Scores Obtained from a Simple Cognitive Test of Visuospatial Episodic Memory Performed Decades before Death Are Associated with the Ultimate Presence of Alzheimer Disease Pathology

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Abstract
Background: Community- or population-based longitudinal studies of cognitive ability with a brain donation end point offer an opportunity to examine relationships between pathology and cognitive state prior to death. Discriminating the earliest signs of dementing disorders, such as Alzheimer disease (AD), is necessary to undertake early interventions and treatments.

Methods: The neuropathological profile of brains donated from The University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age, including CERAD (Consortium to Establish a Registry for Alzheimer's Disease) and Braak stage, was assessed by immunohisto-chemistry. Cognitive test scores collected 20 years prior to death were correlated with the extent of AD pathology present at death.

Results: Baseline scores from the Memory Circle test had the ability to distinguish between individuals who developed substantial AD pathol-ogy and those with no, or low, AD pathology. Predicted test scores at the age of 65 years also discriminated between these pathology groups. The addition of APOE genotype further im-proved the discriminatory ability of the model.

Conclusions: The results raise the possibility of identifying individuals at future risk of the neuropathological changes associated with AD over 20 years before death using a simple cognitive test. This work may facilitate early inter-ventions, therapeutics and treatments for AD by identifying at-risk and minimally affected (in pathological terms) individuals.

Neil Pendleton and David M.A. Mann contributed equally to the study.

Introduction

Currently available drugs used to treat Alzheimer disease (AD) have only limited efficacy in ameliorating its symptoms once disease has been diagnosed. Current research focuses on the pathogenesis of AD in an attempt to develop drugs ideally able to prevent the progression of the pathological process before clinical symptoms develop, or at least able to slow progression once the disease is apparent [1]. Such an approach involving pre-symptomatic diagnosis requires a test which is able to diagnose the disease before it is clinically apparent or to identify a person's risk of developing clinical AD at some later time. Ideally, the test should be related to the presence of the characteristic pathology of the disease. As such, a test could range from question-based tools to biomarkers or brain imaging. Important character-istics of such a test include simplicity, availability, financial cost and tolerability to the subject.

The prediction of clinical symptoms of AD has employed imaging methods [2] to detect early structural changes and has identified changes in levels of tau and amyloid-beta (Aβ) in cerebrospinal fluid [3] and lipidomic profile in blood [4, 5] with only limited success. Cognitive testing offers an alternative, non-invasive, possibility for the prediction of AD: it can be performed easily and safely in a community setting, usually with little or no need for specialist equipment or particular technical skills.

Previous studies have reported associations between clinical dementia and performance scores from a variety of cognitive tests. Measures of executive function, assessed over a 4-year period, predicted the conversion of mild cognitive impairment (MCI) to dementia [6], and scores from tests of episodic, working and semantic memory predicted a similar conversion over a 5-year period [7]. Longer-term studies have shown that changes in scores examining global cognitive function, as measured by the Mini-Mental State Examination (MMSE), visuo-spatial memory and verbal fluency can predict clinical AD 9 years before diagnosis [8], and decreased scores of semantic memory and conceptual formation are predictive of dementia 12 years before symptoms [9]. Most recently, Rajan et al. [10] reported that a low composite test score incorporating episodic memory, executive function and global cognition was asso-ciated with the development of clinical AD over an 18-year follow-up period: individual test scores of these cognitive domains were also predictive of AD over the same follow-up period.

A major drawback in the interpretation of clinical studies relates to the lack of neuro-pathological confirmation of AD. There are correlations between cognitive status and neocor-tical Aβ plaques [11] with densities of neuritic Aβ plaques correlating better than those of diffuse Aβ plaques [12, 13]. Similarly, there are correlations between neocortical neurofi-brillary tangles density and MMSE scores, Blessed scores and the score of global cognitive status [14, 15]. Associations between specific neuropsychological testing scores and AD pathology are less common. Scores in tests assessing episodic memory have been shown to associate with National Institute on Aging-Reagan Institute pathological criteria [16], and scores on the Wechsler Adult Intelligence Score information test, verbal fluency and recog-nition memory correlate with Braak stage [17], as do cumulative scores describing executive function, verbal memory, visuospatial construction and language [18]. However, in all these studies, the period between (the last) cognitive testing and post-mortem brain examination was short, usually only between 1 and 5 years. In addition, selection bias remains an issue regarding the recruitment of subjects into such studies.

In the present study, we investigated associations between 2 neuropathological diag-nostic indices of AD (CERAD [Consortium to Establish a Registry for Alzheimer's Disease] and Braak stage) and a battery of neuropsychological test scores collected many years prior to death. Because the interpretation of test scores is dependent on a person's age, and because the age points at which neuropsychological testing was done varied in this study, we fitted statistical models to individual clinical trajectories and used these to predict an individual's test score at age 65 years for each participant. Associations between neuropathology, baseline test scores and estimated test scores at age 65 years were then examined.

Early stages of AD are characterised clinically by changes in short-term memory (hippo-campal function) as shown by psychological testing, and in spatial awareness, as shown by PET/SPECT imaging of parietal lobe hypometabolism, suggesting that a failure in temporo-parietal pathways might reflect the onset of the disease process [19]. Because of its ability to draw upon elements of temporoparietal function, we predict that the Memory Circle (MC) test employed in the present study may index early failures in the temporoparietal pathway, indicative of the beginnings of the AD pathological process. Data obtained in parallel from the use of other neuropsychological tests were employed as "comparators" in order to determine how well the MC test might perform relative to the other tests.

Materials and Methods

Participants and Study Design

Subjects were participants in The University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age. People with evidence of dementia at the time of recruitment were ineligible for the study. The study began in 1983 and recruited a total of 6,542 healthy individuals, aged between 42 and 92 years, in successive waves between 1983 and 1994. Participants had demographic, lifestyle and health information collected through study-specific self-report questionnaires and undertook biennial alternating batches of cognitive tests (test battery A and B) designed to assess various aspects of cognition including memory, processing speed, fluid intelligence and crystallised intelligence [20]. The MC test from test battery B, which assesses visuospatial episodic memory using an immediate free-recall paradigm, is of particular importance for the present study. Participants were presented with a circle comprising 12 sectors, each containing a line drawing of an easily recognised object, for 30 s. They were then presented with a circle showing the sectors and they had to recall the names of the objects into the correct sectors (Fig. 1). A score out of 12 was calcu-lated using the number of correctly remembered items in the correct location in the circle. Details of educa-tional level were collected using a self-report questionnaire and then standardised using the International Standard Classification of Education (ISCED) guidelines [21].

Between June 2004 and April 2006, surviving participants underwent assessment by the Telephone Instrument for Cognitive Status (TICS), a test of general cognitive function which allows a definition of cognitive impairment. We used 27 items from this test to assign a TICS27 score [22]. Using thresholds defined in this report, we classified participants as follows: 0–6 = dementia; 7–11 = cognitive impairment not dementia; and 12–27 = normal cognition. Cognitive status at death was ascertained using a combination of last TICS27 score and patient notes obtained via the participants' general practitioner.

Eighty-nine brains from the surviving 312 members (in 2003) of the total cohort were accessioned into the study. Following pathological examination, a subset of 75 brains exhibiting AD pathology (without any other co-pathologies) or pathologically normal for age was used for this study. Fourteen individuals had been excluded because of other neuropathological changes (dementia with Lewy bodies [n = 8], corticobasal degeneration [n = 2], argyrophilic grain disease [n = 2], Parkinson disease [n = 1] and aging-related tau astro-gliopathy [n = 1]). Three of the 75 individuals eventually included in this study did not have an MC measure for initial testing.

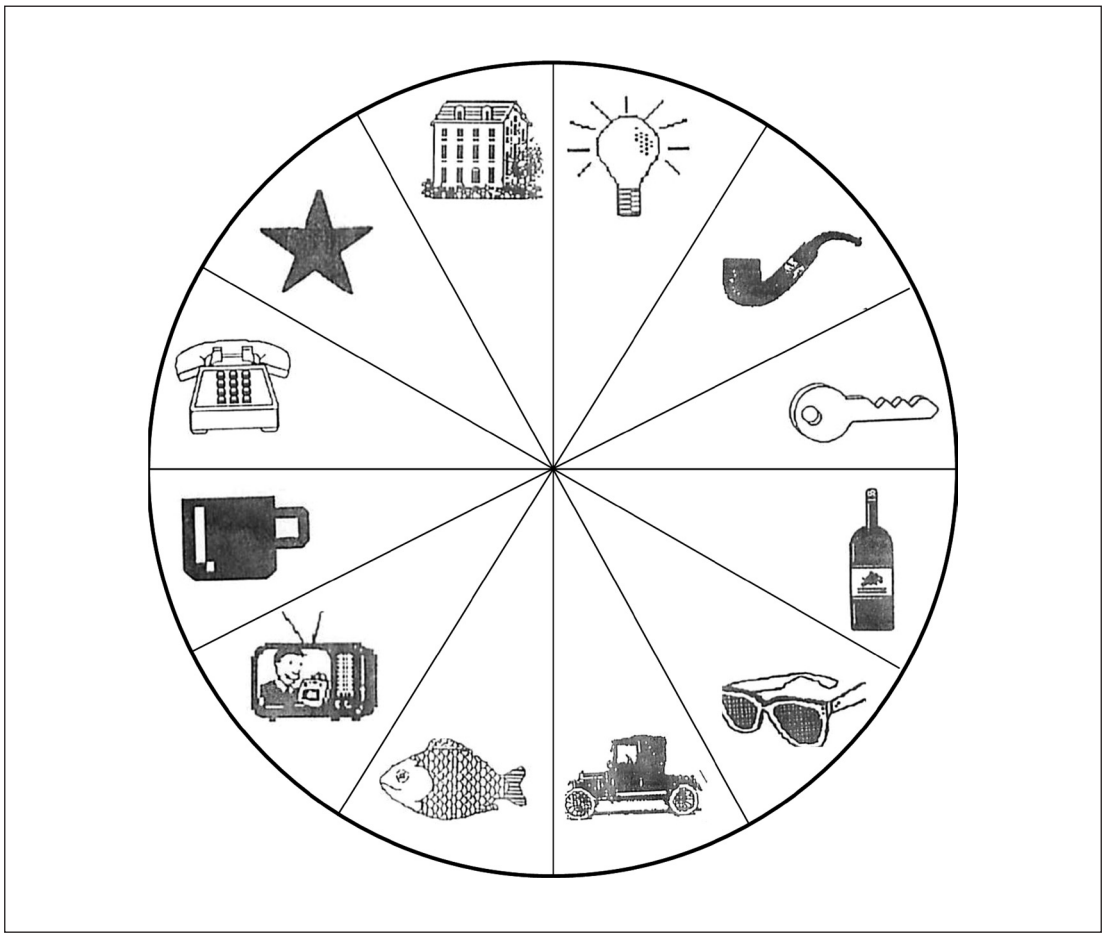

Fig. 1. Memory Circle test. Participants were presented with a circle comprising 12 sectors, each containing a line drawing of an easily recognised object, for 30 s. They were then presented with a blank circle showing the sectors and they had to recall the names of the objects into the correct sectors.

Pathological Methods

One fresh hemi-brain was fixed in 10% neutral formalin for 3–4 weeks with the other hemi-brain frozen at –80 °C. Standard blocks of frontal, cingulate, temporal (with hippocampus), parietal and occipital cortex, amygdala, corpus striatum, thalamus, midbrain, brainstem and cerebellum were cut from the fixed tissue and processed into wax blocks. Paraffin sections (6 μm) were immunostained for Aβ (Cambridge Bioscience, clone 4G8, 1:3,000) and tau proteins phosphorylated at Ser202 and Thr205 (P-tau) (Source Bioscience, clone AT8, 1:750). For antigen retrieval, sections were microwaved in 0.1 M citrate buffer, pH 6.0 (P-tau) or immersed in 70% formic acid for 20 min (Aβ) prior to incubation with primary antibody.

The severity of neuritic plaques in the frontal, temporal and parietal cortex and in the hippocampus was used to assign the CERAD score [23], and the topographical distribution of P-tau pathology was used to assign the Braak stage [24].

DNA was extracted from frozen brain tissue using REDExtract-N-Amp™ Tissue PCR Kit (Sigma) or from blood (3 cases). The *APOE* genotype was determined using routine polymerase chain reaction methods [25]. *APOE* could not be determined for 9 participants because of lack of blood or frozen brain tissue, one of whom also lacked the baseline MC score.

Statistical Analysis

The analysis relates the CERAD score (0–A vs. B–C) and the Braak stage (0–II vs. III–VI) to cognitive test scores at baseline and predicted scores at age 65 years. For demographics, *t* tests assessed differences in mean values at the first test occasion between the CERAD/Braak groups; the χ^2 test was used for nominal variables. The Mann-Whitney test assessed differences in cognitive test scores between pathology groups. A *p* value of <0.05 was considered significant. Scores from only 1 cognitive test (MC test) differed significantly between pathology groups; this was subsequently investigated to ascertain relationships between CERAD and Braak stage groups and MC score in regression analyses which also included sex, education level and *APOE* genotype. Results of these analyses are presented as odds ratios (OR) with 95% confidence intervals (CI) for membership of the CERAD (B–C) or Braak stage (III–VI) groups. Correlations between CERAD score (0, A, B and C), Braak stage (0–VI) and both baseline and predicted MC scores at age 65 years were assessed using the Spearman rank correlation coefficient.

To predict scores at age 65 years for all participants, "random effects" regression models, with age at test as a predictor together with sex, education level and *APOE* genotype and a "learning effect," were fitted to repeated test scores. Previous exposure to a cognitive task may affect future performance, giving the advantage of higher test scores than would be expected. This can bias estimates of cognitive performance in longitudinal studies with repeated test use, attenuating the expected effect of increasing chronological age. This can be termed a practice or learning effect [26, 27]. These models initially allowed both individual differ-ences in level (random intercept) and differences in change (random slope) in test scores with age but reverted to the simpler random intercept models when there was no significant evidence of differences in change over time. The possibility of a non-linear change with age was allowed for by including a quadratic age term in the models. To allow for a learning effect, a binary variable which distinguished between the first test and all later tests was also considered in the model. These models were then used to predict the scores at age 65 years for all participants.

Data were analysed using the statistical software package SPSS (version 20) and the xtmixed software in STATA version 14.

Results

Demographics

Demographic and descriptive characteristics of the 75 participants are shown in Table 1. There were no significant differences in sex, age at death, level of education or age at initial testing of test battery B (which included the MC test) between either CERAD score groups or Braak stage groups. As expected, a significantly greater proportion of individuals cognitively impaired at death were present in the high-severity pathology group (CERAD 56%; Braak 57%) than in the low-severity pathology group (CERAD 21%; Braak 23%) for both CERAD ($p = 0.001$) and Braak stage ($p = 0.003$). Similarly, the proportion of *APOE* ε4 carriers in the high-severity pathology group (CERAD 44%; Braak 46%) was significantly greater than that in the low-severity pathology group (CERAD 21%; Braak 21%) for both CERAD ($p = 0.03$) and Braak stage ($p = 0.04$).

The age at which the initial MC test was conducted ranged from 53 to 78 years, and age at death ranged from 72 to 104 years. The number of years between initial testing and death ranged from 12 to 26 years (mean 21.3 ± 3.5 years).

Assessment of MC Test Scores and Relationship to Pathology

Using scores from the first test, only the MC task was able to differentiate between CERAD 0–A and CERAD B–C groups and between Braak stage 0–II and Braak stage III–VI groups (Table 2). This was only the case for scores reflecting both correct object and correct sector. Scores for objects recalled, regardless of sector assigned, were not able to differentiate between pathology groups, indicating that the spatial aspect of the MC test was the predictive element.

Table 1. Descriptive characteristics, stratified by neuropathological outcome, for the subset of individuals from The University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age cohort who
displayed either AD or normal ageing pathology

	CERAD score		Braak stage		Total cohort
	0–A	B–C	0–II	III–VI	
Male	14 (33%)	7 (22%)	14 (30%)	7 (25%)	21 (28%)
Female	29 (67%)	25 (78%)	33 (70%)	21 (75%)	54 (72%)
CI at death[a]	9 (21%)	18 (56%)	11 (23%)	16 (57%)	27 (36%)
Age at death, years					
Mean ± SD	87.5±5.4	87.7±7.2	87.8±5.5	87.3±7.3	87.6±6.2
Range	24	32	24	32	32
Education in ISCED years					
Mean ± SD	15.5±3.6	14.6±3.5	15.5±3.5	14.5±3.6	15.1±3.5
Range	12	9	12	9	12
APOE					
No ε4 present	29 (67%)	14 (44%)	30 (64%)	13 (46%)	43 (57%)
ε4 present	9 (21%)	14 (44%)	10 (21%)	13 (46%)	23 (31%)
Missing	5 (12%)	4 (12%)	7 (15%)	2 (7%)	9 (12%)
Age at first MC test, years[b]					
Mean ±SD	66.0±5.2	66.8±5.4	65.8±5.3	67.2±5.2	66.3±5.3
Range	22	22	22	22	25
Baseline MC score[b]					
Mean ± SD	9±2	7±2	8±2	7±2	8±2
Range	8	8	8	6	8
Predicted MC score at age 65					
Mean ± SD	8±1	7±2	8±1	7±1	8±1
Range	5	5	5	5	5

AD, Alzheimer disease; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, cognitive impairment; SD, standard deviation; MC, Memory Circle. [a] Two of the subset of 75 individuals did not have clinical information available, and, therefore, no assumption of cognitive impairment could be made. [b] Three of the subset of 75 individuals did not participate in test battery B; therefore, mean age at testing and baseline MC score for this variable is for 72 cohort individuals.

Two approaches were used to assess the relationship between MC scores and pathology: baseline MC scores and predicted MC scores at 65 years. As baseline MC scores cover a wide range of ages (range of 25 years; mean 66.3), knowledge of the ability of scores to distin-guish between pathology groups at a fixed age would be preferable. There were a total of 231 MC test results for the 75 participants (mean 3 tests per person). In the random-effects regression models, there was no evidence of a learning effect (p = 0.45 for learning term). As a result of calculating the standard deviation on the corrected value, the age effect was effectively zero (implying that the rate of decline did not vary between people), but there was evidence that scores changed with age non-linearly (p value for quadratic term in model = 0.02) with a much larger annual decline at older ages compared to younger ages. For example, the model predicted an annual decline of 0.11 at age 70 years but 0.62 at age 80 years. Predicted MC scores at age 65 years were obtained from the quadratic model with no learning effect.

Strong negative correlations were observed between the CERAD score (0, A, B or C) and both baseline (r_s = –0.26, p = 0.03) and predicted (r_s = –0.34, p = 0.003) MC scores. Similarly, strong negative correlations were observed between Braak stage (0–VI) and both baseline (r_s = –0.28, p = 0.02) and predicted (r_s = –0.34, p = 0.03) MC scores. Both baseline MC scores and predicted MC scores at 65 years were able to

Table 2. Median initial test scores (range) for all tests undertaken in The University of Manchester Longitu-dinal Study of Cognition in Normal Healthy Old Age

Cognitive test	CERAD score		*p* value	Braak stage		*p* value
	0–A	B–C		0–II	III–VI	
AH4 test 1	41 (37)	36 (35)	0.10	40 (37)	35 (35)	0.06
AH4 test 2	36 (33)	35.5 (40)	0.93	36 (41)	35 (32)	0.33
Mill Hill A	25 (16)	26 (16)	0.59	25 (16)	25.5 (16)	0.79
Mill Hill B	20 (21)	21 (25)	0.56	20 (23)	20.5 (25)	0.96
VFR 30	9 (12)	10 (16)	0.61	9 (12)	10 (16)	0.75
PR Memory	33 (22)	32 (14)	0.43	33 (22)	32 (14)	0.44
Culture Fair	31 (31)	29.5 (20)	0.41	31.5 (31)	29 (20)	0.19
WAIS	81.1 (55.4)	84.5 (50)	0.49	81.1 (55.4)	85.1 (50)	0.72
Visual Search	208.5 (146)	204 (155)	0.61	219 (146)	202 (155)	0.43
Alphabet Coding	228.5 (192)	222 (167)	0.14	231 (192)	212 (167)	0.06
VFR 10	7 (7)	7 (5)	0.98	7 (7)	7 (5)	0.69
Shapes and Location	36 (12)	36 (13)	0.39	36 (12)	36 (13)	0.17
Propositions/People	7 (10)	6 (7)	0.52	7 (10)	6 (7)	0.36
Memory Circle	9 (8)	8 (8)	0.02	9 (8)	8 (6)	0.03

Comparison by Mann-Whitney *U* test showed that only one cognitive test (Memory Circle) could differentiate between pathology groups for CERAD and Braak stage. CERAD, Consortium to Establish a Registry for Alzheimer's Disease; AH, Alice Heim; VFR, Verbal Free Recall; PR, Pictorial Recognition; WAIS, Wechsler Adult Intelligence Scale.

Table 3. Odds ratios and AUC values for baseline MC test scores and predicted MC test scores at 65 years when comparing individuals with CERAD score 0–A and B–C or Braak stage 0–II and III–VI

	Baseline MC test scores					Predicted MC test scores at 65 years				
	n	OR	95% CI	*p* value	AUC	*n*	OR	95% CI	*p* value	AUC
CERAD score	72	0.78	0.63–0.98	0.04	0.66	75	0.60	0.40–0.90	0.01	0.64
Braak stage	72	0.79	0.63–0.99	0.04	0.65	75	0.51	0.33–0.80	0.003	0.72

AUC, area under the curve; MC, Memory Circle; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; OR, odds ratio; CI, confidence interval.

differentiate between individuals who were in CERAD 0–A group and those in CERAD B–C group, as well as between those in Braak 0–II group and those in Braak III–VI group (Table 3). Specifically, the odds of reaching Braak stage III–VI significantly increased for every unit decrease in baseline MC score (OR = 0.79, 95% CI 0.63–0.99), and similarly for CERAD stage B or C (OR = 0.78, 95% CI 0.63–0.98).

After adjustment for *APOE*, sex and level of education, the ORs for baseline MC scores were unchanged, although significance values decreased slightly as these analyses only included 64 individuals due to missing MC score/*APOE* data. Similarly, for predicted MC scores at 65 years, the OR for CERAD (OR = 0.66, 95% CI 0.42–1.02) and that for Braak stage (OR = 0.54, CI 0.33–0.87) were essentially unchanged – although the MC score for CERAD was no longer significant ($p = 0.06$) due to reduced sample size (Table 4).

Table 4. OR and AUC values for the model incorporating all variables; sex, education level, presence of *APOE* ε4 alleles and baseline MC test scores/predicted MC test scores at 65 years when comparing individuals with CERAD score 0–A and B–C or Braak stage 0–II and III–VI

	Baseline MC test scores						Predicted MC test scores at 65 years					
	CERAD (AUC = 0.73; *n* obs. = 64)			Braak stage (AUC = 0.72; *n* obs. = 64)			CERAD (AUC = 0.73; *n* obs. = 66)			Braak stage (AUC = 0.75; *n* obs. = 66)		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Sex	1.32	0.37–4.66	0.67	1.08	0.30–3.85	0.90	1.53	0.45–5.22	0.50	1.19	0.33–4.25	0.79
Education	0.97	0.82–1.14	0.71	0.97	0.82–1.14	0.71	0.99	0.84–1.16	0.90	1.02	0.86–1.20	0.85
APOE	4.09	1.28–13.05	0.02	3.88	1.22–12.38	0.02	3.08	1.01–9.42	0.05	2.90	0.92–9.15	0.07
MC test	0.78	0.60–1.02	0.07	0.79	0.60–1.03	0.08	0.66	0.42–1.02	0.06	0.54	0.33–0.87	0.01

OR, odds ratio; AUC, area under the curve; MC, Memory Circle; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; obs., observed; CI, confidence interval.

Table 5. Overview of AUC values for all models examined using baseline MC test scores/predicted scores at 65 years and comparing individuals with CERAD score 0–A and B–C or Braak stage 0–II and III–VI

Model	Baseline MC test scores			Predicted MC scores at 65 years		
	n	AUC value (95% CI)		*n*	AUC values (95% CI)	
		CERAD	Braak stage		CERAD	Braak stage
MC only	72	0.66 (0.53–0.79)	0.65 (0.52–0.77)	75	0.67 (0.55–0.80)	0.72 (0.60–0.84)
APOE only	66	0.63 (0.49–0.77)	0.63 (0.48–0.77)	66	0.63 (0.49–0.77)	0.63 (0.48–0.77)
MC + *APOE*	64	0.72 (0.59–0.85)	0.71 (0.59–0.84)	66	0.72 (0.59–0.85)	0.75 (0.62–0.87)
MC + sex + *APOE* + education	64	0.73 (0.60–0.85)	0.72 (0.60–0.85)	66	0.73 (0.60–0.85)	0.75 (0.63–0.88)

The inclusion of *APOE* with baseline MC score/predicted scores at 65 years increases the area under curve. However, the addition of sex and education shows a negligible effect. AUC, area under the curve; MC, Memory Circle; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval.

The area under the curve (AUC) value for baseline MC scores had a similar value to *APOE* for both CERAD (MC test: AUC = 0.66, 95% CI 0.53–0.79; *APOE*: AUC = 0.63, 95% C: 0.49–0.77) and Braak stage (MC test: AUC = 0.65, 95% CI 0.52–0.77; *APOE*: AUC = 0.63, 95% CI 0.48–0.77). Similarly, predicted MC scores at 65 years (AUC = 0.67, 95% CI 0.55–0.80) had a compa-rable value to *APOE* (AUC = 0.63, 95% CI 0.49–0.77) for CERAD. However, when examining Braak stage, predicted MC scores at 65 years (AUC = 0.72, 95% CI 0.60–0.84) performed better than *APOE* (AUC = 0.63, 95% CI 0.48–0.77). The combined baseline MC scores + *APOE* model performed well for both CERAD (AUC = 0.72, 95% CI 0.59–0.85) and Braak stage (AUC = 0.71, 95% CI 0.59–0.84). Similarly, the combined predicted MC scores at 65 years + *APOE* model performed well for both CERAD (AUC = 0.72, 95% CI 0.59–0.85) and Braak stage (AUC = 0.75, 95% CI 0.62–0.87). The addition of sex and education level to these models had a negligible effect (Table 5).

Receiver-operating characteristic curves (ROC) for baseline MC scores and predicted MC scores at age 65 years + *APOE* models are shown in Figure 2. For CERAD and Braak stage, the optimal sensitivity for the predicted MC scores at 65 years + *APOE* model was 75 and 81%, respectively, and optimal specificity was 66 and 53%, respectively.

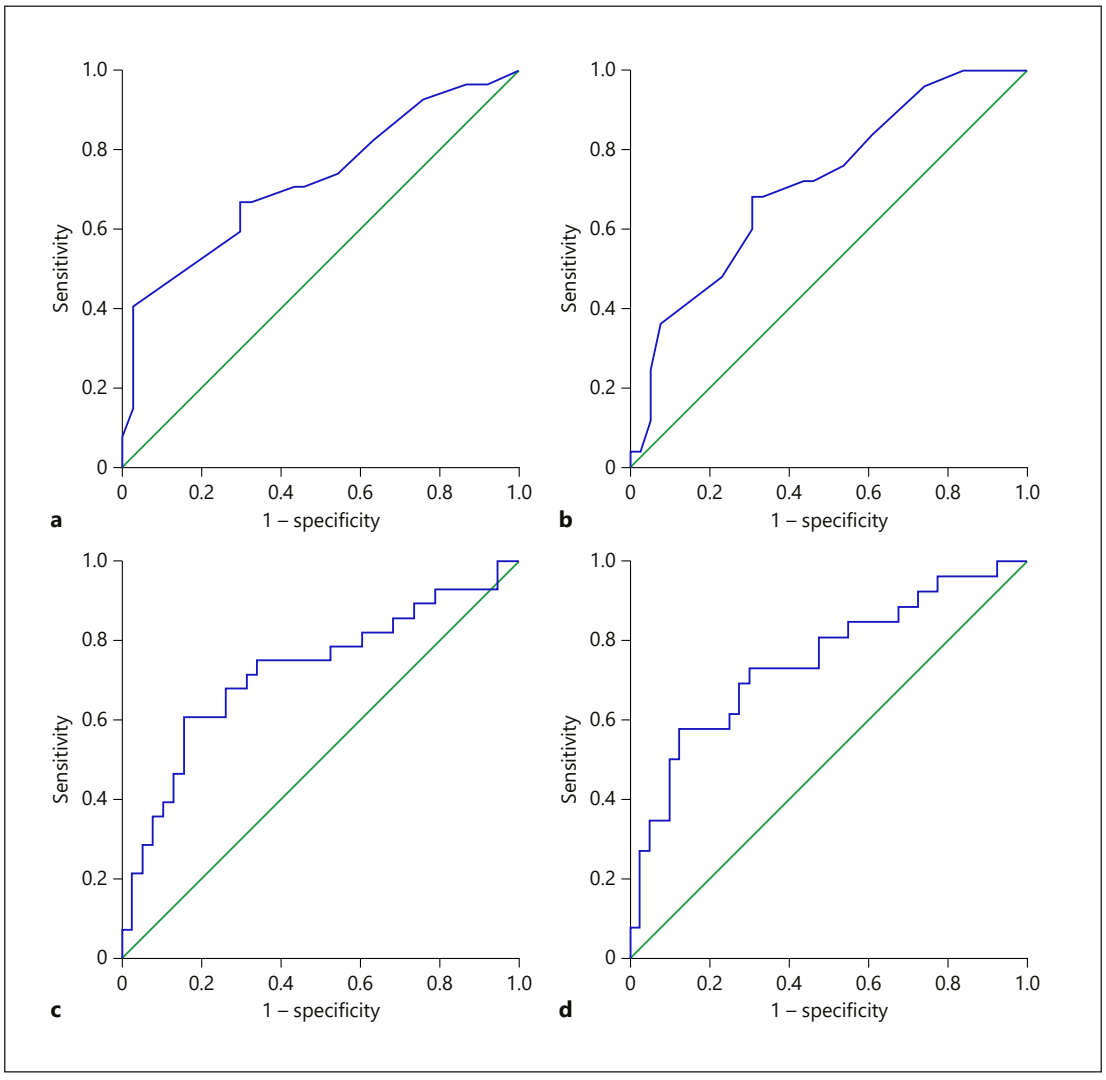

Fig. 2. ROC curves for the baseline MC score + *APOE* (**a**, **b**) and predicted MC score at age 65 years + *APOE* (**c**, **d**) models. The AUC for **a** (AUC = 0.72, 95% CI 0.59–0.85) and **c** (AUC = 0.72, 95% CI 0.59–0.85) shows the level of discrimination between CERAD 0–A and CERAD B–C. The AUC for **b** (AUC = 0.71, 95% CI 0.59–0.84) and **d** (AUC = 0.75, 95% CI 0.62–0.87) shows the level of discrimination between Braak stage 0–II and III–VI. ROC, receiver-operating characteristic; MC, Memory Circle test; AUC, area under the ROC curve; CI, confi-dence interval.

Discussion

This study examines relationships between MC scores, obtained between 12 and 26 years before death (mean 21.3 ± 3.5 years), and the extent of AD-type pathology present at post mortem. Stratification based on Alzheimer-type pathology avoided potential effects of confounders with pathologies other than those associated with AD. We found an association of both baseline MC score and predicted MC score at 65 years with the eventual extent of AD pathology post mortem. Sex, age at testing (for either test battery), age at death and ISCED years of education did not influence pathology. This suggests that the MC test could contribute to a screening exercise to identify individuals at risk of developing sufficient AD-type pathology in future years which would impose clinically apparent dementia.

Previous studies have shown that combinations of cognitive tests are able to predict Braak stage [18]. Furthermore, scores on tests of episodic memory [16] and recognition memory [17] can predict Braak stage independently from other risk factors of dementia. Where previous studies have highlighted the capabilities of a test to distinguish between Braak stages approximately 1–5 years before death, our study greatly extends the length of time between testing and death and shows the possibility of estimating the broad Braak stage of an individual decades before death. That scores from the MC task also associate with the CERAD score has not been previously reported. However, as CERAD scoring criteria are based on densities of neuritic plaques, which contain degenerating neuronal processes along with tau-paired helical filaments, such a finding is unsurprising.

The MC test assesses visuospatial episodic memory, presumably tapping into neural pathways linking temporal lobe and hippocampus (traditionally associated with memory function) with posterior parietal lobe (which governs spatial awareness). It is instructive that memory for *where* objects are located proved a better predictor of later AD pathology than memory for *what* those objects are. This is consistent with reports of topographical memory impairments in MCI and early AD and network-level degeneration incorporating posterior cortical as well as medial temporal structures [19]. Our findings imply that the MC test is indexing changes in connectivity within that network many years earlier than what has been previously recorded.

There are several potential limitations to the study. Brain donation was not initially part of the original study, only being introduced in 2004. This meant that many potential dona-tions were lost. Common to all autopsy-based studies, sample size is a limitation. Although brain donation was offered to all surviving participants in 2004, only 312 individuals agreed to donation. The geographical areas covered by the study (Greater Manchester and Newcastle) could potentially influence outcomes: individuals in large, industrial, northern cities might not reflect society as a whole. As with many observational studies, our cohort is self-selected and may not necessarily be representative of the general population. However, whilst it is possible that test scores of participants in the present study may be higher or lower than the population average, there does not seem to be any evidence that a different relationship would be found in the general population.

Although modest, our findings indicate that a simple test of cognitive function can distin-guish those individuals who are destined to develop sufficient AD-type pathology over subse-quent decades to culminate in clinical dementia from those who would develop only limited changes and remain cognitively unimpaired. Such “at-risk” individuals could be targeted for interventions, including lifestyle adjustments towards cognitively stimulating environments, physical activity, healthy diets [28, 29] or perhaps utilising anti-Aβ therapies [30], long before their level of cognitive change brings them to the attention of medical practice, with a potential influence on the trajectory of their disease.

Importantly, the MC test is cheap, well tolerated and easy to implement, even over the periods of multiple testing needed for the evaluation of drug efficacy, and it can be performed quickly and safely, even at home. This sets it apart from more invasive tests, such as blood/cerebrospinal fluid sampling and brain imaging, which need to be performed in a clinical setting and can be expensive to conduct and evaluate over the extensive periods required in clinical trials. Our findings may facilitate treatments for AD by identifying people “at risk” decades before clinical signs might be anticipated and in whom the prospects of preventing disease might be realistic.

Statement of Ethics

The study was approved by the Manchester Brain Bank Management Committee (REC reference 09/H0906/52 + 5). Under conditions agreed with the Research Ethics Committee, The Manchester Brain Bank can supply tissue or data to researchers without requirement for researchers to apply individually to the REC for approval.

Disclosure Statement

The authors declare that there are no conflicts of interest.

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Author Contributions

All authors have read the manuscript and have agreed to be listed as authors. David M.A. Mann and Neil Pendleton devised and designed the study and helped with writing the paper. Andrew C. Robinson helped to devise and design the study, performed immunohistochemistry, microscopic assessments, genetic analysis and data/statistical analysis and wrote the paper. Roseanne McNamee assisted with statistical analysis. Yvonne S. Davidson helped with immunochemistry. Michael A. Horan provided clinical data and assisted with the preparation of the manuscript. Julie Snowden assisted with neuropsychological overview and preparation of the manuscript. Lynn McInnes helped with neuropsychological overview of the cognitive testing and writing the paper.

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