Visual short-term memory impairments in presymptomatic familial Alzheimer's disease: A longitudinal observational study

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Abstract

Visual short-term memory (VSTM) deficits including VSTM binding have been associated with Alzheimer's disease (AD) from preclinical to dementia stages, cross-sectionally. Yet, longitudinal investigations are lacking. The objective of this study was to evaluate VSTM function longitudinally and in relation to expected symptom onset in a cohort of familial Alzheimer's disease. Ninety-nine individuals (23 presymptomatic; 9 symptomatic and 67 controls) were included in an extension cross-sectional study and a sub-sample of 48 (23 presymptomatic carriers, 6 symptomatic and 19 controls), attending two to five visits with a median interval of 1.3 years, included in the longitudinal study. Participants completed the "What was where?" relational binding task (which measures memory for object identification, localisation and object-location binding under different conditions of memory load and delay), neuropsychology assessments and genetic testing. Compared to controls presymptomatic carriers within 8.5 years of estimated symptom onset, had a faster rate of decline in localisation performance in long-delay conditions (4 seconds) which preceded changes in traditional neuropsychology. This represents the first longitudinal VSTM investigation and shows that changes in memory *resolution* may be sensitive to tracking cognitive decline in preclinical AD.

1. Introduction

Progressive episodic memory impairment is a central, defining feature of Alzheimer's disease (AD) (Dubois et al. 2007; McKhann et al. 1984). Deficits in short-term memory (STM), the ability to temporarily maintain information over seconds (Atkinson and Shiffrin 1968, 1971), have been relatively less well studied. Classically, STM has been tested using 'span' measures where participants are asked to remember a string of stimuli (Groeger et al., 1999). Although such quantal (discrete) measures have been fundamental to developing our understanding of memory function, they are not as sensitive to detect changes in memory *resolution* due to the binary nature of responses measured (correct *vs* incorrect recall). In 2014, Ma and colleagues (Ma et al., 2014) proposed a new approach to study the resolution with which items are retained, arguing that just because an individual fails to recall an item correctly this does not imply they had no memory of it at all. Delayed-reproduction tasks (e.g. (Peich et al., 2013; Pertzov et al. 2012, 2013) rely on remembering a feature and reproducing the exact stored features after a retention period using a *continuous analogue* response space (Bays et al., 2009; Gorgoraptis et al. 2011; Liang et al. 2016). In recent studies, delayed-reproduction tasks have been reported to be more sensitive than conventional span measures of STM, especially in clinical populations (Zokaei et al. 2015).

The concept of 'preclinical AD' continues to evolve and is subject to debate, but current clinical criteria at least on a research basis, allow for it to be diagnosed in asymptomatic individuals without evidence for objective cognitive decline (Sperling et al. 2011) but with accumulation of β-amyloid (Aβ) (Jack and Holtzman 2013). Developing a better understanding of the preclinical changes of AD and improving methods for early detection may offer the best chance for therapeutic success, before irreversible neuronal loss has occurred.

One important line of research has suggested that the ability to bind object features together in visual short-term memory (VSTM) is critically affected in AD (Della Sala et al. 2012; Parra et al., 2010; Parra et al. 2009, 2011; Pavisic et al., 2020). Interest in these tasks increased when studies suggested impairments could be detected at preclinical stages of the condition, more sensitively than other traditional memory measures (Parra et al. 2010). A study by Liang and colleagues found deficits for object-location binding and localisation of the target position in presymptomatic familial Alzheimer's disease (FAD) carriers, in the highest-load condition of the task (Liang et al. 2016). FAD is an autosomal dominant condition caused by mutations in either presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*) or amyloid precursor protein (*APP*) (Ryan et al. 2016) and its pathogenic mutations in these genes are nearly 100% penetrant (Ryman et al. 2014). FAD shares many features (i.e. clinical, radiological and histopathological) with sporadic AD (Rossor et al. 1996; Ryan and Rossor 2010) and the age at onset in FAD is reasonably similar between family members, making this cohort particularly valuable to the study of preclinical stages of AD (Ryman et al. 2014).

In light of these findings, a number of questions remain unanswered:

1. Are the cross-sectional preclinical deficits in VSTM also reflected in longitudinal task performance? ;
2. Given that an individual's expected age at symptom onset may be estimated from their parental onset, what is the relationship between an individual's VSTM performance and proximity to expected years to onset (EYO) at the time of testing? ;

And finally, for comparison:

3. Is longitudinal cognitive decline in presymptomatic and symptomatic mutation carriers seen in other more traditional neuropsychology tasks?

We wished therefore first to extend the work of Liang and colleagues (Liang et al. 2016) in a larger sample and secondly to explore how VSTM in both presymptomatic and symptomatic FAD mutation carriers, changed with EYO. Finally, for comparison we evaluate longitudinal decline in traditional neuropsychology tasks. To our knowledge, no other study has examined VSTM functions longitudinally in a preclinical cohort such as FAD.

2. Methods

2.1. Study design and participants

Participants were recruited from the ongoing longitudinal FAD study at the Dementia Research Centre, University College London, which receives referrals from across the UK, if they had an autosomal dominant family history of AD and a known pathological mutation in *PSEN1* or *APP* genes in at least one affected family member. Healthy individuals (without a family history of AD) were also recruited to the study from our research database. Inclusion criteria also required participants to have normal or

corrected-to-normal visual acuity and colour vision and ≥ 70% average accuracy in identification performance at baseline visit (see (Liang et al. 2016)).

Mutation analysis was carried out using Sanger sequencing (Janssen et al. 2003; Ryan et al. 2016). Genetic results were available for all at-risk individuals, on either a clinical or a research basis. Research genetic results were only shared with the statistician involved in the study and were not disclosed to the participants or to other researchers who remained blind to whether presymptomatic individuals were mutation carriers or non-carriers.

Consequently, the study included symptomatic carriers, presymptomatic carriers and controls: symptomatic individuals were mutation carriers who had cognitive symptoms consistent with AD; presymptomatic individuals were mutation carriers who had not developed symptoms and who scored zero on the Clinical Dementia Rating (CDR) scale (Morris 1993) and control participants consisted of both non-carriers (at-risk individuals who tested negative for pathological mutations) and healthy individuals (from our research database). As per Liang and colleagues, we used EYO as an approximation of how far individuals (presymptomatic and symptomatic) were from symptom onset (Liang et al. 2016). This was based on an individuals' age at the time of assessment subtracted from the age at which their affected parent developed symptoms (Bateman et al. 2012; Ryman et al. 2014). As well as considering how performance varied continuously with EYO, we also grouped individuals by their symptom status and proximity to symptom onset at the baseline assessment into: symptomatic carriers; 'early' presymptomatic mutation carriers (PMCs) (more than 8.5 years from expected onset), 'late' PMCs (at least 8.5 years from expected onset) and controls. The cut-off of 8.5 years corresponded to the median split of PMCs in our dataset. Finally, we considered how performance varied continuously with actual years to/from symptom onset (AYO) for symptomatic carriers and PMCs who converted into symptomatic carriers throughout the study (n=3). Actual age at onset (AAO) was defined as the age at which progressive symptoms of FAD were first noticed by the individual or someone who knew the patient well. Baseline characteristics of the groups are presented in Table 1.

The cross-sectional analysis included 99 individuals: 67 controls (16 non-carrier siblings) and 32 mutation carriers, 9 of whom were symptomatic. Differences between our cross-sectional study and Liang and colleagues (Liang et al. 2016) were: the addition of n=17 at-risk (mutation carriers and non-carriers) individuals; n=1 symptomatic carrier and the exclusion of n=1 at-risk individual (see Supplementary Materials, Fig.e1, for details). Note that mutation status of these at-risk individuals is not disclosed to prevent unblinding of genetic status.

The longitudinal analysis included 48 participants who attended between 2 and 5 visits (median 3), at intervals ranging from 0.5 to 3.9 years (median 1.3): 19 controls (12 non-carrier siblings) and 29 mutation carriers, 6 of whom were symptomatic. (Mean follow-up time: controls= 2.8 [SD 1.7] years, range=1-6; early PMCs= 3.7 [1.7] years, range=1-6 years; late PMCs=3.4 [1.7] years, range=1-6; symptomatic carriers=2.6 [0.7] years, range=2-4)).

All subjects provided written informed consent to participate. The study was approved by The National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee (subsequently, National Research Ethics Service Committee, London Queen Square, Research Ethics Committee ref 11/LO/0753).

2.2. Protocol

The study protocol included a clinical and neuropsychological assessment and the "What was where?" VSTM experiment (Pertzov et al. 2012). Detailed interviews were conducted with individuals at-risk of FAD and their close informants by a neurologist (AOC, YL, PSJW, NSR, NCF) to assess for the presence of cognitive or behavioural symptoms attributable to AD. AD was diagnosed in accordance with the Dubois criteria (Dubois et al. 2007, 2010). Folstein's mini-mental state examination (MMSE) (Folstein et al., 1975), the CDR (Morris 1993) and Hospital Anxiety and Depression scale (HADS) (Zigmond and Snaith 1983) were administered.

The neuropsychological test battery included measures of several cognitive domains: episodic memory (recognition memory test (RMT) for words and faces; (Warrington 1996)); working memory (digit span (Wechsler 1987)); intellectual function (Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999)); executive function (Stroop (Stroop 1935)); confrontational naming (graded naming test (McKenna and Warrington 1983); vocabulary (British picture vocabulary scale (BPVS) (Dunn and Dunn 2009)); arithmetic (Graded Difficulty Arithmetic Test (GNT) (Jackson and Warrington 1986)), visual perception (object decision test from the visual object and space perception (VOSP) battery (Warrington and James 1991)); speed (digit symbol test (Wechsler and De Lemos 1981)) and estimated premorbid intelligence (the National Adult Reading Test) (NART) (Law and O'Carroll 1998; Nelson 1991) (Table 1).

"What was where?" has been described in previous publications (Liang et al. 2016; Pertzov et al. 2012). A depiction of the task is shown in Fig.1. Participants sat approximately 42 cm in front of an interactive touch-sensitive screen (Dell Inspiron One 2320) with a 1920 × 1080-pixel matrix corresponding to approximately 62 × 35° of visual angle. In each trial, participants viewed 1 or 3 fractal objects, each randomly located on the screen and were asked to remember both the objects identity and their locations. A blank screen was then displayed for a 1 or 4 second (s) duration, followed by a test array in which two fractals appeared along the vertical meridian. One of these was in the previous memory array (the target fractal) whereas the other one was a foil (distractor). The foil was not an unfamiliar object, but was part of the general pool of fractal images presented throughout the experiment. Participants were required to select the fractal they remembered from the memory array and drag it to its location. This provided a continuous measure of localisation error. Each participant performed a practice block of 10 trials (not included in the analysis) followed by two test blocks each consisting of 10 trials with 1 fractal and 40 trials with 3 fractals, with a balanced number of trials with 1s or 4s delay between memory and test arrays.

In this paper, findings focus on three outcomes which were included in the previous cross-sectional study (Liang et al. 2016):

- **Identification performance:** proportion of trials where the correct object was chosen.
- **Localisation error:** the distance (in degrees of visual angle) between the centre of the target object once placed in its remembered location and its true (original) location in the memory array (only correctly identified objects).
- **Swap errors:** the percentage of correctly identified objects placed within 4.5° eccentricity of other fractals in the original array-3-item condition only (object-location binding). In accordance with previous studies (Liang et al. 2016; Pertzov et al. 2012), a threshold of 4.5° was used as objects were never presented less than 9° from each other in the memory array and therefore an object could not be swapped with more than one object.

Liang and colleagues also examined the "Nearest item control (NIC)": an index of localisation precision regardless of object identity, calculated as the distance between the centre of the target object once placed in its remembered location and the centre of the nearest location in the memory array- whichever item that was, i.e., it is agnostic to the identity of the nearest fractal. It provided a measure of localisation error discounting the effects of swap errors for the 3-items condition only (Liang et al. 2016; Pertzov et al. 2013). (Results for this outcome are provided in the Supplementary Materials).

2.3. Statistical analysis

Due to a skewed distribution the absolute localisation error was log transformed and proportion of swap errors was square root transformed before analysis. All analysis of VSTM was adjusted for delay (1 *vs* 4s), block (1 *vs* 2), number of items (1 *vs* 3, where relevant), sex, age at baseline, and NART at baseline. Interaction tests were used to examine whether group differences in cross-sectional performance, changes in performance over time, or the relationship with EYO varied by delay, block and number of items.

2.3.1. Cross-sectional analysis

Baseline demographics and neuropsychology scores were compared between symptomatic carriers, early PMCs, late PMCs and controls using ANOVA, or Kruskal-Wallis test where the distribution of the variable was skewed. Fishers' exact test was used to compare the sex distribution between the groups.

VSTM performance at the baseline visit was compared between symptomatic carriers, early PMCs, late PMCs and controls using logistic regression models for object identity and linear regression model for all other measures. Robust standard errors were used to account for repeated measures.

2.3.2. Longitudinal analysis

Change over time in VSTM was investigated in three ways: i) comparison of longitudinal change in VSTM performance between symptomatic carriers, early PMCs, late PMCs and controls; ii) examination of the association between VSTM performance and EYO as a continuous measure (in presymptomatic and

symptomatic mutation carriers); and iii) examination of association between VSTM performance and AYO as a continuous measure in the FAD participants where this was known (symptomatic carriers at baseline and late PMCs who converted into symptomatic throughout the study-'converters'). The models examining proximity to onset (EYO and AYO, as a continuous measure) in mutation carriers included age at visit as a predictor to account for any effects of healthy ageing. Estimation of the effect of age included data from both controls and mutation carriers. Inclusion of controls in the model allowed estimation of the predicted mean difference between controls and mutation carriers by EYO and AYO. The predicted mean performance was calculated for controls and by EYO and AYO in the carriers, setting age and NART at the average of the sample and for an equal balance of sexes and task conditions.

Longitudinal change in object identity was analysed using a mixed effects logistic regression model and analysis of the other VSTM outcomes used a linear mixed effects model.

Finally, analysis was conducted to compare longitudinal change in neuropsychology performance between symptomatic carriers, early PMCs, late PMCs and controls. Mixed effects linear regression was used for analysis of WASI verbal IQ, WASI performance IQ, arithmetic, BPVS, GNT, NART, and Stroop. A mixed effects logistic regression model was used for RMT words, RMT faces and VOSP. Mixed effects ordinal logistic regression model was used for digit span forwards and digit span backwards. All models adjusted for sex, age at baseline, and NART at baseline. Controls were included in all models to allow for changes with increasing age. (See Supplementary Materials for further details on the statistical methods).

For all analysis statistical significance was set at $p<0.05$ and analysis performed on Stata v.14.

3. Results

3.1. Cross-sectional analysis for N=99

3.1.1. Demographics and traditional neuropsychology

Sixty-seven controls and 32 carriers completed the "What was where?" task cross-sectionally. Compared to controls, early PMCs were on average younger, 12.9 years away from their expected onset and had lower scores in: verbal IQ, BPVS and NART measures; late PMCs were on average 5.8 years before expected onset, had lower education, baseline anxiety and depression scores and had significantly lower scores for verbal IQ but similar scores on remaining measures. As expected, symptomatic carriers were older and on average three years after expected onset, had lower MMSE and higher global CDR and had significantly worse scores on neuropsychology tasks including arithmetic, RMT for words, digit span, Stroop and verbal IQ scores compared to controls (Table 1).

3.1.2. VSTM performance

For all groups, VSTM performance was significantly worse with higher-memory load (3 *vs* 1 item) ($p<0.001$ for all metrics). Longer delay (1 *vs* 4s) was also associated with worse localisation performance

(p<0.001) and identification performance (p=0.008) but did not affect swap proportion (p=0.255).

Symptomatic carriers had 44% lower odds of correctly identifying the target (difference in OR=0.57, p<0.001), 46% greater localisation error (p<0.001) and made a greater proportion of swap errors (p<0.001) in comparison to controls (Table 1). There was no significant interaction between group and delay, block or number of items in identification and localisation performance metrics. However, there was a significant interaction between delay and the proportion of swap errors (p=0.039), whereby symptomatic carriers showed larger differences (greater swap errors) compared to controls in the long-delay than the short-delay. Although there was no significant interaction with block (p=0.110), we investigated performance in the first block by delay, following Liang and colleagues finding of a significantly higher proportion of swap errors in the PMC group than controls, in the first block long-delay condition (Liang et al. 2016). Symptomatic carriers made a greater proportion of swap errors than controls in both blocks (both p<0.001), with a larger difference in the 4s delay condition (p=0.027) than 1s delay (p=0.441, Table 1). However, no significant differences emerged at a presymptomatic level (Table 1, Fig.2).

Table 1. Baseline demographics, neuropsychology and VSTM performance by participant group for N=99

	Controls (N=67)	Early PMCs (N=12)	Late PMCs (N=11)	Symptomatic carriers (N=9)
Demographics				
Sex: N (%) Male	34 (50.7)	3 (25.0)	7 (63.6)	6 (66.7)
Age (yrs)	39.4 (8.1)	34.8 (6.4)	37.0 (5.0)	**48.1 (9.8)***
EYO (yrs)	NA	-12.9 (4.7)	-5.8 (1.8)	3.0 (4.1)
AYO (yrs)	NA	NA	NA	3.1 (4.0)
Education (yrs)	15.4 (2.7)	14.3 (2.5)	**13.3 (2.5)***	13.9 (2.9)
MMSE	29.5 (0.8)	29.3 (0.9)	29.5 (0.8)	**25.1 (3.7)****
CDR global	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	**0.6 (0.2)****
Anxiety	6.1 (3.8)	7.9 (4.6)	**3.9 (3.9)***	7.0 (4.5)
Depression	3.2 (2.8)	2.9 (4.0)	**1.3 (1.6)***	2.4 (2.1)
Neuropsychology tests				
Performance IQ	110.5 (16.3)	106.0 (15.7)	101.4 (10.1)	100.4 (12.1)
Verbal IQ	109.9 (14.9)	**96.1 (15.1)***	**95.4 (13.5)****	**99.4 (18.8)***
Arithmetic total/24	16.7 (6.8)	13.9 (5.0)	14.3 (4.6)	**10.3 (5.8)****
RMT faces	41.1 (7.2)	41.0 (4.2)	43.8 (4.5)	40.3 (3.7)
RMT words	47.0 (5.0)	48.7 (2.2)	46.5 (2.8)	**35.3 (10.0)****
Digit span forwards/8	7.1 (1.2)	6.8 (1.0)	7.4 (1.1)	**6.0 (1.5)***
Digit span backwards/7	5.2 (1.2)	5.7 (1.3)	5.4 (1.1)	4.3 (1.6)
BPVS	142.5 (8.8)	**135.0 (14.4)****	139.8 (10.1)	135.9 (11.8)
GNT/30	20.9 (4.6)	17.8 (5.8)	19.2 (5.4)	18.8 (7.2)
NART/50	31.8 (8.9)	**24.1 (8.6)****	27.7 (10.7)	25.4 (13.2)
VOSP OD /20	18.0 (2.8)	17.8 (1.8)	18.3 (1.3)	17.6 (1.5)
Stroop (s)	50.3 (14.0)	45.8 (12.2)	52.6 (14.1)	**78.2 (22.4)****
VSTM performance				
Identification (% correct)				
Overall	91.6 (4.8)	90.2 (6.3)	92.0 (3.9)	**81.9 (5.0)****
Localisation error (deg)				
Overall	4.4 (1.3)	4.5 (1.3)	4.6 (1.1)	**7.8 (1.8)****
Swap error (%)				
Overall	10.6 (5.3)	11.7 (4.7)	10.2 (5.9)	**22.6 (8.1)****

Block 1, 1s delay	12.0 (8.4)	12.4 (9.2)	9.9 (5.0)	21.2 (12.6)
Block 1, 4s delay	13.2 (8.7)	18.7 (9.2)	15.0 (10.8)	**23.2 (18.0)***

Unadjusted mean values are given with SD unless otherwise stated. SD = standard deviation; NA= not applicable; PMC= presymptomatic mutation carrier; EYO=estimated years to/from symptom onset (a negative value indicates a younger age than their estimated age at symptom onset); AYO=actual years to/from onset (positive values indicate years post onset); Anxiety and depression scores from HADS= hospital anxiety and depression scale; IQ=intelligence quotient; MMSE=mini mental state examination; CDR=clinical dementia rating scale; RMT=recognition memory test; GNT=graded naming test; VOSP OD=object decision from the visual object and space perception battery. Digit spans forwards and backwards are taken from the WMS-R= Wechsler Memory Scale. Neuropsychology data were available at baseline for: 64 participants for performance IQ, verbal IQ; 98 for arithmetic total, GNT, NART, VOSP; 99 for RMT faces, RMT words, digit span forwards, digit span backwards; 71 for BPVS; and 78 for Stroop (s). Bold= significant; *: significant at $p<0.05$; **: significant at $p<0.01$.

3.2. Longitudinal analysis for N=48

Forty-eight individuals completing at least two annual visits were included in the longitudinal analysis: 19 controls; 20 individuals who remained PMCs throughout the duration of the study: 12 early PMCs, 8 late PMCs; 3 converters-participants who were late PMCs at baseline but had symptoms at their last follow-up visit and 6 symptomatic carriers. (Baseline performance of the N=48 sample is summarised in the Supplementary Materials, Table e1).

Considering all visits together, longer delay (1 *vs* 4s); higher memory load (3 *vs* 1 item); and block 1 (*vs* block 2) had significant effects on VSTM metrics resulting in worse: localisation, identification and swap error performance (greater error, poorer performance).

3.2.1. Rates of change between late PMCs, early PMCs, symptomatic carriers vs controls

3.2.1.1. Identification performance

Throughout the course of the study, identification performance within controls (p=0.913) and PMCs (early PMC: p=0.850; late PMC: p=0.217) remained similar, whereas performance for symptomatic carriers decreased (p=0.011) (Table 2).

There was no significant difference in the rate of change of identification performance between either PMC group and controls (early PMCs: p=0.830, late PMCs: p= 0.395, Table 2). Symptomatic carriers, showed a faster decline in identification performance over time (p=0.036), with 43% lower odds of correct identification than controls at baseline decreasing to 65% lower by year 3 (Table 2, Fig.3A). There was no significant interaction between group and item number (p=0.451), delay length (p=0.557) or block (p=0.408) in rates of change.

3.2.1.2. Localisation performance

Localisation performance of controls (p=0.737) and early PMCs (p=0.826) generally stayed the same throughout the course of the study, whereas performance for late PMCs (p=0.011) and symptomatic

carriers (p=0.033) decreased (Table 2).

Across task conditions, late PMCs and symptomatic carriers showed a trend towards a faster rate of decline in localisation performance compared to controls (late PMCs: p=0.082; symptomatic carriers: p=0.066). No differences in rates of change were observed between early PMCs and controls (p=0.946) (Table 2).

Both item number (p<0.001) and delay length (p=0.002) had a significant effect on differences in performance between groups. There was a significant interaction between delay and group in the rate of change (p=0.036), whereby for the late PMC group in the 4s delay, but not 1s delay condition (p=0.013), late PMCs showed significantly greater increase in localisation error over time than was seen in the controls (1-item: p=0.043, 3-items: p=0.008, Table 2). This effect was apparent from 2 years after baseline, with the greatest difference in the 3-items, 4s delay condition (difference 11% at baseline, increasing to 35% at 3 years) (Fig.3B).

Symptomatic carriers generally had faster increases in localisation error than controls, but this only reached statistical significance in the 3-items, 1s delay condition (p=0.043, Table 2). No further significant effects were observed.

3.2.1.3. Swap error performance

Swap error performance for all groups, generally stayed the same throughout the course of the study (controls: p=0.937; early PMCs: p=0.231; late PMCs: p=0.943 and symptomatic carriers: p=0.237) (Table 2).

There was no difference in rate of change in swap error performance over time between either PMC groups and controls (early: p=0.389, late: p=0.917). Although symptomatic carriers made a greater proportion of swap errors than controls (p<0.001), there was no difference in the rate of change (p=0.309, Table 2, Fig.3C).

While the evidence for an interaction between group and block (p=0.086) or delay (p=0.089) was weak, we specifically examined the 4s delay of block 1 following Liang and colleagues finding of higher swap errors in PMCs in this condition (Liang et al. 2016). There was a trend for higher swap error proportion for late PMCs compared to controls (p=0.099, Table 2), however this effect did not reach statistical significance and no differences were observed for early PMCs *vs* controls (p=0.830). Despite having a higher proportion of swaps overall (p<0.001), symptomatic carriers showed no difference in rate of change compared to controls in this condition either (p=0.946, Table 2).

Table 2. Rates of change in VSTM function per year.

Change per year	Adjusted mean [95% CI] Group difference [95% CI] (control as reference)			
	Controls	Early PMCs	Late PMCs	Symptomatic carriers
Identification performance: Odds ratio for correct response				
Overall	1.00 [0.92, 1.08]	1.01 [0.93, 1.09]	0.94 [0.86, 1.03]	**0.85 [0.75, 0.96]***
	NA	1.01 [0.91, 1.13]	0.95 [0.84, 1.07]	**0.85 [0.73, 0.99]***
Localisation error: % error				
Overall	0.4 [-2.1, 3.1]	0.3 [-2.4, 3.1]	**4.1 [0.9, 7.4]***	**7.0 [0.6, 13.8]***
	NA	-0.1 [-3.8, 3.7]	4.0 [0.7, 7.5]	7.3 [0.5, 14.6]
3-items	0.4 [-2.2, 3.1]	1.4 [-1.5, 4.3]	**3.6 [-0.4, 7.9]***	**6.5 [-0.4, 13.9]***
	NA	0.9 [-3.0, 5.0]	3.6 [-0.7, 8.1]	6.9 [-0.5, 14.7]
3-items, 1s	0.8 [-2.2, 3.9]	0.0 [-3.3, 3.4]	1.4 [-2.3, 5.3]	**9.9 [1.7, 18.8]***
	NA	-0.8 [-3.0, 5.0]	0.6 [-0.7, 8.1]	**9.0 [0.3, 18.5]***
3-items, 4s	0.0 [-3.0, 3.1]	2.7 [-0.7, 6.2]	**6.9 [2.9, 11.0]****	4.8 [-3.4, 13.6]
	NA	2.7 [-1.9, 7.4]	**6.9 [1.8, 12.2]****	4.7 [-3.9, 14.2]
1-item	0.6 [-3.2, 4.4]	-3.3 [-7.3, 0.8]	4.4 [-0.5, 9.5]	5.5 [-4.7, 16.9]
	NA	-3.9 [-9.1, 1.7]	3.8 [-2.3, 10.3]	5.0 [-5.9, 17.0]
1-item, 1s	0.9 [-3.1, 5.1]	**-4.6 [-8.8, -0.2]***	1.7 [-3.4, 7.0]	8.1 [-3.3, 20.8]
	NA	-5.5 [-11.0, 0.4]	0.7 [-5.6, 7.5]	7.1 [-4.9, 20.5]
1-item, 4s	0.2 [-3.8, 4.3]	-2.0 [-6.3, 2.4]	**7.2 [1.8, 12.8]****	3.0 [-7.7, 15.0]
	NA	-2.2 [-7.9, 3.9]	**7.0 [0.2, 14.2]***	2.8 [-8.6, 15.7]
Swap error: √proportion				
Overall	-0.001 [-0.014, 0.013]	-0.010 [-0.026, 0.006]	0.001 [-0.018, 0.019]	-0.016 [-0.043, 0.011]
	NA	-0.009 [-0.030, 0.012]	0.001 [-0.022, 0.024]	-0.015 [-0.045, 0.014]
Block 1, 4s	-0.014 [-0.035, 0.005]	-0.011 [-0.036, 0.013]	0.014 [-0.014, 0.041]	-0.017 [-0.059, 0.026]
	NA	0.004 [-0.028, 0.036]	0.029 [-0.005, 0.063]	-0.002 [-0.049, 0.045]

Adjusted mean difference in rate of change per year by group and compared to controls. CI= Confidence intervals; NA=not applicable; PMC=presymptomatic mutation carrier. Bold=significant; *: significant at $p<0.05$. **: significant at $p<0.01$.

3.2.2. Relationship between VSTM performance and proximity to symptom onset

3.2.2.1. Identification performance

There was no significant association between identification performance and EYO within FAD carriers (symptomatic and presymptomatic, $p=0.120$, Fig.4A). Nonetheless, identification performance

significantly decreased with AYO in the subgroup analysis of symptomatic carriers and converters (p<0.001) (Fig.4B).

3.2.2.2. Localisation performance

Localisation error significantly decreased with EYO in FAD mutation carriers (presymptomatic and symptomatic, p=0.024). There was a significant interaction with item number (p<0.001) and the delay length (p=0.002) such that the localisation deficit associated with closer proximity to onset was greater in the 3-item and 4s delay conditions (i.e. when the memory demands were greatest), but there was no interaction with block (p=0.137). Results were therefore examined by item and delay. Both 3-item conditions, showed a significant increase in localisation error with increasing EYO (or more years post onset) (1s delay: p=0.036; 4s delay: p=0.002). The association was strongest in longest delay (difference from controls at -5 years: 1s delay 19.1 [95% CI 1.5, 39.8] %, p=0.032 *vs* 4s delay 23.9 [5.5, 45.4] %, p=0.009). In the 3-items, 4s delay model (Fig.4D), a significant difference in mean localisation error between FAD carriers (presymptomatic and symptomatic) and controls was observed from 6 years before expected onset (20.1 [5.5, 41.0] %; p=0.024).

Localisation error also significantly increased with AYO within symptomatic carriers and converters (p<0.001) (Fig.4E).

3.2.2.3. Swap error proportion

There was no significant association between swap error proportion and EYO within FAD carriers (symptomatic and presymptomatic, p=0.123, Fig.4G) nor with AYO in the symptomatic group with converters (p=0.863) (Fig.4H).

3.2.3. Longitudinal change of participants on traditional neuropsychology

Following our findings of a faster rate of decline in localisation performance, we considered rates of change in traditional neuropsychology tasks.

A significant difference between late PMCs and controls on the RMT words was observed approximately 1 year later than the presymptomatic changes observed in localisation performance (i.e. from 3 years after baseline), with 35 [45.6, 22.2] % greater rate of decline per year (p<0.001).

A significant difference between controls and early PMC group was seen for RMT faces but in the opposite direction to that expected (early PMCs: 13.7 [1.0, 28.0] % showed a greater *increase* in performance per year, p=0.034). No further significant group differences emerged at a presymptomatic level. While verbal and performance IQ measures showed lower values for PMCs at baseline, there was no evidence for a faster rate of decline compared to controls (VIQ: early PMCs: 0.9 [-1.1, 2.9] points per year, p=0.398; late PMCs: -0.0007 [-2.3, 2.3], p=1.000; PIQ: early PMCs: 0.07 [-1.5, 1.6] points per year, p=0.930; late PMCs: -0.8 [-2.6, 1.0], p=0.363). Symptomatic carriers had a greater rate of decline than controls in:

performance IQ (-3.9 [-6.1, -1.7] points per year, p<0.001); arithmetic (-1.5 [-2.7, 0.3] points per year, p=0.012) and digit span backwards (66% greater decline per year, OR=0.34 [0.13,0.91], p=0.031).

4. Discussion

The aim of the present study was to investigate VSTM function longitudinally and its relationship to EYO in a preclinical AD cohort like FAD. The main finding was that compared to controls, 'late' PMCs (within 8.5 years of estimated onset) had a significantly faster rate of decline in localisation performance. This effect was observed ~1 year earlier than changes in traditional neuropsychology measures like verbal episodic memory and was strongest in long-delay conditions indicating deficits may relate to maintenance processes. Localisation performance was also the only VSTM metric to show a significant association with EYO, predicting cognitive decline up to 6 years prior to estimated symptom onset. Taken together, these results indicate that the "What was where?" task may be sensitive in tracking preclinical decline earlier than more traditional neuropsychology tests.

Symptomatic participants showed a significant association with AYO and a progressive decline in all VSTM metrics (with faster decline in localisation performance only seen in one condition most likely due to small numbers in this group) but the swap error performance which was poor at every visit.

We speculate that our longitudinal findings may be explained by a 'unified account of hippocampal forgetting across short and long timescales', proposed recently by Sadeh and Pertzov (Sadeh and Pertzov 2020) according to which the similarities between short (interval of a few seconds between study and test, e.g. STM or working memory paradigms) and long timescales (study-test intervals of several minutes to days/months) suggests that a single hippocampus-based mechanism underlies memory in both timescales. This contrasts the once prevailing view that the hippocampus (proposed to be one of the earliest regions affected by AD pathology by some ((Chan et al. 2016; Fox et al. 1996; Liang et al. 2017)) was exclusively involved in memory and forgetting over long timescales. Accelerated forgetting refers to a long-term memory process whereby new material appears to be encoded and retained normally over periods of up to 30 min but is then forgotten at an abnormally rapid rate over the following hours to weeks (Weston et al. 2018). While the exact mechanism for this process is poorly understood, the hippocampus has been implicated in the formation and retention of memories (Squire 2009). Previous reports from our centre have shown strong correlations between localisation performance and hippocampal volume (once adjusted for age, sex and total intracranial volume). As the precision of localisation performance in VSTM for late PMCs declined at an accelerated rate compared to controls, we propose that a process similar to accelerated forgetting may be behind the deficits observed. The effect was specific to localisation performance (a metric measuring the resolution of error in the association between an object's identity to its exact location) indicating that the quality of recall combining the object's identity to *its location* may have been predominantly forgotten at a faster rate. Therefore, there may be processes specific to the hippocampus which underly this 'accelerated forgetting' phenomenon across time-scales. Yet, other studies have shown that atrophy in the entorhinal cortex precedes that in

the hippocampus (Braak and Braak 1991; Liang et al. 2017) and these topics are still under debate in the field of AD.

A critical advantage of longitudinal studies over cross-sectional investigations is the ability to assess when changes occur. Recently, a proposal emerged suggesting that AD progressed in two stages: a sub-hippocampal phase characterised by impairments in context-free memory function such as those assessed by recognition tasks, followed by a hippocampal stage when impairments in context-rich memory functions (such as 'associative memory') are observed and which corresponds clinically to the stage at which cognitive impairment is evident (Parra 2017). In this respect, it is perhaps relevant to note that in this study, longitudinal performance of PMCs was significantly worse than controls in the 'What was where?" task (arguably a context-rich memory function) and in the RMT for words but that changes in the former were observed earlier than the latter. Still, the relative sensitivities of each test certainty affect findings and significant effects were observed in long-delay conditions for localisation performance emphasising the potentially crucial role of delay (i.e. passage of time) as a source of forgetting in PMCs. Longitudinal imaging studies in preclinical AD populations like presymptomatic FAD are required to investigate these questions further.

Unlike reports from our centre by Liang and colleagues showing a higher proportion of swap errors in PMCs (Liang et al. 2016), cross-sectional deficits were only observed in symptomatic carriers here and no differences in the rate change of swap errors were observed for any of the groups compared to controls either. As a relatively accurate localisation is required for a response to count as a swap (i.e. it must be localised 'close enough' to another location), swap errors may have been underrepresented in our sample (in both symptomatic and presymptomatic carriers) especially in light of the localisation error finding. Whilst it is possible that with a larger longitudinal sample, we may have observed relational binding deficits in PMCs, the lack of significant association with EYO suggests other factors such as chance, genetic heterogeneity or lower sensitivity of a binary measure *vs* a continuous one may have also affected results. The non-significant interaction between the rate of swap error proportion and delay in our longitudinal analysis was surprising, yet the worsening localisation particularly for longer delays may have veiled this interaction too.

The current study has several limitations. Firstly, despite the increased sample size in comparison to the previous cross-sectional study (23 presymptomatic carriers in this study *vs* 12 presymptomatic carriers in (Liang et al. 2016)), this remains relatively small due to the low prevalence of FAD. Secondly, disease progression is complex and not well characterised in the literature, especially in FAD (Canevelli et al. 2014; Pavisic et al. 2020; Ryman et al. 2014; Shea et al. 2016). As our study included mutation carriers from pedigrees with different *PSEN1* and *APP* mutations, it is possible that by considering all FAD carriers together, the heterogeneity in the progression of the disease between genes and mutations may have affected our results. However, creating mutation-based subgroups would not have been possible due to issues around validity of modelling such small groups. Furthermore, 'late' PMCs were an heterogenous group in that individuals EYO spanned within 8.5 years before expected onset; mean=-5.8 (SD 1.8) years and these estimations are imprecise given the within-family variation in age at onset (Ryman et al.

2014). Thirdly, the qualitative observation of VSTM performance in ‘converters’ showed that for all VSTM metrics, performance did not follow a unique pattern once participants transitioned into a symptomatic stage (for some participants, scores worsened while for others they remained stable). Reporting this substantial variability possibly resulting from the 100 trials completed by participants at every visit in addition to the limitations previously mentioned, is important as it raises novel considerations of the use of such tasks at an individual level. Lastly, our findings may also be explained by the attention and frontal/executive demands of this task (with the localisation measure being particularly sensitive due to its continuous nature), rather than the visuospatial or memory aspects *per se.* Yet, we did not find longitudinal preclinical evidence this was the case in the more traditional neuropsychology tasks measuring these cognitive functions. This suggests our results may be signalling a somewhat specific VSTM deficit and may hopefully add to the cumulative efforts of tracking preclinical cognitive decline in AD.

Despite the above limitations, to the best of our knowledge, this is the first longitudinal investigation on VSTM function in a preclinical sample like FAD over a period of many years. Future studies looking at correlations with functional outcomes and hippocampal volume or amyloid beta deposition, should investigate its use for screening and monitoring purposes in FAD and other preclinical AD populations more broadly.

Conclusions

Our findings highlight that evaluating the *degree* of error on a continuous scale may be a sensitive measure of longitudinal decline in the presymptomatic stages of FAD. Analogous to the accelerated-forgetting hypothesis, we speculate a similar phenomenon may explain VSTM deficits, whereby the ability to spatially remember and retain a memory representation is forgotten with time at an ‘accelerated rate’ in presymptomatic FAD compared to controls. More broadly, these results merit further exploration particularly in light of the similarities between sporadic and familial AD and the importance of identifying and tracking individuals at-risk of developing AD as early as possible for intervention trials.

Abbreviations

VSTM: visual short-term memory; AD: Alzheimer’s disease; FAD: familial Alzheimer’s disease; PMC: presymptomatic mutation carrier; EYO: estimated years to/from symptom onset; AYO: actual years to/from symptom onset. HADS: hospital anxiety and depression scale; NART: National Adult Reading Test.

Declarations

Declaration of interests

I.M. Pavisic; J.M. Nicholas; Y. Pertzov; A. O'Connor; Y. Liang; J. D. Collins; K. Lu; P.S.J. Weston; N.S. Ryan; M. Husain and S. Crutch report no disclosures relevant to this manuscript. N.C. Fox has provided consultancy for Biogen, Ionis and Roche and serves on a Data Safety Monitoring Committee for Biogen.

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Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

Atkinson, R. C., and R. M. Shiffrin. 1968. "Human Memory: A Proposed System and Its Control Processes." Pp. 89–195 in *Psychol Learn Motiv.* Vol. 2, edited by K. W. Spence and J. T. Spence. Academic Press.

Atkinson, R. C., and R. M. Shiffrin. 1971. "The Control of Short-Term Memory." *Sci Am.* 225(2):82–90. doi: 10.1038/scientificamerican0871-82.

Bateman, Randall J., Chengjie Xiong, Tammie L. S. Benzinger, Anne M. Fagan, Alison Goate, Nick C. Fox, Daniel S. Marcus, Nigel J. Cairns, Xianyun Xie, Tyler M. Blazey, David M. Holtzman, Anna Santacruz, Virginia Buckles, Angela Oliver, Krista Moulder, Paul S. Aisen, Bernardino Ghetti, William E. Klunk, Eric McDade, Ralph N. Martins, Colin L. Masters, Richard Mayeux, John M. Ringman, Martin N. Rossor, Peter R. Schofield, Reisa A. Sperling, Stephen Salloway, John C. Morris, and Dominantly Inherited Alzheimer Network. 2012. "Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease." *N England J Med.* 367(9):795–804. doi: 10.1056/NEJMoa1202753.

Bays, Paul M., Raquel F. G. Catalao, and Masud Husain. 2009. "The Precision of Visual Working Memory Is Set by Allocation of a Shared Resource." *J Vis.* 9(10):7.1-11. doi: 10.1167/9.10.7.

Braak, H., and E. Braak. 1991. "Neuropathological Stageing of Alzheimer-Related Changes." *Acta Neuropathol.* 82(4):239–59. doi: 10.1007/BF00308809.

Canevelli, Marco, Paola Piscopo, Giuseppina Talarico, Nicola Vanacore, Alessandro Blasimme, Alessio Crestini, Giuseppe Tosto, Fernanda Troili, Gian Luigi Lenzi, Annamaria Confaloni, and Giuseppe Bruno. 2014. “Familial Alzheimer’s Disease Sustained by Presenilin 2 Mutations: Systematic Review of Literature and Genotype-Phenotype Correlation.” *Neurosci. Biobehav. Rev.* 42:170–79. doi: 10.1016/j.neubiorev.2014.02.010.

Chan, Dennis, Laura Marie Gallaher, Kuven Moodley, Ludovico Minati, Neil Burgess, and Tom Hartley. 2016. “The 4 Mountains Test: A Short Test of Spatial Memory with High Sensitivity for the Diagnosis of Pre-Dementia Alzheimer’s Disease.” *J. Vis. Exp.* (116). doi: 10.3791/54454.

Della Sala, Sergio, Mario A. Parra, Katia Fabi, Simona Luzzi, and Sharon Abrahams. 2012. “Short-Term Memory Binding Is Impaired in AD but Not in Non-AD Dementias.” *Neuropsychologia* 50(5):833–40. doi: 10.1016/j.neuropsychologia.2012.01.018.

Dubois, Bruno, Howard H. Feldman, Claudia Jacova, Jeffrey L. Cummings, Steven T. DeKosky, Pascale Barberger-Gateau, André Delacourte, Giovanni Frisoni, Nick C. Fox, Douglas Galasko, and others. 2010. “Revising the Definition of Alzheimer’s Disease: A New Lexicon.” *Lancet Neurol.* 9(11):1118–1127.

Dubois, Bruno, Howard H. Feldman, Claudia Jacova, Steven T. Dekosky, Pascale Barberger-Gateau, Jeffrey Cummings, André Delacourte, Douglas Galasko, Serge Gauthier, Gregory Jicha, Kenichi Meguro, John O’brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Yaakov Stern, Pieter J. Visser, and Philip Scheltens. 2007. “Research Criteria for the Diagnosis of Alzheimer’s Disease: Revising the NINCDS-ADRDA Criteria.” *Lancet Neurol* 6(8):734–46. doi: 10.1016/S1474-4422(07)70178-3.

Dunn, Douglas M., and Lloyd M. Dunn. 2009. The British Picture Vocabulary Scale-3rd Ed.

Folstein, M. F., S. E. Folstein, and P. R. McHugh. 1975. “‘Mini-Mental State’. A Practical Method for Grading the Cognitive State of Patients for the Clinician.” *J. Psychiatr. Res.* 12(3):189–98.

Fox, N. C., E. K. Warrington, P. A. Freeborough, P. Hartikainen, A. M. Kennedy, J. M. Stevens, and M. N. Rossor. 1996. “Presymptomatic Hippocampal Atrophy in Alzheimer’s Disease. A Longitudinal MRI Study.” *Brain.* 119(Pt 6):2001–7. doi: 10.1093/brain/119.6.2001.

Gorgoraptis, Nikos, Raquel F. G. Catalao, Paul M. Bays, and Masud Husain. 2011. “Dynamic Updating of Working Memory Resources for Visual Objects.” *J. Neurosci.* 31(23):8502–11. doi: 10.1523/JNEUROSCI.0208-11.2011.

Groeger, John A., David Field, and Sean M. Hammond. 1999. “Measuring Memory Span.” *Int. J. Psychol.* 34(5–6):359–63. doi: 10.1080/002075999399693.

Jack, Clifford R., and David M. Holtzman. 2013. “Biomarker Modeling of Alzheimer’s Disease.” *Neuron* 80(6):1347–58. doi: 10.1016/j.neuron.2013.12.003.

Jackson, M., and E. K. Warrington. 1986. “Arithmetic Skills in Patients with Unilateral Cerebral Lesions.” *Cortex.* 22(4):611–20.

Janssen, J. C., J. A. Beck, T. A. Campbell, A. Dickinson, N. C. Fox, R. J. Harvey, H. Houlden, M. N. Rossor, and J. Collinge. 2003. “Early Onset Familial Alzheimer’s Disease: Mutation Frequency in 31 Families.” *Neurology*. 60(2):235–39.

Law, R., and R. E. O’Carroll. 1998. “A Comparison of Three Measures of Estimating Premorbid Intellectual Level in Dementia of the Alzheimer Type.” *Int. J. Geriatr. Psychiatry* 13(10):727–30.

Liang, Yuying, Yoni Pertzov, Susie Henley, Felix Woodward, Masud Husain, and Sebastian Crutch. 2017. “Visual Short-Term Memory Binding Deficits in Alzheimer’s Disease: A Reply to Parra’s Commentary.” *Cortex.* 88:201–4.

Liang, Yuying, Yoni Pertzov, Jennifer M. Nicholas, Susie M. D. Henley, Sebastian Crutch, Felix Woodward, Kelvin Leung, Nick C. Fox, and Masud Husain. 2016. “Visual Short-Term Memory Binding Deficit in Familial Alzheimer’s Disease.” *Cortex.* 78:150–64. doi: 10.1016/j.cortex.2016.01.015.

Ma, Wei Ji, Masud Husain, and Paul M. Bays. 2014. “Changing Concepts of Working Memory.” *Nature Neurosci.*17(3):347–56. doi: 10.1038/nn.3655.

McKenna, P., and EK Warrington. 1983. The Graded Naming Test. Nelson.

McKhann, G., D. Drachman, M. Folstein, R. Katzman, D. Price, and E. M. Stadlan. 1984. “Clinical Diagnosis of Alzheimer’s Disease: Report of the NINCDS-ADRDA Work Group under the Auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease.” *Neurology.* 34(7):939–44. doi: 10.1212/wnl.34.7.939.

Morris, J. C. 1993. “The Clinical Dementia Rating (Cdr): Current Version and Scoring Rules.” *Neurology* 43(11):2412–14.

Nelson, HE. 1991. National Adult Reading Test Manual. Windsor.

Parra, Mario A., Sharon Abrahams, Katia Fabi, Robert Logie, Simona Luzzi, and Sergio Della Sala. 2009. “Short-Term Memory Binding Deficits in Alzheimer’s Disease.” *Brain: A Journal of Neurology.* 132(Pt 4):1057–66. doi: 10.1093/brain/awp036.

Parra, Mario A., Sharon Abrahams, Robert H. Logie, and Sergio Della Sala. 2010. “Visual Short-Term Memory Binding in Alzheimer’s Disease and Depression.” *J. Neurol.* 257(7):1160–69. doi: 10.1007/s00415-010-5484-9.

Parra, Mario A., Sharon Abrahams, Robert H. Logie, Luis G. Méndez, Francisco Lopera, and Sergio Della Sala. 2010. “Visual Short-Term Memory Binding Deficits in Familial Alzheimer’s Disease.” *Brain.* 133(9):2702–13. doi: 10.1093/brain/awq148.

Parra, Mario A., Sergio Della Sala, Sharon Abrahams, Robert H. Logie, Luis Guillermo Méndez, and Francisco Lopera. 2011. “Specific Deficit of Colour-Colour Short-Term Memory Binding in Sporadic and Familial Alzheimer’s Disease.” *Neuropsychologia* 49(7):1943–52. doi: 10.1016/j.neuropsychologia.2011.03.022.

Parra, Mario Alfredo. 2017. “A Commentary on Liang et al.’s Paper with Regard to Emerging Views of Memory Assessment in Alzheimer’s Disease.” *Cortex.* 88:198–200. doi: 10.1016/j.cortex.2016.06.006.

Pavisic, Ivanna M., Jennifer M. Nicholas, Antoinette O’Connor, Helen Rice, Kirsty Lu, Nick C. Fox, and Natalie S. Ryan. 2020. “Disease Duration in Autosomal Dominant Familial Alzheimer Disease: A Survival Analysis.” *Neurology: Genet*ics 6(5). doi: https://doi.org/10.1212/NXG.0000000000000507.

Pavisic, Ivanna M., Aida Suarez-Gonzalez, and Yoni Pertzov. 2020. “Translating Visual Short-Term Memory Binding Tasks to Clinical Practice: From Theory to Practice. *Front. Neurol*.” doi: 10.3389/fneur.2020.00458.

Peich, Muy-Cheng, Masud Husain, and Paul M. Bays. 2013. “Age-Related Decline of Precision and Binding in Visual Working Memory.” *Psychol. Aging.* 28(3):729–43. doi: 10.1037/a0033236.

Pertzov, Yoni, Mia Yuan Dong, Muy-Cheng Peich, and Masud Husain. 2012. “Forgetting What Was Where: The Fragility of Object-Location Binding.” *PLOS ONE* 7(10):e48214. doi: 10.1371/journal.pone.0048214.

Pertzov, Yoni, Thomas D. Miller, Nikos Gorgoraptis, Diana Caine, Jonathan M. Schott, Chris Butler, and Masud Husain. 2013. “Binding Deficits in Memory Following Medial Temporal Lobe Damage in Patients with Voltage-Gated Potassium Channel Complex Antibody-Associated Limbic Encephalitis.” *Brain.* 136(8):2474–85. doi: 10.1093/brain/awt129.

Rossor, M. N., N. C. Fox, J. Beck, T. C. Campbell, and J. Collinge. 1996. “Incomplete Penetrance of Familial Alzheimer’s Disease in a Pedigree with a Novel Presenilin-1 Gene Mutation.” *Lancet.* 347(9014):1560. doi: 10.1016/s0140-6736(96)90715-1.

Ryan, N. S., J. M. Nicholas, P. S. J. Weston, Y. Liang, T. Lashley, Rita Guerreiro, Gary Adamson, Janna Kenny, Jon Beck, Lucia Chavez-Gutierrez, Bart de Strooper, Tamas Revesz, Janice Holton, Simon Mead, Martin N. Rossor, and Nick C. Fox. 2016. “Clinical Phenotype and Genetic Associations in Autosomal Dominant Familial Alzheimer’s Disease: A Case Series.” *Lancet. Neurol.* 15(13):1326–35. doi: 10.1016/S1474-4422(16)30193-4.

Ryan, Natalie S., and Martin N. Rossor. 2010. “Correlating Familial Alzheimer’s Disease Gene Mutations with Clinical Phenotype.” *Biomark. Med.* 4(1):99–112. doi: 10.2217/bmm.09.92.

Ryman, Davis C., Natalia Acosta-Baena, Paul S. Aisen, Thomas Bird, Adrian Danek, Nick C. Fox, Alison Goate, Peter Frommelt, Bernardino Ghetti, Jessica B. S. Langbaum, Francisco Lopera, Ralph Martins, Colin L. Masters, Richard P. Mayeux, Eric McDade, Sonia Moreno, Eric M. Reiman, John M. Ringman,

Steve Salloway, Peter R. Schofield, Reisa Sperling, Pierre N. Tariot, Chengjie Xiong, John C. Morris, and Randall J. Bateman. 2014. “Symptom Onset in Autosomal Dominant Alzheimer Disease.” *Neurology.* 83(3):253–60. doi: 10.1212/WNL.0000000000000596.

Sadeh, Talya, and Yoni Pertzov. 2020. “Scale-Invariant Characteristics of Forgetting: Toward a Unifying Account of Hippocampal Forgetting across Short and Long Timescales.” *J. Cogn. Neurosci.* 32(3):386–402. doi: 10.1162/jocn_a_01491.

Shea, Yat-Fung, Leung-Wing Chu, Angel On-Kei Chan, Joyce Ha, Yan Li, and You-Qiang Song. 2016. “A Systematic Review of Familial Alzheimer’s Disease: Differences in Presentation of Clinical Features among Three Mutated Genes and Potential Ethnic Differences.” *J. Formos Med. Assoc.* 115(2):67–75. doi: 10.1016/j.jfma.2015.08.004.

Sperling, Reisa A., Paul S. Aisen, Laurel A. Beckett, David A. Bennett, Suzanne Craft, Anne M. Fagan, Takeshi Iwatsubo, Clifford R. Jack, Jeffrey Kaye, Thomas J. Montine, Denise C. Park, Eric M. Reiman, Christopher C. Rowe, Eric Siemers, Yaakov Stern, Kristine Yaffe, Maria C. Carrillo, Bill Thies, Marcelle Morrison-Bogorad, Molly V. Wagster, and Creighton H. Phelps. 2011. “Toward Defining the Preclinical Stages of Alzheimer’s Disease: Recommendations from the National Institute on Aging-Alzheimer’s Association Workgroups on Diagnostic Guidelines for Alzheimer’s Disease.” *Alzheimers Dement.* 7(3):280–92. doi: 10.1016/j.jalz.2011.03.003.

Squire, Larry R. 2009. “Memory and Brain Systems: 1969-2009.” *J. Neurosci.* 29(41):12711–16. doi: 10.1523/JNEUROSCI.3575-09.2009.

Stroop, JR. 1935. “Studies of Interference in Serial Verbal Reactions.”

Warrington, EK, and M. James. 1991. "Visual Object and Space Perception Battery (VOSP)". Pearson Assessment. Thames Valley Test Company.

Warrington, Elizabeth K. 1996. "The Camden Memory Tests Manual". Psychology Press.

Wechsler D. 1987. "Manual for the Wechsler Memory Scale-Revised". New York: The Psychological Corporation.

Wechsler D. 1999. "Wechsler Abbreviated Scale of Intelligence (WASI) Manual". The Psychological Corporation.

Wechsler, D., and MM De Lemos. 1981. "Wechsler Adult Intelligence Scale-Revised." Harcourt Brace Jovanovich.

Zigmond, A. S., and R. P. Snaith. 1983. “The Hospital Anxiety and Depression Scale.” *Acta Psychiatr Scand.* 67(6):361–70.

Zokaei, Nahid, Stephanie Burnett Heyes, Nikos Gorgoraptis, Sanjay Budhdeo, and Masud Husain. 2015. “Working Memory Recall Precision Is a More Sensitive Index than Span.” *J. Neuropsychol.* 9(2):319–29. doi: 10.1111/jnp.12052.

Figures

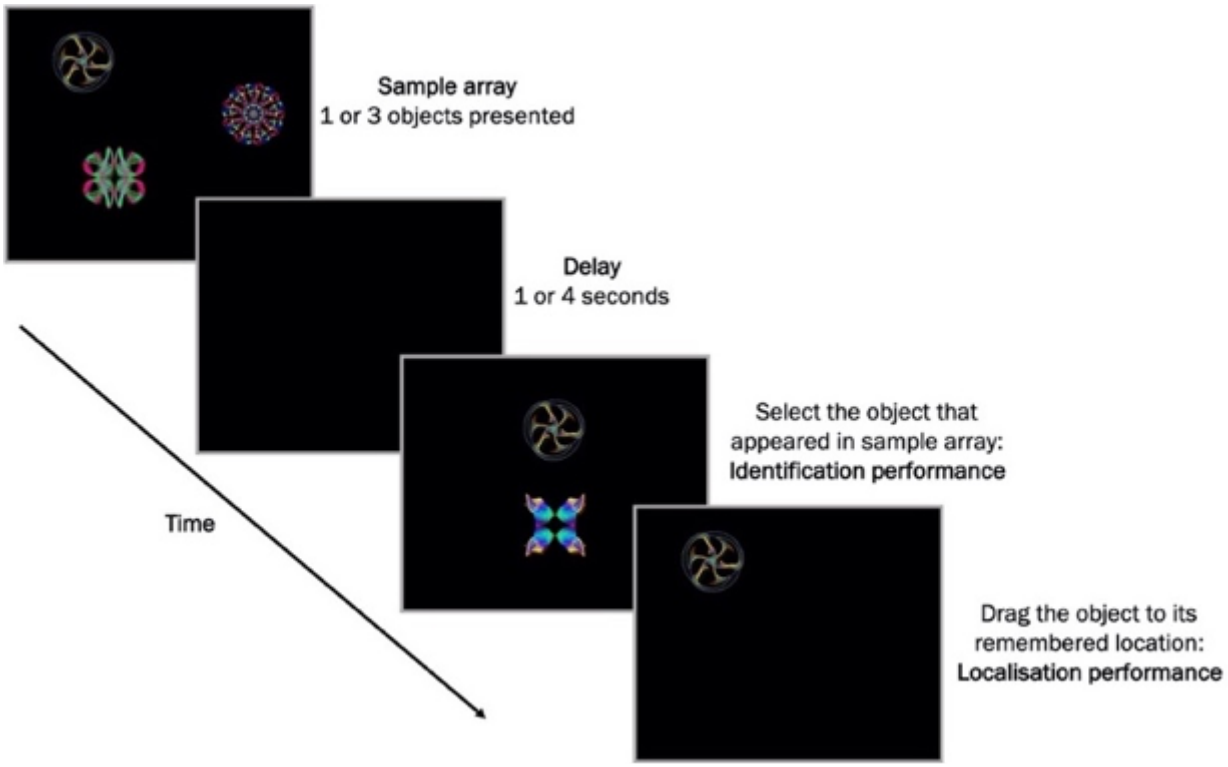

Figure 1

Schematic of “What was there?” (Liang et al. 2016; Pertzov et al. 2012).

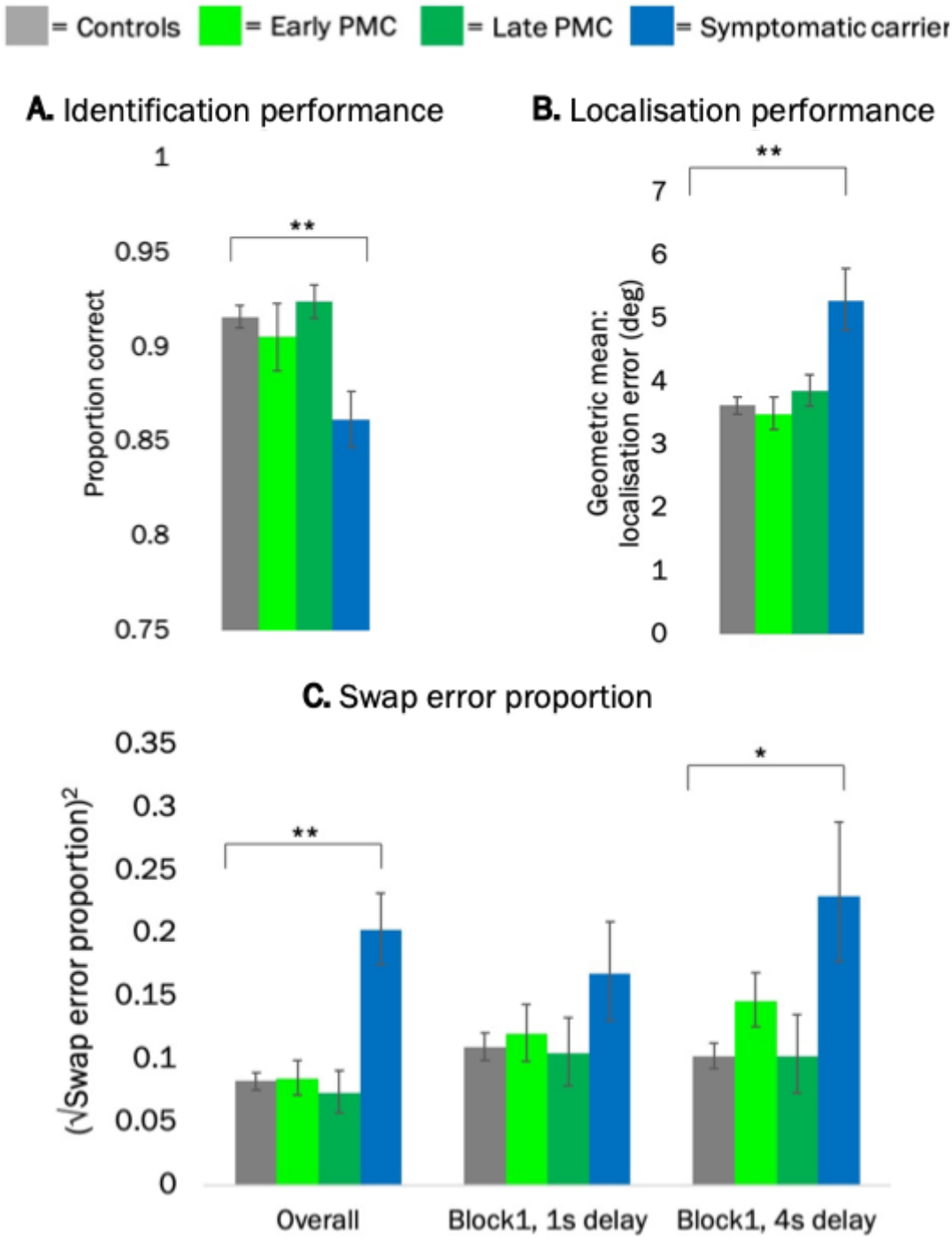

Figure 2

. Cross-sectional adjusted mean performance by group (from model adjusted for age, sex and NART). A. Identification performance (across all conditions); B. Localisation error (across all conditions); C. Swap error proportion across all conditions and by delay in block 1. Error bars show +/- standard error of the mean. PMC=presymptomatic mutation carrier. *= significant at p<0.05; **=significant at p<0.01.

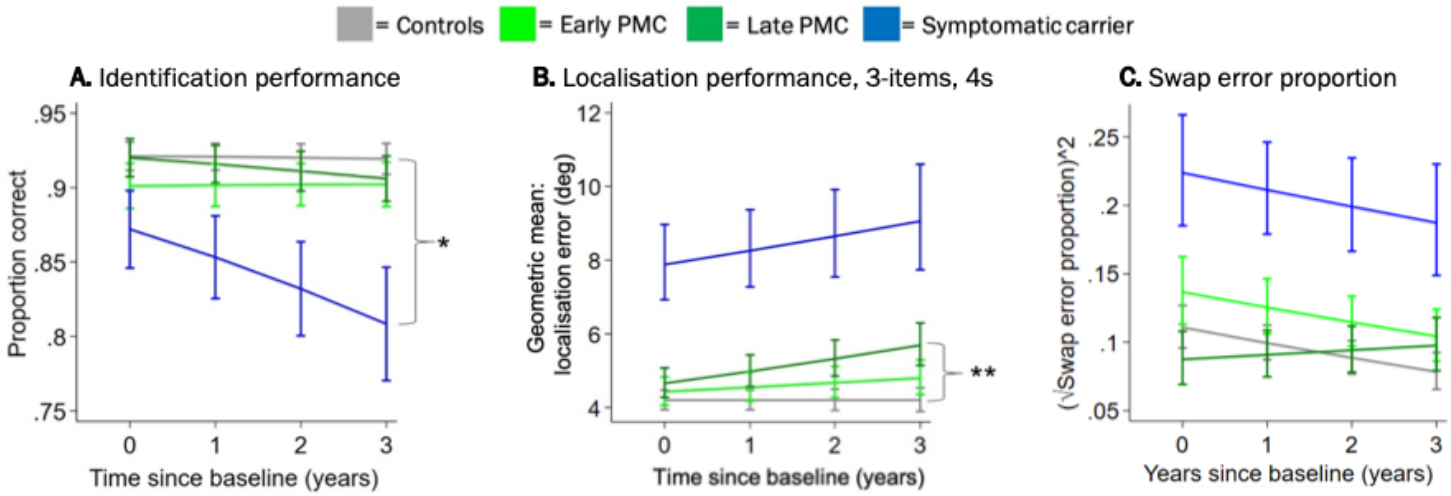

Figure 3

Longitudinal adjusted estimated mean performance by group (from model adjusted for age, sex and NART). A. Identification performance (across all conditions). B. Localisation error performance for the 3-item, 4s delay condition. C. Swap error performance (across all conditions). PMC=presymptomatic mutation carrier. Error bars indicate +/- standard error by time from baseline visit. *= the rate of change between groups was statistically significant at $p<0.05$ (control as reference); **= the rate of change between groups was statistically significant at $p<0.01$ (control as reference).

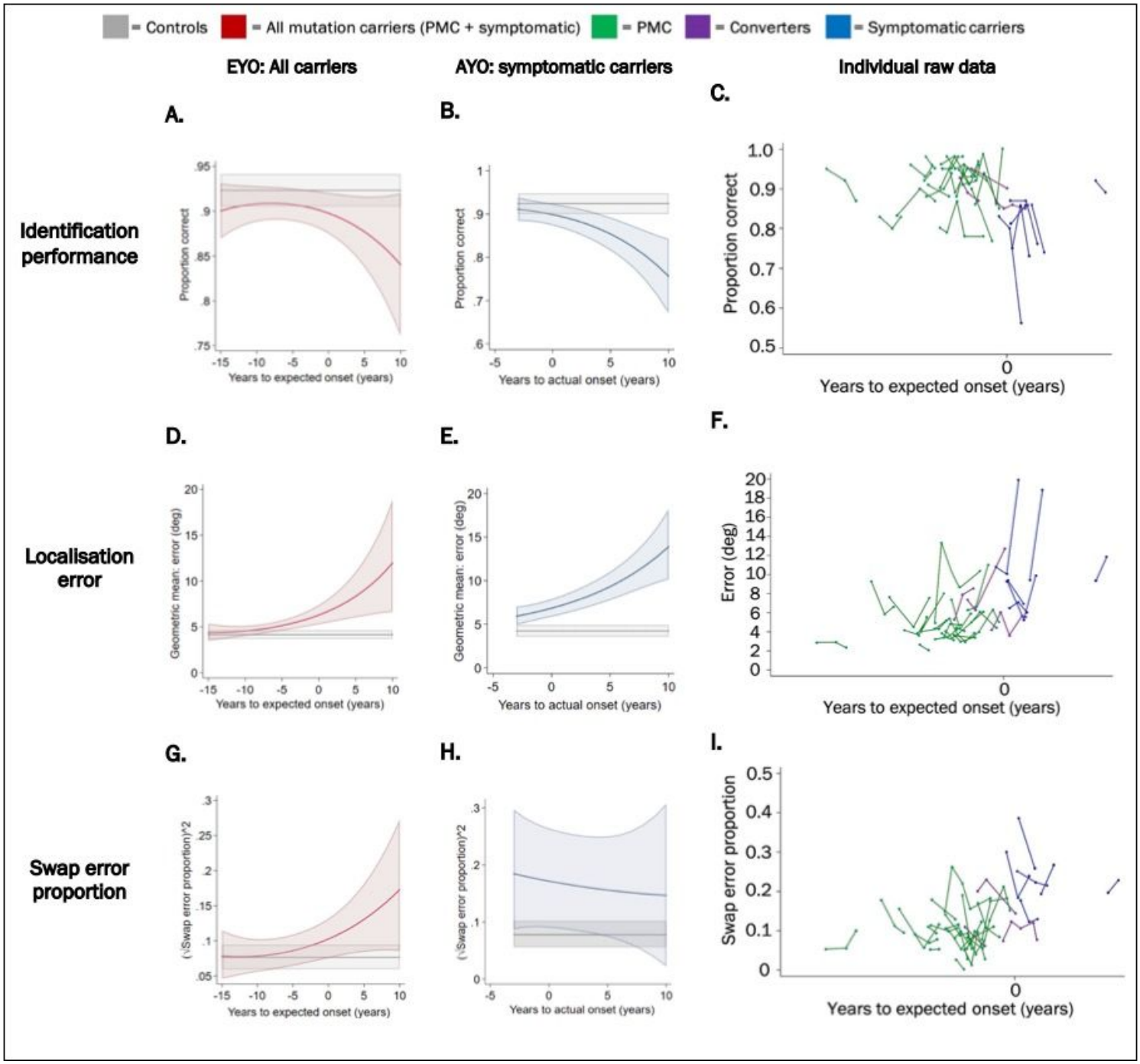

Figure 4

Relationship between VSTM performance and proximity to symptom onset. Panels A., B., D., E., G. and H. show the predicted mean of each VSTM metric (from model adjusted for age, sex and NART) against EYO or AYO. Shaded area indicates 95% confidence intervals. Panels C., F. and I. shows the unadjusted raw data plotted against EYO for each VSTM metric with visits marked as dots and connected for each participant; note there is no scale on the x-axes to preserve participant anonymity. Converters are PMCs who transitioned into a symptomatic stage at their last visit. PMC=presymptomatic mutation carrier. EYO=estimated years to/from symptom onset; AYO=actual years to/from symptom onset.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementarymaterialsPavisicetal.docx