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APOE genotype and cognitive change in young, middle-aged and older adults living in the community

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Abstract

We examined whether the *APOE* ε4 allele was associated with cognitive benefits in young adulthood but reversed to confer cognitive deficits in later life ("antagonistic pleiotropy") in the absence of dementia-related neuropathology. We also tested whether the ε2 allele was associated with disadvantages in early adulthood but offered protection against cognitive decline in early old age. Eight-year cognitive change was assessed in 2,013 cognitively-normal community-dwelling adults aged either 20 to 24, 40 to 44, or 60 to 64 years at baseline. Although cognitive decline was associated with age, multilevel models contrasting the ε2 and ε4 alleles provided no evidence that *APOE* genotype was related to cognitive change in any of the age groups. The findings suggest that in the absence of clinically salient dementia pathology, *APOE* ε2 and ε4 alleles do not exhibit antagonistic pleiotropy in relation to cognition between the ages of 20 and 72 years.

Keywords: *APOE*; cognitive change; age; antagonistic pleiotropy; dementia

Does *APOE* genotype influence the trajectory of cognitive change across the adult lifespan? Importantly, does *APOE*-related variation in cognition over time occur in the absence of the neuropathology associated with dementia? These pressing questions provided the motivation for the present study. *APOE* genotype is determined by three alleles, ε2, ε3 and ε4, resulting in six possible combinations (ε2/2, ε2/3, ε2/4, ε3/3, ε3/4, ε4/4). While possession of the ε4 allele is an established risk factor for dementia (1) and ε2 offers protection against the disease (2), the association between *APOE* genotype and cognition across the adult lifespan is less clear.

A major question concerns whether *APOE* ε4 produces a cognitive phenotype (3) in that the allele directly influences cognition, or whether ε4-related cognitive deficits reflect the preclinical phase of, as yet, undetected dementia and therefore represent an early behavioral marker in persons genetically predisposed to the disease. Meta-analyses (4, 5) suggest the former. However, it is unclear how many of the studies contributing to these analyses included individuals in the prodromal phase of dementia. Longitudinal studies produce mixed findings, some suggesting that there is little ε4-related change in cognitive or mental ability in older adults (6-9), while others suggest greater decline in ε4 carriers (10-15). However, although some of these latter investigations have made some formal attempt to rule out sub-clinical dementia cases (11, 13, 15), in others it is not clear whether ε4-related cognitive decline is due to the undetected disease. Recent research identifying an association between the ε4 allele and mild cognitive impairment (16), widely held to reflect the subclinical phase of dementia, underlines this point.

Against this background, the first major objective of the present investigation, therefore, was to assess 8-year cognitive change as a function of *APOE* genotype in older cognitively-normal adults who at baseline were aged 60 to 64 years. In order to ensure a cognitively healthy sample, we excluded persons with a variety of neurological disorders from the sample. Our particular interest was whether ε4 carriers exhibited more precipitous cognitive decline in this older cognitively intact group.

The second major concern of this study related to the association between *APOE* genotype and cognition across the adult lifespan. A recent proposal, with its origins in evolutionary theory (17), holds that this association is an example of "antagonistic pleiotropy" where advantages in early life are offset by a greater vulnerability to disease in later life (18). Consistent with this suggestion, several studies have shown better cognitive performance in

young ε4-carrying adults compared to those without the ε4 allele (19-21). However, evidence against the hypothesis was reported by two cross-sectional studies in the present population (22, 23). Indeed, Bunce and colleagues (22) specifically tested this hypothesis in over 5,000 participants and found no evidence of ε4-related cognitive benefits in young adulthood or middle age.

Interestingly, it is also suggested that the reverse association may exist in relation to the ε2 allele (24). That is, possession of the ε2 allele may be associated with disadvantages in early life, cognitive and otherwise, but confer greater protection against cognitive decline and neuropathology in later life. In old age, the protective effect of the ε2 allele is widely recognized (e.g., Ref 2). Regarding the hypothesized detrimental effect in early life, Bloss and colleagues (24) reported visuospatial deficits in ε2-carrying children and adolescents relative to their ε3- and ε4-carrying age cohort and there is also work suggesting that ε2 carriers are over-represented in perinatal deaths (25). Although there is little empirical evidence, these studies are consistent with the idea that the ε2 allele may be associated with disadvantages in early life. Conversely, there is evidence that the ε2 allele confers protection in extreme old age (e.g., Ref 26).

Currently, our understanding of the association between *APOE* genotype and cognition across the lifespan is incomplete. There is a need for work that not only assesses the trajectory of cognitive change as a function of *APOE* in early old age, but also in young adulthood and midlife. Such work will provide important insights into what is potentially a major determinant of cognitive aging. Therefore, in addition to investigation of the association between *APOE* and cognitive change in older adults, we also assessed 8-year cognitive change in young and middle-aged adults aged, respectively, 20 to 24, and 40 to 44, years at baseline. Uniquely, we focused our main analyses on persons possessing either the ε2 or ε4 alleles while excluding those with the ε3/3 genotype, held to be of neutral influence. In this way, our intention was to provide the most robust test of the opposing influences of the ε2 and ε4 alleles in the various age groups. The hypotheses we tested was that in older adults, relative to those possessing the ε2 allele, ε4 carriers would exhibit more precipitous cognitive decline. By contrast, in the younger age cohort, any initial ε4-related cognitive benefits relative to ε2 were expected to attenuate over time. As the middle-age cohort represent the hypothesized crossover point for the opposing genetic influences (18), we did not expect any differences in cognitive performance according to *APOE* genotype.

In order to robustly test these associations over time, we directly contrasted the opposing influences of the ε2 and ε4 alleles on cognitive change in 2,013 community-dwelling adults across several domains including processing speed, working memory, lexical decision making and episodic memory. Recent meta-analyses (4, 5) suggest that cognitive tasks placing demands on processing speed, executive function or episodic memory, are particularly sensitive to *APOE* ε4 effects.

Method

Participants

Data were drawn from the Personality and Total Health (PATH) Through Life Project, a longitudinal population-based study of age, mental health and cognition. The study background and procedures for testing have been described in detail elsewhere (27). Participants resided in Canberra or nearby Queanbeyan, and were recruited through electoral rolls, registration for which is compulsory for Australian citizens. Here, three waves of data were used, measured at 4-year intervals over 8 years. At baseline, the number of participants who returned the survey was 7,485, of whom 2,404 were aged 20 to 24 years, 2,530 aged 40 to 44 years and 2,551 60 to 64 years. In each age group, approximately half were female. There was limited sample attrition four (Wave 2 = 6,680) and eight (Wave 3 = 5,996) years later. Approval for the study was obtained from the Human Research Ethics Committee of the Australian National University.

In the present study, there were various exclusions from the baseline sample of 7,485. Participants were removed who were either missing *APOE* data (n = 518) or, following earlier studies in this sample (22, 23), because they did not describe themselves as Caucasian/White (n = 407) as ethnic differences in the frequency of *APOE* genotype have been demonstrated. Earlier work (28) in this dataset suggest that the resulting allelic frequencies do not differ from other Caucasian populations. Additionally, participants were excluded if they reported stroke (n = 178), head injury (n = 827) or epilepsy (n = 51), and older participants scoring <24 on the Mini Mental State Examination (MMSE: 29) at any time point (n = 37). Although the multilevel modeling framework used in the statistical analyses permitted inclusion of all participants regardless of attrition, only participants with available baseline data for all the cognitive variables were included in analyses.

Provisional statistical analyses investigated all six *APOE* genotypes and age in relation to the cognitive measures over time (N = 5,384). However, as the major objective of this investigation was to directly contrast the opposing influences of the ε2 and ε4 alleles, the main statistical analyses involved a robust test of the relative influence of the two alleles. In order to increase statistical power, we combined persons with the ε2/2 and ε2/3 genotypes and contrasted them with participants of the ε3/4 and ε4/4 genotypes. Because of the opposing influence of the *APOE* ε2 and ε4 alleles, individuals possessing the ε2/4 genotype were removed (n = 140) and individuals with Ɛ3/3 genotype were also excluded (n = 3,231) as this genotype is held to be neutral in its influence. Of the resulting 2,013 participants, 55.0%, 53.4% and 50.3% were women for the 20s, 40s and 60s age cohorts, respectively. Mean years of education for the age groups were 14.63 (*SD* = 1.58), 14.62 (*SD* = 1.58) and 14.68 (*SD* = 1.93) for the 20s, 40s and 60s, respectively. The mean length of time in study from baseline to Wave 3 was 8.05 years (*SD* = 0.27). The distribution of *APOE* genotype in this sample is presented in Table 1. A X^2 test did not find *APOE* genotype to vary with age. Further information on attrition and scores according to age and *APOE* genotype across the waves are presented in Table 2.

Cognitive measures

A battery of tests was administered to participants covering a range of cognitive domains including processing speed, working memory, immediate and delayed recall and lexical decision making. This included the *Symbol Digit Modalities Test* (30) in which participants were given 90 s to indicate the appropriate symbol-digit pairings (by writing the number beneath the symbol), and a *backward digit span test* from the Wechsler Memory Scale in which participants repeated a list of three to seven digits backwards (31). Also, *immediate* and *delayed recall* was assessed using the first trial of the California Verbal Learning Test (32). This non-standard version of the task required participants to remember 16 items (e.g., chisel, tangerine, sweater, paprika) and to recall them immediately and again after a brief grip strength task (delayed recall). Finally, *Lexical decision making* was measured through the Spot-the-Word test (33) which is composed of 60 questions and required participants to indicate which of two items was a valid word.

APOE genotyping

At Wave 1, genomic DNA was extracted from buccal swabs using QIAGEN DNA Blood kits (#51162; QIAGEN, Hilden, Germany). Two single-nucleotide polymorphisms (SNPs; *rs429358* and *rs7412*) were genotyped to identify *APOE* genotypes comprised of the *APOE*

ε2, ε3 and ε4 alleles using TaqMan assays (Applied Biosystems [ABI], Foster City, CA) as described elsewhere (23).

Data preparation and statistical analysis

To allow comparison across tasks, all cognitive scores across the three waves were converted into *T*-scores ($M = 50$, $SD = 10$) using the baseline means and standard deviations across age groups. Data were analyzed using the Mixed procedure in SPSS version 18.0.2 (IBM Corporation, 2010). Age group and *APOE* genotype served as fixed time-invariant effects in the multi-level models. Rather than using wave of measurement, time-in-study served as a time-varying fixed effect as not all participants were tested at precise 4-year intervals. The random effects for both the intercept and time-in-study took into account individual differences (within-person variation) in cognition over time. Models used an unstructured covariance matrix structure. Regarding the statistical analyses of primary interest, each cognitive variable was assessed initially using an intercept-only model to provide a baseline index of between- and within-person variation (Model 1). Next, in Model 2, we estimated whether significant change occurred in any of the cognitive measures over the three time points and whether this varied by age cohort. In the third model, we added *APOE* genotype. Importantly, our concern was whether the slopes varied according to *APOE* genotype within each of the age groups. Finally, we reran the models controlling for gender and education.

Results

The critical finding from the provisional multilevel models which included all six *APOE* genotypes was that for each of the cognitive variables, none of the main effects for *APOE*, or Age group x *APOE* genotype x Time interactions, were significant. This latter finding indicates that *APOE* genotype did not affect cognition over time within any of the age groups. In the main analyses that followed, therefore, the opposing effects of the ε2 and ε4 alleles were directly contrasted. Descriptive statistics for the cognitive variables as a function of age, *APOE* genotype and time are presented in Table 1. It can be seen that the number of ε4 carriers in the sample was substantially larger than for ε2 carriers.

Table 1 and 2 about here

Age group differences in intercept and slope

Statistics for Models 1 and 2 are presented in Table 2. Adding age group in Model 2 significantly improved model fit for all of the cognitive variables. Additionally, there were

significant age group differences in both the starting point and slope for the majority of variables. With one exception, the 20s group had the highest initial scores, followed by the 40s and the 60s. For spot-the-word, the opposite was the case, with the 60s cohort recording the highest starting scores followed by the 40s and 20s groups. All age group intercept contrasts were significant with the exception of 60s versus 40s for backward digit span, and 40s versus 20s for immediate recall.

Regarding change over time, with each additional year, the average participant in the 60s group experienced significant decline in symbol digit, and immediate and delayed recall, but improved in spot-the-word performance. The trend for backward digit span was nonsignificant. The 20s group improved over time on all cognitive variables while the 40s group improved on backward digit span, spot-the-word and immediate recall. Between-group contrasts of the slopes suggested significant differences for all variables for 60s versus 20s groups, while for 60s versus 40s all contrasts were significant except for spot-the-word. Significant differences were also evident for all 40s versus 20s contrasts except for backward digit span.

Tables 3 and 4 about here

Does APOE genotype influence the intercept and slope within each age group?

The critical element of the analyses was the addition of *APOE* genotype in Model 3 (see Table 3). Three important findings emerged from this model. First, the addition of *APOE* did not improve overall model fit for any of the cognitive variables ($df_{\Delta} = 6$, χ^2_{Δ} *p*s>.25). Second, neither the Age x *APOE* interactions nor comparison of the slopes for ε2 and ε4 were significant, suggesting that *APOE* genotype did not modify the findings described in Model 2. Finally and most importantly, for all of the cognitive variables, none of the nested ε2 versus ε4 slope contrasts within any of the age cohorts were significant. This suggests that for cognitively normal young, middle-aged and older adults living in the community, neither the ε2 nor ε4 alleles influenced cognitive change over the 8-year study period. Using symbol digit as an example, Figure 1 presents the predicted values for cognitive change as a function of age and *APOE* genotype. As can be seen, there is little evidence of genetic-related variance over time for any of the age groups.

Figure 1 about here

Additionally, we repeated the analyses while controlling for gender and education. The addition of these covariates did not affect the original findings in any way. Finally, we conducted a further test of the opposing effects of ε2 and ε4 by contrasting the ε4/4 group with the ε2/2 + ε2/3 groups (i.e., ε3/4 carriers were excluded). Although two of the models failed to converge (for spot-the-word and immediate recall) due to the small numbers of participants in the ε4/4 group, the pattern of results was very similar to those from the earlier analyses. Importantly, *APOE* genotype did not modify either the intercepts or slopes for any of the cognitive variables.

Discussion

This investigation possesses several unique features. First, the research involved a large-scale population-based sample of over 2,000 persons aged either 20 to 24, 40 to 44, or 60 to 64, years at baseline. Second, we used multilevel modelling to directly contrast the opposing influences of the ε2 and ε4 alleles on cognitive change over an 8-year period in a range of cognitive domains including processing speed, working memory, lexical decision making and episodic memory. Additionally, we were careful to assess only cognitively normal individuals at baseline, excluding from the analyses individuals reporting neurological disorders, and in the older cohort, eliminating persons exhibiting deficits in global cognition that may serve as an early marker of dementia.

Our findings were unequivocal. There was no evidence of cognitive change as a function of *APOE* genotype on any of the measures in any of the age groups. Even in analyses contrasting ε4/4 carriers only, possession of the ε4 allele was not associated with more precipitous cognitive decline in old age and neither was there any evidence of cognitive benefits in young adulthood relative to those with the ε2 allele. Conversely, there was no evidence of ε2-related disadvantages in young adults or benefits in the older cohort. Nor was there evidence of *APOE*-related cognitive change in midlife. Inclusion of the ε3/3 genotype in provisional analyses did not alter these null findings as none of the *APOE* main effects or *APOE* x Time interactions involving this allele were significant. Moreover, taking gender into account did not alter any of these null findings.

The findings have several implications for the potential influence of *APOE* genotype on cognition between the ages of 20 and 72 years. First, they strongly suggest that in old age, rather than representing a cognitive phenotype (3), ε4-related cognitive deficits, where they are found, may reflect the preclinical phase of, as yet, undetected dementia. It is well-

established that the prodromal phase of the disease precedes eventual diagnosis by several years. Indeed, one study (34) has reported cognitive deficits up to ten years in advance of clinical diagnosis, and histopathological studies (35, 36) suggest that the neuropathological hallmarks of dementia are present in early adulthood and middle age. As possession of the ε4 allele is a major risk factor for dementia, it is possible that ε4-related cognitive decline commonly reported (e.g., Refs 10, 11-15) is associated with the subclinical phase of the disease, even though some studies (e.g., Refs 13, 15) removed persons with low global cognition scores. In the present study, we were also careful to eliminate from the analyses individuals with a range of neurological disorders and also low global cognition scores. Although we cannot rule out the possibility that participants will experience dementia in the future, we are cautiously confident that with those exclusions, the sample was cognitively normal. As with studies elsewhere that have taken possible or future dementia into account in relation to cognition (6-8) or the neuroanatomical structures supporting cognition (e.g., Refs 37, 38), the present null findings add to evidence suggesting that ε4-related cognitive deficits reflect the subclinical phase of undetected dementia.

The findings also have important implications for the suggestion that ε4-cognition relations represent an example of "antagonistic pleiotropy" (18) where possession of the ε4 allele is associated with cognitive benefits in young adulthood, but reverses to become a risk factor for more marked cognitive decline in later life. Consistent with earlier cross-sectional studies in this sample (22, 23), we found no evidence of *APOE* genotype-related differences in cognitive performance over time in young or middle-aged cohorts. Equally, the suggestion that the reverse effect may exist in relation to the ε2 allele (24) did not receive support. Indeed, the results indicate that unlike in extreme old age (e.g., Ref 26), the ε2 allele does not moderate cognitive decline in early old age. The present study is one of the largest to test the hypothesis in young adults and those in midlife, and we believe the first to examine these issues longitudinally. Although pleiotropic associations involving the ε4 allele may exist in other domains (e.g., Ref 39) and the ε4 allele may be associated with various benefits such as high vitamin D status (40), our findings clearly suggest that claims of such an association specifically between the ε4 allele and cognition across the ages represented in this study, or indeed the reverse association involving the ε2 allele, should be treated with caution.

There are some limitations to the study that we should acknowledge. The first is that although we did our best to ensure that participants included in the analyses were cognitively normal by excluding individuals with MMSE scores <24, it is still possible that in using this

measure, persons in the preclinical phase of the disease were included in the analyses. However, the null findings in respect to *APOE* make this unlikely. Second, it is possible that our older participants were too young to reveal ε4-related cognitive deficits (the older group ranged 60 to 72 years between Waves 1 and 3). Plans are in place to collect a fourth wave of data that will inform this possibility in the near future. Similarly, it is likely that the youngest group was too old to detect any effects relating to the ε2 allele. For example, a study reporting visuospatial deficits among ε2 carriers tested school-aged children (24), whereas the present study assessed young adults. Additionally, in such large-scale population-based studies, the need for brief but comprehensive assessment of a range of cognitive abilities is a major consideration. It is possible, of course, that studies using alternative measures of memory, and assessment of other cognitive domains such as visuospatial skills and direct measures of executive function, may produce different outcomes. Finally, although not a limitation, the sample had higher educational attainment than their peers of comparable age in other parts of Australia. However, typical patterns of educational attainment are well represented in the sample. Importantly though, educational attainment more closely approximates that of younger individuals who are currently entering the older age ranges studied by the PATH Through Life Study. In this respect, the sample may have greater relevance to current and future aging than many other studies.

To conclude, in this longitudinal population-based study of cognitively normal adults in their early 20s, 40s and 60s at baseline, we found no evidence of cognitive change as a function of *APOE* genotype. The findings suggest that (a) where it is found, ε4-related cognitive decline in older adults is related to the preclinical phase of, as yet, undetected disease in persons genetically vulnerable to dementia, and (b) that the proposal of a pleiotropic association between the ε4 allele and cognition across the ages 20 to 72 years is premature, as are proposals that the reverse effect may operate in relation to the ε2 allele. The results clearly suggest that in the absence of dementia-related neuropathology, *APOE* genotype does not affect cognitive change in early, middle or late adulthood.

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Table 1. Frequency (%) of *APOE* genotype according to age

Age group	ε2/2	ε2/3	ε3/4	ε4/4
20s	7 (0.35)	182 (9.04)	377 (18.73)	49 (2.43)
40s	12 (0.60)	233 (11.58)	432 (21.46)	37 (1.84)
60s	16 (0.80)	214 (10.63)	415 (20.62)	39 (1.94)

Table 2. Descriptive statistics (*t*-scores[1]) for cognitive measures entered into the multilevel models

Age group	Wave	*APOE* genotype	*n*	Symbol digit	Digit backwards	Spot the word	Immediate recall	Delayed recall
20s	1	ε2	189	55.41 (8.53)	51.49 (10.59)	46.70 (8.35)	52.54 (9.47)	52.51 (9.51)
		ε4	426	55.99 (9.05)	51.60 (9.66)	46.73 (8.54)	51.78 (9.53)	52.14 (9.79)
	2	ε2	165	57.20 (8.38)	53.77 (10.06)	48.05 (8.03)	54.69 (9.90)	55.20 (9.90)
		ε4	374	57.44 (8.05)	52.98 (9.27)	48.75 (7.65)	53.40 (10.20)	54.16 (10.34)
	3	ε2	150	57.84 (8.33)	54.38 (10.74)	49.26 (7.45)	55.57 (10.68)	56.75 (9.76)
		ε4	357	57.64 (8.08)	53.80 (9.67)	49.95 (7.32)	54.86 (10.44)	55.12 (10.22)
40s	1	ε2	245	52.93 (8.32)	49.67 (9.72)	51.89 (8.33)	50.66 (9.67)	51.10 (8.99)
		ε4	469	52.36 (7.95)	50.79 (9.96)	51.08 (8.58)	51.67 (9.58)	51.40 (10.25)
	2	ε2	232	53.13 (8.02)	51.13 (9.20)	52.52 (9.35)	51.88 (9.95)	52.45 (10.02)
		ε4	436	52.81 (7.68)	52.37 (9.71)	51.85 (8.94)	51.45 (9.55)	51.78 (9.30)
	3	ε2	213	52.34 (8.05)	51.80 (10.24)	52.87 (9.53)	52.91 (9.02)	52.63 (9.20)
		ε4	396	52.26 (7.33)	52.82 (9.63)	52.38 (8.85)	52.14 (9.44)	52.03 (9.23)
60s	1	ε2	230	43.91 (8.26)	49.57 (10.49)	53.97 (8.88)	48.55 (9.82)	47.93 (9.67)
		ε4	454	44.07 (7.88)	49.55 (9.63)	54.13 (8.88)	48.86 (9.81)	48.71 (10.05)
	2	ε2	199	43.09 (8.08)	51.07 (9.86)	55.91 (7.70)	47.16 (9.08)	47.58 (9.44)
		ε4	399	43.19 (7.72)	50.60 (9.45)	55.55 (8.07)	47.29 (9.46)	47.49 (9.34)
	3	ε2	175	41.80 (7.79)	51.23 (10.22)	55.64 (8.28)	45.88 (10.13)	46.30 (9.62)
		ε4	346	41.43 (8.04)	50.15 (9.52)	55.69 (7.94)	45.73 (9.78)	46.24 (8.95)

Note 1. *T*-score (*M* = 50; *SD* = 10) centered at baseline for entire sample

Table 3. Parameter estimates from multilevel models examining change in cognitive performance as a function of age

	Symbol digit	Digit backwards	Spot-the-word	Immediate recall	Delayed recall
Model 1	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Fixed effect - Intercept	50.54 (.21)*	51.54 (.20)*	51.67 (.19)*	50.75 (.19)*	50.93 (.19)*
Random effect - Residual	15.41 (.37)*	36.20 (.87)*	15.11 (.37)*	48.09 (1.15)*	43.83 (1.05)*
Random effect - Intercept	83.13 (2.82)*	61.22 (2.40)*	65.34 (2.27)*	53.77 (2.31)*	57.50 (2.38)*
Model fit, df = 3	χ^2 = 35869	χ^2 =38401	χ^2 = 35139	χ^2 = 39482	χ^2 = 39218
Model 2					
Fixed Effects (60=ref)					
Intercept	44.15 (.31)*	49.83 (.37)*	54.26 (.32)*	48.75 (.36)*	48.49 (.36)*
Time in Study	-.34 (.03)*	.08 (.05)	.15 (.03)*	-.40 (.05)*	-.29 (.05)*
Intercept x Age Group					
60 vs. 20	11.88 (.45)*	1.86 (.54)*	-7.44 (.47)*	3.37 (.52)*	3.95 (.53)*
60 vs. 40	8.59 (.44)*	.74 (.52)	-2.87 (.45)*	2.50 (.50)*	2.88 (.51)*
40 vs. 20[a]	3.29 (.45)*	1.13 (.53)†	-4.57 (.47)*	.87 (.52)	1.07 (.52)†
Time in Study x Age Group					
60 vs. 20	.55 (.04)*	.21 (.07)$	.19 (.04)*	.76 (.08)*	.69 (.07)*
60 vs. 40	.26 (.04)*	.15 (.06)†	-.02 (.04)	.51 (.07)*	.38 (.07)*
40 vs. 20[a]	.29 (.04)*	.06 (.06)	.22 (.04)*	.25 (.07)*	.31 (.07)*
Random Effects					

Residual	12.93 (.44)*	32.70 (1.12)*	13.76 (.47)*	41.72 (1.41)*	40.04 (1.36)*
Intercept	55.09 (2.12)*	64.77 (3.07)*	59.77 (2.29)*	52.16 (3.01)*	56.45 (3.07)*
Time in Study	.10 (.02)*	.17 (.05)*	.04 (.02)	.30 (.07)*	.16 (.06)†
Model fit, $df_{\Delta} = 7$	$\chi^2_{\Delta} = 1139$*	$\chi^2_{\Delta} = 114$*	$\chi^2_{\Delta} = 408$*	$\chi^2_{\Delta} = 320$*	$\chi^2_{\Delta} = 308$*

Note. †p<.05. $ p<.01. *p<.001. 60s cohort served as reference group in Model 2. [a]Contrast tested in another analysis using same model but different coding for age group.

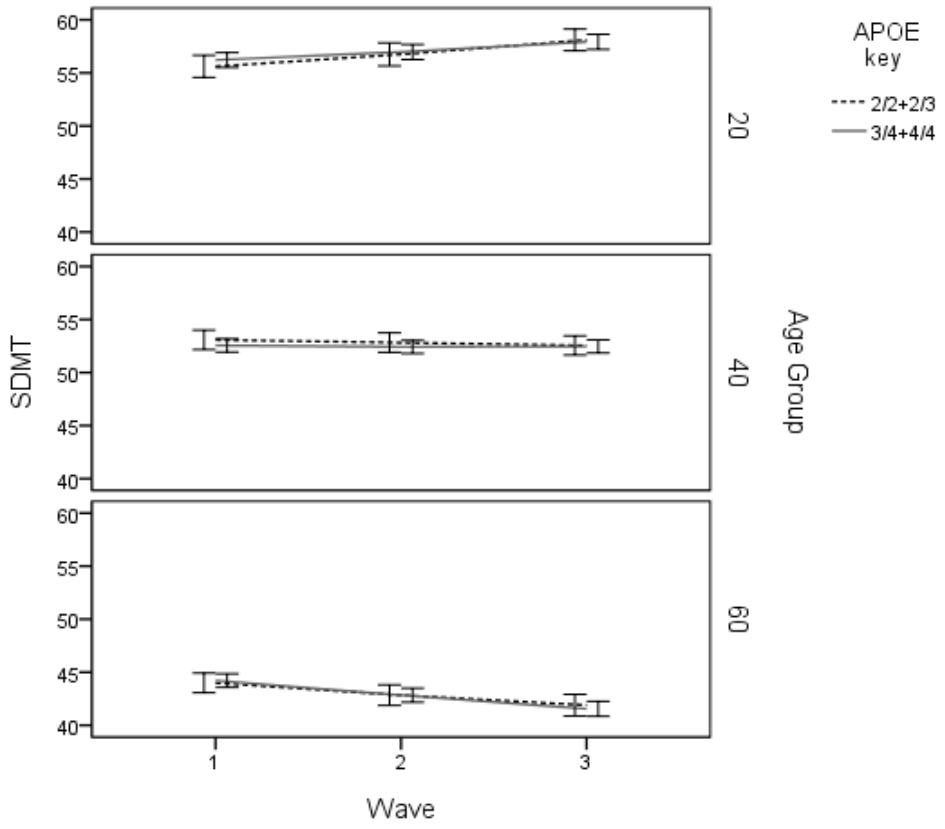
Table 4. Parameter Estimates from Multilevel Models Examining Change in Cognitive Performance as a function of *APOE*

	Symbol Digit	Digit backwards	Spot-the-word	Immediate recall	Delayed recall
Model 3	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Fixed Effects					
Intercept	44.22 (.38)*	49.83 (.45)*	54.29 (.40)*	48.87 (.44)*	48.73 (.45)*
Time in Study	-.37 (.04)*	.06 (.06)	.15 (.04)*	-.43 (.62)*	-.34 (.06)*
Intercept X *APOE* ε2 vs. ε4	-.23 (.66)	-.01 (.78)	-.10 (.69)	-.35 (.76)	-.71 (.77)
Time in Study X *APOE* ε2 vs. ε4	.08 (.06)	.08 (.09)	.01 (.06)	.08 (.11)	.12 (.10)
Age group = 20s ε2 vs. ε4	-.60 (.75)	-.07 (.84)	-.11 (.73)	.85 (.82)	.36 (.83)
Age group = 40s ε2 vs. ε4	.53 (.63)	-1.22 (.75)	.74 (.66)	-.82 (.73)	-.15 (.75)
Age group = 60s ε2 vs. ε4	-.23 (.64)	-.01 (.79)	-.11 (.70)	-.35 (.77)	-.71 (.77)
Age group = 20s Time in Study x ε2 vs. ε4	.06 (.08)	.04 (.10)	-.10 (.06)	-.02 (.12)	.15 (.11)
Age group = 40s Time in Study x ε2 vs. ε4	-.04 (.05)	.01 (.09)	-.03 (.06)	.22 (.21)	.12 (.10)
Age group = 60s Time in Study x ε2 vs. ε4	.08 (.06)	.08 (.10)	.00 (.06)	.08 (.11)	.12 (.10)

Random Effects					
Residual	12.93 (.44)*	32.69 (1.12)*	13.75 (.47)*	41.70 (1.41)*	40.03 (1.36)*
Intercept	55.05 (2.12)*	64.67 (3.07)*	59.73 (2.29)*	52.05 (3.00)*	56.40 (3.07)*
Time in Study	.10 (.02)*	.18 (.05)$^{\$}$	.04 (.02)	.30 (.07)*	.15 (.06)†
Change in Model fit, $df_{\Delta} = 6$	$\chi^2_{\Delta} = 3$	$\chi^2_{\Delta} = 5$	$\chi^2_{\Delta} = 4$	$\chi^2_{\Delta} = 6$	$\chi^2_{\Delta} = 7$

Notes. †p<.05. $ p<.01. *p<.001.

Figure 1. Symbol digit modalities change as a function of *APOE* according to age



Notes. SDMT = Symbol digit modalities task; Error bars = +/- 2 SE