An Investigation of Inhibitory Control and Attention Processes in Alzheimer's Disease:

An Eye Tracking study of Cognitive Impairment, Age and Ethnicity.

By

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Declaration

I declare that this thesis is entirely my own work completed under the supervision of Professor Trevor J. Crawford and Professor Sandra Sunrum-Lea. I declare that no parts of this thesis have been submitted in support of application for the award of a higher degree elsewhere.

The parts of this thesis that have been submitted for publication or published in academic journals throughout the duration of this doctoral degree, have been indicated in the statement of authorship section.

Signed:

Date: 1.07.2022

Abstract

Eye movements are involved in almost all aspects of daily life and can provide valuable insights into an individual's cognitive functioning. The ability to inhibit irrelevant stimuli, engage and disengage attention and successfully execute saccades, are vital processes for most everyday activities. Neurodegenerative diseases such as Alzheimer's results in a decline in executive functioning, working memory and inhibitory control capabilities. Areas of the brain and neuronal pathways that are involved in executing saccades, fixations and gaze patterns are often impaired in Alzheimer's disease (AD) resulting in the deterioration of eye movements, attentional control and inhibitory control. Due to this, dysfunctions and abnormal eye movements can be a useful biological marker of cognitive impairment and decline. The current diagnosis procedure for AD and other forms of cognitive impairment are time consuming, invasive, costly and often lack the sensitivity to provide an early and timely diagnosis. Eye-tracking tasks assessing pro and antisaccades could aid diagnosis and monitoring of AD and provide early indicators of cognitive decline. Further, for a potential diagnosis tool to be successful, it must be robust and generalisable across multiple ethnic and age cohorts. Therefore, in this thesis, chapters 3-5 investigate saccade performance in participants with AD and mild cognitive impairment (MCI). To investigate the robustness and generalisability of novel and established eye-tracking paradigms, chapter 3 and 4 includes younger and older adult populations and both European and South Asian adults allowing the effects to be assessed in relation to ageing, ethnicity and disease effects. I first found that disengagement of attention capabilities were preserved in AD and MCI populations and that the gap paradigm was robust across various clinical groups, age cohorts and ethnic groups. Further studies investigated a novel eye-tracking paradigm designed to assess inhibitory control towards a specific distracter. Here, it was found that the inhibition of a recent distracter (IRD) effect, categorised by faster saccade reaction times towards a target

presented in the location of a previous target compared to the location of a distracter target, was present in AD and MCI populations. This indicates that not all aspects of inhibitory control are impaired in AD populations as previously assumed. Attentional fluctuations when performing pro and antisaccades were investigated using a measure of coefficient of variation (CV) assessing saccade latencies. Results indicated that antisaccade mean latencies can distinguish clinical groups from controls however CV measures may not be sufficiently robust to provide reliable markers for cognitive impairment. In chapter 6 I shifted my focus and investigated the potential of bilateral eye movements to enhance memory and recall processes in healthy adults and clinical groups. It was found that the so-called saccade induced retrieval effect was unable to be replicated in younger and older healthy adults or clinical populations with cognitive impairment bringing into question the robustness of this effect. The work reported in this thesis develops our understanding of oculomotor processes across multiple age cohorts, ethnic groups and clinical populations. In particular, I argue that future research should strive to involve more diverse population samples and provide a greater focus on investigating preserved effects and capabilities in clinical populations.

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Statement of Authorship

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Chapter 1

1. Introduction

1.1. Overview

For many years researchers have been utilising eye tracking techniques to gain insights into individuals cognitive processing. The assessment of eye movements has allowed for a deeper understanding of inhibitory control, problem solving (Knoblich et al., 2001), working memory, attentional engagement and executive functioning processes. Eye tracking is a multifaceted measure of performance providing accuracy, processing speed, variability and latency measures. The vast amount of information and data provided by eye tracking systems creates a valuable tool for assessing cognition in both healthy older and younger adults and in cognitively impaired populations. Biomarkers currently able to detect AD in early stages are either invasive (i.e. lumbar puncture) or costly (i.e. neuroimaging), with these methods being used after multiple stages of cognitive testing. Due to this a low-cost and non-invasive method would be valuable for diagnosis and monitoring of dementia. Eye tracking could offer a low cost, non-invasive and sensitive biomarker for cognitive decline.

This thesis will focus on how eye tracking can be used to assess various forms of cognitive functioning in both healthy adults and adults with cognitive impairment specifically Alzheimer's Disease (AD). A further main focus of this thesis is the extent to which ageing, disease and cultural factors influence eye movements and established eye tracking paradigms. The body of work presented expands upon existing literature of known psychological eye tracking effects such as the "gap effect" by assessing these established paradigms in relation to various cohorts with the implications discussed.

Additionally, research has long focused on what eye movements can inform us about cognition. However, more recently researchers have begun to assess the reciprocal relationship of eye movements on cognition, specifically eye movement enhancements of episodic memory. Here, we expand on existing literature (Christman et al., 2003) by assessing the effectiveness of enhancement methods in older adult populations and in people with AD and Mild Cognitive Impairment (MCI).

1.2   Dementia, Alzheimer's Disease and Mild cognitive impairment.

Dementia is an umbrella term which describes several progressive conditions that affects brain processes. Dementia conditions are often progressive diseases leading to deterioration of cognitive functions including memory, executive functioning, inhibitory control and reasoning. These symptoms often cause significant impact on peoples' everyday life and activities (Jellinger., 2010). Dementia leads to neurones in the brain becoming damaged which prevents effective communication between brain cells. Dementia can affect people at any age but is most common in people over 65 years of age (Alzheimer's Associations, 2015). There are over 200 subtypes and causes of dementia that are currently known, with the four most common being AD, vascular dementia, frontotemporal dementia and Lew bodies dementia (Jellinger & Attems, 2010). In the UK there are over 850,000 people living with dementia with this figure set to rise over the coming years (Price & Jackson, 2009), highlighting the prevalence of dementia and the importance of effective interventions and diagnostic tools to mitigate the impact of dementia on peoples' lives.

AD is the most common cause of dementia resulting in around 50-70% of cases (Alzheimer's Associations, 2015). People with early AD often present with, most noticeably, a reduction in episodic memory capabilities, however research has also demonstrated early impairments in attentional control, executive functioning and inhibitory control (Greenwood et al., 1997; Tse et al., 2010). AD is caused by a build-up of a naturally occurring protein in

the brain called beta-amyloid. Beta-amyloid protein has several molecular forms which collect between neurons in the brain. Beta-amyloid is formed due to a breakdown of a larger protein called amyloid precursor protein (O'Brien & Wong, 2011). An excess of amyloid protein deposits results in the formation of "plaques" and "tangles" that block brain receptors leading to the deterioration of brain cells. Abnormally high levels of beta-amyloid bind together to form larger structures termed "plaques" that disrupts cell functioning by assembling between neurons and binding to cell receptor sites. This blocking of receptor cell sites prevents messages being received at the cell site reducing synaptic transmission. Neurofibrillary "tangles" are formed when abnormal levels of tau protein collect within neurons. Structures called microtubules (that help guide nutrients to the dendrites and axon from the cell body) in healthy adults are stabilised by the tau protein. However, in people with AD the tau protein starts to detach from the microtubules structures and attach to other tau proteins. This results in tangles of tau proteins forming within the neuron blocking the neuron's transport system damaging synaptic communication between cells. AD often results due to a combination of both abnormal levels of beta-amyloid and tau proteins. AD typically affects areas of the brain involved in memory including the hippocampus and entorhinal cortex early in the disease progression resulting in disruption to episodic memory capabilities. It later progresses and affects areas in the cerebral cortex responsible for reasoning, executive functioning, language and social behaviour, such as the temporal, parietal and frontal lobes. Due to the progressive nature of AD, these plaques and tangles spread throughout the brain eventually affecting multiple brain regions, resulting in the individual being unable to function and live independently.

Due to widespread damage caused by beta-amyloid and tau proteins, people with dementia caused by AD have a reduction in inhibitory control and a disengagement of attention which aligns with a decline in working memory and executive functioning

(Baddeley et al., 2001). It is thought that the deterioration of these systems results in abnormal eye movements in people with AD. Extensive research has assessed AD patients eye movements and found abnormalities in visual scan patterns (Bundesen, 1990), longer fixation times, scan durations and a greater number of fixations on selective visual attention tasks in comparison to healthy controls (Rosler et al., 2000). These findings demonstrate the connections between attention, executive functioning, cognition and memory (Freitas Pereira et al., 2014) and how eye movements can provide markers for impairments in these systems.

Mild cognitive impairment (MCI) is a clinical condition classified by cognitive impairments that are abnormal for a person of their age. People diagnosed with MCI are at an increased risk of developing dementia when compared to age-matched healthy adults with as many as 5-10% of people with MCI progressing to a dementia diagnosis each year (Mitchell & Shiri-Feshki, 2009). Although MCI can progress onto dementia, many cases can be reversable, temporarily or static varying due to the cause of the MCI. Previously MCI has been considered a distinct stage of cognitive impairment, however, more recently there is growing support for MCI to be considered a preclinical stage between normal cognitive ageing and AD (McKhann et al., 2011, Sperling et al., 2011, Ritchie et al., 2017). This is due to the high number of people with an MCI diagnosis proceeding to develop a form of dementia (Yaffe et al., 2006). Assessing MCI groups is incredibly informative and offers information of the sensitivity of a diagnostic tool prior to more advanced neurodegeneration. The majority of individuals with AD will be on multiple forms of medication aiming to delay and slow down the advancement of neurodegeneration. MCI populations are an increased risk group for dementia but often have not yet received medicinal interventions providing more accurate baseline data. Current dementia diagnoses are often only established later in the disease progression when irreversible neurodegeneration has occurred. A diagnostic tool able to identify biological markers in a preclinical group would allow for interventions to be

applied at an earlier stage leading to greater preservation of capabilities and improved patient outcomes.

1.3.   Cognitive Assessments

A dementia diagnosis is currently established using a ruling out approach rather than a confirmatory approach. This can be problematic when aiming for an early and timely diagnosis. When diagnosing dementia, self-reports from the patient or a close-relative are often used with the intention of getting an overview of the persons impairments and their severity. Self-reports rely on the informant/patient having an accurate understanding of their problems and being able to accurately articulate these problems to healthcare professionals. This can lead to inaccuracies in diagnoses and monitoring disease progression. Due to the limitations of self-report measures, cognitive assessments are therefore used in conjunction to produce a more accurate reflection of cognitive functioning. Cognitive assessments are used to measure cognitive functioning and identify abnormal changes. Cognitive screening tools are used to detect cognitive impairment in many clinical settings and aim to detect changes that are not "normal" or due to typical age-related cognitive decline. Cognitive assessments aim to offer an objective, quick, low cost and non-invasive evaluation of cognitive abilities. However, these cognitive assessments also have multiple limitations and are sensitive to external factors such as education level and literacy skills. Further, most cognitive assessments have been created based on Western samples, resulting in a lack of cultural relevance to multiple ethnic groups. These external factors greatly influence the validity of these tasks and can result in a lack of sensitivity and performance accuracy.

For cognitive scores to be meaningful a cut-off point and reference must be established based on various demographic factors. This then allows for assessment scores and cut-off points that would be deemed atypical for certain populations and therefore indicative of

cognitive impairment. Impaired performance is often classed as below the 1st or 5th percentile compared with normative data. The Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) is a commonly used cognitive screening tool that aims to differentiate between normal ageing MCI and dementia. The MoCA has been found to have a higher level of sensitivity than other commonly used tasks such as the Mini-Mental State Exam (MMSE, Folstein et al., 1975) but lower specificity. The MoCA test assesses multiple cognitive abilities including visuospatial/executive functioning, naming, attention, language, orientation, abstraction, and memory. The task is scored out of a total of 30 points with a recommended cut-off of 26 with people scoring below 25 indicative of MCI and below 19 indicative of dementia. Although widely used the MoCA has been criticised that the cut-off score of 26 leads to a higher rate of false positives than found in the original study (Kaya et al., 2014; Memoria et al., 2013; Roalf et al., 2013). In addition, education level influences task performance, attempted to be compensated by an additional point added if the person has less than 12 years of formal education. However, the high cut off point of 26/30 increases the risk of false positives particularly in people with a lower education level. Researchers have argued that the 1-point correction for lower education level (<12 years) is inadequate to compensate for education differences (Malek-Ahmadi et al., 2015). This demonstrates one of the many external factors that influences task performance on current paper-based dementia assessments and highlights the problems surrounding current cognitive and diagnostic methods currently used to identify and diagnose cognitive impairment.

1.4 Problem Statement

The current thesis will address the following problems:

- Attentional deficits have been described in patients with AD, but the detailed characteristics of these deficits are unclear.

- Inhibitory control, as measured by the antisaccade test have been reported by a number of studies, including our laboratory at Lancaster. However, it is unclear whether this is a unitary deficit or whether other measures of attentional inhibition are spared in AD.

- The current process for diagnosing AD is often invasive, time consuming and involves several paper-based assessments. These assessments often lack sufficient sensitivity and specificity to detect AD in the early stages.

- The lack of diversity of populations in the literature that have been assessed on novel and established eye tracking paradigms.

1.5 Rationale for Alternative Format

The studies contained in this thesis are presented in publishable manuscript format. Two of the papers have already been published (Chapter 3 in Brain Sciences, Chapter 4 in Cortex). It is appropriate to utilise the alternative format for this thesis due to the nature of these studies and the interesting findings obtained throughout the thesis. Although the chapters presented in this thesis are distinct and self-contained papers, they provide interconnected findings and follow a coherent narrative. The studies presented here all investigate the connection between eye movements and cognitive processes and whether eye movements can be indicative of neurodegenerative disease.

1.6 Thesis Contributions

This thesis investigates both novel and established eye tracking paradigms in relation to ageing, disease and cultural factors. The potential of eye tracking to be used in the diagnosis and monitoring of neurodegenerative disease such as AD is discussed and evaluated across multiple eye tracking tasks. The current thesis will assess whether inhibitory control deficits, often displayed on antisaccade tasks in AD populations, are

present when gaze-aversion is absent and a gaze-directed target alongside a distracter is displayed. Further, the thesis investigates the enhancement effects of bilateral eye movements and the underlying cause of this effect in both healthy adults and in people with AD and MCI.

Four contributions were made in the current thesis:

1.   **The Disengagement of Visual Attention: An Eye-Tracking Study of Cognitive Impairment, Ethnicity and Age.**

Previous research with AD populations has reported inconsistent findings when assessing disengagement of attention specifically on the prosaccade overlap task. The "gap effect" is a method to assess the disengagement of attention and refers to the decrease in prosaccade reaction times due to the inclusion of a temporal gap in the display sequence. This paper assessed the gap effect in wider population samples in relation to ageing, disease and ethnicity effects.

Publication: Polden, M., Wilcockson, T. D., & Crawford, T. J. (2020). The disengagement of visual attention: An eye-tracking study of cognitive impairment, ethnicity and age. *Brain Sciences*, *10*(7), 461.

2.   **Active Visual Inhibition is Preserved in the Presence of a Distracter: A Cross-cultural, Ageing and Dementia Study.**

The inhibition of a recent distracter (IRD) effect has been robustly found in younger adults' groups. Crawford et al (2005) conducted a series of experiments comprising of two consecutive visual displays. Participants were asked to fixate on the target of interest (a red spot) in the first display, and to ignore a distracter (a green spot). In the second display, participants were presented with the red target singularly. The location of the red spot varied and was presented either at the same location as

the previous target (i.e. the previous red spot), the location of the previous distracter (i.e. the previous green spot) or a new location. Reaction times of a saccadic eye movement to the singleton target are significantly slowed when the target is presented at the location of the previous distracter, in comparison to the location of the previous target or a new location. This effect has only been tested in younger European adults and the effects of ageing, disease and ethnicity have not been assessed. Therefore, the current study addresses this by assessing the effects of ageing, ethnicity and disease.

Publication: Polden, M., & Crawford, T. J. (2021). Active visual inhibition is preserved in the presence of a distracter: A cross-cultural, ageing and dementia study. *Cortex*, *142*, 169-185.

3.   **Eye Movement Latency Coefficient of Variation as a Predictor of Cognitive Impairment**

Numerous studies have demonstrated abnormal saccadic eye movements in AD and people with MCI when performing prosaccade and antisaccade tasks. Research has shown that latencies on pro and antisaccade tasks can predict cognitive ability and can indicate cognitive impairment and executive functioning deficits. These eye movements tasks show potential for diagnostic use and for disease progression monitoring, however certain eye tracking parameters, such as latency coefficient of variation (CV) have not been fully investigated and could provide further markers for impairment. Attentional fluctuation can be assessed using a measure of relative variability termed coefficient of variation. CV measures the ratio of standard deviation in relation to the mean.

The current study examined the relationship between latency CV scores on various eye tracking tasks and investigate its potential to distinguish participants with AD, MCI subgroups and older controls.

4.   **On the Effect of Bilateral Eye Movements on Memory Retrieval in Ageing and Dementia**

Bilateral eye movements are repeated saccades made from left to right resulting in bilateral stimulation. Bilateral eye movements have been shown to temporarily enhance episodic memory and cued recall in healthy adults (Christman et al., 2003). Extensive research has been conducted with younger adults, however in more recent years the robustness of the effect has been questioned (Matzke et al., 2015). Limited research has been conducted with older adult populations who may have reduced episodic memory capabilities due to age-related cognitive decline. Further, the effect has not been investigated in patients with memory impairments such as AD patients and mild cognitively impaired patients. It is possible that bilateral eye movements may have a larger effect in AD or MCI populations and could have therapeutic benefits. This study expanded on the current literature by investigating bilateral eye moment effects in relation to ageing and disease effects.

1.7. Thesis Structure

In order to assess novel and established eye tracking paradigms in relation to ageing, disease and ethnicity factors and to assess the potential of eye tracking in the diagnosis and monitoring of neurodegenerative disease, data was collected in younger and older European adults, Southeast Asian older adults and adults with dementia due to AD or MCI. The thesis consists of 4 studies in the form of research manuscripts. In chapter 3, the established "gap effect", an eye tracking paradigm comparing gap and overlap conditions on a prosaccade task was investigated. Previously the gap effect has only been investigated in limited populations mainly younger, educated and Western Adults. To address this, in the current study the effect was assessed in relation to ageing, disease and ethnicity effects. Upon establishing that the gap effect was preserved in AD and MCI, with very few performance variations found when

compared with controls on prosaccade tasks, chapter 4 goes on to discuss some of the limitations surrounding the antisaccade task and introduces a novel paradigm and task termed the Inhibition of a recent distracter (IRD). This task provides a gaze directed target while still allowing assessment of inhibition of a specific distracter rather than general gaze aversion that is present in the antisaccade task. The IRD effect had previously only been assessed in young European populations, the current study expands on this by investigating the effect in multiple populations allowing the assessment of ageing, disease and ethnicity.

Chapter 5 assessed coefficient of variation measures as a possible indicator of cognitive impairment. The study assessed coefficient of variation, a measure of latency variability on pro and antisaccade tasks. Previous studies have shown potential for latency variability to be used as an additional biological marker for impairment on eye tracking tasks and here we assessed this with the additional distinction of MCI subgroups (amnestic MCI and non-amnestic MCI). This allows for the comparison and assessment of low (non-amnestic MCI) and high-risk (amnestic MCI) groups who may go on to receive a dementia diagnosis. Detecting performance distinction in preclinical and early stages is vital for a successful biological marker.

Finally, in chapter 6, the focus shifted from what eye movements can inform us about cognitive impairment to whether eye movements can temporality enhance cognition specifically episodic memory. It has been found that bilateral eye movement stimulation can lead to temporary enhancements on memory and recall tasks however results in more recent years have been mixed bringing into question the robustness of the effect. Research has predominantly focused on establishing this effect in healthy adults with limited research assessing the impacts in people with cognitive and memory impairments. The final study investigates the effect of bilateral eye movement on older and younger adults and in people with AD and MCI assessing any potential therapeutic benefits of bilateral eye movements.

The thesis has the following structure:

- Chapter 2 provides background information on eye tracking and previous eye tracking research involving older adults and people with AD and MCI. Further, relevant established and novel eye tracking paradigms are discussed and the limitations and current gaps in the literature highlighted.

- Chapter 3 reports the first study assessing disengagement of attention using the gap effect paradigm in people with AD and MCI.

- Chapter 4 reports the second study assessing inhibition of a recent distracter. The study assesses inhibitory control while providing a gaze directed target. The IRD effect is assessed in relation to ageing, ethnicity and disease effects.

- Chapter 5 reports the third study investigating latency variability on pro and antisaccade tasks. This study investigates the effectiveness of latency coefficient of variation measure in identifying cognitive impairment.

- Chapter 6 reports the last study on bilateral eye movements and enhancement effects on memory and recall in younger and older adults and in AD and MCI populations.

- Chapter 7 presents a summary and discussion of the thesis work and proposes future directions for research.

Chapter 2

2. Background

2.1 Eye Movements and the Brain

Eye-tracking is the process of measuring eye activity by measuring gaze patterns and movements, fixations and pupil size. Saccadic eye movements are often divided into two categories: 1) fixations and stabilising eye movements which hold the stimulus image on the retina and 2) saccades, that move the eye around bringing different stimuli to the fovea within the visual field (Singh & Singh, 2012). Saccadic eye movements are often measured as degrees of visual angle. Saccades are accurate and rapid eye movements that reposition the fovea in the visual environment. Saccades can reach peak velocities of 400-600 deg/s altering with the saccade amplitude. Further, saccade accelerations can peak up to 40000 deg/s^2 (Singh & Singh, 2012). Fixations are classified when a target image appears on the fovea of the retina. The image is held relatively stable on the retina during fixations for approximately 100-1000ms. The majority of fixations last between 200-500ms, with the time dependant on the amount of visual information being processed and cognitive load required (Bulling et al., 2009; Chen & Newman, 2004).

Multiple areas of the brain are involved in conducting successful eye movements resulting in them being a useful indicator of cognitive functioning (figure 1). Specifically spatial attention has been closely linked to eye movements and motor control. Attention allows observers to simultaneously select relevant stimuli to orient their attention towards while also suppressing the processing of irrelevant stimuli. Premotor theory of attention links spatial attention and the motor system by stating that spatial attention is the consequence of activation of the motor system. It is stated that attentional shifts are achieved by planning goal-directed

actions such as eye movements (Smith & Schenk, 2012). Working memory have also been closely linked to oculomotor processes with neural activity thought to persist in subregions of the prefrontal cortex and posterior parietal cortex during the maintenance working memory representations (Ikkai & Curtis., 2010). It was concluded that this activity is not specific to working memory and instead carried information that can be used to support numerous cognitive functions specifically attention allocation, spatial memory and motor planning, demonstrating the involvement of eye movements in multiple cognitive and attention tasks.

Several neuroimaging studies have demonstrated that areas of the frontal cortex including the frontal eye fields, supplementary eye fields, dorsolateral prefrontal cortex and the prefrontal cortex are employed when generating eye movements (Richards, 2013, McDowell et al., 2008). The areas involved vary between pro and antisaccadic eye movements. Studies using event related potential (ERP) show multiple types of pre-saccade ERP activity that is related to pro and antisaccade eye movements (Everling et al., 1997). Block designs have previously been used alongside neuroimaging to assess which brain areas are involved in prosaccade and antisaccade trials (Fox et al., 1985; Doricchi et al., 1997). Results showed that the multiple areas of the frontal cortex specifically the frontal eye fields, supplementary eye fields, dorsal frontal cortex and ventrolateral prefrontal cortex show greater activity during eye movements than fixations and are more active during antisaccade trials then prosaccade trials. Dyckman et al (2007) used a mixed-choice design that included an antisaccade block; a prosaccade block and a mixed antisaccade and prosaccade trial block. Results revealed several brain areas consistently associated with antisaccades including thalamus, striatum, cuneus, precuneus, lateral and medial frontal eye fields, supplementary eye fields and prefrontal cortex, were more active during antisaccade trials in a single block design than the prosaccade single block design. However, during the mixed block design, variations in brain activations

between pro and antisaccades were not present, and only the areas precuneus, supplementary eye fields and the frontal eye fields showed greater activation during the antisaccade trials.

Results indicate that the precuneus, supplementary eye fields and the frontal eye fields which were active during both single and mixed blocks may be more important for the behavioural eye movement response. Other brain regions such as prefrontal cortex which showed antisaccade related activity during the single task comparison, may be more involved in response selection and context updating (Dyckman et al., 2007). This has been further supported by research suggesting separate brain areas are employed during eye movement planning and generation (Brown et al., 2007, Ettinger et al., 2008).
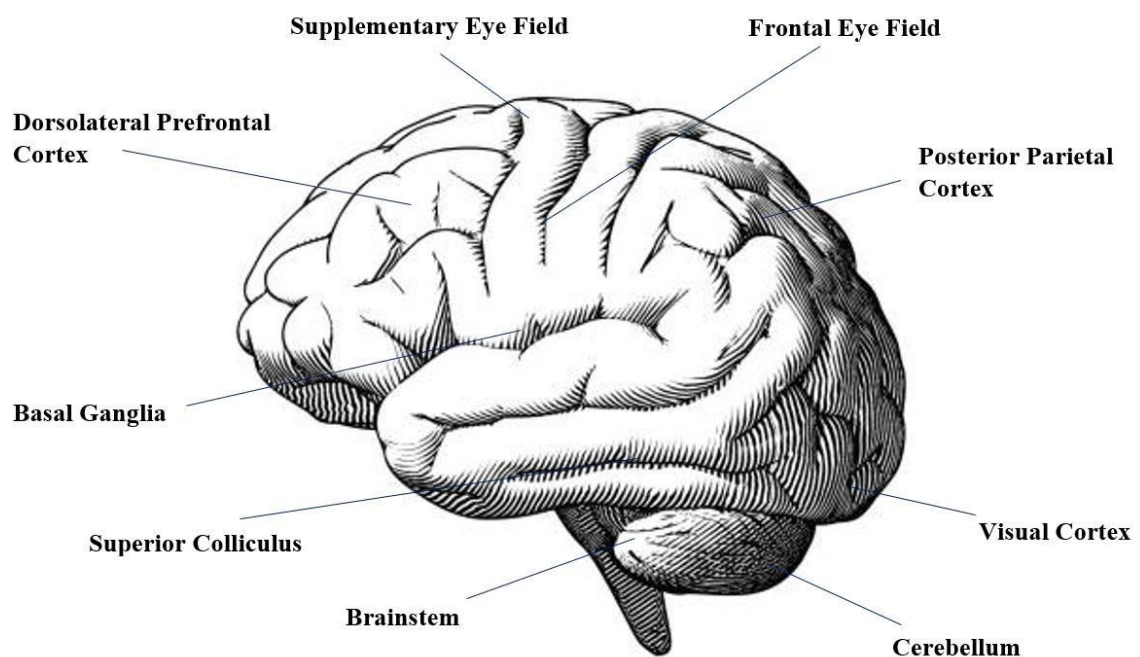
Figure 1. Multiple areas of the brain which are involved in the control of eye movements

Subjective diagnosis methods such as self-reporting, observations and questionnaires can be susceptible to biases such as experimenter bias and demand characteristics impacting on the validity and accuracy of the diagnosis. More objective methods, less susceptible to external influences, are monitoring peoples' physiological responses such as eye movements or brain

activity. Assessing neurophysiological factors is often considered a more objective approach and provides data with reduced bias influence. Physiological measures provide reliable and easily quantified measures of behaviour.

Eye movements can be an insightful tool for investigating cognitive processes and have been increasingly used to monitor and assess cognitive decline (Bowling & Draper, 2014; Molitor et al., 2015; Seligman & Giovannetti, 2015; MacAskill & Anderson, 2016; Chan et al., 2018; Nie et al., 2020). The brain regions and neuronal pathways involved in eye movements, fixation and gaze patterns are controlled by cortical neural networks in the frontal lobe, parietal lobe and downstream pathways project to the cerebellum and brainstem (Anderson and MacAskill, 2013). The frontal eye fields and supplementary eye fields are interconnected systems involved in saccade initiation and saccade generation (Schall et al., 1993; Segraves & Goldburg., 1987). Damage to the frontal eye fields and the midbrain superior colliculus can lead to permanent disruption to saccade initiation (Dias & Segraves, 1999). Studies assessing reversible deactivation of these areas revealed that deactivation of the frontal eye fields resulted in increased saccade reaction times but with the ability to elicit intact saccades. However, deactivation of the superior colliculus resulted in frontal eye fields being unable to elicit saccades indicating that the frontal eye fields signals pass through the superior colliculus to initiate a saccade (Hanes and Wurtz., 2001; Schiller et al., 1980). This highlights the importance of both systems in functioning saccade performance and how damage or neurodegeneration in these areas can lead to measurable behavioural deficits.

Previous research has measured the time a participant takes to complete saccadic and antisaccadic eye movements. When completing a saccadic eye movement there is a decisional process that takes place prior to the eye movement (Hutton, 2008). This decisional process is often measured as the time taken between the onset of the saccade and arrival at the display target. Saccade latency is an important marker to investigate when assessing eye movements

as research has indicated that saccadic eye movement latencies are related to cognitive processes (Pratt et al., 2006). The time required to initiate a saccadic eye movement can rely on executive functioning resources and attentional processing capabilities. Furthermore, it has been found that the antisaccade task involves executive attention and that the ability to complete a correct antisaccade eye movement involves processing speed. Research involving event-related potentials (ERPs) when investigating visuo-spatial attention, found that during the preparation and execution of saccades there were pre-saccadic contra-ipsilateral variations at posterior electrodes (Krebs et al., 2012). This brain activation could be attributed to attentional shifts towards the target. In addition, studies have found activation prior to the execution of the saccade indicating attentional shifts towards the target location before executing the saccade (Gutteling et al., 2010). These prior attention shifts alongside activation in attention areas of the brain support the role of executive functioning and attention when performing eye movement tasks. Due to multiple areas of the brain being involved in controlling, directing and initiating eye movements, this results in a useful method to assess cognitive functioning in a simple and occasionally subconscious way.

2.2 Visuospatial Attention

The Posner & Petersen (1990) 3-attentional abilities framework puts forward 2 basic concepts about the attention system. The first concept states that the attention system is anatomically separate from processing systems that manage incoming stimuli, make decisions, and produce outputs. The second concept states that attention utilises a network of anatomical areas. The third concept states that these anatomical areas conduct different cognitive functions. The framework suggests that the attention system is divided into three networks (alerting network, orienting network and executive network), each representing a different set of attentional processes (Posner & Peterson, 1990). In 2012, Peterson and Posner (2012) reviewed, revised and expanded this framework to include an additional network of self-regulation.

William James (1950 (1890), p. 404) described selective attention as a "withdrawal from some things in order to deal effectively with others." Preferential processing is required due to limited processing resources in the brain and the inability to fully process all sensory information in our environment at a given time. Due to this multiple brain mechanisms, collectively referred to as selective attention, are needed to filter sensory inputs (Buschman & Kastner, 2015). These mechanisms both filter and direct the preferential processing of relevant and irrelevant information. Spatial attention is frequently compared to a spotlight that scans the visual environment, scanning and pausing to highlight potentially relevant stimuli (Posner, 1980). In a natural environment, we typically look where we are attending to and therefore, spatial attention is often coupled to eye position. However, spatial attention can also shift and move independently of the eyes. This indicates that attention networks and oculomotor control are closely linked and intertwined.

2.3 Prosaccade and Antisaccade Tasks

Over the years research has utilised multiple eye tracking paradigms to assess cognitive functioning with the most notable being the Prosaccade and Antisaccade tasks.

Neurodegeneration and natural ageing have been shown to have effects on prosaccade and antisaccadic eye movements (Garbutt et al., 2008) and therefore research has focused on their potential in monitoring and diagnosing neurodegenerative disorders. The prosaccade task is a simple task that requires participants to first focus their attention on a central fixation point and then shift their gaze to a target presented in their peripheral visual area. The prosaccade task can be presented in three variations: the gap paradigm where the central fixation is removed 200 ms prior to the target's appearance (Abel et al., 2002); the step paradigm where the central fixation diminishes and is immediately followed by the targets presentation; and the overlap paradigm where the central fixation and the target are displayed simultaneously for a short period before the central fixation is removed (Figure 2). Latencies are often longer in the overlap paradigm than the gap paradigm which has been termed the 'gap effect'

(Saslow, 1967). Although a short and simple task, it can provide multiple measures such as saccade latency, variability and amplitude.

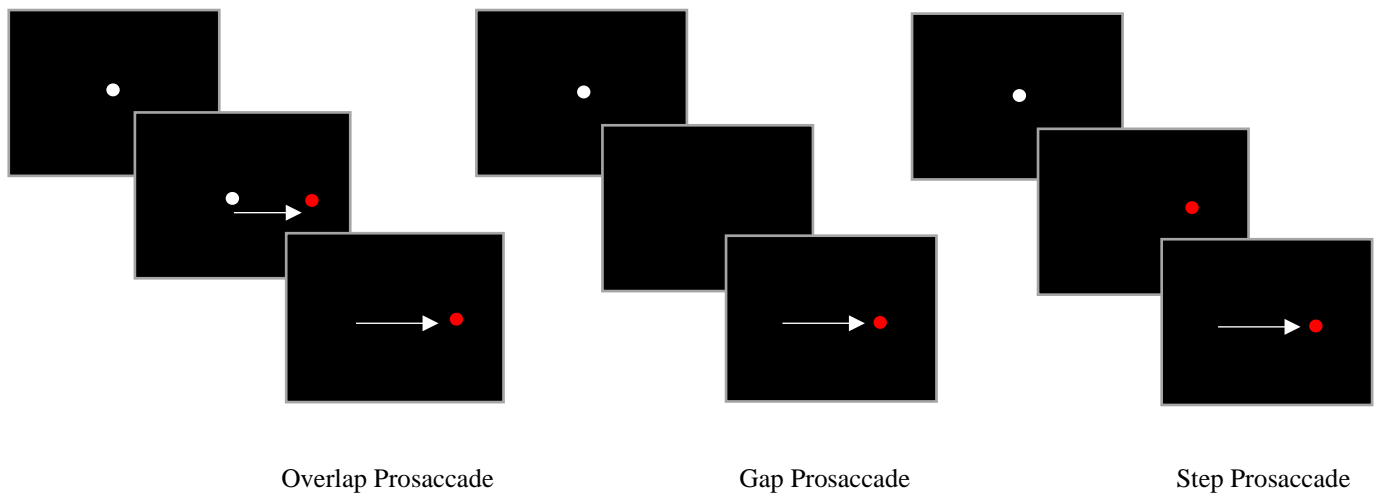Overlap Prosaccade   Gap Prosaccade   Step Prosaccade

Figure 2. Example presentations of gap, overlap and step conditions for the prosaccade task.

The antisaccade task (Hallett, 1978) is more challenging and cognitively demanding then the prosaccade task and has been used to assess cognitive functioning in both clinical populations and healthy adults (Hutton & Ettinger, 2006). The antisaccade task presents a target in the participants peripheral visual field requiring the participant to direct their gaze to the opposite side to the target's location (Munoz & Everling, 2004, Crawford et al., 2013). When a target is presented in an individual's visual field, there is a strong natural impulse to look towards the target resulting in a high inhibitory control demand to resist this impulse. Antisaccade errors are classified as an initial saccade towards the presented target (figure 3a). Antisaccade error rates are often around 20% even in healthy adults further illustrating the high inhibitory control demands of the task (Hutton & Ettinger, 2006; Leigh and Kennard, 2004). However, participants with neurodegenerative disease display abnormally high error rates compared to healthy adults providing a marker for impairment (Crawford et al., 2005;

Anderson & MacAskill, 2013). It is theorised that top-down control is necessary to direct the eye away from the target and this top-down processing requests working memory resources (Crawford et al., 2011). It is thought that working memory capabilities and inhibitory control abilities are closely linked, and both systems are utilised when initiating successful antisaccade eye movements (Kimberg & Farah, 2000). Saccade latency costs are observed when comparing antisaccade and prosaccade eye movements with antisaccadic reaction times increasing by approximately 100-150ms compared to prosaccades. This is due to the increased cognitive demands and resources required to initiate an antisaccade whilst maintaining relative accuracy. The extra challenges associated with antisaccade eye movements are further highlighted when assessing participants with neurodegenerative diseases with impairments in these essential systems.
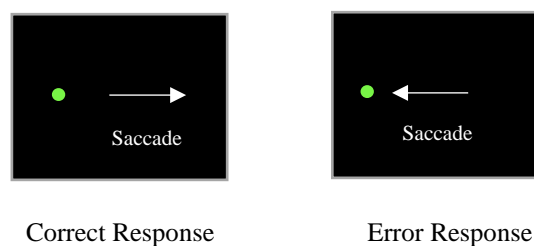

Correct Response   Error Response

Figure 3a. Examples of a correct and error antisaccade response trial. Correct response: antisaccade directing gaze to the opposite location of the presented target. Error response: prosaccade towards the presented target.

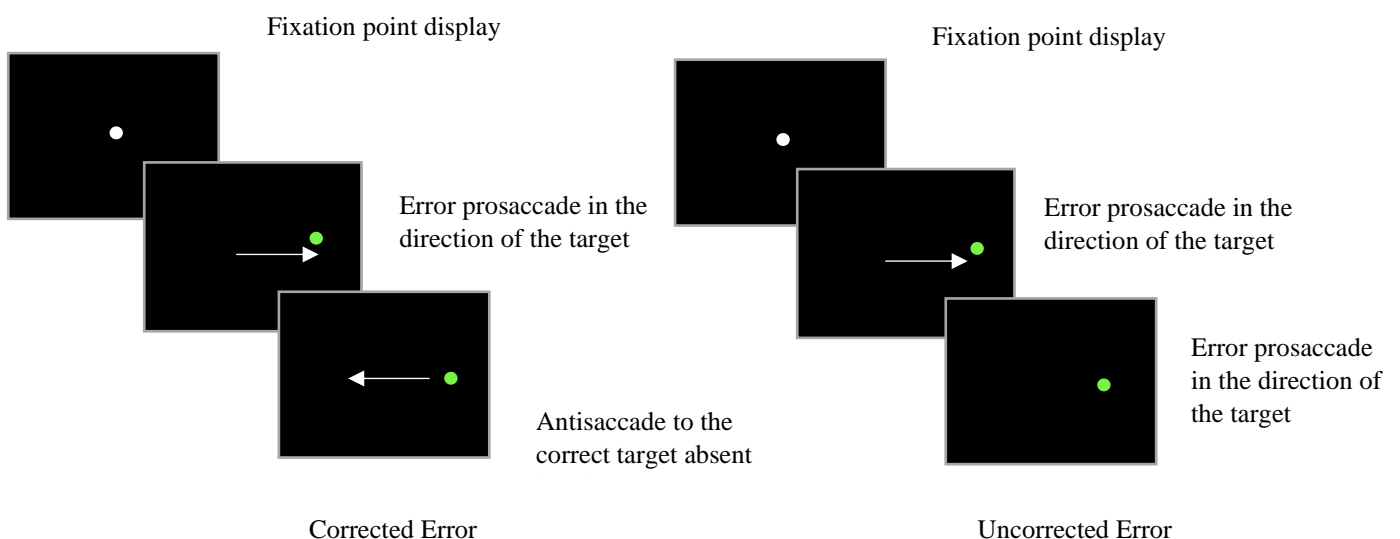Corrected Error   Uncorrected Error

Figure 3b. Corrected error and uncorrected error trials. Arrow indicating the direction of the saccadic eye movement. Corrected errors are classified as a prosaccade towards the target followed by a saccade to correct to the opposite side. Uncorrected errors classified as a saccade toward the target with a failure to make an additional saccade to the correct location.

2.4 Alzheimer's Disease and MCI: Saccadic Eye Movements

Literature has indicated that people with neurodegenerative diseases often display abnormal eye movements (Crawford et al., 2005, Srivastava et al., 2014, MacAskill & Anderson, 2016, Caroline., 2016). Eye tracking has shown potential in distinguishing multiple clinical groups such as people with Schizophrenia, Parkinson's Disease and dementia. Extensive research has demonstrated that Alzheimer's Disease is a neurodegenerative disease that results in abnormal eye movements (Anderson & MacAskill, 2013). People with AD are significantly slower at performing prosaccadic and antisaccadic eye movements and often make an increased number of errors on antisaccade tasks when compared with age matched controls (Crawford et al., 2005., Yang et al., 2013). The prosaccade task has demonstrated that AD participants produce longer saccade latencies compared to healthy controls (Ruthirakuhan et al., 2013). Initial observations of this effect suggested that prosaccade task performance could indicate cognitive impairment (Pirozzolo & Haunsch, 1981), however, more recent research suggests that prosaccadic eye movements alone may not be sufficiently robust to predict AD severity. This is mainly due to the inconsistencies within the literature and the inability of prosaccades to detect more subtle differences in earlier stages of AD limiting its potential and consistency in distinguishing between groups.

The Antisaccade task has produced more reliable and consistent results in distinguishing patient groups. When contrasting AD participants with control participants,

key impairment markers have been found such as increased saccade latencies, error rates and uncorrected errors. AD participants often produce higher saccade latencies resulting from a reduction in processing speed and increased time required to initiate a successful antisaccade (Crawford et al., 2013). It is thought that antisaccade task performance is linked and dependant on working memory capacity. Roberts et al (1994) stated that the working memory hypothesis suggests that to avoid errors it requires the maintenance of current goals and plans while in the presence of competing and distracting stimuli. It has been suggested that throughout the task, the natural response to initiate a saccade towards the target (prosaccade) must be inhibited while also maintaining the correct response (antisaccade) in working memory. The task instructions to avoid the target, must be maintained throughout the task to ensure repeated successful trials. The likelihood of success on the trial would be determined by the strength of the competing target, working memory load and the remaining working memory capacity and resources. A reduction in these systems capabilities could lead to a slowing of antisaccade eye movements or increased errors. This is also consistent in healthy individuals, with research showing participants with a higher working memory span perform faster saccades on the antisaccade task and produce fewer errors compared to participants with a lower working memory span (Nieuwenhuis. et al., 2004; Unsworth et al., 2004). This demonstrates a clear link between working memory and antisaccade performance in both AD patients and healthy adults.

The amount of inhibition errors made on the antisaccade task has been found to be predicted by dementia severity (Abel et al., 2002). Crawford et al (2005) stated that the number of errors displayed in people with AD is abnormally high and not typical of healthy ageing. In addition, a positive correlation was found between dementia severity and mini-mental state examination performance demonstrating the link between the number of antisaccade errors and dementia severity. Crawford et al (2013) found that spatial working

memory highly correlated with antisaccade error rate indicating that inhibition and working memory capacities are employed during the task. The evidence indicates that deficits in the frontal functions in people with AD are involved in programming and initiating the saccade response (Hutton and Ettinger, 2006).

Further, people with AD produce a large number of uncorrected errors on the antisaccade task (Crawford et al., 2005, 2013). This finding is thought to be due to a dysfunction of regulation in the self-monitoring and error correction areas of the brain and neural networks (Crawford et al., 2013). Crawford (2013) compared control participants with Parkinson's disease patients and found no significant differences in the number of uncorrected errors on the antisaccade task. This indicates that the difference in uncorrected errors appears to be AD specific and not generally a factor of healthy ageing or witnessed in other neurodegenerative disorders. The increased prevalence of uncorrected errors found in AD populations has been replicated by multiple research groups (Boxer et al., 2006; Garbutt et al., 2008; Kaufman et al., 2012, Crawford et al., 2013). High levels of specificity and reproducibility as demonstrated in the literature further enhances the validity of the antisaccade task as an AD diagnostic and monitoring tool (Zola et al., 2004).

For eye tracking to be used as a marker for impairment it must also be able to detect subtle indications of cognitive impairment in preclinical and at-risk groups such as people with MCI. People with MCI show key differences in saccade latencies and error rates leading to distinctions between healthy controls and also between MCI subgroups. The classification of MCI can be further split into amnestic (aMCI) and non-amnesic (naMCI). People with aMCI often experience greater memory deficits whereas people with naMCI often had preserved memory but display other cognitive impairment such as inhibitory control or executive functioning deficits. People with aMCI are at a greater risk of progressing to AD than naMCI (Fischer et al., 2007, Ward et al., 2013). Wilcockson et al (2019) demonstrated

that the antisaccade task can distinguish between MCI subgroups with aMCI participants showing slower latencies and higher error rates then naMCI and healthy controls. Interestingly aMCI participants performed more similarly to AD participants and naMCI to healthy controls. This provides further support for the antisaccade task as a useful task to identify and monitor cognitive impairment and is successful in distinguishing subtle differences between MCI subgroups (Wilcockson et al., 2019). Assessing people with a diagnosis of MCI allows investigation into the sensitivity and specificity of biological markers found during antisaccade performance. Further, identifying impairment markers in high-risk MCI populations prior to the presentation of more severe symptoms and disease progression may result in more timely treatment interventions and patient outcomes. Chapters 3,4,5 and 6 will address this issue by assessing eye tracking performance in people diagnosed with MCI and AD. Established and novel eye movement paradigms will be assessed in relation to the effects of neurodegenerative disease and the implications discussed.

2.5 Saccadic Eye Movements and Natural Ageing

Age related cognitive decline has been described as a decrease in processing capabilities in older adults (Salthouse, 2009). It is suggested that there are a variety of age related cognitive deficits including working memory impairments (Baddeley & Hitch, 1974); Inhibitory control (IC) deficits (Hasher & Zacks, 1988, Sweeney et al., 2001, Amer et al., 2022) and reductions in cognitive processing speed (Salthouse, 1996). A recent review suggests that older adults create richer and more "cluttered" memory and event representations compared to younger adults (Amer et al., 2022). These cluttered representations may include key target information, previously relevant information, prior knowledge and irrelevant environment information. It is theorised that cluttered representations can interfere with the retrieval process of target information; however, they may also provide advantages in tasks requiring extensive and more in-depth knowledge.

Reductions in capabilities during the ageing process are often reflected in antisaccade and prosaccade performance (Garbutt et al., 2008). Age-related deficits as seen on the antisaccade task are thought to be due to reductions in working memory capabilities and changes in the efficiency of inhibitory control processes (Hasher and Zacks, 1988). Age-related decline present on the antisaccade task may be due to reduced capabilities with saccade programming and initiation, the inhibition system and saccade fixation or a combination of the two. A study conducted by Raemaekers et al (2006) assessed the effects of ageing on brain systems and inhibition of saccadic eye movements. Functional magnetic resonance imaging (fMRI) was recorded while participants completed tasks designed to active networks of regions known to be involved in the generation and execution of saccadic eye movements. Results showed an age-related shift in brain activity from posterior to frontal regions and a reduction in blood oxygenation level dependant signal in the oculomotor system in older adults. It is hypothesised that older adults increase frontal activation to maintain performance.

Age-related saccade decline is reflected in saccade latencies with research demonstrating a linear relationship between age and onset of saccade latencies (Olincy et al., 1997; Carter et al., 1983). Alongside increased saccade latencies, older adults display higher error rates on antisaccade tasks when compared to younger adults (Sweeney et al., 2001; Nieuwenhuis et al., 2000) but unlike AD participants these errors are often corrected. However, increased error rates due to ageing have been inconsistent across studies with some researchers suggesting that older adults sacrifice speed in order to maintain accuracy. Although Butler et al (1999) when assessing both pro and antisaccades found that the increase in saccade latencies between pro and antisaccade trials were comparable between older and younger adults but error rates where disproportionately high for older adults. This indicates that the saccade inhibition system deteriorates during ageing but not saccade programming systems (Crawford et al., 2017). This is consistent with Hasher and Zacks (1988) and more

recent research by Amer et al (2022) that describes age-related inhibitory control deficits resulting from increased irrelevant task information entering the working memory system and interfering with relevant task information, increasing the likelihood of errors.

The cause of age-related saccade decline has been debated in the literature. Although Amer et al (2022) presents compelling evidence that cluttered memories and interference from irrelevant information contributes to age related cognitive decline, alternative accounts such as the associate deficit hypothesis suggest that difficulties with integrating information are the cause (Naveh-Benjamin et al., 2000). The associate deficit hypothesis suggests that difficulty with binding and integrating information into collective units results in poorer memory retrieval on associated tasks (Castel & Craik., 2003; Naveh-Benjamin et al., 2003). However, conflicting research has found that younger and older adults show comparable memory performance when implicitly accessing target memory associations (Dew & Giovanello, 2010; Davis et al., 2021) proving support for the cluttered memory account (Amer et al., 2022).

Furthermore, the environmental support account presents another approach and suggests that difficulties in maintaining internal cognitive or task representations results in a greater reliance on environmental and external information in older adults (Craik, 1983; Lindenberger & Mayr, 2014). This is supported by research demonstrating that older adults often show progressively poorer performance on memory tasks requiring self-initiated processing compared to tasks with supporting environmental information (La Voie & Light, 1994). However, this theory fails to account for the influence of existing general knowledge, irrelevant information or suitability to interference on cognitive functioning.

Eye tracking research conducted by Eenshuistra et al (2004), assessed the role of inhibitory control and working memory on antisaccade performance in older adults and found that inhibitory functions remained largely intact during ageing, but performance deficits are evident only when their working memory capacity is overstretched by increasing demands.

This suggests that reduced working memory capabilities may be the main driver behind reduced antisaccade performance. This theory could also explain the distinction in antisaccade performance between aMCI and naMCI participants with aMCI participants displaying clearer antisaccade deficits alongside reductions in working memory capabilities. People with naMCI often have preserved working memory capabilities and display less impairments on antisaccade tasks then aMCI participants. However, these deficits could also be explained by the cluttered memory approach (Amer et al., 2022) as people with MCI may have increased susceptibility to irrelevant information due to reduced inhibitory control processes.

It is important to assess ageing effects in relation to disease effects to get a full scope of the portion of deterioration at each stage and to provide a baseline for "typical healthy ageing". To address this, chapter 3,4, and 6 will investigate established and novel eye tracking paradigms in relation to ageing effects allowing assessments of age-related cognitive decline on multiple eye tracking tasks and effects.

2.6 Disengagement of Attention and the "Gap Effect"

Disengaging attention has been defined as "a process that enables shifting of the focus of selective attention from one location to another" (Worden, 2011 in Encyclopaedia of Clinical Neuropsychology). It has been stated that the disengagement of attention process has three stages: 1) disengage attention from the current stimuli, 2) direct attention to a new location, 3) engage attention with the new target or location (Posner, 1982). The Posner model states that attention must be disengaged from the current stimuli in order to shift this attention to the new stimuli. This disengagement procedure requires multiple brain processes, each which contributes to the overall processing time costs (Posner & Petersen., 1990). The "gap effect" as termed by Saslow (1967), is the ability to remove attention from a fixation target and shift to another presented target. The superior colliculus (SC) plays an important role in the

gap effect. Schiller et al (1980) found that removal or damage to the SC results in a lack of

express saccades and leads to an overall increase in saccade latencies. Research has shown that

neurons with fixation related activity in the rostral

SC decrease their firing after the fixation target has been removed on gap trials (Dorries et al.,

1997). Alternately, during the gap period, saccade-related neurons in the caudal SC displays

higher preparatory activity (Sparks et al., 2000). This shift in activity favours the upcoming target

and increases the likelihood of a sufficient surge of activity to trigger the subsequent saccade

(Edelman & Keller, 1996).

The gap effect can be measured by using a dual saccadic paradigm and by assessing gap

and overlap prosaccade eye movements (Fischer & Boch, 1983, Fischer & Weber, 1993,

Goldring & Fischer, 1997, Crawford et al., 2011). Saccadic eye movements are generated by

the activation of saccade-related neurons and by the inhibition of fixation neurons (Dorris and

Munoz, 1995; Dorris et al., 1997). The "gap effect" is thought to be due to an acceleration in

the disengagement of attention from the fixation, leading to the saccade being released early

in comparison to situations where the fixation point remains visible when the peripheral

target is presented (Vernet et al., 2009; Kapoula et al., 2010; Crawford et al., 2015; Crawford

et al., 2011). In the gap condition the central fixation point is removed prior to the

presentation of the display target leading to a temporal gap between the offset of the central

fixation point and the new target being presented. This results in faster reaction times due to

the facilitation of disengagement from the central fixation point. On the other hand, in the

overlap condition the fixation point remains present for a short period of time simultaneously

with the display target. This creates a temporal overlap between the offset of the fixation

point and an onset of the display target. The overlap condition results in delayed reaction

times due to the additional process of disengaging attention from the central fixation point.

The "gap effect" produces an operational index of attentional disengagement and is measured by the difference in mean saccadic reaction times between the gap and overlap conditions.

The Findlay and Walker (1999) model states that the gap effect facilitates the disengagement process by removing the fixation target leading to a reduction in the activation of the fixation neurons removing the inhibition element. When the fixation point remains present (overlap condition) the activation of the fixation cells and the movement of inhibition cells, delays disengagement. Alternatively, others have argued that the gap paradigm yields faster saccade reaction times as it facilitates the disengagement of attention from the fixation point (Crawford et al., 2015). A brief interlude excludes any interaction with a competing target. In contrast the overlap condition slows down the disengagement of attention due to the competing fixation point remaining present and continuing to capture attention for a period when the gaze-directed target is presented. However, alternative perspectives suggest that the gap between trials presentations acts as a warning cue to participants (Klein, 1980). Evidence suggests changes in the visual fixation stimulus such as a gap in presentation reduces saccadic reaction time by acting as a warning signal (Kingstone & Klein, 1993). However, research indicates that the warning signal effect fails to account for all aspects of the gap effect. When assessing the gap effect alongside eye movements, an audio warning cue can diminish the gap effect but often does not remove it entirely (Reuter-Lorenz et al., 1991, 1995). Although, providing an audio warning cue has been shown to eliminate the gap effect when the response is a keypress (Bekkering et al., 1996) suggesting that external factors specific to saccade planning likely contribute to the gap effect when responses involve eye movements.

There have been several studies demonstrating the robustness of the gap effect (Dorris et al., 1997; Rolfs & Vitu 2007, Crawford et al., 2011), however, limited research has been conducted assessing the effect in clinical populations such as AD and MCI. Those that have assessed the effects in AD and MCI populations have yielded conflicting results. Yang et al (2013) reported deficits in disengaging attention in AD participants that correlated with

cognitive assessments indicating a link between the severity of cognitive impairment and the ability to disengage attention. In contrast, Crawford et al (2013, 2015) stated that the gap effect was comparable between AD participants and controls. Additionally, a longitudinal study assessing AD participants over a 12-month period found that the gap effect was similar to that of controls indicating no clear deficits or deterioration of disengagement of attention processes (Crawford et al., 2015). This demonstrates inconsistencies within the literature surrounding the gap effect in clinical populations with neurodegenerative disease. To address these issues, chapter 3 will investigate the robustness and generalisability of the gap effect in

AD and MCI populations.

2.7 Coefficient of Variation

Research has extensively demonstrated the potential of pro and antisaccade eye movements latencies for assessing cognitive impairment. However, another potential marker, that has to date been relatively overlooked, is saccade latency fluctuations. When executing a saccade there is a decisional process prior to the eye movement which is measured by the time taken to initiate the saccade and reaching the goal-directed target (Hutton, 2008). This process can rely heavily on executive functioning and attentional processing resources. Due to this, impairments of these systems can result in reductions in processing speed and increased attentional fluctuations. It is predicted that latency variability could serve as an additional marker for impairment and a measure of attentional fluctuation due to executive functioning capabilities being vital when completing pro and antisaccade tasks. Yang et al (2013) demonstrated that people with attentional deficits tend to show increased fluctuations of task scores and latencies indicating reduced task consistency and sustained attention throughout the task. This reduction in sustained attention is thought to be a result of attentional processing deficits (Kapoula et al., 2010).

Attentional fluctuation can be assessed using a measure of relative variability termed coefficient of variation (CV). CV measures the ratio of standard deviation in relation to the mean. The higher the CV value, the greater the level of variability around the mean. Whereas lower CV percentages indicate less variability and less dispersion around the mean score. Latency CV scores have previously been assessed on prosaccade tasks on gap and overlap conditions with results showing higher latency CV scores for AD than healthy older adults (Yang et al., 2013). AD participants display greater variability in relation to accuracy and speed for vertical and horizontal saccades (Yang et al., 2011). This indicates that AD participants deficits show greater attentional fluctuation on eye movement tasks reflected in higher variability of saccade latencies and increased accuracy fluctuations. These studies indicate the potential of CV scores to be an additional biological marker for impairment in people with AD. Previous research has demonstrated clearer and more consistent distinctions between AD patients and controls on antisaccade tasks compared to prosaccade tasks. To date, the majority of studies assessing CV has focused on prosaccade tasks as opposed to antisaccade tasks. Distinctions in CV scores may be even more evident on the antisaccade task and there may be greater attentional fluctuations in regard to errors and latencies on this more complex eye tracking task. An additional gap in the literature is the assessment of aMCI and naMCI groups. CV has not been fully assessed on multiple tasks when comparing these groups alongside AD participants. Chapter 5 will address this gap by investigating CV measures on multiple eye tracking tasks in aMCI, naMCI and AD populations. Chapter 5 assesses the sensitivity of CV and evaluates whether CV scores can distinguish and identify individuals at greater risk of developing dementia.

2.8 Inhibition of a Recent Distracter

The antisaccade task is a widely used and tested paradigm although not without its limitations. The task suffers from weak ecological validity due to instructed antisaccades, without a goal-directed target, resulting in an uncommon and counterintuitive eye movement.

As the antisaccade task does not offer an alternative target to shift attention to, the task has the additional process of disengaging attention from the central fixation alongside the ability to inhibit the distracter. Further, the antisaccade task involves multiple processes including motor and sensory inhibition and working memory. Previous research has demonstrated that inhibitory control and working memory are disassociated functions with impairments not always being

reflected in both systems in AD (Crawford & Higham, 2016). Due to the complex nature of the antisaccade task, impairments displayed on the task cannot be easily associated with a specific system and it is unclear whether impairments are due to deficits in a single system or a combination of impaired systems.

To address some of these challenges and to assess inhibitory control processes in isolation from working memory systems, a task termed "the inhibition of a recent distracter task (IRD)" was developed (Crawford et al., 2005, Donovan et al., 2012). The IRD task was designed to assess inhibitory control and inhibition of a specific distracter while offering a gaze-directed target (Crawford et al., 2005; Wilcockson et al., 2019). The IRD task consists of two visual displays: the first display presents a red and green target simultaneously with participants required to direct their gaze towards the red target and avoid looking at the green distracter target. The second display presents a single gaze-directed red target that varies in location across trials. The single red target can appear in one of three locations in relation to the first display screen; the same location as the previous target (Target-target (T-T)); the location of the previous distracter (Target-distracter (T-D)) or a new location (target-new (TN)). This design allows reaction times and error rates to be assessed in relation to the various trial types.
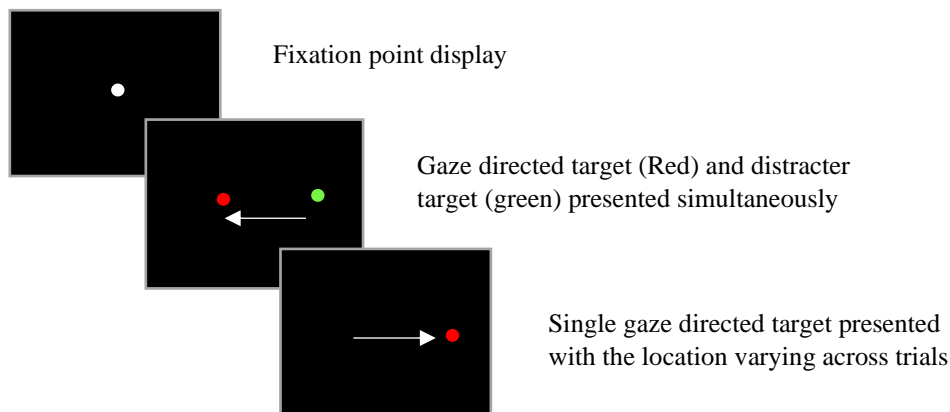
Figure 4a. The series of display screens typically used in the IRD task. The arrow indicates the direction of the required saccade.
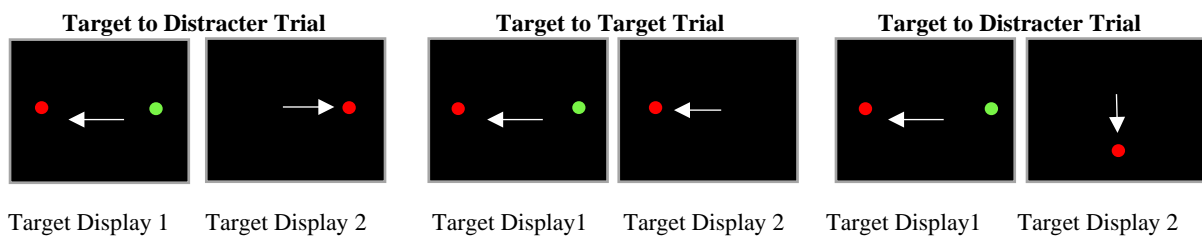
Figure 4b. The three trial variations on the IRD task.

Findings show a reduction in saccadic reaction times to the target in display screen 2 when the target is presented in the location of the previous distracter (T-D) compared to T-T and T-N trial types. Inhibitory control resources employed in display screen 1 remains present for a period of time at the location of the previous distracter. This is evident by its effect on subsequent reaction times to a goal-directed target in that location. Multiple follow up experiments established that the slowing was due to the distracter's location rather than another factor such as colour. Results demonstrated that the slowing, as predicted, was due to the target/distracters location. Donovan et al (2012) expanded on these results and revealed that the effect is not limited to simple light targets but also is present when implementing the task with naturalistic images of animals and objects. The IRD effect supports the idea that a

dual task mechanism of target selection alongside inhibition of a distracter is employed with selective attention of eye movements (Crawford et al., 2005).

The IRD offers a target for the participants to focus and shift their visual attention to and is as a result more representative of everyday gaze behaviour patterns than the antisaccade task. The IRD task does not misinform the participant about the future location of the target or require an unnatural eye movement away from the target. The IRD task measures inhibition by contrasting the reaction times to the new location on display 2 in relation to the location of the distracter on display 1. The task design results in a dual assessment of the facilitation of the eye movement towards the target and the inhibition of the eye movement towards the distracter. There are several key differences between the IRD task and antisaccade task that likely leads to different inhibitory control mechanisms being utilised. A main element of the antisaccade task is gaze aversion, an element that is absent in the IRD task. Additionally, during the antisaccade task a motor signal is required to direct the eyes to the opposite side and to inhibit the target. Donovan et al (2012) stated that a competing distracter, such as in the IRD task, is key for creating distracter inhibition to a specific target which is absent in the antisaccade task and distinct from gaze aversion (Crawford et al., 2005).

Research to date has only assessed the IRD effect in healthy adults and unlike the antisaccade has not been extensively tested in people with cognitive impairment. AD participants show clear deficits on inhibitory control tasks and therefore it is probable that deficits may be evident on the IRD task. AD and MCI may demonstrate a reduced IRD effect or even an absence of the effect altogether due to known inhibitory control deficits. On the other hand, if the IRD is preserved in AD and MCI participants this could indicate a dissociation between general gaze aversion and inhibition of a specific distracter. Presence of the IRD effect in AD populations would indicate that not all areas of inhibitory control are impaired providing an important insight into the inhibitory control deficits frequently reported

in AD populations (Crawford et al., 2019). Chapter 4 addresses this gap in the literature by investigating the IRD effect in AD and MCI populations and the implications on inhibitory control process will be discussed.

2.9   Cross-cultural effects on Eye Movements

The majority of eye tracking research and established paradigm is based on Western industrialized populations and limited research has assessed ethnicity and cultural effects on eye tracking paradigms. Rad et al (2018) discussed a recurring issue in psychological research and highlighted the problems surrounding the lack of diversity of participant samples. The so called WEIRD (western, educated, industrialized, rich and democratic) limitation describes the restricted sample of participants that characterises much of psychological research. In common with most of the published research in Europe and the USA, the majority of eye tracking research has been conducted on young, Caucasian university students. Therefore, we cannot be certain whether these established paradigms are relevant to other age, clinical or ethnic cohorts. Often it is assumed that there is little variation across human populations and that WEIRD samples are representative of the population; however, this is far from accurate. A review conducted by Henrich et al (2010) found considerable variations in experimental effects across different populations and that WEIRD samples are the most unusual and variable presenting frequent outliers, compared to other populations. Conducting psychology studies on a small and select proportion of the population creates problems for generalisability, replicability and interpretive power of many well-known psychological effects originating from WEIRD sample types (Brandy et al., 2018).

Cultural and ethnicity performance variations on eye tracking task is evident. Even in the context of relatively low-level neurocognitive eye-tracking tasks clear ethnic / cultural differences have been observed (Knox et al., 2012; Wolohan & Knox, 2014; Mardanbegi et al.,

2020). Variations in eye movement scan patterns when assessing visual scenes have been demonstrated between native Chinese and Native English-speaking participants (Chua et al., 2005). It was found that English speaking participants tended to first look at foreground objects and made increased fixations compared to Chinese participants who focused on the background visual areas of the scene with fewer fixations. This demonstrates clear strategy and viewing variations between cultures on eye movement tasks and when viewing visual scenes. Further, differences have been found when assessing visual search patterns in scene perception and recognition. When investigating eye movements on a complex search task, Alotaibi et al (2017) found that Saudi participants showed increased fixations and search times compared to British participants. This was attributed to differences in thinking style between analytic (common in individualistic cultures) and holistic thinking (common in collectivist cultures). The thinking style affected determines how people complete the task leading to strategy variations across cultures. This research demonstrates that eye movement techniques deployed by individuals are not universal and cultural factors are likely to influence. During face recognition, eye tracking studies have shown that westerners fixate on the eyes and mouth facial areas whereas easterners fixate more on central regions of the face (Lao et al., 2011). The exact cause for variations in these preferred viewing locations is unknown but is often attributed to cultural factors.

Performance variations between cultural groups could be due to cultural factors or genetic variations. A study by Rayner et al (2007) found evidence suggesting that variations were due to cultural factors rather than genetic variations. The study included native English speakers, native Chinese speakers and bilingual Chinese/English speakers who were either born in China and lived in the US from an early age or born in the US. Differences were found between the native English and native Chinese group and found that the Chinese group often made shorter fixation durations but had a greater number of fixations than the American group. This was in line with previous research, however, no difference was found in the

location of scene that was predominantly focused on (foreground or background). The results for the bilingual groups displayed a greater variation in eye movement behaviour than the other groups, but the results showed greater similarity to the American group than the Chinese. This finding further reinforces that variations, in this case, are likely due to cultural effects and strategy variations than genetic differences. However, not all studies found evidence of cultural differences on eye tracking tasks bringing into question the impact of cultural effects on various eye movement paradigms (Rayner & Castelhano, 2009) and highlights the importance of further investigations into the effects of cultural factors on novel and established paradigms.

Most research conducted assessing cultural effects on eye movements focuses on complex stimuli, likely to produce greater variations in performance and scan patterns. Tasks involving simple stimuli and low-level control processes, such as the pro and antisaccade tasks, may display less variation in task strategy and eye movement parameters. However, research has shown that even on simple tasks, such as the prosaccade task, significant differences in eye movement are present across cultural groups. Performance variations on these tasks can reflect differences in cognitive processes such as memory, attention and inhibitory control. Knox et al, (2012) found that on prosaccade tasks Chinese participants are more likely to exhibit express saccades then UK participants. Express saccades are low latency saccades that have a distant neurophysiological factor (Schiller et al., 1987; Edelman & Keller 1996). Dependant on task design these express saccades will usually fall in the range of 80ms to 130ms (Amatya et al., 2011; Delinte et al., 2002). This variation is fairly robust between these cultural groups and will even occur in situations that greatly decrease the occurrence on express saccades such as prosaccade overlap conditions. Overlap conditions often delays on the onset of the saccade towards the target due to the extra time required to disengage their attention from the central fixation point. However, research has

shown that Chinese participants are far less susceptible to this effect and will continue to make an increased number of express saccades compared to UK participants. It was found that 29% of Chinese participants continued to produce high numbers of express saccades on the overlap task compared to only 3% in the UK group (Amatya et al., 2011). This implies a difference in oculomotor processing across cultures. Further, these variations have been shown to impact on antisaccade performance. Knox et al (2012) found that express saccade maker's produce higher error rates on the antisaccade task. Chinese participants are more likely to be defined as express saccade makers than UK participants and this led to Chinese participants producing higher error rates on the task. However, it should be considered that not all Chinese participants made high numbers of express saccades and performance was not compromised for all Chinese participants. Therefore, the results are difficult to attribute to a cultural explanation as there are specific performance differences within the population. The results could indicate a difference in neurophysiological processing of oculomotor control, not prominently related to cultural factors.

Knox and Wolohan (2014) examined saccades from between Chinese and Caucasian participants and a UK Chinese group who were culturally similar to the Caucasian group. The study aimed to determine whether past dissimilarities found in Chinese and Caucasian groups resulted from cultural differences or other neurophysiological processing factors non-related to culture. Both the Chinese groups performed differently to the Caucasian group with the Chinese groups making an increased number of express saccades and showed overall lower mean latencies compared to the Caucasian group. This difference was particularly evident in the overlap condition where Caucasian participants produced even fewer express saccades due to the task's nature. Despite the cultural dissimilarity between the Chinese groups, their performance on the eye movement tasks was comparable and dissimilar to the Caucasian group indicating that cultural differences are not the sole cause of divergent oculomotor

performance (Knox & Wolohan, 2014). It is currently unclear what the cause of differences in oculomotor systems is, but it is possible they are related to known genetic differences (Kim et al., 2010).

Differences between cultural groups on eye tracking tasks are present and therefore it is important for novel and established paradigms to be investigated in relation to cultural factors. Eye tracking paradigms have shown potential for use as a diagnostic tool for AD and it is vital to ensure that any potential diagnostic tool or indicator of impairment is applicable to multiple cultural groups. Further, multiple studies have looked at variations in eye movements between East Asian participants and Western participants (Knox & Wolohan, 2014) however potential differences between other cultural group such as South Asian participants has not been extensively investigated. It is important to assess whether differences in eye movements span multiple cultures or are exclusive to East Asian cultural groups. In addition, current research that has focused on differences in eye movements between cultural groups has prominently been conducted with younger adults' samples. Due to this it is important that future research addresses these gaps in the literature to assess the generalisability of eye tracking tasks and paradigms. To address this issue, chapters 3 and 4 will include a sample of South Asian adults to investigate potential ethnicity effects on the gap effect and IRD effect.

2.10 Bilateral Eye Movements and Working Memory

Episodic memory has been defined as the process of subjectively "reliving" and recalling past live events (Gardiner et al., 2002; Tulving, 1985, 2002). Episodic memory has been distinguished from semantic memory as episodic memories will contain information relating to the specific time and place of encoding. Semantic memories typically are the knowledge of something e.g. a name or item but will not contain any information of where or when the knowledge was acquired. Research has demonstrated that certain eye movements,

specifically bilateral eye movements can lead to a temporary enhancement in episodic memory retrieval. Bilateral eye movements are the action of shifting your gaze from left to right. Conducting these eye movements repeatedly and in quick succession for as little as 30 seconds can produce an enhancement effect on a subsequent memory and recall task (Christman et al., 2003). The effect of bilateral eye movements on episodic memory retrieval has been replicated on both neutral (Lyle & Martin, 2010) and emotional stimuli (Nieuwenhuis et al., 2013). Research has found evidence that the so-called "saccade induced retrieval enhancement" (SIRE) effect is specific to episodic memory and no effect is found on implicit memory retrieval (Lyle & Martin, 2010). The SIRE effect can lead to increased distinction between targets and lures; enhanced spatial memory (Brunyé et al., 2009); increased recollection of past autobiographical events (Lyle & Martin, 2010) and early childhood memories (Christman et al., 2006). Bilateral eye movements have also been found to reduce the amount of false information and memories recalled during a subsequent memory task (Christman et al., 2004; Parker & Dagnell, 2007). The research investigating eye movements and memory was inspired by research revealing that rapid eye movement (REM) sleep involving repeated horizontal saccades is vital for memory consolidation (Cairney et al., 2014). In addition, research and real-life applications have demonstrated the effects of eye movements on memory in relation to post-traumatic stress disorder (PTSD).

There is a continued debate as to the cause of this enhancement effect with some recent studies questioning the robustness and replicability of the effect. The hemispheric encoding/retrieval asymmetry (HERA) model was presented by Tulving et al (1994) in order to elaborate on episodic memory encoding and retrieval knowledge. Neuroimaging studies showed that the left prefrontal cortex of the brain is more active than the right hemisphere in episodic memory encoding. For episodic memory retrieval, the right hemisphere is more active than the left hemisphere (Gagnon et al., 2010; Shallice et al., 1994). This demonstrates that both hemispheres are involved in episodic memory processes, but each hemisphere has

greater dominance in either encoding or retrieval. Tulving et al (1994) highlighted encoding mechanisms based in the left hemisphere interact with the retrieval mechanisms located in the right hemisphere of the prefrontal regions of the brain to retrieve episodic memories and information (Christman et al., 2006). Due to the memory processes involving both hemispheres, the corpus callosum (a bundle of commissural fibres which connects the right and left hemispheres and allows for communication between hemispheres) must play a vital role in memory retrieval. Christman & Propper (2010) hypothesise that by engaging both hemispheres of the brain and facilitating communication via the corpus callosum aids episodic memory retrieval of encoded information. The interhemispheric interaction hypothesis (IIH) states that the enhancement in memory abilities following bilateral eye movements, is due to an increase in connectivity between the two brain hemispheres via the corpus callosum (Christman et al., 2003; Lyle & Orsborn, 2011; Christman & Propper, 2010).

Support for the IIH theory is derived from case studies on patients who have required a corpus callossotomy procedure, in which the corpus callosum is severed. These patients often display deficits in episodic memory indicating that the corpus callosum is vital for episodic memory processes to function typically (Cronin-Golomb et al., 1996). Additional support for this theory is derived from the evidence that handedness can affect hemispheric interaction and can influence the effect of bilateral eye movements. People who are inconsistent handers show greater interhemispheric interaction compared to consistent handed people (Chase & Seidler., 2008; Lyle & Martin, 2010). Inconsistent handedness has been associated with superior episodic memory retrieval, thought to be due to naturally occurring increased interhemispheric interaction (Gorynia & Egenter, 2000). It is thought that strongly right-handed individuals perform more poorly on interhemispheric interaction tasks than inconsistent handers due to certain regions of the corpus callosum being smaller when compared with inconsistent handers. As a result, the SIRE effect is often only present in

strongly consistent handed individuals as the bilateral eye movements can compensate for the reduced connectivity between brain hemispheres (Propper et al., 2005). As inconsistent handed individuals already experience greater connectivity between hemispheres and superior episodic memory, the benefits of the SIRE effect are less prominent in inconsistent handers (Lyle & Martin, 2010).

Although there is evidence to support the IIH, research has presented some contradictory evidence which does not align with the theory. Lyle and Martin (2010) found no evidence that saccades lead to an enhancement of interhemispheric interaction on across hemisphere trials bringing into question the accuracy of the IIH. However, a methodological issue with Lyle and Martin's (2010) study is that the targets were presented to the left and right visual fields at 1.4 degrees from the central fixation. It was assumed that these targets were only projected to one hemisphere of the brain when presented at 1.4 degrees left/right of the central fixation. However, research has shown that the central area of vision can extend to 1-2 degrees from/around the focal area and this projects to both the right and left visual fields. Due to this, it is likely that the stimuli were projected to both visual fields rather than to a single hemisphere as intended. Visual field paradigms have advised that for stimuli to be presented to only one brain hemisphere and visual field the stimuli should be presented between 2.5 and 3 degrees from the central fixation point (Bourne, 2006). This brings into question whether the results found from Lyle and Martin (2010) suggesting that there is no evidence for interhemispheric interaction caused by saccades are accurate or subject to methodological issues which need to be addressed.

Although there were issues with Lyle and Martins (2010) study addressing the robustness of the SIRE effect, this is not the only research study which has found contradictory evidence against the SIRE effect. EEG studies have been conducted that have found little or no difference in interhemispheric interaction during and after saccadic eye

movements (Propper et al., 2007; Samara et al., 2011). A study conducted by Propper et al (2007) using EEG found that there was no significant change in brain activity and in fact found a reduction of coherence in the gamma frequency band (35-54hz) after completing bilateral eye movements compared to the control condition. Therefore, bilateral eye movements may not produce an increase in connectivity and interhemispheric interaction.

Due to the contradictory evidence and lack of support from neuroimaging studies for the interhemispheric interaction hypothesis, an alternative hypothesis was presented by Lyle and Martin (2010) termed the attentional control hypothesis. This theory states that bilateral eye movements lead to activation in the frontoparietal network in the brain resulting in an enhancement effect following attentional control tasks. Eye movements facilitate top-down control and selection of goal orientated stimuli (Corbetta & Shulman, 2002). The frontoparietal network includes similar regions which are often activated during episodic memory retrieval such as the frontal eye fields, superior parietal lobes and parts of the intraparietal sulcus (Ciaramelli et al., 2008). The hypothesis suggests that bilateral eye movements are a low-level executive control task that engages, and primes required systems for a higher-level top-down control task (Edlin & Lyle, 2013; Lyle and Edlin, 2015; Fleck et al., 2018). Research showed that saccades can be used to increase top-down control and it is thought that SIRE should be more effective when greater top-down control is required for success on the subsequent task (Edlin & Lyle, 2013).

To date no study has directly investigated the neural effects in relation to the attentional control hypothesis (Lyle & Martin, 2010), however research has demonstrated that lateral eye movements have produced activation changes in the frontoparietal attention network and other brain attention pathways. Research conducted with primates has shown that eye movements can result in post-saccadic activity in the prefrontal cortex (Funahashi, 2014). It is argued that residual brain activity resulting from saccades may aid with cognitive

prefrontal cortex processes. Further support for the link between executive attention and eye movements is that when performing attention and memory retrieval tasks activation is found in the frontoparietal attention networks of the brain (Vincent et al., 2008). This is consistent when conducting eye movements (Corbetta & Shulman, 2002). This evidence provides support for SIRE and also indicates that the SIRE effect may not be restricted to bilateral eye movements and other eye movement attention task may be able to elicit the effect.

Over recent years there has been a growing number of studies that have failed to replicate the SIRE effect, and this has led to scepticism as to its validity. Matzke et al (2015) performed a preregistered study attempting to replicate the enhancement effects on free recall by using horizontal eye movements. They designed what they believed was an optimum research design to test the effect based on previous literature. Results showed that the Bayes factor indicated strong evidence in support of the null hypothesis for both horizontal eye movements compared to vertical eye movements and no eye movements. The proposed possible reasons for previous conflicting results in the literature was statistical problems, poor research practices or methodological issues with the research design. However, in response to this paper a p-curve analysis was performed on multiple bilateral eye movement studies to investigate the likelihood of questionable research strategies or possible p-hacking. Simonsohn et al (2014) argued that right-skewed p-curves which show lower significant values e.g. .01, compared to higher significant p-values (0.04) display more evidential value. P-curves that are left-skewed and displayed higher p-values suggest a higher likelihood of phacking e.g. optional stopping. The p-curve analysis on SIRE studies reported a total of 18 statistically significant studies. The results showed that the p-curve was significantly rightskewed with 44.4% of the studies at the 0.01 or less p-value range. This indicates that these studies do contain evidential value. The p-curve analysis included both free recall and cued retrieval studies indicating that both methods have evidential value. However, it must be mentioned

that the p-curve did display a slight increase at the 0.05 p-value level. Overall, this suggests that the SIRE effect is a true effect but there is a possibility that some significant findings within this research area were subject to p-hacking and are not as robust as other findings.

Additionally, the limitations of the Matzke et al (2015) study should also be discussed. The study only investigated the effects of bilateral eye movements on free recall memory and therefore studies that have found the SIRE effect with cued recalled memory cannot be disregarded based on this study. More research needs to be conducted on both younger and older adults to investigate the robustness of the SIRE effect with cued recall in addition to free recall. Another limitation of the study and multiple other studies in this research area is that eye tracking was not implemented to ensure compliance with the eye movements. If attempting to design an optimum study, eye tracking should be implemented as a more objective technique for ensuring eye movement compliance. It is possible that some of the discrepancies in the literature could be due to a lack of compliance and ineffective monitoring of eye movements. In addition, to date no studies have assessed the effects of bilateral eye movements in populations with known memory deficits such as AD and MCI. People with AD and MCI experience memory and executive functioning deficits and the SIRE may be more prominent in impaired populations. Simple techniques that can be used to enhance and temporarily reduce the severity of deficits in AD participants could have a significant impact on daily life and help alleviate symptoms. Chapter 6 will address this gap in the literature by assessing the effect of bilateral eye movements in people with AD and MCI on word recognition.

2.11 Statement of thesis continuous commentary

The majority of eye tracking research has been conducted with Western industrialised population samples and limited research has examined eye tracking paradigms with more diverse samples. Researchers have discussed a recurring issue surrounding the lack of

diversity in psychological research creating problems relating to generalisability and replicability of psychological effects (Rad et al., 2018). The WEIRD (western, educated, industrialized, rich and democratic) limitation describes the restricted sample of participants that characterises much of psychological research and the established eye tracking paradigm termed the "gap effect" is one such paradigm subject to the WEIRD problem. The gap effect is an established eye tracking paradigm which examines disengagement of attention processes using varying display sequences during a prosaccade task. In chapter 3, we acknowledge the WEIRD problem by examining the gap effect in more diverse population samples. In chapter 3, the gap effect is examined in relation to ageing, disease and ethnicity effects.

Chapter 3

Paper one: The Disengagement of Visual Attention: An Eye-Tracking Study of Cognitive

Impairment, Ethnicity and Age.

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The Disengagement of Visual Attention: An Eye-Tracking Study of Cognitive Impairment, Ethnicity and Age

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Abstract: Various studies have shown that Alzheimer's disease (AD) is associated with an impairment of inhibitory control, although we do not have a comprehensive understanding of the associated cognitive processes. The ability to engage and disengage attention is a crucial cognitive operation of inhibitory control and can be readily investigated using the "gap effect" in a saccadic eye movement paradigm. In previous work, various demographic factors were confounded; therefore, here, we examine separately the effects of cognitive impairment in Alzheimer's disease, ethnicity/culture and age. This study included young ($N = 44$) and old ($N = 96$) European participants, AD ($N = 32$), mildly cognitively impaired participants (MCI: $N = 47$) and South Asian older adults ($N = 94$). A clear reduction in the mean reaction times was detected in all the participant groups in the gap condition compared to the overlap condition, confirming the effect. Importantly, this effect was also preserved in participants with MCI and AD. A strong effect of age was also evident, revealing a slowing in the disengagement of attention during the natural process of ageing.

Keywords: cognitive impairment; disengagement; attention; inhibition; "gap effect"; overlap; saccade

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that leads to profound cognitive impairment that includes changes in working memory [1,2]. AD is often diagnosed relatively late in the neuropathology of the disease, due to the lengthy and subjective assessments for the clinical diagnosis that are currently used. Subtle early impairments in executive function, attentional disengagement and other cognitive processes have been reported in people with AD [3,4]. Various attempts have been made to develop specific measures of attentional control in patients with AD [5–8]. However, these have included multiple cognitive operations or have not been grounded in neurophysiological research that has provided insights into the attentional disengagement. An exception is the work by Parasuraman and colleagues [9,10] using the Posner task. Posner [11] stated that orienting of attention comprised three distinct stages: (1) disengagement from the current stimulus; (2) movement to the new location; and (3) re-engagement with the target at the new location. According to the Posner model, attention must be disengaged from the current visual target, in order to facilitate an attentional shift from the old to the new target; just as in driving a car where you disengage from one gear, before moving the gear stick to a new gear. These distinct operations require multiple brain processes, with each contributing to the cost in terms of the overall processing time [12]. Parasuraman and colleagues [9,10] reported that the reaction times to a "valid" cue (that summoned automatic attention towards the target) was equivalent in the AD and control participants. In contrast, the reaction times

to an "invalid" cue (that required disengagement of attention away from the cue) was substantially increased in the AD group. This suggested that the automatic orientation of attention was preserved in AD, but the ability to disengage attention was impaired. However, these results failed to be replicated in several laboratories [13,14].

Mounting research has demonstrated that the attentional operations used in eye tracking tasks can provide an early marker of neurodegenerative disease [15–20]. Importantly, eye movement abnormalities occur earlier than the more noticeable changes in memory, which present relatively late in the progression of the disease [21]. A dual saccadic paradigm is often used to evaluate attentional disengagement [22–25]. In the so-called "gap" condition, the fixation point is removed 200 ms prior to the presentation of the display target, resulting in a temporal "gap" between the offset of the fixation point and the presentation of the new target. This condition yields relatively fast reaction times due to the facilitation of the disengagement operation by the prior removal of the fixation point. In contrast, in the "overlap" condition, the fixation point remains for a period of time while the new target is displayed (see Figure 1a,b). Therefore, in this condition, there is a temporal overlap between the offset of the central fixation point and the onset of the target. The "gap effect" is measured by the difference in the mean saccadic reaction times between the gap and overlap conditions and yields an operational index of attentional disengagement [26,27]. A saccadic eye movement is triggered relatively early in comparison to situations where the fixation point remains visible with the peripheral target, as in the step or overlap conditions [18,25,28,29].

(**a**)

(**b**)
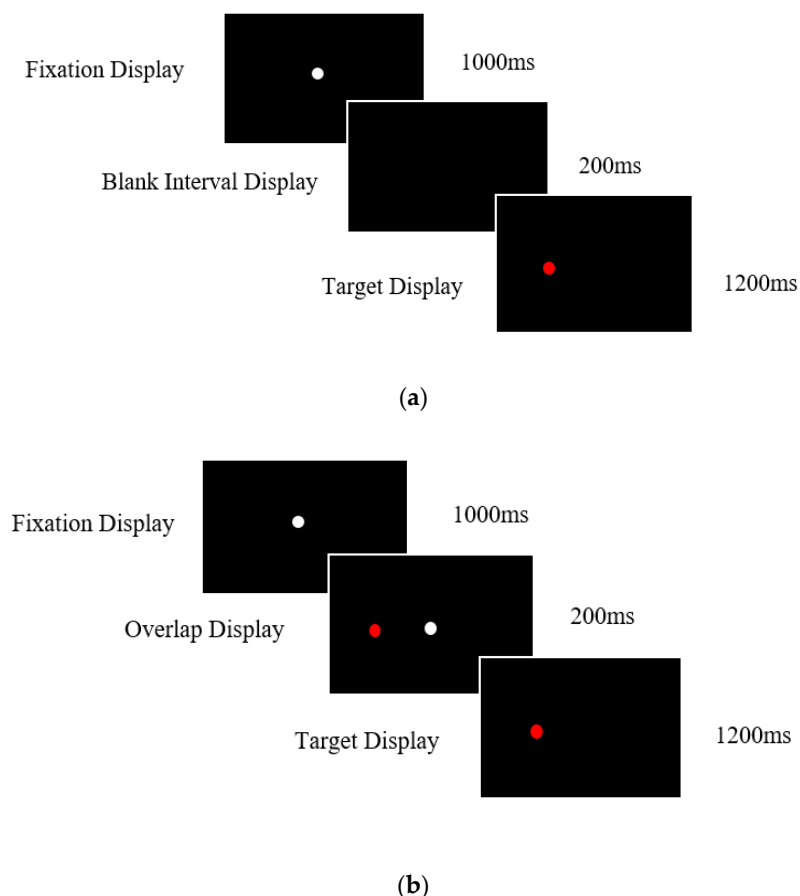
Figure 1. Gap and Overlap Displays (**a**) Timings and sequence of the prosaccade task gap condition. The gap condition facilitates the disengagement of visual attention prior to the target's presentation due to the removal of the central fixation point. (**b**) Timings and sequence of the pro-saccade task overlap condition. The central fixation point remains on for a short period when the target is displayed. This results in a delay in the disengagement of attention, resulting in longer mean saccade reaction times.

There has been relatively little research on the "gap effect" in patients with neurodegenerative disease. Prosaccades have the potential to assess attentional fluctuation in patients with neurodegenerative disease and offer an alternative to more traditional paper-based tests. The few studies that have been reported have yielded conflicting findings. For example, Yang et al. [30] reported in a sample of Chinese AD and mildly cognitively impaired (MCI) participants a substantially larger "gap effect" in comparison to healthy age-matched controls. In contrast, a recent study with Iranian participants revealed no difference in the prosaccade gap effect between AD participants and healthy controls [31]. Crawford et al. [17] found using a longitudinal design with European U.K. participants that the "gap effect" in AD was similar to that of the controls after a 12 month period. These differences could be due to a combination of methodological factors, including the participant populations, since to our knowledge, no study has contrasted different ethnicity groups within a single study design. It is important to examine the effect in various populations to determine the cultural validity of the gap effect. Restricting study populations to Western, educated, industrialized, rich and democratic (WEIRD) samples has contributed to the replicability crisis [32]. Eye movement characteristics have previously differed across ethnicity/cultural groups [33,34], therefore, comparisons across cultures is important.

In summary, this work is an exploration of attentional disengagement, to determine the potential mediating effects of: (a) cognitive impairment (contrasting European participants with AD, MCI and European healthy older participants); (b) healthy ageing (contrasting healthy young and older European participants); and (c) ethnicity/culture (contrasting older European older participants and older South Asian participants).

2. Materials and Methods

2.1. Participants

The study included 32 participants with dementia caused by Alzheimer's disease (AD: mean age = 74.32, SD = 7.57, age range = 59–86 years), 47 participants with mild cognitive impairment (MCI: mean age = 70.83, SD = 8.17, age range = 56–84 years), 96 typically ageing older European participants (mean age = 66.18, SD = 7.94, age range = 55–83 years), 44 younger European adults (mean age = 21.13, SD = 2.87, age range = 18–26 years), and 94 South Asian older adults (mean age = 67.25, SD = 6.13, age range = 55–79 years). Older and younger European participants were white British or European fluent English speakers with a minimum of 11 years in formal education. The older European participants were recruited from the local community, with the younger adults recruited via Lancaster University's Research Participant System. The Asian participants were recruited from local Hindu temples located in the northwest of England, who were born in India or East Africa, but had resided in the U.K. for an average of 46.66 years (SD = 5.94).

The AD and MCI participants were recruited via various NHS sites and memory clinics across the U.K. Participants had received a clinical diagnosis following a full assessment from a dementia specialist. AD participants had a formal diagnosis of dementia due to AD and met the requirements for the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM IV) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) for AD. MCI participants met the following criteria [35] and had a diagnosis of dementia due to mild cognitive impairment: (1) subjective reports of memory decline (reported by the individual or caregiver/informant); (2) memory and/or cognitive impairment (scores on standard cognitive tests were >1.5 SDs below age norms); (3) activities of daily living were preserved. The following exclusion criteria were applied: patients with acute physical symptoms, focal cerebral lesions, history of neurological disease (e.g., Parkinson's disease, multiple sclerosis, epilepsy, amyotrophic lateral sclerosis, muscular dystrophy), cerebrovascular disorders (including ischemic stroke, haemorrhagic stroke, atherosclerosis), psychosis, active or past alcohol or substance misuse/dependence or any physical or mental condition severe enough to interfere with their ability to participate in the study.

All participants retained the capacity to consent to participation in the study and provided written informed consent. Ethical approval was granted by the Lancaster University Ethics committee and by the NHS Health Research Authority, Greater Manchester West Research Ethics Committee.

2.2. Neuropsychological Assessments

The Montreal Cognitive Assessment (MoCA) [36] was administered as an indicator of probable dementia with a score of 26/30 or higher considered normal. The digit [37] and spatial span [37], forward and reverse, were used to estimate short-term memory span and working memory.

2.3. Eye Tracking Tasks

2.3.1. Apparatus

Eye movements were recorded using SR EyeLink Desktop 1000 with a sampling rate of 500 Hz. A chin rest was used to minimise head movements, and participants were seated 55 cm away from the computer screen. Prior to the start of each eye tracking task, a 9 point calibration was used. The stimulus was controlled and created via the use of Experiment Builder Software Version 1.10.1630.

2.3.2. Prosaccade Task

Participants were presented with 36 gap trials followed by 12 overlap trials. A white central fixation point was displayed for 1000 ms, followed by a red target presented randomly at 4° to the left or right for 1200 ms. Participants were instructed to look towards the central fixation point and then when the red target appeared to move their gaze towards it as quickly and accurately as possible. Between trials, a black interval screen was displayed for 3500 ms.

The gap condition included a blank interval screen displayed for 200 ms between the initial appearance of the red target and the extinguishment of the central fixation target. For this condition, the red and white target never appeared on the screen simultaneously (Figure 1). In the overlap condition, the target was presented while the central fixation remained present on the screen for a short period. There was a 200 ms "overlap" in which the target and fixation point were presented simultaneously (Figure 2). After this period, the central fixation was removed, and the target presented singularly for 1200 ms. Previous research [16,18] found that this format works well for patients with neurodegenerative diseases.

2.4. Data Analysis

The raw data were analysed and extracted from the EyeLink using DataViewer Software Version 3.2. The raw data were analysed offline via the use of the software [38]. The software filtered noise and spikes by removing frames with a velocity signal greater than 1500 deg/s or an acceleration signal greater than 100,000 deg^2/s. The fixations and saccadic events were detected by the EyeLink Parser, and the saccades were extracted alongside multiple spatial and temporal variables. Trials in which the participants did not direct their gaze to the fixation point before the target display were removed. Anticipatory saccades made prior to 80 ms and excessively delayed saccades over 700 ms were also filtered from the data.
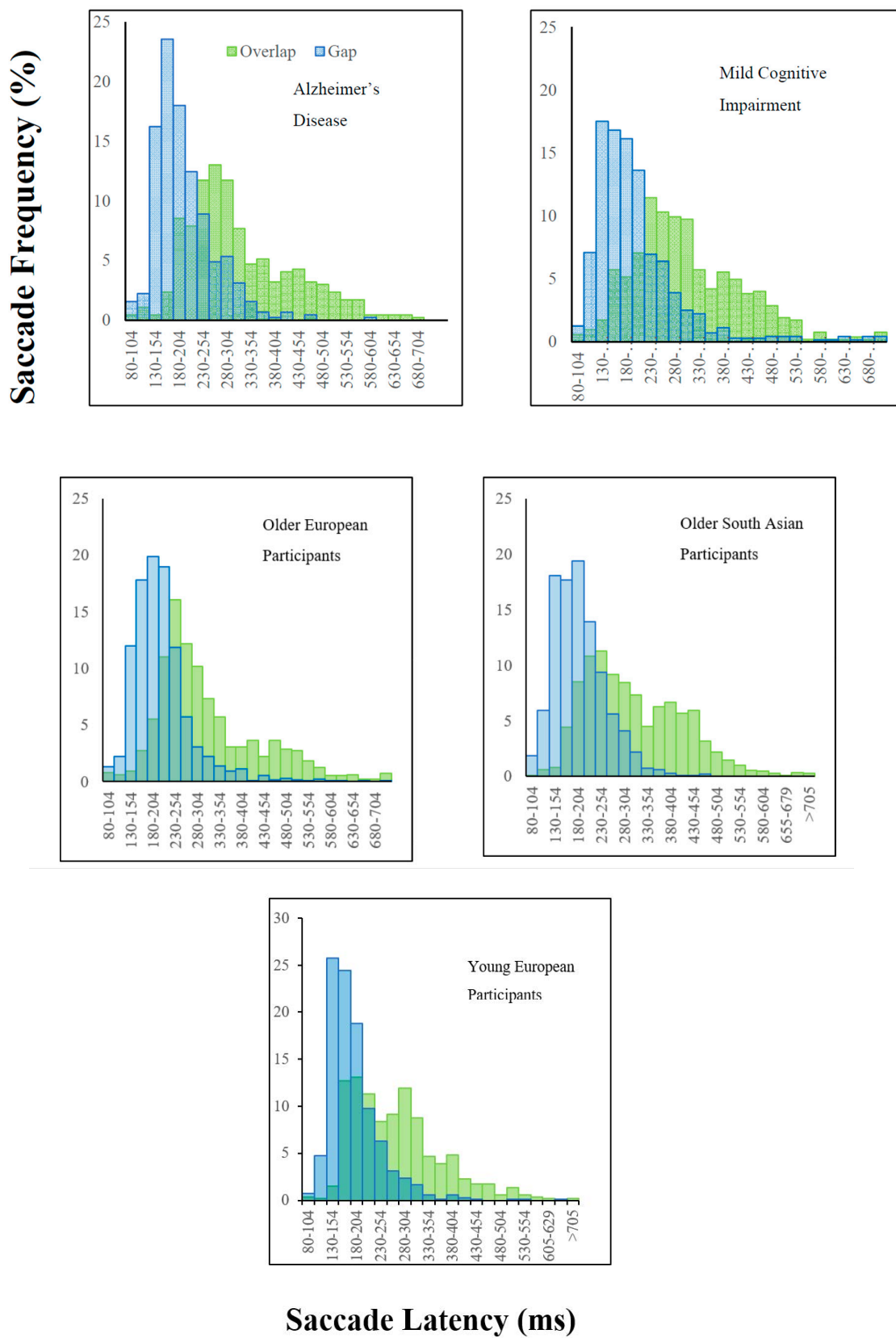
Figure 2. Histograms displaying a shift in the distribution of saccade latencies in the gap condition (blue) compared to the overlap condition (green) for the participant groups: Alzheimer's disease, mild cognitive impairment, older and younger European participants and older South Asian participants.

3. Results

Linear mixed effects model analyses were carried out using RStudio Version 1.2.5033. The models conducted an analysis of the reaction times in the gap and overlap conditions. The "gap effect" value was calculated by subtracting the individuals mean latency in the gap condition from the overlap condition mean latency. The linear mixed effects model also determined the group effects of disease, ageing, and ethnicity. Two participants in the MCI group were excluded from the subsequent analyses due to their mean reaction times in the prosaccade gap and overlap condition being greater than two standard deviations away from the mean.

3.1. Neuropsychological Tests

A linear mixed effects model was conducted to analyse the performance on the neuropsychological tests. Table 1 shows that there was the expected effect of disease on the MoCA test, with lower scores for the AD participants compared to older European participants, $\beta = 6.90$, $t (257) = 7.25$, $p < 0.0001$. AD participants scored significantly lower than the MCI participants, $\beta = 2.83$, $t (257) = 2.72$, $p = 0.007$ (see Table 2). The European older adults produced higher MoCA scores than the MCI group ($\beta = -4.06$, $t (257) = -5.13$, $p < 0.001$) and unexpectedly the South Asian group ($\beta = -6.89$, $t (257) = -7.25$, $p < 0.001$). This difference could be due to the combination of culturally inappropriate test items, linguistics and other cultural factors. There were no significant differences in the MoCA between the healthy European older and younger adults.

Table 1. Table displaying mean reaction times and standard deviations for the neurological assessments. MCI—mild cognitive impairment.

	Older European Participants		Older South Asian Participants		Alzheimer's Disease		MCI		Young European Participants	
	M	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**
MoCA	27.80	2.04	22.04	4.99	20.19	5.45	22.98	5.40	28.14	1.94
Digit Span Task	17.91	4.60	13.27	3.71	15.23	4.56	15.95	4.12	19.86	4.33
Spatial Span Task	13.89	2.44	12.47	2.24	11.42	3.75	12.93	3.08	17.38	2.08

Note: dependent variable: total task score.

Table 2. Table displaying post hoc comparisons for the neurological assessments.

	Post Hoc Contracts (*p* Values)				
	Disease Effects			Ageing Effects	Ethnicity Effects
	AD vs. OEP	**AD vs. MCI**	**MCI vs. OEP**	**OEP vs. YEP**	**OEP vs. OSP**
MoCA	<0.001 *	0.007 *	<0.001 *	0.025	<0.001 *
Digit Span Task	0.015 *	0.496	0.043	0.015 *	<0.001 *
Spatial Span Task	<0.001 *	0.021 *	0.077	<0.001 *	0.002 *

AD—Alzheimer's disease; MCI—mild cognitive impairment; OEP—older European participants; OSP—older South Asian participants. YEP—young European participants. * Significant at $p < 0.05$.

The digit span test (total score forward and backward) revealed that AD participants had a significantly lower mean score than the older European participants, $\beta = 2.38$, $t (254) = 2.46$, $p = 0.015$. No significant differences were found between the AD and MCI group (see Table 2). The older South Asian participants had significantly lower digit span than the older European participants ($\beta = -4.45$, $t (254) = -6.49$, $p < 0.001$). A significant difference was found between younger and older European adults, with a higher mean digit span score for the younger adults ($\beta = 2.25$, $t (254) = 2.45$, $p = 0.015$).

Table 1 shows the results from the spatial span (forward and backward) and revealed that, as expected, the AD participants scored significantly lower compared to the older European participants, $\beta = 2.41$, $t (242) = 3.99$, $p < 0.001$. The AD participants had a significantly lower spatial span score than MCI participants, $\beta = 1.50$, $t (242) = 2.32$, $p = 0.021$. The findings revealed an ageing effect with young

adults producing significantly higher spatial span scores than the European older adults (β = 3.53, *t* (242) = 6.15, *p* < 0.001). The older South Asian participants scored significantly lower than older European participants, β = −1.39, *t* (242) = −3.17, *p* = 0.002 (Table 2).

3.2. The "Gap" Effect

Figure 2 shows the relative shift in the latency distributions in the gap and overlap trials for each of the participant groups. A linear mixed model analysis was conducted to analyse the reaction times in relation to the participant groups. The overlap condition yielded significantly longer reaction times overall, compared to the gap condition, β = 108.21, *t* (8881) = 57.33, *p* < 0.0001 (Figure 2). The "gap effect" was therefore evident in all groups, with significantly faster reaction times in the gap condition, compared to the overlap condition.

3.3. Attentional Disengagement: Effects of Ageing

The older European participants' and the younger European participants' reaction times were compared in the gap and overlap conditions to determine the effects of age. Table 3 reveals that the mean "gap effect" was significantly smaller in the younger European participants (87 ms) compared to the older European participants (110 ms) β = −23.46, *t* (315) = −2.31, *p* = 0.022. Results showed baseline differences in prosaccades with younger European participants having significantly faster reaction times in the gap (β = −8.22, *t* (4624) = −2.70, *p* = 0.007) and overlap conditions (β = −38.46, *t* (4257) = −6.81, *p* < 0.001) compared to older European participants. This indicated that older European participants showed a greater difficulty in disengaging attention from the central fixation in comparison to the younger adults in addition to a general slowing in prosaccades.

Table 3. Table displaying mean reaction times and standard deviations for the prosaccade task gap and overlap conditions.

	Older European Participants *N* = 96		Older South Asian Participants *N* = 94		Alzheimer's Disease *N* = 32		MCI *N* = 45		Young European Participants *N* = 44	
	M	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**
Gap	195	38.87	212	37.06	206	30.93	200	42.18	185	31.60
Overlap	305	75.06	315	75.06	312	51.32	310	66.86	272	58.83
Gap Effect (ms) (Overlap-Gap)	110	57.30	103	58.66	106	48.06	110	59.54	87	48.53

3.4. Attentional Disengagement: Effects of Cognitive Impairment

Table 4 reveals that there was a significant difference between the AD and older European participants' saccadic reaction times in the gap condition (β = −10.20, *t* (4624) = −2.92, *p* = 0.004). There was no significant difference in reaction times in the overlap (β = −2.41, *t* (4257) = −0.361, *p* = 0.718) condition. There was also no significant difference between the "gap effect" between the conditions (β = −4.29, *t* (315) = −0.376, *p* = 0.707). Similarly, there were no significant differences in reaction times in these conditions when comparing the AD group with the MCI group (Table 4). There were no significant differences between the MCI and European older controls in the overlap condition; however, in the gap condition, MCI participants revealed a significant increase in mean saccadic reaction times compared to the European older controls. Thus, prosaccades and the "gap effect" were generally well preserved in people with AD and MCI.

3.5. Attentional Disengagement: Ethnicity/Cultural Effects

The older European group was contrasted with the South Asian older adults to determine the effects of ethnicity on prosaccade reaction times and the "gap effect". The results shown in Table 4 revealed that the European older group generated faster reaction times compared to the South Asian older group (β = 15.78, *t* (4624) = 6.28, *p* < 0.001) in the gap condition and overlap conditions (β = 9.95,

t (4257) = 2.42, p = 0.016). There was no difference in the proportion of the "gap effect" between the groups (Table 4).

Table 4. Table displaying post hoc comparisons for the prosaccade task gap and overlap conditions.

	Post Hoc Contracts (p Values)				
	Disease Effects			Ageing Effects	Ethnicity Effects
	AD vs. OEP	AD vs. MCI	MCI vs. OEP	OEP vs. YEP	OEP vs. OSP
Gap	0.004 *	0.161	<0.001 *	0.007 *	<0.001 *
Overlap	0.718	0.972	0.706	<0.001 *	0.016 *
Gap Effect (Overlap-Gap)	0.707	0.885	0.803	0.022 *	0.383

AD—Alzheimer's disease; MCI—mild cognitive impairment; OEP—older European participants; OSP—older South Asian participants. YEP—young European participants. * Significant at $p < 0.05$.

3.6. Correlations

The neuropsychological measures of memory yielded separate scores: forward, backward and total scores for digit and spatial memory, thus six measures of memory in total. The forward recall score yielded an index for memory span, whilst the backward recall score yielded a more direct measure of working memory, since it relied not simply on pure recall, but also cognitive manipulation of the items in short-term memory. Table 5 reveals that there was a significant negative correlation for backward spatial memory and the gap-effect for the MCI group, such that people with longer attentional disengagement reactions times were associated with lower spatial working memory. Interestingly, this relationship was not evident for digit span, which probed verbal working memory. Curiously, this relationship appeared to be specific to the MCI group, although it was not clear why this relationship was specific to MCI. For many participants, MCI was an intermediate transition state between healthy cognition and Alzheimer's disease. A significant proportion, but by no means all, will unfortunately go on to develop full-blown AD, although we do not yet have a reliable predictive behavioural measure of those people with MCI who will progress to AD. It appears that during this transition period, attentional disengagement may provide a useful index of the decline in working memory, and the progression from MCI to AD. Longitudinal studies will be required to determine the validity of this hypothesis.

Table 5. Correlations of prosaccade conditions and neuropsychological tests.

Variable		MoCA	Digit Span Total	Digit Span Forward	Digit Span Backward	Spatial Span Total	Spatial Span Forward	Spatial Span Backward
Gap Effect (Overlap-Gap)	AD	−0.063	0.120	0.048	0.169	0.157	0.242	0.058
	MCI	−0.096	−0.076	−0.118	−0.015	−0.168	0.021	−0.318 *
	OEP	−0.095	−0.004	−0.014	−0.031	−0.014	0.025	−0.045
	OSP	0.213	0.153	0.144	0.126	−0.024	−0.028	−0.013
	YEP	0.147	−0.013	0.070	−0.088	0.074	0.071	0.043

AD—Alzheimer's disease; MCI—mild cognitive impairment; OEP—older European participants; OSP—older South Asian participants. YEP—young European participants. * Significant at $p < 0.05$.

4. Discussion

This study revealed that the "gap effect" was well preserved in AD and MCI participants. Participants produced significantly faster reaction times when performing pro-saccadic eye movements during the gap condition compared to the overlap condition. Moreover, the effect was robust across both ethnic/cultural groups explored in this study.

4.1. What Does the Gap Effect Reveal about the Integrity of the Alzheimer Brain?

The neurophysiological networks that regulate the control of saccadic eye movements are relatively well understood. The saccadic eye movements are generated by precise reciprocal activation of saccade-related neurons and the inhibition of fixation neurons in the superior colliculus [39,40].

According to the Findlay and Walker [41] model, the removal of the fixation target leads to a reduction in the activation of the fixation units, which releases the saccade from inhibition, and this is reflected by the reduction in reaction times. When the fixation point remains on, the fixation units are tonically active, and the move units are inhibited, causing a delay in the initiation of a saccade. This network is clearly well preserved in early and late stages of the disorder. In previous work, we examined inhibitory control saccades extensively using the antisaccade task. In contrast to the gap and overlap task, the anti-saccade task requires that the observer looks away from the object, in the opposite direction, and is one of the most widely used paradigms assessing inhibitory control in both healthy individuals and clinical disorders [42,43]. These studies have shown that people with dementia generate a high proportion of uncorrected prosaccade errors towards the target in the antisaccade task that correlates with the severity of the dementia [16]. In contrast, when healthy participants make errors, they are normally rapidly corrected, although both AD and MCI adhere to the principle that the frequency of past errors predicts the probability of future errors [44]. People with amnesic MCI are at a greater risk of progressing to dementia [45–47]. Recently, our lab has shown that these errors are also evident in amnesic MCI to a greater extent than non-amnesic MCI participants [20]. We have argued that this error correction implicates a neural network that includes the anterior cingulate. Together with this work, the current evidence of the preservation of the attentional disengagement [16] will help to increase our understanding of the specificity of oculomotor impairment in AD and undermine the idea that the source of the uncorrected errors can be attributed to the inability to disengage attention from the prepotent target. Rather, the inhibition appears to be directly linked to top-down inhibitory control and working memory [16,17]. Clearly, there is a dissociation of impairment of the oculomotor pathways in AD. Evidence from this study revealed a preservation of the superior colliculus pathway, while converging evidence from previous and more recent work [20] indicated that other centres of the network, including the anterior cingulate, that mediate top-down inhibitory control and error monitoring are affected early in the course of the disease [21].

4.2. Ageing

Another key finding was a strong ageing effect on the saccadic reaction times. Although all participant groups displayed the gap effect, the younger adults revealed a significantly faster mean reaction times in the overlap and gap conditions than the older adults. Previous research has reported that eye movements are susceptible to ageing effects, in particular reductions in processing speed, spatial memory and inhibitory control [48–51]. Crawford et al. [17] reported that the "gap effect" increased in older adults compared to younger adults, suggesting that the changes in the attentional engagement are associated with normal ageing, rather than AD. The older adults are apparently more dependent on the removal of the central stimulus to facilitate the shift of attention from fixation and therefore showed a larger benefit following the removal of the fixation point in the gap condition compared to the younger adults. One possible explanation is that may be due to an age-related decrease in the reciprocal inhibitory activity of the fixation and move units [41].

4.3. Ethnicity

As outlined above, the European and the South Asian older adults both demonstrated the gap effect, with significantly faster prosaccades in the gap condition compared to the overlap condition. Clear differences between the groups emerged in the saccade reaction times, specifically for the saccade gap and overlap conditions, with South Asian adults presenting slower saccade reaction times. This raises the possibility that the south Asian group may have a lower proportion of fast and express saccades in the gap and overlap tasks. Express saccades [52,53] are fast reaction time saccades (80 ms−130 ms) with frequencies that vary across cultural groups. The frequency of express saccades was reduced in the overlap task, because the temporal overlap of the fixation-point and the target often inhibited the prosaccade, which may have reduced the difference in the overlap condition. Knox, Amatya, Jiang and Gong [33] demonstrated that Chinese participants showed a higher proportion

of express saccades compared to U.K. participants. Clearly, saccade performance can differ across different cultural groups. If express saccades were a contributory factor to the faster saccade latencies of the European group in the gap condition, this would explain the convergence of saccade latencies for the groups in the overlap condition. However, the combined group latency distributions in Figure 2 suggests that this hypothesis may be flawed and cannot account for the group differences in the gap task and overlap task, although this would be best examined within a design with a larger number of trials, with the distributions of individual participants.

Previous research has also shown differences in eye movements across different cultural and ethnic groups [33,54,55]. Chua, Boland and Nisbett [56] found differences in scan patterns between native Chinese and native English-speaking participants when assessing visual scenes. English participants tended to look first at the foreground object and had an increased number of fixations then Chinese participants, predominantly focused on the background visual areas of the scene. Eye movements are clearly not homogeneous; culture and ethnicity factors can influence specific features of eye movement control.

Knox and Wolohan [57] examined saccades in European, Chinese and U.K.-born Chinese participants who shared similar cultural experiences as the European group. The study investigated whether the differences in the saccadic eye movements of the Chinese and European groups resulted from cultural or culture-unrelated factors. The Chinese participants showed similar pattern results irrespective of the culture exposure. Therefore, cultural differences cannot be the primary cause of the difference in oculomotor characteristics. Although the principal explanatory factors of these differences in oculomotor systems is unclear, they are possibly related to a combination of genetic, epigenetic and environmental factors [58]. A recent study showing very clear differences in the post-saccadic oscillations of Chinese-born and U.K.-born undergraduates concluded that "..genetic, racial, biological, and/or cultural differences can affect the morphology of the eye movement data recorded and should be considered when studying eye movements and oculomotor fixation and saccadic behaviors" [34]. Although there has been increasing eye-tracking research with Chinese participants, research with South Asian populations has been sparse. We hope that this work will encourage future studies to help redress this void.

5. Conclusions

Research scientists have tended to focus on the memory, intelligence and other mental skills that degenerate in AD and understandably have paid less attention to those equally important cognitive functions that may be well preserved. A better understanding of preserved functions in the disease will help to develop potential new early intervention strategies in the treatment of the disease that may improve mental functions and delay the progression of the disease. Patients with AD show large individual differences in the profile of scores across both traditional cognitive assessment and measures of saccadic eye movement. Therefore, in our recent work [18,21], we developed a profile measure of z-scores for each test that captures a patient's performance across a range of measures in relation to the normative scores. This approach takes full advantage of the extensive range of saccadic eye movement parameters to assess and monitor cognitive changes in the evolution of AD and will enhance specificity and sensitivity as a diagnostic tool.

Further, this study demonstrated that prosaccades can be susceptible to disease, ageing and ethnicity effects, and therefore, future research should strive to include non-WEIRD participant groups to create a more comprehensive understanding of the effect and its robustness and generalizability.

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3.1 Statement of thesis continuous commentary

In Chapter 3 I investigated eye tracking performance and the "gap effect" in relation to ageing, ethnicity and disease effects (Abel et al., 2002). Despite previous research suggesting people with AD and MCI often display deficits on eye movement tasks, the gap effect was preserved in AD and MCI participants. This indicated that disengagement of attention capabilities in AD and MCI are comparable to healthy older adults. Additionally, a strong ageing effect was found suggesting a slowing in disengagement of attention processes during natural ageing. Ethnicity was found to affect baseline saccades and it is clear that prosaccades are susceptible to ethnicity, ageing and disease effects.

The inhibition of a recent distracter task (Crawford et al., 2005) was designed to assess inhibitory control abilities while employing prosaccadic eye movements. Findings from chapter 3 indicate that the eye movements are be susceptible to ethnicity, disease and ageing effect and it is possible that eye movements on the inhibition of a recent distracter task may vary across different populations. Research has shown that AD causes deficits on inhibitory control tasks such as the antisaccade task, although to date research has not examined potential inhibitory control deficits, due to AD, on the recent distracter task. Surprising findings from chapter 3 on the preservation of the gap effect indicates that certain aspects of cognitive functioning may be preserved in AD populations and generalisations of impairments should not be assumed. Therefore, chapter 4 assessed the inhibition of a recent distracter effect in relation to ageing, ethnicity and disease.

Chapter 4

Paper two: Active visual inhibition is preserved in the presence of a distracter: A cross-cultural,

ageing and dementia study.

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Active visual inhibition is preserved in the presence of a distracter: A cross-cultural, ageing and dementia study

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ABSTRACT

The current study investigated a novel visual distracter task as a potential diagnostic marker for the detection of cognitive impairment and the extent to which this compares in healthy ageing across two cultures. The Inhibition of a Recent Distracter Effect (IRD) refers to the inhibition of a saccadic eye movement towards a target that is presented at the location of a previous distracter. Two studies compared the IRD across a large cross-cultural sample comprising of young (N = 75), old European participants (N = 119), old south Asian participants (N = 83), participants with Dementia due to Alzheimer's disease (N = 65) and Mild cognitive impairment (N = 91). Significantly longer saccadic reaction times on the target to distracter trials, in comparison to the target to target trials were evident in all groups and age cohorts. Importantly, the IRD was also preserved in participants with Alzheimer's Disease and mild cognitive impairment demonstrating that the IRD is robust across cultures, age groups and clinical populations. Eye-tracking is increasingly used as a dual diagnostic and experimental probe for the investigation of cognitive control in Alzheimer's disease. As a promising methodology for the early diagnosis of dementia, it is important to understand the cognitive operations in relation to eye-tracking that are well preserved as well as those that are abnormal. Paradigms should also be validated across ethnicity/culture, clinical groups and age cohorts.

1. Introduction

Multiple objects and events compete for our attention at any given moment (Crawford, Hill & Higham, 2005; Treisman & Gelade, 1980). In a football match, the object of interest is often the ball and those in possession of the ball; the other competing distracters (such as the advertising animations, the noisy opposition supporters) must be avoided to direct our eyes accurately to the target. The ability to inhibit distracting information and to focus on the task-relevant stimuli is critical for the efficient control of active visual attention. Various studies have suggested that this involves a dual process of

directing spatial attention onto the target together with the inhibition of the distracter (Wilcockson, Mardanbegi, Sawyer, et al., 2019; Zovko & Kiefer, 2013). This ability to inhibit a distracting stimulus appears to decline during the ageing process and in neurodegenerative disease (Crawford, Higham et al., 2005; Crawford et al., 2017).

The inhibition of a "Recent Distracter Task (IRD)" was developed to investigate the characteristics of this competitive process used in the selection of a singleton target that is coupled with a distracter (Crawford, Hill & Higham, 2005; Wilcockson, Mardanbegi, Sawyer, et al., 2019). The IRD comprises two consecutive visual displays (Crawford, Hill & Higham, 2005). The first display screen presents a red target and a green distracter simultaneously: participants are required to fixate on the red target and to avoid the green distracter (Fig. 1). The second display presents a singleton red target after a short interval. The location of the target in the second display can appear at one of three locations relative to the first display; same location as the previous target (i.e., target–target (T–T)), the location of the previous distracter (i.e., target-distracter (T-D)) or a new location (i.e., target-new (T-N)). The key finding was that the reaction time of a saccadic eye movement to the target in the second display (i.e., the probe display) was significantly slowed when the target was presented at the location of the previous distracter (T-D), in comparison to the T–T or the T-N trials. The inhibition of the distracter in the first display apparently carried over from the previous distracter location and was detected by its effect on a subsequent saccade to a probe-target at that spatial location. A series of follow-up experiments revealed that this slowing was derived from the location of the distracter, rather than another co-incidental feature of the distracter, such as its colour. Donovan et al. (2012) demonstrated that this IRD was

also detected with naturalistic images of objects and animals and is therefore not restricted to abstract light targets in a colour display. The IRD supports the view that selective attention for eye movements incorporates a dual mechanism of target selection together with the inhibition of a distracter (Crawford, Hill & Higham, 2005).

1.1. Inhibitory control in Alzheimer's disease

People with AD experience a decline in working memory and executive function, including inhibitory control (Baddeley et al., 2001). The brain regions and neuronal pathways involved in eye movements, fixation and gaze patterns are controlled by cortical neural networks in the frontal lobe, parietal lobe and downstream pathways that project to the cerebellum and brainstem. These areas and pathways are often impaired due to neurodegeneration in disorders such as AD resulting in deterioration of eye movements and inhibitory control processes (Abel et al., 2002). As a result, abnormal eye movements have been shown to be a useful indication of cognitive decline and neurodegeneration (Anderson & MacAskill, 2013). Multiple studies have found that AD patients suffer a reduction in inhibitory control aligning with deterioration in executive functioning and working memory (Baddeley et al., 2001; Parasuraman et al., 1992; Tales et al., 2002).

Impairments of inhibitory control in AD have been reported in several studies using the anti-saccade task (Boxer et al., 2012; Crawford, Higham et al., 2005, Crawford et al., 2019; Heuer et al., 2013; Kaufman et al., 2012; Molitor et al., 2015; Wilcockson, Mardanbegi, Xia, et al., 2019). The anti-saccade task is a widely used task, that explores inhibitory control in healthy individuals and clinical populations (Hutton
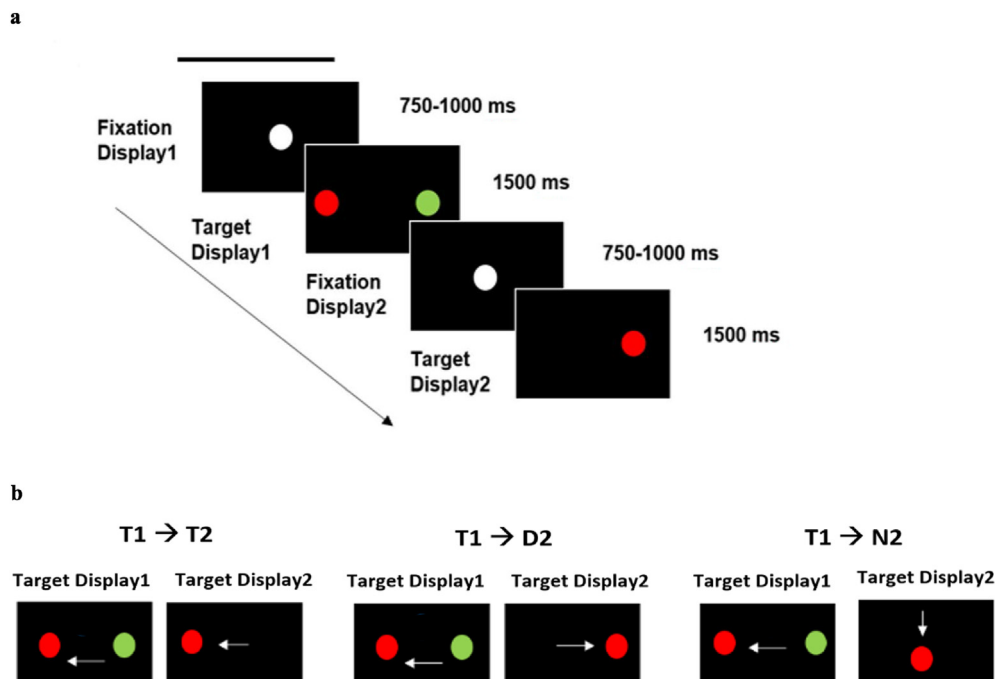

Fig. 1 – a. Timings and sequence of the IRD in experiment 2. b. *Example of the three trial variations in the IRD1. Note.* **The locations of the green and red targets on display screen 1 varied throughout the task.**

& Ettinger, 2006). When an object appears in view, there is a natural impulse to shift your gaze towards the object. The task requires the inhibition of this natural urge and gaze aversion to the opposite side (Crawford, Higham et al., 2005). People with AD show a high proportion of uncorrected error rates and delayed reaction times on the task (Crawford et al., 2019; Wilcockson, Mardanbegi, Xia, et al., 2019). The antisaccade task involves sensory and motor inhibition and incorporates multiple cognitive functions in addition to working memory, with research demonstrating that working memory and inhibitory control are dissociated functions (Crawford & Higham, 2016). The source of the impairment in AD participants is therefore unclear, due to the fact that, in addition to inhibitory control and working memory, the task also comprises stimulus-response incompatibility mapping and top-down volitional action.

Although a widely used paradigm, the anti-saccade task also suffers from weak ecological validity since the overriding goal of looking away from a salient target without a target to foveate is unusual and counterintuitive. More commonly the visual system is required to select a target to fixate from a set of non-targets or distracters, as for example in reading a passage of text where a target word is selected from the competing words. The traditional antisaccade task does not offer a competing target and therefore it also requires the ability to disengage from the target which is holding the participants attention in addition to the ability to inhibit the distractor. In the inhibition of a recent distractor task (IRD) the situation is more comparable to everyday eye movements and visual search tasks, such as reading. Therefore, in the current study we employed the IRD task that was explored in our previous work (Crawford, Hill & Higham, 2005; Donovan et al., 2012).

The IRD addresses some of the challenges presented in the antisaccade task by providing a target to foveate which is more representative of everyday gaze behaviour. The IRD examines the inhibitory trace by probing the spatial effect of the previous distracter on the reaction time of the current saccade towards a subsequent target at that location. The IRD task does not mislead the participant about the future location of the target or require an eye movement away from the target or cue. Instead the participant is presented with two visual displays; the first presents a target and distractor, followed by a second display with a single target that varies in location with respect to the target in the previous display. In the IRD task inhibition is measured implicitly by contrasting the reaction times to the "new" location in relation to the distracter location in the previous display. This design allows for a dual assessment of the facilitation of eye movements directed towards the target and inhibition of eye movements towards a distractor (Crawford, Hill & Higham, 2005).

It cannot be assumed that the IRD and the antisaccade tasks target the same inhibitory control mechanisms. There are some key differences between these tasks which is likely to result in distinct inhibition mechanisms being deployed. The antisaccade task requires a motor signal to direct the eyes to the opposite location rather than a signal to suppress the target per se. In the IRD task the antisaccade, requiring the participant to direct their gaze away from the target, is absent. A competing distractor target is vital for generating the distractor inhibition in the IRD task, (Donovan et al. (2012) which is absent in the antisaccade task. Studies have shown that this is distinct from general gaze aversion which is present in the antisaccade task. Crawford, Hill & Higham 2005 demonstrated that the antisaccade is unable to generate the spatial inhibition at the location of a distractor which is found in the IRD. Donovan et al. (2012) highlighted the importance of the distractor in the display as spatial inhibition is enhanced when a competing target is present. It is possible AD participants may have a loss of inhibitory control towards a distracter that would yield a reduced IRD effect. However, if the IRD effect is preserved in AD and MCI participants this will provide an important insight into the limitations of inhibitory control frequently reported in these disorders (Crawford et al., 2019).

In common with the majority of published research in experimental psychology in Europe and the USA (Barratt, 2020; Rad et al., 2018), the participants in our previous work were exclusively, young British/European/Caucasian university students (Crawford, Hill & Higham, 2005; Donovan et al., 2012). Eye tracking research has demonstrated distinct cross-cultural differences in eye tracking (Alotaibi et al., 2017; Knox et al., 2012). Chua et al. (2005) found differences between native Chinese and native English-speaking in eye movement scan patterns during scene viewing. Growing evidence shows that the eye-tracking characteristics that are deployed by individuals are not a universal constant, but that cultural factors can influence these eye movements. English speaking participants tended to look initially at the foreground objects with an increase in the number of fixations in comparison to Chinese participants who focused on the background visual areas of the scene. Apparently, differences in thinking style lead to variations in the strategy and scanning patterns across cultures. Alotaibi et al. (2017) found more fixations and longer search times for Saudi participants compared to British participants on eye movement tasks. This was attributed to differences between the analytic thinking style (more common in individualistic cultures) and the holistic thinking style (more common in collectivist cultures). In contrast, Rayner and Castelhano (2009) investigated scan patterns in American and Chinese viewers and found no evidence of cultural differences when viewing the presented scenes. This brings into question the true impact of cultural influences on eye movements and scan patterns and it is therefore important to expand further investigations into the range of cultural influences on established and novel paradigms. Recent work in our laboratory (Mardenbegi et al., 2020) revealed that the morphology of post-saccadic oscillations differed between Chinese-born and European-born participants. However, the level of attentional disengagement in South Asian participants (reflected in a similar decrease in mean saccadic latency and overall latency distributions) was comparable to European participants in the saccadic gap/overlap paradigm (Polden et al., 2020). Therefore, in this study, we expanded the diversity to examine the potential effects of age, ethnicity and neurodegenerative disease.

In summary, this work is an exploration of inhibitory control, specifically inhibition of a distracter target, that explored the potential effects of: a) Cognitive impairment (contrasting AD and MCI participants with European healthy

older adults); b) Healthy ageing (contrasting healthy young and older European participants) and c) Ethnicity (contrasting European older adults with South Asian older adults).

2. Experiment 1—materials and methods

2.1. Participants

The study included 269 participants in total, consisting of: 48 young European (mean age = 21 years, SD = 3 years) and 101 older European participants (mean age = 69 years, SD = 2 years) recruited from the local community, all born and residing in the UK and native English speakers; 35 south Asian participants (mean age = 65 years, SD = 5 years) recruited from local Hindu temples in the North-west area of England, born outside of the UK but residing in the UK for an average of 47 years (SD = 6 years). Thirty-three participants with dementia due to Alzheimer's disease (mean age = 74 years, SD = 11 years) and 52 mild cognitive impaired (mean age = 71 years, SD = 7 years) participants were recruited by various National Health Trusts and memory clinics across the UK. Participants had received a clinical diagnosis from a dementia specialist following a full neurocognitive assessment. Participants were white British or European and fluent English speakers with at least 11 years in formal education. The AD participants met the requirements for the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM IV) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) for AD. The MCI participants had received a diagnosis of dementia due to mild cognitive impairment and met the following criteria (Lemos et al., 2015): (1) subjective reports of memory decline (reported by individual or caregiver/informant); (2) memory and/or cognitive impairment (scores on standard cognitive tests were >1.5 SDs below age norms); (3) Activities of daily living were moderately preserved. Participants were excluded from the study if any of the following criteria applied: previous head trauma, stroke, cardiovascular disease, cerebrovascular disease, focal cerebral lesions, physical or mental conditions severe enough to affect their ability to participate, previous and current alcohol or substance misuse. Control participants were excluded if they had previously received a diagnosis of a cognitive or memory impairment. A power analysis was conducted using G*Power software version 3.1.9.7. This was to ensure the tasks offer adequate power. For the analysis the power level was set at .80 with an error of .05 (Faul et al., 2007). The effect size was based on the Crawford, Hill and Higham (2005) study which assessed the IRD effect in young adults. Results revealed a minimum sample size of N = 31 (approximately 6 per condition) per experiment is necessary to achieve a power of .80 at an alpha of .05. However, given that the Crawford, Hill and Higham (2005) sample of participants recruited was a relatively homogeneous group of young, healthy university students this would underestimate the required sample sizes for the current study. This is the first study of IRD using elderly, and neurodegenerative disease therefore we decided to recruit as many participants as we could achieve. Written informed consent was gained with all participants having capacity to provide consent. Ethical approval was granted by Lancaster University Ethics committee and by the NHS Health Research Authority, Greater Manchester West Research Ethics Committee.

2.2. Neuropsychological assessments

Participants were required to complete a series of three cognitive assessments and a computerised eye tracking task termed the "Recent Distracter Task". The Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) was used to assess cognitive impairment and as an indicator of probable dementia or mild cognitive impairment. Verbal working memory was estimated using the digit span task taken from Wechsler Adult Intelligence Scale III (Wechsler, 1997) and spatial memory using the Corsi block spatial memory task (Wechsler, 1997). The neuropsychological measures of memory yielded separate scores: forwards and backwards scores for digit and spatial memory, thus 4 measures of memory in total. The forwards recall score yields an index for memory span, whilst the backwards recall score yields a more direct measure of working memory since it relies not simply on pure recall, but also cognitive manipulation of the items in short term memory. These measures where included to assess baseline working memory, executive functioning and spatial memory abilities for the control participants. In this study we distinguished between verbal and spatial memory span assessments and also between forwards and reverse recall as research has demonstrated these to be distant memory processes. When verbal and spatial items are recalled in the forwards order (in the same order they are presented) there is no requirement to manipulate the memory items. These items are instead held in a temporary buffer and repeated. If the items are asked to be recalled in the reverse order this is a more complex working memory process involving working memory. The forwards version provides a simple measure of memory span whereas the reverse version requires working memory to store, inhibit, and re-sequence the items (Boxer et al., 2006; Garbett et al., 2008). Legal copyright restrictions prevent public archiving of the neuropsychological tests used in this study, which can be obtained from the copyright holders in the cited references.

2.3. The inhibition of a recent distracter (IRD) task

2.3.1. Apparatus

Participant's eye movements were recorded using the EyeLink Desktop 1000 sampling at 500 Hz. The computer monitor size was 24 inches with a resolution of 1366 × 768. Participants were positioned approximately 55 cm from the computer monitor (60 Hz). A chin rest was used to reduce head movements. Participant's gaze was calibrated prior to the start of the tasks using a 9-point calibration. The stimulus was created and controlled via the use of Experiment Builder Software Version 1.10.1630. The data was analysed and extracted using Data Viewer Software Version 3.2.

2.3.2. Procedure

Participants were first presented with a white central fixation point for 750−1000 msec, randomised to prevent anticipatory responses (see Fig. 1). Following this, the fixation point was removed and a red and green circular disk (i.e., target/distracter display 1) presented simultaneously for 1500 msec. Participants were instructed to look towards the red 'light' as quickly and accurately as they could and to ignore the green distracter 'light'. Target display 1 was then removed and the central fixation point re-appeared for a randomised interval of 750−1000 msec (fixation). Finally, a single red target was displayed for 1500 msec (target display 2). The stimulus onset asynchrony between the target display 1 and target display 2 was 2250−2500 msec. A blank interval screen was displayed for 3500 msec between trials. The red target and green distracter were position at 4° from the central fixation both at horizontal and vertical locations. The distance of the targets from the central fixation point was 8 cm. The fixation point and coloured targets measured 15 mm in diameter (visual angle, 1.56°). The mean luminance of the display targets was measured, with the red target measuring at 35.66 lux and the green target at 39.57 lux.

The timing and configurations for target display 1 were randomly selected from one of 18 displays (Fig. 1). The pairings of target display screens created three types of trials: (1) Target → Target (T1 → T2) the target on display 2 was presented at the same location of the previously displayed target in display 1. (2) Target → Distracter (T1 → D2) for this trial type the display 2 target was presented in the location of one of the previous distracter targets in display 1. (3) For the Target → New (T1 → N2) trials the display 2 target was presented in a new location, not previously occupied by the target or distracter in display 1. The task included 120 randomly mixed trials. For 50% of the trials, the target location was repeated in display 2 (T1 → T2 trials) and on 50% of the trials the target varied to the display 2 target (25% T1 → D2 +25% T1 → N2). The complete block of trials included 10 times in which the T1 → T2 was presented in each position and 5 times that the T1 → D2 and T1 → N2 were repeated in each position.

2.3.3. Data processing

EyeLink DataViewer software was used to export the raw eye tracking data and the data was analysed offline using a bespoke software SaccadeMachine (Mardanbegi et al., 2019). The software filtered out noise and spikes by removing all frames with a velocity signal greater than 1,500 deg/s or an acceleration signal greater than 100,000 deg²/sec. The fixations and saccadic events were detected by the EyeLink Parser and the saccades for each trial were extracted alongside multiple spatial and temporal variables. Saccade latency was measured from the onset of the saccade to the target offset. To avoid anticipatory and delayed saccades only saccades made in the time frame of 80−700 msec after the target onset where included in the analysis. Micro saccades that had an amplitude less than .7 deg were removed from the data. Saccade direction errors e.g., correct or incorrect were determined in relation to the target. An error was classified as an eye movement towards the distracter target in Target/distracter display 1 and an eye movement in the opposite direction of the target in Target display 2. The inclusion/exclusion criteria

for the data was determined prior to data analysis. An identical data processing procedure was conducted for experiments 1 and 2. No part of the studies procedure or analysis was pre-registered prior to the research being conducted. The data from this study is accessible via the following link https://doi.org/10.17635/lancaster/researchdata/469. In the study we report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.4. Results

Linear mixed-effects model's analyses were carried out using RStudio version 1.2.5033. The models conducted an analysis on reaction times on the T−T, T-N and T-D trial types to assess the IRD effect. The linear mixed-effects model was also used to determine the group effects of: disease, ageing, and ethnicity.

2.4.1. Cognitive assessments

An ANOVA was conducted assessing the effects of participant group on MoCA score. Table 1 shows an expected significant effect of participant group on MoCA score, $F_{(4, 237)} = 32.39$, $p < .001$, $n^2_p = .35$. As expected, the older European participants produced significantly higher MOCA scores when compared with the AD group ($F_{(1, 101)} = 62.89$, $p < .001$, $n^2_p = .38$) and the MCI group ($F_{(1, 117)} = 26.60$, $p < .001$, $n^2_p = .19$). There were no significant differences in MoCA scores between the older European healthy participants and the young European group. European older participants produced significantly higher MoCA scores compared to the south Asian older adults ($F_{(1, 106)} = 35.40$, $p < .001$, $n^2_p = .25$). This effect on the MOCA may derive from a combination of culturally sensitive test items, linguistic and other cultural-related factors.

Table 1 reveals that there was a significant effect of participant group on digit span score on the forwards ($F_{(4, 197)} = 6.65$, $p < .001$, $n^2_p = .12$) and backwards ($F_{(4, 197)} = 12.20$, $p < .001$, $n^2_p = .25$) versions of the task. Post hoc comparisons revealed that on the digit span tasks, the older European participants yielded significantly higher task scores compared to the south Asian participants for the forwards ($F_{(1, 103)} = 14.69$, $p < .001$, $n^2_p = .12$) and backwards version ($F_{(1, 103)} = 26.96$, $p < .001$, $n^2_p = .20$). On the backwards version of the task as expected the AD group displayed significantly lower task scores compared to the older European participants ($F_{(1, 98)} = 8.76$, $p = .004$, $n^2_p = .08$) although interestingly there was no significant difference on the forwards' version of the task (Table 1). This pattern of results was also repeated for the MCI group, who also differed from the European participants in the backwards ($F_{(1, 113)} = 5.43$, $p = .021$, $n^2_p = 05$.), but not on the forwards' version of the digit span task. This highlights the vulnerability of working memory in dementia rather than memory span per se. No significant differences were found in digit span scores between the other participant groups.

There was an overall significant effect of participant group on spatial span task score for the forwards ($F_{(4, 187)} = 12.58$, $p < .001$, $n^2_p = .21$) and backwards ($F_{(4, 187)} = 17.71$, $p < .001$, $n^2_p = .27$) versions of the task. As expected, AD participants yielded lower spatial memory scores compared to older

Table 1 – Means, standard deviations and post hoc contrasts for MoCA, Digit Span and Spatial span scores for all participant groups in experiment 1.

| | Older European participants | | Older South Asian participants | | Alzheimer's Disease | | MCI | | Young European participants | | Post Hoc Contrasts (P values) | | | | |
| | | | | | | | | | | | Disease | | | Age | Ethnicity |
	M	SD	M	SD	M	SD	M	SD	M	SD	AD versus EP	AD versus MCI	MCI versus EP	EP versus YCP	EP versus OSP
MoCA Score	27.25	2.99	22.64	4.71	19.86	5.39	22.98	5.27	28.16	1.85	<.001[a]	.037[a]	<.001[a]	.066	<.001[a]
Digit Forward	10.54	2.56	8.54	2.07	9.84	2.44	10.02	2.30	11.53	2.34	.678	.764	.262	.341	<.001[a]
Digit Backward	7.24	2.82	4.39	1.82	5.38	2.54	6.02	2.41	8.33	2.50	.004[a]	.304	.021[a]	.234	<.001[a]
Spatial Forward	7.18	1.38	6.67	1.14	5.96	1.89	6.78	1.78	8.60	1.10	.001[a]	.078	.194	<.001[a]	.570
Spatial Backward	6.65	1.50	6.21	1.18	5.46	2.31	6.05	1.75	8.70	1.20	.005[a]	.243	.074	<.001[a]	.776

Note. Dependent variable: Task score.
AD–Alzheimer's disease; MCI–mild cognitive impairment; EP–older European participants; OSP- older south Asian participants. YCP–young European participants.
[a] Significant at p < .05 level.

European participants on the forwards (F (1, 90) = 11.75, $p = .001$, $n^2{}_p = .12$) and backwards (F (1, 90) = 8.45, $p = .005$, $n^2{}_p = .09$) versions of the task (Table 1). Young European participants produced significantly higher spatial span scores compared the older European participants on both the forwards (F (1, 94) = 24.52, $p < .001$, $n^2{}_p = .21$) and backwards versions (F (1, 94) = 42.98, $p < .001$, $n^2{}_p = .31$). No significant differences were found between the other participant groups.

2.4.2. Eye tracking data

The eye-tracking data was analysed using linear mixed-effects models comparing the effects of participants group on reaction times for the three trial types: TT, TN and TD. Comparisons were conducted to explore the effects of ageing, ethnicity and disease.

2.4.2.1. THE INHIBITION OF A RECENT DISTRACTER EFFECT (IRD). The groups were first examined to determine whether the IRD was evident in each of the participant groups. Fig. 2 confirmed that this was indeed the case. The mean saccade reactions times significantly increased on TD compared to TT trials: AD (37 msec), MCI (30 msec), EP (25 msec), OSP (43 msec), YC (13 msec) ($\beta = -10.26$, t (13,497) = -5.78, $p < .001$). Saccadic reaction times were also significantly longer on TD trials compared to TN ($\beta = -11.27$, t (13,497) = -6.56, $p < .001$) (Fig. 2). Clearly, the participants were slower in directing their gaze towards the target on display 2 when it was positioned at the location of the distracter target on display 1. There was no significant difference in the mean reaction times for the TN and TT trials ($\beta = 1.01$, t (13,497) = .50, $p = .615$).

An analysis was conducted to explore the size of the effect across the groups. The mean reaction times for the TN trials were subtracted from the TD trials mean to provide an IRD score for each participant. To explore the facilitation effect, the TT mean reaction times were subtracted from the TN mean reaction times (Table 2). The analyses revealed that there were no significant effects of the participant group on the IRD score or facilitation (Table 2).

2.4.2.2. OVERALL SACCADE REACTION TIMES: AGEING EFFECTS. Overall saccade times for the older European participants were contrasted with the young European participants to determine the effects of healthy ageing. The analyses revealed a significant ageing effect (Fig. 2) with older participants yielding longer mean reaction times across the three trial types, compared to the young participants (TT = -26 msec, TN = -28 msec, TD = -38 msec).

2.4.2.3. OVERALL SACCADE REACTION TIMES: DISEASE EFFECTS. We contrasted the AD, MCI and older European groups to examine the effect of Alzheimer's disease on the mean reaction times. The results (Table 3) revealed a significant group effect between the AD participants and older European participants: with AD participants had significantly longer reaction times across the three trial types (34 msec). AD participants also had longer reaction times compared to the MCI participants across the three trial types. The MCI participants had significantly longer reaction times on the TT, TN and TD trials with an average increase in reaction times of 18 msec compared to older European participants.
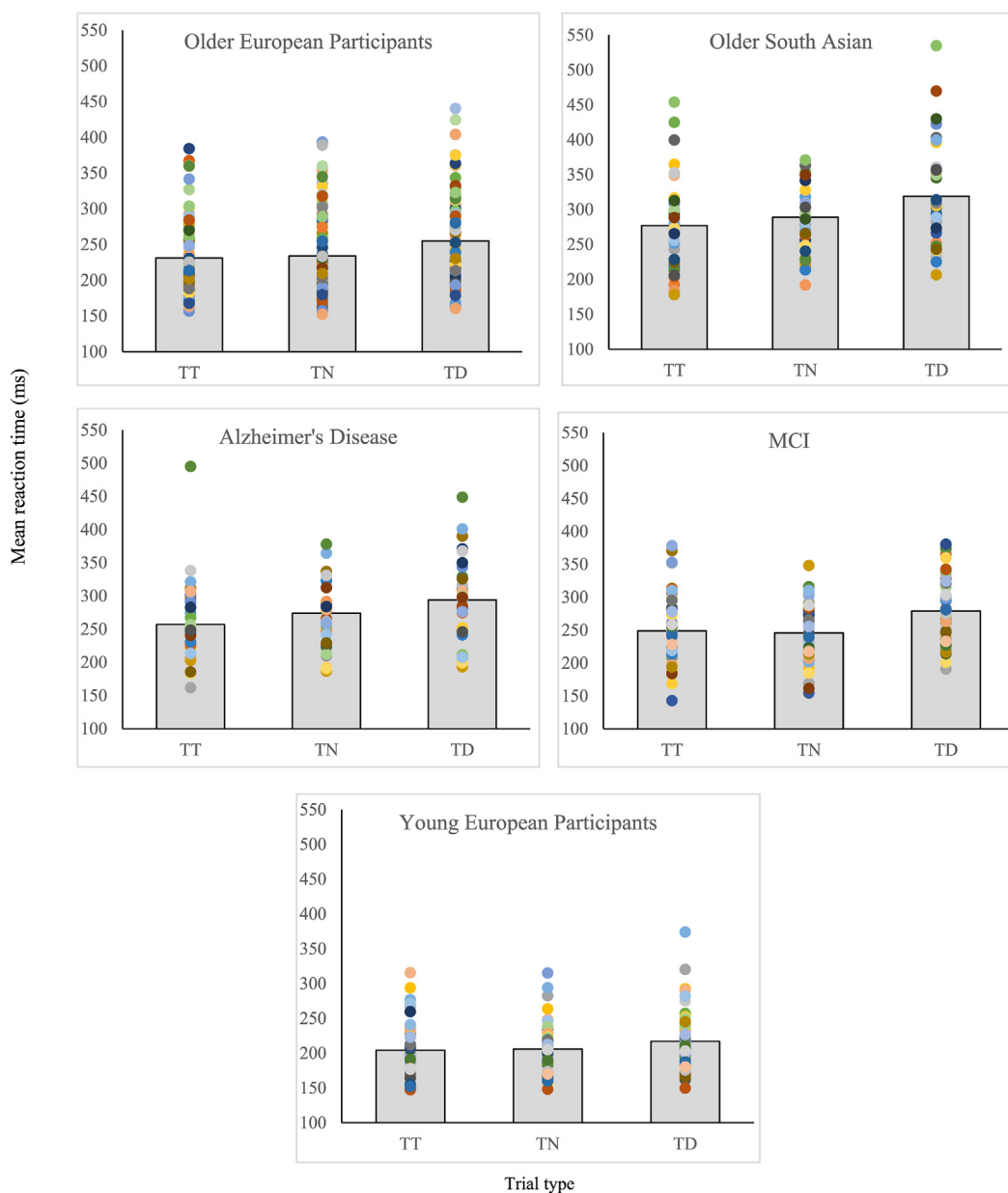
Fig. 2 — Mean reaction times and individual participant RTs on target to target, target to new and target to distracter trials for participant groups.

2.4.2.4. OVERALL SACCADE REACTION TIMES: ETHNICITY EFFECTS. In comparison to the older European participants, the south Asian participants revealed significantly longer reaction times across the three trial types (52 msec increase in overall reaction times, Table 3).

2.4.2.5. PERCENTAGE ERROR RATES. The mean percentage error rates were derived from saccade direction errors to the green distracter (rather than the red target) in display 1. As expected, the young European participants generated significantly fewer errors compared to the AD group ($\beta = -10.08$, t (131) $= -2.12$, $p = .036$). The young European group also generated significantly fewer errors compared error than the older South Asian

group. There were no significant differences between the young and older European participants (Table 4). The results revealed a significant increase in the errors generated by the AD compared to the MCI group ($\beta = -9.42$, t (131) $= -2.18$, $p = .031$). No significant differences were found between the other participant groups (Table 4).

2.5. Discussion

The IRD requires the participant to program a saccade towards the singleton target and to inhibit the distracter. This yields a significantly longer response time to a new target that is presented at the distracter location shortly afterwards.

Table 2 – Reaction time means and post hoc contrasts for the inhibition and facilitation effect on the IRD1.

	Older European participants		Older South Asian participants		Alzheimer's Disease		MCI		Young European participants		Post Hoc Contracts (P values)				
											Disease			Age	Ethnicity
	M	SD	M	SD	M	SD	M	SD	M	SD	AD versus EP	AD versus MCI	MCI versus EP	EP versus YCP	EP versus OSP
Inhibition Effect (TD-TN)	21.57	28.99	30.61	57.27	19.74	46.14	32.86	25.81	11.11	23.92	.999	.168	.051	.466	.726
Facilitation Effect (TN-TT)	2.99	31.37	11.94	45.46	17.37	52.71	-3.01	44.30	1.57	28.18	.344	.059	.356	1.00	.769

Note. Dependent variable: mean reaction time difference.
AD—Alzheimer's disease; MCI—mild cognitive impairment; EP—older European participants; OSP- older south Asian participants. YCP–young European participants.
*Significant at p < .05 level.

Thus, in the healthy participants, there was an inhibitory carry-over from the previous trial, that results in the slowing of gaze towards the distracter location in the subsequent trial. Crawford, Hill & Higham (2005) report that this inhibition remains active between 2 and 5 sec after the target is removed. The current study investigated whether this effect was preserved in people with dementia, across ageing and different cultural/ethnic groups. The results revealed that the IRD was clearly evident across all the participant groups. The south Asian participants revealed the largest slowing on the TD versus TT trials, whilst the young European participants showed the smallest effect of trial type. Although differences were detectable in the baseline saccade latencies, there were no significant effects of disease, ageing and ethnicity/culture on the magnitude of the IRD effect.

3. Experiment 2

Experiment 1 replicated the previous research (Crawford, Hill & Higham, 2005; Wilcockson, Mardanbegi, Sawyer, et al., 2019) and revealed that the IRD effect is robust across both age, culture and cognitive impairment. Nonetheless, given the previous reports of the impairment of inhibitory control on the anti-saccade task (Boxer et al., 2012; Crawford et al., 2019) it is curious that the participants with MCI and AD revealed a similar pattern of distracter inhibition as the age-matched healthy participants. The results from experiment 1 reveals that the suppression of a visual distracter is distinct from the inhibitory operations, of the anti-saccade task. Alternatively, it may be that the inhibitory load was not sufficiently demanding in this task. Therefore, in experiment 2 the distracter load was increased by employing two distinct colour distracters that were presented simultaneously with the target (Fig. 3). The experiment aimed to determine whether an increase in the inhibitory load will perturb the IRD and to what extend will this more challenging version of the IRD moderate any effects of ageing, ethnicity or disease.

3.1. Materials and methods

3.1.1. Participants
Experiment 2 included 27 young (mean age = 24 years, SD = 5 years) and 18 older European participants (mean age = 69 years, SD = 7 years), 48 south Asian participants (mean age = 67 years, SD = 6 years), 32 AD participants (mean age = 72, SD = 7 years) and 39 MCI (mean age = 71 years, SD = 6 years) participants.

3.1.2. Procedure
Participants were required to complete three cognitive assessments and the eye tracking task as in experiment 1. Participants completed the MoCA, digit span task and spatial span task both forwards and backwards versions (see experiment 1 above). The key distinctive feature here was an additional distracter target which aimed to increase the inhibitory control demand and the difficulty of the task (see Fig. 3). Participants were presented first with a white central fixation target and instructed to fixate on the centre marker.

Table 3 – Mean reaction times and standard deviations and post hoc comparisons for the IRD1 for the TT, TN and TD trials in msec.

| | Older European participants | | Older South Asian participants | | Alzheimer's Disease | | MCI | | Young European participants | | Post Hoc Contracts (P values) | | | | |
| | | | | | | | | | | | Disease | | | Age | Ethnicity |
	M	SD	M	SD	M	SD	M	SD	M	SD	AD versus EP	AD versus MCI	MCI versus EP	EP versus YCP	EP versus OSP
TT	231	50.10	277	66.87	257	62.99	249	51.21	204	38.52	<.001[a]	.028[a]	.034[a]	<.001[a]	<.001[a]
TD	255	56.63	319	77.48	294	62.15	279	51.10	217	43.33	.001[a]	.005[a]	<.001[a]	<.001[a]	<.001[a]
TN	234	50.94	289	45.20	274	51.61	246	43.14	206	36.09	<.001[a]	.002[a]	.034[a]	<.001[a]	<.001[a]

Note. Dependent variable: Reaction time.
AD—Alzheimer's disease; MCI—mild cognitive impairment; EP—older European participants; OSP- older south Asian participants. YCP—young European participants.
[a] Significant at $p < .01$ level.

Table 4 – Means, standard deviations and post hoc contrasts for percentage error rates on target-display screen 1.

| | Older European participants | | Older South Asian participants | | Alzheimer's Disease | | MCI | | Young European participants | | Post Hoc Contracts (P values) | | | | |
	M	SD	M	SD	M	SD	M	SD	M	SD	AD versus EP	Disease AD versus MCI	MCI versus EP	Age EP versus YCP	Ethnicity EP versus OSP
% Error Rate	16.63	21.11	20.20	19.39	18.44	18.11	9.03	14.39	8.09	11.06	.757	.029[a]	.137	.102	.554

Note. Dependent variable: percentage error rate.
AD—Alzheimer's disease; MCI—mild cognitive impairment; EP—older European participants; OSP- older south Asian participants. YCP—young European participants.
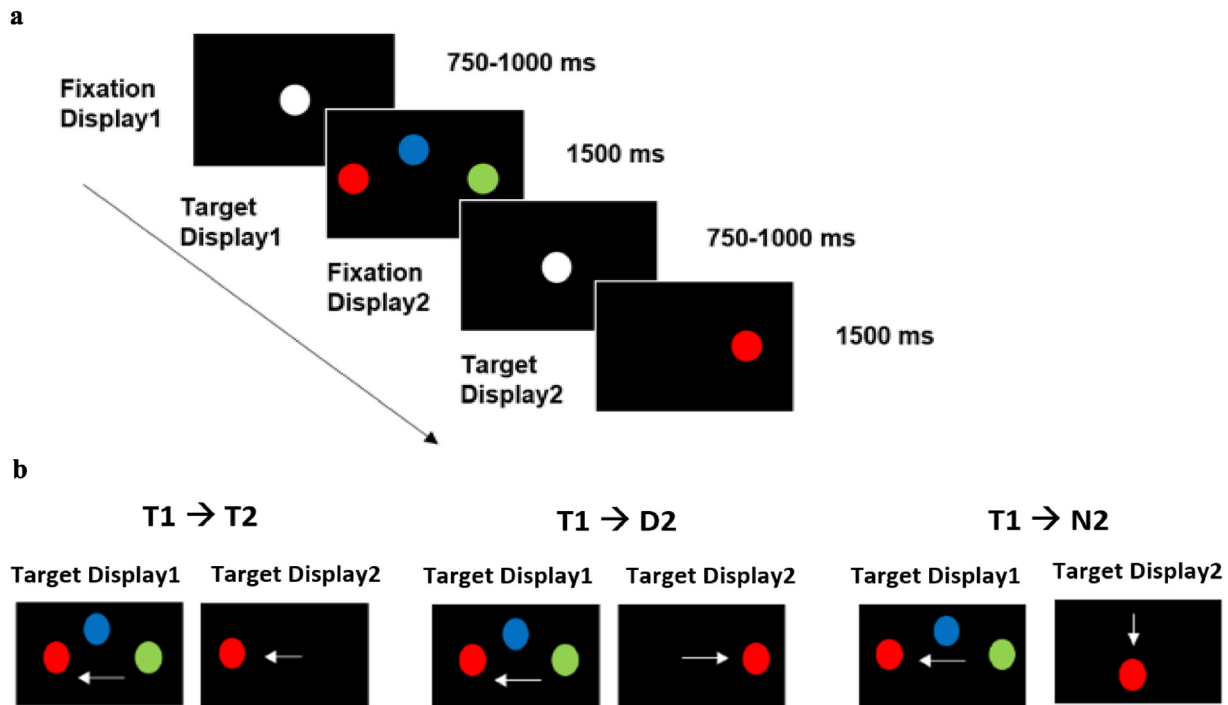[a] Significant at $p < .05$ level.

a

b

Fig. 3 — a. Timings and sequence of the IRD in experiment 2. b. Example of the three trial variations in the IRD2. The locations of the green, red and blue targets on display screen 1 varied throughout the task.

Following this, a red, green and a blue circular disk appeared simultaneously (target display 1). A second central fixation was then displayed, followed by a single red target (target display 2). Participants were instructed to look towards the red "light" and to ignore the green and the blue "lights". The single red target was presented at one of three locations: the location of the target on the previous display 1 screen (T1 → T2), location of the green distracter target on the previous screen (T1 → D2) or at a new location not previously occupied by the target or distracter on target display 1 (T1 → N2). The blue distracter target was positioned 4° from the central fixation both at horizontal and vertical locations (see Fig. 3). The timing and parameters for this IRD task were identical to the experiment 1 task. The luminance of the blue display target measured at 36.81 lux.

3.2. Results

The analyses conducted for experiment 2 were consistent with the procedures used in experiment 1. One participant was removed from the older European adult group due to their mean reaction times being greater than 2 standard deviations from the mean.

3.2.1. Cognitive assessments

An ANOVA was conducted to examine the effect of participant group on the MoCA scores. The results revealed a significant effect of participant group $F (4, 132) = 23.105, p < .001, n^2_p = .41$) (Table 6). As expected, the AD group ($F (1, 38) = 35.59, p < .001, n^2_p = .48$) and MCI group ($F (1, 37) = 13.29, p = .001, n^2_p = .26$) scores were significantly lower on the

MoCA than the older European participants. There was a significant difference between MCI and AD performance on the MoCA ($F (1, 41) = 8.85, p = .005, n^2_p = .18$). There was no difference in task scores between the European healthy older participants and the young participants. The European older participants generated significantly higher scores on the MoCA than the south Asian participants ($F (1, 66) = 29.15, p < .001, n^2_p = .31$).

On the Digit Span task, there was a significant effect of participant group on both the forwards ($F (4, 159) = 14.34, p < .001, n^2_p = .27$) and backwards ($F (4, 159) = 10.45, p < .001, n^2_p = .21$) versions of the task. For the forwards ($F (1, 48) = 7.76, p = .008, n^2_p = .14$) and backwards $F (1, 48) = 15.10, p < .001, n^2_p = .24$) version of the task there was a disease effect, as expected the AD participants had lower memory scores than the older European participants. An ethnicity effect was also revealed; the European older participants generated higher scores on the task than south Asian older adults for both the forwards ($F (1, 66) = 44.87, p < .001, n^2_p = .40$) and backwards version ($F (1, 66) = 27.96, p < .001, n^2_p = .30$). No effect of healthy ageing (young *vs* older Europeans) was found on the digit span task.

The Spatial Span task revealed a significant effect of participant group on the forwards ($F (4, 148) = 14.98, p < .001, n^2_p = .29$) and backwards ($F (4, 148) = 11.53, p < .001, n^2_p = .24$) task. The AD participants, as expected, had reduced spatial span scores compared to the older European participants on both the forwards ($F (1, 43) = 11.54, p = .001, n^2_p = .21$) and backwards ($F (1, 43) = 8.13, p = .007, n^2_p = .16$) versions of the task. There was an effect of ethnicity on the backwards version of the task ($F (1, 64) = 9.01, p = .004, n^2_p = .12$), but not on the forwards' version of the task. No effect of healthy

Table 5 – Means and standard deviations and post hoc comparisons for task score on the MoCA, digit Span and Spatial Span for all participant groups in experiment 2.

| | Older European participants | | Older South Asian participants | | Alzheimer's Disease | | MCI | | Young European participants | | Post Hoc Contracts (P values) | | | | |
| | | | | | | | | | | | Disease | | | Ageing | Ethnicity |
	M	SD	M	SD	M	SD	M	SD	M	SD	AD versus EP	AD versus MCI	MCI versus EP	EP versus YCP	EP versus OSP
MoCA Score	27.72	1.78	21.26	4.94	20.64	4.77	24.43	3.46	28.50	1.18	<.001*	.005*	.001*	.398	<.001*
Digit Forward	12.39	2.38	8.58	1.95	10.31	2.61	10.62	2.44	11.89	2.14	.008*	.613	.018*	.951	<.001*
Digit Backwards	8.33	2.59	4.80	2.37	5.50	2.41	6.19	2.48	7.63	2.45	<.001*	.248	.005*	.787	<.001*.
Spatial Forward	7.39	1.38	6.52	1.24	5.93	1.44	6.45	1.30	8.44	1.42	.001*	.141	.014*	.077	.136
Spatial Backwards	7.28	2.14	5.73	1.76	5.59	1.80	5.48	1.73	8.04	1.70	.007*	.815	.003*	.637	.004*

Note. Dependent variable: Task score.
AD—Alzheimer's disease; MCI—mild cognitive impairment; EP—older European participants; OSP- older south Asian participants. YCP—young European participants.
Significant at *p* < .05 level.

Table 6 – Reaction times means, standard deviations and post hoc contrasts for the inhibition and facilitation effect on the IRD2.

| | Older European participants | | Older South Asian participants | | Alzheimer's Disease | | MCI | | Young European participants | | Post Hoc Contracts (P values) | | | | |
| | | | | | | | | | | | Disease | | | Age | Ethnicity |
	M	SD	M	SD	M	SD	M	SD	M	SD	AD versus EP	AD versus MCI	MCI versus EP	EP versus YCP	EP versus OSP
Inhibition Effect (TD-TN)	4.54	21.56	3.12	34.26	10.99	26.23	11.59	35.17	4.71	16.81	.946	.937	.305	1.00	1.00
Facilitation Effect (TN-TT)	9.50	39.93	17.41	40.87	14.88	41.83	9.33	44.86	7.84	38.93	.990	.597	.972	1.00	.949

Note. Dependent variable: Mean reaction times difference.
AD—Alzheimer's disease; MCI—mild cognitive impairment; EP—older European participants; OSP- older south Asian participants. YCP—young European participants.
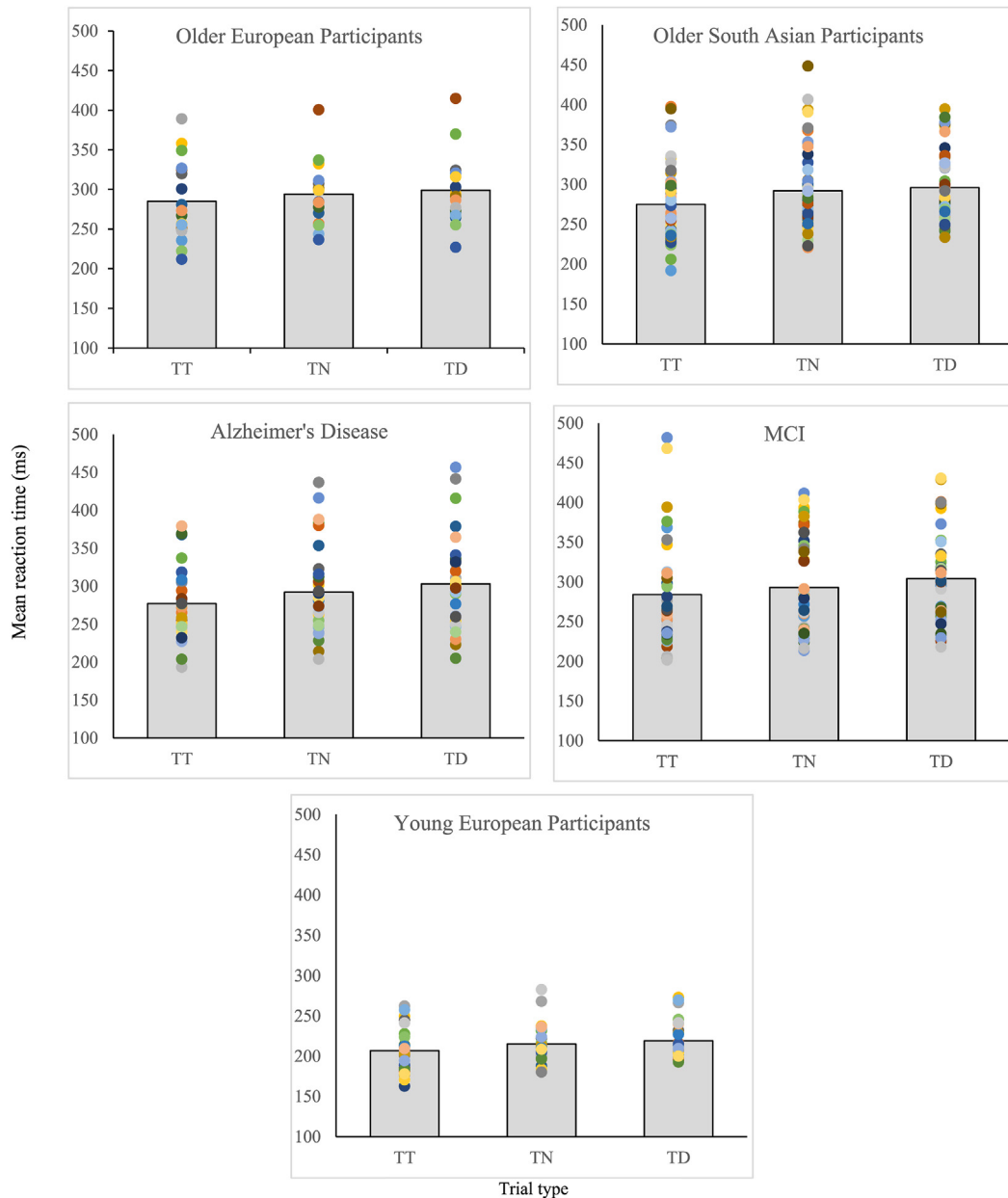*Significant at *p* < .05 level.

Fig. 4 – **Mean reaction times and individual participant RTs on target to target, target to new and target to distracter trials for participant groups.**

ageing (young *vs* older Europeans) was found for the spatial span task (Table 5).

3.2.2.   *Eye tracking data*

3.2.2.1. THE INHIBITION OF RECENT DISTRACTER EFFECT (IRD). The results revealed a significant effect of trial type on the mean reaction times. Participants were slower at directing their gaze towards the target in display 2 (TD) when it was located in the position of the previous distracter (Fig. 4) compared the location of the previous target ($\beta = -12.26$, t (16,789) $= -7.55$, $p < .001$), with an increase in mean RT on TD trials for each group, AD (26 msec), MCI (21 msec), EP (14 msec), OSP (21 msec) & YC (13 msec). The young participants displayed

significantly faster reaction times on the three trial types compared to the older participants. There were no significant group effects between the other participant groups.

The mean reaction times for the TN trials were subtracted from the TD trials mean to provide an IRD score for each participant. To explore a potential facilitation effect, the TT mean reaction times were subtracted from the TN mean re-action times. The results revealed no significant difference between participant groups for the IRD score, F (4, 158) $= .655$, $p = .624$, $\eta^2_p = .016$ or facilitation scores, F (4, 158) $= .401$, $p = .808$, $\eta^2_p = .01$. Overall, the participant groups revealed a similar relative difference in the reaction times between the target-distracter conditions (Table 6).

3.2.2.2. OVERALL SACCADE REACTION TIMES: AGEING EFFECTS. The results revealed that there was a significant effect of age between the healthy European older participants and the young participants (Fig. 4). Young participants displayed significantly faster mean reaction times compared to the older European participants (TT = −78 msec, TN = - 79 msec, TD = − 79 msec).

3.2.2.3. OVERALL SACCADE REACTION TIMES: ETHNICITY EFFECTS. No significant differences in mean reaction times were found between older European participants and the older south Asian participants (Table 7).

3.2.2.4. OVERALL SACCADE REACTION TIMES: DISEASE EFFECTS. There was no significant difference between the mean reaction times for the older European participants and the MCI and AD group (Table 7).

3.2.2.5. PERCENTAGE ERROR RATES. An analysis was conducted to explore the effect of participant group on the proportion of erroneous saccades towards the distracters. An error was classified as a primary saccade in the direction of either of the distracter target on display 1. Comparisons between the participant groups revealed no significant differences in error rates (Table 8).

3.2.3. *Comparison of IRD effect in IRD1 and IRD2*

Several previous studies (Hulleman, 2010; Kazanovich & Borisyuk, 2017; Palmer et al., 2011; Proulx & Egeth, 2006; Wolfe, 2007) have shown that reaction times increase to a greater or lesser extent with increasing number distracters in the display. Therefore, we felt it was important to explore to a limited extent whether an increase in the competing distractor would enhance or interact with inhibitory control in the IRD task. In order to explore the impact of the additional distractor on the inhibitory controls demands of the task, we ran an ANOVA analysis comparing the reaction times, inhibition effect sizes and error rates between IRD experiment 1 and IRD experiment 2. There was a main effect of distractor condition (TT, TN, TD trial type) on reaction times across both experiments ($F (2, 433) = 17.16$, $p < .001$, $n^2_p = .039$). As expected, reaction times were longer on the TD trials compared to the TT trials. There was a significant main effect of experiment $F (1, 433) = 16.30$, $p < .001$, $n^2_p = .037$) with IRD experiment 2 producing higher RTs on all trial conditions. There was no interaction between the distractor condition and experiment ($F (1, 433) = 3.50$, $p = .062$, $n^2_p = .008$). Therefore, this data reveals that the additional distractor in IRD2 increased the overall difficulty of the task.

However, we explored whether the additional distractor also increased the level of the inhibitory demand. This was clearly not the case. To the contrary, the inhibition effect was actually significantly larger on experiment 1 than experiment 2 ($F (1, 433) = 22.30$, $p < .001$, $n^2_p = .05$) (Table 9). Experiment 1 with just a single distractor elicited a stronger inhibitory control demand than experiment 2 with two distractors. It appears that a single distracter generated a stronger effect due to the increased saliency of the singleton distractor. In

Table 7 – Mean reaction times, standard deviations and post hoc comparisons for the TT, TN and TD trials.

| | Older European participants | | Older South Asian participants | | Alzheimer's Disease | | MCI s | | Young European participants | | Post Hoc Contrasts (P values) | | | | |
| | | | | | | | | | | | Disease | | | Age | Ethnicity |
	M	SD	M	SD	M	SD	M	SD	M	SD	AD versus EP	AD versus MCI	MCI versus EP	EP versus YCP	EP versus OSP
TT	285	48.59	275	48.59	277	44.94	284	66.83	207	26.64	.222	.089	.867	<.001[a]	.467
TD	299	43.13	296	45.94	303	60.77	304	59.78	219	23.12	.432	.899	.490	<.001[a]	.806
TN	294	38.41	292	51.21	292	57.38	293	61.61	215	23.06	.243	.919	.275	<.001[a]	.886

Note. Dependent variable: Reaction time.
AD–Alzheimer's disease; MCI–mild cognitive impairment; EP–older European participants; OSP- older south Asian participants. YCP–young European participants.
[a] Significant at $p < .05$ level.

Table 8 — Means, standard deviations and post hoc contracts for percentage error rates on target display 1 on the IRD2.

| | Older European participants | | Older South Asian participants | | Alzheimer's Disease | | MCI | | Young European participants | | Post Hoc Contracts (P values) | | | | |
| | | | | | | | | | | | Disease | | | Age | Ethnicity |
	M	SD	M	SD	M	SD	M	SD	M	SD	AD versus EP	AD versus MCI	MCI versus EP	EP versus YCP	EP versus OSP
% Error Rate	15.23	20.17	14.07	12.22	21.88	25.43	14.53	14.11	4.36	3.78	.117	.136	.889	.092	.782

Note. Dependent variable: percentage error rate.
AD—Alzheimer's disease; MCI—mild cognitive impairment; EP—older European participants; YCP—young European participants. YCP—young European participants. OSP- older south Asian participants.
*Significant at p < .05 level.

Table 9 — Mean values for the inhibition and facilitation effects, error rates and reaction times on the IRD1 and IRD2.

	IRD1	IRD2
Inhibition effect (TD-TN)	24.19	5.88
Facilitation effect (TN-TT)	2.52	12.73
Error rates	14.48	15.70
TT Reaction time (msec)	240	267
TN Reaction time (msec)	242	280
TD Reaction time (msec)	267	286

contrast the analysis of the facilitation effect, revealed a larger effect in experiment 2 compared to experiment 1 (F (1, 433) = 6.05, p = .014, n^2_p = .01). Error rates were also compared between the experiments, with no significant differences were found (F (1, 285) = .334, p = .564, n^2_p = .001). Thus, although the additional distractor appears to generate significantly longer reaction times in experiment 2, the evidence does not show a change in the inhibitory control demands.

3.3. Discussion

Experiment 1 explored the effects of disease, ageing and ethnicity on the IRD. Experiment 2 aimed to increase the inhibitory load of the IRD task to determine whether this would reveal a change in the effect, particularly in the cognitively impaired groups however results revealed this increase in inhibitory control in the IRD2 was not evident. The results revealed that a strong IRD effect was evident in all the participants' groups, and across both of the experiments.

The IRD clearly requires a form of implicit representation or memory that tags the location of an irrelevant distracter across consecutive displays. Crawford, Hill and Higham (2005) established that this representation was based on the spatial location of the distracter, and not some other coincidental feature, such as its colour. Critically the inhibitory impact of the distracter is relatively long-lasting (2–5 sec). IRD was originally reported in young, healthy university students, and is remarkably robust and well-preserved in atypical participants (e.g., dyslexia, Wilcockson, Mardanbegi, Sawyer, et al., 2019) and with both simple shapes as well as naturalistic stimuli (Donovan et al., 2012). The current work demonstrates the validity of IRD across age groups, ethnicity and cognitive impairment. Although the neural correlates of the IRD are yet to be explored, the effect is consistent with models of visual orienting which feature competitive interactions between the target and a distracter (e.g., Duncan et al., 1997; Trappenberg et al., 2001).

Given the pervasive and progressive nature of the cognitive impairments, it is remarkable that the IRD is so well preserved in AD and MCI participants. This presents a stark contrast with previous research with AD participants using the anti-saccade task (Crawford, Higham et al., 2005, Crawford et al., 2013, 2019; Boxer et al., 2012; Noiret et al., 2018; Wilcockson, Mardanbegi, Xia, et al., 2019). In the anti-saccade task, participants' are required to look away from the prepotent target, to the opposite side of the display. It has been extensively used as a method to examine inhibitory control in both healthy adults and clinical

populations (Broerse et al., 2001; Hutton & Ettinger, 2006; Crawford et al., 2015; Crawford et al., 2017). Patients generate a high proportion of erroneous saccade towards the prepotent target and fail to self-correct many of these errors, consistent with an impairment of inhibitory control and error monitoring. This impairment correlated with the severity of dementia (Crawford, Higham et al., 2005; Faust, 1997). When healthy adults make errors on the task, they are quickly corrected and are very rarely left uncorrected. Our lab has recently demonstrated that these errors are more prominent in amnesic MCI in comparison to non-amnesic MCI participants (Wilcockson, Mardanbegi, Xia, et al., 2019). The key aspect of this finding is linked to the fact that people with Amnesic MCI are at an increased risk of progressing to develop dementia in the future (Fischer et al., 2007; Ward et al., 2013; Yaffe et al., 2006). Inhibitory control is clearly not a unitary concept and has multiple forms that can be dissociated at many levels of the visuomotor control networks. The IRD and the anti-saccade tasks clearly do not target identical inhibitory control mechanisms. The anti-saccade task focuses on gaze aversion requiring an eye movement directed away from the target. The motor requirement to generate an anti-saccade eye movement is not present in the IRD. The IRD uses a distracter that competes with the target to generate inhibition at the spatial location of the distracter, a key distinction from the anti-saccade task. This competition for attention is a significant factor for inhibition of the distracter and has been demonstrated in multiple negative priming studies. Research has shown that the distracter in the probe display in addition to the prime displays is also required for object inhibition (Donovan et al., 2012). In a series of experiments Donovan et al. (2012) demonstrated that when there is no competing distracter in the probe display, there was a lack of negative priming for the visual objects and no inhibition to the location of the distracter. Crawford, Hill and Higham (2005) demonstrated that the anti-saccade task per se does not generate spatial inhibition of the distracter, as witnessed in the IRD. Together, these findings demonstrate that the fundamental nature of the IRD "inhibition" is quite distinct from the top–down processes of the anti-saccade task. The current study undermines the idea that uncorrected errors and deficits demonstrated on the anti-saccade task are due primarily to a failure to inhibit a distracter target and the inhibition appears to be linked to top-down inhibitory control and working memory capabilities (Crawford, Higham et al., 2005; Crawford et al., 2013).

3.3.1. Ageing

Another key finding was a clear effect of age on the mean saccadic reaction times for both versions of the IRD. Although the IRD effect was present in the European older adults, the young adults revealed significantly faster saccadic reaction times on the three trial types. This indicates an overall slowing in prosaccade eye movements during natural ageing. This is consistent with previous research and demonstrates that eye movements are susceptible to ageing effects, in particular to reductions in processing speed, inhibitory control and spatial memory (Crawford et al., 2017; Peltsch et al., 2011; Salthouse, 1996, 2009).

3.3.2. Ethnicity

As previously stated, the European and South Asian older adults both demonstrated the IRD effect, with a slowing in reaction times when the target was presented in the location of a previous distracter. Experiment 1 revealed significant differences in mean reactions time between the groups with faster reaction times for the European group across the three trial types. Interestingly, this difference was not evident using the double distracter display in experiment 2. The differences were present on the three trials types demonstrating that this may be due to baseline differences in the prosaccade eye movements. Previous research has uncovered clear differences in eye movements across ethnic and cultural groups (Alotaibi et al., 2017; Knox et al., 2012; Rayner et al., 2007). Differences in scanning patterns between native Chinese and native English-speaking participants were reported using visual scenes (Chua et al., 2005). English participants focused on the foreground objects and showed an increased number of fixations than Chinese participants who often focused on the background areas of the scene demonstrating clear strategy differences. Evidently, specific features of eye movement control are subject to the influence of culture and ethnicity.

Knox and Wolohan (2014) explored whether the variations in saccadic eye movements were due to culture or culture-unrelated factors. This study examined saccades in Chinese, European and UK born Chinese participants with similar cultural experiences to the European group. Interestingly, the Chinese participants showed similar eye movement patterns regardless of cultural experience demonstrating that culture must not be the primary cause of variations in oculomotor processes. These variations in oculomotor characteristics may result from a combination of genetic, environmental and epigenetic factors (Kim et al., 2010; Mardanbegi et al., 2020). A recent study demonstrated clear differences in post-saccadic oscillations between UK-born adults and Chinese-born adults. It was concluded that "… genetic, racial, biological and/or cultural difference can affect the morphology of the eye movement data recorded" (Mardanbegi et al., 2020). These factors should be considered when assessing eye movement saccades and fixations. Research involving South Asian populations is clearly lacking and future research should attempt to address this void leading to a deeper understanding of eye movement variations that are attributable to ethnicity and culture.

4. Conclusions

Traditionally in this field, scientists have focussed primarily on the mnemonic and cognitive skills that degenerate in AD and understandably have paid less attention to those equally important cognitive functions that may be well preserved. We suggest that a similar research priority should be aimed at the cognitive operations that may be preserved in the disease as this will help to develop potential new early intervention strategies for the treatment of the disease, that will improve cognitive functions and hopefully delay the

progression of the disease. This study has demonstrated that inhibition of a distracter is preserved in people with early and chronic AD. The current evidence on preservation of the IRD will aid our understanding of oculomotor impairment in AD and MCI, in particular, the specificity of inhibitory control deficits.

Author contributions

Conceptualization, methodology, software, validation, investigation, writing, review and editing, contributions and project administration contributions were made by T.C., and M.P. The formal analysis, data curation, writing, original draft preparation contributions were made by T C. and M.P. Supervision and funding acquisition were conducted by T.C. All authors read and agreed to the published version of the manuscript.

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Open practices

The study in this article earned an Open Data badge for transparent practices. Data for this study are available at https://doi.org/10.17635/lancaster/researchdata/418.

Declaration of competing interest

The authors declare no conflict of interest.

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4.1 Statement of thesis continuous commentary

Chapter 4 demonstrated the robustness of the IRD effect and provided evidence for a dissociation between general gaze aversion as seen in the antisaccade task and inhibition of a specific distracter. Chapter 5 continued to assess eye movements in relation to disease and ageing effects. Chapter 4 indicated that prosaccades and inhibitory control processes were comparable between healthy older adults and people with AD and MCI, however, research has indicated that differences may be evident when assessing the level of attentional fluctuations during these tasks (Yang et al., 2013). Chapter 5 used coefficient of variation measures in order to assess attentional fluctuations on prosaccade and antisaccade tasks. Coefficient of variation scores were assessed in healthy older adults, AD populations and MCI subgroups. The sensitivity of the measure was assessed and its potential to reliably distinguish populations with cognitive impairment.

Chapter 5

Paper three: Eye Movement Latency Coefficient of Variation as a Predictor of Cognitive Impairment

Polden, M., and Crawford, T.J

Abstract

Numerous studies have demonstrated abnormal saccadic eye movements in Alzheimer's disease (AD) and people with mild cognitive impairment (MCI) when performing prosaccade and antisaccade tasks. Research has shown pro and antisaccade latencies can predict cognitive ability and can indicate executive functioning deficits. These tasks show potential for diagnostic use, however certain markers, such as coefficient of variation have not been fully investigated. For biological markers to be reliable they must be able to detect abnormalities in preclinical stages of the disorder. MCI is often viewed as a predecessor to AD with certain classifications of MCI more likely than others to progress to AD. The current study examined the potential of coefficient of variation scores on pro and antisaccade tasks to distinguish participants with AD, amnestic MCI (aMCI), non-amnesiac MCI (naMCI) and healthy older controls. No significant differences in coefficient of variation scores were found across the groups on the antisaccade task, however coefficient of variation scores on the prosaccade task showed promising results in distinguishing people with MCI from older controls. MCI groups showed higher CV scores indicating greater attentional fluctuation when compared with older controls. Interestingly, this distinction was not found in the AD group. Antisaccade mean latencies were able to robustly distinguish participants with AD and between the MCI subgroups showing high sensitivity. Future research is needed into coefficient of variation measures and attentional fluctuations in AD and MCI individuals to fully assess the measures potential to robustly distinguish clinical groups with high sensitivity and specificity.

Keywords: Alzheimer's disease; Saccades; Eye movements; Latencies; Coefficient of variation

Eye Movement Latency Coefficient of Variation as a Predictor of Cognitive Impairment

Eye movements are a powerful tool for assessing cognitive functioning capacities. Alzheimer's disease is a prominent neurodegenerative disease that results in atypical eye movements. Due to the current clinical diagnostic tests, AD often goes undiagnosed until later stages making treatments and interventions less effective. Treatments for AD are most effective when administered in the earliest stages of the disease prior to neurodegeneration in the brain becoming widespread rendering treatments ineffective (Sperling et al., 2011). Current diagnosis methods which are capable of detecting AD in the early stages are either invasive (lumbar puncture for cerebrospinal fluid sample) or expensive (neuroimaging). Eye tracking could provide an invaluable indicator for neurodegenerative disorders and impaired cognitive functioning offering a cost effective and non-invasive alternative (Crawford et al., 2013, Molitor et al., 2015). Multiple eye tracking markers for impairment have been found however, the sensitivity and robustness of these markers on multiple tasks has not been assessed or compared. The current study aims to assess recognised impairment markers on pro and antisaccade tasks and their sensitivity in identifying established dementia and preclinical stages such as mild cognitive impairment.

In clinical populations and healthy adults, the antisaccade task can be used to assess inhibitory control abilities (Hutton & Ettinger, 2006). The antisaccade task requires a participant to inhibit shifting their gaze towards the displayed target and instead look towards the opposite side (Munoz & Everling, 2004, Crawford et al., 2013). Due to a reduction in inhibitory control, disengagement of attention and a decline in working memory and executive functioning (Baddeley et al., 2001), AD patients are significantly slower at performing pro and antisaccadic eye movements resulting in an increase in mean latencies (Crawford et al., 2005., Yang et al., 2013). In an addition to cognitive slowing, Crawford et al (2013) showed higher error rates on antisaccade tasks which can predict dementia severity. It is theorised that top-down executive control is required to inhibit the eye gaze from shifting towards the target and this top-down processing requires working memory resources often impaired in people with AD (Crawford et al., 2011). As a result, error rates and

latencies, on inhibitory control tasks such as the antisaccade task, have shown potential in predicting dementia severity and identifying cognitive impairment.

Deficits in eye tracking performance are evident when assessing antisaccades in AD patients, however, this has not been fully investigated in earlier, preclinical stages such as aMCI and naMCI groups. For a biological marker to be beneficial it must be sensitive enough to detect subtle signs of impairment in preclinical stages. MCI is a clinical syndrome characterised by cognitive impairments which are atypical for a person's age. MCI has traditionally been classed as a distinct stage of dementia due to the deficits not being sufficiently severe to significantly impact on an individuals daily living and capabilities (Peterson, 2004). However, there is a growing argument that MCI should be classed as a preclinical stage between healthy ageing and AD. There are two subgroups of MCI, amnesic MCI (aMCI) and non-amnesic MCI (naMCI). People with aMCI suffer greater memory impairments than naMCI whereas people with naMCI often have preserved memory but display other cognitive impairments such as executive functioning deficits. People with aMCI are deemed at a greater risk of progressing to AD then naMCI (Fischer et al., 2007, Ward et al., 2013). Previous research assessing MCI subtypes in relation to eye movement performance found that eye movement parameters such as latencies and error rates were able to distinguish between naMCI and aMCI. Interestingly results showed aMCI participants performed more similarity on the antisaccade task to AD participants and naMCI more similarity to healthy controls. This provided further support for the antisaccade task as a useful task to identify and monitor cognitive impairment and even be successful in distinguishing subtle differences between MCI subgroups (Wilcockson et al., 2019).

Research to date indicates that fluctuations of eye movement latencies could serve as an additional impairment marker. When completing a saccadic eye movement there is a decisional process that takes place prior to the eye movement (Hutton, 2008). This decisional process is often measured as the time taken between saccade onset and reaching the goal-directed target. The time required to initiate a saccadic eye movement can rely on the resources of executive functioning and attentional processing capabilities therefore impairments in these areas can result in reductions in

processing speed and increased latency fluctuations. Due to executive functioning and processing speed systems being employed when completing pro and antisaccade eye movements, it is thought that latency variability could be an indicator of attentional fluctuation when completing these tasks. Participants with attentional deficits often show a greater fluctuation of task latencies and scores (Yang et al., 2013). This indicates less consistency and reductions in sustained attention across the course of the task indicating attentional processing deficiencies (Kapoula et al., 2010). A measure of latency variability on pro and antisaccade tasks could offer markers for further distinctions between healthy adults and people with memory impairments.

The current study will assess participants attentional fluctuations using a measure of relative variability termed coefficient of variation (CV). The measure takes the ratio of the standard deviation in relation to the mean. The higher the CV, the greater the level of dispersion around the mean score. The lower the CV percentage the more precise and less variability the measure is. CV could be an additional biological marker for impairment, alongside existing eye tracking makers such as mean latencies and error rates. Yang et al (2013) assessed CV scores on prosaccade eye movements on a gap and overlap version of the task. Results showed higher CV in latencies for AD participants than for healthy adults and aMCI participants. Increased variability of accuracy and speed was also abnormally high in AD participants in both vertical and horizontal saccades (Yang et al., 2011). This indicates the potential for CV latencies on the prosaccade task to distinguish between AD and healthy adults. The current study expanded on this research by assessing CV latencies on a wider range of tasks (prosaccade and antisaccade task) and in a wider group of participants with the addition of naMCI participants. The addition of the naMCI will provide information on the potential of latencies CV scores to distinguish between subgroups of MCI participants which is vital in identifying more at-risk groups for AD.

In summary, the current study assesses the potential of mean latencies, latency CV measures and error rates as biological markers for impairment on prosaccade and antisaccade tasks. These measures will be evaluated on their sensitivity and reliability in detecting cognitive impairment

particularly in distinguishing preclinical stages of AD. The study includes AD, aMCI, naMCI and healthy older adult participants to assess these measures.

1. Methods

1.1. Participants

The study included 65 participants with diagnosis of dementia due to AD (Mean age =74.15, SD= 7.75), 42 with aMCI (Mean age =73.71, SD=7.42) and 47 naMCI (Mean age = 69.26, SD = 6.89) and 96 older adult controls (Mean age =67.80, SD= 8.10).

The AD and MCI participants were recruited from various NHS sites and memory clinics across the UK. The AD participants met the requirements for the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM IV) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) for AD. All AD and MCI participants had received a full assessment from a qualified NHS dementia specialist. The MCI participants had a formal diagnosis and met the following criteria (Lemos et al., 2015): (1) subjective reports of memory decline (reported by individual or caregiver/informant); (2) memory and/or cognitive impairment (scores on standard cognitive tests were >1,5 SDs below age norms); (3) Activities of daily living were moderately preserved. To subgroup the MCI participants into aMCI and naMCI, the Free and Cued Selective Reminding test with Immediate Recall (FCSR-IR) task (see below) scores were used for classification (Lemos et al., 2015).

Control participants were recruited via opportunity sampling. Participants with focal cerebral lesions, history or neurological disorders, neurodegenerative disease, cerebrovascular disease or alcoholism were excluded. Control participants who scored less than 26 on the Montreal Cognitive Assessment (MoCA) were excluded from the final analysis. All participants were deemed to have capacity to consent to participation in the study and provided written informed consent. Ethical approval was granted by Lancaster University Ethics committee and NHS Health Research Authority, Greater Manchester West Research Ethics Committee.

1.2 .Neurological assessments.

Participants completed four neurological assessments. The Montreal Cognitive Assessment (MoCA, Nasreddine, 1966) assessed cognitive impairment with a score lower than 26 an indicator of probable dementia. The digit span assessed verbal working memory taken from the Wechsler Adult Intelligence Scale III (Wechsler, 1997a) both forwards and backwards versions of the task. Spatial memory was assessed using the Spatial Span task via the use of the Corsi block (Wechsler, 1997b) for both forwards and backwards versions. As recommended by the International Working Group on Alzheimer's Disease, the FCSR-IC task was conducted (Grober & Buschke, 1987) due to its high sensitivity in differentiating between AD and MCI subgroups (Cummings et al., 2013). The task provides a measure of free recall and cued recall for correct responses (a total of 48 for both scores). MCI participants who scored equal to or below 27 on the free recall score were classified as aMCI and scores over 28 classified as naMCI as recommended by Lemos et al (2015).

1.3. Eye Tracking Tasks

1.3.1. Apparatus

Eye movements were recorded via the EyeLink Desktop 1000 at 500Hz. A chin rest was used to reduce head movements. Participants sat approximately 55cm away from the computer monitor (60Hz). Participant's gazes were calibrated and validated using 9-point calibration prior to each task. The stimulus was created and controlled via the use of Experiment Builder Software Version 1.10.1630. The data was analysed and extracted using Data Viewer Software Version 3.2

1.3.2. Prosaccade task

Participants were presented with 36 gap trials followed by 12 overlap trials. A white fixation target was displayed for 1000ms in order to centre the participants gaze, followed by a red target presented randomly to the left or right at 4° for 1200ms. Participants were instructed to first look towards the white fixation point at the centre of the screen and then towards the red target as quickly

and accurately as possible. For the gap condition, there was a blank interval screen displayed for 200ms between the extinguishment of the white fixation target and the initial appearance of the red target. This resulted in a temporal gap in stimuli presentation (figure 1a). In the overlap condition, the target was presented while the central fixation point remained on the screen for 200ms. There was an overlap in stimuli presentation resulting in the target and the fixation point being displayed simultaneously for 200ms (figure 1b). After a short period, the central fixation was removed, and the target presented singularly for 1200ms.

Figure 1a. Timings and display presentation screens for the prosaccade task gap condition. Task instructions required participants to look towards the red target.
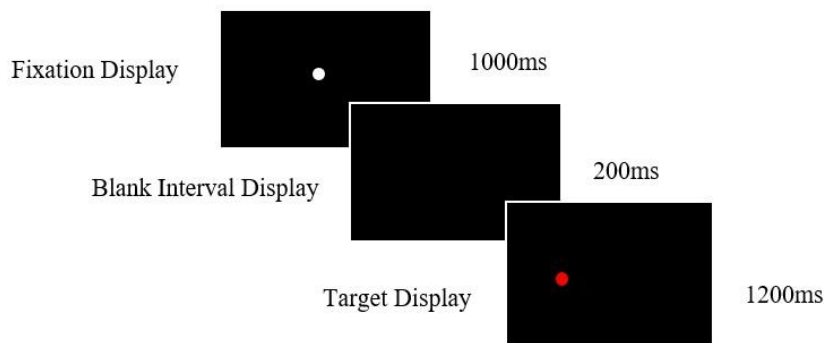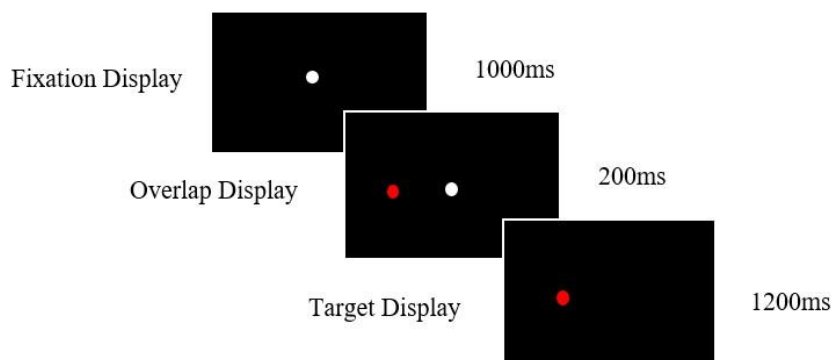

Figure 1b. Timings and display presentation screens for the prosaccade task overlap condition. Task instructions required participants to look towards the red target.

1.3.3. Antisaccade task.

Participants completed 24 gap trials and 4 practice trials. Participants were presented with a central white fixation for 1000ms followed by a green target on the left or right side of the screen presented for 2000ms. Participants were instructed to direct their gaze and attentional focus to the opposite side of the screen to which the target appeared (figure 2). There was a 200ms gap in presentation of the fixation point and the target in which a blank interval screen appeared. Participants needed to generate the saccade to the opposite side of the screen to which the target was displayed to perform a successful antisaccade.

Figure 2. Timings and display presentation screens for the antisaccade task. Task instructions required participants to ignore the green target and move their gaze to the opposite side of the screen.
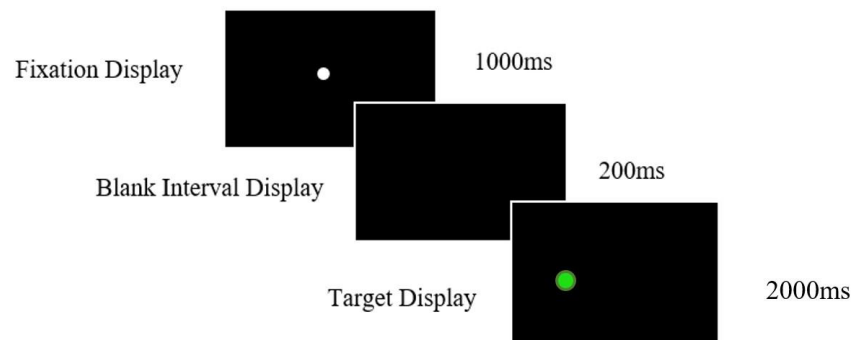
1.4. Data Processing.

The raw data was extracted and analysed via EyeLink using DataViewer Software Version 3.2. A bespoke software (Mardanbegi et al., 2019) was then used to analyse the data offline. This software removed spikes and noise by filtering out frames with a velocity signal greater than 1,500 deg/s or with an acceleration signal greater than 100,000 deg^2/sec. The EyeLink Parser was used to detect the fixations and saccadic events and the saccades were extracted alongside multiple temporal and spatial variables. Trials were removed in cases when the participant did not direct their gaze to the central fixation. The temporal window of 80-700ms used and measured from the onset of the

target display. Anticipatory saccades made prior to 80ms and excessively delayed saccades made after 700ms were removed.

Results

The results were analysed using regression models via RStudio version 1.2.5033. Participants eye tracking mean latencies and latency standard deviations were compared with performance on the cognitive assessments and group effects were assessed. One MCI participant was excluded from the analysis due insufficient eye tracking data.

2.1. Cognitive Assessments

An ANOVA was performed to assess the effects of group on cognitive performance on the MoCA, Digit span, spatial span and FCSR task. For the MoCA results revealed a significant effect of participant group, $F(3, 247) = 73.99$, $p < .001$. Post hoc comparisons revealed AD produced significantly lower scores compared to older adults and naMCI participants. There was no significant difference between AD and aMCI participants on MoCA score. There was a significant difference between the MCI subgroups with naMCI producing significantly higher scores than aMCI. Further aMCI and naMCI participants also expectedly scored lower when compared to older controls (table 1).

For the digit span task, there was an effect of participant group $F(3, 228) = 6.98$, $p < .001$) with AD participants scoring lower than older controls on the task. Further aMCI also scored significantly lower than controls on the task, although no significant difference was found between controls and naMCIs. There were no further significant differences between the groups.

There was a significant group effect on spatial task performance, $F(3, 222) = 15.10$, $p < .001$. AD participants scored lower compared to controls and naMCI participants. Both MCI subgroups produced significantly lower scores when compared with controls. There were no further significant differences between the MCI subgroups.

The FCSR task has a significant effect of participant group $F(3, 163) = 20.96$, $p < .001$ when assessing total task score with AD participants scoring lower than controls and both MCI subgroups. There were no significant differences between the MCI subgroups and the controls.

Table 1. *Table displaying means, standard deviations and post hoc contrasts for MoCA, Digit Span, Spatial span and FCRS task score for all participant groups.*

	Alzheimer's Disease (n=65)		aMCI (n=42)		naMCI (n=47)		Healthy Older Controls (n=96)		Post Hoc Contracts (P values)					
											Disease Effects			
	M	SD	M	SD	M	SD	M	SD	AD vs OC	AD vs aMCI	AD vs naMCI	aMCI vs naMCI	aMCI vs OC	naMCI vs OC
MoCA	19.98	5.71	20.93	4.46	25.34	2.17	28.02	1.79	<.001*	.577	<.001*	<.001*	<.001*	<.001*
Digit Span	15.64	4.12	16.35	3.66	16.66	4.79	18.72	4.48	<.001*	.850	.631	.988	.023*	.050
Spatial Span	11.34	3.12	12.58	3.10	13.00	2.55	14.56	2.81	<.001*	.178	.022*	.919	.004*	.021*
FCSR-IC	36.48	14.72	45.10	4.41	47.39	1.29	47.73	0.94	<.001*	<.001*	<.001*	.592	.401	.996

Note. Dependent variable: Task score.

*Significant at p<.05 level

2.2. Prosaccade Task - Gap Condition

An ANOVA was performed comparing the effects of participant group on prosaccade means and coefficient of variation. Pearson Correlations assessed the relationship between the eye-tracking markers and cognitive assessment performance.

2.2.1. Mean Reaction Times and Coefficient of Variation Group Effects

Results revealed no significant effects of participant group on prosaccade mean reaction times, $F(3, 169) = 1.78$, $p = .153$ (Table 2). When assessing coefficient of variation (CV) measures, there was a significant effect of participant group on CV scores, $F(3, 169) = 2.70$, $p = .047$. Post hoc comparisons

revealed that the older adult group displayed lower coefficient of variation scores indicating less

variation in prosaccade reaction times during the task however this was not statistically significantly.

Interestingly there was no significant difference between AD and older controls.

Table 2. *Table displaying means and standard deviations for mean latencies and coefficient of variation scores and post hoc contracts for the prosaccade task gap condition.*

	Alzheimer's Disease (n=43)		aMCI (n=29)		naMCI (n=27)		Healthy Older Controls (N=71)		Post Hoc Contracts (P values)					
												Disease Effects		
	M	SD	M	SD	M	SD	M	SD	AD vs OC	AD vs aMCI	AD vs naMCI	aMCI vs naMCI	aMCI vs OC	naMCI vs OC
Mean Latencies	215	31.88	201	39.14	226	60.33	203	48.56	.648	.770	.826	.351	.997	.163
Coefficient of Variation	23.14	10.03	26.93	17.09	25.57	15.62	19.77	12.41	.627	.687	.916	.720	.060	.271

Note. Dependent variable: Reaction times.

2.2.2. Correlations between Prosaccade markers and cognitive assessments.

Correlations were conducted to compare the eye tracking measures (mean latencies and CV scores) and the cognitive assessment scores. Due to the variations between the participant groups, correlations were assessed for the groups individually. Interestingly there was no single task which consistently correlated with mean latencies or CV across the groups. The aMCI group showed correlations between CV score and the digit span task backwards version ($r(17) = -.486$, $p = .048$) and for the spatial span task, forwards ($r(17) = -.492$, $p = 046$), backwards ($r(17) = -.512$, $p = .036$) and total scores ($r(17) = -.548$, $p = .023$) and also for MoCA task score ($r(17) = -.551$, $p = .022$). Participants with higher task scores produced lower CV indicating less variation in latencies across prosaccade trials. The aMCI group also showed a significant correlation between mean latencies and MoCA task score ($r(17) = -.543$, $p = .024$). However, this was not consistent across the other groups.

The controls showed a significant correlation between CV score and backwards digit span score ($r(56) = -.299$, $p = .025$) and total score ($r(56) = -.268$, $p = .046$), again with higher task score correlating with less fluctuation in latencies. Further the AD and naMCI group did not show any correlations between eye tracking latencies and cognitive assessments indicating a weak link between these markers.

2.3. Prosaccade Task – Overlap Condition

The analysis performed for the overlap condition remained consistent with the gap condition.

2.3.1 Mean Reaction Times and Coefficient of Variation Group Effects

When assessing group effects on mean reaction times table 3 revealed there were no significant differences between the groups, $F(3, 167) = 2.55$, $p = .058$. The overlap condition often leads to a delay in disengaging attention from the fixation point which may have resulted in less variation between groups when initiating the saccade. Table 3 revealed no significant differences in CV scores across the participant groups ($F(3, 167) = .354$, $p = .786$), indicating limited potential for distinction between participants groups for this task.

Table 3. *Table displaying means and standard deviations for mean latencies and coefficient of variation scores and post hoc contracts for the prosaccade task overlap condition.*

	Alzheimer's Disease (n=43)		aMCI (n=29)		naMCI (n=27)		Healthy Older Controls (n=69)		Post Hoc Contracts (P values)					
												Disease Effects		
	M	SD	M	SD	M	SD	M	SD	AD vs OC	AD vs aMCI	AD vs naMCI	aMCI vs naMCI	aMCI vs OC	naMCI vs OC
Mean Latencies	274	57.61	234	62.45	273	74.51	254	71.51	.462	.070	.999	.127	.509	.601
Coefficient of Variation	37.94	19.29	38.96	18.20	36.44	19.04	34.93	18.15	.857	.997	.989	.966	.814	.986

Note. Dependent variable: Reaction times.

2.3.2. Correlations between Prosaccade markers and cognitive assessments-overlap

Similar to the prosaccade gap condition there was little consistency across groups when assessing correlations. The aMCI group showed a correlation between mean latencies and spatial span total score ($r(23) = .454$, $p = .030$) and FCSR free recall score ($r(29) = .418$, $p = .024$) but unlike the gap condition there were no correlations between CV scores and cognitive task score. The control group showed a significant correlation between mean latencies and the FCSR total score with participants who score higher on the task displaying lower mean latencies ($r(31) = -.442$, $p = .013$). There were no significant correlations found for the AD and naMCI consistent with the gap condition.

2.4. Antisaccade task

The analysis performed for the antisaccade task was consistent with the analysis for the prosaccade task.

2.4.1. Correct Trials Mean Reaction Times and Coefficient of Variation Group Effects

Results revealed a significant effect of participant group on antisaccade mean reaction times, $F(3, 238) = 13.54$, $p < .001$. Post hoc comparisons revealed that the AD group produced significantly slower saccade reaction times compared to healthy older adults (Table 4), indicating reductions in processing speed and inhibitory control deficits. The AD and aMCI group produced comparable saccade reaction times supporting previous research that AD and aMCI show similar impairments and deficits. The AD and naMCI produced significantly different results with the AD group producing slower saccade reaction times then the naMCI group. The naMCI group performed similarly to healthy controls with no significant difference in saccade reaction times. The aMCI group produced significantly slower saccade reaction times than the naMCI group which again supports previous research on distinctions between naMCI and aMCI participants with aMCI performing more similarly to the AD and the naMCI more similarity to the healthy older controls (Table 4).

There were no significant differences in measures of coefficient of variation between the participant groups, $F(3, 238) = 2.21$, $p = .087$. This indicates that the variability of scores and performance on the antisaccade task is not affected by disease. The AD and MCI group do not display differences in coefficient of variation when compared to healthy adults indicating comparable and typical levels of attentional fluctuation on the task.

Table 4. *Table displaying means and standard deviations for mean latencies and coefficient of variation scores and post hoc contracts.*

	Alzheimer's Disease (n=65)		aMCI (n=42)		naMCI (n=47)		Healthy Older Controls (n=88)		Post Hoc Contracts (P values)					
									Disease Effects					
	M	SD	M	SD	M	SD	M	SD	AD vs OC	AD vs aMCI	AD vs naMCI	aMCI VS naMCI	aMCI vs OC	OC vs naMCI
Mean Latencies	404.34	86.34	418.91	81.70	363.05	61.61	338.12	83.91	<.001*	.804	.041*	.008*	<.001*	.320
Coefficient of Variation	23.57	10.43	20.55	5.80	25.04	6.79	24.74	10.30	.858	.376	.854	.133	.080	.998

Note. Dependent variable: Reaction times.

*Significant at p<.05 level

2.4.2. Correlations between Antisaccade Markers and Cognitive Assessments

Unlike for the prosaccade task, the AD group showed a significant correlation between antisaccade mean latencies and the digit span forwards score ($r(60) = -.324$, $p = .011$). Further CV score correlated with FCSR total scores ($r(44) = -.389$, $p = .009$). Participants who score higher on these cognitive tasks produced lower and less variable mean latencies. The only correlation found for the aMCI group was between CV score and digit span forwards task score with again higher task score indicating lower CV scores and less variable latencies ($r(38) = -.357$, $p = .028$). For the naMCI, the only correlation was between CV score and spatial span forward score ($r(43) = -.416$, $p = .006$). The control group showed correlations between saccadic mean latencies and MoCA score ($r(88) = -

.294, $p = .005$). These results indicate that there is not a sole cognitive task that consistently correlate with the eye tracking markers across the groups. However, it is clear from the results that higher cognitive functioning and higher task scores often leads to lower mean latencies and saccadic processing speeds and less variation in latencies indicating less attentional fluctuation.

2.5. Error rates

An error was defined as a saccade in the direction of the presented distracter target. This was determined based on the first saccade in the direction of left or right. An ANOVA was performed to assess the group effects on percentage of error trials. Results revealed a significant effect of participants group on percentage error rate ($F(3, 243) = 12.96$, $p < .001$). Post hoc comparisons revealed that AD participants displayed a significantly higher number of errors compared to naMCI and controls (table 5). AD participants produced a similar number of errors on the task to aMCI resulting in no significant difference between AD and aMCI participants. The aMCI group produced significantly higher percentage error rates compared to naMCI and controls, indicating that they performed more similarly to the AD group then the naMCI group. Further there was no significant difference between error rates when comparing the naMCI and the control group. This indicates that naMCI produce error rates more similarly to controls than aMCI and AD participants. Error rates on the antisaccade task may be successful at distinguishing between AD and aMCI participants from naMCI and controls.

Table 5. *Table displaying mean and standard deviations and post hoc contracts for percentage error rates for all participant groups.*

	Alzheimer's Disease		aMCI		naMCI		Healthy Older Controls		Post Hoc Contracts (P values)					
									Disease Effects					
	M	SD	M	SD	M	SD	M	SD	AD vs OC	AD vs aMCI	AD vs naMCI	aMCI VS naMCI	aMCI vs OC	OC naMCI VS
Percentage error rate	26.13	28.80	30.11	30.02	12.40	10.75	10.36	10.98	<.001*	.773	.004*	.001*	<.001*	.951

Note. Dependent variable: Percentage error rate.

*Significant at p<.05 level

Discussion

The current study assessed the effectiveness coefficient of variation as an additional biological marker alongside well-founded measures such as mean latencies and antisaccade error rates. The study assessed mean latencies and CV on the prosaccade and antisaccade tasks. The CV measure allowed for the assessment of latency fluctuations throughout the task. It was predicted that AD and MCI participants may show higher CV scores due to greater attentional fluctuation. Results showed no significant differences in CV measures across the groups on the antisaccade task although CV measures on the prosaccade task indicated promising results in terms of distinguishing MCI participants from older controls. CV scores on the prosaccade task were significantly higher for the aMCI and naMCI group compared to older controls indicating a greater level of fluctuation of prosaccade latencies in MCI populations. Interestingly this was not the case for the AD group with no significant difference from controls.

Another key finding revealed that antisaccade mean latencies were able to robustly distinguish participants with AD from older controls and between the MCI subgroups showing high sensitivity. Participants with AD produced significantly slower mean latencies indicating a greater difficulty in

generating the saccade and a reduction in processing speed. This finding is supported by previous research showing inhibitory control impairments resulting in difficulties performing correct antisaccades leading to speed reductions and increased difficulty in triggering saccades (Boxer et al., 2012, Crawford et al., 2005, Kaufman et al., 2012). Previous research (Clark et al., 2015) has demonstrated eye movement latencies greatly rely on attentional processes, often impaired in AD patients. The slowing in saccade latencies is likely the result of these attentional impairments (Levinoff et al., 2004). The current study provides further support for the effectiveness of mean latencies and indicates sufficient sensitivity to distinguish between MCI subgroups and preclinical stages of AD.

It has been previously demonstrated that patients show more variable latencies then older controls and MCI patients which suggests that higher latency variability is related to greater attentional fluctuation (Kapoula et al., 2010). More variable latencies on the task indicate that AD patients have less sustained attentional focus on the task compared to older controls and MCI participants and this is likely to be due to damage to regions of the brain responsible for executive functioning and attentional processing. Yang et al (2013) found a higher coefficient of latency variation, increased variability of accuracy and abnormally high latencies for AD patients compared to healthy adults and MCI participants. It was stated that the latency and latency variability abnormalities reflect deficits of cerebral areas involved in the execution and triggering of saccades. However, the results from the current study do not support these findings and instead showed that levels of variation and CV scores were comparable across the groups. It is possible that variations in attentional fluctuation is only evident in more advanced stages of AD and therefore is not sensitive enough to show noticeable difference in early to moderate stages of AD. However, research has shown higher CV scores and increased attentional fluctuation in MCI participants which does not support this conclusion. These inconsistent findings indicate that CV may not be a reliable and robust marker for cognitive impairment as previously thought in the literature. More research is needed to

assess CV scores and their robustness for distinguishing clinical and non-clinical groups on eye tracking tasks

A further key finding was the clear distinction seen on the antisaccade task between the MCI subgroups. The aMCI group produced significantly higher antisaccade mean latencies compared to naMCI. This indicates that aMCI have greater deficits in generating and executing saccadic eye movements and the decisional process prior to an eye movement. The time required to initiate a saccade relies on executive functioning and attentional processing capabilities and therefore impairments in these areas results in a slowing in processing speed and increased latencies. The current study indicates reduced capabilities in executive functioning and attentional processes in aMCI compared to naMCI. Antisaccade mean latencies were comparable for the AD and aMCI and significantly different from the naMCI and controls, indicating similar processing and executive functioning capabilities between aMCI and AD participants. The naMCI group performed more similarly to controls again further emphasising this MCI distinction. Patients with aMCI are more likely to progress to develop AD whereas naMCI are less likely to progress to an AD diagnosis and the pattern of results in the current study supports this deviation. The antisaccade task appears to be a useful tool at highlighting the distinction between these MCI subgroups and provide support for the argument of MCI particularly aMCI to be assessed as a preliminary stage prior to AD or full-blown dementia. The clear distinctions between these groups on the antisaccade task is valuable when assessing biological markers between MCI subgroups to provide vital information on the likelihood of an individual developing AD and an indication on the severity of this progression.

The relationship of eye tracking mean latencies and CV with paper-based cognitive assessments was assessed. The results revealed that cognitive task scores correlated with mean latencies and CV scores, however the specific cognitive assessment correlating with the eye tracking measure varied for each participant group. The overall trend showed that higher scores on the cognitive assessments correlated with faster mean latencies and lower CV scores. This finding adhered with previous research findings that cognitive ability is reflected in prosaccade and

antisaccade eye movement performance (Boxer et al., 2006., Garbutt et al., 2008). However, these results also indicate that different cognitive tasks are more effective in predicting mean latencies and CV depending on the participant's group. This brings into question the robustness of eye tracking measure in directly predicting cognitive ability as mean latencies and CV score only correlate with certain cognitive assessments which vary depending on participant group and ability. Further it must also be considered that the cognitive assessments are not sensitive enough to correlate with more subtle variations and changes in mean latencies and CV scores across the groups. This should be assessed with a wider battery of cognitive assessments to further assess consistency between groups.

In summary, the current study assessed the disease effect on pro and antisaccade eye movement latencies, CV and error rates. Certain parameters on the antisaccade task are capable of distinguishing between AD patients, MCI subgroups and older control participants but it is clear that research into the effectiveness of CV as a biological marker for impairment is required further as results do not provide clear evidence of increase attentional fluctional in AD and MCI participants. This conflicts with previous findings which have shown promising findings for CV as an additional biological marker however more research is required to fully assess the robustness and true potential of this variable.

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5.1 Statement of thesis continuous commentary

In chapters 3-5 I investigated the potential of eye movements to provide biomarkers and early indications of cognitive impairments and how eye movements can be used to inform on cognitive processes. In chapter 6, I shifted my focus and explored oculomotor processes that could mitigate symptoms of cognitive impairment and offer therapeutic benefits. Specifically, this chapter focused on whether eye movements could be used to temporarily enhance memory recognition (Christman et al., 2003). Previous research in young adult populations has found that performing bilateral eye movements for a short period of time results in performance enhancements on a subsequent memory task. To date the enhancement of memory capabilities as a result of bilateral eye movements has not been investigated in clinical populations and there may be potential for therapeutic benefits. In chapter 6, I investigate the robustness of bilateral eye movements to produce an enhancement effect on memory recognition in younger adults and whether the saccade induced retrieval effect applies to older adults and clinical populations.

Chapter 6

Paper four: On Effect of Bilateral Eye Movements on Memory Retrieval in Ageing and Dementia

Polden, M., and Crawford, T.J

Article

On the Effect of Bilateral Eye Movements on Memory Retrieval in Ageing and Dementia

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Abstract: It has been reported that performing bilateral eye movements for a short period can lead to an enhancement of memory retrieval and recall (termed the "saccade induced retrieval effect (SIRE)"). The source of this effect has been debated within the literature and the phenomenon has come under scrutiny as the robustness of the effect has recently been questioned. To date investigations of SIRE have largely been restricted to younger adult populations. Here, across two experiments, we assess the robustness and generalisability of the SIRE specifically in relation to disease and ageing. Experiment 1 employed a between subject's design and presented younger and older participants with 36 words prior to completing one of three eye movement conditions (bilateral, antisaccade or a fixation eye movement). Participants then performed a word recognition task. Experiment 2 assessed the SIRE in individuals diagnosed with Alzheimer's, Mild cognitive impairment and Parkinson's by employing an online within subject's design. Results showed no significant difference between groups in the number of words recognised based on eye movement condition. Neither experiment 1 or 2 replicated the SIRE effect therefore the findings from this study add to the growing number of studies that have failed to replicate the SIRE effect.

Keywords: bilateral eye movements; saccades; memory retrieval; word recognition; Alzheimer's; mild cognitive impairment; Parkinson's

1. Introduction

Traditionally eye movements and memory have been studied in quite separate domains. There is now growing evidence of a close interaction between eye movements and working memory. For example, evidence derived from neuropsychological studies of people with dementia revealed that eye movements can be indicative of memory and cognitive impairment [1,2]. One line of research purports that eye movements interfere and disrupt working memory processes [3]. Pearson & Sahraie [4] across 5 experiments contrasting the effects of eye movements, limb movements and attention shifts on working memory, demonstrated a crucial role for oculomotor control processes during rehearsal of location representations in working memory. Later research assessing this claim more specifically revealed that it was eye movement attentional control processes (involved in retrieval, encoding or formation of images) and not the movement per se that produced disruptive effects and that these effects are limited to spatial working memory [5]. However, there is an emerging discord in understanding the relationship between eye movements and memory. The critical role of eye movement activity in spatial memory was highlighted using the abducted eye paradigm by Pearson et al. [6], although as the effects may include combined influences of both prospective planning and sensory representation of memory items [5]. Ryan and colleagues [7] stated that "eye movements may be functional for the formation, retrieval and reconstruction of memory" claiming a close interaction in which eye movements directly facilitate working memory [7]. It is suggested that gaze fixations during encoding processes is related to neural markers of memory formation and functional

activity in the hippocampus, with the restriction of eye movements during encoding negatively impacting subsequent memory [8,9]. However, whereas voluntary eye movements were interruptive in the studies above [4,5], it has also been claimed that intrusive voluntary eye movements can actually lead to enhancements in memory processes [10]. This claim is critical as it suggests there is a potential for eye movements to facilitate working memory processes in both healthy and clinical populations.

Christman et al. [10] hypothesised that bilateral eye movements can lead to enhancements on subsequent memory and recall tasks due to increasing interhemispheric interaction which plays a role in episodic memory processes [11]. These bilateral eye movements incorporate the sequential gaze shift from left to right visual field in quick succession (Figure 1). They demonstrated that a sequence of bilateral eye movements for as little as 30 s can produce an enhancement effect on episodic memory specifically word recall. The so-called "saccade induced retrieval effect" (SIRE) has been replicated [12,13] and applied to various stimulus's types such as autobiographic memory, spatial memory and episodic future thinking [14–16]. Although current literature has focused on assessing the SIRE effect across various stimuli, the effect has predominately been assessed in young adult populations and has not yet been applied to populations with cognitive deficits. Here, across two experiments we examined the SIRE effect in older adult populations and clinical populations with known cognitive and memory deficits (people with Alzheimer's Disease, Mild cognitive impairment and Parkinson's Disease) assessing the effect in relation to ageing and disease.
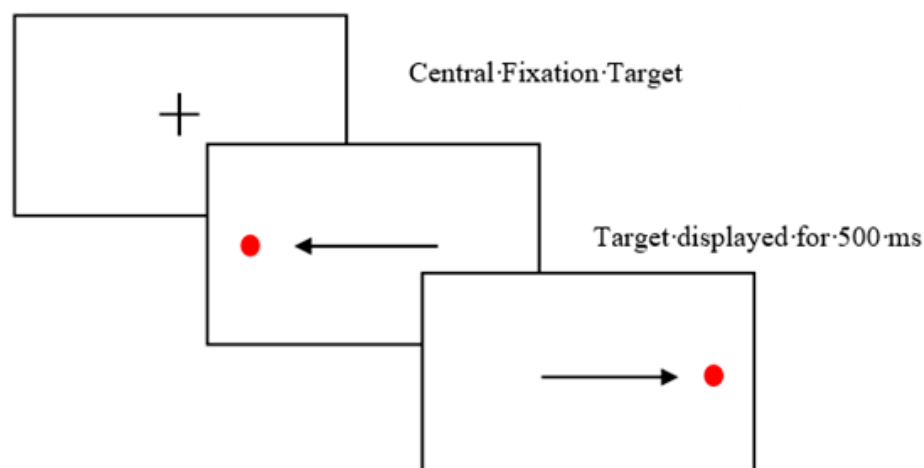

Figure 1. Bilateral eye movement task. Red target flashes from the left side of the screen to the right repeatedly for 30 s. The target moves every 500 ms resulting in 2 horizontal saccades per second. Arrows indicate the direction of the horizontal saccade.

Lyle and Martin [17] suggest that activation of the frontoparietal attention network could be the cause of the SIRE. If this is the case, attentional control tasks such as the antisaccade task, could elicit the SIRE effect. The antisaccade task presents participants with a single target and requires participants to shift their gaze and attentional focus to the opposite side. This task employs top-down control processes including inhibitory control, working memory and other executive operations. Regions of the frontoparietal network are activated during the task similar to episodic memory retrieval potentially making the task an effective priming method for a subsequent memory retrieval task. In the current study we assess the potential of antisaccade eye movements to enhance memory retrieval.

Experiment 1 examined antisaccadic (top-down control task) and bilateral eye movements and their ability to enhance word memory retrieval, utilising eye tracking to objectively monitor the eye movements. If the enhancement effect is specific to simple bilateral eye movements this will provide support for the interhemispheric interaction hypothesis [10] however if only the more complex anti saccadic eye movements are able to elicit the SIRE effect, then this would provide support for the attentional control hypothesis [17].

A more accurate understanding of the cause of the SIRE effect will help to produce a more reliable, robust, and replicable effect. As older adults are generally more susceptible to memory decline and reductions in cognitive processes [18,19], the effects of bilateral eye movements may increase with age. Younger adults may be more prone to ceiling effects on memory recall tasks and reduced ceiling effects as a result of memory decline in older adult populations may result in increased enhancements effects following bilateral eye movements. Due to this, the current study explored the SIRE in relation to ageing by including both healthy younger and older adults.

2. Materials and Methods

2.1. Participants

The study included 68 younger adults (mean age = 23.03, SD = 3.91, age range = 18–35 years) and 59 older adults (mean age = 63.55, SD = 6.71, age range = 55–90 years). The participants were white British or European fluent English speakers with a minimum of 11 years in formal education. The younger adults were recruited via the Lancaster University Research Participation System and the older adults were recruited from the local community. The younger and older adults were assigned to one of three experimental conditions: Bilateral prosaccadic eye movements, antisaccade eye movements and a fixation condition with no eye movements (Fixation condition). Participants were counterbalanced across the conditions. Only strongly right-handed individuals were included in the study due to research demonstrating inconsistent results of the SIRE effect in left-handed and ambidextrous individuals [17,20,21].

The following exclusion criteria was applied: previous head trauma, stroke, cardiovascular disease, physical or psychological conditions severe enough to affect their ability to participate, previous and current alcohol or substance misuse. Participants with focal cerebral lesions, history of neurological disorders (e.g., Parkinson's disease, multiple sclerosis, epilepsy, amyotrophic lateral sclerosis, muscular dystrophy), neurodegenerative or cerebrovascular disease (including ischemic stroke, haemorrhagic stroke, atherosclerosis).

The G*Power software version 3.1.9.7 was used to conduct a power analysis to determine the minimum sample size to ensure adequate power. The power level was set at 0.80 with an error of 0.05 for the analysis [22]. The effect size used (d = 0.495) was based on the Christman et al. [10] article for the comparison of horizontal eye movements to no eye movements. The analysis indicated a required sample size of 45 participants for a between subject's design. A between subject's design was used to replicate and maintain consistency with the Christman et al. [10] study. Therefore, we aimed to collect a minimum of 45 participants in experiment 1. All participants included in the study had normal or corrected to normal vision. Written informed consent was gained from all participants. Ethical approval was granted by Lancaster University Ethics committee in May 2018.

2.2. Neuropsychological Assessments

The memory recognition task consisted of 72 words (see Supplementary Materials) which were sourced from Friendly's (1996) online word list generator consisting of 925 nouns collated by Paivio et al. [23] and scaled for print frequency, meaningfulness, imagery, concreteness. Two-word lists were created, a target and a foil word list both consisting of 36 words controlled for moderate meaningfulness, frequency, concreteness, and imagery scores. The words ranged from five to eight letters and included 2–4 syllables. The 36 target words were displayed via Microsoft PowerPoint, version 2013, singularly on the centre on the screen for 5 s per word automatically being replaced by the next word. Participants were informed that they would be asked to identify the words in a later task and asked to remember as many words as possible. Participants were later presented with a randomly mixed list of the total 72 words (36 target and 36 foil words) and were given 2 min to select the words they remembered. The memory recognition task produced two scores which are assessed here: correct words identified, and false (incorrect) words identified. An overall task score was calculated by subtracting the total number of false

words identified from the total number of correct words identified for each participant. This measure allows for differences in task strategy to be controlled for.

The digit and spatial span [24], forwards and reversed, were performed to assess working memory and acted as a distractor task to prevent rehearsal of the words. The Edinburgh Handedness Inventory [25] assessed handiness dominance. Participants scoring below >80 and not classed as strongly right-handed were excluded from the final analysis.

2.3. Eye Movement Tasks

The study was a between factor design with participants randomly allocated to one of three eye movement conditions: bilateral prosaccade eye movement, antisaccade eye movement and a fixation condition. The Saccadometer Advanced software version A358 was used to record participants eye movements for the bilateral and antisaccade eye movement conditions to ensure compliance. Participants were seated 5 ft away from a plain white wall in which the lights from the Saccadometer were presented. A calibration trial was completed prior to the task. For the bilateral eye movement condition, participants were presented with a red target that moved from left to right repeatedly. The target moved every 500 ms resulting in two eye movements per second. Participants completed 70 trials lasting approximately 30–40 s.

For the antisaccade task, participants were presented with a central green fixation target presented for 100 ms followed by a single red target presented for 100 ms. There was a 100 ms gap between trials. Participants were instructed to avoid looking at the red target and instead look to the opposite side. Participants completed 40 antisaccade trials. The Saccadometer data was extracted and analysed using Latency Meter version 6.3.

The fixation condition was presented using PowerPoint. The fixation condition consisted of a central red dot that flashed every 500 ms presented on a white background. The dot remained in the same central location throughout the 30 s eye movement display. The fixation eye movement was designed as a control condition and provided the flashing stimulation without the bilateral movement. Participants were instructed to maintain their gaze on the presented target as it flashed at the centre of the screen for 30 s. Compliance was monitored visually by the experimenter due to the absence of an eye movement for this condition.

3. Results

A multivariate ANOVA was conducted investigating the effect of eye movement condition and ageing on correct and false words identified. A total of 11 people from the younger group and 1 person from the older group were excluded from the analysis due to scoring below 80 on the Edinburgh Handedness Inventory [25]. No participants were removed from the analysis due to poor compliance with the eye movement task.

3.1. Memory Assessments

An ageing effect was found on the spatial span task (total score), $F(1,113) = 5.097$, $p = 0.026$, with younger participants recalling longer spatial patterns (Table 1). There were no significant differences in digit span task score (total score), $F(1,113) = 0.011$, $p = 0.916$.

Table 1. Means and standard deviations for the neurological assessments.

	Digit Span Forward		Digit Span Backwards		Digit Span Total		Spatial Span Forwards		Spatial Span Backwards		Spatial Span Total	
	M	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**
Young Adults (n = 57)	12.19	2.29	8.14	2.66	20.33	4.12	8.17	2.70	7.35	1.49	14.88	3.38
Older Adults (n = 58)	12.48	2.13	8.10	2.75	20.41	4.05	7.12	1.69	6.47	1.35	13.59	2.72

Note. Dependent variable: Task score.

3.2. Correct Words Identified

Results showed that there was no significant effect of eye movement condition on the number of correct words identified on the recognition task, for the younger (F(2,54) = 1.66, p = 0.20, partial η^2 = 0.58) or older adult group (F(2,55) = 0.099, p = 0.91, partial η^2 = 0.004) (Table 2). Results showed no significant difference in the number of correct words identified based on age group, F(1,113) = 1.25, p = 0.27, partial η^2 = 0.011.

Table 2. Mean and standard deviations for the correct words identified following the eye movement conditions.

	Bilateral		Antisaccade		Fixation	
	M	**SD**	**M**	**SD**	**M**	**SD**
Young Adult group (n = 57)	26.70	5.66	25.79	5.44	23.50	5.49
Older Adult group (n = 58)	23.90	5.47	24.05	6.88	24.21	5.70

Note. Dependent variable: Number of words recognised.

3.3. False Words Identified

Results showed no significant effect of eye movement condition on false word recognition for the younger adult group, F(2,54) = 0.26, p = 0.77, partial η^2 = 0.09 or the older adults group, F(2,55) = 0.023, p = 0.98, partial η^2 = 0.001 (Table 3). There was a significant ageing effect on the number of false words identified, (F(1,113) = 5.66, p = 0.019, partial η^2 = 0.048) with older participants (M = 5.55, SD = 4.14) identifying significantly more false words than the younger participant group (M = 3.88, SD = 3.37). This indicates a performance ageing effect or a difference in task strategy across the groups.

Table 3. Mean and standard deviations for the false words identified following the eye movement conditions.

	Bilateral		Antisaccade		Fixation	
	M	**SD**	**M**	**SD**	**M**	**SD**
Young Adult group (n = 57)	4.15	3.72	3.42	3.06	4.06	3.40
Older Adult group (n = 58)	5.40	5.18	5.68	3.35	5.58	4.14

Note. Dependent variable: Number of false words recognised.

3.4. Task Score Words

Participant task score was calculated by deducting the number of false words from the number of correct words identified for each participant. This was to control for strategy differences. There was no significant effect on task score due to the eye movement condition for the younger (F(2,54) = 1.47, p = 0.24, partial η^2 = 0.052) or older adults (F(2,55) = 0.057, p = 0.95, partial η^2 = 0.002) (Table 4).

Table 4. Mean and standard deviations for task score following the eye movement conditions.

	Bilateral		Antisaccade		Fixation	
	M	**SD**	**M**	**SD**	**M**	**SD**
Young Adult group (n = 57)	22.55	6.71	22.37	6.19	19.44	5.55
Older Adult group (n = 58)	18.50	7.80	18.37	6.95	19.10	6.80

Note. Dependent variable: Task score.

Results showed that there was a significant effect of age on memory task scores, $F(1,113) = 5.24$, $p = 0.024$, partial $\eta^2 = 0.044$. Older participants (M = 18.66, SD = 7.09) scored significantly lower than younger adult participants (M = 21.51, SD = 6.24). This indicates a potential strategy difference between older and younger participants. Older participants select a higher number of false words impacting on the overall task score. Younger participants may be more reserved in their selections and therefore select fewer false words.

4. Discussion

Bilateral eye movements have previously been shown to elicit memory retrieval enhancement effects in younger adult populations. The cause of the SIRE effect has been debated in the current literature with conflicting accounts. The current study assessed the effect of bilateral and antisaccade eye movements on the number of words younger and older participants were able to recognise. Results from the current study did not replicate the enhancement effect of bilateral eye movements on word memory recognition and recall [10,17]. The effect was not found in younger or older adults indicating that the effect may not be as robust as previously evidenced in the literature. Results showed that neither bilateral eye movements nor antisaccadic eye movements produced a performance enhancement on the word recognition task. There was no significant difference between the groups in the number for correct words identified or false words identified. This indicates that bilateral stimulation or performing a top-down control task (antisaccade task) may be ineffective at producing an enhancement effect on a word recognition task in healthy younger and older adults.

An ageing effect was found when assessing word recognition task score, with younger adults producing higher task scores and identifying less false words than older adults. This indicates an age-related deterioration in memory recognition and recall capabilities. It is also possible that this result is due to a strategy variation between the age groups. Younger adults may be more conservative when selecting words and therefore may only select words they are more certain are correct resulting in the selection of less false words. However, if older adults are less reserved in their judgements, they may select a greater number of words or be more inclined to guess on the task.

In recent years, there has been a growing literature that has failed to replicate the SIRE effect, bringing into question the robustness and replicability of the effect. Matzke et al. [26] conducted a preregistered study with the aim to replicate the enhancement effect originally found in the Christman et al. [10] study. After reviewing the literature, they attempted to design an optimum research design to investigate the robustness of the effect and used Bayesian statistics to analyse the results. Results revealed no significant variations in the number of words recognised depending on the eye movements condition leading to questions surrounding the robustness of the effect and the conditions in which the effect is optimised. The researchers suggested that previous significant results could be due to the use of *p* values rather than Bayesian statistics which are arguably a more stringent technique [27]. However, many studies displaying the effect have yielded robust *p* values [10,12,17]. Roberts et al. [28] conducted two experiments aiming to replicate the SIRE effect. In their first experiment they successfully replicated the SIRE effect found in the Christman et al. [10] study, however results showed weak Bayesian evidence indicating weak support for the experimental effect found. However, their second experiment that expanded the sample size and assessed vertical and horizontal saccades separately failed to replicate the effect. It was concluded that the SIRE effect is prone to inconsistencies and is very sensitive to experimental design. This study further highlights the inconsistencies and apparent lack of robustness of the SIRE effect. Nevertheless, the failure to replicate should not diminish the extensive literature that has supported this effect and further research is needed to examine the effects systematically.

A recent systematic review [29] assessing the SIRE effect in relation to horizontal and vertical saccades reported that across 22 studies there was a significant facilitation of

horizontal on memory performance providing strong evidence for the SIRE effect. There was no significant effect of vertical saccades on memory retrieval performance and found that handedness influenced the effect with strongly right-handed individuals benefiting more from horizontal saccades than inconsistent handers. These results provide support for the interhemispheric interaction hypothesis and demonstrates the potential for horizontal saccades to enhance memory performance. This systematic review provides strong evidence for the SIRE effect across multiple studies and indicates the effects validity. However, it should be noted that systematic reviews are highly susceptible to publication bias that may have influenced this result. Future research and replications are required to establish the validity and replicability of the SIRE effect. Research should also be conducted with wider populations and participant samples of various ages, ethnicities and clinical groups to investigate the generalisability of the effect.

5. Experiment 2

Experiment 2 expanded on experiment 1 by investigating the potential of bilateral eye movements in people with memory impairments and neurodegenerative disease. Bilateral eye movements have previously demonstrated an enhancement effect in neurotypical adults however current literature has not investigated the effect in people with mild cognitive impairment (MCI) or dementia due to Alzheimer's. Disease (AD). AD is one of the most common causes of Dementia and is a prominent neurodegenerative disease [30]. People with AD often show reduced episodic memory, attentional control and executive functioning [31]. Due to the reduced episodic memory, AD participants may show greater benefit from the SIRE effect and enhanced susceptibility. Further, research has shown that people with AD often display abnormal eye movements on tasks such as pro and antisaccade tasks [1,32]. Cognitive impairment is also well-recognised in Parkinson's (PD) and similar to AD populations display abnormal eye movements on pro and antisaccade tasks [33–35]. Due to eye movement variations on well-established paradigms, it cannot be assumed that the previously found SIRE effect will generalise. Therefore, assessing the SIRE effect in people with AD and MCI is important to establish the robustness of the effect in populations with reduced memory capabilities and the potential benefits of the SIRE effect for these populations.

Although experiment 1 did not yield the enhancement effect, this may have been due to the highly educated sample used leading to a ceiling effects on memory performance. The potential therapeutic benefits of the SIRE may not be fully known due to the lack of research in populations with reduced memory capabilities. The reduced memory recognition and recall capabilities in people with Alzheimer's and mild cognitive impairment may facilitate the enhancement effect due to lower baseline memory capabilities. People with Alzheimer's disease experience memory and executive functioning deficits and techniques to aid and enhance memory capabilities which even temporarily could have a great impact on everyday life and activities.

Therefore, the current experiment compared bilateral eye movements against an eye fixation movement condition in both older healthy adults and people with Alzheimer's disease and mild cognitive impairment and in people with Parkinson's disease, a population who often experience motor deficits alongside cognitive deficits. Assessing the SIRE in clinical populations will allow investigation into potential therapeutic benefits from bilateral eye movements.

Due to the COVID-19 pandemic restricting face to face testing, experiment 2 was converted to an online study using the online testing tool Gorilla. Given the high level of compliance with the eye movement tasks in experiment 1, eye tracking was not implemented in experiment 2.

6. Materials and Methods

6.1. Participants

Experiment 2 included 27 Healthy older adults (Mean age = 69.74 years, SD = 7.57 years), 10 participants with Dementia due to Alzheimer's Disease or mild cognitive impairment (Mean age = 75.6 years, SD = 5.10 years), and 31 participants with Parkinson's Disease (Mean age = 64.35 years, SD = 7.95 years). The inclusion and exclusion criteria and recruitment strategy were kept consistent with experiment 1 for healthy older controls.

The AD and MCI participants were recruited via various National Health Trusts and memory clinics in the UK who distributed the online task. Participants had previously received a clinical diagnosis following a full neurocognitive assessment with a dementia specialist. The AD participants met the requirements for the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM IV) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) for AD.

The MCI participants had received a diagnosis of dementia due to mild cognitive impairment and met the following criteria [36]: (1) subjective reports of memory decline (reported by individual or caregiver/informant); (2) memory and/or cognitive impairment (scores on standard cognitive tests were >1.5 SDs below age norms); (3) Activities of daily living were moderately preserved. The inclusion and exclusion criteria and recruitment methods for the older adults was consistent with experiment 1. Ethical approval was granted by Lancaster University Ethics committee and by the NHS Health Research Authority, Greater Manchester West Research Ethics Committee.

Participants with Parkinson's Disease had received a formal diagnosis of Parkinson's Disease and were recruited through the local community and Parkinson's UK database. All PD participants were receiving parkinsonian medication and completed the study while under their usual medication regime. The Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [37] was used to assess Parkinsonian symptoms. Of the 31 PD participants the average length of time since diagnosis was 5 years and 4 months. All 31 participants with Parkinson's were receiving Parkinsonian medication and were tested under their normal medication regime. Fifteen participants were taking a dopamine agonist (e.g., ropinirole), 11 participants were taking combination (containing levodopa and a peripheral dopadecarboxylase inhibitor, e.g., Madopar), 11 were taking a monoamine oxidase inhibitor (e.g., rasagiline) and 2 patients were taking a catechol-O-methyl transferase inhibitor (e.g., entacapone).

Consistent with experiment 1, G*Power software version 3.1.9.7 was used to conduct a power analysis with the power level set at 0.80 and an error of 0.05. The effect size used was d = 0.495 based on the Christman et al. [10] article. The analysis indicated a required sample size of 33 participants for a within-subjects design.

6.2. Memory Assessments

For experiment 2, a within subject design was employed to control for the variability of memory abilities in AD and MCI participants. A within study design was employed due to the increase variability in patient groups. The study was created and controlled via the online testing tool Gorilla Experiment Builder (www.gorilla.sc, accessed on 21 September 2022). Due to the within study design a further word list was created. The criteria and procedure for creating the second word list was consistent with experiment 1. The presentation of the eye movement conditions, and the word lists were counterbalanced across the groups. Participants were randomly assigned to one of four sequences for completing the study. Participants were provided with two links, to access the online experiment and a Zoom call with the researcher. The researcher remained present on the call while participants completed the study to ensure understanding and compliance with the study and eye movement tasks. The Montreal Cognitive Assessment (MOCA) [38] was completed to indicate probable dementia. Scores below 26 are indicative of MCI and scores below 21, indicative of AD. The MoCA was completed verbally with the experiment.

6.3. Online Tasks

Participants accessed the experiment task via a URL link sent to the participant. The Edinburgh Handedness Inventory [25] was completed with the procedure consistent with experiment 1. The subjective memory complaints questionnaire (SMCQ) was performed to assess the participants perception of their memory impairment [39]. The SMCQ consisted of 14 questions in which the participant responded either yes or no, for example "Do you have difficulty in remembering a recent event?".

The word memory task was converted to an online version with the procedure kept consistent with experiment 1. Participants were presented 36 words that they were instructed to remember and recognise in a later task. Each word was shown on the screen individually for 5 s and automatically changed to the next word consistent with experiment 1. The digit span task [24] was converted to an online version in which each number in the sequence would be individually displayed on the screen for 3 s before changing to the next number in the sequence. Participants were then presented with an entry box where they were instructed to type the number sequence, they had been shown using their keyboard. This procedure was used for both the forwards and backwards version of the task. The digit span task acted as a baseline memory assessment but also to prevent rehearsal of the words prior to the recognition tasks. Following the completion of the assigned eye movement, participants completed a word recognition task consistent with experiment 1. Participants were presented with 72 words (36 target words and 36 false words) and asked to select the words they could recognise from the previous presentation. The same procedure was then repeated for the second word list and eye movement (Figure 2). There was a 5 min delay period between conditions to avoid carry-over effects [40].
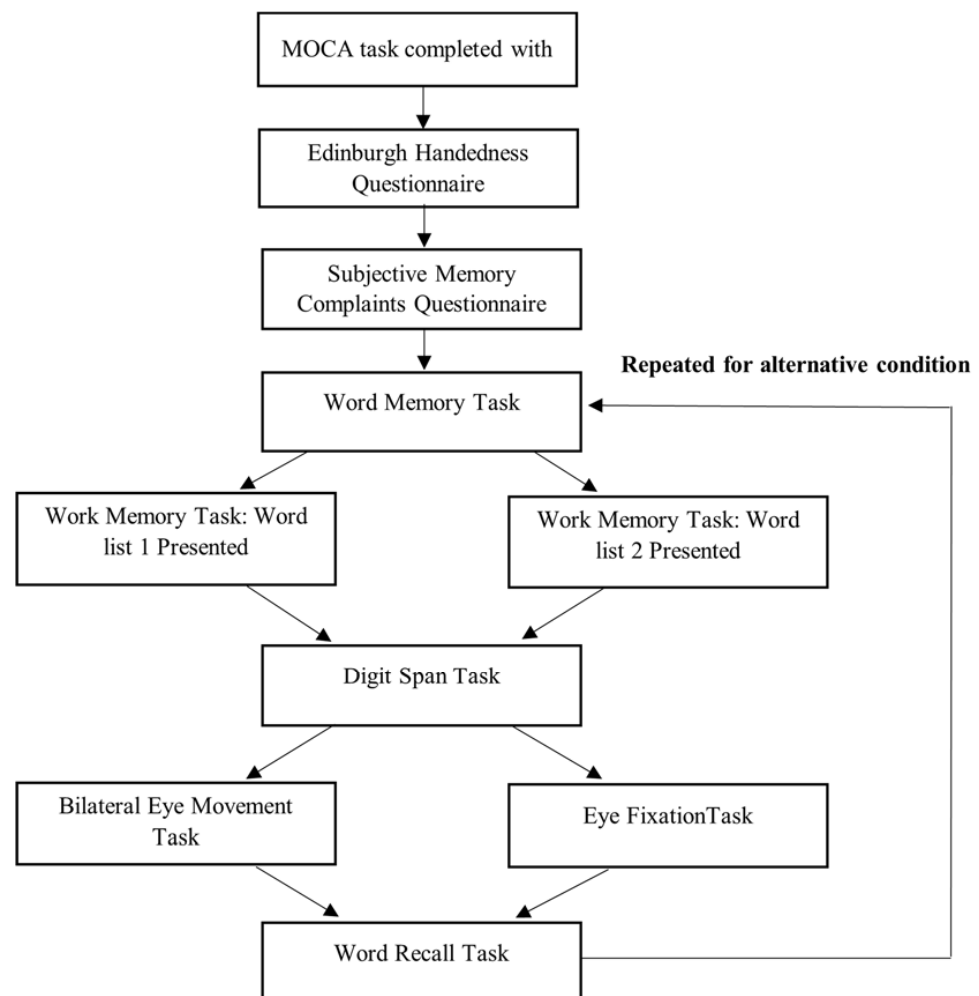

Figure 2. Study Flow Diagram for Experiment 2.

6.4. Eye Movements

The eye movement task included two conditions: Eye fixation and bilateral eye movement. Participants were instructed to sit 55 cm away from the computer screen to maintain a consistent visual angle.

For the bilateral condition participants were presented with a central cross fixation for 250 ms to centre their eye prior the start of the task. A red dot then flashed from the left side of the screen to the right side every 500 ms creating two eye movements per second for 60 trials. The distance of the red target from the central fixation point was 5 cm. The red dot measured 15 mm in diameter (visual angle, 1.56). Participants were instructed to follow the red dot with their eyes as accurately as possible. For the fixation eye movement condition, the fixation was displayed at the centre of the screen for 250 ms. This was replaced by a red dot that flashed at the centre of the screen repeatedly, once every 500 ms. Participants were instructed to maintain their gaze on the target as it flashed in the centre of the screen for 30 s. Participants completed 60 trials lasting approximately 30 s. To monitor compliance with the eye movements, the researchers visually observed the participant completing the eye movements via their webcam.

7. Results

The data was extracted from the online testing tool Gorilla and analysed using SPSS version 27. A multivariate ANOVA was conducted investigating performance variation and potential bilateral enhancement effects on the groups. Group variations between the number of correct and number of false words identified, and overall task score was compared using an ANOVA analysis. For the analysis, participants with AD and MCI were combined into a cognitively impaired group (CI) due to the small sample sizes of these groups individually. Three participants from the older control group and three participants from the Parkinson's group were excluded from the analysis due to scoring <80 on the Edinburgh Handedness Inventory [25] indicating inconsistent handedness. No participants were removed from the analysis due to poor compliance with the eye movement tasks.

7.1. Memory Assessments

Results revealed a significant group effect on MOCA task score, ($F_{(2,65)}$ = 17.82, $p < 0.0001$) with the CI group producing significantly lower task scores compared to the PD and OC group (Table 5). The PD group produced significantly lower task scores compared to the OC group on the MOCA. For the digit span task, significant groups effects were found on both the forwards $F_{(2,65)}$ = 21.86, $p = 0.023$) and backwards $F_{(2,65)}$ = 37.87, $p = 0.001$) versions of the task. For the forwards digit span, the PD group scored significantly lower on the task compared to the OC group. There were no significant differences between the other participant groups. For the backwards version of the task, results revealed that the CI group and the PD group scored significantly lower than the control group. There was a significant group effect on the SMCQ reporting ($F_{(2,65)}$ = 79.34, $p < .0001$) with expectedly the CI group reporting more subjective memory impairments compared to the PD and the OC group.

Table 5. Mean and standard deviations and group post hoc comparisons for the cognitive assessments.

	Participants with Cognitive Impairments (n = 10)		Parkinson's Group (n = 31)		Older Control Group (n = 27)		Post Hoc Comparisons		
							CI vs. PD	CI vs. OC	PD vs. OC
	M	**SD**	**M**	**SD**	**M**	**SD**			
MOCA Task Score	22.40	4.95	25.26	2.19	28.04	2.03	0.013 *	<0.001 *	0.001 *
Digit Span Forward	9.50	2.22	9.61	2.09	11.22	2.62	0.990	0.122	0.029 *
Digit Span Backwards	6.50	1.72	7.22	1.94	9.15	2.44	619	0.004 *	0.003 *
SMCQ score	7.40	3.50	3.87	3.10	2.74	2.31	0.004 *	<0.001 *	0.301

Note. Dependent variable: Task score. CI—Participants with cognitive impairment; OC—older control group; PD—Parkinson's group. * Significant at $p < 0.05$ level.

7.2. Correct Word Identified

When assessing the effect of eye movement condition across the groups on the number of correct words identified, results revealed no significant main effects for participant group ($F(2,65) = 2.11$, $p = 0.130$, partial $\eta^2 = 0.061$) or eye movement condition ($F(1,65) = 1.08$, $p = 0.303$, partial $\eta^2 = 0.016$). There were no significant interaction effects between participant group and eye movement condition ($F(2,65) = 0.772$, $p = 0.466$, partial $\eta^2 = 0.023$) (Table 6).

Table 6. Mean and standard deviations and group post hoc comparisons for the correct words identified following the eye movement conditions.

	Participants with Cognitive Impairments (n = 10)		Parkinson's Group (n = 31)		Older Control Group (n = 27)		Post Hoc Comparisons		
							CI vs. PD	CI vs. OC	PD vs. OC
	M	SD	M	SD	M	SD			
Bilateral Eye Movement	20.10	9.15	24.03	6.79	23.26	7.97	0.339	0.507	0.922
Fixation Eye Movement	17.30	11.80	23.71	7.21	23.52	7.35	0.081	0.101	0.996

Note. Dependent variable: Correct words identified. CI—Participants with cognitive impairment; OC-older control group; PD—Parkinson's group.

7.2.1. Participants with Cognitive Impairment

The effects of the eye movement condition (bilateral vs. Fixation) may affect the individual groups differently or to varying extents. Due to this we assessed the effect of the eye movement condition separately for each participant group. Although the AD and MCI participants recognised a larger number of words during the bilateral condition compared to the fixation condition the change was not significant, $F(1,9) = 1.549$, $p = 0.245$, partial $\eta^2 = 0.147$. This non-significant result may be due to a lack of power due to the small sample size.

7.2.2. Participants with Parkinson's Disease

Results revealed no significant effect of eye movement condition on the number of correct words recognised for the Parkinson's group, $F(1,30) = 0.109$, $p = 0.743$, partial $\eta^2 = 0.004$.

7.2.3. Older Control Participants

There was no significant difference in the number of correct words recognised as a result of eye movement condition for the control group, $F(1,26) = 0.030$, $p = 0.864$, partial $\eta^2 = 0.001$.

7.3. False Word Identified

When assessing the effects of eye movement condition and participant group on the number of false words participants recognised, results revealed no significant effect of eye movement condition ($F(1,65) = 1.89$, $p = 0.174$, partial $\eta^2 = 0.028$) or participant group ($F(2,65) = 0.941$, $p = 0.395$, partial $\eta^2 = 0.028$). No significant interactions were found, $F(2,65) = 0.924$, $p = 0.402$, partial $\eta^2 = 0.028$ (Table 7).

Table 7. Mean and standard deviations and group post hoc comparisons for the false words identified following the eye movement conditions.

	Participants with Cognitive Impairment (n= 10)		Parkinson's Group (n = 31)		Older Control Group (n = 27)		Post Hoc Comparisons		
							CI vs. PD	CI vs. OC	PD vs. OC
	M	SD	M	SD	M	SD			
Bilateral Eye Movement	7.30	4.47	5.03	5.16	4.74	5.12	0.438	0.364	0.974
Fixation Eye Movement	5.60	4.35	5.23	5.28	3.81	3.87	0.973	0.555	0.484

Note. Dependent variable: False words identified. CI–Participants with cognitive impairment; OC—older control group; PD—Parkinson's group.

7.3.1. Participants with Cognitive Impairment

AD and MCI participants recognised a higher number of false words during the bilateral condition compared to the fixation eye movement condition, however this difference was not significant, $F(1,9) = 1.340$, $p = 0.277$, partial $\eta^2 = 0.130$.

7.3.2. Participants with Parkinson's Disease

There was no significant effect of eye movement condition on the number of false words recognised for the PD group, $F(1,30) = 0.084$, $p = 0.773$, partial $\eta^2 = 0.003$.

7.3.3. Older Control Participants

Similar to the AD, MCI and Parkinson's participants, the older controls showed no significant effect of eye movement condition on the number of false words recognised, $F(1,26) = 1.013$, $p = 0.323$, partial $\eta^2 = 0.038$.

7.4. Task Score

Task score was calculated by subtracting the number of false words identified from the number of correct words recognised. This was to adjust for variations in strategy across participants. Consistent with the results for the correct and false words identified, there was no significant effect of eye movement condition ($F(1,65) = 0.133$, $p = 0.717$, partial $\eta^2 = 0.002$) or participant group ($F(2,65) = 2.45$, $p = 0.094$, partial $\eta^2 = 0.071$) on task score. There were no significant intervention effects, $F(2,65) = 0.572$, $p = 0.567$, partial $\eta^2 = 0.018$ (Table 8).

Table 8. Mean and standard deviations and group post hoc comparisons for task score following the eye movement conditions.

	Participants with Cognitive Impairments (n= 10)		Parkinson's Group (n = 31)		Older Control Group (n = 27)		Post Hoc Comparisons		
							CI vs. PD	CI vs. OC	PD vs. OC
	M	SD	M	SD	M	SD			
Bilateral Eye Movement	12.80	5.79	18.22	10.61	18.51	10.50	0.304	0.280	0.993
Fixation Eye Movement	11.70	8.82	17.23	11.1	19.70	8.73	0.283	0.081	0.616

Note. Dependent variable: Task score. CI—Participants with cognitive impairment; OC—older control group; PD—Parkinson's group.

7.4.1. Participants with Cognitive Impairment

Results showed no significant difference between task score between the bilateral and fixation eye movement conditions, $F(1,9) = 0.226$, $p = 0.646$, partial $\eta^2 = 0.025$.

7.4.2. Participants with Parkinson's Disease

There was no significant effect of eye movement condition on task score for the PD group, $F(1,30) = 0.826$, $p = 0.371$, partial $\eta^2 = 0.028$.

7.4.3. Older Control Participants

Results showed that there was no significant difference in task score based on eye movement condition for the older control participants, $F(1,26) = 0.298$, $p = 0.590$, partial $\eta^2 = 0.011$.

8. Discussion

Experiment 2 investigated the SIRE effect in populations with memory impairments and in healthy older adult populations. Previous research has only investigated the SIRE effect in healthy older and younger adult populations [10,17] and has failed to assess the potential of the SIRE effect in populations with cognitive impairments. The benefits and effects of bilateral eye movements could have even greater benefit to disease populations

and elicit stronger retrieval enhancements. Results from experiment 2 which assessed the SIRE effect in people with AD, MCI, PD and healthy older adults failed to replicate the SIRE effect. There was no significant difference in the number of correct or false words recognised across the participants groups based on the eye movement condition. Conducting bilateral eye movements failed to induce an enhancement in memory retrieval in AD, MCI, PD and older adult populations. This result was consistent with experiment 1 that also failed to replicate the SIRE effect in younger and older populations. These results add to the growing amount of literature that has failed to replicate the SIRE effect [26,28] and provides new knowledge that the SIRE effect may not be beneficial in populations with memory impairments and may not generalise to clinical populations. The inconsistent findings and the growing number of failures to replicate undermines the robustness of the effect and its potential as a clinical tool.

Research involving the SIRE effect have used a variety of methodologies with one of the main variations being between vs. within study designs. Here, experiment 1, employed a between study design and experiment 2 employed a within study design due to the increased variability in cognitive abilities in AD, MCI and PD populations. The majority of SIRE literature has used a between-subjects design although studies have successfully demonstrated the SIRE effect in within-subjects designs [40]. Brunye et al. [40] employed a 10 min delay between conditions and did not report finding carry-over effects. Additionally, Roberts et al. [28] used a five-minute delay between conditions and although did not find the SIRE effect, they did not find any reliable order effects indicating that carry-over effects were unlikely. Based on previous literature using a within-subjects design as opposed to a between-subjects design, should not significantly influence or diminish the effect. Further due to a reduced overall variance, particularly high in clinical populations, within-subjects designs could even increase the likelihood of finding an effect providing carry-over and order effects are controlled for. Here, the SIRE effect was unable to be replicated with either a between subject or a within-subjects design indicating that the lack of an enhancement effect found in this study was unlikely a result of subject design variations.

It should be noted that although experiment 1 and 2 closely mimicked previous experimental designs [10], they were not direct replications due to the attempt to expand on existing literature. Methodological variations employed in this study may have weakened or diminished the effect for example the addition of the antisaccade condition and eye tracking in experiment 1 and the shift to an online study with a within study design in experiment 2. Recent evidence [28] suggests that the SIRE effect is highly sensitive to experimental methodology and only appears to be present in specific conditions. The effect appears to only be present in people with certain handedness conditions (strong right-handers), it may be more effective when between methodologies are employed and may only be present in certain lab conditions due to slight variations in methodologies. With so many factors that weaken or diminish the effect, it is clear that the effect lacks reliability and stability. Experiment 2 was conducted online and although there are benefits to online studies, certain methodological parameters can be more difficult to control, such as computer screen size and distance seated from the screen. Research suggests that the SIRE effect may lack robustness and stability and may not lend itself well to being tested in an online setting due to greater potential variations in experiment equipment and set up and less stringent experimental methods. A lab setting can employ a higher level of control and consistency and therefore may increase the likelihood of replicating the SIRE effect. However, here we accessed the SIRE effect in both a lab and online setting and failed to replicate the effect. Repeated failures to replicate can often indicate a nuance in participant demographics or methodology that has not been identified or considered. These nuances could be integral to the effect and until specific boundary conditions are clearly specified, the effect may continue to lack robustness. Direct replications should be conducted to assess the robustness of the effect and to document specific boundary conditions of the effect.

It should be considered that certain individuals may be more susceptible to enhancement effects than others and methodologies that look at enhancement effects on an individ-

ual level may show more promise [41]. It is clear from the literature that the effect is more evident in strongly right-handed individuals [10] and it is possible that other unknown characteristics may mediate the effect.

To date, research has not examined the potential enhancement effect on memory retrial when employing multimodal stimuli rather not solely oculomotor involvement. Marandi et al. [41] demonstrated that auditory input potentially improves the visual recall process. Combining enhancement effects (e.g., oculomotor and auditory techniques) in a multimodal stimuli approach may result in greater enhancement effects on memory retrieval creating a more robust and replicable effect. Future research should examine enhancement effects on memory recall and retrieval by employing a multimodal stimuli approach and examining the effect on an individual level rather than population level.

Across the literature, multiple tasks and stimulus types have been employed when assessing the enhancement effects of eye movements on cognition with mixed results [10,13,42,43]. Future research should examine enhancement effects on memory recall and retrieval by employing a multi-modal stimuli approach and examining the effect of stimulus variables, such as emotional valence. Additional research is also required to examine the SIRE effect on multiple task types and stimuli due to the vast about of literature employing different methodologies.

It is well known that clinical populations are often more variable than the general population. Effects that lack robustness can be even more unstable in clinical populations. Due to this, the clinical applications of the SIRE effect should be questioned. The current study failed to demonstrate the SIRE effect in populations with memory and cognitive impairments and fails to provide evidence for bilateral eye movements to have therapeutic benefits for AD, MCI or PD populations. However, due to the small sample sizes in experiment 2, particularly for the AD and MCI group, clinical application should not be ruled out. The study may have lacked sufficient power, and this could likely have caused the null result observed in experiment 2. The cognitive impairment group included only 10 participants and power analysis indicating a sample size of 33 (approximately 11 per group) to produce a significant result at the $p < 0.05$ level. The AD and MCI group recognised more correct words during the bilateral conditions compared with the no eye movement condition although not significant. This null result could be due to a lack of power from low participant samples and therefore results from experiment 2 should not rule out the potential benefits of the SIRE effect in clinical populations. Future research should continue to assess the SIRE effect in people with AD, MCI and PD with adequate sample size to achieve sufficient power. Although, prior to clinical applications, consistent replications are required to demonstrate a stable and robust effect with clear boundary conditions.

9. Conclusions

Future research should focus on establishing the robustness of the SIRE effect by performing direct pre-registered replications to validate the effect. Research should aim to establish clear and precise boundary conditions in which the effect is present, robust, and replicable. Such replications could provide a deeper understanding of the literature and findings could help re-examine and enhance existing theories.

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Chapter 7

7. General Discussions and Conclusions

7.1 Summary of Studies

Inhibitory control, disengagement of attention and working memory processes are vital to everyday tasks and for successfully navigating daily events and activities (Baddeley & Hitch, 1974, Salthouse, 2009). Neurodegenerative diseases such as dementia and Alzheimer's leads to a deterioration of cognitive processes, making simple everyday tasks more complex, challenging, and burdensome (Crawford et al., 2013). A vast amount of research has documented the varying types of cognitive impairment, neurodegenerative and decline that accompany AD and dementia. Cognitive processes can be assessed in multiple ways with eye-tracking being an effective tool for assessing cognitive functioning in both healthy individuals and individuals with cognitive impairment (KahanaLevy et al., 2018). Key distinctions and markers for impairment have been found on multiple eye tracking tasks when comparing healthy individuals to people with AD (Opwonya et al., 2021)). These findings highlight the potential for eye tracking to aid with the diagnosis and monitoring of AD and dementia (Readman et al., 2021). Eye-tracking tasks such as the antisaccade task have been shown to successfully distinguish AD individuals and healthy controls however, the task is often criticized for being unintuitive and largely unnaturalistic. Due to this, across chapters 3-5 I investigated the potential of alternative eye-tracking paradigms and measures, including gap and overlap prosaccade tasks, the IRD task and latency coefficient of variation, to provide robust markers for cognitive impairment. These paradigms were assessed in populations with varying levels of cognitive impairment (AD and MCI), across multiple ethnic groups (South Asian adults and European Adults) and age groups (younger and older adults). Following this in chapter 6, I shifted my focus to whether eye movements could aid with the enhancement of cognition and memory processes in healthy and clinical populations. Cognition and memory enhancement effects have been found in healthy adult populations after conducting bilateral eye movements (Christman et al., 2003). Current literature has not assessed this

enhancement effect in clinical populations and if present, real-life therapeutic benefits could be developed from this effect.

In chapter 3 I showed, using the gap effect paradigm, that the ability to engage and disengage attention is preserved in people with MCI and AD. This was demonstrated by a clear reduction in saccade reaction times when disengagement was facilitated. A strong ageing effect was evident, revealing cognitive slowing in disengagement of attention processes during natural ageing. This study found that the gap effect was present in South Asian older adults but found baseline variations in reaction times when compared to European older adults, with South Asian participants showing slower reaction times.

Previous research has demonstrated clear inhibitory control deficits in people with AD and dementia (Crawford et al., 2005) and it was assumed that these deficits were present across all aspects of inhibitory control. In chapter 4, it was found that the IRD effect, resulting in longer saccadic reaction times towards a location where a previous distracter target was located compared to the location of a previous target, was present across all participant groups and preserved in individuals with AD and MCI. These findings demonstrated the robustness of the IRD and that it generalises across various clinical, age and ethnic groups. Additionally, the demonstration of the IRD in people with AD and MCI indicates that the antisaccade task and the IRD task target different inhibitory control mechanisms and not all aspects of inhibitory control capabilities are impaired in people with AD and MCI.

In chapter 5, results indicated that coefficient of variation measures on pro and antisaccade tasks are not a robust indicator of cognitive impairment although may be effective at distinguishing subgroups of people with MCI. Antisaccade mean latencies were able to robustly distinguish people with AD from older controls and between MCI subgroups with a high level of sensitivity. These results add to the growing body of literature that highlights antisaccade mean latencies as a marker for cognitive impairment.

In chapter 6, the previously reported saccade induced retrieval effect (Christman et al., 2003) failed to replicate. Across two methodologies, there was no effect of eye movement on the number of words participants were able to recall in a subsequent task. This effect was assessed in younger and older adults and people with AD, MCI and PD. Results indicated the need for further research to establish the effects robustness and replicability before assessment of therapeutical benefits in clinical populations.

Taken as a whole, these findings suggest that eye movements can be highly informative of cognitive functioning and a useful indicator of preserved cognitive functioning in addition to impairment and deficits. These findings indicate that specific aspects of attention and inhibitory control process are not impaired in people with AD as previous literature suggests. Therefore, based on these findings I suggest that research into AD should look deeper into specific aspects of inhibitory control and attentional disengagement and urge researchers not to make broad generalisations when discussing systems that may be impaired in people with AD.

Here, I will first discuss the effects of ageing on cognition and the use of eye-tracking to measure age-related cognitive decline. Following this, I will discuss findings related to disease effects on memory, cognition and eye-tracking performance, specifically areas of cognition and effects that this thesis found to be preserved in people with AD. This thesis will then discuss the findings relating to ethnicity and emphasise the need for further research investigating established paradigms in wider and non-WEIRD populations.

7.2 Effects of Ageing on Cognition and Eye Movements

Research demonstrates that people experience a reduction in processing capabilities, inhibitory control and working memory due to age-related cognitive decline (Baddeley & Hitch, 1974; Hasher & acks, 1988; Salthouse, 2009). Eye movements can provide an indication of general cognitive functioning and parameters such as increased saccade latencies and error rates can be markers for cognitive impairment. The link between age-related cognitive decline and saccadic eye movements has

been well documented in the literature and the findings from this thesis provide more specific details on how ageing affects eye movement paradigms. Across the eye-tracking paradigms (gap effect, IRD effect, saccade latencies) assessed in this thesis an ageing effect was found. Consistently, ageing did not diminish or alter the effects however there was a clear reduction in saccade latencies and reaction times. When executing a saccade there is a decisional process needed to accumulate and process information to decide when to trigger the saccade (Hutton, 2008). The amount of decisional processing time required to trigger the saccade is contingent on processing efficiency and the level of cognitive processing such as working memory or attentional control required for the task. It is theorised that due to age-related cognitive decline, this decisional process required to trigger a saccade, is longer and delayed in older adults. This finding has been consistently found across multiple studies assessing pro and antisaccade eye movements (Yang et al., 2006; Abel & Douglas, 2007; Litvinova et al., 2011). It is often assumed that the increase in saccade latency is related to a decline in processing speed, however, an alternative suggestion is that neuronal degeneration of key cortical areas involved in triggering saccadic eye movements could be causing the increase in latencies (Kapoula et al., 2010). Research has demonstrated an age-related anterior-posterior cortical decline (Dennis & Cabeza, 2008) which is consistent with changes in the frontal eye fields, the dorsolateral prefrontal cortex and other cortical areas involved in the saccade execution (Domagalik et al., 2012; Munoz & Everling, 2004, Matsuda et al., 2004). Age-related cognitive decline in the brain areas and systems referenced above would explain the increased difficulty in disengaging attention and the greater reliance on external facilitation of disengaging attention and increased saccade latencies found in chapter 3.

Increased error rates on inhibitory control tasks such as antisaccade tasks has been linked to age-related cognitive decline (Klein et al., 2000; Peltsch et al., 2011). The IRD task assessed in chapter 4 provided a measure of error rates on an inhibitory control task and findings did not align with previous literature showing increased error rates in older adult populations. The age-related decline, which is evident in the current thesis, particularly in chapter 4, does not appear to generate performance deficits related to accuracy. For example, participants often did not display an increased number of errors on

the tasks or the diminishment of the effect, however processing speeds were often affected. Older adults may forfeit processing speed in order to maintain accuracy and successfully complete the task. This processing speed compromise may only be effective when processing demands are moderate and if the task becomes too difficult or demanding errors may increase. Processing demands on the antisaccade task are likely higher than the IRD task due to the requirement to generate an antisaccadic eye movement and therefore may explain why age related deficits are more evident.

7.3 Effects of Disease Related Cognitive Impairment on Eye Movements

Multiple studies have demonstrated an association between abnormal eye movements and cognitive decline (Crawford et al., 2013, Anderson & MacAskill, 2013). However, in the current study eye movements were surprisingly well preserved across the paradigms assessed in this thesis. It was evident that the main distinction between the AD, MCI and healthy control groups across the studies was increased mean latencies and saccade reaction times. Mean latencies on the antisaccade task appeared the most robust at distinguishing AD from healthy adults and between people with AD and MCI. This finding from chapter 5 adds to the growing body of literature demonstrating the robustness of mean latencies on the antisaccade task in distinguishing participant groups. This finding provides support for eye tracking, specifically mean latencies on the antisaccade tasks, to aid the diagnosis of AD and MCI by providing an early marker for impairment. Research on prosaccades has produced inconsistent findings in clinical populations with some studies finding increased saccade latencies in AD populations while others failing to find significant differences. In studies 3 and 5, mean latencies on the prosaccade task were not impaired in AD populations (gap and overlap conditions) further highlighting that prosaccade mean latencies lack the sensitivity and specificity to robustly distinguish between AD and healthy adult populations.

Increased variability in task performance can indicate impairments and the lack of ability to sustain attention, maintain accuracy and consistency. Increased variation in saccade latencies has previously been linked to cognitive impairment (Yang et al., 2013). Study 5 predicted that AD and MCI

participants may show increased coefficient of variation scores due to greater attentional fluctuation caused by cognitive impairment. However, we found no evidence for increased attentional fluctuation in AD populations when performing pro and antisaccade tasks. Variations in attentional fluctuation may be more prominent in advanced stages of AD indicating that CV measures may lack sufficient sensitivity to detect variations in early to moderate stages of AD. Conversely, previous research and in chapter 5, increased attentional fluctuation was found in MCI participants which fails to support the above conclusion. These inconsistent findings bring into question the robustness of CV as a reliable marker for impairment. It is clear more research is needed to evaluate attentional fluctuations on eye tracking tasks in AD and MCI to understand their true potential in distinguishing clinical and nonclinical groups.

One of the most interesting findings of this thesis was the unexpected level of preservation of capabilities in AD and MCI populations. Chapter 3 demonstrated that the gap effect was preserved in AD and MCI populations. Similar to healthy controls, AD and MCI populations produced significantly faster prosaccade reaction times during the gap condition compared to the overlap condition. Saccadic eye movements are regulated by the neurophysiological networks and are generated by reciprocal activation of saccade-related neurons and the inhibition of fixation neurons in the superior colliculus (Dorris et al., 1995, 1997). The Findlay and Walker model (Findlay & Walker, 1999) states that removing the fixation target, as seen in the gap condition, leads to a reduction in the activation of the fixation units. This in turn removes the saccade inhibition element of the task reflected by a reduction in saccade reaction times. In overlap conditions when the fixation point remains present, the fixation units continue to be active and move units are inhibited leading to a delay in the initiation of the saccade. This study indicates that this network in people with AD and MCI is well preserved.

Furthermore, chapter 4 discovered that the IRD effect was also well preserved in people with AD and MCI. AD and MCI populations presented with longer saccade reaction times when shifting their gaze to the location of a previous distracter target when compared with the location of the previous gaze-directed target. The IRD effect was remarkably well preserved in AD and MCI individuals

demonstrating the strong robustness of this effect. Furthermore, it provides evidence for a dissociation between inhibition of a specific distracter and more general gaze aversion as employed in the antisaccade task displaying clear performance deficits. The evidence of preservation of attentional disengagement and inhibition processes found in this thesis will increase our understanding of the specificity of oculomotor impairment in AD. Additionally, it indicates that impairments evident on the antisaccade task should not be generalised to all elements of inhibitory control or disengagement of attention. It is clear that there is a dissociation of impairment of the oculomotor pathways and inhibitory control pathways in people with AD.

7.4 Effects of Ethnicity on Cognition and Eye Movements

Previous research has demonstrated variations in eye movement latencies, fixations and scan patterns across different ethnic groups (Knox et al., 2012; Wolohan & Knox, 2014; Mardanbegi et al., 2020), however, multiple established eye-tracking paradigms have failed to assess these effects in relation to ethnicity or cultural effects. To address this gap, chapters 3 and 4 investigated eye-tracking paradigms in South Asian older adults. Results revealed that both effects (gap effect and IRD effect) generalised to South Asian adults. Consistent with European older adults in chapter 4, South Asian adults demonstrated faster saccade reaction times when trials included a short temporal gap facilitating disengagement compared to overlap conditions. Additionally, in chapter 4, South Asian adults demonstrated that the IRD effect generalised across different ethnic groups by displaying faster saccade reaction times to a target presented in the location of a previous target as opposed to a distracter target. These findings support the robustness and generalisability of these effects. However, across both studies, variations were found when assessing saccade latencies. South Asian adults produced slower saccade latencies on both the overlap and gap trial types compared to European adults. This was consistent with results on the IRD effect that also found slower saccade latencies in South Asian adults in experiment 1 across the three trial types compared to European adults. These findings suggest baseline variations in saccade latencies across different ethnicities aligning with previous research (Alotaibi et al., 2017; Knox et al., 2012; Rayner et al., 2007). Surprisingly, experiment 2 when assessing

the IRD effect did not demonstrate this variation in saccade latencies across the groups despite variations found in experiment 1. The exact reason for this inconsistency is not known but may have been due to increased task difficulty in experiment 2. These findings highlight the importance of assessing new and established eye movement paradigms in relation to ethnicity effects. Further, it is clear that genetic, biological and cultural differences can affect eye movement parameters (Mardanbegi et al., 2020) and future research should consider these factors when assessing eye movement performance. Additionally, it is evident that research involving South Asian populations is lacking and future research should attempt to address this gap which would lead to a greater understanding of eye movement variations attributed to ethnicity factors.

7.5 Clinical Implications

To date, research surrounding clinical populations has prominently focused on impairments and reductions in capabilities and rarely focuses on capabilities that are well preserved. Assessing capabilities and functions that are preserved in clinical populations can in some situations be as informative to distinguishing clinical groups and monitoring disease progression as assessing impairments. For example, a person with AD may show performance deficits on the antisaccade task but preserved functioning on the IRD task whereas a person with Parkinson's disease may demonstrate impaired or preserved functioning on both tasks. Establishing a profile of impairments and preserved capabilities could aid in the distinction of various types of neurodegenerative diseases that can often be difficult to distinguish and diagnose accurately. This thesis provides support for the use of eye tracking to aid in the monitoring and diagnosis of cognitive impairment and provides new insights into preserved inhibitory control and attention functioning in AD and MCI populations.

7.6 Future Applications of Eye Tracking

A vast amount of literature has demonstrated the potential of eye tracking to aid in the early diagnosis of multiple neurodegenerative disease, most notably dementia and AD (Crawford et al., 2013). Existing diagnosis tools for dementia and AD often are unable to detect AD in very early stages

of the disorder and eye tracking may be able to detect subtle biomarkers of impairment prior to a formal diagnosis. Although in this thesis we found that many eye tracking effects were preserved in AD populations and surprisingly comparable to healthy controls, there were still markers for AD impairment such as increased mean latencies and error rates on the antisaccade task. Furthermore, collating research to create profiles of oculomotor control that are preserved and impaired in various neurodegenerative diseases may be a useful method to distinguish AD populations from not only healthy controls but also other similarly presenting neurodegenerative diseases such as PD. Future research should examine the literature to determine the robustness of these measures and potential eye tracking profiles of impairments and preserved functions for various neurodegenerative disorders.

For eye tracking to be truly beneficial in AD diagnosis, it needs to be sufficiently sensitive to detect markers in pre-clinical stages. Previous research and results in this thesis using aMCI and naMCI groups have demonstrated that people with aMCI (are more likely to progress to an AD diagnosis) perform more similarly to AD populations when examining eye movement parameters and naMCI more similarity to healthy controls (Wilcockson et al., 2019). This demonstrates that eye tracking may be able to detect variations in subgroup of MCI and may have potential in determining increased risk MCI populations. However, there is a strong need for longitudinal data to follow older adults prior to diagnosis and examine at what stage eye tracking makers are evident to understand the true potential of eye tracking in AD diagnosis.

One of the main challenges of using eye tracking technology in diagnosis is the accessibility to eye tracking technology in clinical or home-based settings. With ever growing advances in technology and a wider availability of low-cost eye trackers, the potential for larger-scale longitudinal eye tracking studies is becoming progressively more feasible. Home-based eye tracking studies using built-in computer webcams have become increasingly popular and advancements in eye tracking technology has improved the quality and reliability of eye tracking data obtained via webcams (Wisiecka et al., 2022, Schröter et al., 2021). Additionally recent research examining home-based eye tracking studies using built-in webcams demonstrate the feasibility of these methods in older adult and AD populations and provide recommendations for future delivery (Greenway et al., 2021). These methods could offer a

low-cost and widely accessible way to examine eye tracking performance in older adults and identify early biomarkers and individuals who may be at greater risk of progressing to a diagnosis of MCI or AD. Although future research is needed to examine the utility of these methods, home-based webcam eye tracking offers exciting opportunities for advancements in MCI and AD diagnosis and monitoring.

7.7 Conclusions

Overall, this thesis expands on existing literature by assessing established eye-tracking paradigms (gap effect, IRD effect and latency coefficient of variation) in relation to ageing, disease and ethnicity. It is vital to understand the robustness and generalisability of both novel and established eye-tracking paradigms. Additionally, this thesis provided new insights into effects that are surprisingly well preserved in people with AD and MCI. Research has primarily focused on cognitive skills that degenerate in AD and capabilities that are preserved often draw less attention. However, here we argue that it is equally important to assess cognitive functions and capabilities that are well-preserved as this can offer their own insights. We suggest that future research should aim to offer a similar focus to cognitive capabilities that are preserved in AD and MCI as this will aid in the development of new early intervention strategies for treatment, diagnosis and monitoring of the disease.

Chapter 8

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