Peripheral reaching in Alzheimer's disease and mild cognitive impairment

Alexandra G. Mitchell*, Stephanie Rossit, Suvankar Pal, Michael Hornberger, Annie Warman, Elise Kenning, Laura Williamson, Rebecca Shapland & Robert D. McIntosh

ABSTRACT

Recent evidence has implicated areas within the posterior parietal cortex (PPC) as among the first to show pathophysiological changes in Alzheimer's disease (AD). Focal brain damage to the PPC can cause optic ataxia, a specific deficit in reaching to peripheral targets. The present study describes a novel investigation of peripheral reaching ability in AD and mild cognitive impairment (MCI), to assess whether this deficit is common among these patient groups. Individuals with a diagnosis of mild-to-moderate AD, or MCI, and healthy older adult controls were required to reach to targets presented in central vision or in peripheral vision using two reaching tasks; one in the lateral plane and another presented in radial depth. Pre-registered case-control comparisons identified 1/10 MCI and 3/17 AD patients with significant peripheral reaching deficits at the individual level, but group-level comparisons did not find significantly higher peripheral reaching error in either AD or MCI by comparison to controls. Exploratory analyses showed significantly increased reach duration in both AD and MCI groups relative to controls, accounted for by an extended Deceleration Time of the reach movement. These findings suggest that peripheral reaching deficits like those observed in optic ataxia are not a common feature of AD. However, we show that cognitive decline is associated with a generalised slowing of movement which may indicate a visuomotor deficit in reach planning.

Keywords: Alzheimer's disease; visuomotor; cognitive impairment; reaching; optic ataxia

1. INTRODUCTION

Alzheimer's disease (AD) is a progressive, neurodegenerative condition most often associated with cognitive decline and symptoms of memory loss, limited attention and poor spatial navigation. However, the pathophysiological cascade that leads to AD can begin 20 years before the onset of these behavioural markers (Dubois et al., 2014; Jack et al., 2013; Pike et al., 2007) and early neurological changes have been identified in both autosomal (familial) and sporadic forms of AD (Gordon et al., 2018; Villemagne et al., 2013). The precuneus, in the medial posterior parietal cortex (PPC), has been identified as one of the first brain areas to show patterns of change preceding cognitive impairment in amnestic AD (Chételat et al., 2005; Gordon et al., 2018; Hämäläinen et al., 2007; Huang et al., 2018; Pennanen et al., 2005). Longitudinal modelling identified altered Amyloid-β levels in the precuneus at around 21 years before the onset of memory loss; metabolic changes around 18 years prior to memory loss and reduced cortical thickness around 13 years prior to memory loss (Gordon et al., 2018). As well as structural changes, functional changes to neural activity within the PPC have been identified in individuals with AD and MCI (Fernandez & Duffy, 2012; Hawkins & Sergio, 2014; Thiyagesh et al., 2009). These data concern typical amnestic forms of AD, not the atypical variant Posterior Cortical Atrophy (PCA) which is associated with major changes in visuospatial, attentional and visuomotor abilities (Crutch et al., 2017). The more subtle pathophysiological changes of the PPC in typical AD might be expected to lead to changes in visually-guided behaviour, but these have not been extensively examined.

The PPC is a major component of the dorsal visual stream, a network of brain areas involved in the processing of visuospatial information, especially the guidance of goal-directed actions, such as reaching to visual targets (Clower et al., 1996; Culham & Valyear, 2006; Kertzman et al., 1997; Konen et al., 2013). We might, therefore, expect impairments in visuomotor control of simple reaching actions in typical AD, even at prodromal and pre-clinical stages. However, action impairments are not a prominent clinical feature of typical AD, and such individuals perform tasks such as target-directed reaching with similar levels of spatial accuracy to age-matched controls (de Boer et al., 2016; Salek et al., 2011; Tippett et al., 2007, 2012; Tippett & Sergio, 2006). More cognitively complex reaching tasks may expose differences in accuracy between patients with AD and healthy older adults (Hawkins et al., 2015; Hawkins & Sergio, 2014, 2016; Mollica et al., 2017). For instance, patients with mild-to-moderate AD make large spatial errors if the plane of response is dissociated from the plane of the screen (Tippett et al., 2007, 2012; Tippett & Sergio, 2006) and removing visual feedback from both the hand and cursor during simple guided actions has been found to increase spatial error in AD (Ghilardi et al., 2000; Felice Ghilardi et al., 1999). Alongside this, AD patients are slower to initiate goal-directed actions, and have longer movement durations compared to healthy, older adults (Tippett et al., 2007; Tippett & Sergio, 2006). This general pattern of slowed movement in typical AD has been reproduced in a number of studies (de Boer et al., 2016; Ghilardi et al., 1999; Tippett et al., 2012; Verheij et al., 2012), in individuals with MCI (Salek et al., 2011) and in adults with increased risk of AD (Hawkins et al., 2015; Hawkins & Sergio, 2014, 2016). It is therefore possible that degeneration in the PPC, along the dorsal visual stream, in early stages of the disease does result in disrupted visuomotor processing.

The prototypical visuomotor disorder associated with damage to the PPC is optic ataxia (Balint, 1909; Karnath & Perenin, 2005; Rossetti et al., 2019). Patients with optic ataxia typically have little trouble reaching accurately to targets in central vision, but show large spatial errors when reaching for targets in their peripheral visual field (Perenin & Vighetto, 1988; Ratcliff & Davies-Jones, 1972). During clinical testing, patients are required to reach to lateralised targets, both when they are allowed to look

directly at the target and when they are required to fixate straight-ahead so the target is in peripheral vision (Borchers et al., 2013; Perenin & Vighetto, 1988). Optic ataxia is indicated by a pronounced increase in spatial errors to targets presented in peripheral vision. However, as misreaching is typically confined to the periphery and accuracy is maintained to targets in central vision, it may go unnoticed in daily life and clinicians will not observe signs of optic ataxia unless specifically trying to elicit them. Given that signs of optic ataxia are not expressly assessed in individuals with cognitive impairment, the presence of this specific visuomotor deficit could go unnoticed in early AD. It has been noted that patients with optic ataxia are also impaired in cognitively complex reaching conditions, such as plane-dissociated reaching and reaching with reduced visual feedback (Blangero et al., 2007; Granek et al., 2013; Jeannerod, 1986; Pisella et al., 2009). This similarity with typical, amnestic AD impairment (Tippett et al., 2007, 2012; Tippett & Sergio, 2006) makes it plausible that patients with AD may also have problems with peripheral misreaching if this ability were specifically assessed.

Optic ataxia has been noted as a feature of PCA, but no previous study has systematically tested for signs of optic ataxic misreaching in patients with typical, amnestic AD. The purpose of the present study is to fill this surprising knowledge gap. Two different, complementary tasks were used to assess reaching ability. The first was a tablet-based reaching task presented on the lateral (fronto-parallel) plane. This task was designed for potential future translation into clinical settings. The second was a motion-tracked, lab-based task with targets presented in radial depth that allowed for more detailed kinematic analysis. This radial reaching task was similar to typical laboratory assessments of optic ataxia in experimental neuropsychology (e.g. Milner et al., 2003). We plan to evaluate the possible presence of peripheral misreaching in patients with mild-to-moderate typical AD and in individuals with amnestic MCI, by comparison with a group of age-matched controls. The methods in the current paper have been pre-registered and published as a study protocol (Mitchell et al., 2020). We hypothesise that individuals with AD, and possibly those with MCI, will show deficits reaching to targets presented in peripheral vision similar to what is observed in optic ataxia. A multiple-case approach of testing for deficits at the individual patient level is complemented by group-based comparisons, and more exploratory analyses of reaching kinematics. The present study, therefore, aims to clarify whether visually guided reaching to peripheral targets is affected in early clinical stages of AD, laying groundwork for further investigation into action guidance in dementia.

2. MATERIALS & METHODS

2.1 Participants

Patients were tested at the University of Edinburgh (UOE) and the University of East Anglia (UEA), recruited via the Anne Rowling Regenerative Neurology Clinic, (Edinburgh) and the Julian Hospital (Norwich). Patients in the MCI group (N = 10) had a clinical diagnosis of amnestic MCI but had not yet progressed to AD. Patients in the AD group (N = 17) had a clinical diagnosis of AD and an ACE-III score of 50 or above, indicating mild to moderate impairment (Bruno & Schurmann Vignaga, 2019). Criteria for diagnoses of both MCI and AD groups were determined by the National Institute of Ageing-Alzheimer's Association (NIA-AA) guidelines at both sites (Jack et al., 2011). Patients were excluded if they presented with clinical features suggestive of Lewy body pathology (e.g. visual hallucinations or rapid eye movement sleep disorder), significant difficulty communicating or understanding English, significant uncorrected visual impairment (e.g. cataract, macular degeneration or scotoma) or conditions that could interfere with smooth hand movements (e.g. ataxia, essential tremor and severe arthritis).

Healthy controls (N = 24) for both lateral and radial reaching tasks were tested at the University of Edinburgh. An additional 8 healthy controls were tested at UEA, to allow for differences in set-up between sites for the radial reaching task. Healthy controls were aged 50-80, had normal or corrected-to-normal vision, and no reported neurological or neurodegenerative conditions. Two AD patients were left-handed, and all other participants were right-handed by self-report. Demographic characteristics for participant groups are summarised in Table 1.

This research was approved by the UK Health Research Authority, the East of England Central Cambridge Research Ethics Committee and Research & Development for NHS Lothian and NHS Norfolk & Suffolk Trusts, in accordance with guidelines from the Declaration of Helsinki.

2.2 Pre-registered protocol

The protocol for this study was pre-registered on Open Science Framework on 17-10-2019 (https://osf.io/mtqck) and subsequently published in BMJ Open (Mitchell et al., 2020). The materials and methods for the present study follow the published protocol, except for the following details. First, the COVID pandemic forced an early close to patient testing (from 23-03-2020), prior to the end of the period of funded research, so our planned sample of 24 participants per group could not be achieved (see *Section 2.4*). Second, the pre-registered plan for outlier removal flagged over 7/24 UOE control participants as outliers in the lateral reaching task. As we could not justify removing 29% of our controls from this task, we adjusted our analysis to omit the outlier removal step. As we planned to remove control outliers only, this step affected our pre-registered analysis of healthy controls only. Third, the pre-registered analyses included a factor of target side. However, as no significant differences were observed across side at the group level, data are averaged across right and left sides for simplicity of presentation. Fourth, age was added as a covariate to single case analyses (Crawford et al., 2011) and all ANOVAs. Finally, as single case analyses revealed no cases with borderline peripheral reaching deficit ($.05 < P < .025$, see Mitchell et al., 2020), borderline deficits are not reported here. A document reporting the analysis performed exactly according to pre-registered plan is archived at https://osf.io/bxnqs/.

Open materials, data & code
Anonymised data, stimulus and analysis code are available at https://osf.io/bxnqs/.

Table 1: Demographic information for healthy controls (HC), mild cognitive impairment (MCI) and Alzheimer's disease (AD) for both tasks. HC (radial) include 8 additional UEA control participants

Group	N	F/M	Age	Education[1]	ACE score	Weeks since diagnosis
HC lateral	24	15/9	63.8 (6.47)	22.0 (2.82)	-	-
HC radial	32	22/10	63.4 (6.80)	20.7 (3.88)	-	-
MCI	10	6/4	70.3 (8.35)	20.3 (3.80)	85.8 (8.01)	34.1 (30.29)
AD	17	5/12	65.8 (7.81)	17.7 (4.65)	75.5 (9.84)	66.5 (65.52)

[1]The age participants were when they left full-time education in years
Standard deviation displayed in brackets for mean age, education, ACE score and time since diagnosis.

2.3 Tasks

To assess peripheral reaching, two different set ups were used: a tablet-based reaching task in the fronto-parallel plane (lateral reaching) and a motion-tracked reaching task in radial depth (radial reaching). Participants completed two versions of each task; a condition in which they were instructed to look directly at targets before reaching (free reaching) and a condition in which central fixation was required (peripheral reaching). The inflation of absolute reaching error in peripheral reaching relative to free reaching was the critical dependent measure in each task.

Tasks were performed in a fixed order, to allow for direct comparisons of individual patients against the control group. Lateral reaching was always performed before radial reaching. Within each task, free reaching was performed before peripheral reaching, and both free and peripheral reaching were completed first with the dominant hand, followed by the non-dominant hand. Targets were always presented in the peripheral visual field on the same side as the reaching hand in both tasks. The reason for this arrangement is that peripheral misreaching errors in optic ataxia tend to be largest when the contralesional hand is used to reach to targets on contralesional side (Blangero et al., 2010; Perenin & Vighetto, 1988). In the present study, by having each hand reach to targets on the same side, we could be sure to include the conditions most likely to be most affected, regardless of whether the PPC was more affected on the right or left side in a given patient.

2.3.1   Lateral reaching

Stimuli & Apparatus

Stimuli were presented on a HP Pavillion x260 touch screen (310 x 175mm, 1920 x 1080pix). Tasks were coded in OpenSesame, version 3.2.8 (Mathôt et al., 2012). Participants were seated 400mm away from the screen, positioned with either the right or left edge of the screen aligned to the body midline (Fig. 1). A start box (white rectangle, 2x2°) appeared at the centre edge (right or left) of the screen, aligned to the participant's midline. For peripheral reaching, a fixation cross (1x1°) was presented 5° directly above the start box. Targets were presented as white circles (diameter = 2°) along radial spokes at either 28, 33 or 38° (200, 240, 275mm) to the left or right of fixation (Fig. 1B & 1C). Movements were recorded at the screen refresh rate of 60Hz. The experimenter sat directly opposite the participant and directly monitored eye movements throughout the task, matching methods used in testing for optic ataxia in clinical settings (Borchers et al., 2013).

Free reaching

For free reaching, no fixation cross was presented. Participants initiated a trial by pressing and holding down the start box with either their right (right-sided reaching) or left (left-sided reaching) index finger. Once the screen was touched, the start box disappeared, and, after a short delay (250 – 750ms, randomised 100ms intervals), a target appeared at one of nine possible locations. Participants were required to look directly at the target and lift their finger off the start box to make one smooth, reaching movement to touch it. Participants were instructed to reach as soon as they were looking directly at the target and to be as accurate as possible, however movement time was not restricted. The target remained on screen until a touch was recorded, after which it disappeared with a short beep (100ms, 440Hz). If no eye-movement was made to the target, the trial was repeated immediately. The block ended after a minimum of 27 valid trials (3 per target position), or after a total of 50 trials.
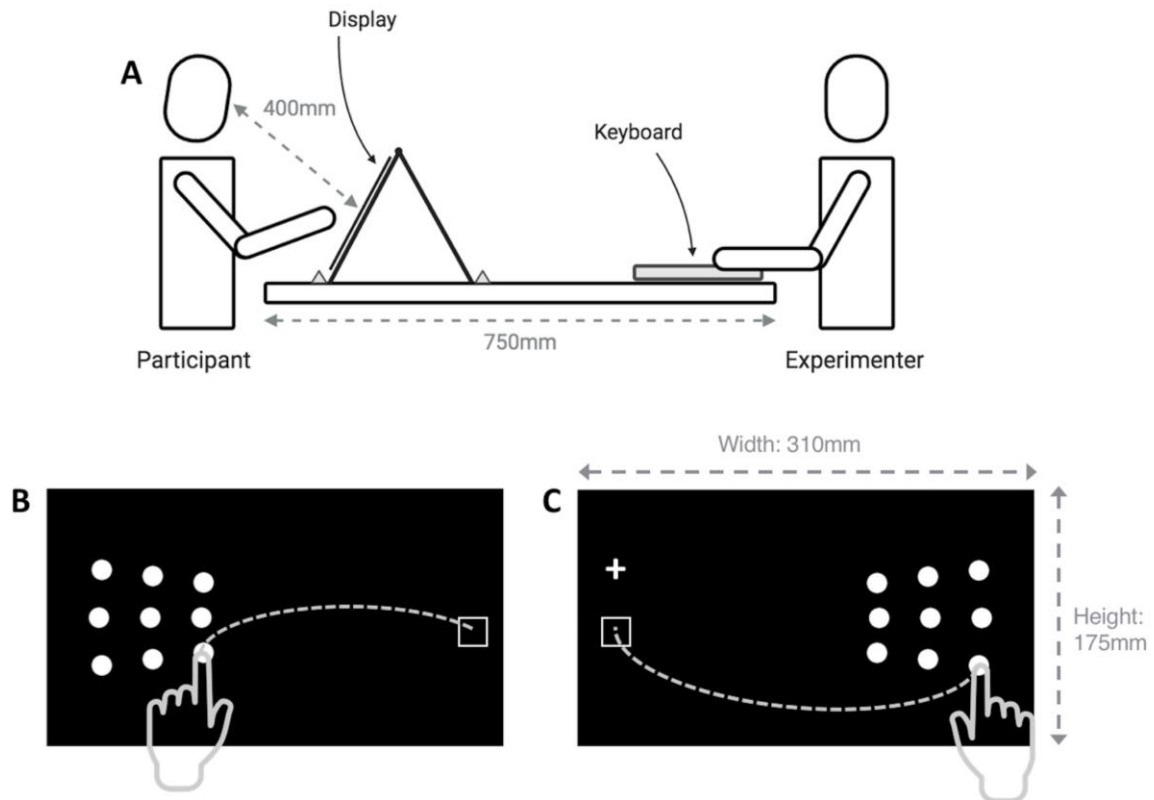
Figure 1: lateral reaching task. (A) Stimuli were displayed on a tablet laptop in the fronto-parallel plane. The experimenter sat directly opposite the participant to monitor eye-movements. Target locations, on radial spokes at 28, 33 & 38° are shown during (B) left-hand free-reaching and (C) right-hand peripheral reaching. All possible target positions are shown in the figure, but only one was presented per trial.

Visual detection

This task was used to confirm that the participant was capable of detecting the targets in peripheral vision. The participant gazed at the fixation cross, which cycled between white and red at a rate of 60Hz to assist steady fixation. To initiate a trial, they pressed the start box which disappeared when touched. After a short delay (250-750ms), a target appeared at one of the nine locations, or no target appeared (catch trial). After 1000ms, a short beep indicated the end of the trial and the target (if present) disappeared. The participant verbally reported whether or not they had seen a target. The trial was repeated immediately if an eye-movement was detected. The block ended after 15 valid trials: one for each of the nine target locations, and six catch trials. To progress to the peripheral reaching task, participants had to detect at least 6/9 targets and correctly reject at least 3/6 catch trials.

Peripheral reaching

As with visual detection, the participant gazed at the fixation cross and initiated a trial by pressing on the start box, which disappeared when touched. After a short delay (250-750ms) a target appeared at one of nine possible locations. Participants were required to make one smooth reaching movement to touch the target. The target remained on the screen until a touch was recorded, at which point a short beep was played to indicate the trial end. If an eye-movement was detected, the trial was immediately repeated. The block ended after a minimum of 27 trials (3 per target position), or after a total of 50 trials.

2.3.2   Radial reaching[1]

Stimuli & Apparatus

For the radial reaching task, an infrared motion-tracking camera (Optotrak Certus, Northern Digital Inc) was used to track the reaching movement. Infra-red-emitting diodes (IREDs) were taped to the right and left index fingernails of each participant. The Optotrak sampled the IRED's 3D position at 100Hz throughout each 2000ms trial. The task was controlled by custom software written in LabVIEW 2013 SR1 (National Instruments).

Participants were seated with their head placed in a chinrest in line with the middle of the display. Stimuli were back-projected via a mirror onto a flat screen surface (1000mm wide x 750mm deep). A webcam was placed on the screen 500mm directly in-front of the participant, as a fixation point (Fig. 2A). The live webcam image fed into a separate laptop, allowing the experimenter to monitor gaze continuously. A start-button was aligned to the centre of the screen, positioned 100mm in-front of the participant, 400mm away from fixation. Targets were white circles (diameter = 1.60°, 13.96mm) presented at 4 eccentric locations (10-40°, 100-400mm from centre) on the left and right sides (Fig. 2B).

Prior to radial reaching, a calibration procedure was run to identify target locations relative to the IRED camera (Mitchell et al., 2020).

---

[1] The set-up reported here is for data collection at UOE. For UEA reaching movements were recorded using a Qualysis 6 Motion Capture System (Qualysis, Sweden) and IRED positions were sampled at 179Hz throughout each trial. The task was coded in MATLAB R2010a using Psychtoolbox Version 3.0.11 (Brainard, 1997). The fixation webcam was placed 450mm directly in front of the participant, 350mm away from the start-button. Stimuli were green LEDs (diameter 0.60°, 15mm) embedded within a purpose-built table and only visible when lit. All other details matched the UOE set-up.
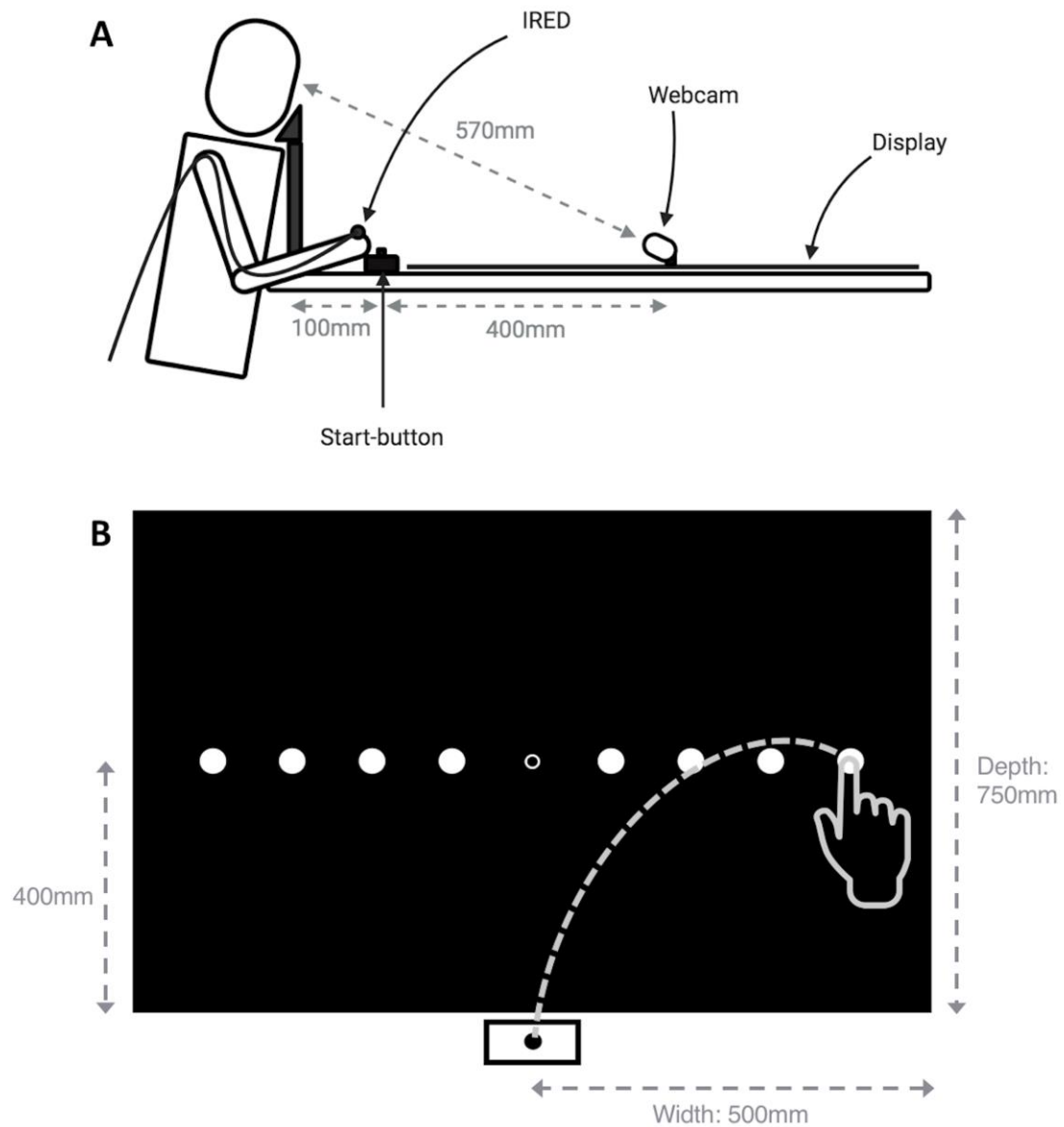
Figure 2: radial reaching task. (A) set-up for UOE with stimuli displayed in radial plane 500mm in-front of participant. Eye-movements were monitored via a live feed from webcam placed at centre of display. (B) target locations were 100, 200, 300 and 400mm to the left and right of fixation (webcam). All possible target locations are shown in the figure, but only one was presented per trial.

Free reaching

Participants initiated a trial by pressing and holding down the start button, 250-750ms later a target appeared. Participants were required to look directly at the target, then to reach and touch it in one smooth movement, leaving their finger on its landing position until they heard a short beep (100ms, 400Hz), 2000ms after target onset. If no eye movement was detected prior to the reach response, the trial was recycled at the end of the block. If participants did not respond or failed to reach within two seconds, the trial was marked as void and recycled to the end of the block. The block ended after 28 valid trials (7 per target location) or after a total of 50 trials.

Peripheral reaching

The peripheral reaching task was performed in the same manner as the free reaching task (*Section 2.2.2c*) except participants were required to gaze at the webcam throughout all trials. If an eye-movement was detected prior to completion of reach response, or the participant did not execute a reach in time, the trial was recycled to the end of the block. The block ended after 28 valid trials, or after 50 trials.

2.4 Power considerations

The individual, patient-level assessments were performed using case-control Bayesian test of deficit (Crawford & Howell, 1998). The UOE control sample size of 24 provides close to the maximum power for these tests, but such a test can only achieve a high level of power (>.80) if the behavioural deficit is large (>2.5 standard deviations from the control mean (McIntosh & Rittmo, 2021)). It should therefore be emphasised that our assessment of patient-level deficits is concerned with large behavioural aberrations, not with subtle signs. The UEA control sample of 8 provides ≥ .70 power to detect a deficit >2.5 standard deviations from the mean.

We then applied a binomial test to assess whether the rate of reaching deficits in patient groups exceeds that which would be expected by chance (chance level = .05). The planned patient group size of 24 would provide > .90 power, provided that the true proportion is at least .25 (1 in 4). The achieved group size of 17 for AD and 10 for MCI would provide .65 and .47 power respectively if the true proportions were at least .25. The reduced sample size, and consequent reduction in power, was an unavoidable consequence of the COVID-19 pandemic.

2.5 Statistical analyses
2.5.1 Lateral reaching task

Data processing and exclusions

One patient with AD had difficulty understanding and following instructions and was unable to complete the lateral reaching task. Two patients (1 MCI, 1 AD) failed the visual detection task on the right-side, so peripheral reaching was tested on the left (non-dominant) side only for these patients. For free-reaching, trials in which no eye movement was detected were removed from analysis, whilst for the peripheral reaching analysis, trials in which an eye movement *was* detected were removed. For the included sample, the percentage of free-reaching trials in which no eye movement was detected was 0% for HC, 0.18% for MCI and 2.2% for AD. For peripheral reaching, the percentage of trials in which an eye movement was detected was 1.7% for HC, 7.9% for MCI and 9.6% for AD.

The reach endpoint was defined as the touch coordinates at the end of the reach in the x (horizontal) and y (vertical) dimensions, and Absolute Error (in mm) was recorded as the 2D distance from the centre of the target. The median Absolute Error was calculated for each target eccentricity, for each combination of viewing condition (free, peripheral) and side (dominant, non-dominant). The average Absolute Error was then calculated as mean of medians across target eccentricities to give a single measure of reaching accuracy for each viewing condition and side. Data were then compressed to a *Peripheral Misreaching Index* by subtracting reaching accuracy in the free vision condition from the peripheral condition. This index provides a single measurement of peripheral reaching ability per side, for each participant.

Confirmatory analyses

We compared each individual patient's Peripheral Misreaching Index against the distribution of the Peripheral Misreaching Index in the control group (N = 24) using Crawford's Bayesian Test of Deficit with age as a covariate (Crawford et al., 2011), implemented in the *singcar* package for R (Rittmo &

McIntosh, 2020). Two one-tailed tests were run per participant, on the dominant and non-dominant sides. To constrain Type I error rate to < .05 per patient, across the two sides, the alpha level was set to .025. Patients were classified as showing peripheral misreaching if they showed a significant deficit ($p < .025$) on at least one side. Binomial tests were then run to test whether observed rate of peripheral misreaching exceeded that expected by chance (i.e. the per-patient adjusted alpha level of .05).

A one-way between-subjects ANOVA of reaching accuracy (Peripheral Misreaching Index) with a factor of group (HC, MCI, AD) and participant age as a covariate was also conducted.

Exploratory analyses
Exploratory analyses were conducted on Absolute Error, Reaction Time (time from target onset to touch offset at start of reach) and Movement Time (time from touch offset at to touch onset at end of reach). For each exploratory outcome measure, the median was calculated for each target eccentricity, for each combination of viewing condition (free, peripheral) and side (dominant, non-dominant). Three mixed measures ANOVAs were conducted to explore the effect of eccentricity on Absolute Error, Reaction Time and Movement Time, with a between-subject factor of group and within subject factors of viewing condition (free, peripheral) and eccentricity (28, 33, 38°), with age as a covariate. Similar exploratory analyses were also conducted on.

2.5.2 Radial reaching task
Data processing and exclusions
For free-reaching, trials in which no eye movement was detected were removed from analysis, whilst for the peripheral reaching analysis, trials in which an eye movement *was* detected were removed. The percentage of free reaching trials in which no eye movement was detected was 0.2% for HC, 0.2% for MCI and 0.1% for AD. The percentage of peripheral reaching trials in which an eye movement was detected was 3.2% for HC, 10.5% for MCI and 10.8% for AD. Eighteen trials (9 HC, 2 MCI, 7 AD) were excluded as extreme outliers (Absolute Error > 4 within-participant standard deviations from the mean).

The raw movement data were filtered by a dual pass through a Butterworth filter with a low-pass cut-off of 20 Hz. Movement onset was defined as the first frame in which the IRED speed exceeded 50mm/s, provided that it did not fall below this level for at least 100ms. Movement offset was defined as the first subsequent frame the IRED speed fell below 50mm/s.

The reach endpoint was defined as the landing coordinates in the x (horizontal) and y (depth) dimensions in the final frame of movement, and the Absolute Error (in mm) was calculated as the 2D distance in this plane from the target location determined during the calibration step (Mitchell et al., 2020). The Peripheral Misreaching Index was calculated using reaching error for the two most eccentric target locations (300 and 400mm) only, as these locations are within a similar eccentricity range to those in the lateral reaching task. Due to slight differences in viewing distance between sites, target eccentricity is reported in mm (rather than degrees of visual angle).

Confirmatory analyses
Case-control comparisons were conducted in the same manner as for lateral reaching to estimate rates of peripheral misreaching in MCI and AD groups. Each patient was referenced to control data from the same site to account for slight differences in set-up between the two sites.

A between-groups ANOVA of Peripheral Misreaching Index was also conducted with site (UOE, UEA) and participant age as covariates.

Exploratory analyses
To explore the effect of eccentricity on peripheral radial reaching, the median Absolute Error was calculated for each target eccentricity, for each combination of viewing condition (free, peripheral) and side (dominant, non-dominant). A mixed measures ANOVA was run on absolute reaching error across all target locations, with a between-subjects factor of group, within subject factors of viewing condition (free, peripheral) and eccentricity (100, 200, 300 and 400mm), and site (UOE, UEA) and age as covariates.

Similar exploratory analyses were conducted on Reaction Time (time from target onset to movement onset) and Movement Time (time from movement onset to movement offset). As the entire reach movement was tracked, further exploratory analyses were conducted on Peak Speed, Acceleration Time (time to Peak Speed) and Deceleration Time (time after Peak Speed).

3. RESULTS

3.1 Lateral reaching

3.1.1 Confirmatory analyses

Case-control comparisons on Peripheral Misreaching Index detected significant peripheral reaching deficits in 1/10 (10.0%) MCI patients and in 1/16 (6.25%) AD patients (Fig. 3, Supplementary T1). Binomial tests found that this observed rate of peripheral misreaching was not significantly above chance for either the MCI ($p = .40$) or AD group ($p = .56$). An ANOVA revealed no significant effect of group on the Peripheral Misreaching Index ($F_{2,47} = 0.01$, $p = .99$, $\eta_p^2 = 0.00$).

3.1.1 Exploratory analyses

For Absolute Error (Fig. 4A), significant main effects of viewing condition ($F_{1,47} = 103.96$, $p < .001$, $\eta_p^2 = 0.69$) and eccentricity ($F_{1.5,70.3} = 21.28$, $p < .001$, $\eta_p^2 = 0.31$) were observed, as well as a significant interaction of view by eccentricity ($F_{1.5,70.3} = 17.40$, $p < .001$, $\eta_p^2 = 0.27$). This suggests that reaching error increases with target eccentricity, in the peripheral reaching condition only. No significant effect of group was found ($F_{2,47} = 0.62$, $p = 0.94$, $\eta_p^2 = 0.00$).

For Reaction Time (Fig. 4B), there was a significant increase for peripheral, compared to free reaching ($F_{1,47} = 52.23$, $p < .001$, $\eta_p^2 = 0.52$). No significant main effect of group ($F_{2,47} = 0.54$, $p = .59$) or other main effects or interactions were identified.

For Movement Time, a significant main effect of group (Fig. 4C) was found ($F_{2,47} = 8.17$, $p = .001$, $\eta_p^2 = 0.26$) and pairwise comparisons showed that overall Movement Time was significantly higher in patients with AD compared to MCI ($p < .001$) and HC groups ($p < .001$), and significantly higher in MCI compared to HC ($p < .001$). Movement Time significantly decreased in peripheral, compared to free reaching ($F_{1,47} = 79.16$, $p < .001$, $\eta_p^2 = 0.63$) and significantly increased at higher target eccentricities ($F_{1.9,88.6} = 132.84$, $p < .001$, $\eta_p^2 = 0.74$). A significant interaction of viewing condition by eccentricity was observed ($F_{1.9,90.8} = 3.54$, $p = .03$, $\eta_p^2 = 0.07$).
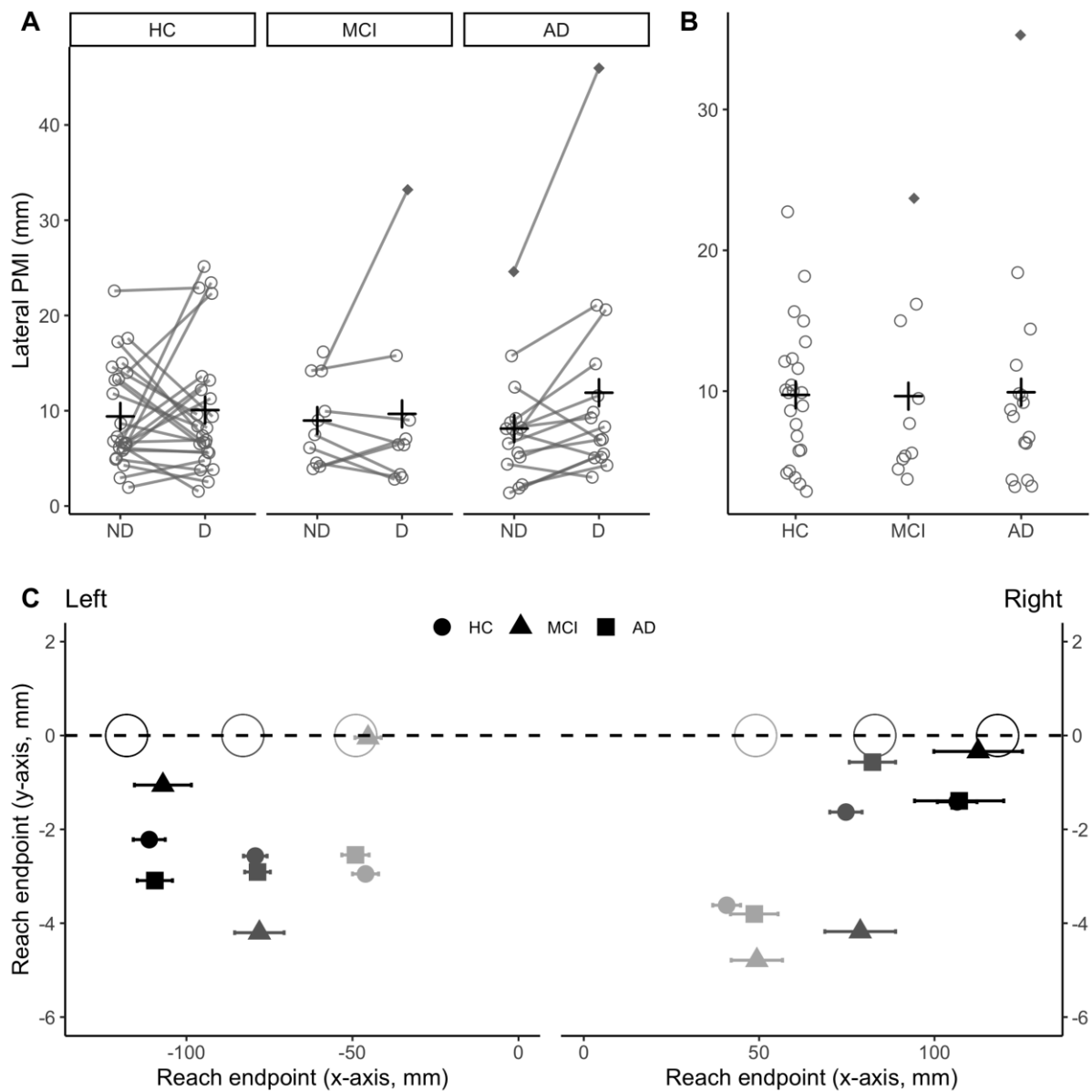
Figure 3: Peripheral reaching error for the lateral reaching task. (A) Lateral Peripheral Misreaching Index (PMI) for each participant, for non-dominant (ND) and dominant (D) sides. (B) PMI averaged across side for each participant. Diamonds show significant deficits in case-control comparisons. Crosses show mean Peripheral Misreaching Index within groups and side (A) and within groups across side (B). (C) Peripheral reaching endpoint (mm) along the x and y-axes for each group relative to target position, collapsed across three target locations per eccentricity (empty circles), for both right and left sided targets. Target position along the x-axis is plotted from the centre of the screen, 150mm to the left or right of fixation. Error bars represent 95% confidence intervals for Reach Endpoint along the x-axis. Note the scale differences between the x and y-axes.
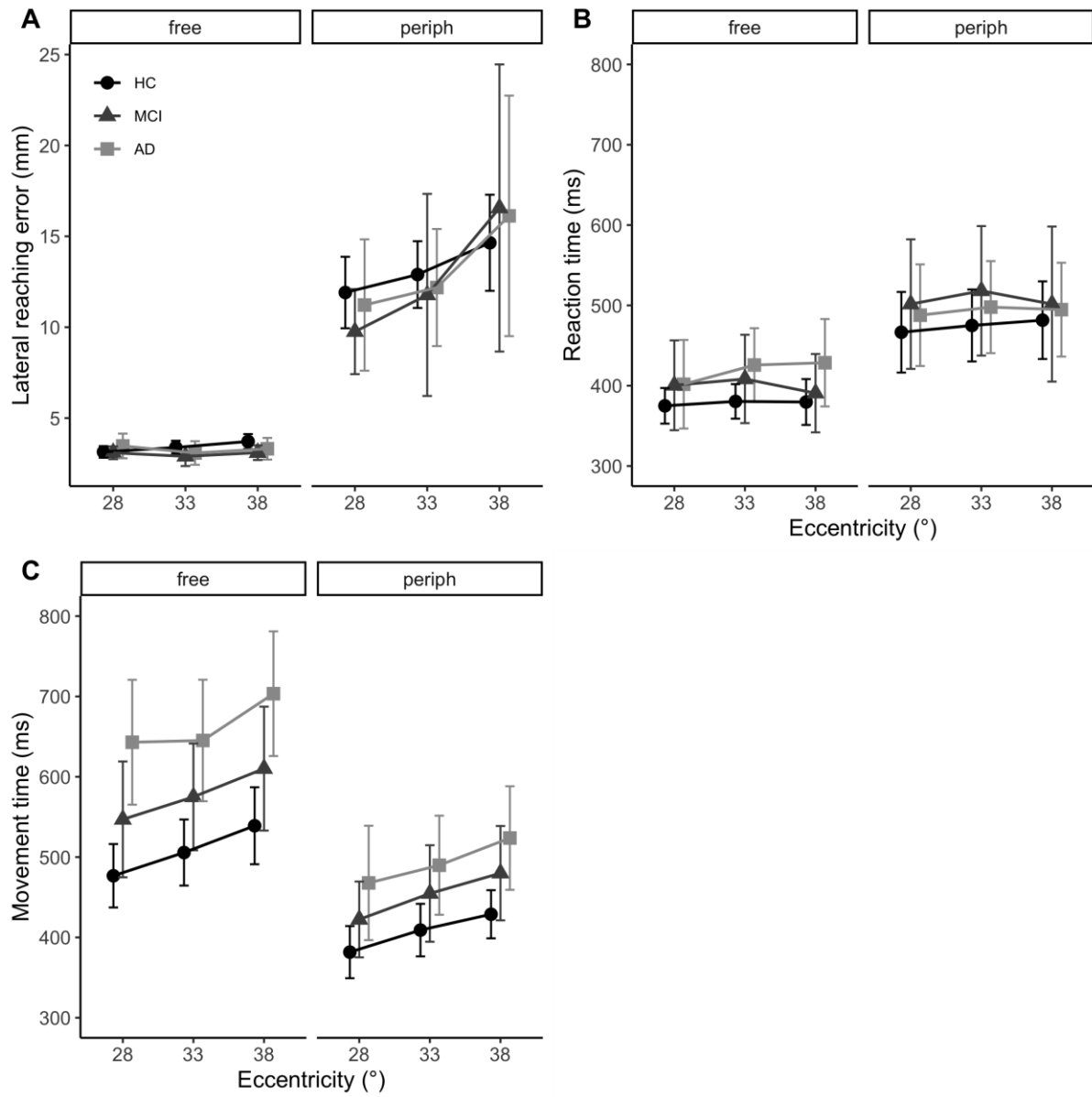
Figure 4: Exploratory results for the lateral reaching task, showing differences in (A) Lateral Reaching Error, (B) Reaction Time and (C) Movement Time between patient groups, across viewing conditions and target eccentricities. Error bars show 95% between-subject confidence intervals.

3.2 Radial reaching

3.2.1 Confirmatory analyses

Case-control comparisons on Peripheral Misreaching Index detected significant peripheral reaching deficits in 1/10 (10.0%) MCI patients and in 3/17 (17.65%) AD patients (Fig. 5, Supplementary T2). Binomial tests found that this observed rate of peripheral misreaching was not significantly above chance for MCI ($p = .40$), nor convincingly above chance for the AD group ($p = .05$). An ANOVA found no significant difference in peripheral reaching errors between groups ($F_{2,56} = 0.81$, $p = .45$, $\eta_p^2 = 0.01$).
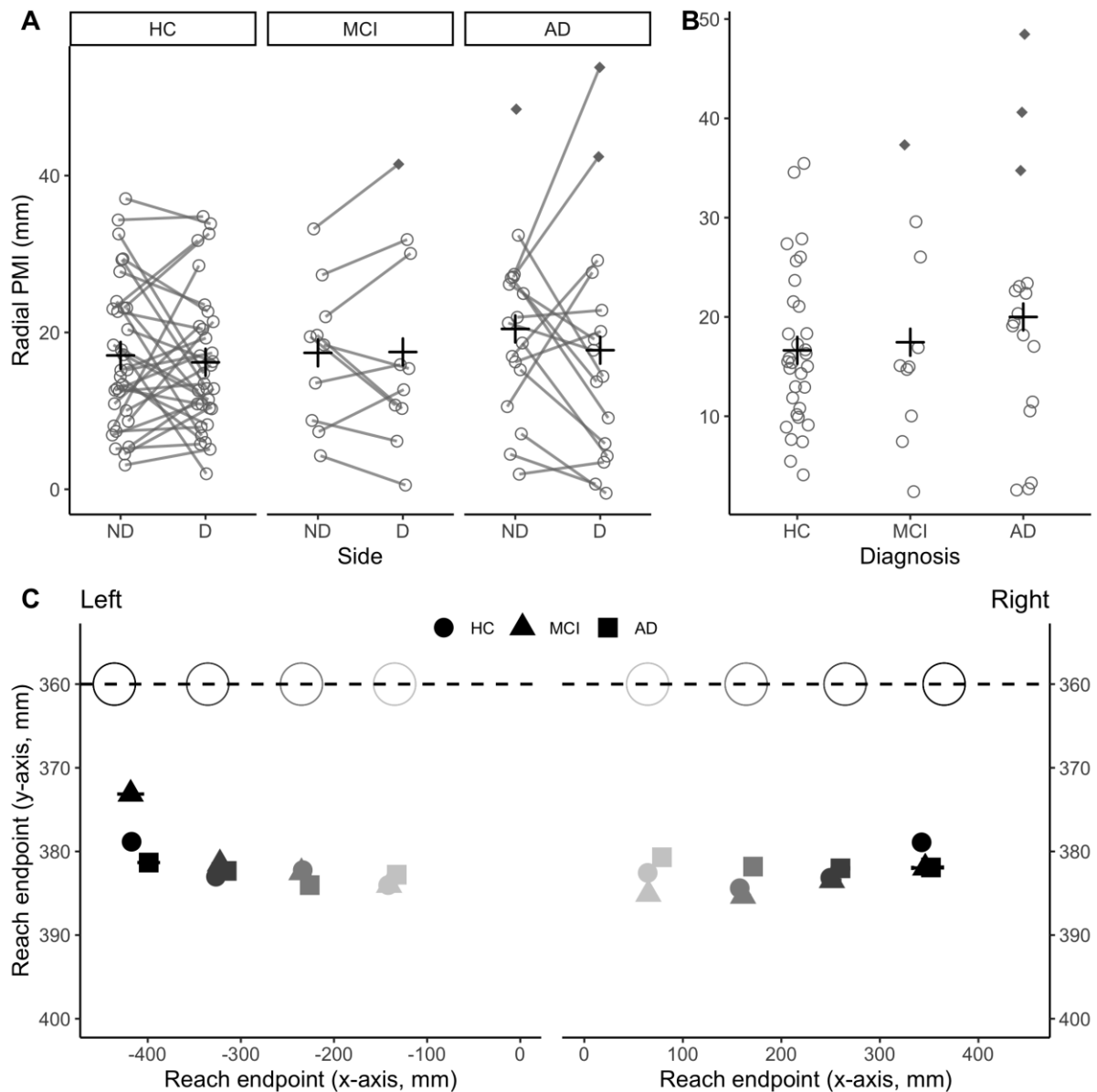

Figure 5: Peripheral reaching error for the radial reaching task. (A) Radial Peripheral Misreaching Index (PMI) for each participant for non-dominant (ND) and dominant (D) sides. (B) PMI averaged across side for each participant. Diamonds show significant deficits in case-control. Crosses show mean Peripheral Misreaching Index within groups and side (A) and within groups across side (B). (C) Peripheral reaching endpoint (mm) along the x and y-axes for each group relative to target position at each eccentricity (empty circles) for both right and left sided targets. Target position is plotted from the centre of the screen. Error bars represent 95% confidence intervals for Reach Endpoint along the x-axis. Note the scale differences between the x and y-axes.

3.2.2 Exploratory analyses

Absolute Error (Fig. 6A) increased significantly with target eccentricity ($F_{1.9,104.2} = 101.32$, $p < .001$, $\eta_p^2 = 0.64$) and in peripheral compared to free reaching ($F_{1,56} = 184.34$, $p < .001$, $\eta_p^2 = 0.77$). A significant interaction of viewing condition by eccentricity was also found ($F_{1.6,88.5} = 74.99$, $p < .001$, $\eta_p^2 = 0.57$). However, there was no significant main effect of group ($F_{2,56,} = 2.40$, $p = .10$, $\eta_p^2 = 0.08$).

RT (Fig. 6B) increased significantly for peripheral compared to free reaching ($F_{1,56} = 18.68$, $p < .001$, $\eta_p^2 = 0.25$) and with target eccentricity ($F_{3,168} = 20.40$, $p < .001$, $\eta_p^2 = 0.27$). A significant interaction effect was also found between viewing condition and eccentricity ($F_{3,168} = 9.18$, $p = .002$, $\eta_p^2 = 0.14$). However, there was no significant effect of group ($F_{1.4,76.4} = 0.07$, $p = .94$, $\eta_p^2 = 0.00$)

For Movement Time (Fig. 6C), a significant effect of group was observed ($F_{2,56} = 5.42$, $p = .01$, $\eta_p^2 = 0.16$). Pairwise-comparisons revealed that Movement Time was significantly higher in both AD ($p < .001$) and MCI ($p < .001$) compared to HC. Movement Time was found to be significantly lower in peripheral reaching, compared to free reaching ($F_{1,65} = 16.74$, $p = .001$, $\eta_p^2 = 0.23$) and increased with target eccentricity ($F_{2.4,135.8} = 41.99$, $p < .001$, $\eta_p^2 = 0.43$). A significant interaction of viewing condition by eccentricity was also observed ($F_{2.7,149.4} = 9.86$, $p < .001$, $\eta_p^2 = 0.15$).

Peak Speed (Fig. 6D) was significantly higher during free reaching, compared to peripheral reaching ($F_{1,65} = 54.19$, $p < .001$, $\eta_p^2 = 0.45$) and for larger target eccentricities ($F_{1.6,89.1} = 817.04$, $p < .001$, $\eta_p^2 = 0.93$). A significant interaction effect of view by eccentricity was also identified ($F_{2.4,138.4} = 15.23$, $p < .001$, $\eta_p^2 = 0.19$). No significant difference was observed between groups ($F_{2,56} = 0.82$, $p = .45$).

Acceleration Time (Fig. 6E) was significantly greater for free reaching, compared to peripheral reaching ($F_{1,56} = 7.37$, $p = .001$, $\eta_p^2 = 0.12$) and significantly increased as a function of target eccentricity ($F_{1.9,105.9} = 82.38$, $p < .001$, $\eta_p^2 = 0.60$). Although no significant main effect of group was identified ($F_{2,56} = 1.81$, $p = .17$), a significant interaction between group, viewing condition and eccentricity was found ($F_{5.2,146.5} = 2.98$, $p = .001$, $\eta_p^2 = 0.10$).

Deceleration Time (Fig. 6F) was significantly greater for patient groups than healthy controls ($F_{2,56} = 10.36$, $p = .001$, $\eta_p^2 = 0.27$). Pairwise comparisons showed that Deceleration Time was greater in both AD ($p < .001$) and MCI ($p < .001$) compared to HC, but did not differ significantly between MCI and AD ($p > .99$). Deceleration Time was also significantly shorter in peripheral reaching compared to free reaching ($F_{1,56} = 34.12$, $p < .001$, $\eta_p^2 = 0.38$) and differed across target eccentricities ($F_{2.3,130.1} = 18.20$, $p < .001$, $\eta_p^2 = 0.25$). A significant interaction effect of view by eccentricity was also found ($F_{2.7,150.3} = 13.81$, $p < .001$, $\eta_p^2 = 0.20$).
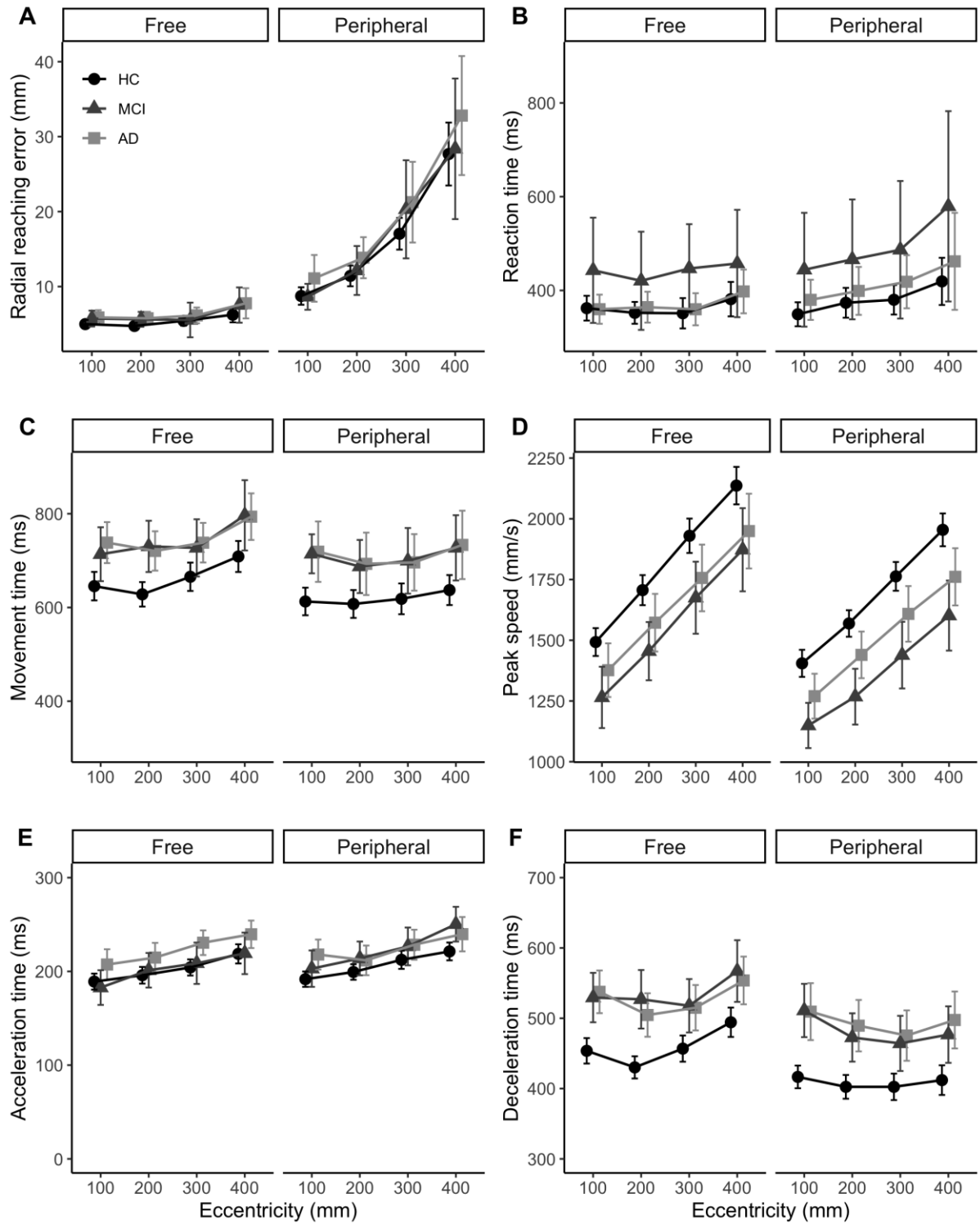
Figure 6: Exploratory results for the radial reaching task, showing differences in (A) Absolute Error, (B) Reaction Time, (C) Movement Time, (D) Peak Speed, (E) Acceleration Time and (F) Deceleration Time between patient groups, across viewing conditions and target eccentricities. Error bars show 95% between-subject confidence intervals.

4. DISCUSSION

The present study tested the impact of AD on the ability to reach to targets in peripheral vision, a symptom that characterises optic ataxia, the classic visuomotor deficit following damage to the PPC. When reaching towards objects we typically look towards the object prior to the reach, therefore, deficits of peripheral reaching could easily go unnoticed unless specifically tested. Two tasks were used to assess whether impairments of reaching to targets in the peripheral visual field is a prominent feature of AD and amnestic MCI. In both the lateral and radial reaching tasks, single-case comparisons to the range of performance in older adult controls revealed significant peripheral misreaching in a small number of patients only, and differences did not emerge at the group level. Therefore, gross peripheral reaching deficits similar to what is observed in optic ataxia seem not to be a characteristic symptom of AD or amnestic MCI. This result is perhaps surprising, given metabolic and structural changes observed in AD in brain areas closely associated with the control of visually guided reaching (Gordon et al., 2018; Jacobs et al., 2012). The preservation of accuracy during reaching is in line with other studies of visuomotor control in AD (Salek et al., 2011; Tippett et al., 2007; Tippett & Sergio, 2006). Our data suggest that this preservation of spatial accuracy extends even to the considerably more demanding condition of reaching to targets in peripheral vision.

Although spatial accuracy was preserved, exploratory analyses did reveal consistent differences in the timing of reaches between patients and older adult controls. Individuals diagnosed with MCI and AD had significantly longer Movement Times than those healthy controls, and in the lateral task those with AD had longer Movement Times than those with MCI. This is consistent with a graded increase in reach duration associated with increasing cognitive impairment. These findings support previous studies that found longer reach durations during simple, visually guided reaching in early stage AD and MCI (de Boer et al., 2016; Salek et al., 2011; Tippett et al., 2007; Verheij et al., 2012). Alongside this, increased Movement Time has been previously associated with parietal lobe damage (Rossit et al., 2009, 2012), which suggests that these results are indicative of a visuomotor impairment associated with changes to the PPC.

Extended Movement Time could be suggestive of a more general bradykinesia associated with cognitive decline in AD and MCI (Bologna et al., 2020; Ott et al., 1995; Scarmeas et al., 2005). However, more detailed analysis of the kinematic reaching profiles found that patients reached a similar Peak Speed to healthy participants, at a similar time, and that the increased Movement Time was chiefly attributable to an extended phase of reaching after this point of Peak Speed (Fig. 6F). This effect was equally present in free and peripheral reaching, pointing to a general change in reach execution, rather than a specific problem with peripheral targets. The Deceleration Time is strongly associated with the implementation of feedback-based corrections as the hand approaches the target, in both simple reaching (Bootsma et al., 1994; Soechting, 1984) and more complex grasping tasks (Jeannerod, 1986; McIntosh et al., 2018).

There are two obvious candidate explanations for this extended Deceleration Time. The first is that initial movement programming is less accurate in patient groups. As a result, individuals may depend more heavily on visual and proprioceptive feedback to maintain terminal accuracy during reaching. This is supported by previous studies showing that reducing visual feedback significantly reduces reaching accuracy in AD (Ghilardi et al., 2000; Felice Ghilardi et al., 1999). A second, non-mutually exclusive, possibility is that the efficiency of feedback-based control is itself reduced, so that an extended Deceleration Time is required for these feedback processes to operate. Either account would predict that limiting the amount of time patients have to reach to visual targets, would result in inflated spatial error to visual targets. This could be tested by using fast-paced reaching tasks,

preventing strategic prolongation of deceleration time. Both possibilities support the notion that cognitive impairment in AD may be accompanied by subtle deficits of visuomotor control, which may be exposed as spatial inaccuracies under certain task constraints. Alongside this, in the future, tracking eye-movements during free reaching could provide insight into possible abnormalities of oculomotor responses in visually acquiring the target (Anderson & MacAskill, 2013; Garbutt et al., 2008; Shakespeare et al., 2015), which could be potentially related to slowed or inaccurate reaching.

Another thing to note is the reduced Movement Time for peripheral compared to free reaching in all groups, which may be linked to increased dependence on visual feedback during goal-directed movements. There is a body of literature that shows healthy older adults slow down goal-directed reaching movements and depend more on visual feedback than younger adults (Mason et al., 2019; Zanto & Gazzaley, 2014). This could lead to increased response time under conditions where rich visual feedback is available (e.g. free reaching) compared to conditions were it is reduced (e.g. peripheral reaching). As visual feedback is reduced in the peripheral reaching task, it is possible that the movements are less carefully monitored than in free reaching, and that less use is made of feedback-based corrections. The extended durations for free reaching, providing more opportunity for closed-loop feedback-based control, may also help explain the very high spatial accuracy in this condition.

In our sample, 3/17 individuals with AD showed severe peripheral reaching deficits in the radial task, compared with 1/16 for lateral reaching. This pattern of heterogeneity in AD symptoms has been previously identified in visual motion processing (Mapstone et al., 2008; O'Brien et al., 2001) and may suggest that severe visuomotor deficits are present in a small sub-population of individuals with typically developing AD. It is possible that these patients present with a differential impairment to the PPC similar to what can be observed in PCA and further investigations of structural and functional brain changes in such patients are required. However, the number of patients with significant peripheral misreaching was too few to rule out the possibility that the difference is simply due to sampling variability. It is also possible that a generalised reduction in visual acuity in the peripheral field of patients with AD decreases the accuracy of reaching to peripheral targets. We included a visual detection task to confirm that participants could see the reaching targets, but we did not formally assess visual acuity at peripheral target locations. A more detailed visual assessment is required to rule out a primary visual contribution in these patients.

The purpose of this study was to determine whether optic ataxia-like deficits were present in AD and MCI. On the basis of our preliminary findings, we conclude that substantial peripheral reaching deficits are not a common feature of AD. However, increased duration of reaching movement was observed in both AD and MCI, attributable to an extended Deceleration Time in both groups. This suggests that individuals with cognitive impairment may strategically prolong visually guided movements to maintain accuracy and it highlights a relatively subtle visuomotor impairment in AD, consistent with findings from previous studies (de Boer et al., 2016; Ghilardi et al., 1999; Tippett et al., 2007, 2012; Tippett & Sergio, 2006; Verheij et al., 2012). Future research should focus on understanding whether changes to the PPC in prodromal AD contribute to this deficit. It may also be prudent to investigate whether timing differences identified in AD match those observed in individuals with optic ataxia and other forms of parietal damage.

5. References

Anderson, T. J., & MacAskill, M. R. (2013). Eye movements in patients with neurodegenerative disorders. *Nature Reviews Neurology*, *9*(2), 74–85. https://doi.org/10.1038/nrneurol.2012.273

Balint, R. (1909). Seelenlähmung des "Schauens", optische Ataxie, räumliche Störung der Aufmerksamkeit. Pp. 67–81—Abstract—European Neurology 1909, Vol. 25, No. 1—Karger Publishers. *Monatsschr Psychiatr Neurol*, *25*, 67–81.

Blangero, A., Ota, H., Delporte, L., Revol, P., Vindras, P., Rode, G., Boisson, D., Vighetto, A., Rossetti, Y., & Pisella, L. (2007). Optic ataxia is not only 'optic': Impaired spatial integration of proprioceptive information. *NeuroImage*, *36*, T61–T68. https://doi.org/10.1016/j.neuroimage.2007.03.039

Blangero, A., Ota, H., Rossetti, Y., Fujii, T., Ohtake, H., Tabuchi, M., Vighetto, A., Yamadori, A., Vindras, P., & Pisella, L. (2010). Systematic retinotopic reaching error vectors in unilateral optic ataxia. *Cortex*, *46*(1), 77–93. https://doi.org/10.1016/j.cortex.2009.02.015

Bologna, M., Guerra, A., Colella, D., Cioffi, E., Paparella, G., Di Vita, A., D'Antonio, F., Trebbastoni, A., & Berardelli, A. (2020). Bradykinesia in Alzheimer's disease and its neurophysiological substrates. *Clinical Neurophysiology*, *131*(4), 850–858. https://doi.org/10.1016/j.clinph.2019.12.413

Bootsma, R. J., Marteniuk, R. G., MacKenzie, C. L., & Zaal, F. T. J. M. (1994). The speed-accuracy trade-off in manual prehension: Effects of movement amplitude, object size and object width on kinematic characteristics. *Experimental Brain Research*, *98*(3), 535–541. https://doi.org/10.1007/BF00233990

Borchers, S., Müller, L., Synofzik, M., & Himmelbach, M. (2013). Guidelines and quality measures for the diagnosis of optic ataxia. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00324

Brainard, D. (1997). The Psychophysics Toolbox. *Spatial Vision*, *4*(10). https://brill.com/view/journals/sv/10/4/article-p433_15.xml

Bruno, D., & Schurmann Vignaga, S. (2019). Addenbrooke's cognitive examination III in the diagnosis of dementia: A critical review. *Neuropsychiatric Disease and Treatment*, *15*, 441–447. https://doi.org/10.2147/NDT.S151253

Chételat, G., Landeau, B., Eustache, F., Mézenge, F., Viader, F., de la Sayette, V., Desgranges, B., & Baron, J.-C. (2005). Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: A longitudinal MRI study. *NeuroImage*, *27*(4), 934–946. https://doi.org/10.1016/j.neuroimage.2005.05.015

Clower, D. M., Hoffman, J. M., Votaw, J. R., Faber, T. L., Woods, R. P., & Alexander, G. E. (1996). Role of posterior parietal cortex in the recalibration of visually guided reaching. *Nature*, *383*(6601), 618–621. https://doi.org/10.1038/383618a0

Crawford, J. R., Garthwaite, P. H., & Ryan, K. (2011). Comparing a single case to a control sample: Testing for neuropsychological deficits and dissociations in the presence of covariates. *Cortex*, *47*(10), 1166–1178. https://doi.org/10.1016/j.cortex.2011.02.017

Crawford, J. R., & Howell, D. C. (1998). Comparing an Individual's Test Score Against Norms Derived from Small Samples. *The Clinical Neuropsychologist*, *12*(4), 482–486. https://doi.org/10.1076/clin.12.4.482.7241

Crutch, S. J., Schott, J. M., Rabinovici, G. D., Murray, M., Snowden, J. S., van der Flier, W. M., ... & Fox, N. C. (2017). Alzheimer's association ISTAART atypical Alzheimer's Disease and associated syndromes professional interest area. *Consensus classification of posterior cortical atrophy. Alzheimers Dement*, *13*(8), 870-84.

Culham, J. C., & Valyear, K. F. (2006). Human parietal cortex in action. *Current Opinion in Neurobiology*, *16*(2), 205–212. https://doi.org/10.1016/j.conb.2006.03.005

de Boer, C., van der Steen, J., Mattace-Raso, F., Boon, A. J. W., & Pel, J. J. M. (2016). The Effect of Neurodegeneration on Visuomotor Behavior in Alzheimer's Disease and Parkinson's Disease. *Motor Control*, *20*(1), 1–20. https://doi.org/10.1123/mc.2014-0015

Dubois, B., Feldman, H. H., Jacova, C., Hampel, H., Molinuevo, J. L., Blennow, K., DeKosky, S. T., Gauthier, S., Selkoe, D., Bateman, R., Cappa, S., Crutch, S., Engelborghs, S., Frisoni, G. B., Fox, N. C., Galasko, D., Habert, M.-O., Jicha, G. A., Nordberg, A., … Cummings, J. L.

(2014). Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. *The Lancet Neurology*, *13*(6), 614–629. https://doi.org/10.1016/S1474-4422(14)70090-0

Fernandez, R., & Duffy, C. J. (2012). Early Alzheimer's disease blocks responses to accelerating self-movement. *Neurobiology of Aging*, *33*(11), 2551–2560. https://doi.org/10.1016/j.neurobiolaging.2011.12.031

Garbutt, S., Matlin, A., Hellmuth, J., Schenk, A. K., Johnson, J. K., Rosen, H., Dean, D., Kramer, J., Neuhaus, J., Miller, B. L., Lisberger, S. G., & Boxer, A. L. (2008). Oculomotor function in frontotemporal lobar degeneration, related disorders and Alzheimer's disease. *Brain*, *131*(5), 1268–1281. https://doi.org/10.1093/brain/awn047

Ghilardi, M. F., Alberoni, M., Marelli, S., Rossi, M., Franceschi, M., Ghez, C., & Fazio, F. (1999). Impaired movement control in Alzheimer's disease. *Neuroscience Letters*, *260*(1), 45–48. https://doi.org/10.1016/S0304-3940(98)00957-4

Ghilardi, M.-F., Alberoni, M., Marelli, S., Marina Rossi, Franceschi, M., Ghez, C., & Fazio, F. (1999). Impaired movement control in Alzheimer's disease. *Neuroscience Letters*, *260*(1), 45–48. https://doi.org/10.1016/S0304-3940(98)00957-4

Ghilardi, M.-F., Alberoni, M., Rossi, M., Franceschi, M., Mariani, C., & Fazio, F. (2000). Visual feedback has differential effects on reaching movements in Parkinson's and Alzheimer's disease. *Brain Research*, *876*(1–2), 112–123. https://doi.org/10.1016/S0006-8993(00)02635-4

Gordon, B. A., Blazey, T. M., Su, Y., Hari-Raj, A., Dincer, A., Flores, S., Christensen, J., McDade, E., Wang, G., Xiong, C., Cairns, N. J., Hassenstab, J., Marcus, D. S., Fagan, A. M., Jack, C. R., Hornbeck, R. C., Paumier, K. L., Ances, B. M., Berman, S. B., … Benzinger, T. L. S. (2018). Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: A longitudinal study. *The Lancet Neurology*, *17*(3), 211–212. https://doi.org/10.1016/S1474-4422(18)30028-0

Granek, J. A., Pisella, L., Stemberger, J., Vighetto, A., Rossetti, Y., & Sergio, L. E. (2013). Decoupled Visually-Guided Reaching in Optic Ataxia: Differences in Motor Control between Canonical and Non-Canonical Orientations in Space. *PLOS ONE*, *8*(12), e86138. https://doi.org/10.1371/journal.pone.0086138

Hämäläinen, A., Tervo, S., Grau-Olivares, M., Niskanen, E., Pennanen, C., Huuskonen, J., Kivipelto, M., Hänninen, T., Tapiola, M., Vanhanen, M., Hallikainen, M., Helkala, E. L., Nissinen, A., Vanninen, R., & Soininen, H. (2007). Voxel-based morphometry to detect brain atrophy in progressive mild cognitive impairment. *NeuroImage*, *37*(4), 1122–1131. https://doi.org/10.1016/j.neuroimage.2007.06.016

Hawkins, K. M., Goyal, A. I., & Sergio, L. E. (2015). Diffusion Tensor Imaging Correlates of Cognitive-Motor Decline in Normal Aging and Increased Alzheimer's Disease Risk. *Journal of Alzheimer's Disease*, *44*(3), 867–878. https://doi.org/10.3233/JAD-142079

Hawkins, K. M., & Sergio, L. E. (2014). Visuomotor Impairments in Older Adults at Increased Alzheimer's Disease Risk. *Journal of Alzheimer's Disease*, *42*(2), 607–621. https://doi.org/10.3233/JAD-140051

Hawkins, K. M., & Sergio, L. E. (2016). Adults at Increased Alzheimer's Disease Risk Display Cognitive-Motor Integration Impairment Associated with Changes in Resting-State Functional Connectivity: A Preliminary Study. *Journal of Alzheimer's Disease*, *53*(3), 1161–1172. https://doi.org/10.3233/JAD-151137

Huang, X., Hu, Y., Zhou, F., Xu, X., Wu, Y., Jay, R., Cheng, Y., Wang, J., & Wu, X. (2018). Altered whole-brain gray matter volume in high myopia patients: A voxel-based morphometry study. *NeuroReport*, *29*(9), 760–767. https://doi.org/10.1097/WNR.0000000000001028

Jack, C. R., Albert, M. S., Knopman, D. S., McKhann, G. M., Sperling, R. A., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(3), 257–262. https://doi.org/10.1016/j.jalz.2011.03.004

Jack, C. R., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., Shaw, L. M., Vemuri, P., Wiste, H. J., Weigand, S. D., Lesnick, T. G., Pankratz, V. S., Donohue, M. C., & Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: An

updated hypothetical model of dynamic biomarkers. *The Lancet Neurology*, *12*(2), 207–216. https://doi.org/10.1016/S1474-4422(12)70291-0

Jacobs, H. I. L., Van Boxtel, M. P. J., Jolles, J., Verhey, F. R. J., & Uylings, Harry. B. M. (2012). Parietal cortex matters in Alzheimer's disease: An overview of structural, functional and metabolic findings | Elsevier Enhanced Reader. *Neuroscience & Biobehavioural Reviews*, *36*(1), 297–309. https://doi.org/10.1016/j.neubiorev.2011.06.009

Jeannerod, M. (1986). Mechanisms of visuomotor coordination: A study in normal and brain damaged subjects. *Neuropsychologia*, *24*(1), 41–78.

Karnath, H.-O., & Perenin, M.-T. (2005). Cortical Control of Visually Guided Reaching: Evidence from Patients with Optic Ataxia. *Cerebral Cortex*, *15*(10), 1561–1569. https://doi.org/10.1093/cercor/bhi034

Kertzman, C., Schwarz, U., Zeffiro, T. A., & Hallett, M. (1997). The role of posterior parietal cortex in visually guided reaching movements in humans: *Experimental Brain Research*, *114*(1), 170–183. https://doi.org/10.1007/PL00005617

Konen, C. S., Mruczek, R. E. B., Montoya, J. L., & Kastner, S. (2013). Functional organization of human posterior parietal cortex: Grasping- and reaching-related activations relative to topographically organized cortex. *Journal of Neurophysiology*, *109*(12), 2897–2908. https://doi.org/10.1152/jn.00657.2012

Mapstone, M., Dickerson, K., & Duffy, C. J. (2008). Distinct mechanisms of impairment in cognitive ageing and Alzheimer's disease. *Brain*, *131*(6), 1618–1629. https://doi.org/10.1093/brain/awn064

Mason, A. H., Grabowski, P. J., & Rutherford, D. N. (2019). The Role of Visual Feedback and Age When Grasping, Transferring and Passing Objects in Virtual Environments. *International Journal of Human–Computer Interaction*, *35*(19), 1870–1881. https://doi.org/10.1080/10447318.2019.1574101

Mathôt, S., Schreij, D., & Theeuwes, J. (2012). OpenSesame: An open-source, graphical experiment builder for the social sciences. *Behavior Research Methods*, *44*(2), 314–324. https://doi.org/10.3758/s13428-011-0168-7

McIntosh, R. D., MonWilliams, M., & Tresilian, J. R. (2018). Grasping at laws: Speed-accuracy trade-offs in manual prehension. *Journal of Experimental Psychology: Human Perception and Performance*, *44*(7), 1022–1037.

McIntosh, R. D., & Rittmo, J. Ö. (2021). Power calculations in single-case neuropsychology: A practical primer. *Cortex*, *135*, 146–158. https://doi.org/10.1016/j.cortex.2020.11.005

Milner, A. D., Dijkerman, H. C., McIntosh, R. D., Rossetti, Y., & Pisella, L. (2003). Delayed reaching and grasping in patients with optic ataxia. In *Progress in Brain Research* (Vol. 142, pp. 225–242). Elsevier. https://doi.org/10.1016/S0079-6123(03)42016-5

Mitchell, A. G., McIntosh, R. D., Rossit, S., Hornberger, M., & Pal, S. (2020). Assessment of visually guided reaching in prodromal Alzheimer's disease: A cross-sectional study protocol. *BMJ Open*, *10*(6), e035021. https://doi.org/10.1136/bmjopen-2019-035021

Mollica, M. A., Navarra, J., Fernández-Prieto, I., Olives, J., Tort, A., Valech, N., Coll-Padrós, N., Molinuevo, J. L., & Rami, L. (2017). Subtle visuomotor difficulties in preclinical Alzheimer's disease. *Journal of Neuropsychology*, *11*(1), 56–73. https://doi.org/10.1111/jnp.12079

O'Brien, H. L., Tetewsky, S. J., Avery, L. M., Cushman, L. A., Makous, W., & Duffy, C. J. (2001). Visual mechanisms of spatial disorientation in Alzheimer's disease. *Cerebral Cortex*, *11*(11), 1083–1092. https://doi.org/10.1093/cercor/11.11.1083

Ott, B. R., Ellias, S. A., & Lannon, M. C. (1995). Quantitative assessment of movement in Alzheimer's disease. *Journal of Geriatric Psychiatry and Neurology*, *8*(1), 71–75.

Pennanen, C., Testa, C., Laakso, M. P., Hallikainen, M., Helkala, E. L., Hänninen, T., Kivipelto, M., Könönen, M., Nissinen, A., Tervo, S., Vanhanen, M., Vanninen, R., Frisoni, G. B., Soininen, H., & Tuomainen, S. (2005). A voxel based morphometry study on mild cognitive impairment. *Journal of Neurology, Neurosurgery and Psychiatry*, *76*(1), 11–14. https://doi.org/10.1136/jnnp.2004.035600

Perenin, M.-T., & Vighetto, A. (1988). OPTIC ATAXIA: A SPECIFIC DISRUPTION IN VISUOMOTOR MECHANISMSI. DIFFERENT ASPECTS OF THE DEFICIT IN

REACHING FOR OBJECTS. *Brain*, *111*(3), 643–674.
https://doi.org/10.1093/brain/111.3.643

Pike, K. E., Savage, G., Villemagne, V. L., Ng, S., Moss, S. A., Maruff, P., Mathis, C. A., Klunk, W.
E., Masters, C. L., & Rowe, C. C. (2007). β-amyloid imaging and memory in non-demented
individuals: Evidence for preclinical Alzheimer's disease. *Brain*, *130*(11), 2837–2844.
https://doi.org/10.1093/brain/awm238

Pisella, L., Sergio, L., Blangero, A., Torchin, H., Vighetto, A., & Rossetti, Y. (2009). Optic ataxia and
the function of the dorsal stream: Contributions to perception and action. *Neuropsychologia*,
47(14), 3033–3044. https://doi.org/10.1016/j.neuropsychologia.2009.06.020

Ratcliff, G., & Davies-Jones, G. A. (1972). Defective visual localization in focal brain wounds. *Brain:
A Journal of Neurology*, *95*(1), 49–60. https://doi.org/10.1093/brain/95.1.49

Rittmo, J., & McIntosh, R. D. (2020). *Singcar* (CRAN Patent). https://cran.r-
project.org/package=singcar

Rossetti, Y., Pisella, L., & McIntosh, R. D. (2019). Definition: Optic ataxia. *Cortex; a Journal
Devoted to the Study of the Nervous System and Behavior*, *121*, 481.
https://doi.org/10.1016/j.cortex.2019.09.004

Rossit, S., Malhotra, P., Muir, K., Reeves, I., Duncan, G., Birschel, P., & Harvey, M. (2009). The
neural basis of visuomotor deficits in hemispatial neglect. *Neuropsychologia*, *47*(10), 2149–
2153. https://doi.org/10.1016/j.neuropsychologia.2009.04.015

Rossit, S., McIntosh, R. D., Malhotra, P., Butler, S. H., Muir, K., & Harvey, M. (2012). Attention in
action: Evidence from on-line corrections in left visual neglect. *Neuropsychologia*, *50*(6),
1124–1135. https://doi.org/10.1016/j.neuropsychologia.2011.10.004

Salek, Y., Anderson, N. D., & Sergio, L. (2011). Mild Cognitive Impairment Is Associated with
Impaired Visual-Motor Planning When Visual Stimuli and Actions Are Incongruent.
European Neurology, *66*(5), 283–293. https://doi.org/10.1159/000331049

Scarmeas, N., Albert, M., Brandt, J., Blacker, D., Hadjigeorgiou, G., Papadimitriou, A., Dubois, B.,
Sarazin, M., Wegesin, D., Marder, K., Bell, K., Honig, L., & Stern, Y. (2005). Motor signs
predict poor outcomes in Alzheimer disease. *Neurology*, *64*(10), 1696–1703.
https://doi.org/10.1212/01.WNL.0000162054.15428.E9

Shakespeare, T. J., Kaski, D., Yong, K. X. X., Paterson, R. W., Slattery, C. F., Ryan, N. S., Schott, J.
M., & Crutch, S. J. (2015). Abnormalities of fixation, saccade and pursuit in posterior cortical
atrophy. *Brain*, *138*(7), 1976–1991. https://doi.org/10.1093/brain/awv103

Soechting, J. F. (1984). Effect of target size on spatial and temporal characteristics of a pointing
movement in man. *Experimental Brain Research*, *54*(1), 121–132.
https://doi.org/10.1007/BF00235824

Thiyagesh, S. N., Farrow, T. F. D., Parks, R. W., Accosta-Mesa, H., Young, C., Wilkinson, I. D.,
Hunter, M. D., & Woodruff, P. W. R. (2009). The neural basis of visuospatial perception in
Alzheimer's disease and healthy elderly comparison subjects: An fMRI study. *Psychiatry
Research: Neuroimaging*, *172*(2), 109–116.
https://doi.org/10.1016/j.pscychresns.2008.11.002

Tippett, W. J., Krajewski, A., & Sergio, L. E. (2007). Visuomotor Integration Is Compromised in
Alzheimer's Disease Patients Reaching for Remembered Targets. *European Neurology*,
58(1), 1–11. https://doi.org/10.1159/000102160

Tippett, W. J., & Sergio, L. E. (2006). Visuomotor integration is impaired in early stage Alzheimer's
disease. *Brain Research*, *1102*(1), 92–102. https://doi.org/10.1016/j.brainres.2006.04.049

Tippett, W. J., Sergio, L. E., & Black, S. E. (2012). Compromised visually guided motor control in
individuals with Alzheimer's disease: Can reliable distinctions be observed? *Journal of
Clinical Neuroscience*, *19*(5), 655–660. https://doi.org/10.1016/j.jocn.2011.09.013

Verheij, S., Muilwijk, D., Pel, J. J. M., van der Cammen, T. J. M., Mattace-Raso, F. U. S., & van der
Steen, J. (2012). Visuomotor Impairment in Early-Stage Alzheimer's Disease: Changes in
Relative Timing of Eye and Hand Movements. *Journal of Alzheimer's Disease*, *30*(1), 131–
143. https://doi.org/10.3233/JAD-2012-111883

Villemagne, V. L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K. A., Salvado, O., Szoeke, C.,
Macaulay, S. L., Martins, R., Maruff, P., Ames, D., Rowe, C. C., & Masters, C. L. (2013).
Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's

disease: A prospective cohort study. *The Lancet Neurology*, *12*(4), 357–367. https://doi.org/10.1016/S1474-4422(13)70044-9

Zanto, T. P., & Gazzaley, A. (2014). *Attention and Ageing* (A. C. (Kia) Nobre & S. Kastner, Eds.; Vol. 1). Oxford University Press. https://doi.org/10.1093/oxfordhb/9780199675111.013.020

Competing interests

None declared.