

Cognitive Ability at Age 11 and 70 Years, Information Processing Speed, and *APOE* Variation: The Lothian Birth Cohort 1936 Study

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The $\epsilon 4$ allele of the apolipoprotein E (*APOE*) gene confers risk of Alzheimer's disease and, in some studies, relates to cognitive ability and decline in older people without Alzheimer's disease. Its relationship with processing speed, a contributor to cognitive decline with age, is largely unknown. This study tests the association of *APOE* with cognition and speed, with and without covarying childhood mental ability. The 1,013 participants were tested on cognitive ability at age 11 as part of the Scottish Mental Survey of 1947 and, at age 70, were tested on reasoning, working memory, information processing speed, and executive function. The results showed that *APOE* was associated with the general cognitive factor, 2 nonverbal tests, and choice reaction time (RT) variability; as expected, the $\epsilon 4$ allele was the risk allele. RT measures and a general speed factor were nonlinearly related to *APOE* when factoring childhood ability ($p < .05$): The correlation between childhood ability and speed was lower in $\epsilon 4$ allele carriers. *APOE* has an influence on nonverbal cognition in old age and interacts with childhood IQ to influence processing speed.

Keywords: cognitive ability, processing speed, *APOE*, cognitive aging, normal population

The apolipoprotein E (*APOE*) gene, located on 19q13.2, is a susceptibility gene for late-onset Alzheimer's disease (Corder et al., 1993). Its potential role in brain functioning is wide-ranging, and there is some evidence (Small, Rosnick, Fratiglioni, & Backman, 2004) that its effects extend to variation in normal cognitive aging rather than specifically to Alzheimer's disease. In the present study we investigate the effects of *APOE* genotype variability in normal cognitive aging with a special focus on information processing speed, which is theorized to play an important role in individual differences in memory and broader cognitive ability.

There are three major allelic variants of *APOE* ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$) that produce ApoE isoforms with different functional and biological prop-

erties; the $\epsilon 4$ variant increases risk of Alzheimer's disease (Corder et al., 1993). ApoE is involved in removing excess cholesterol from the blood for transport to the liver for processing. As a lipid transporter, it is important in neuronal growth and remodeling to maintain synaptodendritic connections; in the brain it is produced mostly in the astrocytes and in the peripheral nervous system in the glia surrounding sensory and motor neurons and in nonmyelinating Schwann cells (Boyles, Pitas, Wilson, Mahley, & Taylor, 1985; Mahley, Weisgraber, & Huang, 2006; Nathan et al., 2002; Weisgraber & Mahley, 1996). ApoE deficiency contributes to neurodegeneration (Masliah et al., 1995), and lipoproteins containing ApoE4 offer less protection to retinal ganglion cells from apoptosis (Hayashi, Campenot, Vance, &

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Vance, 2007). Studies of the brain tissue of people with Alzheimer's disease show an increased number of amyloid plaques in those with the e4 allele (Schmechel et al., 1993).

Associations between *APOE* and normal variation in cognitive ability have been found in population samples of adults. A meta-analysis (Small et al., 2004) including more than 20,000 adults ranging in age from 45 to around 89 years showed that the *APOE* e4 allele contributed to worse performance on measures of general cognitive ability ($N = 28$ studies), episodic memory ($N = 24$ studies), and executive functioning ($N = 8$ studies). However, *APOE*'s effect on normal cognitive ability during middle adulthood and into old age was small ($SD = .10$) compared with its effect on Alzheimer's disease risk (*APOE* e4 heterozygotes have a fourfold risk) and dementia. As episodic memory was shown to be especially affected by *APOE*, Small et al. (2004) suggested that the hippocampus (important in episodic memory) was a major biological target of *APOE*'s effects, citing prior work in which *APOE* e4 carriers showed smaller hippocampal volumes than noncarriers (e.g., Cohen, Small, Lalonde, Friz, & Sunderland, 2001). The more general effects of *APOE* e4 were attributed to the e4-related changes in β -amyloid metabolism, impairments to neuronal integrity and rejuvenation, and cardiovascular-related effects. Presumably, these effects do not occur in childhood because *APOE* is unrelated to measures of general cognitive ability at this stage of life (Deary et al., 2003; Turic, Fisher, Plomin, & Owen, 2001). Small et al.'s (2004) meta-analysis of samples ranging in average age of 55 to around 85 years showed a trend of age as a moderator of *APOE* effects on general cognition. The correlation between age and *APOE* effect size was such that increasing age was associated with smaller group differences between e4 carriers and noncarriers. Similarly, in Alzheimer's disease the e4 allele is less of a risk factor in older people, with prevalence decreasing to around .28 in e4 heterozygotes aged between 85 and 89 years and in e4 homozygotes aged 85 years and older (Breitner et al., 1999; Farrer et al., 1997). Thus, the effects of *APOE* on normal cognition appear to be curvilinear throughout the lifespan.

Although there has been much interest in the effects of *APOE* on memory and general cognitive ability, little research has focused on information processing speed. This is a serious omission because of the pivotal position that speed of information processing occupies in some influential accounts of cognitive aging (Salthouse, 2000). Behavioral studies implicate an age-related slowing in general information processing speed as a partial cause of related declines in cognitive functions such as memory (Salthouse, 1996) and general fluid intelligence (Eysenck, 1982; Jensen, 1993). Working memory has been proposed as a crucial link between speed and higher order cognition (Eysenck, 1987; Jensen, 1982; Vernon, 1987): A fast speed of information processing allows a person to carry out the component processes required for problem solving before the items to be manipulated in memory storage are lost owing to decay. A biological interrelationship between speed, executive functioning, and cognitive processes such as episodic memory has been highlighted in a study that measured cognition and regional brain volume in young and older adults (Head, Rodrigue, Kennedy, & Raz, 2008). Age was linked to reduction in brain volumes and cognitive performance, and importantly, its effect on memory was shown to be entirely mediated by cognitive speed, executive function, and neural factors.

Potential determinants of the speed of information processing include neurological factors such as oscillation speed of neuronal excitatory potentials and myelination of neurons (Jensen, 1998). For example, a greater degree of myelination might promote a faster speed and efficiency of information processing, because myelinated fibers in the brain (i.e., white matter) are responsible for transmitting neural information to differing regions of the brain and across the corpus callosum. With normal aging, atrophy in regions of the corpus callosum and degradation of white matter integrity occur (e.g., Reuter-Lorenz & Stanczak, 2000; Ryberg et al., 2008; Sullivan, Rohlfing, & Pfefferbaum, in press). The structural integrity of white matter tracts (especially in parietal and temporal cortices and left middle frontal gyrus) has also been related to cognitive speed (Digit-Symbol test) in healthy young adults measured by diffusion tensor imaging (Turken et al., 2008). Other biobehavioral imaging studies show that the influence of white matter integrity on cognitive ability in old age is mediated by reaction time (RT), a processing speed measure (Deary et al., 2006). Age-related slowing of RT (and more generally cognitive processing speed) may therefore stem from deterioration in white matter tracts in the brain, accounting for some of the *APOE* effects on age-related cognitive decline and the risk of Alzheimer's disease (Bartzokis et al., 2006; Deary et al., 2006). Importantly, a neuroimaging study of healthy participants showed a decline in white matter integrity in the posterior corpus callosum of e4 carriers compared with noncarriers (Persson et al., 2006). Biological evidence is accumulating to support a role of *APOE* in brain myelination, which we predict, and others have found (Turken et al., 2008), to be central to speed of information processing.

APOE studies that have included information processing speed measures have typically used psychometric tasks of processing speed such as digit-symbol substitution and number comparison. A meta-analysis of 10 of these studies showed that *APOE* did not influence processing speed (Small et al., 2004). Although these tasks tap speed, they are not simple and probably also invoke complex cognitive processing. More elementary cognitive tasks, such as RT and inspection time, are conceptually simpler and may serve as better proxies of the physiological properties of the central nervous system (Deary, 2000). RT, especially choice RT, is associated with higher cognitive abilities, slows in old age, and is associated with cognitive decline (Deary, Der, & Ford, 2001; Der & Deary, 2006; Salthouse, 1996, 2000). Inspection time is a psychophysical task assessing the efficiency of visual processing. It usually takes the form of a two-alternative, forced-choice, backward-masking procedure in which participants are asked to indicate which of two markedly different parallel lines is longer (Nettelbeck, 2001). The stimuli are presented for different durations; accuracy at shorter stimulus durations indicates faster information processing, which is associated with higher scores on psychometric intelligence tests (Grudnik & Kranzler, 2001). Inspection time partially mediates the association between age and the decline in various cognitive functions (Deary, 2000; Nettelbeck & Rabbitt, 1992) and is markedly poorer in older adults with mild cognitive impairment (Bonney et al., 2006; Lu, Neuse, Madigan, & Doshier, 2005) and dementia (Deary, Hunter, Langan, & Goodwin, 1991).

Processing efficiency tests such as RT and Inspection Time have been proposed as useful early detectors—clinical markers—of age-related cognitive decline (Nettelbeck & Wilson, 2004), yet they have been largely overlooked in studies of *APOE*. One recent,

small study ($N = 51$) that measured RT found no association between accuracy on a battery of memory tasks (except immediate memory) and *APOE* $\epsilon 4$ variation in participants aged 62 to 85 years. There was, however, an association with response time measures from the four memory tasks and a simple RT task. The authors suggested that speed measures may be more sensitive indicators of memory deficits (O'Hara et al., 2008). Obviously, there is a need for replication of such findings and investigation of more extensive batteries of processing speed tasks.

The cognitive traits typically studied in older people in *APOE* research reflect the variation in both lifelong cognitive ability and cognitive aging per se because they rarely adjust for stable cognitive ability. Almost half of the variance in cognitive ability in old age overlaps with that in childhood. For example, raw correlations between general cognitive ability in childhood and varied cognitive ability measures in old age have been estimated in the range of .58–.66 in two Scottish samples (Deary, Whiteman, Starr, Whalley, & Fox, 2004). To capture variation in cognitive change in old age, some studies have incorporated prior mental ability in their analyses. However, most of these studies have used premorbid IQ estimates as proxies for earlier cognitive functioning rather than original measures of IQ (e.g., Bertheau-Pavy, Park, & Raber, 2007; Henderson et al., 1995). Here we use the more reliable measure of IQ measured at age 11 as an index of adult mental ability prior to cognitive aging (with which it strongly correlates).

The aim of our study is to examine the influence of *APOE* variation in normal cognitive aging. We are especially interested in its effects on information processing speed, which is theoretically tied to biological functions (e.g., brain myelination) that are potentially affected by *APOE*; to this end we use assessments of processing speed at different levels of complexity: psychometric, cognitive-experimental, and psychophysical.

Method

Sample

The sample was the Lothian Birth Cohort 1936 (LBC1936), which comprises 1,091 surviving participants of the Scottish Mental Survey 1947 (SMS1947) who undertook medical and cognitive testing at age 70. Recruitment was accomplished with the assistance of the Lothian Health Board, which identified all individuals listed on the Lothian Community Health Index who were born in 1936, that is, individuals who might have taken part in the Scottish Mental Survey of 1947. At the start of the study, 3,810 people born in 1936 were identified. Of the 3,686 individuals invited to hear about the study, 1,703 responded (46.2% of those contacted), some of whom were not interested, were medically unfit to participate, or had not sat the SMS1947. After subsequent mailings, 1,226 individuals were interested and eligible for the study; of these, 1,091 participated. See Deary et al. (2007) for full details on participant recruitment.

All participants lived independently in the community and were able to travel to the Wellcome Trust Clinical Research Facility. Medical history was obtained in a structured interview. For this study, 13 individuals were identified as having potential dementia (a score of <24 on the Mini-Mental State Examination; Folstein, Folstein, & McHugh, 1975), 1 reported a history of dementia, and 1 had incomplete test data; they were excluded from analyses. A further 63 individuals did not have *APOE* genotype data owing to

the lack of a good-quality DNA sample ($N = 13$) or failed genotyping ($N = 50$). Therefore, the final sample for analysis included 508 women and 505 men, ranging in age from 67.7 to 71.5 years, with a mean age of 69.6 years ($SD = 0.8$ years; all were Caucasian). Their years of full-time education ranged between 8 and 14, with the average being 10.7 years ($SD = 1.1$ years).

APOE Genotyping

Genomic DNA was isolated from whole blood. The target sequence for each single-nucleotide polymorphism—two polymorphic sites (rs7412 and rs429358) that account for the three alleles $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ (Wenham, Price, & Blandell, 1991)—was genotyped with TaqMan technology by the Wellcome Trust Clinical Research Facility Genetics Core, Western General Hospital, Edinburgh.

Cognitive Tests

Full details of all cognitive and information processing tasks are given in a free-access LBC1936 protocol article (Deary et al., 2007). Briefer descriptions of the relevant tests are given here.

The Mini-Mental State Examination (MMSE) was used to screen for possible dementia (Folstein et al., 1975). A general measure of verbal cognitive ability and verbal reasoning (Moray House Test No. 12; MHT) had been administered when participants were age 11 in the SMS1947 (Scottish Council for Research in Education, 1949). It was readministered in this sample at a mean age of almost 70 years, under the same instructions and 45-min time limit. The other cognitive tests in the battery administered at age 70 and investigated in the present study included Backward Digit Span (working memory) from the Wechsler Memory Scale–IIIUK (WMS–IIIUK) and Letter–Number Sequencing (working memory), Matrix Reasoning (nonverbal reasoning) and Block Design (constructional ability) from the Wechsler Adult Intelligence Scale–IIIUK (WAIS–IIIUK; Wechsler, 1998). The Verbal Fluency test provided a measure of executive function (Lezak, 2004). A full description of these tests can be found in the Lothian Birth Cohort 1936 protocol article (Deary et al., 2007).

The information processing speed battery comprised two psychometric tests from the WAIS–IIIUK, Digit Symbol–Coding and Symbol Search, and two elementary cognitive tasks, RT and Inspection Time, which are described briefly here; a full account of each test is given in Deary et al. (2007).

Simple and four-choice RT. Mean and standard deviation of correct trials on a simple RT (20 trials) and four-choice RT (40 trials) task were used to assess speed and variability of simple information processing. For Simple RT, the participant was required to press a response key as fast as possible following the occurrence of 0 on the LCD screen. The four-choice condition required the participant to press the corresponding response key when a target of 1, 2, 3, or 4 appears on the LCD screen. These task measures have been shown to be reliable over a 1-day test interval with an average test–retest correlation of .63 reported (Deary & Der, 2005a, 2005b). A full description and illustration of the RT tasks can be found in Deary, Der, and Ford (2001).

Inspection Time. Inspection Time is a two-alternative, forced-choice, backward-masking visual discrimination task. It was used to assess speed of elementary visual processing, requiring participants to make a simple visual discrimination: to indicate, with no

pressure on response time, which of two parallel, vertical lines of markedly different lengths was longer. The stimuli and psychophysical procedure were the same as those used in Deary, Simonotto, et al. (2004), with a prescribed number of trials given at different stimulus durations. The correctness of each response across the 150 trials was recorded; increased accuracy indicated that more trials were correct, especially at the more difficult, shorter stimulus durations. See Deary et al. (2007) for more detail on the Inspection Time task.

Statistical Analysis

A general cognitive ability factor (*g* factor) was derived from principal components analysis of the WMS-IIIUK subtest (Backward Digit Span) and five WAIS-IIIUK subtests (Letter–Number Sequencing, Matrix Reasoning, Block Design, Digit Symbol, Symbol Search). Regression scores were calculated for the first unrotated principal component with SPSS 14.0 for Windows. A general speed factor was similarly derived for the set of speed measures (Symbol Search, Digit Symbol, Simple RT mean, Choice RT mean, Inspection Time); RT standard deviation measures that were strongly correlated with RT mean scores were excluded. Note that that general speed factor contains two of the tests that are included in the general cognitive factor (Digit Symbol and Symbol Search). Thus, the two factors will necessarily overlap somewhat, reflecting the well-established finding that cognitive speed is a group factor with a moderately high *g* loading. However, the *g* factor will contain only variance that is common to all tests (and not the speed-specific variance) and the speed factor only variance that is common to the speed tests. General linear models were used to test the fixed effect of *APOE* e4 on the dependent measures. Genotypes were recoded for presence or absence of at least one e4 allele, consistent with a model of gene action where e4 is dominant to other alleles, as previously investigated (Small et al., 2004). Full factorial models were specified including gender and age at cognitive testing as covariates. Analyses were repeated with and without childhood IQ (residualized on age at cognitive testing in childhood) as a covariate so that the effects on cognitive aging as well as stable cognitive ability could be investigated.

Because we tested a large number of correlated variables, we used permutation tests to evaluate how significant our overall findings were. Empirical *p* values for the *APOE* main effect (in the model covarying for MHT at age 11) were derived by running 100,000 tests in which the *APOE* genotype was randomly permuted across individuals. We counted the number of times that multiple cognitive measures (1, 2, 3, etc.), excluding the factor scores, showed significance of the *APOE* main effect in the same test by chance alone (alpha of .05).

Results

Descriptive

Allele frequencies in the sample were e2 = 7.4%, e3 = 76.7%, and e4 = 15.9%, and the following genotype frequencies were observed: e2e2 = 5 (0.5%), e2e3 = 117 (11.5%), e2e4 = 22 (2.2%), e3e3 = 592 (58.4%), e3e4 = 258 (25.5%), and e4e4 = 19 (1.9%). Thus, at least one copy of the e4 allele was present in 299 (29.5%) of the 1,013 participants. An exact test of Hardy–Weinberg

equilibrium (HWE) performed in PEDSTATS (Wigginton & Abecasis, 2005) confirmed that *APOE* was in HWE ($p = .62$).

Data were normally distributed for all variables, with the exception of Simple RT measures, which were positively skewed and transformed by a logarithmic (Base 10) function to improve their distribution. Outliers—scores exceeding $\pm 3 z$ —were removed from analysis: For three of the tests there were no outliers, and a maximum of 18 outliers were identified for Simple RT mean and standard deviation scores. The first unrotated principal components for the general cognitive factor and the general speed factor explained 51% and 49% of variance, respectively. Significant intercorrelations (ranging .12–.61 with a mean of .31) were observed among all variables.

The range of correlations among the speed variables was .13–.61 with a mean of .33. Medical conditions—including diagnosed diabetes, history of stroke, Parkinson’s disease, reported high cholesterol and high blood pressure, and history of cardiovascular disease—with potential impact on cognitive ability were assessed separately for the speed and *g* factors. Those with diabetes ($N = 85$) showed lower *g* scores. Those with a history of stroke ($N = 47$) showed slower processing speed. Cardiovascular disease history ($N = 230$) negatively affected speed and the *g* factor. Those with high blood pressure ($N = 383$) showed lower *g* factor scores. Additional analyses therefore covaried for these medical conditions and years of education (which was significantly correlated with the cognitive measures).

No significant difference existed between those with and without a copy of the *APOE* e4 allele in MHT IQ at age 11 (MHT11) years, $t(945) = -.34, p = .73$, or MMSE scores at age 70 years, $t(1011) = -.10, p = .92$. Respective mean scores for those with and without a copy of the e4 allele were 49.7 ($SD = 10.9$) and 49.4 ($SD = 11.0$) for the MHT11 and 28.9 ($SD = 1.3$) and 28.8 ($SD = 1.3$) for the MMSE.

General Linear Modeling

Univariate linear models (SPSS Version 14.0), including gender and age as covariates, were run for each of the dependent variables with *APOE* e4 status as a fixed effect and repeated with MHT11 as a covariate and testing the interaction between *APOE* and MHT at age 11.

Main Effects of Gender, Age, and Childhood IQ

The *F* statistics and effect sizes for the gender, age and childhood IQ main effects are shown in Appendixes A and B. The main effect of gender—from the model without MHT11—was significant for six tests, with a female advantage observed for Verbal Fluency, whereas a male advantage was observed for Matrix Reasoning, Block Design, Digit Symbol, Choice RT standard deviation, and Inspection Time. Means for women and men are shown in Table 1. It should be noted that in the model including the *APOE* \times MHT11 interaction term, main effects of gender were present for MHT and *g* factor scores (male advantage) but not Verbal Fluency. Age effects, despite the small age range, were significant ($p < .01$) for all measures except Simple RT mean and standard deviation, Choice RT standard deviation, and Inspection Time; increasing age was related to lower cognitive performance.

Table 1

Means and Standard Deviations of the Cognitive Measures and the Derived General Processing Speed and General Cognitive Ability (g) Factors Separately for Female and Male Participants and for APOE e4 Carriers (e4+) and Noncarriers (e4-)

Dependent variable	Women		Men		e4+ allele		e4- allele	
	N	M (SD)	N	M (SD)	N	M (SD)	N	M (SD)
Moray House Test	530	64.35 (7.80)	523	65.38 (7.52)	292	64.65 (7.79)	700	64.95 (7.60)
Matrix Reasoning	539	12.99 (5.03)	533	14.17 (5.12)	297	13.03 (4.97)	713	13.76 (5.12)
Verbal Fluency	535	43.11 (12.34)	535	41.67 (12.31)	298	42.79 (12.32)	709	42.33 (12.29)
Letter-Number Sequence	534	10.90 (3.02)	529	11.05 (3.12)	295	10.74 (2.93)	706	11.05 (3.12)
Backward Digit Span	539	7.71 (2.21)	536	7.83 (2.29)	299	7.69 (2.11)	713	7.79 (2.30)
Block Design	539	32.11 (9.71)	531	35.72 (10.46)	297	33.34 (10.36)	711	34.06 (10.15)
Symbol Search	535	24.78 (5.84)	530	24.87 (6.20)	293	24.12 (5.86)	711	25.11 (6.09)
Digit Symbol	537	58.60 (12.19)	533	55.03 (12.95)	299	56.11 (12.39)	708	57.18 (12.89)
Simple RT M	530	-0.57 (0.07)	525	-0.57 (0.07)	294	-0.57 (0.06)	701	-0.57 (0.07)
Raw	530	0.27 (0.04)	525	0.27 (0.04)	299	0.27 (0.05)	710	0.28 (0.05)
Simple RT SD	528	-1.28 (0.17)	525	-1.27 (0.19)	295	-1.28 (0.18)	697	-1.27 (0.19)
Raw	528	0.06 (0.03)	525	0.06 (0.03)	299	0.06 (0.04)	710	0.06 (0.05)
Choice RT M	535	0.64 (0.07)	527	0.63 (0.08)	297	0.64 (0.08)	703	0.64 (0.08)
Choice RT SD	532	0.14 (0.03)	526	0.13 (0.03)	295	0.14 (0.03)	701	0.13 (0.03)
Inspection Time	505	110.86 (10.22)	513	114.33 (9.99)	280	111.83 (10.49)	680	112.88 (10.07)
Speed factor	494	-0.03 (0.96)	495	0.03 (1.04)	271	-0.08 (0.96)	663	0.02 (1.02)
g factor	528	-0.05 (0.96)	519	0.05 (1.03)	288	-0.10 (0.94)	698	0.04 (1.00)

Note. APOE = apolipoprotein E; RT = reaction time.

APOE e4+ Versus APOE e4- Models Without Controlling for Childhood IQ

APOE e4 allele status contributed significantly to Matrix Reasoning, Symbol Search, Choice RT standard deviation, and the g factor (see Table 2 for *F* statistic, *p* value, η^2). The mean differences were in the predicted direction, with poorer performance observed for those possessing an e4 allele (see Table 1). Permutation testing showed that the probability of attaining three significant tests (as observed) by chance was .032, indicating that our results ($p \leq .02$) were robust. To test the stable or reliable variance

of the MHT (for which childhood and adult scores were available), a repeatability analysis was performed with the mean gender and age residualized MHT scores at age 11 and 70; this test was nonsignificant ($p = .80$).

APOE e4+ Versus APOE e4- Models Controlling for Childhood IQ

A significant main effect of APOE e4 allele status, although with a larger effect size, was found for the same variables reported in the previous analysis, that is, Matrix Reasoning, Symbol Search,

Table 2

Analysis of Variance Results for APOE (e4 Allele Status) Factor Models Without Controlling for Moray House Test at Age 11 (MHT11) and Controlling for MHT11

Dependent variable	APOE with MHT11								
	APOE without MHT11 main effect			APOE main effect			APOE \times MHT11 effect		
	<i>F</i>	<i>p</i>	η^2	<i>F</i>	<i>p</i>	η^2	<i>F</i>	<i>p</i>	η^2
Moray House Test	(1, 988) = 0.35	.56	.000	(1, 922) = 1.73	.19	.002	(1, 922) = 0.21	.65	.000
Matrix Reasoning	(1, 1006) = 4.85	.03	.005	(1, 938) = 7.25	.01	.008	(1, 938) = 0.00	.99	.000
Verbal Fluency	(1, 1003) = 0.42	.52	.000	(1, 935) = 0.10	.75	.000	(1, 935) = 2.47	.12	.002
Letter-Number Sequence	(1, 997) = 2.12	.15	.002	(1, 932) = 1.96	.16	.002	(1, 932) = 1.86	.17	.002
Backward Digit Span	(1, 1008) = 0.38	.54	.000	(1, 940) = 0.60	.44	.001	(1, 940) = 0.60	.44	.001
Block Design	(1, 1004) = 1.44	.23	.001	(1, 936) = 2.60	.11	.003	(1, 936) = 0.10	.75	.000
Symbol Search	(1, 1000) = 5.30	.02	.005	(1, 933) = 6.25	.01	.007	(1, 933) = 0.44	.50	.000
Digit Symbol	(1, 1003) = 1.05	.30	.001	(1, 933) = 1.96	.16	.002	(1, 932) = 2.21	.14	.002
Simple RT M	(1, 991) = 0.60	.44	.001	(1, 924) = 0.96	.33	.001	(1, 924) = 7.91	.005	.008
Simple RT SD	(1, 988) = 0.45	.50	.000	(1, 920) = 0.98	.32	.001	(1, 920) = 5.07	.02	.005
Choice RT M	(1, 996) = 0.79	.37	.001	(1, 928) = 0.90	.34	.001	(1, 928) = 5.75	.02	.006
Choice RT SD	(1, 992) = 4.64	.03	.005	(1, 924) = 5.85	.02	.006	(1, 924) = 1.24	.27	.001
Inspection Time	(1, 956) = 2.93	.09	.003	(1, 890) = 2.43	.12	.003	(1, 890) = 0.47	.49	.001
Speed factor	(1, 930) = 2.09	.15	.002	(1, 866) = 1.94	.16	.002	(1, 866) = 6.35	.01	.007
g factor	(1, 981) = 4.24	.04	.004	(1, 918) = 6.59	.01	.007	(1, 918) = 0.75	.39	.001

Note. *P* values in bold indicate significance. APOE = apolipoprotein E; RT = reaction time.

Choice RT standard deviation, and the g factor. An interaction effect between *APOE* and MHT11 was observed for several processing speed measures: Simple RT mean and standard deviation, Choice RT mean, and the general speed factor (see Table 2). The interaction was such that the group of participants carrying an $e4$ allele showed a weaker relationship (which was nonsignificant for Simple RT) between MHT11 and the dependent speed measure than the group of participants who did not possess an $e4$ allele. In other words, the correlation between IQ at age 11 and speed was attenuated in the group possessing an $e4$ allele. Figure 1 depicts the interaction effect for the general speed factor. The correlation between MHT11 and the processing speed factor at age 70 was .28 ($SE = 0.06$) in $e4$ carriers compared with .45 ($SE = .04$) in noncarriers.

APOE e4+ Versus APOE e4- Models Adjusted for Medical and Education Variables

Analyses for *APOE* $e4$ status adjusted for medical and education variables produced very similar results (available on request) to those without adjustment. Subsidiary analyses also showed that there were no differences in age, education, or medical conditions between $e4$ carriers and noncarriers.

APOE Common Genotype Models

Models in which *APOE* $e4$ allele status was replaced with a three-level fixed factor representing the common genotypes ($e2e3$,

$e3e3$, $e3e4$) showed similar results as the $e4$ dominant models in that lower tests scores were observed for the $e3e4$ genotype group than in the other two genotypic groups. However, the results were of lesser significance owing to lower power resulting from the smaller sample size and test on two degrees of freedom (data not shown).

Discussion

We found evidence of allelic association between *APOE* and both psychometric and information processing speed indices of cognitive ability in relatively healthy, community-dwelling older people ranging in age from 67 to 71 years. Consistent with past findings, carriers of the $e4$ allele demonstrated lower task performance on the associated measures of reasoning, processing speed, and general ability. Several processing speed measures showed an interaction effect between childhood IQ (an indicator of the life-long trait of general cognitive ability) and *APOE* $e4$ variation. We speculate that *APOE*'s effect on brain myelination may be a source of this interaction effect, as discussed below.

APOE has been implicated in normal cognitive aging, and here we replicate this association for the g factor, Matrix Reasoning, and Symbol Search psychometric tests and extend its influence to the new measure of Choice RT variability. Association with the $e4$ allele was significant even after controlling for childhood IQ, suggesting that *APOE* allelic variation is relevant to aspects of cognitive aging irrespective of stable general cognitive ability. But the finding that *APOE* allelic variation was not associated with IQ at age 11 suggests that the *APOE* gene may not be important for cognitive ability until later in life. This null finding in childhood has been reported elsewhere (Deary et al., 2002). In our sample, not all psychometric tests showed significant association with *APOE*; effects were mostly observed for those tests relying less on acculturated learning. For instance, the g factor we extracted was based on reasoning, working memory, and spatial tasks and the individual tests of Matrix Reasoning, Symbol Search, and Inspection Time were all nonverbal tasks. It is possible that *APOE* especially influences visuospatial perception and attention processes that are less dependent on motor responses, as tasks requiring visual-motor coordination (i.e., Digit Symbol) were not affected by *APOE*. This would be consistent with reports by Greenwood and colleagues (Greenwood, Lambert, Sunderland, & Parasuraman, 2005; Greenwood, Sunderland, Friz, & Parasuraman, 2000), who found that nondemented, asymptomatic middle-aged individuals with an $e4$ allele showed specific and selective deficits in visual attention but not in general executive functioning (as indexed by nonspecific neuropsychological tasks).

Like ours, a previous study focusing on 80-year-olds did not find association between the Verbal Fluency test and *APOE* (Deary, Whiteman, Pattie, et al., 2004), but they did report an association between *APOE* and MHT scores (Deary et al., 2002), which we did not replicate here. This inconsistency between studies is of interest in view of the fact that both samples came from the same region in Scotland but were initially measured in different decades (1930s vs. 1940s) and that both analyses adjusted for IQ at age 11. The possibility that this older sample included participants who were closer to incipient dementia than ours might explain this discrepancy. At age 70 the prevalence of dementia in the population is relatively low (Knapp & Prince, 2007), so our

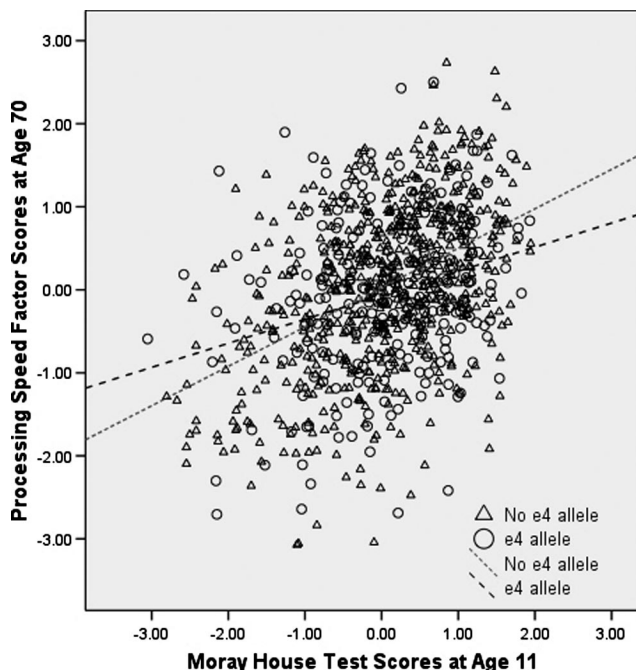


Figure 1. The interaction effect of the Moray House Test at age 11 (residualized for age and gender) and apolipoprotein E $e4$ status ($e4+$ vs. $e4-$) on the general speed factor at age 70 (residualized for age and gender). Graph depicts the linear regression of speed on childhood IQ, separately for $e4+$ and $e4-$ groups. Note that positive speed factor scores represent faster speed of processing.

sample was unlikely to have included people with incipient Alzheimer's dementia, and furthermore, we excluded participants with low scores on the MMSE and with a reported history of dementia.

The present study is the first to investigate processing speed in old age while accounting for premorbid general cognitive ability. With the exception of Choice RT variability, we did not observe any main effect of *APOE* on the processing speed measures. This is consistent with the null associations reported by Jorm et al. (2007) for Simple and Choice RT mean in groups of participants varying in age from 20 to 64 years but not adjusting for premorbid IQ. For Simple RT mean and standard deviation, Choice RT, and the general speed factor we observed an interaction between *APOE* e4 and childhood IQ such that in e4 carriers the relationship between childhood IQ and speed at age 70 was significantly diminished (see Figure 1). In e4 noncarriers, 20% of the variance in the general speed factor overlapped with childhood IQ, indicating that the relationship between speed and IQ is not simply state dependent but relies on stable underlying processes. Because early general cognitive function is significantly less predictive of later processing speed in e4 carriers, this suggests that *APOE* affects some of the underlying processes contributing to this continuity into old age. That is, one must seek how variation in *APOE* leads to different causal structures between childhood intelligence and processing speed in later life. How this occurs is not straightforward, because *APOE* does not affect the mean level of childhood IQ or those speed measures showing the interaction.

The long-standing continuity between childhood IQ and processing speed in e4 noncarriers suggests relatively high stability of the biological causes across long periods of time, as would occur in a brain whose efficiency of repair retained existing baseline structures. However, if neuronal repair in e4 carriers is less efficient (Mahley et al., 2006), compensatory remodeling might lead to more brain restructuring to achieve the same behavioral ends. Therefore, it is possible that *APOE* affects a biological process important for determining speed of processing but that ensuing behavioral deficits (i.e., performance on speed tasks) in e4 carriers are somehow compensated by invoking other biological pathways or strategies or cognitive processes that are associated with general ability. This may explain why mean levels are retained and why the correlation between childhood IQ and speed in old age is still significant in e4 carriers but of weaker strength than in e4 noncarriers, at least for choice RT and general speed.

Brain myelination might be one such biological factor that is affected by *APOE* and thus contributes to the weaker association between childhood IQ and processing speed in early old age. A study of *APOE* effects on age-related myelin breakdown showed that the severity and rate of myelin breakdown, measured by magnetic resonance imaging and transverse relaxation, in a healthy sample aged 55 to 75 years was associated with *APOE* variation (Bartzokis et al., 2006). *APOE* e4 genotype carriers exhibited a steeper slope of decline in transverse relaxation with age than participants with the *APOE* e2 genotype or *APOE* e3 homozygotes. The association between cognitive processing speed and myelin breakdown was later investigated and found to be correlated only in the group of *APOE* e4 carriers (Bartzokis et al., 2007). If in e4 carriers brain myelination is related to processing speed, then this would be a source of variance that would weaken the correlation between childhood IQ and speed, because myelin breakdown does not occur in childhood and therefore might be an

influence relatively unrelated to childhood IQ. Further evidence for the role of *APOE* in brain myelination comes from studies of white matter hyperintensities (WMH), which have been linked to amyloid β plasma levels (affected in Alzheimer's disease) in *APOE* e4 carriers (van Dijk et al., 2004). A review of studies investigating the association between the *APOE* e4 allele and WMH confirmed that in nondemented cohorts the e4 allele was associated with greater WMH volumes (Cherbuin, Leach, Christensen, & Anstey, 2007). Lower levels of cerebrospinal *APOE* have also been found in individuals with WMH and in dementia cases (Skoog et al., 1997).

Although the exact neurobiological effects are unclear, it is possible that brain myelination is involved in *APOE*'s effects on processing speed. An exciting future direction of this study will be to link variation in speed and *APOE* with white matter tract integrity; measures of diffusion tensor and magnetization transfer magnetic resonance imaging are currently being collected from the LBC1936 cohort. We will have the potential to extend Turken et al.'s (2008) finding of a relationship between white matter integrity and processing speed to a wider range of speed measures and, importantly, to undertake large-scale genetic analyses.

In our study, *APOE* e4 variation explained around 0.5% of variance in the psychometric measures and 1% of variance in the speed measures. These effect sizes are smaller than those reported by Deary, Whiteman, Pattie, et al. (2004) but are slightly larger than those reported in the most recent meta-analysis (Small et al., 2004) of *APOE* and cognitive ability, in which the largest significant correlation was $-.03$. Our results significant at the more conservative two-tailed probability level are particularly robust considering that there was prior evidence for a directional effect of the e4 allele. The effect of *APOE* genotype on normal cognitive ability is small, so there are likely to be many other genes of similar or smaller effect size involved in cognition (because no major genes have been discovered through linkage analysis). Furthermore, there are likely to be interaction effects among genes and between genes and environmental factors on cognitive ability. Also, there are likely to be multiple environmental effects.

In summary, our results supported an influence of *APOE* variation on cognitive traits especially tapping nonverbal abilities. Moreover, we showed an influence of *APOE* variation on information processing speed measures of cognition, whereby the relationship between childhood IQ and processing speed in old age was attenuated in carriers of the e4 allele. Ideally, studies that measure processing speed in childhood and in groups of people younger than 70 years of age are needed to confirm when the putative change in information processing abilities affected by *APOE* occurs.

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(Appendixes follow)

Appendix A

Analysis of Variance Results for Gender and Age From the Model Excluding Moray House Test at Age 11 as a Covariate

Dependent variable	Gender main effect			Age main effect		
	<i>F</i>	<i>p</i>	η^2	<i>F</i>	<i>p</i>	η^2
Moray House Test	(1, 988) = 3.53	.06	.000	(1, 988) = 18.85	<.001	.019
Matrix Reasoning	(1, 1006) = 11.34	.001	.009	(1, 1006) = 18.70	<.001	.018
Verbal Fluency	(1, 1003) = 4.84	.03	.005	(1, 1003) = 19.44	<.000	.019
Letter–Number Sequence	(1, 997) = 0.09	.76	.000	(1, 997) = 31.12	<.001	.030
Backward Digit Span	(1, 1008) = 0.05	.83	.000	(1, 1008) = 23.81	<.001	.023
Block Design	(1, 1004) = 27.85	.00	.024	(1, 1004) = 17.85	<.001	.017
Symbol Search	(1, 1000) = 0.07	.79	.001	(1, 1000) = 55.56	<.001	.053
Digit Symbol	(1, 1003) = 23.77	<.001	.020	(1, 1003) = 34.10	<.001	.033
Simple RT <i>M</i>	(1, 991) = 0.03	.87	.000	(1, 991) = 3.24	.07	.003
Simple RT <i>SD</i>	(1, 988) = 2.11	.15	.002	(1, 988) = 2.39	.12	.002
Choice RT <i>M</i>	(1, 996) = 0.45	.50	.001	(1, 996) = 11.17	.001	.011
Choice RT <i>SD</i>	(1, 992) = 32.42	<.001	.032	(1, 992) = 1.78	.18	.002
Inspection Time	(1, 956) = 29.27	<.001	.030	(1, 956) = 1.68	.19	.002
Speed factor	(1, 930) = 0.20	.66	.000	(1, 930) = 27.03	<.000	.028
<i>g</i> factor	(1, 982) = 0.84	.36	.001	(1, 982) = 57.81	<.001	.056

Note. *P* values in bold indicate significance. RT = reaction time.

Appendix B

Analysis of Variance Results for Gender, Age, and Moray House Test at Age 11 (MHT11) From the Model Including the *APOE* × MHT11 Interaction Term

Dependent variable	Gender main effect			Age main effect			MHT11 main effect		
	<i>F</i>	<i>p</i>	η^2	<i>F</i>	<i>p</i>	η^2	<i>F</i>	<i>p</i>	η^2
Moray House Test	(1, 922) = 16.07	<.001	.017	(1, 922) = 6.18	.01	.007	(1, 922) = 695.48	<.001	.430
Matrix Reasoning	(1, 938) = 22.63	<.001	.024	(1, 938) = 10.55	.001	.011	(1, 938) = 219.61	<.001	.190
Verbal Fluency	(1, 935) = 1.25	.26	.001	(1, 935) = 8.03	.005	.009	(1, 935) = 140.31	<.000	.130
Letter–Number Sequence	(1, 932) = 0.99	.32	.001	(1, 932) = 23.06	<.001	.024	(1, 932) = 153.70	<.001	.142
Backward Digit Span	(1, 940) = 0.83	.36	.001	(1, 940) = 15.60	<.001	.016	(1, 940) = 135.86	<.001	.126
Block Design	(1, 936) = 47.94	<.001	.049	(1, 936) = 10.07	<.001	.011	(1, 936) = 214.91	<.001	.187
Symbol Search	(1, 933) = 0.10	.76	.073	(1, 933) = 47.19	<.001	.048	(1, 933) = 152.11	<.001	.140
Digit Symbol	(1, 936) = 23.03	<.001	.048	(1, 936) = 25.22	<.001	.026	(1, 933) = 131.52	<.001	.123
Simple RT <i>M</i>	(1, 924) = 0.15	.69	.000	(1, 924) = 2.11	.15	.002	(1, 924) = 19.79	<.001	.021
Simple RT <i>SD</i>	(1, 920) = 1.17	.28	.001	(1, 920) = 1.39	.24	.002	(1, 920) = 13.03	<.001	.014
Choice RT <i>M</i>	(1, 928) = 1.29	.26	.001	(1, 928) = 6.74	.01	.007	(1, 928) = 37.38	<.001	.039
Choice RT <i>SD</i>	(1, 924) = 39.40	<.001	.041	(1, 924) = 0.27	.60	.000	(1, 924) = 26.71	<.001	.028
Inspection Time	(1, 890) = 26.73	<.001	.029	(1, 890) = 0.60	.44	.001	(1, 890) = 6.94	.009	.008
Speed factor	(1, 866) = 0.40	.53	.000	(1, 866) = 20.40	<.001	.023	(1, 866) = 108.39	<.001	.111
<i>g</i> factor	(1, 918) = 5.49	.02	.006	(1, 918) = 54.01	<.001	.056	(1, 918) = 417.19	<.001	.312

Note. *P* values in bold indicate significance. *APOE* = apolipoprotein E; RT = reaction time.

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