Visual Short-term Memory Impairments in Presymptomatic Familial Alzheimer's Disease: a Longitudinal Observational Study

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Abstract

Background: Cross-sectional studies in presymptomatic familial Alzheimer's disease (FAD), have associated binding deficits with preclinical AD. How impairments in visual-short term memory (VSTM) relate to longitudinal change and proximity to expected symptom onset (EYO) is less characterized.

Methods: Thirty-two FAD mutation carriers (23 presymptomatic; 9 symptomatic) carrying a mutation in either presenilin 1 or amyloid precursor protein genes and 67 healthy controls were included in an extension VSTM cross-sectional study. Forty-eight participants (23 presymptomatic carriers, 6 symptomatic and 19 healthy controls) who had at least two annual visits (median= 3), were 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.

Results: While cross-sectionally only symptomatic carriers (N=9) showed significant impairments in VSTM performance, longitudinally, presymptomatic carriers within 8.5 years of estimated symptom onset (mean=5.8 years ±SD [1.8], N=11) showed a faster rate of decline in localisation performance in long-delay conditions (4s) compared to controls: increase/year in localisation error was 6.9% greater in the high-memory load condition (p=0.008) and 7.0% greater for the low-memory load condition (p=0.043). Change in this metric preceded presymptomatic changes in traditional measures of verbal episodic memory. Symptomatic carriers had 15% faster reduction in identification performance per year compared to controls (p=0.036) and some evidence of faster increase in localisation error (6.5% increase/year; p=0.066). The earliest significant difference in VSTM performance between FAD mutation carriers (presymptomatic and symptomatic) and controls was in localisation performance, six years prior to estimated symptom onset (p=0.024).

Conclusions: This longitudinal study of FAD, suggests changes in VSTM resolution, which measure precision and thus quality of recall of the memory presentation, may be sensitive markers for tracking and predicting cognitive decline in preclinical AD.

Background

Progressive episodic memory impairment is a central, defining feature of Alzheimer's disease (AD) (1,2). Deficits in short-term memory (STM), the ability to temporarily *maintain* information over seconds (3,4), have been relatively less well studied.

Classically, STM has been tested using 'span' measures where participants are asked to remember a string of stimuli (5). 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 (6) 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. (7–9) rely on remembering a feature and reproducing the exact stored features after a retention period using a *continuous analogue* response space (10–12). In recent studies, delayed-reproduction tasks have been reported to be more sensitive than conventional span measures of STM, especially in clinical populations (13).

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 (14) but with accumulation of β-amyloid (Aβ) (15). 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. 2009; Parra et 2010; Parra et al. 2011; Pavisic, Suarez-Gonzalez, and Pertzov 2020). Interest in these tasks increased, when studies suggested impairments could be detected at asymptomatic 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 (12). FAD is an autosomal dominant condition caused by mutations in either presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*) or amyloid precursor protein (*APP*) (22) and its pathogenic mutations in these genes are nearly 100% penetrant (23). FAD shares many features (i.e. clinical, radiological and histopathological) with sporadic AD (24,25) 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 (23).

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

1. Are the cross-sectional deficits in VSTM binding in preclinical AD also reflected in longitudinal decline in 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 their expected years to onset (EYO) at the time of testing?
3. For comparison, is longitudinal decline of cognition 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 (12) 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 like FAD.

Methods

Study design and participants

Participants were recruited from an ongoing longitudinal FAD study at the Dementia Research Centre, University College London (UCL), 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 for this study 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 (12)).

Mutation analysis was carried out using Sanger sequencing (22,26). 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.

The study thus 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 (27). 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 (12). This was based on an individuals' age at the time of assessment subtracted from the age at which their affected parent developed symptoms (23,28). 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 (PMC) (more than 8.5 years from expected onset), 'late' PMC (at least 8.5 years from expected onset) and controls. The cut-off of 8.5 years corresponded to the median split of PMC in our dataset. Finally, we considered how performance varied continuously with actual years to/from symptom onset (AYO) for symptomatic carriers and PMC 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 non-carriers (16 non-carrier siblings) and 32 mutation carriers, 9 of whom were symptomatic. Differences between our cross-sectional study and Liang and colleagues (12) 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 the supplementary materials for more 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 non-carriers (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 PMC= 3.7 [1.7] years, range=1-6 years; late PMC=3.4 [1.7] years, range=1-6; symptomatic carriers=2.6 [0.7] years, range=2-4)).

Protocol

The study protocol included a clinical and neuropsychological assessment and the *"*What was where?" VSTM experiment (8). Detailed interviews were conducted with individuals at-risk of FAD and their close informants by a neurologist (AOC, YL, PW, NR, NF) to assess for the presence of cognitive or behavioural symptoms attributable to AD. AD was diagnosed in accordance with the Dubois criteria (1,29). Folstein's mini-mental state examination (MMSE) (30), the CDR (27) and Hospital Anxiety and Depression scale (HADS) (31) were administered.

The neuropsychological test battery included measures of several cognitive domains: episodic memory (recognition memory test (RMT) for words and faces; (32)); working memory (digit span (33)); intellectual function (Wechsler Abbreviated Scale of Intelligence (WASI) (34)); executive function (Stroop (35)); confrontational naming (graded naming test (36); vocabulary (British picture vocabulary scale (BPVS) (37)); arithmetic (Graded Difficulty Arithmetic Test (GNT) (38)), visual perception (object decision test from the visual object and space perception (VOSP) battery (39)); speed (digit symbol test (40)) and estimated premorbid intelligence (the National Adult Reading Test) (NART) (41,42) (Table 1).

A depiction of the task is shown in Fig.1 (8,12). 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, they 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 across the experiment.

Participants were required to touch the fractal they remembered from the memory array and drag it on the touch screen to its location. This provided a continuous measure of localisation error. Each participant performed a practice block of 10 trials followed by two test blocks. Each test block consisted 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.

Figure 1. Schematic of "What was there?" (8,12).

In this paper, findings focus on three outcomes which were included in the previous cross-sectional study (12):

- **Identification performance:** proportion of trials where the correct object was chosen.
- **Localisation error:** the distance (in 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 (8,12), 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 (9,12). Results for this outcome are provided in the supplementary materials.

Statistical analysis

Baseline demographics and neuropsychology scores were compared between the symptomatic carriers, early PMC, late PMC 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.

Due to a skewed distribution the absolute localisation error was log transformed and proportion of swap errors was square root transformed before analysis.

a) Cross-sectional analysis

VSTM performance at the baseline visit was compared between symptomatic carriers, early PMC, late PMC 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.

b) Longitudinal analysis

Change over time in VSTM was investigated in three ways: i) comparison of longitudinal change in VSTM performance between symptomatic carriers, early PMC, late PMC 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 VTSM performance and AYO as a continuous measure in the FAD participants where this was known (symptomatic carriers at baseline and late PMC who converted into symptomatic throughout the study-‘converters’). The models examining proximity to onset (EYO and AYO) 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 block and delay 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.

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.

Finally, analysis was conducted to compare longitudinal change in neuropsychology performance between symptomatic carriers, early PMC, late PMC 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).

Results

a) Cross-sectional analysis for N=99

i) Demographics and traditional neuropsychology

Sixty-seven controls and 32 carriers with cross-sectional data were available for the VSTM binding task. Early PMC were on average slightly younger than controls and 12.9 years away from their expected onset. Late PMC were on average 5.8 years before expected onset and had lower education, baseline anxiety and depression scores compared to controls. As expected, symptomatic carriers were older, had lower MMSE and higher global CDR and were on average three years after expected onset at baseline (Table 1).

Early PMC had lower scores in verbal IQ, BPVS and NART measures compared to controls. Late PMC had significantly lower values for verbal IQ compared to controls but similar scores on remaining measures. Symptomatic individuals were on average, significantly worse than controls on arithmetic, RMT for words, digit span, Stroop and verbal IQ scores.

ii) Cross-sectional 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 swaps 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 compared to controls, in the first block longer delay condition (12). Symptomatic carriers made a greater proportion of swap errors than controls in both blocks (both blocks p<0.001), with a larger difference in the 4s delay condition than 1s delay. No significant differences from controls emerged in either PMC group (Fig.2).

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.

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

	Controls (N=67)	Early PMC (N=12)	Late PMC (N=11)	Symptomatic carriers (N=9)	*p* value			
					3-way comparison	Early PMC *vs* controls	Late PMC *vs* controls	Symptomatic carriers *vs* controls
Demographics								
Sex: N (%) Male	34 (50.7)	3 (25.0)	7 (63.6)	6 (66.7)	0.199	0.125	0.524	0.486
Age (yrs)	39.4 (8.1)	34.8 (6.4)	37.0 (5.0)	48.1 (9.8)	**0.001**	0.062	0.341	**0.026**
EYO (yrs)	NA	-12.9 (4.7)	-5.8 (1.8)	-3.0 (4.1)	NA	NA	NA	NA
AYO (yrs)	NA	NA	NA	-3.1 (4.0)	NA	NA	NA	NA
Education (yrs)	15.4 (2.7)	14.3 (2.5)	13.3 (2.5)	13.9 (2.9)	0.053	0.226	**0.023**	0.107
MMSE	29.5 (0.8)	29.3 (0.9)	29.5 (0.8)	25.1 (3.7)	**0.002**	0.297	0.708	**<0.001**
CDR global	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.6 (0.2)	**<0.001**	NA	NA	**<0.001**
Anxiety	6.1 (3.8)	7.9 (4.6)	3.9 (3.9)	7.0 (4.5)	0.083	0.269	**0.035**	0.473
Depression	3.2 (2.8)	2.9 (4.0)	1.3 (1.6)	2.4 (2.1)	0.115	0.355	**0.020**	0.543
Neuropsychology tests								
Performance IQ	110.5 (16.3)	106.0 (15.7)	101.4 (10.1)	100.4 (12.1)	0.192	0.406	0.082	0.109
Verbal IQ	109.9 (14.9)	96.1 (15.1)	95.4 (13.5)	99.4 (18.8)	**0.010**	**0.014**	**0.007**	**0.010**
Arithmetic total/24	16.7 (6.8)	13.9 (5.0)	14.3 (4.6)	10.3 (5.8)	**0.032**	0.160	0.236	**0.007**
RMT faces	41.1 (7.2)	41.0 (4.2)	43.8 (4.5)	40.3 (3.7)	0.254	0.451	0.172	0.354
RMT words	47.0 (5.0)	48.7 (2.2)	46.5 (2.8)	35.3 (10.0)	**<0.001**	0.355	0.124	**<0.001**
Digit span forwards/8	7.1 (1.2)	6.8 (1.0)	7.4 (1.1)	6.0 (1.5)	**0.029**	0.125	0.451	**0.014**
Digit span backwards/7	5.2 (1.2)	5.7 (1.3)	5.4 (1.1)	4.3 (1.6)	0.151	0.166	0.666	0.092
BPVS	142.5 (8.8)	135.0 (14.4)	139.8 (10.1)	135.9 (11.8)	**0.034**	**0.004**	0.205	0.227
GNT/30	20.9 (4.6)	17.8 (5.8)	19.2 (5.4)	18.8 (7.2)	0.332	0.103	0.342	0.439
NART/50	31.8 (8.9)	24.1 (8.6)	27.7 (10.7)	25.4 (13.2)	**0.036**	**0.007**	0.196	0.226
VOSP OD /20	18.0 (2.8)	17.8 (1.8)	18.3 (1.3)	17.6 (1.5)	0.847	0.890	0.550	0.657

Stroop (s)	50.3 (14.0)	45.8 (12.2)	52.6 (14.1)	78.2 (22.4)	**0.007**	0.611	0.586	**0.001**
VSTM performance								
Identification (% correct)								
Overall	91.6 (4.8)	90.2 (6.3)	92.0 (3.9)	81.9 (5.0)	**<0.001**	0.569	0.453	**<0.001**
Localisation error (deg)								
Overall	4.4 (1.3)	4.5 (1.3)	4.6 (1.1)	7.8 (1.8)	**0.002**	0.663	0.410	**<0.001**
Swap error (%)								
Overall	10.6 (5.3)	11.7 (4.7)	10.2 (5.9)	22.6 (8.1)	**<0.001**	0.895	0.615	**<0.001**
Block 1, 1s delay	12.0 (8.4)	12.4 (9.2)	9.9 (5.0)	21.2 (12.6)	**0.441**	0.671	0.865	0.124
Block 1, 4s delay	13.2 (8.7)	18.7 (9.2)	15.0 (10.8)	23.2 (18.0)	**0.027**	0.057	0.996	**0.010**

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 (negative 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 at $p<0.05$.

b) 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 PMC throughout the duration of the study: 12 early PMC, 8 late PMC; 3 converters-participants who were late PMC 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.

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).

i) Rates of change between late PMC, early PMC, symptomatic carriers vs controls

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) (see supplementary materials for more details).

There was no significant difference in the rate of change of identification performance between either PMC group (early or late PMC) and the controls (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.

Localisation performance

Localisation performance of controls (p=0.737) and early PMC (p=0.826) generally stayed the same throughout the course of the study, whereas performance for late PMC (p=0.011) and symptomatic carriers (p=0.033) decreased (see supplementary materials for more details).

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

There was a significant interaction between delay and group in the rate of change (p=0.036), and both item number and (p<0.001) and delay length (p=0.002) had a significant effect on differences in performance between groups. There was a significant interaction of the effect of delay on rate of change in the late PMC group (p=0.013) such that in the 4s delay, but not 1s delay conditions, the late PMC 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). The late PMC group had significantly higher localisation error than controls 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 interaction effects on the rate of change were observed. There were no significant differences between early PMC and controls in any condition.

Swap error performance

Swap error performance for all groups, generally stayed the same throughout the course of the study (controls: p=0.937; early PMC: p=0.231; late PMC: p=0943 and symptomatic carriers: p=0.237) (see supplementary materials for more details).

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

Although there was only weak evidence towards an interaction of block (p=0.086) and delay (p=0.089) for their effects on the differences in rate of change between groups, we specifically examined the 4s delay of block 1 following Liang and colleagues finding of higher swap errors in presymptomatic carriers in this condition (12). While there was a trend for higher swap error proportion for the late PMC group compared to controls (p=0.099, Table 2), this effect did not reach statistical significance. No differences were observed for the early PMC *vs* controls and despite 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. Comparison in the rates of change of VSTM metrics compared to controls.

Change per year	Early PMC		Late PMC		Symptomatic carriers	
	Mean* [95% CI]	*p* value	Mean* [95% CI]	*p* value	Mean* [95% CI]	*p* value
Identification performance: Odds ratio						
Overall	1.01 [0.91, 1.13]	0.830	0.95 [0.84, 1.07]	0.395	0.85 [0.73, 0.99]	**0.036**
Localisation error: %						
Overall	-0.1 [-3.8, 3.7]	0.946	3.6 [-0.4, 7.9]	0.082	6.5 [-0.4, 13.9]	0.066
3-items	0.9 [-3.0, 5.0]	0.644	3.6 [-0.7, 8.1]	0.099	6.9 [-0.5, 14.7]	0.068
3-items, 1s delay	-0.8 [-5.2, 3.8]	0.732	0.6 [-4.1, 5.6]	0.800	9.0 [0.3, 18.5]	**0.043**
3-items, 4s delay	2.7 [-1.9, 7.4]	0.252	6.9 [1.8, 12.2]	**0.008**	4.7 [-3.9, 14.2]	0.295
1-item	-3.9 [-9.1, 1.7]	0.169	3.8 [-2.3, 10.3]	0.230	5.0 [-5.9, 17.0]	0.384
1-item, 1s delay	-5.5 [11.0, 0.4]	0.065	0.7 [-5.6, 7.5]	0.825	7.1 [-4.9, 20.5]	0.260
1-item, 4s delay	-2.2 [-7.9, 3.9]	0.467	7.0 [0.2, 14.2]	**0.043**	2.8 [-8.6, 15.7]	0.640
Swap error: √proportion						
Overall	-0.009 [-0.030, 0.012]	0.389	0.001 [-0.022, 0.024]	0.917	-0.015 [-0.045, 0.014]	0.309
Block 1, 4s delay	0.004 [-0.028, 0.036]	0.830	0.029 [-0.005, 0.063]	0.099	-0.002 [-0.049, 0.045]	0.946

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

Figure 3.Longitudinal adjusted estimated meanperformance 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.

ii) Relationship between VSTM performance and proximity to symptom onset

Identification performance

Considering symptomatic and presymptomatic carriers together, no significant association between identification performance and EYO emerged ($p=0.120$, Fig.4A), nor were there any significant interactions between task-conditions. However, identification performance significantly decreased with AYO in the subgroup analysis of symptomatic carriers and converters ($p<0.001$) (Fig.4B).

Localisation performance

For symptomatic and PMCs (early and late) together, a significant association between EYO and worse localisation error ($p=0.024$) was observed. 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 statistically 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 significantly increased with AYO within symptomatic carriers and converters (p<0.001) (Fig.4E).

Swap error proportion

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

Figure 4. Relationship between VSTM performance and proximity to symptom onset.. Predicted mean (from model adjusted for age, sex and NART) performance. The first row shows **identification performance** results (across all conditions): **A.** Against EYO. **B.** Against AYO and **C.** individual unadjusted data per visit (each line represents a participant). The second row shows **localisation error** results (for the 3-items, 4s delay condition): **D.** Against EYO; **E.** Against AYO and **F.** individual unadjusted data (each line represents a participant). The third row shows **swap error proportion** results (across all conditions): **G.** Against EYO; **H.** Against AYO and **I.** individual unadjusted data (each line represents a participant). Converters are PMC who converted to 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. Shaded area indicates 95% confidence intervals.

iii) 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.

Evidence for a greater reduction in task performance for late PMC *vs* controls was observed in recognition memory test (RMT) for words with 35 [45.6-22.2]% greater rate of decline per year, (p<0.001) and a significant difference from controls 3 years after baseline (71.2 lower odds of correct response [22.9-89.3]%). A difference between controls and early PMC group was seen for RMT for faces although in the opposite direction to that expected (early PMC: 13.7 [1.0-28.0]% greater *increase* in performance per year, p=0.034). No further significant group differences emerged. While verbal and performance IQ measures showed lower values for presymptomatic carriers at baseline, there was no evidence for a faster rate of decline compared to controls (VIQ: early PS: 0.9 [-1.1, 2.9] points per year, p=0.398; late PS: -0.0007 [-2.3, 2.3], p=1.000; PIQ: early PS: 0.07 [-1.5, 1.6] points per year, p=0.930; late PS: -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 (62% greater decline per year, OR=0.34 [0.13,0.91], p=0.031)

Discussion

Summary of results

In this longitudinal study of VSTM in FAD we show that late' PMC (within 8.5 years of estimated onset) had a faster decline in the rate of localisation performance in long-delay conditions, compared to controls, with a significant difference apparent approximately 2 years after the baseline visit. This effect preceded changes in traditional measures of verbal episodic memory, which were observed approximately 3 years after the baseline visit. Localisation error was also the only VSTM metric to show a significant association with EYO with strongest effects observed in long-delay conditions up to 6 years prior to estimated symptom onset. As these effects were predominantly present in longer delay conditions, the impairment may be related to difficulty in maintenance processes rather than memory encoding or retrieval. Taken together, findings suggest localisation performance may be sensitive to tracking decline in the preclinical stages of the disease.

Symptomatic carriers showed progressive increases in localisation errors over time but we only found significant effects in one condition, most likely due to small numbers in this group. Identification performance showed a significant difference in the rate of change between symptomatic carriers and controls and a significant association only with AYO (as opposed to

EYO and AYO). Although such findings may be due to perceptual difficulties, the significantly faster rate of decline in the digit span backwards task but not in visual perception (VOSP) in traditional neuropsychology tests, suggests perceptual difficulties unlikely explain all effects.

Integrating VSTM results with previous literature

Cross-sectional findings revealed VSTM impairments for object identity, localisation and binding in symptomatic carriers but not in PMC groups. Unlike data reported from our centre by Liang and colleagues, there was no evidence in the cross-sectional study for a binding deficit in our sample of PMC (12). No differences in the rate change of swap errors were observed from controls either. As a relatively accurate localisation is required for a response to count as a swap (it must be localised 'close enough' to another location), binding deficits may have been underrepresented in our sample (in both symptomatic and PMC) especially in light of the localisation error finding. Whilst it is possible that with a later longitudinal sample, we may have observed relational binding deficits in PMC, the lack of significant association with EYO suggests other factors (i.e. chance, gene and mutation heterogeneity or lower sensitivity of a binary measure *vs* a continuous one) may also contribute. The non-significant interaction between the rate of swap error proportion and delay was surprising however, repetitive exposure to the task over time, may have predisposed individuals to develop strategies specific to the binding of the object's identity to its location. In addition, the worsening localisation particularly for longer delays may have veiled this interaction.

We speculate our longitudinal findings may be explained by a 'unified account of hippocampal forgetting across short and long timescales', proposed recently (43). 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). As the precision of localisation performance gradually declined with time (instead of demonstrating a complete loss of access), we propose that a process similar to accelerated forgetting may be behind the deficits observed in 'late' PMC, whereby forgetting over just a few seconds is associated with decreases in precision at an abnormally rapid rate in this group with time. As this effect was observed for the localisation error measure this suggests the association of the object's identity to *its location* may have been predominantly forgotten at a faster rate.

A previous study in sporadic AD (as opposed to FAD), compared the performance of VSTM change detection performance (detecting whether successive images changed or not) and visuospatial STM (VSSTM) (detecting whether the same image had changed in location or not) in MCI and AD groups (44) and concluded VSSTM deficits appeared in earlier phases of AD (i.e. in MCI patients *vs* AD) and were more likely to have memory rather than attentional origins. As localisation error had perhaps the greatest sensitivity to spatial resolution-measured in a continuous scale, at the resolution of pixels, it is possible that it was the only metric sensitive enough to detect subtle cognitive change in this patient cohort.

Limitations

The current study has several limitations. First, despite the increased sample size in comparison to the previous cross-sectional study (23 presymptomatic carriers in this study *vs* 12 presymptomatic carriers in (12)), 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 (23,45–47). 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. In addition, the 'late' PMC was 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 inevitable imprecise given the within-family variation in age at onset (23). Lastly, the qualitative observation of VSTM performance in 'converters' showed that for all VSTM metrics, performance did not follow a unique pattern. For some participants, scores worsened while for others they remained stable. This provides important information on the value of this task at an individual level, although more data points are needed to evaluate this further.

Conclusion

In summary we present the first longitudinal study of a VSTM binding in FAD, to the best of our knowledge. Our findings highlight that evaluating the *degree* of error on a continuous scale may be a sensitive measure of longitudinal decline in the preclinical stages of FAD, worth further exploration. Analogous to the accelerated-forgetting hypothesis, we speculate a similar phenomenon may explain VSTM deficits in presymptomatic FAD-whereby the ability to spatially remember and retain information is forgotten with time at an 'accelerated rate' compared to controls. Future studies considering correlations with functional outcomes and hippocampal volume or amyloid beta deposition, should determine its use as a clinical tool both in the screening and monitoring of the conditions like FAD.

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

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Authors contributions

IMP: drafted the manuscript; acquired and interpretated the data; critically revised the manuscript. JMN: analysed the data; provided statistical support for interpretation of results; critically revised the manuscript. YP: conception/design of the study; data interpretation; critically revised the manuscript. AOC: acquired clinical data; critically revised the manuscript. YL: acquired the data; critically revised the manuscript. JDC: acquired the data; critically revised the manuscript. KL: provided support for the interpretation of the data; critically revised the manuscript. PSJ: acquired the clinical data; critically revised the manuscript. NSR: acquired the clinical data; critically revised the manuscript. MH: conception/design of the study; critically revised the manuscript. SJC: conception/design of the study; data interpretation; critically revised the manuscript. NCF: conception/design of the study; data interpretation; principal investigator of the study; critically revised the manuscript. All authors have read and approve of the final manuscript.

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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.

Ethics approval and consent to participate

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, REC ref 11/LO/0753).

Consent for publication

Not applicable.

Declaration of interests

I.M. Pavisic; J.M. Nicholas; Y. Pertzov; A. O'Connor; Y. Liang; J. 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.

Competing interests

The authors have no competing interests to report.

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Figures

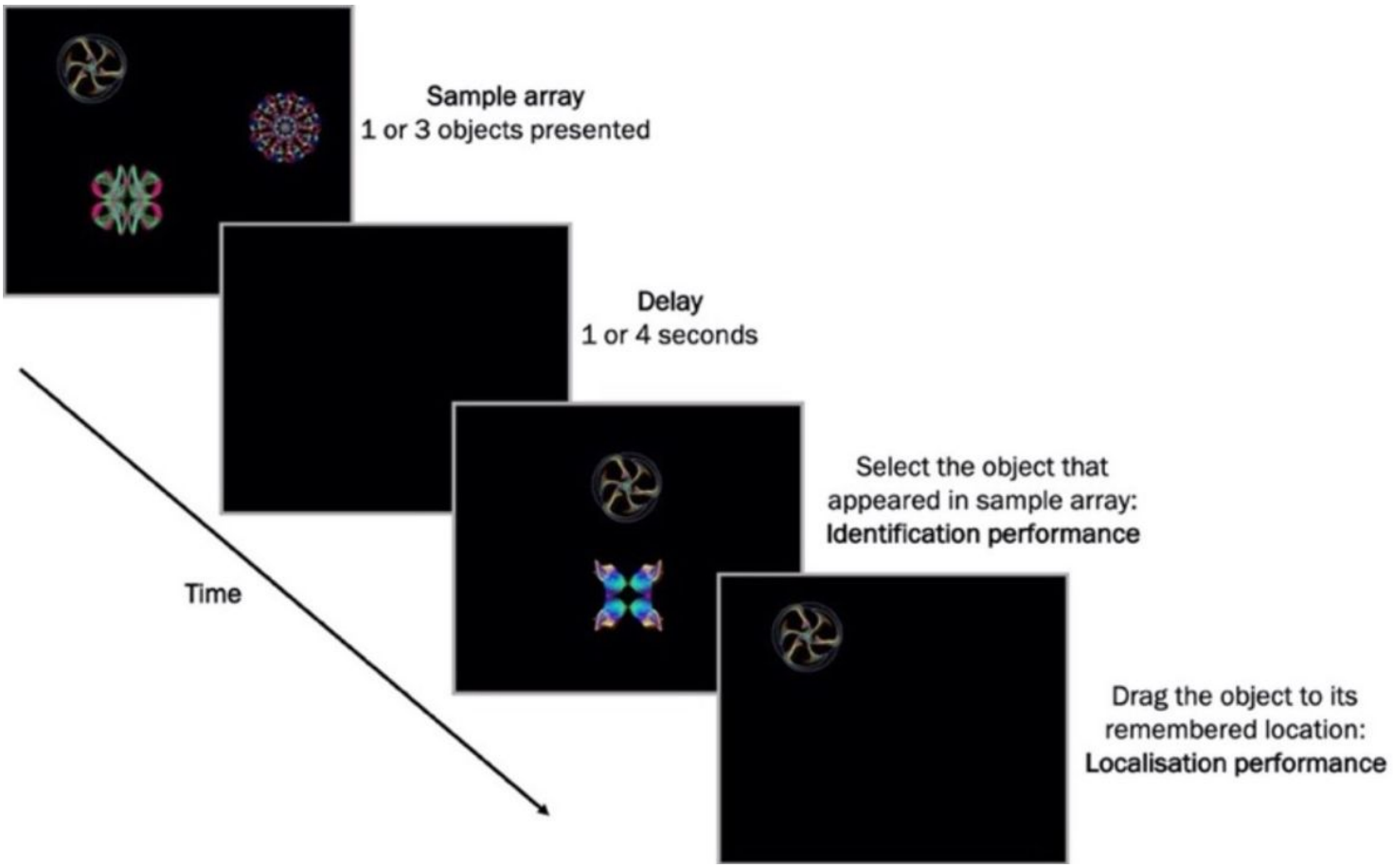

Figure 1

Schematic of "What was there?" (8,12).

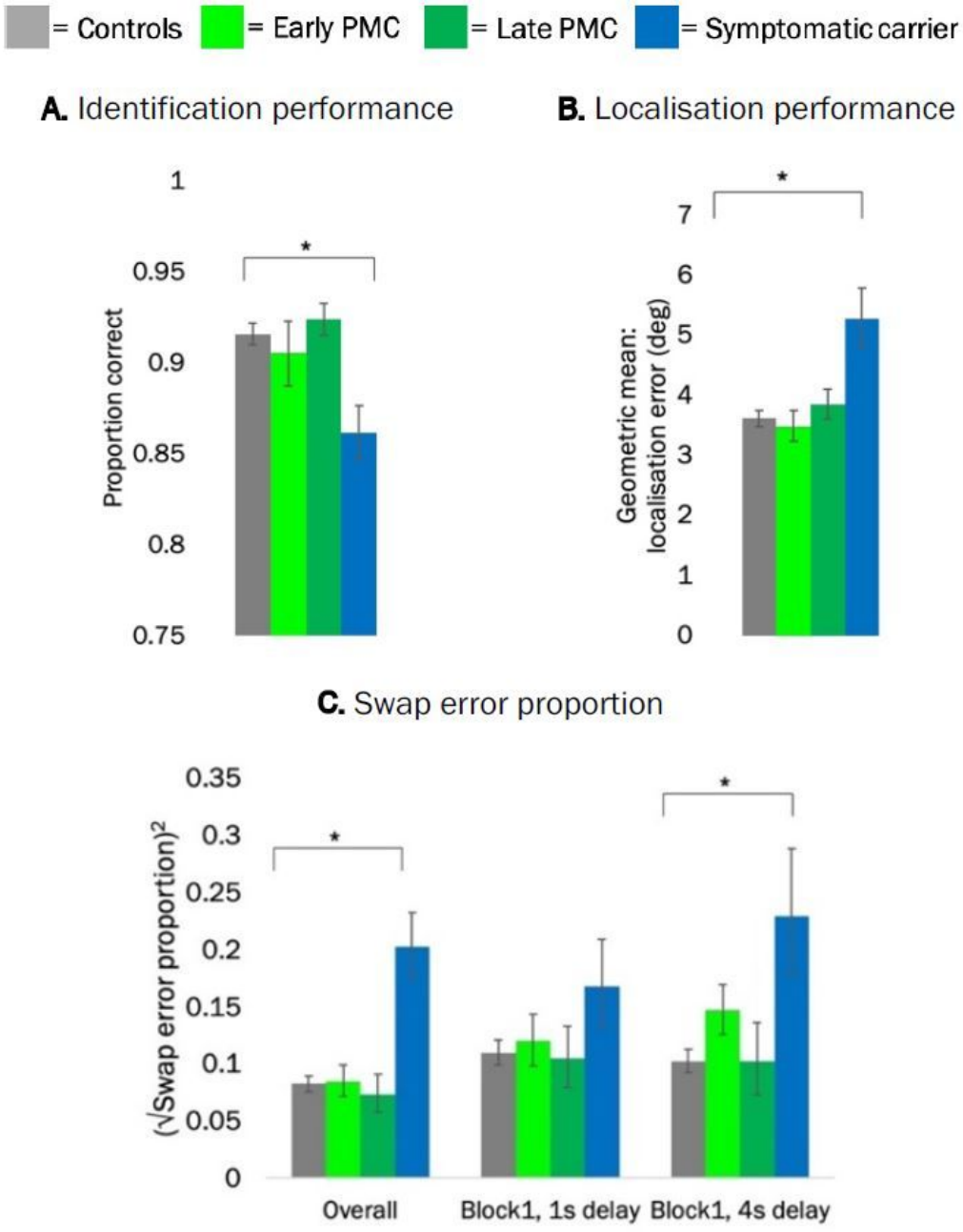

Figure 2

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 $p<0.05$.

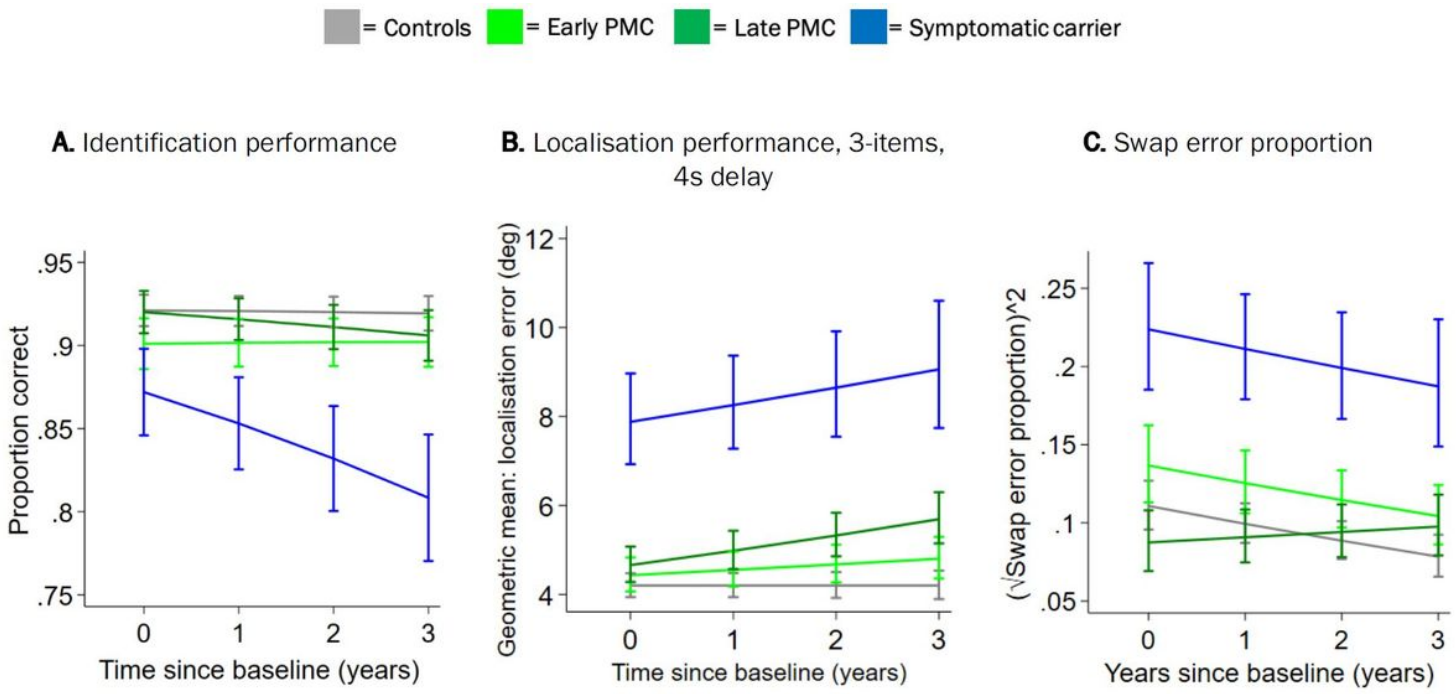

Figure 3

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.

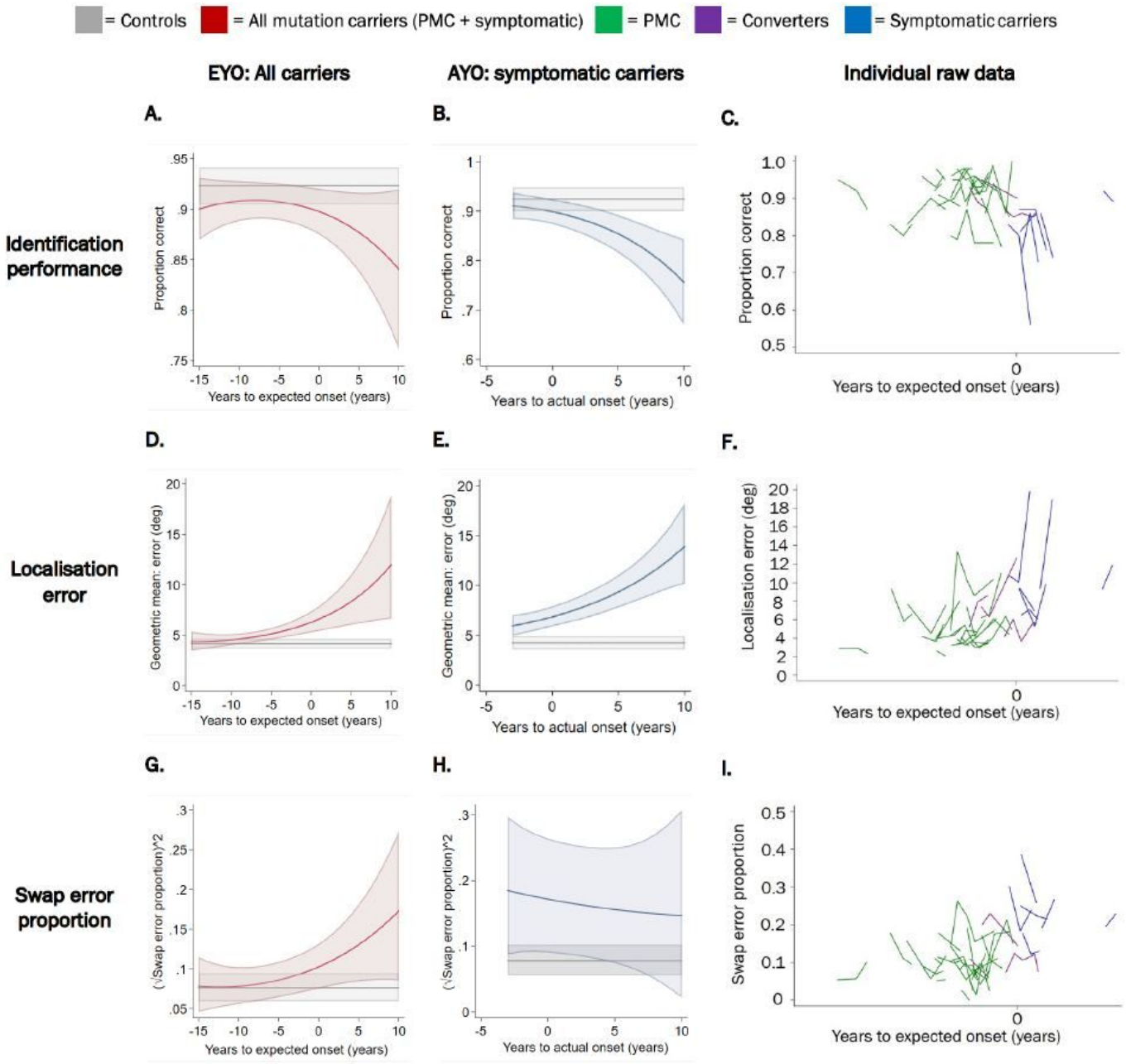

Figure 4

Relationship between VSTM performance and proximity to symptom onset. Predicted mean (from model adjusted for age, sex and NART) performance. The first row shows identification performance results (across all conditions): A. Against EYO. B. Against AYO and C. individual unadjusted data per visit (each line represents a participant). The second row shows localisation error results (for the 3-items, 4s delay condition): D. Against EYO; E. Against AYO and F. individual unadjusted data (each line represents a participant). The third row shows swap error proportion results (across all conditions): G. Against EYO; H. Against AYO and I. individual unadjusted data (each line represents a participant). Converters are PMC who converted to 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. Shaded area indicates 95% confidence intervals.

Supplementary Files

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