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Apolipoprotein ε4 and neuropsychological performance in Alzheimer's disease and vascular dementia

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ABSTRACT

The apolipoprotein (APOE) ε4 allele is a genetic risk factor for the development of Alzheimer's disease (AD). It has also been associated with vascular dementia (VaD) in some but not all studies. Previous studies have examined the role of APOE in predicting performance on cognitive tests in both demented and non-demented populations. In cognitively intact individuals, statistically significant group differences between APOE ε4 carriers and non-carriers have been demonstrated for several cognitive domains. In AD studies of the impact of APOE ε4 on cognition have been conflicting while no previous study has assessed cognition and impact of APOE ε4 in VaD. In this study we investigated the impact of APOE ε4 on performance in neuropsychological tests including information processing speed in patients with mild-moderate AD and VaD. We incorporated both computerized and pen and paper tests to ensure a sensitive method of assessing cognition. 109 patients participated in the study (VaD = 41, AD = 68). Neurocognitive performance of 44 ε4 present AD patients was compared to 24 ε4absent patients and performance of 23 ε4 present VaD patients was compared to 18 ε4 absent patients. There was evidence that APOE ε4 conferred a risk of poorer cognitive functioning in both patient groups. In the AD group presence of ε4 conferred a negative impact on some measures of speed of information processing and immediate recall while in the VaD group ε4 present patients had evidence of poorer accuracy on tasks such as choice reaction time and spatial working memory. In AD and VaD groups ε4 present patients showed impairment in selective attention. These findings provide further support of the negative impact of the ε4 allele in cognition.

Alzheimer's disease (AD) and vascular dementia (VaD) constitute the most common forms of dementia. AD is thought to account for 50–60% of all cases and VaD for 25–30% of cases: mixed forms also occur [8,34]. The apolipoprotein (APOE) ε4 allele is a genetic risk factor for the development of AD [5]. Meta-analysis has shown that the APOE ε4 allele increases the risk of the disease by three times in heterozygotes and by 15 times in homozygotes [9]. It acts mainly by modifying age of onset, with each copy of the allele lowering the age of onset by almost 10 years [5]. APOE is involved in neuronal repair and acts as a cholesterol transporter in the brain [33]. APOE is encoded by a gene on chromosome 19, with three allelic variants (ε2, ε3, and ε4) yielding six possible genotypes. AD patients homozygous for the ε4 allele demonstrate greater senile plaque density and amyloid burden than ε3/ε3 or ε3/ε4 patients [25].

Studies have examined the role of APOE in predicting performance on cognitive tests in both demented and non-demented populations. As AD usually appears later in life and progresses slowly, the APOE ε4 allele may exert its effect prior to the clinical diagnosis of AD. Studies using information–processing approaches to dissect cognition into component operations found impairments in attention and working memory in individual carriers of the APOE ε4 gene [13,24]. These changes were found in healthy middle-aged adults in their 50s who were clinically without dementia. In contrast, some studies observed no association between the ε4 allele and performance on any neuropsychological measure [30,29]. However, a meta-analysis of 38 studies in cognitively intact individuals demonstrated statistically significant group differences between APOE ε4 carriers and non-carriers for several domains of cognitive performance. Specifically, the presence of a ε4 allele was associated with poorer performance on tests of global cognitive functioning, episodic memory and executive functioning. No differences were observed however, on tests of perceptual speed, attention, short-term memory and visuospatial skills [31]. The absence of any significant observed effects, especially in the domain of attention, was thought to relate to the use of tests that were not sensitive enough to detect subtle impairments. A further more recent study [21] used a battery of computerized cognitive tests that included measures of information processing speed. On stan-

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dard neuropsychological tests, there was no significant difference in performance between the ε4 positive and ε4 negative groups. However, on the computerized battery, individuals with the ε4 allele were significantly slower performing all the cognitive tests, with the exception of a visuospatial task.

In AD, the findings from studies examining the impact of APOE ε4 on cognition have been conflicting. Several studies have shown a relatively selective effect of the ε4 allele on episodic memory [32,35] and attention [24], especially in the early stages of the disease. A cognitive phenotype characterized by memory and verbal comprehension deficits has been claimed for APOE ε4 homozygotes with AD as well as those with mild cognitive impairment [32]. Several studies have also focused on the effect of APOE genotype on AD patients' cognition over time. Frisoni et al. [11] found ε4 absent patients actually had greater rates of decline in MMSE than ε4 present patients. In contrast, another study found no association between ApoE ε4 dose and any retrospective or prospective measure of cognitive or functional decline [15]. A further study again found rate of decline in AD patients over time did not vary significantly across APOE genotypes on any cognitive test. The authors speculated that ε4 genotype exerts its effect on cognition either prior to the onset or at an early point in the AD process [14]. In VaD, the APOE ε4 allele has been associated with the disease in some [2,6] but not all studies [22]. If APOE ε4 influences cognitive performance in healthy adults, it may also affect neuropsychological performance in patients with VaD. A study on neuropsychological changes and impact of APOE ε4 in VaD has not previously been reported in the literature.

In this study we investigated the effect of APOE ε4 on performance in neuropsychological tests in patients with mild-moderate AD and VaD. We incorporated both computerized and pen and paper tests to ensure both a sensitive and comparative method of assessing cognition in these patients.

The Research Ethics Committee of the Queen's University Belfast approved this study (Application No. 249/03). It was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and assent from carers was obtained if necessary. The 109 participants in the study (VaD = 41, AD = 68) were recruited from the memory clinic at the Belfast City Hospital.

Patients were assessed using a structured interview, physical examination, routine biochemical screening and CT scan of brain. A detailed corroborative history was taken from the carer (usually a family member). A diagnosis of probable AD or probable VaD was made using the NINCDS-ADRDA [18] and NINDS-AIREN [26] criteria, respectively. Patients with findings suggestive of mixed dementia, Lewy body dementia, frontotemporal dementia and/or an additional standardized diagnosis of depression were excluded from the study. No patients were being treated with cholinesterase inhibitors at the time of testing.

Premorbid IQ was estimated using the National Adult Reading Test (NART) [20]. All subjects underwent testing using the Cognitive Drug Research (CDR) computerized cognitive assessment system [4] as well as a battery of pen and paper tests. These tests were selected to ensure a comprehensive assessment of all major cognitive domains was carried out accurately and within time constraints for the patient.

The three attention/information processing tasks used from the CDR test battery were simple reaction time, choice reaction time, and digit vigilance. Measures of speed and accuracy were recorded. Mean speeds from spatial working memory and numeric working memory along with delayed word recall and delayed picture recall tasks were also recorded. Three paper and pencil tests were used to assess additional aspects of attention: Colour Trails A and Colour Trails B [7] and the Stroop test [12]. Colour Trails A primarily involves perceptual tracking and simple sequencing. Colour Trails B is a test of executive divided attention and sequencing. It more directly assesses frontal systems functioning than part A due to the alternating sequence pattern. The Stroop test primarily measures executive selective attention as the participant must ignore the distraction of the non-congruent colour words during the test phase.

Pen and paper tests were used to assess executive function. These were: the Executive Interview (EXIT25) [27], Clock Drawing (CLOX 1) [28] and the Controlled Oral Word Association Test (COWAT) of verbal fluency [3].

A numeric working memory [NWM-CDR battery] task assessed the articulatory loop sub-system of working memory and a spatial working memory [SWM-CDR battery] task assessed the visuospatial sub-loop of working memory [1]. A sensitivity index was recorded. The sensitivity index was calculated from the formulae derived by Frey and Colliver [10]: it combines accuracy scores from familiar as well as novel (distractor) information contained within the tasks. By combining the ability to identify previously presented items and to correctly reject items that were not previously presented, it represents the ability of the participant to discriminate (or be sensitive to) the task information. The scores ranged from 0 to 1, and a score of 1 represented perfect discrimination.

Immediate word recall was measured by ability to recall a list of 15 words (CDR battery). Episodic memory was assessed by ability to store and recall verbal information, ability to discriminate novel from previously presented words and ability to discriminate novel from previously presented pictorial information (CDR battery).

CLOX 2 [28] and the COWAT of category fluency [3] were used to assess visuospatial function and semantic fluency respectively.

Genomic DNA was extracted from peripheral blood leucocytes using the salting out method [19]. APOE genotyping was carried out essentially as described [17].

Study data were analysed using SPSS Version 15 (Chicago, IL, 2008). The groups were analysed according to presence or absence of the ε4 allele. Homozygozity for ε4 ($n = 12$) was not separated from heterozygozity ($n = 55$) on ε4 due to the numbers involved. Demographic data were compared between groups using independent samples t-tests (two-tailed). In the AD group, there was a significant difference in age between the ε4 groups. Hence, neurocognitive data were analysed using Analysis of Covariance (ANCOVA) with age as a covariate. Neurocognitive data in the VaD group were analysed using independent samples t-tests. Power was based on a previous study in which significant differences in cognition were found with 18 ε4 present and 33 ε4 negative participants [21]. Effect sizes were also calculated (Cohen's d), 0.2 indicating a small effect, 0.5 a moderate effect, and 0.8 a large effect. Missing neurocognitive data (<5%) were imputed using the expectation–maximization method.

We collected data on 109 patients [AD $n = 68$ (44 ε4 present, 24 ε4 absent); VaD $n = 41$ (23 ε4 present, 18 ε4 absent)]. The AD patients did not differ in terms of gender, age leaving school, MMSE or premorbid IQ (Table 1). The VaD patients did not differ significantly in terms of age, gender, age leaving school, MMSE or premorbid IQ (Table 1).

Neurocognitive data for the AD group is shown in Table 2. ε4 present patients demonstrated a significantly slower choice reaction time than ε4 negative patients ($p = 0.02$; Cohen's $d = 0.62$). There was evidence of an effect on delayed word recall reaction time ($p = 0.06$, Cohen's $d = 0.51$) and delayed picture recall reaction time ($p = 0.06$, Cohen's $d = 0.51$). We did not demonstrate any significant difference between the ε4 present and ε4 absent groups on any other measure of speed of information processing. In addition, the ε4 present patients performed significantly less well on the Stroop test ($p = 0.04$, Cohen's $d = 0.57$) and on a test of immediate word recall ($p = 0.01$, Cohen's $d = 0.79$).

Table 1
Characteristics of AD and VaD APOE ε4 groups.

AD patients	ε4 Present (n = 44)	ε4 Absent (n = 24)	t	df	p
Male:Female	18:26	5:19	X^2 = 2.8	1	0.1
Age	76.2 (6.0)	81.1 (6.1)	−3.2	65	<0.01
Age leaving school	15.4 (2.0)	15.0 (2.0)	0.60	65	0.56
MMSE	22.5 (3.4)	22.7 (3.4)	−0.19	65	0.85
IQ	109.5 (9.0)	108.8 (8.1)	0.30	65	0.77
VaD patients	ε4 Present (n = 23)	ε4 Absent (n = 18)	t	df	p
Male:Female	9:14	11:7	X^2 = 1.95	1	0.16
Age	76.9 (6.2)	76.4 (7.9)	0.23	40	0.82
Age leaving school	14.8 (1.2)	15.7 (3.2)	−1.1	40	0.30
MMSE	22.0 (3.5)	22.7 (3.8)	−0.63	40	0.53
IQ	110.5 (5.9)	108.1 (8.9)	1.04	40	0.30

Mean (standard deviation).

Neurocognitive data for the VaD group is shown in Table 3. We concentrated on moderate-large effect sizes as evidence of potentially clinically significant group differences due to the small numbers involved. There was evidence of an effect of ε4 on simple reaction time, with ε4 present patients actually performing better than ε4 absent patients (p = 0.12, Cohen's d = 0.56). Despite this, there was also evidence of a negative effect of ε4 on choice reaction time accuracy and the Stroop test with ε4 present patients showing trends for poorer performance on these tasks (p = 0.11, Cohen's d = 0.54; p = 0.11, Cohen's d = 0.59, respectively). Patients with an ε4 allele also had significantly poorer spatial working memory (p = 0.04, Cohen's d = 0.69).

There were no interactions between gender, APOE status and any of the neurocognitive measures. There were also no interactions between premorbid IQ and APOE status. Correlations were also carried out between the number of APOE alleles and neurocognitive performance; no significant correlations were observed.

The results from this study demonstrated that the presence of an ε4 allele confers a risk of poorer cognitive functioning in both AD and VaD patients.

In AD, choice reaction time and delayed memory reaction times were moderately more impaired in ε4 present patients, suggesting a negative impact on speed of information processing, particularly where decision-making and memory were required. There was also evidence of a moderately large effect of ε4 on immediate memory as measured by immediate word recall. The ε4 allele was also associated with a greater impairment in selective attention in AD: ε4 present patients performed significantly less well on the Stroop test. In VaD, ε4 present patients had similar or somewhat poorer information processing speeds when compared to ε4 absent patients despite their simple reaction times being superior. However, comparable information processing speed may have come at the expense of poorer accuracy on tasks such as the choice reaction time and spatial working memory, both of which showed a moderately greater impairment. In common with the AD patients, there

Table 2
Neurocognitive functioning in AD patients according to APOE ε4 status (ANCOVA analysis).

	ε4 Present (n = 44)	ε4 Absent (n = 24)	F	df	p	Cohen's d
Speed of information processing						
Simple reaction time (ms)	546.6 (210.3)	470.2 (215.1)	1.87	1,65	0.18	0.37
Choice reaction time (ms)	675.2 (151.2)	582.1 (154.3)	5.38	1,65	0.02	0.62
Digit vigilance (ms)	564.2 (95.5)	523.1 (97.5)	2.64	1,65	0.11	0.43
Colour Trails A (s)	118.8(63.7)	108.7 (64.2)	0.36	1,65	0.55	0.16
Colour Trails B (s)	230.3 (76.3)	204.9 (74.5)	1.64	1,65	0.21	0.34
Spatial working memory reaction time (ms)	3159.8 (1988.6)	2583.1 (2031.6)	1.19	1,65	0.28	0.29
Numeric working memory reaction time (ms)	1659.9 (947.9)	1600.9 (956.8)	0.06	1,65	0.81	0.06
Delayed word recall reaction time (ms)	2134.9 (934.6)	1664.9(954.8)	3.58	1,65	0.06	0.51
Delayed picture recall reaction time (ms)	2452.4 (1503.1)	1691.8 (1535.3)	3.63	1,65	0.06	0.51
Attention						
Choice reaction accuracy (percentage correct)	95.5(6)	94.2 (5.9)	0.64	1,65	0.43	0.22
Digit vigilance accuracy (percentage correct)	93.0 (11.9)	93.7 (11.8)	0.05	1,65	0.82	0.06
Stroop colour word (number)	15.7 (7.96)	20.2 (8.3)	4.43	1,65	0.04	0.57
Executive functioning and working memory						
EXIT 25	17.4 (5.3)	15.4 (5.4)	1.81	1,65	0.18	0.38
CLOX 1	8.71 (2)	8.9 (2.4)	0.16	1,65	0.69	0.09
COWAT letter fluency	9.4 (4)	9.3 (4.4)	0.01	1,65	0.97	0.02
Spatial working memory sensitivity index	0.35 (0.7)	0.38 (0.5)	0.09	1,65	0.77	0.05
Numeric working memory sensitivity index	0.86 (0.7)	0.85 (0.5)	0.05	1,65	0.82	0.02
Immediate and delayed memory						
Immediate word recall (number)	1.6 (1.3)	2.7 (1.5)	8.60	1,65	0.01	0.79
Delayed word recall (number)	0.0 (0.7)	0.2 (0.5)	3.51	1,65	0.07	0.35
Delayed word recall sensitivity index	0.31 (0.7)	0.41 (0.5)	1.58	1,65	0.21	0.17
Delayed picture recall sensitivity index	0.51 (0.7)	0.49 (0.5)	0.05	1,65	0.83	0.03
Visuospatial functioning and semantic fluency						
CLOX 2	10.8 (2.7)	11.4 (2.4)	0.63	1,65	0.43	0.24
COWAT category fluency	10.3 (3.3)	10.1 (3.9)	0.01	1,65	0.92	0.06

Marginal mean (±standard deviation).
ms = milliseconds.

Table 3
Neurocognitive functioning in VaD patients according to APOE ε4 status (independent samples *t*-test).

	ε4 Present (*n* = 23)	ε4 Absent (*n* = 18)	*t*	*df*	*p*	Cohen's *d*
Speed of information processing						
Simple reaction time (ms)	460.3 (148.4)	581.1 (287.8)	1.62	24[a]	0.12	0.56
Choice reaction time (ms)	723.4 (253.3)	697.4 (171.1)	−0.37	39	0.71	0.12
Digit vigilance (ms)	553.7 (99.7)	541.4 (78.8)	−0.43	39	0.66	0.14
Colour Trails A (s)	111.5 (59.5)	110.8 (42.5)	−0.04	34[a]	0.97	0.01
Colour Trails B (s)	229.5 (117.1)	203.2 (60.3)	−0.79	32[a]	0.44	0.28
Spatial working memory reaction time (ms)	2733.0 (1386)	2393.0 (1201)	−0.83	39	0.42	0.27
Numeric working memory reaction time (ms)	1675.5 (854.7)	1587.3 (673.9)	−0.36	39	0.73	0.12
Delayed word recall reaction time (ms)	1902.1 (791.1)	1686.8 (530.6)	−0.99	39	0.32	0.32
Delayed picture recall reaction time (ms)	2056.1(761.4)	1887.7 (543.1)	−0.79	39	0.45	0.26
Attention						
Choice reaction accuracy (percentage correct)	94.5 (4.3)	96.7 (4.1)	1.63	39	0.11	0.54
Digit vigilance accuracy (percentage correct)	91.8 (11.6)	87.9 (15.3)	−0.93	39	0.36	0.30
Stroop colour word (number)	14.7 (6.9)	18.2 (4.9)	1.63	32[a]	0.11	0.59
Executive functioning and working memory						
EXIT 25	18.4 (5.2)	17.9 (5.1)	−0.30	39	0.77	0.10
CLOX 1	9.1 (3.2)	8.9 (3.3)	−0.20	38[a]	0.85	0.06
COWAT letter fluency	8.1 (2.6)	7.2 (3.5)	−1.02	39	0.31	0.31
Spatial working memory sensitivity index	0.32 (0.4)	0.54 (0.2)	2.19	37[a]	0.04	0.69
Numeric working memory sensitivity index	0.86 (0.2)	0.81 (0.2)	−0.70	39	0.48	0.26
Immediate and delayed memory						
Immediate word recall (number)	2.0 (1.4)	1.9 (1.4)	−0.23	39	0.82	0.07
Delayed word recall (number)	0.3 (0.7)	0.5 (1.2)	0.64	39	0.53	0.22
Delayed word recall sensitivity index	0.42 (0.2)	0.48 (0.3)	0.73	39	0.47	0.25
Delayed picture recall sensitivity index	0.54 (0.3)	0.55 (0.3)	0.23	39	0.82	0.03
Visuospatial functioning and semantic fluency						
CLOX 2	10.9 (3.3)	11.2 (2.7)	0.27	38[a]	0.79	0.10
COWAT category fluency	10.0 (2.7)	9.4 (3.8)	−0.54	39	0.59	0.19

Mean (±standard deviation).
ms = milliseconds.
[a] Equal variance not assumed.

was evidence of a moderate effect of ε4 on selective attention, with ε4 present patients performing less well on the Stroop task.

Slower speed of processing in individuals with the ε4 allele has been demonstrated previously in a small cohort (*n* = 51) of non-demented older adults [21]. In these participants, there were no significant differences noted between the ε4 present and ε4 absent groups on absolute performance except on a measure of immediate memory, with the ε4 group exhibiting greater numbers of errors. Likewise we found impairment in immediate memory in the AD patients suggesting APOE is still exerting a detectable effect at an early-moderate stage of the disease state in patients with AD. Significant differences were seen in reaction times between the two groups in the domains of physical reflexes, immediate memory, delayed memory recognition, and working memory in this study. We likewise found evidence of impairment on speed of information processing in AD patients. VaD patients exhibited a different pattern with poorer simple reaction times in ε4 absent patients but poorer accuracy in ε4 present patients.

We demonstrated an effect of ε4 on attention in both patient groups with ε4 present patients performing less well in Stroop. This has been demonstrated previously in a large cohort of patients (*n* = 5804) taking part in the PROSPER study [23]. Again, most of the participants were free of dementia (89.3% of ε4 present and 92.8% of ε4 absent participants had MMSE scores >24 at their final assessment). Of note, participants in the ε4 present group performed less well on the Stroop and recall tests than subjects in the ε4 absent group at baseline but over the average 3.2 years of follow-up, APOE status only significantly influenced change in scores on memory tests, not attention tests. This suggests APOE exerts its effect on attention prior to diagnosis.

In a further very large (*n* = 1013) recently published study, participants were tested on cognitive ability at age 11 as part of the Scottish Mental Survey of 1947 and at age 70 on reasoning, working memory, information processing speed and executive function [16]. APOE was found to have an influence on non-verbal cognition in old age and interacted with childhood IQ to influence processing speed measures, whereby the relationship between childhood IQ and processing speed in old age was attenuated in carriers of the ε4 allele. We found no interaction with APOE and premorbid IQ as measured by NART [20] but the NART is not as sensitive as an original measure of childhood IQ available in the Scottish Mental Survey.

These three studies were carried out on dementia-free participants; this is the first study looking at information processing speed and other neurocognitive measures and impact of APOE in a group of patients with AD and VaD. The numbers were small and did not permit examination of differences across the six different genotypes. There were no significant correlations seen however between number of ε4 alleles and neurocognitive measures. Significant effects, however, were seen in the previously cited study with *n* = 51 [21].

One disadvantage of this study is lack of data from a control group, this does limit data interpretation but we were primarily interested in effects of APOE on cognition in dementia.

In conclusion we found APOE had an effect on attention in both patient groups. We also found evidence of an effect on information processing speed and immediate recall in AD patients and on accuracy in VaD patients with mild-moderate disease. It would be useful to expand this study to examine larger numbers of patients with dementia, especially those with VaD and also compare to a control group.

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