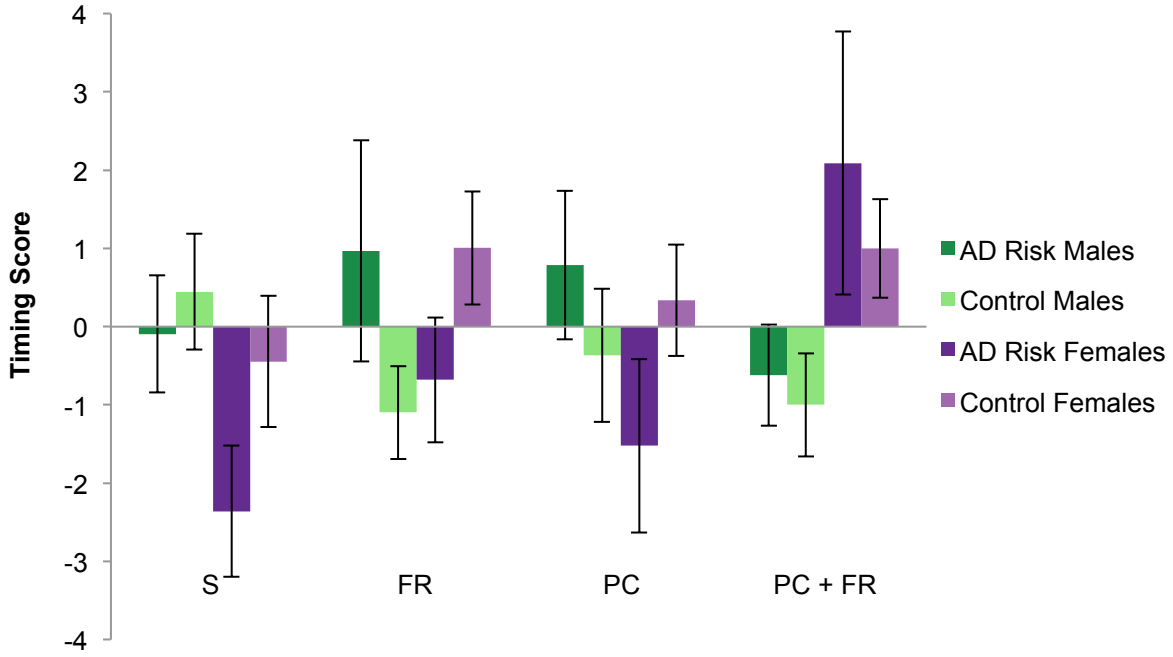


Figure 5. Mean timing score results for group (at-risk males: dark green, control males: light green, at-risk females: dark purple, control females: light purple) across all four conditions (S: standard, FR: feedback reversal, PC: plane-change, PC+FR: plane-change + feedback reversal). Kruskal-Wallis test revealed that there is no statistically significant effect by group in any of the conditions. Error bars represent SEM.

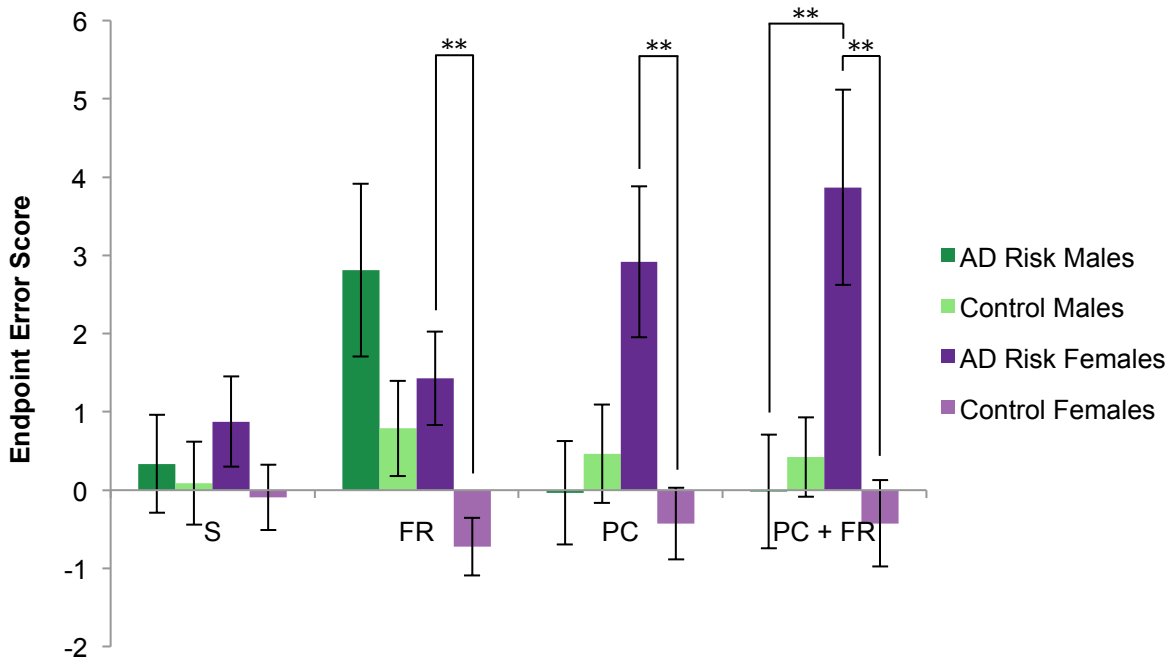


Figure 6. Mean endpoint error score results for group (at-risk males: dark green, control males: light green, at-risk females: dark purple, control females: light purple) across all four conditions (S: standard, FR: feedback reversal, PC: plane-change, PC+FR: plane-change + feedback reversal). Kruskal-Wallis test revealed a statistically significant effect by group in the plane-change + feedback reversal condition. Error bars represent SEM.

*p < 0.05; **p < Bonferroni criterion = 0.0125

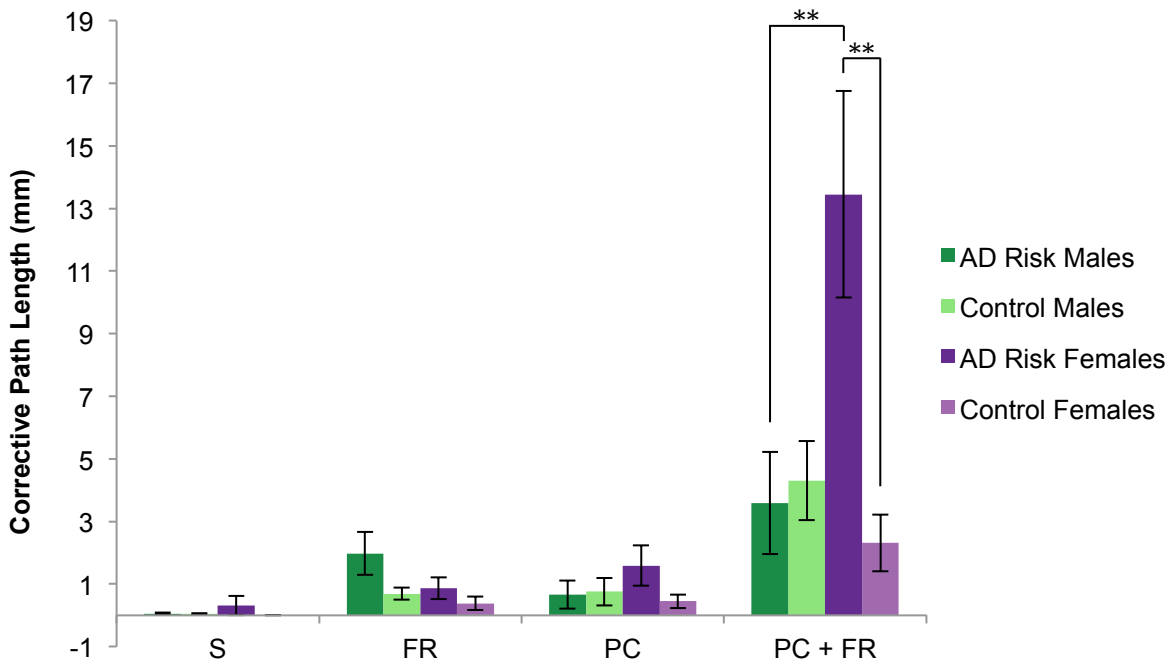


Figure 7. Mean corrective path length results for group (at-risk males: dark green, control males: light green, at-risk females: dark purple, control females: light purple) across all four conditions (S: standard, FR: feedback reversal, PC: plane-change, PC+FR: plane-change + feedback reversal). Kruskal-Wallis test revealed a statistically significant effect by group in the plane-change + feedback reversal condition. Error bars represent SEM.

*$p < 0.05$; **$p <$ Bonferroni criterion = 0.0125

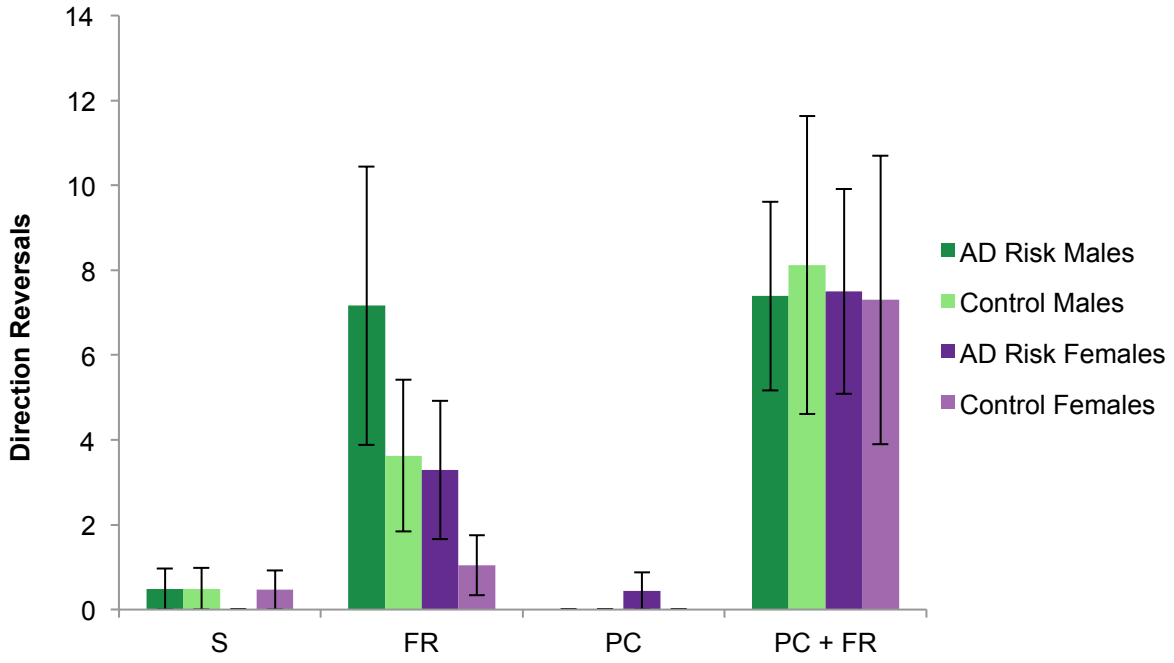


Figure 8. Mean percent direction reversals results for group (at-risk males: dark green, control males: light green, at-risk females: dark purple, control females: light purple) across all four conditions (S: standard, FR: feedback reversal, PC: plane-change, PC+FR: plane-change + feedback reversal). Kruskal-Wallis test revealed that there is no statistically significant effect by group in any of the conditions. Error bars represent SEM.

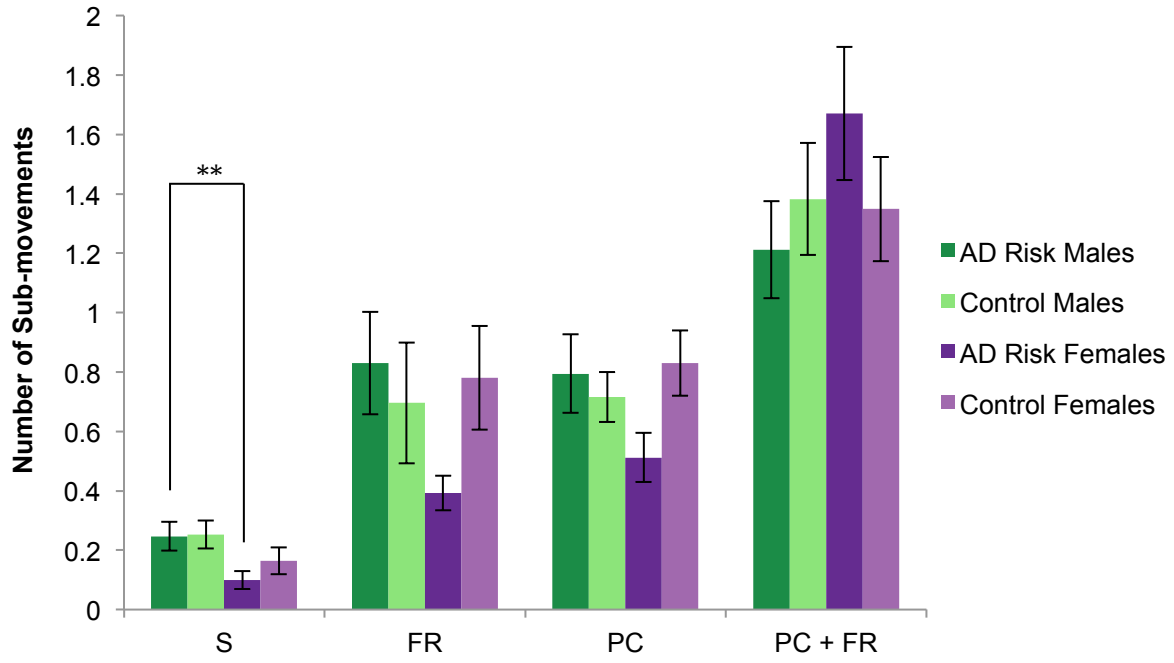


Figure 9. Mean number of corrective sub-movements results for group (at-risk males: dark green, control males: light green, at-risk females: dark purple, control females: light purple) across all four conditions (S: standard, FR: feedback reversal, PC: plane-change, PC+FR: plane-change + feedback reversal). Kruskal-Wallis test revealed a statistically significant effect by group only in the standard condition. Error bars represent SEM.

*$p < 0.05$; **$p <$ Bonferroni criterion = 0.0125

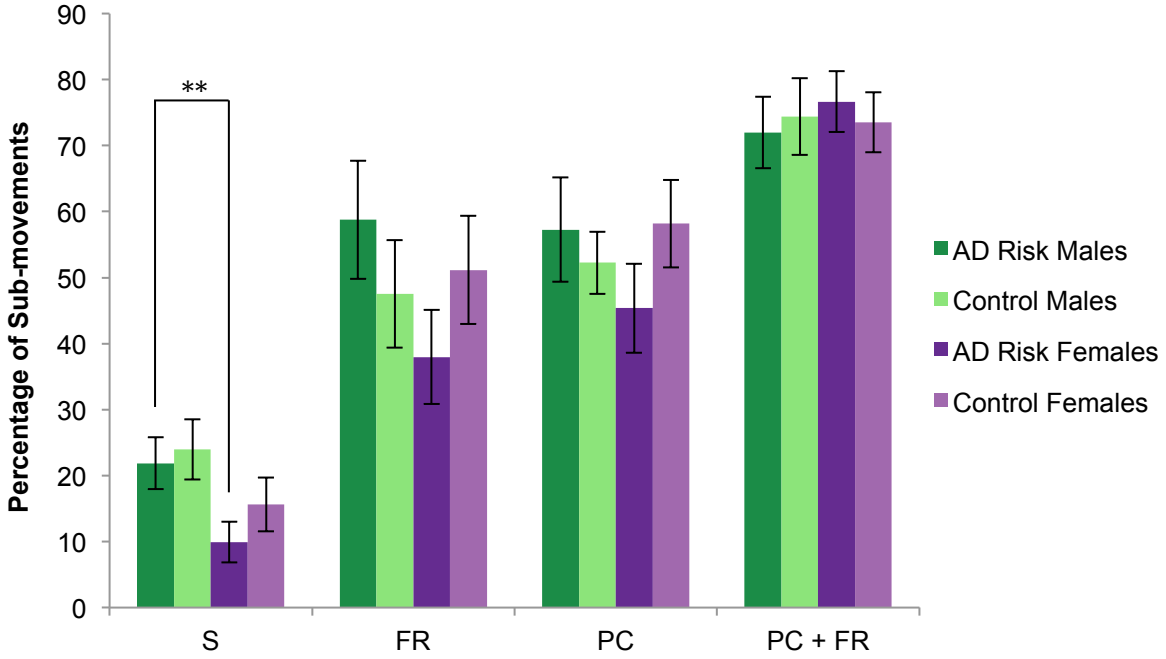


Figure 10. Mean percentage of corrective sub-movements results for group (at-risk males: dark green, control males: light green, at-risk females: dark purple, control females: light purple) across all four conditions (S: standard, FR: feedback reversal, PC: plane-change, PC+FR: plane-change + feedback reversal). Kruskal-Wallis test revealed a statistically significant effect by group only in the standard condition. Error bars represent SEM.

*$p < 0.05$; **$p <$ Bonferroni criterion = 0.0125

DISCUSSION

The aims of this study were to expand on previous findings from the female population by looking at males at high- and low-risk for dementia likely due to Alzheimer's disease, and to characterize any sex-differences in performance on behavioural tasks. As predicted, performance in the standard condition of an eye-hand coordination task showed no significant differences across the groups for any of the kinematic measures. The standard condition reflects the ability to interact directly with objects (or, standard reaching), which in everyday life is not typically impaired in early AD relative to health aging. Rather, the results of this study demonstrate a disruption in certain components of movement in the more cognitively-demanding non-standard conditions that require frontoparietal cognitive-motor integration brain networks. Further, I observed sex-differences in the behavioural expression of these disruptions to rule-based action control.

The results suggest that measurable impairments in visuomotor control are present in individuals at increased risk of dementia who do not yet show any cognitive deficits. Revisiting the hypotheses, they were partially supported. Contrary to findings in the previous female-based study, there were no cognitive-motor impairments for increasingly dissociated visually-guided reaching tasks in at-risk males when compared to healthy controls. Analyses of the females in their ability to perform accurate movements to targets supported previous findings, where at-risk females had less accurate movements compared to control females in the non-standard conditions (Hawkins and Sergio, 2014). As predicted, there were no behavioural differences between the control male and female groups. This supports previous findings from our laboratory, where behavioural performance did not differ between the sexes of cognitively healthy young adults on CMI tasks (Gorbet and Sergio, 2007). Instead, any differences were seen

in brain imaging results. The underlying brain networks that control thinking and moving at the same time were different between the sexes for the same behavioural performance. As previously mentioned, in healthy populations women typically outperform men in tasks requiring accuracy, while men excel in tasks requiring speed (Fozard et al., 1994; Kimura, 1993; Kimura and Harshman, 1984). While not statistically significant, the results for the healthy control participants in the current study reflected these findings. In general, the women had lower endpoint error scores (representing greater accuracy and precision), while the men had faster timing scores. However, the dementia-risk male and female groups did differ significantly in their performance of the CMI tasks, discussed below.

Timing and endpoint error scores. The introduction of the three non-standard mapping conditions did not result in any significant changes to timing scores in the at-risk groups compared to their respective sex-matched controls. Furthermore, there were no significant sex-differences in timing scores between the at-risk participants nor the control participants. Timing scores were composed of the RT, MTf, and PV. RT and MTf functionally involve the registration of a sensory stimulus, followed by the translation of this information to a motor response, and finally the motor execution. No significant differences in timing scores suggest that when task complexity was increased, participants did not have trouble with the planning and initiation phases of the appropriate hand movement. This supports findings from a previous study investigating patients with probable AD compared to healthy controls on a plane-change movement task with little to no feedback of their limb (Ghilardi et al., 1999). They found that compared to the control participants, AD patients had fragmented velocity profiles and increased movement times both with and without visual cursor feedback, suggesting that AD patients rely on continuous sensory monitoring of their limbs. Furthermore, without visual feedback the AD

patients had more inaccurate movements; because the initial directions of the movements were more accurate than the endpoint locations, the authors suggested that patients could successfully plan but not maintain an accurate motor plan in the early stages of the disease. This is further reflected in the current study, where similar timing scores across groups indicate normal movement initiation, but increased endpoint error scores indicate an inability to then execute an accurate and precise movement in at-risk females. The multiple correction model of limb control suggests that movements towards a single target are composed of multiple sub-movements, each responsible for reducing the error made in the preceding sub-movement. (Crossman and Goodeve, 1983; Keele, 1968). It takes time to detect the error visually, feed it back for a correction, and initiate a corrective sub-movement - this is the speed-accuracy trade-off, where longer movements are assumed to generally be more accurate. This may be the mechanism underlying our results from the female population, where the at-risk females showed greater endpoint error scores but faster timing scores compared to controls. The opposite appears to be true for the males, where at-risk males had consistently slower timing scores but smaller endpoint error scores compared to controls on most of the non-standard tasks. Furthermore, patients with AD have been shown to have problems in cognitive processes requiring higher-level control involving attention networks (Baddeley et al., 2001; Sheridan and Hausdorff, 2007). In the current study, increased endpoint errors during non-standard tasks requiring higher-level cognition may reflect problems with attention networks. Disruptions to these networks would divide attention (and require more neural resources) between incongruent eye and hand movements during non-standard tasks.

Corrective path lengths and sub-movements. Movement performance was compared across groups by examining corrective path lengths, as movements with curves and deviations from a

straight trajectory would result in longer path lengths. As the task difficulty increased from the standard to non-standard conditions, there was also an increase in corrective path lengths. Specifically, the two non-standard tasks with one level of dissociation (FR and PC) had comparably larger corrective path lengths compared to the standard condition. The PC+FR condition with two levels of dissociation had the greatest corrective path lengths compared to the other three conditions. Work in our laboratory has shown something similar in individuals with mild cognitive impairment, where behavioural deficits became apparent only for the CMI conditions having two levels of dissociation between the motor output and the guiding visual information (Salek et al., 2011). Across all conditions, the at-risk groups also showed greater corrective path lengths, and thus greater hand path variability, compared to their respective controls. In a study investigating visual feedback control in young adults and the elderly, visual feedback was removed (Seidler-Dobrin and Stelmach, 1998). Following practice, the elderly continued to show persistently lower endpoint accuracy unlike younger controls. This suggests that older adults rely more heavily on visual online feedback than younger controls, as reported by a number of other studies (Haaland et al., 1993; Lyons et al., 1996). Moreover, older adults show impairments in monitoring online movement trajectories through visual feedback (Sarlegna, 2006). Younger and older adults reached to targets that were either stationary or unexpectedly displaced. Their results showed that movement accuracy towards stationary targets was enhanced by visual information in both age groups. However, when large movement adjustments were required following target displacement, young adults used visual information of the target locations more efficiently compared to older adults to correct hand trajectories. Taken together, these studies demonstrate how older adults rely more on visual online feedback, but are also less efficient in their use of online feedback when making movement adjustments.

Participants in the current study had a greater number and percentage of corrective sub-movements in the three non-standard tasks compared to the standard task. Furthermore, the condition with two levels of dissociation had the greatest number and percentage of sub-movements. This further showed that older adults are more reliant on feedback control; an internal feedback loop is needed for comparing and updating relative hand and target locations in the cognitive-motor integration tasks, which rely on properly functioning frontoparietal connections (Vesia et al., 2008). Pohl et al., (1996) similarly postulated that older adults are more reliant on feedback control, as they made a greater number of corrective movements compared to younger controls. In the current study, larger endpoint error scores and corrective path lengths specifically in the at-risk individuals suggest that disruptions to online feedback control seen in healthy aging may be further impaired in the patient population. Further support for disruptions to online corrective mechanisms comes from direction reversal results.

Direction Reversals. The largest numbers of direction reversals were in the two non-standard conditions requiring strategic control, FR and PC + FR. At-risk females had more direction reversals than control females in both strategic control conditions, while at-risk males had more direction reversals compared to control males only in the FR condition. The strategic control conditions require participants to pay attention to the location of target appearance, and then inhibit the initial reaction to move towards the target and instead move in the opposite direction. Therefore, an increased number of direction reversals may reflect inhibitory dysfunction in the at-risk individuals, which has been shown by other studies in AD patients via abnormal prosaccadic behaviour. One study investigated changes in partially directed attention in patients with probable AD, where subjects had to attend to targets appearing in one of four peripheral locations around a central marker (Scinto et al., 1994). Perseveration errors were

defined as “wrong-way saccades” where subjects had trouble disengaging attention from central or previous trial targets, or performed saccades to the opposite direction of the new target. Patients with probable AD displayed greater errors of perseveration compared to controls, and the authors suggested that damage to the posterior lobes may be responsible. In another study, AD patients and healthy controls were tested in part on a go/no-go task that required participants to saccade towards targets (go) or maintain central fixation during target presentation (no-go) (Crawford et al., 2005). There were also anti-saccade trials in which participants had to saccade in the opposite direction of target appearance. AD patients had more inhibition errors in the no-go, go/no-go, and anti-saccade tasks. Inhibition errors in the anti-saccade tasks positively correlated with dementia severity. Their findings suggest that problems with online corrective movements may account for the direction reversal findings in the current study. In an anti-point paradigm, when subjects were required to deliberately reach in the opposite direction of target displacement they produced an initial movement in the direction of the target before being corrected away (Day and Lyon, 2000). These online adjustments towards the target at the start of the movement were labelled as automatic responses that were then susceptible to voluntary modification away from the target. They suggested that a possible mechanism for this automatic response is that it is mediated by subcortical brain regions, while the later voluntary adjustment involves cortical premotor areas that establish a non-standard relationship (i.e., moving left when the target displaces to the right).

Now that we’ve established possible explanations for behavioural differences across conditions and between groups, let’s look more in depth at what mechanisms may underlie these differences.

Potential mechanisms underlying diagnostic differences. There are several models used to describe movement control - feedfoward, feedback, or hybrid. Feedforward models propose that a motor plan is created prior to a movement, and feedback loops are then used near the end of movement to modulate the initial motor command when it is inaccurate (Meyer et al., 1988). Feedback models propose that there is no production of an initial motor plan, but rather it is generated in real-time during the course of the movement whereby an error signal compares the locations of the hand and target relative to each other (Flanagan et al., 1993). However, optimal movement control is likely a result of a combination of these two models and is represented by a hybrid model. A hybrid model proposes that a crude initial motor plan is created (feedfoward), and because this motor plan is imprecise it is then continuously adjusted in real-time (feedback) (Desmurget and Grafton, 2000). Support for this model comes from findings that online control by visual and non-visual information is seen early in a hand movement. The coordination of eye, head, and hand movement during a goal-directed reach appear sequential - the eyes move first, followed by the head, and finally the hand (Prablanc et al., 1979). Biguer et al., (1982) showed that while behaviourally the movements appear sequential, they actually occur at the same time and any differences are due to inertial factors. Looking at EMG discharge of the eyes, head, and arm during reaching tasks towards a visual target, they found that the EMG discharges were synchronous. A motor command is sent to all effectors at the same time, but the arm moves last, as it has to overcome the greatest inertia. Studies investigating eye-hand coordination have reported a lag of 60-100 ms between eye and hand movement (Angel et al., 1970; Prablanc et al., 1979). This is consistent with the electromechanical delay of 50-100 ms seen between agonist muscle activation and contraction. It has been shown that motor plans created and executed from peripheral vision do not provide as accurate a target location as foveal vision (Bock, 1993).

Therefore, following a saccade to a target there need to be adjustments to the motor plan based on foveal information.

An area hypothesized as being critical for updating hand trajectory is the posterior parietal cortex (PPC) (Desmurget et al., 1999; Desmurget et al., 2001; Pisella et al., 2000). In one study, participants had to reach towards a visual target that either remained stationary, or was moved (Desmurget et al., 1999). Transcranial magnetic stimulation (TMS) was applied over the left PPC during the presentation of the target; stimulation caused a disruption in trajectory corrections, which otherwise normally occurred in tasks where the target moved. In tasks where the target remained stationary and normally did not require corrective movements, stimulation of the left PPC had no effect. Normal aging appears to show a frontal dominance in its effects; there is shrinkage in several brain regions among which are areas of the frontal lobe, there is loss of white matter tracts in the frontal lobe but a preservation in the posterior regions, and finally there are decreases in metabolism seen in the frontal lobe (O'Sullivan et al., 2001; Pfefferbaum et al., 2005; Raz et al., 2005; Tumeh et al., 2007). Conversely, AD pathology appears to be concentrated in posterior cortical regions. Brun and Gustafson (1976) examined the brains of AD patients and found that maximal cortical degeneration spanned the posterior temporal areas, as well as the parietal and occipital lobes. Both the superior and inferior regions of the PPC have also shown hypoperfusion in patients with AD (Buck et al., 1997). Based on the findings from AD patients in conjunction with the current study's results, I propose that the PPC is impaired to a greater degree in at-risk individuals relative to those not at-risk. Damage to the PPC may cause problems with online corrective mechanisms and may explain why the at-risk participants have greater corrective path lengths and endpoint error scores.

It is not known exactly where in the brain abnormal Aβ accumulation begins in individuals with AD. In a recent imaging study investigating non-demented individuals, researchers used PET scans to measure fibrillar Aβ pathology, and CSF samples to measure the levels of Aβ-42, total tau, and phosphorylated tau (Palmqvist et al., 2017). Using these approaches, they were able to identify the earliest preclinical AD stage in participants, and showed that Aβ accumulation preferentially began in the precuneus, posterior cingulate cortex, and medial orbitofrontal cortex. This early Aβ accumulation predominantly overlapped with the DMN, as well as with the frontoparietal network. While a correlation between decreased functional connectivity in these networks and Aβ pathology has been shown previously, Palmqvist et al., (2017) were the first to demonstrate this relationship in the earliest stages of AD for individuals who are still cognitively healthy (Elman et al., 2016; Koch et al., 2014). This could be a mechanism to explain why performance differences are seen between females at-risk for dementia versus those that are not at-risk in tasks requiring the frontoparietal network.

Potential mechanisms underlying sex-differences. The question remains - why are the at-risk females affected behaviourally to a greater extent than the at-risk males? According to the Alzheimer's Society of Canada, 72% of Canadians living with AD are women. It's not yet clear why this is. One possible explanation is that differences in the prevalence of AD between the sexes may be due to hormonal changes. Converging evidence suggests that low levels of estrogens could lead to cognitive decline. Specifically, low estrogen levels have been linked to the etiology of dementia in women, where estrogen seems to have a neuroprotective effect against cognitive decline (Rocca et al., 2014). Women with surgically induced menopause following bilateral oophorectomy - the surgical removal of both ovaries - undergo an abrupt decline in estrogen, progesterone, and testosterone (Morrison et al., 2006). Several studies

looking at women who had surgically induced menopause showed an increased risk of cognitive impairment and dementia (Phung et al., 2010; Rocca et al., 2007). In the study by Rocca et al., (2007), women who then received estrogen treatment following the surgery no longer showed an increased risk of cognitive impairments or dementia. Natural menopause shows high variability in the age of onset, with some women experiencing premature menopause (before 40 years old) or early menopause (between 40 and 45 years old) (Rocca et al., 2011; Shuster et al., 2010). The females in the current study were 50 to 68 years of age, and so it is highly likely that most (if not all) would be undergoing, or have already gone through, menopause and therefore potentially showing exacerbated cognitive-motor integration declines compared to the males.

There also appears to be an interaction of APOE e4 with hormone levels and menopause. A study by Jacobs et al., (2013) collected data from post-menopausal women, half of which were on hormone replacement therapy (HRT) while the other half had been off of it for two years. They investigated the effects of having the APOE e4 allele on telomere length, a measure of biological aging. APOE e4 carriers had greater telomere shortening that was an equivalent of 10 years of aging compared to non-carriers. There was also a modulatory effects of hormone therapy, where e4 carriers on HRT did not show as much cellular aging as e4 carriers no longer on HRT. This further suggests that hormones in women serve as a buffer against cell aging in at-risk women. Furthermore, APOE e4 risk for developing AD is greater for women than men. Women with just one copy of the APOE e4 allele showed an increased dementia risk equivalent to the one seen in men with two copies of the APOE e4 allele (Payami et al., 1994). This finding was supported in another study that found that there was not a significant difference in disease risk for men with one copy of the APOE e4 allele compared to men without any copies of the e4

allele (Farrer et al., 1997). In contrast, women who had one copy of the e4 allele had the same increase in risk as men who had two copies of the allele.

Finally, our laboratory has previously shown that the brain regions used by males and females for tasks requiring cognitive-motor integration are different (Gorbet and Sergio, 2007). Females showed higher activity in the right dorsal premotor cortex in the frontal lobe, and, importantly, in the right superior parietal lobule and left sensorimotor cortex in the parietal lobe. At the same levels of performance, males showed greater bilateral activation solely in the superior temporal gyri. As was previously mentioned, frontal regions show declines in volume, white matter integrity, and metabolism in healthy aging and there is a further degeneration of the parietal regions associated with AD. As women appear to rely on these regions more heavily compared to men, it points to a possible neural mechanism explaining sex-differences seen in the at-risk individuals, where females are affected to a greater extent.

FUTURE DIRECTIONS

Future work will examine the exact nature of these task-related brain networks and their relationship to individual genetics using collected brain imaging and genetic data. Imaging data were collected for all of the participants with a magnetic resonance imaging (MRI) scanner. Diffusion tensor imaging (DTI) and resting-state functional MRI (fMRI) data will be used to identify and compare the spatial maps of the DMN between the at-risk and the control groups. Preliminary research findings from the female population did show deficits in visuomotor performance in more cognitively demanding tasks with alterations in the DMN typically seen in individuals with AD (Hawkins and Sergio, 2016). Given the online control deficits observed behaviourally in the current study, the previous imaging work could be extended to look in

particular at network level interactions with the cerebellum. The cerebellum, in addition to the PPC, has been shown to be important in the visual guidance of movement, as well as for feedback loops and online control of movement (Schweighofer et al., 1998; Stein, 1986; Wolpert et al., 1998).

All participants were also asked to provide a saliva sample to genotype for APOE e4, an allele of the APOE gene that is associated with a 2 to 3 fold increased risk for AD (Reitz and Mayeux, 2014). Genetic results will be used to assess risk of the individuals, and whether it is correlated with their visuomotor performance.

Estrogen has also been shown to mediate cognitive deficits associated with AD (Emilien et al., 2000), yet there is very little research on brain neurophysiology of post-menopausal women. Comparing healthy females pre-menopause and post-menopause would provide some insight since estrogen levels show large and rapid declines in perimenopause, while sex hormone levels in men decline only marginally with age (Burger et al., 1995; Harman and Tsitouras, 1980). The results from females could then be compared to data collected from healthy age-matched males, and eventually translated to the at-risk population. Additionally, there is evidence of a further increased risk of AD in women with APOE e4 (a genetic marker of AD) associated with events occurring at midlife and onward. Due to sex-specific fluctuations seen in APOE e4 concentration synergistic with hormonal changes at puberty onset and menopause in women, it would be interesting to look at the impact of sex steroid levels on brain activity and performance on CMI tasks in females pre- and post-menopause. Estrogen in particular has been shown to impact APOE gene expression and brain metabolism differently between the sexes as a result of the greater sex hormone changes seen in women post-menopause (Li et al., 2014; Shiele et al., 2000).

LIMITATIONS

The selection of male participants was not supervised by a medical professional. Groupings into the at-risk versus control groups were based on the participants' self-reports, and no medical charts or official clinical diagnoses were obtained. While some participants did have a definitive diagnosis of AD for their parent(s) and/or family member(s) following autopsies, most participants' parents were still alive. It is not possible to diagnose someone with AD before death, and so most of the parents were diagnosed by a clinician with dementia due to probable AD. It is possible that some of the participants' parents had another form of dementia and we were not aware. Furthermore, this study was cross-sectional in nature. As we are looking at individuals that are at an increased risk for developing AD later in life, it would be interesting to do a longitudinal study to follow these participants and see what proportion develop AD from both groups. It would then be possible to also look at whether these individuals that develop AD were the ones with the poorest CMI performance on non-standard tasks.

CONCLUSION

While research in the last decade has led to developments in the early detection of dementia risk, these techniques involve invasive and costly procedures such as PET scans and taking blood samples. Our laboratory uses a fairly quick paradigm (approximately 20 minutes) that is neither invasive nor costly, and one that would be easily accessible to the public and straightforward to administer. The goal of the current research was to test the efficacy of this tablet-based tool in measuring deficits in visuomotor control of individuals at-risk for dementia before the onset of clinical symptoms. By the hybrid model of movement control, the feedfoward component involving the creation of the initial motor plan was not affected early on in the disease as reflected by timing scores not being significantly different across groups. Rather, it

appears to be the feedback component required for continuous online updating of the motor plan that was disrupted early in the disease. This is evident in the increased endpoint error scores, corrective path lengths, and direction reversals in the non-standard conditions, especially in the condition involving two levels of dissociation. Disruptions in online feedback control are seen in the at-risk individuals, particularly in the females. These data suggest that the underlying brain networks that control thinking and moving at the same time are different between men and women, and that dementia risk may affect female cognitive-motor integration performance to a greater extent. These findings provide insight into the mechanisms underlying disease- and sex-related changes in cognitive-motor control. Importantly, the results may potentially translate into a behavioural biomarker for early dementia detection.

REFERENCES

Albines D, Granek JA, Gorbet DJ, Sergio LE. 2016. Bimanual Coordination Development Is Enhanced in Young Females and Experienced Athletes. J Mot Learn Dev. 4(2):274-286.

Alexander GE, Crutcher MD. 1990. Neural Representations of the Target (Goal) of Visually Guided Arm Movements in Three Motor Areas of the Monkey. J Neurophysiol. 64(1):164-178.

American Psychiatric Association. 2013. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.

Andersen RA, Essick C, Siegel R. 1985. Encoding of spatial location by posterior parietal neurons. Science. 230:456-458.

Andersson C, Blennow K, Johansson SE, Almkvist O, Engfeldt P, Lindau M, Eriksdotter-Jönhagen M. 2007. Differential CSF biomarker levels in APOE-epsilon4-positive and -negative patients with memory impairment. Dement Geriatr Cogn Disord. 23(2):87-95.

Angel RW, Alston W, Garland H. 1970. Functional relations between the manual and oculomotor control systems. Exp Neurol. 27(2):248-257.

Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. 1992. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology. 42:631-639.

Baddeley AD, Baddeley HA, Bucks RS, Wilcock GK. 2001. Attentional control in Alzheimer's disease. Brain. 124(8):1492-1508.

Battaglia-Mayer A, Ferraina S, Mitsuda T, Marconi B, Genovesio A, Onorati P, Lacquaniti F, Caminiti R. 2000. Early coding of reaching in the parietooccipital cortex. J Neurophysiol. 83(4):2374-2391.

Bedford FL. 1993. Perceptual and cognitive spatial learning. J Exp Psychol Hum Percept Perform. 19(3):517-530.

Beery AK, Zucker I. 2011. Sex bias in neuroscience and biomedical research. Neurosci Biobehav Rev. 35(3):565-572.

Bierer LM, Hof PR, Purohit DP, Carlin L, Schmeidler J, Davis KL, Perl DP. 1995. Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. Arch Neurol. 52:81-88.

Biguer B, Jeannerod M, Prablanc C. 1982. The coordination of eye, head, and arm movements during reaching at a single visual target. Exp Brain Res. 46(2):301-304.

Blangero A, Menz MM, McNamara A, Blinofski F. 2009. Parietal modules for reaching. Neuropsychologia. 47(6):1500-1507.

Blennow K, de Leon MJ, Zettenberg H. 2006. Alzheimer's disease. Lancet. 368:387-403.

Bock O. 1993. Localization of objects in the peripheral visual field. Behav Brain Res. 56(1):77-84.

Braak H, Braak E. 1991a. Alzheimer's disease affects limbic nuclei of the thalamus. Acta Neuropathol. 81:261-268.

Braak H, Braak E. 1991b. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82(4):239-259.

Braak H, Braak E. 1995. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging. 16(3):271-278.

Braak H, Braak E. 1996. Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. Acta Neuropathol. 92(2):197-201.

Braskie MN, Jahanshad N, Stein JL, Barysheva M, McMahon KL, de Zubicaray GI, Martin NG, Wright MJ, Ringman JM, Toga AW, Thompson PM. 2011. Common Alzheimer's disease risk variant within the CLU gene affects white matter microstructure in young adults. J Neurosci. 31(18):6764-6770.

Brun A, Gustafson L. 1976. Distribution of cerebral degeneration in Alzheimer's disease. Archiv für Psychiatrie und Nervenkrankheiten. 223(1):15-33.

Buck BH, Black SE, Behrmann M, Caldwell C, Bronskill MJ. 1997. Spatial-and object-based attentional deficits in Alzheimer's disease. Relationship to HMPAO-SPECT measures of parietal perfusion. Brain. 120(7):1229-1244.

Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, Sheline YI, Klunk WE, Mathis CA, Morris JC, MA Mintun. 2005. Molecular, structural, and functional characterization of Alzheimer’s disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci. 25:7709-7717.

Burns A, Iliffe S. 2009. Dementia. BMJ. 338.

Cahill L. 2006. Why sex matters for neuroscience. Nature Rev Neurosci. 7(6):477.

Campion D, Flaman JM, Brice A, Hannequin D, Dubois B, Martin C, Moreau V, Charbonnier F, Didierjean O, Tardieu S, et al. 1995. Mutations of the presenilin gene in families with early-onset Alzheimer's disease. Hum Mol Gen. 4(12):2373-2377.

Cavanna AE, Trimble MR. 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain. 129:564-583.

Cirrito JR, Yamada KA, Finn MB, Sloviter RS, Bales KR, May PC, Schoepp DD, Paul SM, Mennerick S, Holtzman DM. 2005. Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. Neuron. 48:913-922.

Clower DM, Boussaoud D. 2000. Selective use of perceptual recalibration versus visuomotor skill acquisition. J Neurophysiol. 84(5):2703-2708.

Conway JM, Huffcutt AI. 2003. A review and evaluation of exploratory factor analysis practices in organizational research. Organ Res Methods. 6(2):147-168.

Crawford JD, Henriques DY, Medendorp WP. 2011. Three-dimensional transformations for goal-directed action. Annu Rev Neurosci. 34:309-331.

Crawford TJ, Higham S, Renvoize T, Patel J, Dale M, Suriya A, Tetley S. 2005. Inhibitory control of saccadic eye movements and cognitive impairment in Alzheimer's disease. Biol Psychiatr. 57(9):1052-1060.

Crossman ER, Goodeve PJ. 1983. Feedback control of hand-movement and Fitts' law. Q J Exp Psychol A. 35(2):251-278.

Darling WG, Cooke JD, Brown SH. 1989. Control of simple arm movements in elderly humans. Neurobiol Aging. 10:149-157.

Day BL, Lyon IN. 2000. Voluntary modification of automatic arm movements evoked by motion of a visual target. Exp Brain Res. 130(2):159-168.

Desmurget M, Epstein CM, Turner RS, Prablanc C, Alexander GE, Grafton ST. 1999. Role of the posterior parietal cortex in updating reaching movements to a visual target. Nature Neurosci. 2(6):563.

Desmurget M, Grafton S. 2000. Forward modeling allows feedback control for fast reaching movements. Trends Cogn Sci. 4(11):423-431.

Desmurget M, Gréa H, Grethe JS, Prablanc C, Alexander GE, Grafton ST. 2001. Functional anatomy of nonvisual feedback loops during reaching: a positron emission tomography study. J Neurosci. 21(8):2919-2928.

Dickerson BC, Goncharova I, Sullivan MP, Forchetti C, Wilson RS, Bennett DA, Beckett LA, deToledo-Morrell L. 2001. MRI-derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. Neurobiol Aging. 22(5):747-754.

Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, et al. 2007. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 6(8):734-746.

Elman JA, Madison CM, Baker SL, Vogel JW, Marks SM, Crowley S, O'Neil JP, Jagust WJ. 2014. Effects of beta-amyloid on resting state functional connectivity within and between networks reflect known patterns of regional vulnerability. Cerebral Cortex. 26(2):695-707.

Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, Duijn CM. 1997. Effects of age, sex, and ethnicity on the association between Apolipoprotein E genotype and Alzheimer disease: A meta-analysis. J Am Med Assoc. 278(16):1349-1356.

Field A. 2009. Discovering statistics using SPSS. Sage publications.

Fischer FU, Wolf D, Scheurich A, Fellgiebel A. 2015. Altered whole-brain white matter networks in preclinical Alzheimer's disease. Neuroimage Clin. 8:660-666.

Flanagan JR, Ostry DJ, Feldman AG. 1993. Control of trajectory modifications in target-directed reaching. J Motor Behav. 25(3):140-152.

Flanders M, Soechting JF, Tillery SIH. 1992. Early stages in a sensorimotor transformation. Behav Brain Sci. 15:309-362.

Fozard JL, Vercryssen M, Reynolds SL, Hancock PA, Quilter RE. 1994. Age differences and changes in reaction time: The baltimore longitudinal study of aging. J Gerontol. 49:P179-89.

Galletti C, Fattori P, Kutz DF, Gamberini M. 1999. Brain location and visual topography of cortical area V6A in the macaque monkey. Eur J Neurosci. 11:575-582.

Geller SE, Adams MG, Carnes M. 2006. Adherence to federal guidelines for reporting of sex and race/ethnicity in clinical trials. J Womens Health. 15(10):1123-1131.

Ghilardi MF, Alberoni M, Marelli S, Rossi M, Franceschi M, Ghez C, Fazio F. 1999. Impaired movement control in Alzheimer's disease. Neurosci Lett. 260:45-48.

Ghilardi MF, Alberoni M, Rossi M, Franceschi M, Mariani C, Fazio F. 2000. Visual feedback has differential effects on reaching movements in Parkinson's and Alzheimer's disease. Brain Res. 876:112-123.

Ghilardi M, Gordon J, Ghez C. 1995. Learning a visuomotor transformation in a local area of work space produces directional biases in other areas. J Neurophysiol. 73:2535-2539.

Gielen CC, Van den Heuvel PJ, Van Gisbergen JA. 1984. Coordination of fast eye and arm movements in a tracking task. Exp Brain Res. 56(1):154-161.

Gorbet DJ, Mader LB, Staines WR. 2010. Sex-related differences in the hemispheric laterality of slow cortical potentials during the preparation of visually guided movements. Exp Brain Res. 202(3):633-646.

Gorbet DJ, Sergio LE. 2007. Preliminary sex differences in human cortical BOLD fMRI activity during the preparation of increasingly complex visually guided movements. Eur J Neurosci. 25:1228-1239.

Gorbet DJ, Sergio LE. 2009. The behavioural consequences of dissociating the spatial directions of eye and arm movements. Brain Res. 1284:77-88.

Gorbet DJ, Staines WR. 2011. Inhibition of contralateral premotor cortex delays visually guided reaching movements in men but not in women. Exp Brain Res. 212(2):315-325.

Gorbet DJ, Staines WR, Sergio LE. 2004. Brain mechanisms for preparing increasingly complex sensory to motor transformations. Neuroimage. 23(3):1100-1111.

Granek JA, Sergio LS. 2015. Evidence for distinct brain networks in the control of rile-based motor behavior. J Neurophysiol. 114:1298-1309.

Greicius MD, Srivastava G, Reiss AL, Menon V. 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci USA. 101:4637-4642.

Grieve SM, Clark CR, Williams LM, Peduto AJ, Gordon E. 2005. Preservation of limbic and paralimbic structures in aging. Hum Brain Mapp. 25:391-401.

Gron G, Wunderlich AP, Spitzer M, Tomczak R, Riepe MW. 2000. Brain activation during human navigation: Gender-different neural networks as substrate of performance. Nat Neurosci. 3:404-408.

Guillozet AL, Weintraub S, Mash DC, Mesulam MM. 2003. Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. Arch Neurol. 60:729-736.

Haaland KY, Harrington DL, Grice JW. 1993. Effects of aging on planning and implementing arm movements. Psychol Aging. 8(4):617.

Hardy J, Selkoe DJ. 2002. The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics. Science. 297(5580):353–356.

Hawkins KM, Goyal AI., Sergio LE. 2015. Diffusion tensor imaging correlates of cognitive-motor decline in normal aging and increased Alzheimer's disease risk. J Alzheimer's Dis. 44(3):867-878.

Hawkins KM, Sayegh P, Yan X, Crawford JD, Sergio LE. 2013, Neural activity in superior parietal cortex during rule-based visual-motor transformations. J Cogn Neurosci. 25(3):436-454.

Hawkins KM, Sergio LE. 2014. Visuomotor impairments in older adults at increased Alzheimer's disease risk. J Alzheimer's Dis. 42(2):607-621.

Hawkins KM, Sergio LE. 2016. Adults at Increased Alzheimer's Disease Risk Display Cognitive-Motor Integration Impairment Associated with Changes in Resting-State Functional Connectivity: A Preliminary Study. J Alzheimer's Dis. 53:1161-1172.

Hebert LE, Bienias JL, McCann JJ, Scherr PA, Wilson RS, Evans DA. 2010. Upper and Lower Extremity Motor Performance and Functional Impairment in Alzheimer's Disease. Am J Alzheimers Dis Other Demen. 25(5):425-431.

Helsen WF, Elliott D, Starkes JL, Ricker KL. 1998. Temporal and spatial coupling of point of gaze and hand movements in aiming. J Motor Behav. 30(3):249-59.

Honea RA, Swerdlow RH, Vidoni ED, Burns JM. 2011. Progressive regional atrophy in normal adults with a maternal history of Alzheimer's disease. Neurology. 76:822-829.

Honea RA, Swerdlow RH, Vidoni ED, Goodwin J, Burns JM. 2010. Reduced gray matter volume in normal adults with a maternal family history of Alzheimer disease. Neurology.74(2):113-120.

Hua X, Hibar DP, Ching CR, Boyle CP, Rajagopalan P, Gutman BA, Leow AD, Toga AW, Jack CR, Harvey D, et al. 2013. Unbiased tensor-based morphometry: improved robustness and sample size estimates for Alzheimer's disease clinical trials. Neuroimage. 66:648-661.

Hugenschmidt CE, Peiffer AM, Kraft RA, Casanova R, Deibler AR, Burdette JH, Maldjian JA, Laurienti PJ. 2008. Relating imaging indices of white matter integrity and volume in healthy older adults. Cereb Cortex. 18(2):433-442.

Hyman SE. 2007. Can neuroscience be integrated into the DSM-V? Nat Rev Neurosci. 8(9):725-732.

Inoue K, Kawashima R, Sugiura M, Ogawa A, Schormann T, Zilles K, Fukuda H. 2001. Activation in the ipsilateral posterior parietal cortex during tool use: A PET study. Neuroimage. 14:1469-1475.

Jack CR, Lowe VJ, Senjem ML, Weigand SD, Kemp BJ, Shiung MM, Knopman DS, Boeve BF, Klunk WE, Mathis CA, Petersen RC. 2008. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. Brain. 131:665-680.

Jack CR, Wiste HJ, Weigand SD, Knopman DS, Vemuri P, Mielke MM, Lowe V, Senjem ML, Gunter JL, Machulda MM, et al. 2015. Age, Sex, and APOE ε4 Effects on Memory, Brain Structure, and β-Amyloid Across the Adult Life Span. J Am Med Assoc Neurol. 72(5):511-519.

Jacobs EG, Kroenke C, Lin J, Epel ES, Kenna HA, Blackburn EH, Rasgon NL. 2013. Accelerated cell aging in female APOE-ε4 carriers: implications for hormone therapy use. PloS one. 8(2):e54713.

Jordan K, Wustenberg T, Heinze HJ, Peters M, Jancke L. 2002. Women and men exhibit different cortical activation patterns during mental rotation tasks. Neuropsychologia. 40:2397-2408.

Kaiser HF. 1960. The application of electronic computers to factor analysis. Educ Psychol Meas. 20(1):141-51.

Kakei S, Hoffman DS, Strick PL. 2003. Sensorimotor transformations in cortical motor areas. Neurosci Res. 46(1):1-10.

Kalaska JF. 1996. Parietal cortex area 5 and visuomotor behavior. Can J Physiol Pharmacol. 74(4):483-498.

Kalaska JF, Crammond DJ. 1992. Cerebral cortical mechanisms of reaching movements. Science. 255(5051):1517-1523.

Kalaska JF, Scott SH, Cisek P, Sergio LE. 1997. Cortical control of reaching movements. Curr Opin Neurobiol. 7(6):849-859.

Kalaska JF, Sergio LE, Cisek P. 1998. Cortical control of whole-arm motor tasks. Novartis Found Symp. 218:176-90; discussion 190-201.

Kantarci K, Avula R, Senjem ML, Samikoglu AR, Zhang B, Weigand SD, Przybelski SA, Edmonson HA, Vemuri P, Knopman DS, et al. 2010. Dementia with Lewy bodies and Alzheimer disease: neurodegenerative patterns characterized by DTI. Neurology. 74:1814-1821.

Kantarci K, Schwarz CG, Reid RI, Przybelski SA, Lesnick TG, Zuk SM, Senjem ML, Gunter JL, Lowe V, Machulda MM, et al. 2014. White matter integrity determined with diffusion tensor imaging in older adults without dementia: influence of amyloid load and neurodegeneration. J Am Med Assoc Neurol. 71:1547-1554.

Karow DS, McEvoy LK, Fennema-Notestine C, Hagler DJ, Jennings RG, Brewer JB, Hoh CK, Dale AM. et al. 2010. Relative capability of MR imaging and FDG PET to depict changes associated with prodromal and early alzheimer disease. Neuroradiol. 256(3):932-942.

Keele SW, Posner MI. 1968. Processing of visual feedback in rapid movements. J Exp Psychol. 77(1):155.

Kemppainen NM, Aalto S, Wilson IA, Nagren K, Helin S, Brück A, Oikonen V, Kailajärvi M, Scheinin M, Viitanen M, et al. 2007. PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. Neurology. 68:1603-1606.

Ketcham CJ, Seidler RD, Van Gemmert AW, Stelmach GE. 2002. Age-related kinematic differences as influenced by task difficulty, target size, and movement amplitude. J Gerontol B Psychol Sci Soc Sci. 57:P54-64.

Kim ES, Carrigan TP, Menon V. 2008. Enrollment of women in National Heart, Lung, and Blood Institute-funded cardiovascular randomized controlled trials fails to meet current federal mandates for inclusion. J Am Coll Cardiol. 52(8):672-673.

Kimura D. 1993. Neuromotor mechanisms in human communication. New York: Oxford University Press.

Kimura D, Harshman RA. 1984. Sex differences in brain organization for verbal and non-verbal functions. Prog Brain Res. 61:423-441.

Koch K, Myers NE, Göttler J, Pasquini L, Grimmer T, Förster S, Manoliu A, Neitzel J, Kurz A, Förstl H, Riedl V. 2014. Disrupted intrinsic networks link amyloid-β pathology and impaired cognition in prodromal Alzheimer's disease. Cerebral Cortex. 25(12):4678-4688.

Kuczynski B, Targan E, Madison C, Weiner M, Zhang Y, Reed B, Chui HC, Jagust W. 2010. White matter integrity and cortical metabolic associations in aging and dementia. Alzheimers Dement. 6:54-62.

Lackner JR, Dizio P. 1994. Rapid adaptation to coriolis force perturbations of arm trajectory. J Neurophysiol. 72(1):299-313.

Leduc V, Jasmin-Bélanger S, Poirier J. 2010. APOE and cholesterol homeostasis in Alzheimer's disease. Trends Mol Med. 16(10):469-477.

Liu CC, Kanekiyo T, Xu H, Bu G. 2013. Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. Nature Reviews. Neurology. 9(2):106-118.

Lustig C, Snyder AZ, Bhakta M, O'Brien KC, McAvoy M, Raichle ME, Morris JC, Buckner RL. 2003. Functional deactivations: change with age and dementia of the Alzheimer type. Proc Natl Acad Sci USA. 100:14504-14509.

Lyons J, Elliott D, Swanson LR, Chua R. 1996. The use of vision in manual aiming by young and older adults. J Aging Phys Act. 4(2):165-178.

Mahley RW, Weisgraber KH, Huang Y. 2009. Apolipoprotein E: structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. J Lipid Res. 50(Suppl):S183-S188.

Martin JJ, Gheuens J, Bruyland M, Cras P, Vandenberghe A, Masters CL, Beyreuther K, Dom R, Ceuterick C, Lubke U, et al. 1991. Early-onset Alzheimer's disease in 2 large Belgian families. Neurology. 41:62-68.

Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, Herukka SK, van der Flier WM, Blankenstein MA, Ewers M. 2009. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. J Am Med Assoc. 302:385-393.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS–ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 34(7):939-944.

McKhann G, Knopmanc DS, Chertkowd H, Hymanf BT, Jack CR, Kawash CH, Klunkk WE, Koroshetzl WJ, Manly JJ, Mayeux R, et al. 2011. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 7(3):263-269.

Meyer DE, Abrams RA, Kornblum S, Wright CE, Keith Smith JE. 1988. Optimality in human motor performance: ideal control of rapid aimed movements. Psychol Rev. 95(3):340.

Morris JC. 2005. Early-stage and preclinical Alzheimer disease.Alzheimer Dis Assoc Disord. 19(3):163-165.

Morrison JH, Brinton RD, Schmidt PJ, Gore AC. 2006. Estrogen, menopause, and the aging brain: how basic neuroscience can inform hormone therapy in women. J Neurosci. 26(41):10332-10348.

Mosconi L, Brys M, Switalski R, Mistur R, Glodzik L, Pirraglia E, Tsui W, de Santi S, de Leon MJ. 2007. Maternal family history of Alzheimer's disease predisposes to reduced brain glucose metabolism. Proc Natl Acad Sci. 104(48):19067-19072.

Munoz DP, Broughton JR, Goldring JE, Armstrong IT. 1998. Age-related performance of human subjects on saccadic eye movement tasks. Exp Brain Res. 121:391-400.

Murray EA, Bussey TJ, Wise SP. 2000. Role of prefrontal cortex in a network for arbitrary visuomotor mapping. Exp Brain Res. 133:114-129.

Nierenberg J, Pomara N, Hoptman MJ, Sidtis JJ, Ardekani BA, Lim KO. 2005. Abnormal white matter integrity in healthy apolipoprotein E epsilon4 carriers. Neuroreport. 16:1369-1372.

Nir TM, Jahanshad N, Toga AW, Bernstein MA, Jack CR, Weiner MW, Thompson PM, ADNI. 2012. Connectivity network breakdown predicts imminent volumetric atrophy in early mild

cognitive impairment. In Yap PT, et al. (Eds.), Multimodal Brain Image Analysis. Nice, FR: Springer-Verlag Berlin Heidelberg.

Nowrangi MA, Lyketsos CG, Leoutsakos JM, Oishi K, Albert M, Mori S, Mielke MM. 2013. Longitudinal, region-specific course of diffusion tensor imaging measures in mild cognitive impairment and Alzheimer's disease. Alzheimers Dement. 9:519-528.

O'Sullivan MR, Jones DK, Summers PE, Morris RG, Williams SC, Markus HS. 2001. Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. Neurology. 57(4):632-638.

Palmqvist S, Schöll M, Strandberg O, Mattsson N, Stomrud E, Zetterberg H, Blennow K, Landau S, Jagust W, Hansson O. 2017. Earliest accumulation of β-amyloid occurs within the default-mode network and concurrently affects brain connectivity. Nat Commun. 8(1):1214.

Panegyres PK, Chen HY. 2013. Differences between early and late onset Alzheimer's disease. Am J Neurodegener Dis. 2(4):300-306.

Panegyres PK, Goldblatt J, Walpole I, Connor C, Liebeck T, Harrop K. 2000. Genetic testing for Alzheimer's disease. Med J Aust. 172(7):339-343.

Payami H, Montee KR, Kaye JA, Bird TD, Yu C, Wijsman EM, Schellenberg GD. 1994. Alzheimer's Disease, Apolipoprotein E4, and Gender. J Am Med Assoc. 271(17):1316-1317.

Pfefferbaum A, Adalsteinsson E, Sullivan EV. 2005. Frontal circuitry degradation marks healthy adult aging: evidence from diffusion tensor imaging. Neuroimage. 26(3):891-899.

Phung TK, Waltoft BL, Laursen TM, Settnes A, Kessing LV, Mortensen PB, Waldemar G. 2010. Hysterectomy, oophorectomy and risk of dementia: a nationwide historical cohort study. Dement Geriatr Cogn Dis. 30(1):43-50.

Pisella L, Grea H, Tilikete C, Vighetto A, Desmurget M, Rode G, Boisson D, Rossetti Y. 2000. An 'automatic pilot' for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. Nature Neurosci. 3(7):729.

Pohl PS, Winstein CJ, Fisher BE. 1996. The locus of age-related movement slowing: sensory processing in continuous goal-directed aiming. J Gerontol B Psychol Sci Soc Sci. 51(2):94-102.

Prablanc C, Echallier JF, Komilis E, Jeannerod M. 1979. Optimal response of eye and hand motor systems in pointing at a visual target. Biol Cybern. 35(2):113-124.

Prescott JW, Guidon A, Doraiswamy PM, Choudhury KR, Liu C, Petrella JR. 2014. The Alzheimer structural connectome: changes in cortical network topology with increased amyloid plaque burden. Radiology. 273:175-184.

Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. 2015. The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. World Alzheimer Report 2015, Alzheimer's Disease International (ADI), London.

Public Health Agency of Canada. 2014. Mapping Connections: An Understanding of Neurological Conditions in Canada – The National Population Health Study of Neurological Conditions [Internet]. Ottawa: Public Health Agency of Canada; [cited 2017 May 31]. Available from: http://www.phac-aspc.gc.ca/publicat/cd-mc/mc-ec/assets/pdf/mc-ec-eng.pdf

Puglielli L, Tanzi RE, Kovacs DM. 2003. Alzheimer's disease: the cholesterol connection. Nat Neurosci. 6:345-351.

Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D, Acker JD. 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cerebral Cortex. 15(11):1676-1689.

Redding GM, Rossetti Y, Wallace B. 2005. Applications of prism adaptation: A tutorial in theory and method. Neurosci Biobehav Rev. 29(3):431-444.

Redding GM, Wallace B. 1996. Adaptive spatial alignment and strategic perceptual-motor control. J Exp Psychol Hum Percept Perform. 22(2):379-394.

Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minoshima S, Thibodeau SN, Osborne D. 1996. Preclinical evidence of Alzheimer's disease in persons homozygous for the e4 allele for apolipoprotein E. N Engl J Med. 334:752-758.

Reisberg B. 2006. Diagnostic criteria in dementia: a comparison of current criteria, research challenges, and implications for DSM-V. J Geriat Psych Neurol. 19(3):137-146.

Reitz C, Mayeux R. 2014. Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers. Biochem Pharmacol. 88(4):640–651.

Riedel BC, Thompson PM, Brinton RD. 2016. Age, APOE and sex: Triad of risk of Alzheimer's disease. J Steroid Biochem Mol Biol. 160:134-147.

Roalf D, Lowery N, Turetsky BI. 2006. Behavioral and physiological findings of gender differences in global-local visual processing. Brain Cogn. 60:32-42.

Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, De Andrade M, Melton LJ. 2007. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology. 69(11):1074-1083.

Rocca WA, Grossardt BR, Shuster LT. 2011. Oophorectomy, menopause, estrogen treatment, and cognitive aging: clinical evidence for a window of opportunity. Brain Res. 1379:188-198.

Rocca WA, Grossardt BR, Shuster LT. 2014. Oophorectomy, estrogen, and dementia: a 2014 update. Mol Cell Endocrinol. 389(1-2):7-12.

Rombouts SA, Barkhof F, Goekoop R, Stam CJ, Scheltens P. 2005. Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. Hum Brain Mapp. 26:231-239.

Sabes PN. 2000. The planning and control of reaching movements. Curr Opin Neurobiol. 10(6):740-746.

Sadato N, Ibanez V, Deiber MP, Hallett M. 2000. Gender difference in premotor activity during active tactile discrimination. Neuroimage. 11:532-540.

Salek Y, Anderson ND, Sergio L. 2011. Mild cognitive impairment is associated with impaired visual-motor planning when visual stimuli and actions are incongruent. Eur Neurol. 66(5):283-293.

Sarlegna FR. 2006. Impairment of online control of reaching movements with aging: a double-step study. Neurosci Lett. 403(3):309-314.

Sayegh PF, Gorbet DJ, Hawkins KM, Hoffman KL, Sergio LE. 2017. The Contribution of Different Cortical Regions to the Control of Spatially Decoupled Eye–Hand Coordination. J Cog Neurosci. 29(7):1194-1211.

Sayegh PF, Hawkins KM, Hoffman KL, Sergio LE. 2013. Differences in spectral profiles between rostral and caudal premotor cortex when eye-hand actions are decoupled. J Neurophysiol. 110(4):952-963.

Sayegh PF, Hawkins KM, Neagu B, Crawford JD, Hoffman KL, Sergio LE. 2014. Decoupling the actions of the eyes from the hand alters beta and gamma synchrony within SPL. J Neurophysiol. 111(11):2210-2221.

Scahill RI, Schott JM, Stevens JM, Rossor MN, Fox NC. 2002. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. Proc Natl Acad Sci USA. 99:4703-4707.

Schroeter ML, Stein T, Maslowski N, Neumann J. 2009. Neural correlates of alzheimer's disease and mild cognitive impairment: A systematic and quantitative meta-analysis involving 1351 patients. NeuroImage. 47(4):1196-1206.

Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ. 2012. The Aging Brain. In: Principles of Neural Science. 5th Ed. New York: McGraw-Hill. p. 1328-1346.

Schweighofer N, Arbib MA, Kawato M. 1998. Role of the cerebellum in reaching movements in humans. I. Distributed inverse dynamics control. Eur J Neurosci. 10(1):86-94.

Scinto LF, Daffner KR, Castro L, Weintraub S, Vavrik M, Mesulam MM. 1994. Impairment of spatially directed attention in patients with probable Alzheimer's disease as measured by eye movements. Arch Neurol. 51(7):682-688.

Seidler-Dobrin RD, Stelmach GE. 1998. Persistence in visual feedback control by the elderly. Exp Brain Res. 119(4):467-474.

Sekuler AB, Bennett PJ, Mamelak M. 2000. Effects of aging on the useful field of view. Exp Aging Res. 26:103-120.

Selkoe DJ. 2006. The ups and downs of Aβ. Nat Med. 12(7):758-759.

Sergio LE, Kalaska JF. 2003. Systematic changes in motor cortex cell activity with arm posture during directional isometric force generation. J Neurophysiol. 89(1):212-228.

Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, Bis JC, Smith AV, Carrasquillo MM, Lambert JC, et al. 2010. Genome-wide analysis of genetic loci associated with Alzheimer disease. J Am Med Assoc. 303(18):1832-40.

Seurinck R, Vingerhoets G, de Lange FP, Achten E. 2004. Does egocentric mental rotation elicit sex differences? Neuroimage. 23:1440-1449.

Sheridan PL, Hausdorff JM. 2007. The role of higher-level cognitive function in gait: executive dysfunction contributes to fall risk in Alzheimer's disease. Dement Geriatr Cogn Dis. 24(2):125-137.

Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. 2010. Premature menopause or early menopause: long-term health consequences. Maturitas. 65(2):161-166.

Small SA, Duff K. 2008. Linking Aβ and tau in late-onset Alzheimer's disease: a dual pathway hypothesis. Neuron. 60:534-542.

Soechting JF, Flanders M. 1989a. Errors in pointing are due to approximations in sensorimotor transformations. J Neurophysiol. 62:595-608.

Soechting JF, Flanders M. 1989b. Sensorimotor representations for pointing to targets in three-dimensional space. J Neurophysiol. 62:582-594.

Song MK, Lin FC, Ward SE, Fine JP. 2013. Composite variables: when and how. Nursing Res. 62(1):45.

Snyder LH. 2000. Coordinate transformations for eye and arm movements in the brain. Curr Opin Neurobiol. 10(6):747-754.

Stein JF. 1986. Role of the cerebellum in the visual guidance of movement. Nature. 323(6085):217.

Stelmach GE, Goggin NL, Garcia-Colera A. 1987. Movement specification time with age. Exp Aging Res. 13:39-46.

Stricker NH, Schweinsburg BC, Delano-Wood L, Wierenga CE, Bangen KJ, Haaland KY, Frank LR, Salmon DP, Bondi MW. 2009. Decreased white matter integrity in late-myelinating fiber pathways in alzheimer's disease supports retrogenesis. NeuroImage. 45(1):10-16.

Strittmatter W, Weisgraber K, Goedert M, Saunders A, Huang D, Corder E, Dong L, Jakes R, Alberts M, Gilbert J. 1994. Hypothesis: microtubule instability and paired helical filament formation in the Alzheimer disease brain are related to apolipoprotein E genotype. Exp Neurol. 125(2):163–171.

Tang MX, Maestre G, Tsai WY, Liu XH, Feng L, Chung WY, Chun M, Schofield P, Stern Y, Tycko B, Mayeux R. 1995. Effect of age, ethnicity, and head injury on the association between APOE genotypes and Alzheimer's disease. Ann N Y Acad Sci. 802(1):6-15.

Tippett WJ, Krajewski A, Sergio LE. 2007. Visuomotor integration is compromised in Alzheimer's disease patients reaching for remembered targets. Eur Neurol. 58(1):1-11.

Tippett WJ, Sergio LE. 2006. Visuomotor integration is impaired in early stage Alzheimer's disease. Brain Res. 1102(1):92-102.

Tippett WJ, Sergio LE, Black SE. 2012. Compromised visually guided motor control in individuals with Alzheimer's disease: Can reliable distinctions be observed? J Clin Neurosci. 19(5):655-660.

Tumeh PC, Alavi A, Houseni M, Greenfield A, Chryssikos T, Newberg A, Torigian DA, Moonis G. 2007. Structural and functional imaging correlates for age-related changes in the brain. Semin Nucl Med. 37(2):69-87.

Vesia M, Yan X, Henriques DY, Sergio LE, Crawford JD. 2008. Transcranial magnetic stimulation over human dorsal–lateral posterior parietal cortex disrupts integration of hand position signals into the reach plan. J Neurophysiol. 100(4):2005-2014.

Villain N, Desgranges B, Viader F, de la Sayette V, Mezenge F, Landeau B, Baron JC, Eustache F, Chetelat G. 2008. Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. J Neurosci. 28(24):6174-6181.

Wang L, Zang Y, He Y, Liang M, Zhang X, Tian L, Wu T, Jiang T, Li. 2006. Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. NeuroImage. 31:496-504.

Weiss E, Siedentopf CM, Hofer A, Deisenhammer EA, Hoptman MJ, Kremser C, Golaszewski S, Felber S, Fleischhacker WW, Delazer M. 2003. Sex differences in brain activation pattern during a visuospatial cognitive task: A functional magnetic resonance imaging study in healthy volunteers. Neurosci Lett. 344:169-172.

Wise SP, di Pellegrino G, Boussaoud D. 1996. The premotor cortex and nonstandard sensorimotor mapping. Can J Physiol Pharmacol. 74(4):469-482.

Wolpert DM, Miall RC, Kawato M. 1998. Internal models in the cerebellum. Trends Cogn Neurosci. 2(9):338-347.

APPENDIX

A: Entrance Questionnaire

BrDI Study: Entrance Questionnaire

BrDI HARDWARE USED: _____ FILE NAME: _____

NAME: _____ DIAGNOSIS: _____

AGE: _____ SEX: F M HANDEDNESS: _____

VISION: _____ MOCA SCORE: _____ FIRST LANGUAGE: _____

YEARS OF EDUCATION: _____ ETHNICITY: _____

OCCUPATION: _____

MEDICATION: _____

TYPE I OR II DIABETES: _____

SMOKING HISTORY: _____

ACQUIRED BRAIN INJURY (STROKE, TBI): _____

AD FAMILY HISTORY: _____

OTHER HISTORY: _____

DO YOU USE COMPUTERS? YES NO

IF YES, HOW MANY HOURS/WEEK?

1-5 (RARELY) 5-10 (O CCASIONALLY) MORE THAN 10 (OFTEN)

HAVE YOU USED A TOUCHSCREEN? YES N O

IF YES, HOW MANY HOURS/WEEK?

1-5 (RARELY) 5-10 (OCCASIONALLY) M ORE THAN 10 (OFTEN)

DO YOU PLAY VIDEO/COMPUTER GAMES? (CIRCLE ONE)

NO

RARELY

OCCASIONALLY

OFTEN

IF YES WHAT DO YOU PLAY WITH? (CIRCLE ALL THAT APPLY)

JOYSTICK

KEYBOARD

MOUSE

STAND ALONE MACHINE

GAMEPAD/CONTROLLER

WII REMOTE/KINECT

HOW DO YOU USUALLY DO YOUR BANKING? (CIRCLE ALL THAT APPLY)

ONLINE

IN PERSON AT A BRANCH (WITH A TELLER)

USING ABMS

HAVE YOU EVER USED A TOUCHSCREEN? (E.G. BUYING MOVIE TICKETS, GAS STATION, SMART PHONE, IPAD) – LIST TOUCHSCREEN EXPERIENCE

_____

_____

_____ _____

_____ ____

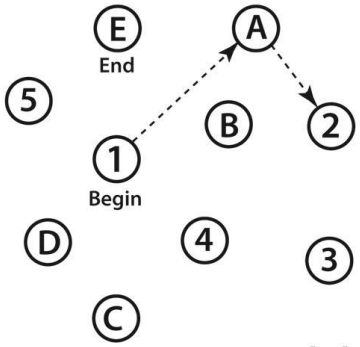
_____

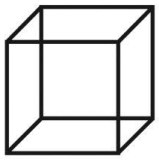
B: Montreal Cognitive Assessment (MoCA)

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS





Copy cube

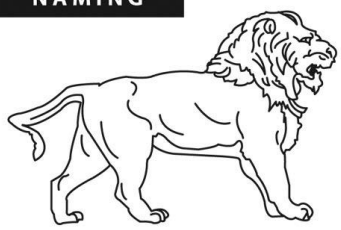
[ ] [ ]

Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING



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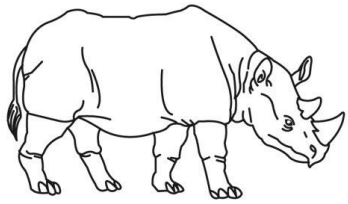

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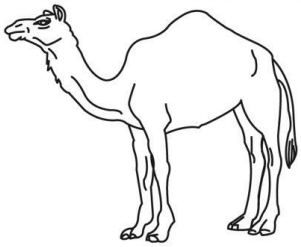

[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 — __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** — __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] — __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) — __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler — __/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — __/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____