The mid-life cognitive profiles of adults at high risk of late-onset Alzheimer's disease: the PREVENT Study

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Abstract

While biomarker studies of late-onset Alzheimer's disease suggest pathology to be present decades before diagnosis, little is known about cognitive performance at this stage. A sample of 210 adults (aged 40-59) of whom 103 have a parent diagnosed with dementia (FH sub-group), underwent computerized cognitive testing. ApoE status was determined and 193 subjects had magnetic resonance (MR) imaging. Distance from dementia onset was estimated in relation to age of parental diagnosis and CAIDE Dementia Risk Scores were calculated. Lower hippocampal volumes ($p=0.04$) were associated with poorer spatial location recall and higher DRS with poorer visual recognition ($p=0.0005$), and lower brain and hippocampal volume (($p<0.0001$) ; $p=0.04$ respectively). FH participants closer to dementia onset had lower scores on visual working memory ($p=0.05$) while those with an ApoEε4 allele performed better on form perception ($p=0.005$). Middle-aged adults at risk of dementia show evidence of poorer cognitive performance, principally in visuospatial functions.

Introduction

Both epidemiological and biomarker studies of high risk groups suggest that late-life Alzheimer's disease (AD) pathology may be present decades before a clinical diagnosis of dementia [1-3]. These observations are further supported by autopsy studies tracking amyloid and tau pathology from childhood through mid-life [4] . Furthermore as exposure to the principal cardiovascular and metabolic risk factors commonly begins in mid-life, this preclinical period is increasingly considered to constitute a critical window for secondary prevention [5]. Theoretical models of the temporal order of changes in these markers have hypothesized that amyloid-β (Aβ) accumulation is an early change followed by markers of neurodegeneration (tau accumulation and structural/metabolic abnormalities), with cognitive decline occurring only at the end of this pre-clinical period in a prodromal phase just prior to a dementia diagnosis [6]. The construction of biomarker and cognitive trajectories in the decade preceding diagnosis based on empirical observations has suggested an alternative model in which cognitive changes may not only parallel but also interact with biomarker changes [7].

A recent review of pre-clinical neuroimaging studies and prospective cohorts concluded that alterations in cognitive function may be detected at this stage but on a much narrower range of functions than in dementia, with patterns of deficit changing with distance from (i.e. length of time before) dementia diagnosis [8]. While longitudinal studies indicate amyloid load to be frequently associated with episodic and semantic memory and executive functions [9,10], these changes are observed principally in the prodromal period. A central problem has been that the cognitive measures used in AD research, being based on tests used to detect dementia rather than on the underlying neuropathological changes, may be insufficiently sensitive to the subtle focal brain changes occurring in the pre-clinical phase.

With increasing interest in the development of public health strategies to reduce dementia risk and drug development for up-stream secondary prevention, the middle-aged offspring of recently diagnosed persons with dementia, especially those at genetically higher risk, are an obvious target group for investigation and ultimately therapeutic intervention. A central methodological problem is the improbabilityof being able to track young at-risk cohorts for decades following an intervention until dementia diagnosis in order to be able to establish efficacy. Intermediary outcome measures are therefore required, but while a number of clinical, cognitive and biomarkers have now been demonstrated to show changes in the years immediately preceding dementia, we have little knowledge as to how well they perform at such an early stage. The PREVENT Dementia Programme [11], initiated in 2013, is a prospective study of the adult children of persons with dementia designed to seek out clinical and biological changes which may subsequently be used as short-term outcome measures for mid-life secondary preventions. This multi-centre study has incorporated both cerebral imaging and a battery of computerized cognitive tests designed to cover a much wider range of cognitive functions than is normally used in studies of pre-clinical dementia. The baseline results from the pilot phase of the PREVENT Dementia programme carried out in West London are used within the present study to examine associations between cognitive performance and multiple indicators of dementia risk (family history, genetic vulnerability, brain biomarkers and a composite dementia risk score based on cardiovascular measures). The principal hypothesis of the study is thus that persons with a high probability of manifesting pre-clinical AD may manifest subtle cognitive changes in comparison to persons with low risk on testing procedures designed to assess cognitive processing rather than to detect dementia.

METHODS

The protocol for the PREVENT study has been described in detail elsewhere [11] **http://bmjopen.bmj.com/cgi/content/full/bmjopen-2012-001893.** Participants aged 40 to

59 were recruited through multiple sources. Initially they were identified from the dementia register (DemReg) database held at West London Mental Health NHS Trust (WLMHT), part of the U.K. National Health Service. This registry holds information on patients with dementia and cognitive impairment who have consented to be approached for clinical research and their carers (often children). Other participants were recruited via the Join Dementia Research website (https://www.joindementiaresearch.nihr.ac.uk/), through information about the study on the internet and public presentations. Of the 210 persons (62 men; 148 women) now recruited at baseline, 103 have at least one parent with a dementia diagnosis, referred to as the family history (FH sub-group).

Consent and organisation of examinations

Consented participants were seen at the West London Cognitive Disorders Treatment and Research Unit, WLMHT where they were given a standardized neuropsychiatric interview and life-style questionnaires. Blood was taken for ApoE genotyping with all members of the research and clinical teams remaining blind to the result. Approval for the study has been given by the NHS Research Ethics Committee London Camberwell St-Giles.

Cognitive testing

The COGNITO neuropsychological battery is designed to examine cognitive processing across a wide range of cognitive functions in adults of all ages, and not restricted to those functions usually implicated in dementia detection in the elderly . The cognitive areas assessed by COGNITO, by order of presentation, are Reaction Time; Reading; Comprehension of Phonemes, Phrases and Syntax; Focused and Divided Attention in both visual and auditory modalities; Visual Working Memory (visual tracking with auditory interference); the Stroop test; Immediate, Delayed and Recognition trials for Verbal Recall (name list); Delayed Recognition of Spatial stimuli (faces); Visuospatial Associative Learning; Visuospatial span; Form perception; Denomination of common objects; Spatial reasoning; Copying of meaningful and meaningless figures; Verbal Fluency with semantic and phonetic

prompts; Immediate Recall of a narrative; Immediate Recall of a description of the relative position of objects; Vocabulary; Implicit Memory (recognition of new and previously learnt material). The full battery takes approximately 40 minutes and is described in detail in the manual

http://inserm-neuropsychiatrie.fr/sites/default/files/documents/COGNITO_MANUAL.pdf

A detailed description of the neuropsychological basis of test construction and item selection is given in Ritchie et al. [12]. Participants respond using a touch-sensitive screen which records correct responses and response latencies.

Imaging

Participants underwent multimodal 3T structural MRI on a single scanner including volumetric T1-weighted scans (176 slices, 1.0 x 1.0 mm, 1.0 mm slice thickness, TR = 2300ms, TE = 2.98ms, flip angle 9°). Brain tissue segmentation into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) was performed using the Gaussian mixture model in VBM toolbox of SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The GM maps were then normalized using the DARTEL algorithm [13]. Hippocampal region of interests (ROIs) were selected using AAL atlas in MNI space [14], and then inverse normalized back to each subject's native space using the participant-specific diffeomorphic parameters estimated from the previous DARTEL procedure. The resulting ROIs were also masked using the thresholded GM probability maps (at threshold $p > 0.8$) before the total hippocampal volume was calculated. Finally in order to control for global volume effects, the hippocampal volumes were normalized by the estimated total intracranial volume (ICV).

Genotyping

Taqman Genotyping was carried out on QuantStudio12K Flex to establish ApoE variants. Genomic DNA was isolated from whole blood and genotyping was performed in 384 well-plates, using the TaqMan polymerase chain reaction-based method. The final volume PCR

reaction was 5 µl using 20 ng of genomic DNA, 2.5 µl of Taqman Master Mix and 0.125µl of 40x Assay By design Genotyping Assay Mix, or 0.25µl of 20x Assay On Demand Genotyping Assay. The cycling parameters were 95° for 10 minutes, followed by forty cycles of denaturation at 92° for 15 seconds and annealing/extension at 60° for 1 minute. PCR plates were then read on ThermoFisher QuantStudio 12K Flex Real Time PCR System instrument with QuantStudio 12K Flex Software or Taqman Genotyper Software v1.3.

Statistical analyses

Hypothesized distance to a dementia diagnosis for FH participants was calculated from the difference between the participant's age and the age of dementia diagnosis in their parent following Bateman et al. [15] as a proxy for stage of pre-clinical disease progression.

Dementia Risk Scores (*DRS*) were calculated for each participant irrespective of family history of dementia using the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score [16]. This is a risk score validated within prospective population studies composed of cohort-based weightings by reference to the following variables: age, education, sex, systolic blood pressure, body mass index, total cholesterol, physical activity, ApoE status. Scores vary from 0 to 15 and are treated as a continuous variable in the present analyses.

Comparisons of sociodemographic characteristics and prevalent pathologies between FH and non FH groups were performed using Chi square tests for categorical variables and Wilcoxon two-sample tests for those continuous variables (age and BMI) which were not normally distributed.

Ten cognitive summary variables from the COGNITO battery were considered as dependent variables: [1] working memory (total number of correct answers for form recognition in double task design and difference of the mean time in milliseconds between the double task and the simple task), [2] narrative recall (total number of correct answers), [3] description recall (total number of correct answers), [4] implicit memory (difference in the number of steps in the

progressive build-up of names on the screen between the number of names never seen and the number of names already learnt), [5] name-face association (number of correctly recognized faces and visual recognition of their corresponding names), [6] form perception (number of correct answers) and [7] (mean time for correct answers), [8] phoneme comprehension (total correct responses) and [9] (mean time for correct response), [10] verbal fluency (sum of the number of words generated using both a semantic and phonemic cue). If normally distributed these variables were analyzed with linear regression, otherwise with logistic regression models after dichotomization according to the median. Linear regression models adjusted for gender were used for analyzing brain volumes as dependent variables.

RESULTS

Sample description

The participants were principally white (90%). Educational levels were post-graduate (29%), trade or technical skills (15%), college graduates (33%), high school (23%) and one person with no education. No statistically significant differences were found between persons with and without a family history of dementia in relation to age, gender, hypertension, depressive symptomatology, diabetes or BMI (Table 1). The FH sub-group (n=103) had a lower level of education (p=0.003) and a higher prevalence of the ApoE $\varepsilon 4$ allele (65%) than the non-FH group (28%). High rates of head injury were observed for the group as a whole (38.6%), but no statistically significant difference was found between participants with and without a family history (p=0.56). Overall DRS mean (SD) was 5.94 (2.90) in the range 0 to 15. For the FH group, the mean age of dementia diagnosis in parents was 76.2 years, (SD 7.49). Type of dementia in the parents as declared by the children were AD for 56 participants, mixed AD for 20, vascular dementia for 16 and unknown for 11 participants.

Table 1 here

Associations between indicators of dementia risk and brain volumes

The FH group was observed to have a significantly higher DRS than controls (mean (SD) of 6.51 (2.51) vs 5.40 (3.15), p=0.0055). No significant association was observed between brain volumes and either FH or ApoE status (ANOVA, p≥0.25), but in simple linear regression DRS in the whole sample was significantly associated with total brain volume (R-squared=0.016, p=0.08), whole brain GM volume normalized by total intracranial volume (R-squared=0.094, p<0.0001) and hippocampal volume (average of left and right hemispheres and normalized by total intracranial volume) (R-squared=0.022, p=0.04). However, the R-squared are low suggesting that only a small part of DRS variability is explained by brain volumes. In the FH group no significant association was found between DRS and estimated time to dementia (linear regression, n=100, p=0.26).

Cognitive performance and indicators of dementia risk in the whole sample

The association between cognitive outcomes and age, family history, ApoE status, education and head injury was first examined individually by univariate analyses (Table 2). It was observed that while age, education and head injury were significantly associated with performance on some cognitive tasks, neither family history of dementia nor ApoE status alone were found to differentiate cognitive performance in the group as a whole.

TABLE 2

When indicators significantly associated with cognitive performance were included together in a multivariate model the results were only slightly modified: age (p=0.03) and years of education (p=0.003) for name-face association, years of education (p=0.0003) and loss of consciousness (p=0.03) for narrative recall and years of education (p<0.0001) and loss of consciousness (p=0.09) for description recall.

A higher DRS was associated with poorer performance on name-face associative learning (OR=1.4 CI 1.04-1.26 p=0.008) and phoneme comprehension time (β(SE)=16.7(7.24) p=0.02), approaching significance on form perception (response time) (β(SE)=64.4(34) p=0.06) within univariate models (Table 2). Multivariate linear regression with stepwise selection of cognitive variables showed DRS to be associated with significantly poorer performance on visually presented name recognition (F=12.61 p=0.0005) and a very slight association with response speed on comprehension (F=5.28 p=0.02).

Cognitive performance and indicators of dementia risk in the FH group

A statistical interaction between FH of dementia and ApoE ε4 was found for the number of correct answers in the form perception task (p=0.007). In the FH group only, participants with an ApoE ε4 allele had more correct responses, the probability of having poor performance being lower (OR=0.29; CI 0.12-0.69; p=0.005). This association was not significant in the non FH group (p=0.32). In the FH group, estimated closer distance to dementia diagnosis was found to be associated with poorer performance in visual working memory (difference in mean time between the double task and the simple task) (β(SE)=80.3(40.0) p=0.05) in a simple linear model.

Cognitive performance and brain volumes

Univariate analyses showed gender-adjusted associations between description recall and both total brain volume and hippocampal volume (Table 3).

TABLE 3

Age was found to be significantly associated with brain volume/cranial volume only. After adjusting for gender and age the association between brain volume/cranial volume ratio and comprehension response time lost significance (β(SE)=0.0006%(0.0004) p=0.13).

DISCUSSION

Overall we observed in this middle-aged cohort that persons with a family history of dementia have a higher dementia risk according to the CAIDE criteria, and also higher rates of the ApoE ε4 allele as previously reported by Scarabino et al. [17]. However, we observed no difference in relation to cognitive performance between FH and non-FH groups. Bateman et al. [15] have previously demonstrated that the difference between current age of persons with a family history of dominantly inherited AD and parental age of AD onset may be used as a proxy for pre-clinical staging. Given that age of onset of late-onset AD has also recently been shown to have a strong genetic component, with greater genetic influence being related to earlier onset [17 18], we have used this difference as a means of refining familial risk to incorporate a possible pre-clinical staging indicator. Interestingly we observed that FH participants closer to estimated age of onset showed poorer performance on visual working memory. It should be noted, however, that "time to dementia" is an exploratory measure designed only as a proxy for sub-clinical disease progression (if there is any) and requires validation within longer term prospective studies. FH participants with an ApoEε4 allele were observed surprisingly to perform better on a geometric form matching task. This task measures form perception with no recall component. We have no clear explanation of why this should be performed better in this normally high risk group. This does not appear to be because at risk subjects were taking longer to perform a task they found more difficult and therefore making less errors, as we observed no differences in response time. A possible explanation may be the young age of our cohort, given that previous research has suggested that the ApoE e4 allele, while being associated with a number of poorer health outcomes in old age, may have a positive effect earlier in life, being associated with higher IQ and a more economic use of memory-related neural resources in young healthy humans [19].

For the cohort as a whole a high CAIDE dementia risk score was found to be associated with

poorer visual association learning, and a decrease in both brain volume/cranial volume ratios and hippocampal volume. The latter observation is consistent with recent findings by Enache et al. [20] reporting an association between CAIDE score and medial temporal atrophy. Poorer performance on a test requiring recall of spatial configuration was found to be associated with both total smaller brain volume and smaller hippocampal volumes in the group as a whole. While the original CAIDE validation study was carried out on a population cohort likely to be closer to dementia diagnosis (up to 20 years before) than the PREVENT participants, a recent study by Exalto et al [21] has demonstrated its validity up to 40 years before thus making it relevant to this study. It is an important observation from our work that the CAIDE score is already impacting on measures of brain health both in terms of biology (brain volumes) and behavior (cognition) in mid-life. This suggests a therapeutic opportunity by which reduction in an individual's CAIDE score or avoidance of its increase through better cardiovascular health may affect longer-term outcomes.

Overall our results suggest that having a parent with recently diagnosed dementia is not in itself associated cross-sectionally with poorer cognitive performance at this early stage. However, having either a) a family history and being closer to hypothesized age of onset b) having smaller hippocampal and/or whole brain volumes, or c) a higher dementia risk score is associated with poorer performance on a very small number of cognitive tests which have notably a strong spatial component. A weak association also reported between comprehension response time and dementia risk score may reflect either a slowing in syntactic comprehension or also given the spatial component of this task (identifying the position of stimuli) be related to spatial analysis. The pattern of cognitive deficit differs, however, according to the definition of risk used (family history, ApoE allele, dementia risk score or estimated distance to dementia).

Previous cross-sectional studies of pre-clinical AD have shown virtually no association between cognitive performance and brain changes [22-24], but it may be that this is due to

the limited range of tests which have been used. While some prospective studies indicate differences in slope in episodic memory, semantic fluency and executive functions [25 26] these associations are mostly observed in the period up to 5 years before dementia diagnosis [27-30]. A case control study with ten year follow-up by Laukka et al. found a range of deficits could be observed up to ten years before diagnosis with visuospatial deficits preceding changes in episodic and semantic memory [31]. Bilgel et al. [32] on the other hand observed verbal episodic memory to be impaired before visuospatial memory, however, the visual stimuli used were geometric shapes which tend to be memorized by verbal mediating processes. The authors also noted that immediate recall is more sensitive than delayed recall in pre-clinical AD. We observed no association at this preclinical stage in the tests most commonly used previously to assess immediate episodic memory. However, the COGNITO battery also includes immediate recall of a description which does not rely on logical verbal sequencing but rather on capacity to visualize and recall the relative spatial location of random objects, the length and semantic structuring of this test being comparable to that of narrative recall. This test, but not narrative recall, was found to be associated with both total brain volume and smaller hippocampal size, again suggesting the increased sensitivity at this stage of spatial tests. This difference in performance between two tests of similar difficulty level but different content, normally performed at a similar level in normal adults, is suggestive of an early decrement, probably in spatial memory and analysis, however the difference is small and may also be due to other factors such as poorer recall of non-logically related events.

One of the most striking features of previous studies of pre-clinical AD overall has been their focus on tests of executive functions and verbal episodic memory and the relative absence of purely spatial tasks. While spatial navigation tasks in particular are considered to be highly sensitive to changes in this area of the hippocampus, only one recent study has investigated the potential of spatial navigation in the pre-clinical stage of AD; showing significant

decrements between cerebrospinal $A\beta_{42}$ positive and negative persons [33]. In this younger group we did not have a specific navigational task but found some modest differences in tests which rely predominantly on more general visuospatial processing. It is possible that more significant differences may have emerged had we used this type of task. Histopathological studies point to the transentorhinal cortex as the first anatomical region affected by AD followed by the entorhinal cortex and hippocampus, with evidence from lesion studies in these areas in humans and experimental animals [34 35] and functional neuroimaging in normal adults [36] indicating that a decline in visuospatial memory and spatial location to be primary candidates for an early marker. Longitudinal studies of prodromal dementia and MRI imaging suggest that mediotemporal lobe atrophy in preclinical cases may be demonstrated by tests of visuospatial analysis tasks even before evidence on brain imaging [37].

While the hippocampal formation is recognized as one of the first brain regions to be compromised by AD-related pathology, there has been a tendency to focus on its role in episodic memory while neglecting its other pivotal functions, notably in spatial navigation, spatial memory and the integration of spatial location with episodic memory [38]. Examining persons at risk decades before likely dementia onset we were unable to detect an association between dementia risk and cognitive performance on most of the tests commonly used in studies of prodromal AD, but some evidence of decrements were observed in tests implicating predominantly spatial functions. Our preliminary results underline the need for improved spatial testing procedures able to target regions implicated in spatial analysis and binding such as the entorhinal cortex, precuneus and retrosplenial cortex; regions in which both tau and abeta pathology both initially co-occur [39 40].

CONCLUSION

Middle aged adults with at least one parent recently diagnosed with dementia are prime targets for intervention strategies, not only because they are highly motivated but also because they are entering a period of exposure to a number of well-established risk factors such as diabetes and cardiovascular disease. They may also be showing the first brain changes. While such interventions may be assessed in relation to biomarkers, cognitive functioning will always remain a central clinical concern and a principal outcome measure. Findings from the present study suggest that persons with a high risk for late-onset dementia show some evidence of poorer cognitive performance in a number of areas, varying according to the definition of type of risk (family history, genetic vulnerability, estimated time to dementia diagnosis, dementia risk score). These changes appear to have in common a strong spatial component. Our findings draw attention to two important points: first, that many of the dementia-based cognitive tests now being integrated into research protocols for pre-clinical AD do not appear to be discriminative at this early stage and second, that future pre-clinical test development should focus more on spatial and navigational tasks. The aim of this study is to provide exploratory descriptive data for research purposes and which may ultimately be used to improve early clinical diagnosis but at present cannot be used for individual examinations or to inform persons of their risk status. Furthermore the study is cross-sectional and requires confirmation from prospective follow-up of the cohort as decline across time may prove to be a more sensitive measure. There is also the possibility that some of our negative results have been due to lack of power as power calculations have been based on studies with slightly older participants. Moreover, some of the parents of the participants have probably had non-AD dementia (according to the reports of their offspring around 15%) and this may have weakened some of the associations described here.

The PREVENT Dementia Program is ongoing with recruitment eventually of 700 further participants by 2017 and incorporating in the second wave new tests designed to be more sensitive to spatial and navigational abilities and a wider range of AD biomarkers. Two-year

follow up has started and then follow up every 5 years in the entire cohort is planned. As the sample increases in size and longitudinal change data can be entered into our modeling work, the findings presented here can be validated and expanded upon.

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