Possible positive effect of the APOE ε2 allele on cognition in early to mid-adult life

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ABSTRACT

Background: ε4 allele possession is associated with an increased risk of Alzheimer’s disease. Its effects earlier in life are less well understood. Previous studies have reported both detrimental effects and a lack of effect on cognition outside dementia. We used genotype based recall from the ALSPAC study to investigate whether APOE genotype influences cognition in earlier adult life.

Methods: We invited all individuals with the rarer ε22 or ε44 genotypes and equal numbers of those with ε32, ε33 or ε34 APOE genotypes (total n invited = 1936, ages 23–67). Participants were screened for dementia using the Addenbrooke’s Cognitive Examination Revised (ACE-R). Participants were asked to complete a 3 h battery of neuropsychological tests covering a range of cognitive domains. The primary outcome was performance on the Rey Auditory Verbal Learning Test (RAVLT). Transformation of variables was used where required to permit objective cognitive testing.

Results: 114 participants were recruited to the study (39 ε33, 27 ε34, 15 ε44, 26 ε32 & 7 ε22). ε4+ participants had higher scores on the cognitive failures questionnaire (10 point increase, p = 0.006) but no deficits on objective cognitive testing. ε2 carriers had slightly better episodic memory performance (p = 0.016), slightly improved n-back accuracy and better executive functioning (trails A & B, p = 0.005).

Conclusions: It is intriguing that the ε2+ group performed better as this group have a lower risk of Alzheimer’s disease. Most previous studies have analysed as ε4/non ε4 so may have missed this effect.

1. Introduction

The human APOE gene has three alleles: ε2, ε3 and ε4. Possession of an ε4 allele (compared to ε3) has been linked to a higher risk of developing and earlier age at onset of late onset Alzheimer’s disease (AD) (Corder et al., 1993) with evidence of an allele dose effect (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007). One ε4 allele confers a threefold increase in risk and possession of two ε4 alleles confers an over tenfold increase in risk (Bertram et al., 2007). Possession of an ε2 allele has been linked with a lower risk of AD and may also slow progression of vascular cognitive impairment (Blacker, Lee, Muzikansky, et al., 2007; Corder et al., 1994; Kim et al., 2017; Talbot et al., 1994).

Possession of an ε4 allele is neither necessary nor sufficient for the development of AD and many ε4 allele carriers live to advanced ages with no evidence of dementia (Bunce, Fratiglioni, Small, Winblad, & Bäckman, 2004). It has been suggested that ε4 reduces the age at onset of AD but does not influence whether someone develops it (Meyer et al., 1998). Studies over several decades have reported that ε4 allele possession may have more of a deleterious effect in women (reviewed in Ungar, Altmann, & Greicius, 2014).

It has been shown in post-mortem brain studies and in PET studies of older adults that ε4 allele possession is associated with higher levels of amyloid plaques (Caselli, Walker, Sue, Sabbagh, & Beach, 2010; Wirth, Villeneuve, La Joie, Marks, & Jagust, 2014). In one study this effect was seen even in middle-aged individuals (Ghebremedhin, Schultz, Braak, & Braak, 1998). ε4 effects on neurofibrillary tangles are much less consistent (Raber, Huang, & Ashford, 2004). In contrast individuals with the ε2 variant have less AD neuropathology before extreme old age (Berlau, Corrada, Head, & Kawas, 2009; Ohm, Scharnagl, Marz, & Bohl, 1999).

Most previous studies of the effect of ε4 on cognition in non-demented adults have included older participants. Relatively few have studied younger people (only 8 studies with a mean age of under 50 y in a 2017 meta-analysis) or reported the presence of the ε2 allele (Lancaster, Tabet, & Rusted, 2017). Indeed in one study possession of ε2 was an exclusion criterion (Evans et al., 2014). A meta-analysis in 2011 found evidence of improved episodic memory in ε2 carriers from 6 studies (mean effect size 0.09, 95% CI –0.05 to 0.22) (Wisdom, http://dx.doi.org/10.1016/j.nlm.2017.10.008
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Callahan, & Hawkins, 2011). The same meta-analysis reported that the adverse effects of $e_4$ on cognition (in the absence of dementia) increases with age, yet many previous studies have not adequately screened for dementia (Wisdom et al., 2011). In particular many studies have used the mini mental state examination (MMSE) which is much less sensitive to the presence of early dementia (or mild cognitive impairment) than other tests such as the Addenbrooke’s cognitive examination revised (ACE-R) (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006).

Although compromised by lack of phenotypic precision, a GWAS meta-analysis which analysed a general cognitive ability score from heterogeneous individual studies found that the effect of $e_4$ was minimal in middle age and increased with age (Davies et al., 2015). Other studies have reported that the separation between $e_4$ carriers and non-$e_4$ carriers on cognitive tests starts in the mid 50s (Caselli et al., 2009) and as early as 35 years old (Bunce, Anstey, Burn, Christensen, & Easteal, 2011). The largest recent study of middle aged adults, which used data from the Generation Scotland study, showed detrimental effects of $e_4$ on logical memory and processing speed. These effects appeared to be larger in those aged $> 60$ y in a sensitivity analysis (Marioni et al., 2016).

There remains considerable debate as to whether the changes seen in some previous studies reflect genuine $e_4$ effects in the absence of dementia, or merely the early stages of a demencing process. The latter is entirely possible as amyloid can be found in the brain at least 10 years before the diagnosis of a dementia (Fouquet, Besson, Gonneaud, La Joie, & Chételat, 2014; Morris et al., 2010). Evidence of cognitive decline has been shown 10 and 12 years before the onset of AD (Amieva et al., 2009; Tierney, Yao, Kiss, & McDowell, 2005).

Perhaps unsurprisingly, given the known relationship of $e_4$ to AD risk, most previous studies have included a measure of episodic memory. The cognitive domains of attention, executive function and visuospatial function have been much less well studied (Wisdom et al., 2011). In the 2011 meta-analysis by Wisdom et al. the mean effect size for $e_4$ homozygotes on episodic memory was $-0.18$ (95% CI $-0.34$ to $-0.02$) and for $e_3$4 participants it was $-0.04$ (95%CI $-0.09$ to 0.01). There was also evidence of small $e_4$ effects on executive functioning (effect size $-0.06$, 95% CI $-0.12$ to $-0.04$) and perceptual speed (effect size $-0.07$, 95% CI $-0.13$ to $-0.01$) (Wisdom et al., 2011). Although episodic memory is the major cognitive process affected early in LOAD, it is not the only process affected early in the disease process (Backman, Jones, Berger, Laukka, & Small, 2005). Poor working memory performance has been reported as one of the earliest deficits seen in Alzheimer’s disease (McKhan et al., 1984). The current study builds on previous work by including younger participants, including a relatively large number of $e_2$+ participants, rigorously screening for dementia (to exclude this as a cause of any differences observed) and by testing multiple domains of cognition.

Whilst some individual studies have suggested that there is a positive pleiotropic effect of $e_4$ in younger adults (e.g. Hubacek et al., 2001) a meta-analysis found no evidence of such an effect (Ihle, Bunce, & Kliegel, 2012). The authors suggested that this may have been because several of the studies used less difficult tasks that may have failed to pick up subtle effects.

We wished to study the effects of $APOE$ genotype on cognition independent of dementia. We hypothesised that cognitive function is reduced in young to middle aged adults without dementia from the ALSpac study with an $e_4$ allele compared to those without.

Recall by genotype is an efficient study design which allows causal inference, precision phenotyping and maximises statistical power (Ware, Timpson, Davey Smith, & Munafò, 2014). It involves selecting a defined number of participants with each genotype at random from an existing study with genetic data. These participants are then invited to take part in the recall study. Dense phenotyping can be performed in the recall study which would be impracticable to perform on the whole study cohort.

2. Methods and materials

2.1. Ethics

Ethical approval for this study and approval for substantial amendments was provided by the ALSPAC ethics and law committee (study ref E201109). Both researchers and participants were blind to $APOE$ genotype status. All participants gave written informed consent to take part in this study following assessment of their capacity to do so by a Psychiatrist (LIS).

2.2. The Avon longitudinal study of parents and children

The Avon Longitudinal Study of Parents and Children (ALSPAC) as described previously in detail is a prospective study which was established in 1991 (Boyd et al., 2012; Fraser et al., 2012). Initially 14,541 women were enrolled, resulting in 14,062 live births and 13,988 children alive at one year. At age 7/8 further eligible children were added to the sample, giving a total sample size of 15,247 eligible pregnancies and 14,775 live births. Data were collected from self-report questionnaires, teacher report questionnaires, medical, educational and other records, birth registries, and hands on assessment. Detailed information has been collected since birth via questionnaires and at regular clinics. The study website contains details of all the available data through a freely searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

2.3. APOE genotyping

Genotyping of all study participants for $APOE$ was undertaken by integrated single label liquid phase assay as previously described (Abdollahi et al., 2006). DNA samples were available in 2009 for 7091 children, 63% of the 11343 ALSPAC children with potential DNA samples available. In total 95% of these samples were genotyped (Taylor et al., 2011). After siblings and children of known non-white ethnicity were excluded there was genotype data for 5995 children. DNA samples were available in 2010 for 9763 mothers: 83.6% of the 11,679 mothers with potential DNA samples available. In total 87.9% of these samples were able to be genotyped. There was no strong evidence of a sex difference in genotype distribution or of a deviation from Hardy Weinberg Equilibrium for either the mothers or young people ($p > 0.05$).

2.4. Recall by genotype

Inclusion criteria for this study were that participants had previously taken part in the ALSpac study and that they had a known $APOE$ genotype. Exclusion criteria were: drop out from ALSPAC; living > 50 miles away; already taking part in an ALSPAC sub-study; very poor command of English; lack of capacity to consent; and dementia.

Recruitment to the study is summarised in Fig. 1. The planned strategy was to identify whether a per-genotype difference existed between the homozygotes and then to ascertain whether there was an allele dose effect by inviting heterozygotes in a second wave. Due to a very poor response rate to the first wave the invitations to the second case selection were sent earlier than planned.

Participants in each batch of invitations were chosen at random from the case selection. They were sent an initial invitation, a reminder postcard after 3 weeks (if they had not replied) and if they had still not replied were contacted by telephone. All participants were reminded the day prior to their appointment. In order to maintain double blinding as to participant genotype, all invitation letters, case selections, telephone calls and participant contact other than the study visit were carried out by ALSPAC staff and not by the researchers.

Despite all of these measures the final response rate (either positive
or negative) was only 16%. Participants and the rest of the ALSPAC study population were compared (see Supplementary Table 1).

2.5. Co-variates

Information was available on a range of possible confounders including IQ, blood pressure, serum cholesterol, past medical history, mood rating scales and demographic variables.

2.6. The study visit

The study visit lasted for up to 3 h. Participants were screened for dementia using the ACE-R, which incorporates the MMSE (Mioshi et al., 2006). Information was gathered on head injuries, history of mental illness, current medication, caffeine consumption, alcohol intake, illicit drug use and family history of dementia. All young people completed the mood and feelings questionnaire (Angold et al., 1995). All mothers completed the Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden, & Sagovsky, 1987) and the Crown-Crisp Inventory (Crown & Crisp, 1966). These questionnaires were chosen to allow comparison with data previously collected by ALSPAC. All participants completed the Depression, anxiety and stress scale (DASS) and the Cognitive Failures Questionnaire (CFQ) (Broadbent, Cooper, FitzGerald, & Parkes, 1982; Lovibond & Lovibond, 1995a; Lovibond & Lovibond, 1995b). The DASS may be downloaded from www.psych.unsw.edu.au/dass/. Full scale IQ was measured using the Wechsler abbreviated scale of intelligence (WASI) (Wechsler, 2011). 

All analyses were carried out in STATA v13. There was no evidence to support an association of any demographic variables or potential confounders with APOE genotype (Table 1). Given that participants with each genotype were selected at random and that genotypes are unlikely to be confounded in any case, it was decided not to include any co-variates in the analysis.

A power calculation estimated a total n of 350 i.e. 70 in each genotype group to ensure 80% power with an α of 0.05. It soon became apparent that this was not going to be possible so numbers were maximised wherever possible. To maximise study power an analysis strategy of combining ε32 and ε22 to form an ε2+ group and combining ε34 and ε44 to form an ε4+ group was used with ε33 as the reference group.

Transformation of variables was used where necessary to permit parametric testing. Where parametric testing was possible the data was initially analysed using ANOVA and subsequently by linear regression. Non-parametric testing was performed using the Kruskal-Wallis and Dunn’s post hoc tests. Effect sizes were calculated, where possible, using the post hoc size command in Stata after ANOVAs.

For the N-back data multi-level regression was used, as described previously (Sinclair, Button, Munafo, Day, & Lewis, 2015). Unfortunately reaction times were not available for target/non-target so the reaction time data was only re-shaped according to the difficulty level. It was not possible to use multilevel regression for accuracy in the visual motion task as the data had a truncated normal distribution, but it was possible to use a repeated measures ANOVA.
For the simple reaction time all unfeasibly long (> 1000 ms) or short (< 120 ms) reaction times were excluded before calculation of mean and median reaction times. A further corrected (C-mean) mean reaction time was calculated by excluding all reaction times > 2SD away from the sub-mean. The C-mean was then used in analyses. For the choice reaction time task the same procedure was followed, except that the upper limit for excluding unfeasibly long reaction times was raised to 2000 ms. The difference between the choice C-mean and simple C-mean was calculated and used in the analysis as this is a purer measure of choice than the choice reaction time alone.

We made an a priori decision to exclude individuals with an ε42 genotype from analyses as this group mixes the high and lowest risk alleles. This is standard practice in APOE research (e.g. Alexander et al., 2007) We also made an a priori decision to exclude those who scored < 82 on the ACE-R as this has optimal sensitivity for dementia (Mioshi et al., 2006).

3. Results

3.1. Demographics

The study population differed by APOE genotype from those in the case selection who did not take part (see Table 1). In particular homozygotes for rare alleles were more likely to participate. The cause for this is unknown. Although homozygotes were invited first and then heterozygotes in the second wave of invitations the case selection was performed at random (other than for homozygotes for rare genotypes who were all invited to participate) and participants were then invited in a random order. There was no difference in the rate of family history of dementia between the groups. The expected effect of APOE genotype on serum LDL cholesterol was observed (Zacho et al., 2008). The age range of those who took part was 23–24 (young people) and 42–67 (mothers). There were 33 individuals with an ε2+ genotype and an age range of 23–24 (young people) and 43–67 (mothers). There were 39 individuals with an ε33 genotype whose ages ranged from 23 to 24 (young people) and 42 to 62 (mothers). Finally there were 42 individuals with an ε4+ genotype, with ages ranging from 23 to 24 (young people) and 42 to 62 (mothers).

Table 1

| Variable                                      | ε2+ | ε33 | ε4+ | Statistical evidence (ANOVA or Mann Whitney) |
|-----------------------------------------------|-----|-----|-----|---------------------------------------------|
| Mean (SD)                                     | 33  | 39  | 42  |                                             |
| Did not take part in study                    | 721 | 661 | 788 |                                             |
| Mean age of mothers at visit (yrs)            | 51.42 ± 4.867 | 50.28 ± 3.993 | 51.14 ± 4.459 | p = 0.513 |
| Gender                                        |     |     |     |                                             |
| Male                                          | 20  | 15  | 20  | X² = 3.521                                  |
| Female                                        | 13  | 24  | 22  | p = 0.172                                   |
| Young Person (YP)                             | 22  | 21  | 23  | X² = 1.473                                  |
| Mother                                        | 11  | 18  | 19  | p = 0.479                                   |
| IQ                                            | 114.333 ± 7.292 | 112.921 ± 11.741 | 113.488 ± 10.107 | X² = 0.208 |
| Mini Mental State Examination (MMSE) score     | 29.788 ± 0.415 | 29.553 ± 0.86 | 29.667 ± 0.612 | p = 0.961 |
| Addenbrooke's Cognitive Examination (ACE-R) score | 93.909 ± 3.076 | 93.676 ± 4.137 | 93.167 ± 3.963 | X² = 0.460 |
| Positive family history of dementia (%)       | 0.394 | 0.297 | 0.415 | p = 0.795 |
| History of a significant head injury (%)      | 0.152 | 0.263 | 0.195 | X² = 1.488 |
| No. of participants who use cannabis regularly | 3.500 ± 0.707 | 0 ± 0 | 0.750 ± 1.5 | N/A |
| No. of participants who use stimulants regularly | 0.500 ± 0.707 | 0 ± 0 | 0 ± 0 | N/A |
| No. of cups of caffeine containing drink usually consumes per day | 2.604 ± 0.24 | 3.459 ± 2.34 | 3.839 ± 3.144 | X² = 3.034 |
| No. of cups of caffeine containing drink consumed that day | 0.613 ± 0.715 | 0.73 ± 0.871 | 0.902 ± 1.934 | X² = 0.046 |
| Units of alcohol per week                     | 10.348 ± 12.519 | 9.456 ± 10.997 | 7.488 ± 8.092 | X² = 0.708 |
| Personal history of epilepsy                  | 0.061 | 0.026 | 0.024 | p = 0.702 |
| History of anxiety disorder                   | 0.121 | 0.237 | 0.190 | X² = 0.895 |
| History of depression                         | 0.121 | 0.184 | 0.262 | p = 0.639 |
| History of psychotic disorder                 | 0 ± 0 | 0 ± 0 | 0 ± 0 | N/A |
| Cognitive Failures Questionnaire Score        | 25.697 ± 36.987 | 35.526 ± 38.2 | 32.667 ± 36.701 | X² = 3.006 |
| Last available cholesterol (mothers) mmol/L   | 4.813 ± 0.9 | 5.202 ± 0.913 | 5.049 ± 0.536 | p = 0.001 |
| Depression, Anxiety and Stress Scale (DASS) total score | 9.424 ± 9.572 | 7.553 ± 6.769 | 17.214 ± 16.389 | X² = 7.487 |
| Edinburgh Postnatal Depression Scale (EPDS) total score | 4.212 ± 6.413 | 5.789 ± 6.338 | 5.69 ± 6.426 | X² = 1.022 |
| Moods & Feelings total score                  | 3.061 ± 2.85 | 2.421 ± 2.937 | 3.524 ± 4.49 | X² = 0.375 |

For the simple reaction time all unfeasibly long (> 1000 ms) or short (< 120 ms) reaction times were excluded before calculation of mean and median reaction times. A further corrected (C-mean) mean reaction time was calculated by excluding all reaction times > 2SD away from the sub-mean. The C-mean was then used in analyses. For the choice reaction time task the same procedure was followed, except that the upper limit for excluding unfeasibly long reaction times was raised to 2000 ms. The difference between the choice C-mean and simple C-mean was calculated and used in the analysis as this is a purer measure of choice than the choice reaction time alone.

We made an a priori decision to exclude individuals with an ε42 genotype from analyses as this group mixes the high and lowest risk alleles. This is standard practice in APOE research (e.g. Alexander et al., 2007) We also made an a priori decision to exclude those who scored < 82 on the ACE-R as this has optimal sensitivity for dementia (Mioshi et al., 2006).
3.2. Test battery results

There was little evidence of a per genotype difference in performance on the reaction time, digits forwards/backwards task, the Rey-Osterrieth complex figure task or the Stroop test (see Table 2). Although the initial ANOVA was suggestive of a per genotype difference in phonemic fluency (p = 0.047) no evidence of a difference was seen in a subsequent linear regression. There was no evidence of a per genotype difference in category fluency (p = 0.647).

### 3.3. Episodic memory

In the main analysis there was no evidence of a per genotype difference in performance at the long delay timepoint in the RAVLT (see Fig. 2B). As shown in Fig. 2A the ε2+ group remembered slightly more words in the first 5 trials of the RAVLT (5.1 more words, $X^2 = 6.663$, p = 0.036) In addition there was evidence from both the Kruskal-Wallis and Dunn’s tests that ε2 carriers performed better on the episodic list learning task (1.6 more words, $X^2 = 6.842$, p = 0.016) (see Fig. 3). This was an immediate recall task. There was no evidence of a per-genotype difference in the paired associative learning task.

### 3.4. Executive functioning

There was reasonable strength evidence that those with an ε2 allele were faster (i.e. performed better) in the trails A & B test ($X^2 = 11.704$, p = 0.003, see Fig. 4). The Kruskal-Wallis and Dunn’s post hoc test suggested that there was a difference between the ε2+ group and the ε33 (p = 0.005) and the ε4+ group (p < 0.001). This should be interpreted with caution.

### 3.5. Working memory

As would be expected the participants had almost perfect accuracy on the 1-back task (see Table 3). Accuracy was lower for the 2-back and much lower for the 3-back, as anticipated. Neither the accuracy variable nor d’ were normally distributed (truncated normal distribution with an upper limit of 1.0) and it was not possible to transform them. It was not possible to calculate d’.

The regression was therefore performed with bootstrapping as this method does not require a normal distribution. The residuals from this regression were normally distributed. The results were unchanged with bootstrapping. There appeared to be improved accuracy (3.6% increase, $\beta = 0.036$ (95% CI = 0.003–0.069), p = 0.034) in the ε2 group, although the overall likelihood test for an effect of APOE suggested that there was no effect (p = 0.091, see Table 3). The overall r2 was 0.473.

There was no evidence that APOE genotype influenced reaction time to target in the 2- or 3-back n-back task (p = 0.888, see Table 3).

### Table 2

Results from the neuropsychological test battery. $X^2$ refers to statistical evidence from the Kruskal Wallis test.

| Variable                     | $\epsilon^2+$ | $\epsilon^33$ | $\epsilon^4+$ | Statistical evidence (ANOVA or Kruskal Wallis) |
|------------------------------|---------------|---------------|---------------|---------------------------------------------|
|                              | Mean  | SD    | Mean  | SD    | Mean  | SD    | p value | Effect size |
| Digits forwards               | 6.061 | 1.029 | 5.925 | 1.185 | 5.907 | 1.25  | p = 0.835 | 0.003       |
| Digits backwards              | 4.576 | 1.437 | 4.3   | 1.381 | 4.186 | 1.367 | p = 0.496 | 0.013       |
| RAVLT trials I-V recall (errors) | 1.636 | 2.133 | 1.425 | 2.024 | 1.419 | 1.918 | $X^2 = 1.205$ | p = 0.547 |
| RAVLT trials I-V recall (repetitions) | 15.424 | 12.281 | 9.05  | 10.583 | 13.791 | 15.239 | $X^2 = 4.650$ | p = 0.098 |
| RAVLT trials I-V recall (total) | 57.848 | 7.484 | 52.7  | 10.118 | 53.884 | 7.582 | $X^2 = 6.663$ | p = 0.036 |
| RAVLT trial VII delayed recall (errors) | 11.969 | 2.901 | 10.75 | 3.095 | 11.214 | 2.968 | $X^2 = 0.523$ | p = 0.770 |
| RAVLT trial VII delayed recall (total) | 11.969 | 2.901 | 10.75 | 3.095 | 11.214 | 2.968 | $X^2 = 2.980$ | p = 0.225 |
| Verbal fluency (FAS) total no. words | 43.697 | 8.432 | 41.25 | 11.047 | 41.186 | 11.065 | Effect size = 0.010 | p = 0.375 |
| Category fluency (animals)    | 23.636 | 3.959 | 21.85 | 5.323 | 23.093 | 4.83  | p = 0.018 |
| Paired associative learning (errors) | 1.667 | 1.931 | 1.725 | 1.961 | 2.465 | 2.693 | $X^2 = 2.907$ | p = 0.234 |
| Paired associative learning (total) | 51.242 | 7.08  | 45.7  | 13.921 | 46.651 | 9.768 | $X^2 = 4.722$ | p = 0.094 |
| Rey-Osterrieth figure delayed recall | 22.788 | 4.697 | 20.075 | 7.604 | 21.093 | 6.045 | p = 0.317 |
| Rey-Osterrieth figure immediate recall | 23.561 | 5.275 | 19.738 | 8.252 | 21.244 | 6.073 | Effect size = 0.029 | p = 0.104 |
| Trails B – Trails A (secs)     | 20.595 | 9.636 | 36.745 | 41.301 | 33.835 | 23.521 | $X^2 = 11.704$ | p = 0.005 |
| Episodic list learning total recalled | 11.697 | 2.687 | 10.075 | 3.214 | 10   | 3.471 | $X^2 = 6.842$ | p = 0.033 |
| Episodic list learning errors | 0.424 | 0.792 | 0.475 | 0.816 | 0.31  | 0.643 | $X^2 = 0.781$ | p = 0.677 |
| C-mean simple reaction time (ms) | 292.049 | 38.829 | 284.925 | 34.884 | 289.379 | 29.281 | $X^2 = 0.839$ | p = 0.657 |
| C-mean choice reaction time (ms) | 438.109 | 59.592 | 440.356 | 60.409 | 446.225 | 53.149 | $X^2 = 0.778$ | p = 0.004 |
| Choice RT error rate | 0.036 | 0.021 | 0.041 | 0.029 | 0.047 | 0.042 | $X^2 = 1.990$ | p = 0.670 |
| Stroop interference effect (ms) | 91.878 | 95.07 | 124.454 | 94.421 | 109.775 | 84.805 | Effect size = 0.020 |

- $\epsilon^2$ refers to statistical evidence from the Kruskal Wallis test.
- $\epsilon^2$ refers to statistical evidence from the ANOVA test.
3.6. Visual motion task

The motion task had 3 levels of speed and 2 levels for target i.e. present/absent. One participant was excluded because they had a large number of unfeasibly fast reaction times (< 120 ms) and their accuracy was at chance level. When calculating the reaction time all unfeasibly short (< 120 ms) reaction times were excluded before calculation of mean and median reaction times. A further corrected (C-mean) mean reaction time was calculated by excluding all reaction times > 2SD away from the sub-mean. Only 1 trial from one participant was excluded because of a reaction time < 120 ms.

Multi-level regression of accuracy was not possible because a normal distribution could not be obtained. The analysis proceeded using d' as this takes account of both accuracy to target and false alarms. The discriminability index (better known as d') is a measure of signal strength that takes account of signal and "noise". To prevent a false alarm rate of 0 (and thus an infinitely large d') where the false alarm rate was zero it was adjusted to be 1/N where N was the number of valid trials for that participant.

Because the within subject co-variance of the d' data structure was compound symmetric it was possible to use a repeated measures ANOVA. There was no evidence that APOE genotype had an effect on d' (see Table 4 and supplementary Tables 4 and 5).

Multilevel regression for reaction time was possible by inverse transformation of reaction time (see Table 4 and supplementary Table 6). There was no evidence of an APOE effect on reaction time.

3.7. Self-reported cognitive difficulties

There was evidence from the cognitive failures questionnaire (CFQ) that self-reported cognition was worse in those with an ε4 allele (X² = 6.051, p = 0.006, see Fig. 5A). Those with an ε4 allele also scored somewhat higher on the depression anxiety and stress scale (DASS). The overall Kruskal-Wallis test and the Dunn’s post-hoc test (see Fig. 5B) suggested that those with an ε4 allele scored higher on this scale than either of the other two groups (increase = 9.7 points, overall p value = 0.024, X² = 7.487, comparison to ε33 group p = 0.009).

3.8. Effect of age group

The dichotomised age groups in this study allowed us to examine differences in observed APOE genotype effects between young people and middle aged women. Unfortunately low numbers precluded statistical analysis, but the data are presented graphically in Supplementary Figs. 1–7. It would seem that the ε2+ positive effect on episodic memory was seen predominantly in the young people and the ε2+ effect in the trails A & B test was seen in both age groups. It appears that ε4 had slightly more effect on DASS scores in the mothers, which is surprising as there were no per genotype effects on either the Crown-Crisp or the EPDS which overlap somewhat with the DASS.
Finally it seems that the higher scores on the CFQ for individuals with an ε4+ genotype was driven by the young people. Due to low numbers these findings are speculative and impossible to prove.

4. Discussion

We found evidence to suggest that ε4 allele possession is associated with more self-reported cognitive failures, but minimal objective difference in cognitive performance compared to the reference ε33 group. We also found that possession of an ε2 allele is associated with slightly better episodic memory performance, slightly improved accuracy on the n-back task and better executive functioning (as measured by trails A & B) than the reference ε33 group. There was no evidence of a per genotype difference in reaction time, attention, verbal fluency or working memory. Effect sizes, where it was possible to calculate them, were very low. It is intriguing that the ε4 carriers, who have an up to 50% reduction in the risk of AD should demonstrate advantage in working memory. ε2 carriers, although at least 15% of its cohort developed AD during the 8 y follow-up period (Wilson, Bienias, Berry-Kravis, Evans, & Bennett, 2002). A similar Finnish community based study with a 3 y follow-up had similar results (Helkala et al., 1996). In a secondary analysis of data from an existing longitudinal study aimed at examining the effect of cardiovascular risk factors Blair et al. demonstrated that individuals with an ε2 allele had the least cognitive decline over a 6 y period (Blair et al., 2005). This was a large study, with mixed ethnicity and a mean participant age of 55. Its main weaknesses were a loss to follow-up and a limited test battery. Conversely, the HALCYON study, a combination of ageing cohorts, found no meta-analytic evidence of an ε2 effect on episodic memory or verbal fluency, although this was largely based on cross-sectional measures (Alfred et al., 2014). The majority of participants came from studies with a mean age in the mid 50 s. Given that many previous studies have analysed their results as ε4+ vs. ε4 − it is possible that if ε2 does have a beneficial effect on cognition then including them in the ε4 − (control) group may have possibly inflated findings that ε4 allele possession has a detrimental effect on cognition.

A meta-analysis in 2011 found a small effect of ε4 on episodic memory in adults without dementia, but gave the caveat that many studies had not adequately screened for dementia. Most of the studies had included mainly older adults. More recent studies have also found an effect of APOE genotype on episodic memory in later adult life, for example the limited GWAS by Andrews et al. (mean cohort age 62 y). (Andrews, Das, Cherbuin, Anstey, & Eastal, 2016) A recent meta-analysis of the effects of APOE genotype on cognition in mid life reported no per genotype effect (Lancaster et al., 2017). Only 8 studies with a mean participant age of less than 50 y were included.

Several studies have reported that subjective memory complaints in ε4 carriers aged over 60 are associated with greater decline in episodic memory (Dang, 2017; Dik et al., 2001; Samieri et al., 2014). Caselli et al. found an increased rate of subjective memory complaints in ε4 carriers in their 60 s and older (Caselli et al., 2014). Very recent work

Table 3
Results from the n-back task at levels 1, 2 and 3 back.

| ε2+ | ε33 | ε4+ |
|-----|-----|-----|
| Accuracy | | | |
| Multi-level regression | Co-efficient | 0.036 (0.003-0.069) | Co-efficient | 0.034 | Co-efficient | 0.008 (-0.23 to 0.040) |
| LR test for overall effect | p = 0.091 | P-value | 0.034 | Reference group | P-value | 0.008 |
| Reaction time | Co-efficient | -0.001 (-0.111 to 0.110) | Co-efficient | 0.987 | Co-efficient | -0.021 (-0.125 to 0.083) |
| Statistical evidence from multi-level regression | LR test for overall effect | p = 0.888 | p = 0.007 |

Table 4
C mean reaction times and accuracy rates for the different conditions in the visual motion task. * denotes p < 0.05.

| ε2+ | ε33 | ε4+ |
|-----|-----|-----|
| Accuracy | | | |
| Target absent | Fast | 0.989 | 0.02 | 0.945 | 0.108 | 0.974 | 0.033 |
| | Medium | 0.98 | 0.029 | 0.961 | 0.078 | 0.981 | 0.029 |
| | Slow | 0.983 | 0.027 | 0.952 | 0.097 | 0.977 | 0.040 |
| Target present | Fast | 0.954 | 0.054 | 0.929 | 0.100 | 0.940 | 0.068 |
| | Medium | 0.939 | 0.055 | 0.921 | 0.107 | 0.930 | 0.085 |
| | Slow | 0.939 | 0.066 | 0.943 | 0.085 | 0.946 | 0.091 |
| Repeated measures ANOVA | APOE genotype | Interaction between APOE genotype and level | p = 0.588 | p = 0.027 |
| C mean reaction time (msec) | Target absent | Fast | 1235.67 | 756.354 | 1072.34 | 820.401 | 1065.691 | 411.334 |
| | Medium | 1351.498 | 1173.153 | 1065.149 | 781.691 | 1079.731 | 456.079 |
| | Slow | 1371.326 | 1114.924 | 1108.585 | 879.918 | 1089.68 | 483.82 |
| Target present | Fast | 819.296 | 301.045 | 740.199 | 324.114 | 730.257 | 252.855 |
| | Medium | 828.271 | 316.083 | 747.454 | 258.899 | 783.043 | 264.319 |
| | Slow | 993.369 | 488.757 | 847.204 | 324.114 | 868.535 | 306.196 |
| Statistical evidence from multi-level regression | Co-efficient | -0.014 (-0.30 to 0.002) | Co-efficient | 0.106 | Co-efficient | -0.007 (-0.023 to 0.008) |

- Table 3 Results from the n-back task at levels 1, 2 and 3 back.
- Table 4 C mean reaction times and accuracy rates for the different conditions in the visual motion task. * denotes p < 0.05.
been demonstrated that the E2 isoform of ApoE increased synaptic
kinesis by Minett et al. suggests that the 
 recent work of Minett et al., 2014; Suri, Heise, Trachtenberg, & Mackay, 2013). Recent work
has reduced a
ferences in
strongly to A
β carries. The E2 protein is more abundant than the E4,
ε 2 and
ε 4 carriers were not more likely to
ε 2+ group (p = 0.015). As shown in
ε 4+ group had higher scores on the DASS.* denotes p < 0.05.

There are a number of possible biological explanations for the dif-
ferences in e2 carriers. The E2 protein is more abundant than the E4, possibly because it is more resistant to degradation (Conejero-Goldberg et al., 2014). It has reduced affinity for LDL receptors and binds more strongly to Aβ than other ApoE isoforms, which may lead to more ef-
cient clearance of Aβ from cerebral blood vessels (Conejero-Goldberg et al., 2014; Suri, Heise, Trachtenberg, & Mackay, 2013). Recent work
by Minett et al. suggests that the e2 and e4 alleles may have opposite
acter migration and atrophy (Minett et al., 2016). It has also recently
been demonstrated that the E2 isoform of ApoE increased synaptic
phagocytosis by astrocytes (with possible evidence of fewer senescent
synapses (Chung et al., 2016). It has been shown in post-mortem brain

from the Australian Womens Healthy Ageing project (age of partici-
pants mid 64–77) found that whilst e4 carriers were not more likely to
report subjective memory complaints in response to a single question those that did had more decline in their episodic memory at 2 year follow up (Dang, 2017). Several of these individuals subsequently
developed mild cognitive impairment. It is important to note though that there is no consistent relationship between subjective memory complaints and objective decline (Lenehan, Klekociuk, & Summers, 2012). In our study it appears that the increase in subjective memory complaints was also seen in the young people, which runs counter to the suggestion that subjective memory complaints are an early marker of cognitive decline in e4+ individuals.

There are a number of possible biological explanations for the dif-
fferences in e2 carriers. The E2 protein is more abundant than the E4, possibly because it is more resistant to degradation (Conejero-Goldberg et al., 2014). It has reduced affinity for LDL receptors and binds more strongly to Aβ than other ApoE isoforms, which may lead to more ef-
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been demonstrated that the E2 isoform of ApoE increased synaptic
phagocytosis by astrocytes (with possible evidence of fewer senescent
synapses (Chung et al., 2016). It has been shown in post-mortem brain

studies and in PET studies of older adults that e4 allele possession is
associated with a higher amyloid plaque load (Caselli et al., 2010; Wirth et al., 2014). In one study this effect was seen even in middle-
age 
aged individuals (Ghebremedhin et al., 1998). e4 effects on neurofi-
brillary tangles are much less consistent (Raber et al., 2004). Cumula-
tively this cell biological and neuropathological evidence goes some 
way towards explaining the opposing effects on the risk of AD seen with the e2 and e4 genotypes.

Strengths of this study include adequate screening for dementia,
examination of a range of cognitive functions and prospective
information on possible confounders. Eleven individuals in this study
scored between 82 and 88 on the ACE-R and ten of them were young
people. The mother who scored in this range had a borderline low IQ.
Educational level is known to affect performance on the ACE-R
(Amaral-Carvalho & Caramelli, 2012; Garcia-Caballero et al., 2006; Strydom & Hassiotis, 2003). All of these individuals had an MMSE score of 28 (2 young people) or higher. It is extremely unlikely that an
individual in their 20 s would suffer with dementia. We can therefore
be confident that no individuals with dementia were included in this
study. There were more female than male participants, principally due
to the study design. It is possible that e4 effects on cognition might be
more pronounced in women, but this benefit of our study design was
almost certainly offset by poor recruitment (Ungar et al., 2014).

The main weakness of this study was poor recruitment. Recall by
genotype is an efficient study design which maximises statistical power
(Ware et al., 2014). One drawback is that if recruitment is a problem
then it is an inflexible design. Despite strenuous efforts to improve re-
cruitment we were unable to recruit further participants. Participants in
this study were better educated (mothers), more likely to come from a
family that owned its own home and had higher IQs (young people)
than the rest of the ALSPAC cohort. The phenomenon of differential loss
to follow-up in longitudinal cohort studies is well known and it is the
most likely explanation for this finding. It does however limit the
generalisability of our findings. There was little evidence of a differ-
etial loss to follow-up by APOE genotype as the genotypes of all re-
mainig available participants were in Hardy Weinberg Equilibrium (p
= 0.016).

In conclusion this study used recall by genotype to study individuals
with the full range of APOE genotypes. We studied younger individuals
than most previous studies and used a wider range of cognitive tests.
We did not find any effect of e4 allele possession on objective cognitive
test performance in young to middle aged adults, but they scored higher
on the cognitive failures questionnaire (although this seemed to be
more prominent in the younger age group). Our findings support the
existing literature which suggests that objective e4 effects do not de-
velop until later adult life and may reflect the earlier onset of AD seen in
this genotype group. In addition we found evidence to suggest that e2
carriers (who have a lower risk of AD) may have mildly superior per-
formance in executive functioning, working memory and episodic
memory tasks, domains known to be affected early in the AD disease
process.

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