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# BMJ Open

## The assessment of visually guided misreaching in prodromal Alzheimer's disease: study protocol

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3 1 **The assessment of visually guided misreaching in prodromal Alzheimer's disease:**  
4  
5 2 **study protocol**

6  
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50 26 Word count: 3,593

## 1 Abstract

27 *Introduction:* Recent evidence has implicated the precuneus of the medial parietal lobe  
28 as one of the first brain areas to show pathological changes in Alzheimer's disease (AD).  
29 Damage to the precuneus through focal brain injury is associated with impaired visually  
30 guided reaching, particularly for objects in peripheral vision. This raises the hypothesis  
31 that peripheral misreaching may be detectable in patients with prodromal AD. The aim  
32 of this study is to assess the frequency and severity of peripheral misreaching in  
33 patients with mild cognitive impairment (MCI) and AD.  
34

35  
36 *Methods and Analysis:* Patients presenting with amnesic MCI, mild-to-moderate AD, and  
37 healthy older-adult controls will be tested (target N=24 per group). Peripheral  
38 misreaching will be assessed using two set ups: a tablet based task of lateral reaching,  
39 and motion-tracked radial reaching (in depth). There are two versions of each task,  
40 where participants can look directly at targets (free reaching), and when they must  
41 maintain central fixation (peripheral reaching). All tasks will be conducted first on their  
42 dominant and then their non-dominant side. For each combination of task and side, a  
43 peripheral misreaching index (PMI) is then calculated as the increase in absolute  
44 reaching error between free and peripheral reaching. Each patient will be classified as  
45 showing peripheral misreaching if their PMI is significantly abnormal, by comparison to  
46 control performance on either side of space. We will then test whether the frequency of  
47 peripheral misreaching exceeds the chance level in each patient group, and compare the  
48 overall severity of misreaching between groups.  
49

50 *Ethics and Dissemination:* Ethical approval was provided by the NHS East of England,  
51 Cambridge Central Research Ethics Committee (REC 19/EE/0170).  
52

53 **Key words:** Alzheimer's disease, cognitive impairment, visually guided action,  
54 peripheral reaching, optic ataxia  
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3 57 **2 Article Summary**  
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5 58 *Strengths and Limitations of this study*  
6

- 7 59 • The first study to systematically assess visually guided reaching in patients with  
8 cognitive impairment  
9 60  
10 61 • Includes a simple tablet-based task (lateral reaching) that could be readily  
11 translated to clinical to assess the presence of peripheral misreaching  
12 62  
13 63 • Case-control statistical tests of deficit are inherently low-powered, subtle deficits  
14 of misreaching may not be detected at the level of individual patients  
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### 65 3 Introduction

66 The pathophysiological cascade that leads to Alzheimer's disease (AD) can begin 20  
67 years before the onset of cognitive problems such as memory loss (1). Longitudinal  
68 modelling of these changes has highlighted the precuneus, in the medial superior  
69 parietal lobe, as one of the first regions to be affected in this wave of change (Gordon et  
70 al., 2018). Focal damage in and around this area is known to be associated with deficits  
71 of visually guided action (3). One example of such a condition is optic ataxia, an  
72 impairment of misreaching typically reflected in peripheral vision (4,5). Patients with  
73 optic ataxia often do not often complain of this symptom and it is rarely assessed in  
74 clinical settings, and it can therefore go undetected (6). The changes observed in the  
75 precuneus in prodromal AD, and the link between the precuneus and optic ataxia, raise  
76 the hypothesis that optic ataxic misreaching may be detectable in patients with  
77 prodromal AD.

#### 79 3.1 Specific hypothesis

80 The hypothesis that peripheral misreaching is a feature of AD predicts that individual  
81 patients with AD, and possibly those with MCI, will show an abnormally large inflation  
82 of reaching errors when aiming for targets in peripheral vision, as compared with  
83 targets in free vision. At a group level, patients with AD, and possibly MCI, may show  
84 significantly greater peripheral misreaching than healthy controls.

## 87 4 Methods

### 88 4.1 Study setting

89 The study is a collaboration between clinicians and University staff at the University of  
90 Edinburgh (UoE) and University of East Anglia (UEA). Details of recruitment and site  
91 information can be found in the supplementary materials. Data collection for this study  
92 began on 03/10/2019 and 8/48 patients have taken part. Data for healthy controls have  
93 already been collected.

94

### 95 4.2 Participants

96 Patients with a diagnosis of amnesic MCI or typical (amnesic) mild-to-moderate AD  
97 will be invited to take part. Mild to moderate AD will be defined by a score of at least 50  
98 in the most recent administration of Addenbrooke's Cognitive Examination (ACE-III,  
99 Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000) If there is no recorded ACE-III  
100 score, clinical opinion of patient's condition will be used to assess eligibility.

101

102 Older adults without any known neurological disorders will be tested as a healthy  
103 control (HC) group. To achieve our target of 24 full data-sets per group (*Section 5.3*), we  
104 plan to test up to 30 participants in each group, allowing for possible withdrawals.

105

#### 106 4.2.1 Inclusion criteria

107 For all participant groups, the ability to give informed consent is the initial inclusion  
108 criterion. Additional inclusion criteria are then applied to each group.

109

110 Control group inclusion criteria:

- 111 • Aged 50 – 75<sup>1</sup>
- 112 • No reported neurological or neurodegenerative conditions

113

114 MCI group inclusion criteria:

- 115 • Aged 45 – 85
- 116 • Clinical diagnosis of MCI with an amnesic pattern of presentation

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<sup>1</sup> NB. The age-range for controls is targeted at the expected age range for patients, but the allowable range of ages for patients is wider than this, in order not to restrict recruitment unnecessarily.



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5 118 AD group inclusion criteria:

- 6  
7 119
  - Aged 45 – 85

8  
9 120
  - Clinical diagnosis of AD

10 121

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12 122 *4.2.2 Exclusion criteria*

13  
14 123 For all participant groups, the following exclusion criteria are applied:

- 15 124
  - Significant difficulty communicating or understanding instructions in English

16  
17 125
  - Significant, uncorrected visual impairment (e.g., cataract, macular degeneration,

18 126 scotoma, amblyopia, strabismus)

19  
20 127
  - Conditions that could interfere with smooth hand movements (e.g. ataxia,

21 128 essential tremor, severe arthritis)

22  
23 129
  - Prior history of stroke or TIA

24 130

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26 131 *4.2.3 Public and Patient involvement*

27  
28 132 Patients with MCI or AD and their carers were involved in the early stages of planning  
29 133 and development. A focus group was held at the Anne Rowling Clinic in Edinburgh  
30 134 where patients and carers had the opportunity to try out prototypes of the tablet-based  
31 135 reaching task and provide feedback on task design. This feedback was used to optimise  
32 136 the final task for patient accessibility and clarity.

33  
34 137

35  
36 138 *4.3 Tasks*

37 139 Two different set-ups will be used to assess peripheral reaching: a tablet-based  
38 140 assessment of reaching in the frontoparallel plane (lateral reaching), and a motion-  
39 141 tracking assessment of reaching in radial depth (radial reaching). Participants will  
40 142 complete two versions of each reaching task: a version in which participants look  
41 143 directly at targets before reaching to them (free reaching); and a version where central  
42 144 fixation is maintained (peripheral reaching). The critical outcome is a measure of the  
43 145 inflation of absolute reaching error in peripheral reaching relative to free reaching.

44  
45 146

46 147 Before testing, the participant's dominant writing hand is identified (by self-report). All  
47 148 tasks are completed first on the dominant side, using the dominant hand, followed by

1  
2  
3 149 the non-dominant side and hand. Lateral reaching is completed first, followed by radial  
4  
5 150 reaching. All tasks are performed in the same order for all participants.  
6  
7 151

#### 8 152 4.3.1 *Lateral reaching tasks*

##### 9 153 *i. Stimuli & Apparatus*

10 154 Stimuli are presented on a HP Pavillion x360 touch screen (active display 310x175mm,  
11  
12 155 resolution 1920x1080 pixels). Tasks are controlled by a custom program written in  
13  
14 156 OpenSesame version 3.2.8 *Kafkesque Koffka* (8). Participants are seated 40cm away  
15  
16 157 from the screen which is positioned with either the right edge of the screen aligned to  
17  
18 158 their midline (left-sided reaching, Figure 1A) or the left edge (right-sided reaching,  
19  
20 159 Figure 1B). A start box (white rectangle, 2x2°, 13.96x13.96mm) is drawn at the centre  
21  
22 160 edge (right or left) of the screen, aligned to participant's midpoint. In some tasks  
23  
24 161 (detailed below) a white fixation cross is present (1x1°, 6.98x6.98mm), located 34.9mm  
25  
26 162 (5°) directly above the start box. Targets are white circles (diameter = 2°, 13.96mm)  
27  
28 163 presented along radial spokes at 28, 33 and 38° to the left (Figure 1A) or right (Figure  
29  
30 164 1B) of fixation. The experimenter sits across the table and monitors eye movements  
31  
32 165 directly.  
33

##### 34 166 *ii. Free reaching*

35 167 For the first block in the lateral reaching task participants are not required to fixate,  
36  
37 168 therefore the fixation cross is absent.  
38  
39 169

40 170  
41  
42 171 Participants initiate a trial by pressing and holding down the start box, which  
43  
44 172 disappears at touch. At this point they are may search the screen for a target. After a  
45  
46 173 short delay (250-750ms, randomised 100ms intervals) a target appears at one of nine  
47  
48 174 possible locations. As soon as the target appears, participants look at it and make one  
49  
50 175 smooth reach to try to touch the target. The target remains on the screen until a touch is  
51  
52 176 recorded at any location, then the target disappears and a short beep (100ms, 440Hz) is  
53  
54 177 played. The validity of the trial is then coded by the experimenter using a keyboard; 'y' –  
55  
56 178 valid trial, 'e' – the participant did not move their eyes to the target, 'v' – invalid trial,  
57  
58 179 and the start box reappears to begin another trial.  
59  
60 180

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2  
3 181 If the experimenter presses 'e' or 'v' that trial is repeated until a valid trial is recorded.  
4  
5 182 The block ends after a minimum of 27 valid trials (3 per target location), or after 50  
6  
7 183 valid and 'no eye-movement' trials.  
8

9 184

10 185 *iii. Visual detection*

11  
12 186 This is a simple check to confirm that the participant is capable of detecting the targets  
13  
14 187 when presented in peripheral vision, to be allow for a meaningful test of peripheral  
15  
16 188 reaching (*Section 4.3.1iv*).  
17

18 189

19 190 Throughout each trial the participant must gaze at the fixation cross. They initiate the  
20  
21 191 trial by pressing and holding down the start box, which disappears when touched. In  
22  
23 192 order to aid the maintenance of fixation, the fixation cross cycles between white and red  
24  
25 193 at the screen refresh rate (60Hz). After a short delay (250-750ms), a target can appear  
26  
27 194 at one of the nine locations for one second, or no target appears. This is followed by a  
28  
29 195 short beep to indicate the end of the trial. The participant must verbally report whether  
30  
31 196 or not a target was seen in that interval. The experimenter records the response using  
32  
33 197 the keyboard ('y' – yes, 'n' – no). If the participant makes an eye-movement, the  
34  
35 198 experimenter presses 'e' and the trial is repeated. The block ends after 15 valid (no eye-  
36  
37 199 movement) trials, one for each of the nine target locations, and six catch trials with no  
38  
39 200 target.  
40

41 201

42 202 To progress to the peripheral reaching task, participants are required to detect at least  
43  
44 203 6/9 targets and correctly rejects at least 3/6 catch trials. Otherwise, testing is  
45  
46 204 discontinued on that side of space.  
47

48 205

49 206 *iv. Peripheral reaching*

50 207 For peripheral reaching participants are required to gaze at the fixation cross  
51  
52 208 throughout each trial. A trial begins by pressing and holding down the start box. When  
53  
54 209 touched, the start box disappears and the fixation cross cycles between white and red  
55  
56 210 (at a rate of 60Hz) until the trial ends. After a short delay (250-750ms) a target appears  
57  
58 211 at one of nine locations. Whilst maintaining fixation, participants make one smooth  
59  
60 212 reaching movement to try to touch the target. The target remains on the screen until a  
61  
62 213 touch is recorded at any location, and a short beep is played once the target disappears.

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3 214 The experimenter then records the validity of the trial; 'y' – valid, 'e' – participant  
4 215 moved their eyes away from fixation, 'v' – invalid trial.

6 216

8 217 Invalid ('e' or 'v') trials are repeated until a valid trial is recorded. The block ends after a  
9 218 minimum of 27 valid trials (3 per target location), or after 50 valid and 'eye-movement'  
11 219 trials.

13 220

#### 15 221 4.3.2 Radial reaching tasks

##### 17 222 i. Stimulus & Apparatus<sup>2</sup>

19 223 An infrared motion-tracking camera (Optotrak Certus, Northern Digital Inc) is used to  
20 224 track the reaching movement. Infra-red-emitting diodes (IREDs) are taped to the tip of  
22 225 the right and left index fingers of each participant to track the reach in each hand. The  
24 226 Optotrak samples the IRED's 3D position at 100Hz throughout each 2000ms trial. The  
26 227 task is controlled by custom software written in LabView (National Instruments)  
28 228 programming environment.

29 229

31 230 Participants are seated with their head placed in a chin-rest in line with the middle of  
32 231 the display. Stimuli are back-projected via a mirror onto a screen (1000mm wide x  
34 232 750mm deep) that lies flat in-front of the participant. A webcam is placed on the screen  
36 233 50cm directly in-front of the participant, as a fixation point. The live webcam image  
38 234 feeds into a separate laptop, allowing experimenter to monitor gaze. A start-button is  
40 235 aligned to the centre of the screen, positioned 10cm in-front of the participant, 40cm  
42 236 away from fixation (Figure 2). Targets are white circles (diameter = 1.60°, 13.96mm)  
44 237 presented at 4 eccentric locations (11.4, 22.6, 33.4 and 43.6° away from centre) on each  
46 238 side (Figure 2).

47 239

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55 <sup>2</sup> The stimuli and apparatus reported here are specific to UoE. At the second site, UEA, motion  
56 tracking was performed a Qualisys AB system (Gothenburg, Sweden). Targets are green LEDs  
57 (diameter = 0.68°, 6mm). The experiment is presented on a grey table (100x100cm) and the  
58 experiment is run through Psychophysics Toolbox (11) in MATLAB (Mathworks, USA).  
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3 242 *ii. Calibration*  
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5 243 A calibration procedure is carried out before the reaching tasks to record the IRED  
6 244 position at the actual target location. A target is displayed at one target location and the  
7 245 participant is instructed to cover it completely with their reaching finger. Once the  
8 246 target is covered, the experimenter presses the start button and the finger location is  
9 247 recorded for 2000ms. A beep plays after 2000ms, indicating that the participant can  
10 248 move their hand away from the target position. Another target appears at the next  
11 249 location and the same procedure is repeated. Calibration is run using the ipsilateral  
12 250 hand for four targets on the left side, and four on the right.  
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20 252 *iii. Free reaching*  
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22 253 Participants initiate a trial by pressing and holding down the start button. As soon as  
23 254 they push the button down, participants may look around the screen for a target. After  
24 255 250-750ms a target appears, participants then look directly at the target and reach to  
25 256 touch the target in one smooth movement. Optotrak recording is initiated  
26 257 simultaneously with target appearance, and the target disappearance is the  
27 258 simultaneous with the end of the recording after 2000ms. When the target disappears a  
28 259 short beep (100ms, 440Hz) plays, the participant leaves their finger at its landing  
29 260 position until they hear the beep. After the trial, the experimenter codes the trial  
30 261 validity with a key-press; 'Return' – valid, 'F1' – no eye-movement, 'Esc' – invalid trial. If  
31 262 an invalid trial ('F1' or 'Esc') is coded the trial gets recycled to the end of the shuffled  
32 263 trial.  
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44 265 The block ends once 28 valid trials (7 per target location) are recorded, or after 50 valid  
45 266 and 'no eye-movement' trials.  
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48 267

49 268 *iv. Peripheral reaching*  
50

51 269 To assess reaching accuracy in the periphery participants are required to look directly  
52 270 at central fixation (the webcam) throughout each trial. Participants initiate a trial by  
53 271 pressing and holding down the start button. After 250-750ms a target appears. Whilst  
54 272 maintaining gaze on the webcam participants make one smooth reaching movement to  
55 273 try to touch the target. After the reach, participants leave their finger at its landing  
56 274 position until a short beep (100ms, 440Hz). The target remains on screen for 2000ms  
57  
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3 275 after the trial begins. The motion-tracker records the reach throughout the 2000ms  
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5 276 trial. At the end of the trial, the experimenter codes trial validity; 'Return' – valid trial,  
6  
7 277 'F1' – eye movement during trial, 'Esc' – invalid trial. If an invalid trial ('F1, 'Esc') is  
8  
9 278 recorded then the trial is recycled to the end of the shuffled trial list.  
10  
11 279  
12 280 The block ends after 28 valid trials (7 per target location) are recorded, or after 50 valid  
13  
14 281 and 'eye-movement' trials.  
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## 282 5 Analysis plan

### 283 5.1 Lateral reaching task

284 For the critical analyses, a single measure of *reaching accuracy* is taken for each  
285 participant, for each combination of viewing condition (free, peripheral) and side (non-  
286 dominant, dominant). For each response, the absolute error (in mm, x and y axis) is  
287 recorded as the distance of the reach endpoint from the target midpoint. The median  
288 absolute error is then calculated for each target eccentricity, across responses to the 3  
289 targets at that eccentricity, for each combination of viewing condition and side. The  
290 average absolute error is then calculated as the mean of the medians for the 3  
291 eccentricities, to give the single measure of reaching accuracy for each viewing  
292 condition at each side.

293  
294 For the comparison of individual patients against control performance, the data are  
295 further compressed to a single index of performance per side, by subtracting reaching  
296 accuracy in the free vision condition from the peripheral condition. We call this value  
297 the *peripheral misreaching index (PMI)*.

#### 299 5.1.1 Analysis of single case deficits

300 We will screen the control group for outliers that might suggest abnormalities, as such  
301 values would reduce the (already low, see Figure 3) power to detect single-case deficits.  
302 We will use a robust method of outlier detection based on the median absolute  
303 deviation (MAD). The MAD can be multiplied by the consistency constant 1.4826 to  
304 estimate the standard deviation, assuming a normal distribution. Each control  
305 participant's PMI can be expressed a modified Z-score ( $Z'$ ) by subtracting the group  
306 median, divided by the median absolute deviation \*1.4826. If  $Z'$  exceeds 2.5, that  
307 participant will be excluded, and replaced. Our simulations suggest that, for a group size  
308 of 24, we would expect to exclude (on average) < 1 participant (~0.67) by this criterion.

309  
310 We will next assess, for each side, whether the PMI of controls is related to age or sex,  
311 by computing Pearson's correlations. If the correlation is  $\geq .3$  on either side, then that  
312 variable will be included as a covariate in the subsequent case-control comparisons for  
313 both sides.

314



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2  
3 315 Case-control comparisons will then be run to compare each patient's PMI against  
4  
5 316 control performance. These comparisons will be based upon Crawford & Howell's  
6  
7 317 (1998) modified t-test; or, if covariates are included, we will use the updated test of  
8  
9 318 deficit (Crawford, Garthwaite and Ryan, 2011). As we are testing for an increased PMI in  
10  
11 319 each patient, the tests will be one-tailed, with alpha level set to .025, to constrain the  
12  
13 320 expected Type I error rate to .05 across the two sides. If a patient shows a significant  
14  
15 321 deficit on either side, they will be classed as showing peripheral misreaching. If a  
16  
17 322 patient meets an unadjusted criterion for a deficit (.05), but not the adjusted criterion  
18  
19 323 (.025), they will be classified as showing borderline peripheral misreaching.  
20

21 324  
22 325 Finally, a binomial test will test whether the rate of observed peripheral misreaching  
23  
24 326 exceeds the rate expected by chance (i.e. the per-patient adjusted alpha level of .05). A  
25  
26 327 significant outcome ( $p < .05$ ) for either patient group will indicate that peripheral  
27  
28 328 misreaching is a feature of this patient group. The observed rate of peripheral  
29  
30 329 misreaching will provide an estimate of how common it is. We will run a further  
31  
32 330 analysis including borderline cases, and compare the rate of peripheral misreaching in  
33  
34 331 each patient group against the appropriate chance level of (i.e. the per-patient  
35  
36 332 unadjusted alpha level of .10).  
37

38 333

### 39 334 *5.1.2 Group-level analysis*

40 335 The case control approach will be complemented by a group-level ANOVA of reaching  
41  
42 336 accuracy, as measured by the PMI, with the between-subject factor of group (HC, MCI,  
43  
44 337 AD) and the within subject factor of side (non-dominant, dominant). This analysis will  
45  
46 338 test whether the average severity of peripheral misreaching in each patient group  
47  
48 339 significantly exceeds that observed in healthy controls.  
49

50 340

### 51 341 *5.1.3 Exploratory analyses*

52 342 More detailed analyses will be run with a between subject factor of group and within  
53  
54 343 subject factors of side, eccentricity and viewing condition. These analysis will be  
55  
56 344 conducted using dependent variables of absolute reaching error, directional (signed)  
57  
58 345 reaching error, reaction time and movement time. The expectation is that peripheral  
59  
60 346 misreaching will manifest as a fixation-directed bias, which is exacerbated at higher  
347 eccentricities.



348

### 5.2 Radial reaching task

350 IRED speed is used to determine onset and offset of the reaching movement. Movement  
351 onset is defined as the first frame in which the IRED's speed exceeds 50mm/s (and  
352 maintains that speed for up to 100ms). Movement offset is defined as the first  
353 subsequent frame in which IRED speed falls below 50mm/s. The landing position of the  
354 movement is defined by the x and y coordinates in the final frame of the movement, and  
355 will be recorded as errors relative to true target locations recorded during calibration  
356 for each participant.

358 An initial analysis of PMI for the radial reaching task will be performed, restricted to the  
359 two most eccentric target positions (33.4 and 43.6°). Case-control comparisons follow  
360 the plan for the lateral reaching task (*Section 5.1.1*), to estimate the rates of peripheral  
361 misreaching, and borderline peripheral misreaching, in the two patient groups. Due to  
362 different experimental set ups between the two test sites (UoE, UEA), each patient will  
363 be referenced to the same-site control data for case-control comparisons.

365 A group level ANOVA of PMI, restricted to the two most eccentric target positions, will  
366 similarly follow the plan for lateral reaching (*Section 5.1.2*). We will include site (UoE,  
367 UEA) as an additional covariate. Subsequent, more detailed analyses, will also follow the  
368 plan for lateral reaching (*Section 5.1.2*) Since motion tracking also provides kinematic  
369 variables on reaching trajectories, we also aim to examine the dependent variables peak  
370 speed and time to peak speed, as well as average spatial trajectory of reach.

### 5.3 Power considerations

373 The target sample sizes (N=24 per group) are based on power considerations related to  
374 the main inferential analyses, the case-control comparisons, and binomial tests of rates  
375 of peripheral misreaching deficits for the lateral reaching task.

377 The control sample size of 24 will provide close to the maximum power for case-control  
378 tests of deficit (figure 3A). Note that high power for these comparisons is inherently  
379 unachievable unless the deficit being tested for is very large. We do not know how large  
380 any misreaching deficits may be in our patient groups, but our control sample size will

1  
2  
3 381 provide close to the maximum achievable power to detect them if they exist. Figure 3B  
4  
5 382 illustrates more fully the relationship between deficit size (D) and power, for the  
6  
7 383 adjusted alpha level (.025) and unadjusted alpha level (.05) by which we will determine  
8  
9 384 peripheral misreaching deficits and borderline cases respectively (*Section 5.1.1*).

10 385

11  
12 386 The main hypothesis is that peripheral misreaching will be found in a significant  
13  
14 387 proportion of patients with AD and MCI. For one-sample binomial test to determine  
15  
16 388 whether the observed rate of peripheral misreaching exceeds the chance level of .05, a  
17  
18 389 sample size of 24 has > .9 power. Provided that the true population proportion is at  
19  
20 390 least .2 (1 in 5). This is appropriate to our aims, since peripheral misreaching would be  
21  
22 391 of limited significance in these clinical populations if its prevalence were less than 1 in  
23  
24 392 5.

## 393 6 Ethics and dissemination

394 This protocol was approved by UK Health Research Authority, by the East of England,  
395 Cambridge Central Research Ethics Committee on 13 June 2019 (REC reference  
396 19/EE/0170).

397  
398 All patients will provide informed consent, highlighting the voluntary nature of the  
399 study and their right to withdraw. If there is any doubt about the ability of the patient to  
400 provide informed consent, then this patient will not be recruited. There are no direct  
401 risks associated with taking part.

402  
403 Careful consideration will be taken to maintain patient's confidentiality. After consent is  
404 provided, an anonymous code will be assigned to each patient. Some patient details  
405 such as CHI number, age, gender and time of diagnosis, will need to be accessed by the  
406 research team, these details will be stored alongside patient code in a password-  
407 protected document.

408  
409 At the end of the study, a lay summary of results will be provided to patients who have  
410 expressed a further interest. Project results will be made publically available on the  
411 Open Science Framework (<https://osf.io/bxnqs/>) within three months after study end-  
412 date (30/06/2020).

## 414 7 Footnotes

415 **Author Contributions:** Each author has contributed significantly one or more aspects  
416 of the study. All authors contributed to study development and design. RDM, SR and  
417 AGM were involved in implementation of study protocol and analysis design. All authors  
418 contributed to data acquisition for MCI and AD, with SP and MH leading patient  
419 recruitment. AGM and SR were involved in data acquisition for HC. AGM and RDM  
420 drafted the manuscript and all authors provided critical revisions and approved the  
421 final version.

422  
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1  
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3 425

4 426 **Competing interests:** there are no conflicts or competing interests for AGM, SP, MH, SR  
5 427 or RDM.  
6  
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11 429 **8 References**

- 12 430 1. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for  
13 431 Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*2014;13(6):614–29.  
14 432 [doi.org/10.1016/S1474-4422\(14\)70090-0](https://doi.org/10.1016/S1474-4422(14)70090-0)  
15  
16 433 2. Gordon BA, Blazey TM, Su Y et al. Spatial patterns of neuroimaging biomarker  
17 434 change in individuals from families with autosomal dominant Alzheimer's  
18 435 disease: a longitudinal study. *Lancet Neurol*.2018;17(3):211–2.  
19 436 [doi.org/10.1016/S1474-4422\(18\)30028-0](https://doi.org/10.1016/S1474-4422(18)30028-0)  
20  
21 437 3. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and  
22 438 behavioural correlates. *Brain*2006;129(3):564–83.  
23 439 [doi.org/10.1093/brain/awl004](https://doi.org/10.1093/brain/awl004)  
24  
25 440 4. Karnath H-O, Perenin M-T. Cortical Control of Visually Guided Reaching: Evidence  
26 441 from Patients with Optic Ataxia. *Cereb Cortex*2005;15(10):1561–9.  
27 442 [doi.org/10.1093/cercor/bhi034](https://doi.org/10.1093/cercor/bhi034)  
28  
29 443 5. Perenin MT, Vighetto A. Optic Ataxia: A Specific Disorder in Visuomotor  
30 444 Coordination. In: *Spatially Oriented Behavior*New York, NY: Springer New York;  
31 445 1983 p. 305–26.  
32 446 6. Rossetti Y, Pisella L, McIntosh RD. Definition: Optic ataxia. *Cortex*2019;in press.  
33 447 7. Mathuranath PS, Nestor PJ, Berrios GE, et al. A brief cognitive test battery to  
34 448 differentiate Alzheimer's disease and frontotemporal dementia.  
35 449 *Neurology*2000;55(11):1613–20.  
36 450 [doi.org/10.1212/01.wnl.0000434309.85312.19](https://doi.org/10.1212/01.wnl.0000434309.85312.19)  
37  
38 451 8. Mathôt S, Schreij D, Theeuwes J. OpenSesame: An open-source, graphical  
39 452 experiment builder for the social sciences. *Behav Res Methods*2012;44(2):314–24.  
40 453 [doi.org/10.3758/s13428-011-0168-7](https://doi.org/10.3758/s13428-011-0168-7)  
41  
42 454 9. Crawford JR, Howell DC. Comparing an Individual's Test Score Against Norms  
43 455 Derived from Small Samples. *Clin Neuropsychol*1998;12(4):482–6.  
44 456 [doi.org/10.1076/clin.12.4.482.7241](https://doi.org/10.1076/clin.12.4.482.7241)  
45  
46 457 10. Crawford JR, Garthwaite PH, Ryan K. Comparing a single case to a control sample:

1  
2  
3 458 Testing for neuropsychological deficits and dissociations in the presence of  
4 covariates. *Cortex*2011;47(10):1166–78.

5 459  
6 [doi.org/10.1016/j.cortex.2011.02.017](https://doi.org/10.1016/j.cortex.2011.02.017)

7 460  
8 461 11. Brainard DH. The Psychophysics Toolbox. *Spat Vis*1997;10:433–6.

9 462  
10 [doi.org/10.1163/156856897X00357](https://doi.org/10.1163/156856897X00357)

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## 12 464 **9 Figure legends**

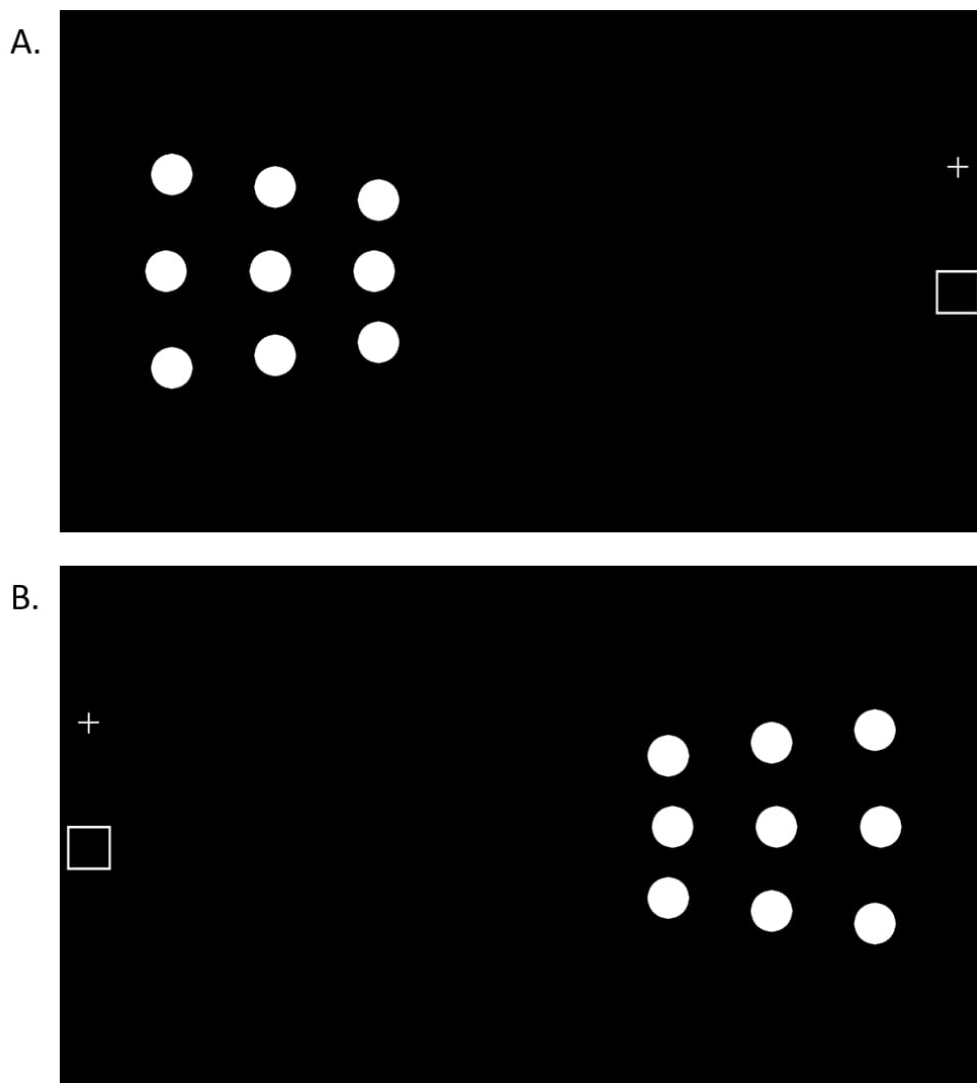
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14 465 Figure 1: 9 target positions during the lateral reaching task for left (A) and right (B)  
15 hand sides. At a viewing distance of 40cm targets are presented at approximately 28, 33  
16 466 and 38° of eccentricity  
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19 469 Figure 2: target positions during the radial reaching task, shown here on both the right-  
20 and left-hand sides, at 11.4, 22.6, 33.4 and 43.6° from fixation. The start-button is  
21 470 positioned at the bottom of the screen 40cm away from central fixation. A webcam is  
22 471 placed at the point of central fixation (midpoint).  
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24 473

25 474 Figure 3: (a) Relation between control sample size and power to detect a single-case  
26 475 deficit in a one-tailed test, for different size of deficit (D, expressed as standard  
27 476 deviations of control mean), (b) Relation between deficit size (D) and power to detect a  
28 477 single case deficit, given a control sample size of 24, for adjusted and unadjusted alpha  
29 478 criteria.  
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Figure 1: 9 target positions during the lateral reaching task for left (A) and right (B) hand sides. At a viewing distance of 40cm targets are presented at approximately 28, 33 and 38° of eccentricity

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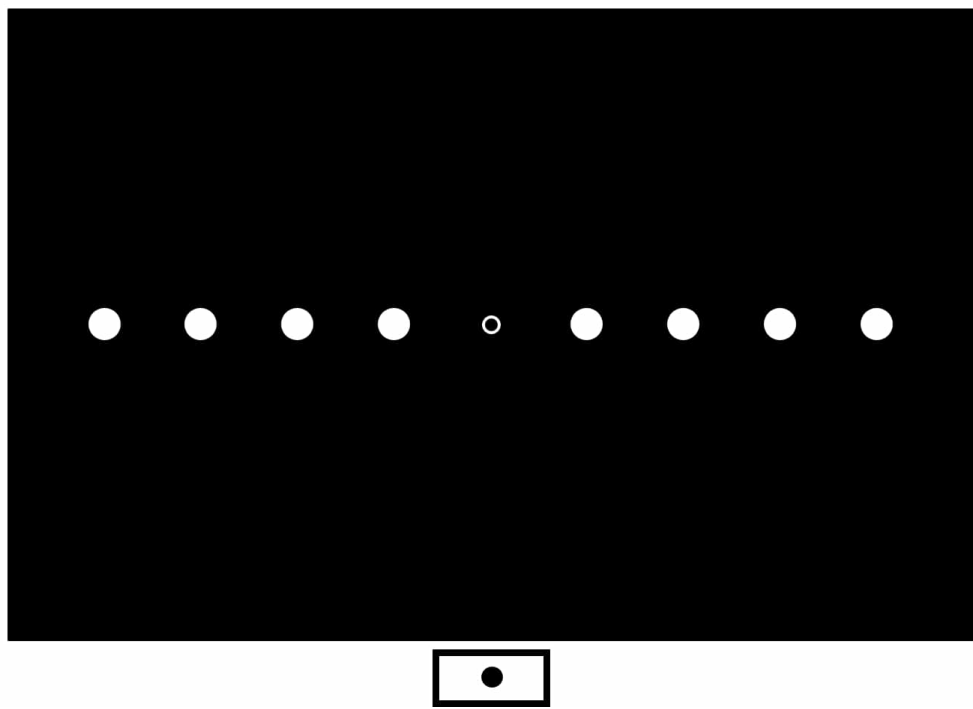


Figure 2: target positions during the radial reaching task, shown here on both the right- and left-hand sides, at 11.4, 22.6, 33.4 and 43.6° from fixation. The start-button is positioned at the bottom of the screen 40cm away from central fixation. A webcam is placed at the point of central fixation (midpoint).

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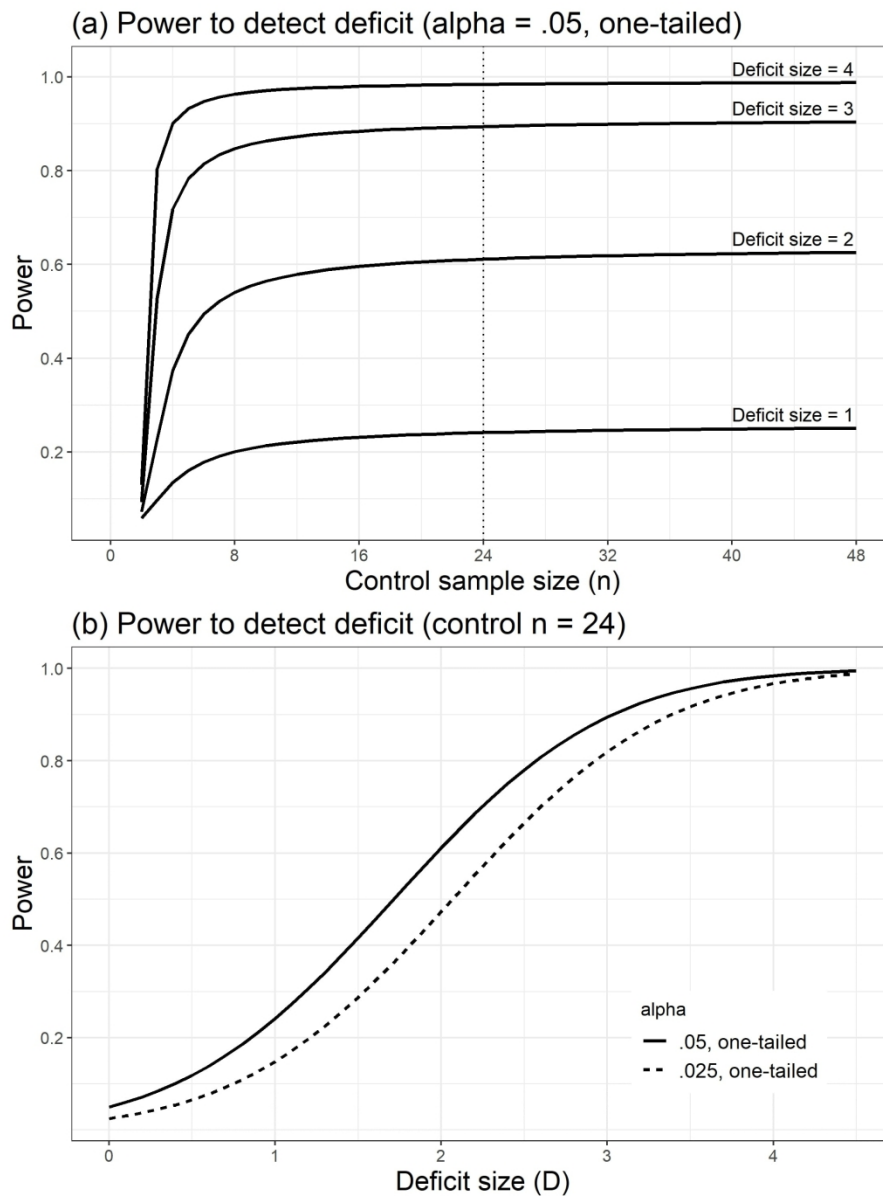


Figure 3: (a) Relation between control sample size and power to detect a single-case deficit in a one-tailed test, for different size of deficit (D, expressed as standard deviations of control mean), (b) Relation between deficit size (D) and power to detect a single case deficit, given a control sample size of 24, for adjusted and unadjusted alpha criteria.

190x254mm (300 x 300 DPI)



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2  
3 **The assessment of visually guided misreaching in prodromal Alzheimer's disease:**  
4 **study protocol**  
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6

7 **Site-specific information**

8 *Site 1: Edinburgh*

9  
10 Patient recruitment in Edinburgh will take place at the Anne Rowling Regenerative  
11 Neurology Clinic (NHS Lothian), through a team led by Dr. Suvankar Pal. Patients who fit  
12 the recruitment criteria will be identified through the Rowling CARE-register and  
13 provided an information sheet and a notification of interest form.  
14  
15

16  
17 All testing (patient and control) takes place in the Human Movement Laboratory,  
18 Department of Psychology, The University of Edinburgh.  
19

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21 *Site 2: Norfolk*

22 Patient recruitment will take place in the Julian Hospital in Norwich (NHS Norfolk &  
23 Suffolk). A team of research nurses will identify suitable participants who will be  
24 provided an information sheet and a notification of interest form.  
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28 All testing takes place in the Vision and Action Laboratory, Department of Psychology,  
29 The University of East Anglia.  
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## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

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60**Results**

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

**Discussion**

Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results

**Other information**

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
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\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## The assessment of visually guided reaching in prodromal Alzheimer's disease: a cross-sectional study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035021.R1
Article Type:	Protocol
Date Submitted by the Author:	26-Feb-2020
Complete List of Authors:	Mitchell, Alexandra; The University of Edinburgh, School of Psychology, Philosophy & Language Sciences McIntosh, Robert; The University of Edinburgh, School of Psychology, Philosophy & Language Sciences Rossit, Stephanie; University of East Anglia, School of Psychology Hornberger, M; University of East Anglia, School of Medicine Pal, Suvankar; The University of Edinburgh, Anne Rowling Regenerative Neurology Clinic, Centre for Clinical Brain Sciences
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Mental health, Pathology
Keywords:	Dementia < NEUROLOGY, Adult neurology < NEUROLOGY, Neurophysiology < NEUROLOGY, NEUROPATHOLOGY

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3 **1 The assessment of visually guided reaching in prodromal Alzheimer's disease: a**  
4 **2 cross-sectional study protocol**

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7 3 *Alexandra G. Mitchell<sup>1</sup>, Robert D. McIntosh<sup>1</sup>, Stephanie Rossit<sup>2</sup>, Michael Hornberger<sup>3,4</sup> &*  
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26 Word count: 3,593

## 1 Abstract

27 *Introduction:* Recent evidence has implicated the precuneus of the medial parietal lobe  
28 as one of the first brain areas to show pathological changes in Alzheimer's disease (AD).  
29 Damage to the precuneus through focal brain injury is associated with impaired visually  
30 guided reaching, particularly for objects in peripheral vision. This raises the hypothesis  
31 that peripheral misreaching may be detectable in patients with prodromal AD. The aim  
32 of this study is to assess the frequency and severity of peripheral misreaching in  
33 patients with mild cognitive impairment (MCI) and AD.  
34

35  
36 *Methods and analysis:* Patients presenting with amnesic MCI, mild-to-moderate AD, and  
37 healthy older-adult controls will be tested (target N=24 per group). Peripheral  
38 misreaching will be assessed using two set ups: a tablet-based task of lateral reaching,  
39 and motion-tracked radial reaching (in depth). There are two versions of each task,  
40 where participants can look directly at targets (free reaching), and when they must  
41 maintain central fixation (peripheral reaching). All tasks will be conducted first on their  
42 dominant and then their non-dominant side. For each combination of task and side, a  
43 peripheral misreaching index (PMI) is then calculated as the increase in absolute  
44 reaching error between free and peripheral reaching. Each patient will be classified as  
45 showing peripheral misreaching if their PMI is significantly abnormal, by comparison to  
46 control performance on either side of space. We will then test whether the frequency of  
47 peripheral misreaching exceeds the chance level in each patient group and compare the  
48 overall severity of misreaching between groups.  
49

50 *Ethics and dissemination:* Ethical approval was provided by the NHS East of England,  
51 Cambridge Central Research Ethics Committee (REC 19/EE/0170). The results of this  
52 study will be published in a peer reviewed journal and presented at academic  
53 conferences.  
54

55 Key words: Alzheimer's disease, cognitive impairment, visually guided action,  
56 peripheral reaching, optic ataxia  
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58

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3 59 **2 Article Summary**  
4

5 60 *Strengths and Limitations of this study*  
6

- 7 61 • The first study to systematically assess visually guided reaching in patients with  
8 cognitive impairment  
9 62  
10 63 • Includes a simple tablet-based task (lateral reaching) that could be readily  
11 translated to clinical settings to assess the presence of peripheral misreaching  
12 64  
13 65 • Case-control statistical tests of deficit are inherently low-powered, subtle deficits  
14 of misreaching may not be detected at the level of individual patients  
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### 67 3 Introduction

68 The pathophysiological cascade that leads to Alzheimer's disease (AD) can begin up to  
69 20 years before the onset of cognitive problems in both autosomal and sporadic AD (1–  
70 5). In dominant and early onset cases, there is evidence that the precuneus is one of the  
71 earliest regions to be affected (6,7). Focal damage in and around this brain area is  
72 known to be associated with deficits of visually guided action (8). One example of such a  
73 condition is optic ataxia, an impairment of misreaching typically reflected in peripheral  
74 vision (9,10). Patients with optic ataxia often do not often complain of this symptom and  
75 it is rarely assessed in clinical settings, and it can therefore go undetected (11). The  
76 changes observed in the precuneus in prodromal AD, and the link between the  
77 precuneus and optic ataxia, raise the hypothesis that optic ataxic misreaching may be  
78 detectable in patients with prodromal AD.

79

#### 80 3.1 Specific hypothesis

81 The hypothesis that peripheral misreaching is a feature of AD predicts that individual  
82 patients with AD, and possibly those with MCI, will show an abnormally large inflation  
83 of reaching errors when aiming for targets in peripheral vision, as compared with  
84 targets in free vision. At a group level, patients with AD and, to a lesser extent, patients  
85 with MCI will show significantly greater peripheral misreaching than healthy controls.

86

87

## 88 4 Methods

### 89 4.1 Study setting

90 The study is a collaboration between clinicians and University staff at the University of  
91 Edinburgh (UoE) and University of East Anglia (UEA). Details of recruitment and site  
92 information can be found in the supplementary materials. Data collection for this study  
93 began on 03/10/2019 and 8/48 patients have taken part. Data for healthy controls have  
94 already been collected.

### 96 4.2 Participants

97 Patients with a diagnosis of amnesic MCI or typical (amnesic) mild-to-moderate AD  
98 will be invited to take part. Mild to moderate AD will be defined by a score of at least 50  
99 in the most recent administration of Addenbrooke's Cognitive Examination (ACE-III)  
100 (12) If there is no recorded ACE-III score, clinical opinion of patient's condition will be  
101 used to assess eligibility.

102  
103 Older adults without any known neurological disorders will be tested as a healthy  
104 control (HC) group. To achieve our target of 24 full data-sets per group (*Section 5.3*), we  
105 plan to test up to 30 participants in each group, allowing for possible withdrawals.

#### 107 4.2.1 Inclusion criteria

108 For all participant groups, the ability to give informed consent is the initial inclusion  
109 criterion. Additional inclusion criteria are then applied to each group.

110  
111 Control group inclusion criteria:

- 112 • Aged 50 – 75<sup>1</sup>
- 113 • No reported neurological or neurodegenerative conditions

114  
115 MCI group inclusion criteria:

- 116 • Aged 45 – 85

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<sup>1</sup> NB. The age-range for controls is targeted at the expected age range for patients, but the allowable range of ages for patients is wider than this, in order not to restrict recruitment unnecessarily.

- 1  
2  
3 117 • Clinical diagnosis of MCI with an amnesic pattern of presentation. This includes  
4  
5 118 an observed deficit on cognitive/neuropsychological testing suggesting amnesic  
6  
7 119 and visuospatial profile deficit, low  $\beta$ -amyloid, elevated phosphorylated Tau,  
8  
9 120 regional atrophy on MR brain imaging and/or regional perfusion changes on  
10  
11 121 HMPAO-SPECT  
12  
13

14 123 AD group inclusion criteria:

- 15  
16 124 • Aged 45 – 85  
17  
18 125 • Clinical diagnosis of AD  
19  
20 126

#### 21 127 4.2.2 Exclusion criteria

22  
23 128 For all participant groups, the following exclusion criteria are applied:

- 24 129 • Significant difficulty communicating or understanding instructions in English  
25  
26 130 • Significant, uncorrected visual impairment (e.g., cataract, macular degeneration,  
27  
28 131 scotoma, amblyopia, strabismus)  
29  
30 132 • Conditions that could interfere with smooth hand movements (e.g. ataxia,  
31  
32 133 essential tremor, severe arthritis)  
33  
34 134 • Prior history of stroke or TIA  
35  
36 135 • Clinical features suggested of Lewy body pathology (e.g. visual hallucinations or  
37  
38 136 REM sleep disorder)  
39  
40 137

#### 41 138 4.2.3 Public and Patient involvement

42 139 Patients with MCI or AD and their careers were involved in the early stages of planning  
43  
44 140 and development. A focus group was held at the Anne Rowling Clinic in Edinburgh  
45  
46 141 where patients and carers had the opportunity to try out prototypes of the tablet-based  
47  
48 142 reaching task and provide feedback on task design. This feedback was used to optimise  
49  
50 143 the final task for patient accessibility and clarity.  
51  
52 144

#### 53 145 4.3 Tasks

54 146 Two different set-ups will be used to assess peripheral reaching: a tablet-based  
55  
56 147 assessment of reaching in the frontoparallel plane (lateral reaching), and a motion-  
57  
58 148 tracking assessment of reaching in radial depth (radial reaching). Participants will  
59  
60 149 complete two versions of each reaching task: a version in which participants look

1  
2  
3 150 directly at targets before reaching to them (free reaching); and a version where central  
4  
5 151 fixation is maintained (peripheral reaching). Any general factors affecting motor  
6  
7 152 accuracy should influence both free and peripheral reaching, so we will treat the free  
8  
9 153 reaching condition as a baseline condition, to be subtracted from peripheral reaching  
10  
11 154 performance, to isolate the specific increase in error due to peripheral target  
12  
13 155 presentation (13). The critical outcome measure is therefore the inflation of absolute  
14  
15 156 reaching error in peripheral reaching relative to free reaching.  
15  
16 157

17 158 Before testing, the participant's dominant writing hand is identified (by self-report). All  
18  
19 159 tasks are completed first on the dominant side, using the dominant hand, followed by  
20  
21 160 the non-dominant side and hand. Lateral reaching is completed first, followed by radial  
22  
23 161 reaching. All tasks are performed in the same order for all participants.  
24  
25 162

#### 26 163 4.3.1 Lateral reaching tasks

##### 27 164 i. Stimuli & Apparatus

28  
29 165 Stimuli are presented on a HP Pavillion x360 touch screen (active display 310x175mm,  
30  
31 166 resolution 1920x1080 pixels). Tasks are controlled by a custom program written in  
32  
33 167 OpenSesame version 3.2.8 *Kafkesque Koffka* (14). Participants are seated 40cm away  
34  
35 168 from the screen which is positioned with either the right edge of the screen aligned to  
36  
37 169 their midline (left-sided reaching, Figure 1A) or the left edge (right-sided reaching,  
38  
39 170 Figure 1B). A start box (white rectangle, 2x2°, 13.96x13.96mm) is drawn at the centre  
40  
41 171 edge (right or left) of the screen, aligned to participant's midpoint. In some tasks  
42  
43 172 (detailed below) a white fixation cross is present (1x1°, 6.98x6.98mm), located 34.9mm  
44  
45 173 (5°) directly above the start box. Targets are white circles (diameter = 2°, 13.96mm)  
46  
47 174 presented along radial spokes at 28, 33 and 38° to the left (Figure 1A) or right (Figure  
48  
49 175 1B) of fixation. The experimenter sits across the table and monitors eye movements  
50  
51 176 directly.  
51  
52 177

##### 53 178 ii. Free reaching

54  
55 179 For the first block in the lateral reaching task participants are not required to fixate,  
56  
57 180 therefore the fixation cross is absent.  
58  
59 181  
60

1  
2  
3 182 Participants initiate a trial by pressing and holding down the start box, which  
4  
5 183 disappears at touch. At this point they may search the screen for a target. After a  
6  
7 184 short delay (250-750ms, randomised 100ms intervals) a target appears at one of nine  
8  
9 185 possible locations. As soon as the target appears, participants look at it and make one  
10  
11 186 smooth reach to try to touch the target. The target remains on the screen until a touch is  
12  
13 187 recorded at any location, then the target disappears and a short beep (100ms, 440Hz) is  
14  
15 188 played. The validity of the trial is then coded by the experimenter using a keyboard; 'y' –  
16  
17 189 valid trial, 'e' – the participant did not move their eyes to the target, 'v' – invalid trial,  
18  
19 190 and the start box reappears to begin another trial.

19 191

20  
21 192 If the experimenter presses 'e' or 'v' that trial is repeated until a valid trial is recorded.  
22  
23 193 The block ends after a minimum of 27 valid trials (3 per target location), or after 50  
24  
25 194 valid and 'no eye-movement' trials.

26 195

27  
28 196 *iii. Visual detection*

29  
30 197 This is a simple check to confirm that the participant is capable of detecting the targets  
31  
32 198 when presented in peripheral vision, to be allow for a meaningful test of peripheral  
33  
34 199 reaching (*Section 4.3.1iv*).

35 200

36  
37 201 Throughout each trial the participant must gaze at the fixation cross. They initiate the  
38  
39 202 trial by pressing and holding down the start box, which disappears when touched. In  
40  
41 203 order to aid the maintenance of fixation, the fixation cross cycles between white and red  
42  
43 204 at the screen refresh rate (60Hz). After a short delay (250-750ms), a target can appear  
44  
45 205 at one of the nine locations for one second, or no target appears. This is followed by a  
46  
47 206 short beep (100ms, 440Hz) to indicate the end of the trial. The participant must verbally  
48  
49 207 report whether or not a target was seen in that interval. The experimenter records the  
50  
51 208 response using the keyboard ('y' – yes, 'n' – no). If the participant makes an eye-  
52  
53 209 movement, the experimenter presses 'e' and the trial is repeated. The block ends after  
54  
55 210 15 valid (no eye-movement) trials, one for each of the nine target locations, and six  
56  
57 211 catch trials with no target.

56 212

1  
2  
3 213 To progress to the peripheral reaching task, participants are required to detect at least  
4 214 6/9 targets and correctly rejects at least 3/6 catch trials. Otherwise, testing is  
5 215 discontinued on that side of space.  
6  
7 216

8  
9  
10 217 *iv. Peripheral reaching*

11 218 For peripheral reaching participants are required to gaze at the fixation cross  
12 219 throughout each trial. A trial begins by pressing and holding down the start box. When  
13 220 touched, the start box disappears and the fixation cross cycles between white and red  
14 221 (at a rate of 60Hz) until the trial ends. After a short delay (250-750ms) a target appears  
15 222 at one of nine locations. Whilst maintaining fixation, participants make one smooth  
16 223 reaching movement to try to touch the target. The target remains on the screen until a  
17 224 touch is recorded at any location, and a short beep is played once the target disappears.  
18 225 The experimenter then records the validity of the trial; 'y' – valid, 'e' – participant  
19 226 moved their eyes away from fixation, 'v' – invalid trial.  
20  
21 227

22 228 Invalid ('e' or 'v') trials are repeated until a valid trial is recorded. The block ends after a  
23 229 minimum of 27 valid trials (3 per target location), or after 50 valid and 'eye-movement'  
24 230 trials.  
25  
26 231

27  
28  
29 232 *4.3.2 Radial reaching tasks*

30 233 *i. Stimulus & Apparatus<sup>2</sup>*

31 234 An infrared motion-tracking camera (Optotrak Certus, Northern Digital Inc) is used to  
32 235 track the reaching movement. Infra-red-emitting diodes (IREDS) are taped to the tip of  
33 236 the right and left index fingers of each participant to track the reach in each hand. The  
34 237 Optotrak samples the IRED's 3D position at 100Hz throughout each 2000ms trial. The  
35 238 task is controlled by custom software written in LabView (National Instruments)  
36 239 programming environment.  
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<sup>2</sup> The stimuli and apparatus reported here are specific to UoE. At the second site, UEA, motion tracking was performed a Qualisys AB system (Gothenburg, Sweden). Targets are green LEDs (diameter = 0.68°, 6mm). The experiment is presented on a grey table (100x100cm) and the experiment is run through Psychophysics Toolbox (15) in MATLAB (Mathworks, USA)

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2  
3 241 Participants are seated with their head placed in a chin-rest in line with the middle of  
4  
5 242 the display. Stimuli are back-projected via a mirror onto a screen (1000mm wide x  
6  
7 243 750mm deep) that lies flat in-front of the participant. A webcam is placed on the screen  
8  
9 244 50cm directly in-front of the participant, as a fixation point. The live webcam image  
10  
11 245 feeds into a separate laptop, allowing experimenter to monitor gaze. A start-button is  
12  
13 246 aligned to the centre of the screen, positioned 10cm in-front of the participant, 40cm  
14  
15 247 away from fixation (Figure 2). Targets are white circles (diameter = 1.60°, 13.96mm)  
16  
17 248 presented at 4 eccentric locations (11.4, 22.6, 33.4 and 43.6° away from centre) on each  
18  
19 249 side (Figure 2).

20 250

21 251

22 252

23 253 *ii. Calibration*

24  
25  
26 254 A calibration procedure is carried out before the reaching tasks to record the IRED  
27  
28 255 position at the actual target location. A target is displayed at one target location and the  
29  
30 256 participant is instructed to cover it completely with their reaching finger. Once the  
31  
32 257 target is covered, the experimenter presses the start button and the finger location is  
33  
34 258 recorded for 2000ms. A beep plays after 2000ms, indicating that the participant can  
35  
36 259 move their hand away from the target position. Another target appears at the next  
37  
38 260 location and the same procedure is repeated. Calibration is run using the ipsilateral  
39  
40 261 hand for four targets on the left side, and four on the right.

41 262

42 263 *iii. Free reaching*

43  
44 264 Participants initiate a trial by pressing and holding down the start button. As soon as  
45  
46 265 they push the button down, participants may look around the screen for a target. After  
47  
48 266 250-750ms a target appears, participants then look directly at the target and reach to  
49  
50 267 touch the target in one smooth movement. Optotrak recording is initiated  
51  
52 268 simultaneously with target appearance, and the target disappearance is the  
53  
54 269 simultaneous with the end of the recording after 2000ms. When the target disappears a  
55  
56 270 short beep (100ms, 440Hz) plays, the participant leaves their finger at its landing  
57  
58 271 position until they hear the beep. After the trial, the experimenter codes the trial  
59  
60 272 validity with a key-press; 'Return' – valid, 'F1' – no eye-movement, 'Esc' – invalid trial. If



1  
2  
3 273 an invalid trial ('F1' or 'Esc') is coded the trial gets recycled to the end of the shuffled  
4  
5 274 trial.

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7 275

8 276 The block ends once 28 valid trials (7 per target location) are recorded, or after 50 valid  
9  
10 277 and 'no eye-movement' trials.

11  
12 278

13  
14 279 *iv. Peripheral reaching*

15 280 To assess reaching accuracy in the periphery participants are required to look directly  
16  
17 281 at central fixation (the webcam) throughout each trial. Participants initiate a trial by  
18  
19 282 pressing and holding down the start button. After 250-750ms a target appears. Whilst  
20  
21 283 maintaining gaze on the webcam participants make one smooth reaching movement to  
22  
23 284 try to touch the target. After the reach, participants leave their finger at its landing  
24  
25 285 position until a short beep (100ms, 440Hz). The target remains on screen for 2000ms  
26  
27 286 after the trial begins. The motion-tracker records the reach throughout the 2000ms  
28  
29 287 trial. At the end of the trial, the experimenter codes trial validity; 'Return' – valid trial,  
30  
31 288 'F1' – eye movement during trial, 'Esc' – invalid trial. If an invalid trial ('F1, 'Esc') is  
32  
33 289 recorded then the trial is recycled to the end of the shuffled trial list.

34  
35 290

36 291 The block ends after 28 valid trials (7 per target location) are recorded, or after 50 valid  
37  
38 292 and 'eye-movement' trials.



## 293 **5 Analysis plan**

### 294 *5.1 Lateral reaching task*

295 For the critical analyses, a single measure of *reaching accuracy* is taken for each  
296 participant, for each combination of viewing condition (free, peripheral) and side (non-  
297 dominant, dominant). For each response, the absolute error (in mm, x and y axis) is  
298 recorded as the distance of the reach endpoint from the target midpoint. The median  
299 absolute error is then calculated for each target eccentricity, across responses to the 3  
300 targets at that eccentricity, for each combination of viewing condition and side. The  
301 average absolute error is then calculated as the mean of the medians for the 3  
302 eccentricities, to give the single measure of reaching accuracy for each viewing  
303 condition at each side.

304

305 For the comparison of individual patients against control performance, the data are  
306 further compressed to a single index of performance per side, by subtracting reaching  
307 accuracy in the free vision condition from the peripheral condition. We call this value  
308 the *peripheral misreaching index (PMI)*.

309

#### 310 *5.1.1 Analysis of single case deficits*

311 We will screen the control group for outliers that might suggest abnormalities, as such  
312 values would reduce the (already low, see Figure 3) power to detect single-case deficits.  
313 We will use a robust method of outlier detection based on the median absolute  
314 deviation (MAD). The MAD can be multiplied by the consistency constant 1.4826 to  
315 estimate the standard deviation, assuming a normal distribution. Each control  
316 participant's PMI can be expressed a modified Z-score ( $Z'$ ) by subtracting the group  
317 median, divided by the median absolute deviation \*1.4826. If  $Z'$  exceeds 2.5, that  
318 participant will be excluded, and replaced. Our simulations suggest that, for a group size  
319 of 24, we would expect to exclude (on average) < 1 participant ( $\sim 0.67$ ) by this criterion.

320

321 We will next assess, for each side, whether the PMI of controls is related to age or sex,  
322 by computing Pearson's correlations. If the correlation is  $\geq .3$  on either side, then that  
323 variable will be included as a covariate in the subsequent case-control comparisons for  
324 both sides.

325

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2  
3 326 Case-control comparisons will then be run to compare each patient's PMI against  
4  
5 327 control performance. These comparisons will be based upon Crawford & Howell's (16)  
6  
7 328 modified t-test; or, if covariates are included, we will use the updated test of deficit (17).  
8  
9 329 The individual tests will be one-tailed, with an alpha-level set to .025, in order to  
10  
11 330 constrain per-patient alpha level (across the two sides) to .05. If a patient shows a  
12  
13 331 deficit on either side that would meet the unadjusted criterion (.05), but not the  
14  
15 332 adjusted criterion (.025), they will be classified as showing borderline peripheral  
16  
17 333 misreaching.

17 334  
18  
19 335 Finally, a binomial test will test whether the rate of observed peripheral misreaching  
20  
21 336 exceeds the rate expected by chance (i.e. the per-patient adjusted alpha level of .05). A  
22  
23 337 significant outcome ( $p < .05$ ) for either patient group will indicate that peripheral  
24  
25 338 misreaching is a feature of this patient group. The observed rate of peripheral  
26  
27 339 misreaching will provide an estimate of how common it is. We will run a further  
28  
29 340 analysis including borderline cases and compare the rate of peripheral misreaching in  
30  
31 341 each patient group against the appropriate chance level of .10.

### 31 342 32 33 343 *5.1.2 Group-level analysis*

34  
35 344 The case control approach will be complemented by a group-level ANOVA of reaching  
36  
37 345 accuracy, as measured by the PMI, with the between-subject factor of group (HC, MCI,  
38  
39 346 AD) and the within subject factor of side (non-dominant, dominant). This analysis will  
40  
41 347 test whether the average severity of peripheral misreaching in each patient group  
42  
43 348 significantly exceeds that observed in healthy controls.

### 43 349 44 45 350 *5.1.3 Exploratory analyses*

46  
47 351 Any lateralisation that occurs in MCI/AD is likely to be limited, therefore, any  
48  
49 352 impairment in peripheral reaching may be similarly non-lateralised. An average PMI  
50  
51 353 (across both sides) will therefore be calculated to assess peripheral reaching ability  
52  
53 354 overall. More detailed analyses will be run with a between subject factor of group and  
54  
55 355 within subject factors of side, eccentricity and viewing condition. These analyses will be  
56  
57 356 conducted using dependent variables of absolute reaching error, directional (signed)  
58  
59 357 reaching error, reaction time and movement time. The expectation is that peripheral  
60

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3 358 misreaching will manifest as a fixation-directed bias, which is exacerbated at higher  
4  
5 359 eccentricities significantly more so in patient groups than in age-matched controls.  
6  
7 360

### 8 361 *5.2 Radial reaching task*

9  
10 362 IRED speed is used to determine onset and offset of the reaching movement. Movement  
11  
12 363 onset is defined as the first frame in which the IRED's speed exceeds 50mm/s (and  
13  
14 364 maintains that speed for up to 100ms). Movement offset is defined as the first  
15  
16 365 subsequent frame in which IRED speed falls below 50mm/s. The landing position of the  
17  
18 366 movement is defined by the x and y coordinates in the final frame of the movement and  
19  
20 367 will be recorded as errors relative to true target locations recorded during calibration  
21  
22 368 for each participant.  
23

24 369  
25 370 An initial analysis of PMI for the radial reaching task will be performed, restricted to the  
26  
27 371 two most eccentric target positions (33.4 and 43.6°). Case-control comparisons follow  
28  
29 372 the plan for the lateral reaching task (*Section 5.1.1*), to estimate the rates of peripheral  
30  
31 373 misreaching, and borderline peripheral misreaching, in the two patient groups. Due to  
32  
33 374 different experimental set ups between the two test sites (UoE, UEA), each patient will  
34  
35 375 be referenced to the same-site control data for case-control comparisons.  
36

37 376  
38 377 A group level ANOVA of PMI, restricted to the two most eccentric target positions, will  
39  
40 378 similarly follow the plan for lateral reaching (*Section 5.1.2*). We will include site (UoE,  
41  
42 379 UEA) as an additional covariate. Subsequent, more detailed analyses will also follow the  
43  
44 380 plan for lateral reaching (*Section 5.1.2*). Since motion tracking also provides kinematic  
45  
46 381 variables on reaching trajectories, we also aim to examine the dependent variables peak  
47  
48 382 speed and time to peak speed, normalised time after peak speed until reach endpoint  
49  
50 383 and number of secondary movements.  
51

52 384

### 53 385 *5.3 Power considerations*

54 386 The target sample sizes (N=24 per group) are based on power considerations related to  
55  
56 387 the main inferential analyses, the case-control comparisons, and binomial tests of rates  
57  
58 388 of peripheral misreaching deficits for the lateral reaching task.  
59  
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2  
3 390 The control sample size of 24 will provide close to the maximum power for case-control  
4  
5 391 tests of deficit (figure 3A). Note that high power for these comparisons is inherently  
6  
7 392 unachievable unless the deficit being tested for is very large. We do not know how large  
8  
9 393 any misreaching deficits may be in our patient groups, but our control sample size will  
10  
11 394 provide close to the maximum achievable power to detect them if they exist. Figure 3B  
12  
13 395 illustrates more fully the relationship between deficit size (D) and power, for the  
14  
15 396 adjusted alpha level (.025) and unadjusted alpha level (.05) by which we will determine  
16  
17 397 peripheral misreaching deficits and borderline cases respectively (*Section 5.1.1*).  
18  
19 398

19 399 The main hypothesis is that peripheral misreaching will be found in a significant  
20  
21 400 proportion of patients with AD and MCI. For one-sample binomial test to determine  
22  
23 401 whether the observed rate of peripheral misreaching exceeds the chance level of .05, a  
24  
25 402 sample size of 24 has > .9 power. Provided that the true population proportion is at  
26  
27 403 least .2 (1 in 5). This is appropriate to our aims, since peripheral misreaching would be  
28  
29 404 of limited significance in these clinical populations if its prevalence were less than 1 in  
30  
31 405 5.

## 6 Ethics and dissemination

This protocol was approved by UK Health Research Authority, by the East of England, Cambridge Central Research Ethics Committee on 13 June 2019 (REC reference 19/EE/0170).

All patients will provide informed consent, highlighting the voluntary nature of the study and their right to withdraw. If there is any doubt about the ability of the patient to provide informed consent, then this patient will not be recruited. There are no direct risks associated with taking part.

Careful consideration will be taken to maintain patient's confidentiality. After consent is provided, an anonymous code will be assigned to each patient. Some patient details such as CHI number, age, gender and time of diagnosis, will need to be accessed by the research team, these details will be stored alongside patient code in a password-protected document.

At the end of the study, a lay summary of results will be provided to patients who have expressed a further interest. Project results will be made publicly available on the Open Science Framework (<https://osf.io/bxnqs/>) within three months after study end date (30/06/2020). Alongside this, we plan to publish the results of this protocol will be published in a peer reviewed journal and presented at academic conferences.

## 7 Footnotes

**Author Contributions:** Each author has contributed significantly one or more aspects of the study. All authors contributed to study development and design. RDM, SR and AGM were involved in implementation of study protocol and analysis design. All authors contributed to data acquisition for MCI and AD, with SP and MH leading patient recruitment. AGM and SR were involved in data acquisition for HC. AGM and RDM drafted the manuscript and all authors provided critical revisions and approved the final version.

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2  
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5 438  
6 439

7  
8 440 **Competing interests:** there are no conflicts or competing interests for AGM, SP, MH, SR  
9 or RDM.  
10 441  
11 442

## 12 443 **8 References**

- 13  
14 444 1. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al.  
15 445 Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria.  
16 446 Lancet Neurol [Internet]. 2014 Jun 1 [cited 2019 Aug 29];13(6):614–29. Available  
17 447 from: <https://www.sciencedirect.com/science/article/pii/S1474442214700900>  
18 448 2. Pike KE, Savage G, Villemagne V, Ng S, Moss S, Maruff P, et al.  $\beta$ -amyloid imaging  
19 449 and memory in non-demented individuals: evidence for preclinical Alzheimer's  
20 450 disease. Brain [Internet]. 2007 [cited 2020 Feb 20];130(11):2837–44. Available  
21 451 from: <https://academic.oup.com/brain/article/130/11/2837/331929>  
22 452 3. Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al.  
23 453 Tracking pathophysiological processes in Alzheimer's disease: An updated  
24 454 hypothetical model of dynamic biomarkers. Vol. 12, The Lancet Neurology.  
25 455 Elsevier; 2013. p. 207–16.  
26 456 4. Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, et al.  
27 457 Amyloid  $\beta$  deposition, neurodegeneration, and cognitive decline in sporadic  
28 458 Alzheimer's disease: A prospective cohort study. Lancet Neurol. 2013 Apr  
29 459 1;12(4):357–67.  
30 460 5. Gordon BA, Blazey TM, Su Y, Hari-Raj A, Dincer A, Flores S, et al. Spatial patterns  
31 461 of neuroimaging biomarker change in individuals from families with autosomal  
32 462 dominant Alzheimer's disease: a longitudinal study. Lancet Neurol [Internet].  
33 463 2018 Mar 1 [cited 2019 Mar 27];17(3):241–50. Available from:  
34 464 <https://www.sciencedirect.com/science/article/pii/S1474442218300280>  
35 465 6. Gordon BA, Blazey TM, Su Y, Hari-Raj A, Dincer A, Flores S, et al. Spatial patterns  
36 466 of neuroimaging biomarker change in individuals from families with autosomal  
37 467 dominant Alzheimer's disease: a longitudinal study. Lancet Neurol.  
38 468 2018;17(3):211–2.  
39 469 7. Möller C, Vrenken H, Jiskoot L, Versteeg A, Barkhof F, Scheltens P, et al. Different

- 1  
2  
3 470 patterns of gray matter atrophy in early- and late-onset Alzheimer's disease.  
4  
5 471 Neurobiol Aging. 2013 Aug 1;34(8):2014–22.  
6  
7 472 8. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and  
8  
9 473 behavioural correlates. Brain [Internet]. 2006 Mar 1 [cited 2019 Aug  
10  
11 474 29];129(3):564–83. Available from:  
12  
13 475 [http://academic.oup.com/brain/article/129/3/564/390904/The-precuneus-a-](http://academic.oup.com/brain/article/129/3/564/390904/The-precuneus-a-review-of-its-functional-anatomy)  
14  
15 476 [review-of-its-functional-anatomy](http://academic.oup.com/brain/article/129/3/564/390904/The-precuneus-a-review-of-its-functional-anatomy)  
16  
17 477 9. Karnath H-O, Perenin M-T. Cortical Control of Visually Guided Reaching: Evidence  
18  
19 478 from Patients with Optic Ataxia. Cereb Cortex [Internet]. 2005 Oct 1 [cited 2019  
20  
21 479 Aug 29];15(10):1561–9. Available from:  
22  
23 480 [http://academic.oup.com/cercor/article/15/10/1561/396841/Cortical-Control-](http://academic.oup.com/cercor/article/15/10/1561/396841/Cortical-Control-of-Visually-Guided-Reaching)  
24  
25 481 [of-Visually-Guided-Reaching](http://academic.oup.com/cercor/article/15/10/1561/396841/Cortical-Control-of-Visually-Guided-Reaching)  
26  
27 482 10. Perenin MT, Vighetto A. Optic Ataxia: A Specific Disorder in Visuomotor  
28  
29 483 Coordination. In: Spatially Oriented Behavior [Internet]. New York, NY: Springer  
30  
31 484 New York; 1983 [cited 2019 Aug 29]. p. 305–26. Available from:  
32  
33 485 [http://link.springer.com/10.1007/978-1-4612-5488-1\\_17](http://link.springer.com/10.1007/978-1-4612-5488-1_17)  
34  
35 486 11. Rossetti Y, Pisella L, McIntosh RD. Definition: Optic ataxia. Cortex. 2019;in press.  
36  
37 487 12. Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR. A brief cognitive  
38  
39 488 test battery to differentiate Alzheimer's disease and frontotemporal dementia.  
40  
41 489 Neurology [Internet]. 2000 Dec 12 [cited 2019 Oct 15];55(11):1613–20. Available  
42  
43 490 from: <http://www.ncbi.nlm.nih.gov/pubmed/8190290>  
44  
45 491 13. Borchers S, Müller L, Synofzik M, Himmelbach M. Guidelines and quality measures  
46  
47 492 for the diagnosis of optic ataxia. Front Hum Neurosci [Internet]. 2013 Jul 2 [cited  
48  
49 493 2019 Mar 27];7:324. Available from:  
50  
51 494 <http://journal.frontiersin.org/article/10.3389/fnhum.2013.00324/abstract>  
52  
53 495 14. Mathôt S, Schreij D, Theeuwes J. OpenSesame: An open-source, graphical  
54  
55 496 experiment builder for the social sciences. Behav Res Methods [Internet]. 2012  
56  
57 497 Jun 16 [cited 2019 Oct 10];44(2):314–24. Available from:  
58  
59 498 <http://www.springerlink.com/index/10.3758/s13428-011-0168-7>  
60  
61 499 15. Brainard DH. The Psychophysics Toolbox. Spat Vis [Internet]. 1997 [cited 2019  
62  
63 500 Oct 11];10:433–6. Available from:  
64  
65 501 <http://color.psych.upenn.edu/brainard/PsychToolbox.pdf>  
66  
67 502 16. Crawford JR, Howell DC. Comparing an Individual's Test Score Against Norms



1  
2  
3 503 Derived from Small Samples. Clin Neuropsychol [Internet]. 1998 Nov 9 [cited  
4 504 2019 Sep 13];12(4):482–6. Available from:  
5 505 <https://www.tandfonline.com/doi/full/10.1076/clin.12.4.482.7241>  
6  
7  
8 506 17. Crawford JR, Garthwaite PH, Ryan K. Comparing a single case to a control sample:  
9 507 Testing for neuropsychological deficits and dissociations in the presence of  
10 508 covariates. Cortex. 2011;47(10):1166–78.  
11  
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## 17 511 **9 Figure legends**

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19 512 Figure 1: 9 target positions during the lateral reaching task for left (A) and right (B)  
20 513 hand sides. At a viewing distance of 40cm targets are presented at approximately 28, 33  
21 514 and 38° of eccentricity  
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27 516 Figure 2: target positions during the radial reaching task, shown here on both the right-  
28 517 and left-hand sides, at 11.4, 22.6, 33.4 and 43.6° from fixation. The start-button is  
29 518 positioned at the bottom of the screen 40cm away from central fixation. A webcam is  
30 519 placed at the point of central fixation (midpoint).  
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36 521 Figure 3: (a) Relation between control sample size and power to detect a single-case  
37 522 deficit in a one-tailed test, for different size of deficit (D, expressed as standard  
38 523 deviations of control mean), (b) Relation between deficit size (D) and power to detect a  
39 524 single case deficit, given a control sample size of 24, for adjusted and unadjusted alpha  
40 525 criteria.  
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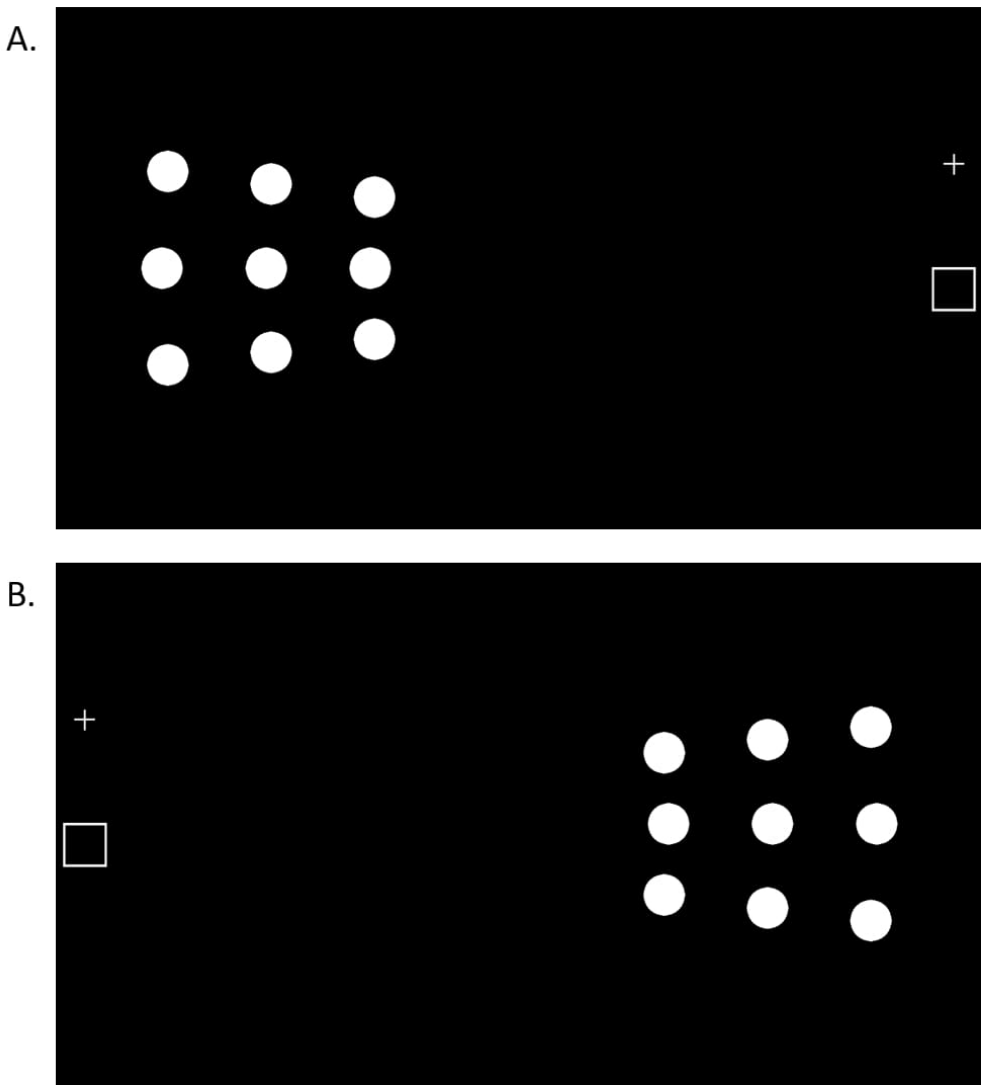


Figure 1: 9 target positions during the lateral reaching task for left (A) and right (B) hand sides. At a viewing distance of 40cm targets are presented at approximately 28, 33 and 38° of eccentricity  
83x90mm (300 x 300 DPI)

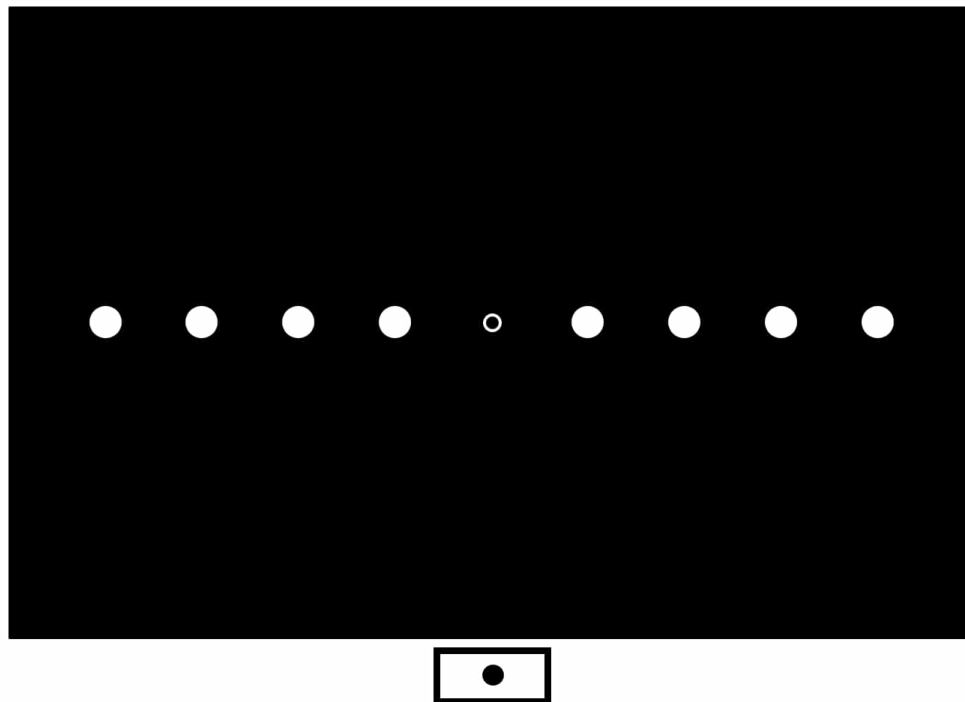
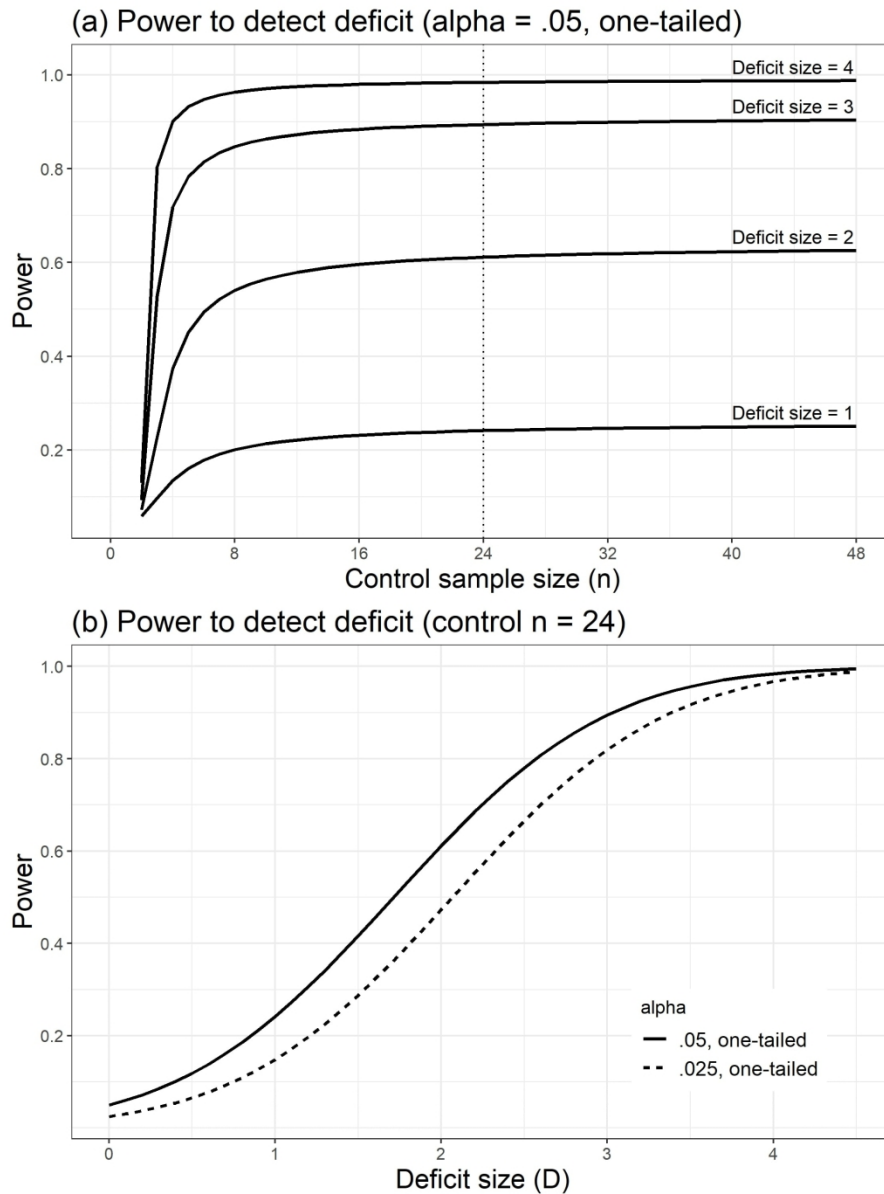


Figure 2: target positions during the radial reaching task, shown here on both the right- and left-hand sides, at 11.4, 22.6, 33.4 and 43.6° from fixation. The start-button is positioned at the bottom of the screen 40cm away from central fixation. A webcam is placed at the point of central fixation (midpoint).

112x80mm (300 x 300 DPI)



45 Figure 3: (a) Relation between control sample size and power to detect a single-case deficit in a one-tailed  
 46 test, for different size of deficit (D, expressed as standard deviations of control mean), (b) Relation between  
 47 deficit size (D) and power to detect a single case deficit, given a control sample size of 24, for adjusted and  
 48 unadjusted alpha criteria.

49 190x254mm (300 x 300 DPI)

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3 **The assessment of visually guided misreaching in prodromal Alzheimer's disease:**  
4 **study protocol**  
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7 **Site-specific information**

8 *Site 1: Edinburgh*

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10 Patient recruitment in Edinburgh will take place at the Anne Rowling Regenerative  
11 Neurology Clinic (NHS Lothian), through a team led by Dr. Suvankar Pal. Patients who fit  
12 the recruitment criteria will be identified through the Rowling CARE-register and  
13 provided an information sheet and a notification of interest form.  
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17 All testing (patient and control) takes place in the Human Movement Laboratory,  
18 Department of Psychology, The University of Edinburgh.  
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21 *Site 2: Norfolk*

22 Patient recruitment will take place in the Julian Hospital in Norwich (NHS Norfolk &  
23 Suffolk). A team of research nurses will identify suitable participants who will be  
24 provided an information sheet and a notification of interest form.  
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28 All testing takes place in the Vision and Action Laboratory, Department of Psychology,  
29 The University of East Anglia.  
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## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

Continued on next page

**Results**

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

**Discussion**

Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results

**Other information**

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
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\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).