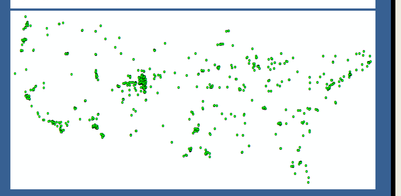
# APOE Effects On Cognition From Middle Childhood To The Cusp Of Middle Adulthood

Chandra A. Reynolds [1], Andrew Smolen [2], Brett C. Haberstick [2], John C. DeFries [2], Sally J. Wadsworth [2]
1. University of California, Riverside, Riverside, CA, United States; 2. University of Colorado Boulder, Boulder, CO, United States

## Abstract

*APOE* is a well-established genetic risk factor for cognitive aging and dementia, but its influence on cognition in childhood through early adulthood is inconclusive. We examined cross-sectional and longitudinal associations of *APOE* genotypes with cognitive performance in individuals now approaching midlife (30-45 years) from the ongoing Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging study (CATSLife), with over 30 years of follow-up from parent studies (Colorado Adoption Project, Longitudinal Twin Study). We conducted an analysis on a subset of participants who participated in cognitive assessments between middle childhood and early adulthood with available *APOE* genotyping. Cross-sectional analyses of WAIS IQ scores indicated that with each ε4 allele, full IQ scores were lower by 1.66 points compared to ε33 individuals ($p < .01215$; $d = -.11$). Consistent but weaker effects were found for Verbal and Performance IQ. Longitudinal trajectory analyses of specific memory, spatial and speed abilities between middle childhood and early adulthood (9 – 46 years; $N = 1339$) suggested that *APOE* ε4 was associated with poorer performance on a paired associates task (Names and Faces, Immediate & Delayed, $p \leq 1.10E-06$). Specifically, for each ε4 allele, a lower asymptote was achieved ($p \leq .023$) and faster rate of change to the asymptote ($p = .000$), typically achieved by 14.5 years, was observed for both immediate and delayed recall, adjusting for *APOE* ε2, sex, study, practice and mode of administration. Our findings suggest that *APOE* ε4 genotypes may be associated with lower general cognitive ability and hippocampal-dependent memory abilities, and that these differences may be manifested earlier than midlife.

**CATSLife participants span the US.**
Current address plotted in ArcGIS, points jiggled for de-identification. (AK & HI not shown)



Contact: Chandra A. Reynolds
CATSLife – UC Riverside
chandra.reynolds@ucr.edu
bbr.ucr.edu
www.colorado.edu/ibg/human-research-studies/catslife

## Introduction

"Cognitive health begins at conception."[1] This implies that early influences accumulate over the life course to impact how well we age[2].

- For example, *APOE* ε4, the established genetic risk for Alzheimer's disease, may predict brain differences as early as infancy[3-4]; however, it is equivocal as to when detrimental cognitive effects emerge[5,6].

We examined associations of *APOE* genotypes with cognitive performance in individuals now approaching midlife (30-45 years) from CATSLife, evaluating middle-childhood to the cusp of middle adulthood.

## Methods and Materials

**Participants**

*Colorado Adoption Project (CAP).* Initiated 1975: 245 adoptive & 245 control families.

*Longitudinal Twin Study (LTS).* Initiated in 1985: 483 twin pairs.

- Nearly annual assessments between infancy – adolescence, periodic assessments into adulthood.

*CATSLife assessment.* Enrolls CAP & LTS participants between ~30-45 years.

- Target N = 1600, Current N as of May 2017 = 667.

**Measures**

Standardized IQ measures (Year 16 assessment).

- WAIS-R [CAP]; WAIS-III [LTS]

Specific Cognitive Abilities (Years 9[t], 10[t], 12, 14[t], 16, 21*, 30*, CATSLife)

[t] telephone assessments. * CAP only assessments.

- Names & Faces Paired Associates Task, Immediate & Delayed (NFI, NFD)
- Picture Memory, Immediate & Delayed (PMI, PMD)
- ETS Card Rotations (ROTA)
- Colorado Perceptual Speed (CPS)

*APOE* Genotyping. Taqman assays of APOE SNPS, rs7412 and rs429385, were performed using existing buccal cell derived DNA. Success rate was 97%. HWE was achieved in both the CAP and LTS samples ($p \geq .082$)

**Table 1.** Sample descriptions.

| | CAP (N=947) | | | LTS (N=910) | | |
|---|---|---|---|---|---|---|
| Sex | 53% male | | | 49% male | | |
| Assessment | *N* | *Mage* | *SD* | *N* | *Mage* | *SD* |
| Year 9 | 625 | 9.48 | 0.37 | 796 | 8.94 | 0.45 |
| 10 | 629 | 10.45 | 0.37 | 752 | 9.96 | 0.40 |
| 12 | 628 | 12.47 | 0.40 | 754 | 12.43 | 0.37 |
| 14 | 598 | 14.50 | 0.38 | 632 | 13.93 | 0.42 |
| 16 | 908 | 17.04 | 2.31 | 813 | 16.58 | 0.79 |
| 21 | 568 | 21.56 | 1.18 | . | . | . |
| 30 | 274 | 31.87 | 1.29 | . | . | . |
| CATSLife (Current) | 246 | 38.34 | 2.48 | 363 | 28.88 | 0.99 |

**Table 2.** *APOE* genotype frequencies.

| CAP | | | LTS | | |
|---|---|---|---|---|---|
| *APOE* | *N* | *freq* | *APOE* | *N* | *freq* |
| ε22 | 5 | 1.02 | ε22 | 9 | 1.03 |
| ε23 | 51 | 10.41 | ε23 | 105 | 12.07 |
| ε24 | 15 | 3.06 | ε24 | 16 | 1.84 |
| ε33 | 292 | 59.59 | ε33 | 536 | 61.61 |
| ε34 | 118 | 24.08 | ε34 | 197 | 22.64 |
| ε44 | 9 | 1.84 | ε44 | 7 | 0.80 |
| Current *N* | 490 | | | 870 | |

*Note*. The available *N* for *APOE* is higher than the current *N* tested at CATSLife given availability of archived DNA.

## Results

**APOE ε4 and cross-sectional performance at age 16.** Multilevel regression models were fitted to WAIS IQ scores (SAS Proc Mixed) of those with available *APOE* genotyping at the at year 16 assessment ($N = 1160$; $M$age = 16.36, $SD = .44$; range limited to 16 – 18 years), accounting for sibling clustering, study (CAP/LTS), sex, age, and *APOE* ε2 alleles. Results suggested that for each ε4 allele, Full scale IQ scores were lower by -1.66 points compared to ε33 ($p = .01215$, 1-tailed; $d = -.11$). Consistent effects were found for Verbal and Performance IQ ($p \leq .0375$, 1-tailed; $d$'s = -.10 and -.09).

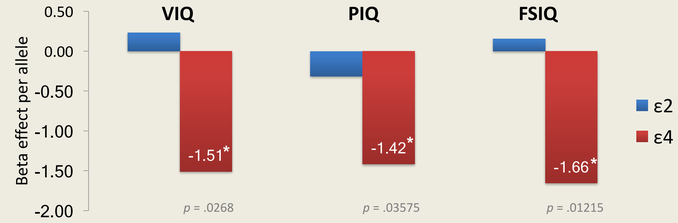



**Figure 1. Expected IQ differences by *APOE* ε4 at age 16**. ε4 allele effects relative to ε33, adjusted for ε2.
* p < 0.038 is significant with adjustments for number of tests (3) and correlation among tests (.74).

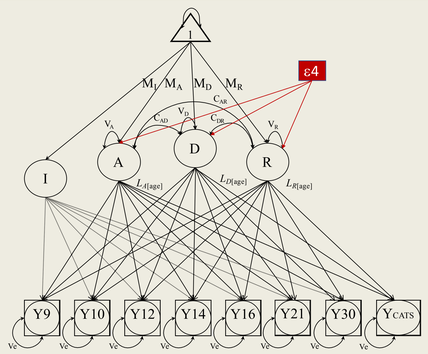
**APOE ε4 and Cognitive Trajectories.** A Gompertz sigmoid model[7,8] was fitted in Mplus 7.4 (Figure 2A), to test for emergent differences by *APOE* ε4 alleles on cognitive trajectories ($N = 1339$). Possible *APOE* ε4 differences were observed for the Names & Faces paired associates task (see Figures 2B, 3). Adjusted for *APOE* ε2, sex, study (CAP/LTS), practice and mode of administration.

Names & Faces Immediate (NFI): For each ε4 allele, a lower asymptote (p=.023) and faster rate of change to the asymptote (p=.000). $\Delta\chi2(3) = 54.28$, p = 9.80E-12.

Names & Faces Delayed (NFD): For each ε4 allele, a lower asymptote (p=.008) and faster rate of change to the asymptote (p=.000). $\Delta\chi2(3) = 30.46$, p = 1.10E-06. The trajectory pattern is nearly identical for immediate (not shown) and delayed (shown, see Figure 3).

No significant effects for picture memory (PMI, PMD), perceptual speed (CPS), or card rotations (ROTA).

A.




B.

| Test | I9 | A | ε4 | R | ε4 | D | ε4 | LRT | df | p |
|---|---|---|---|---|---|---|---|---|---|---|
| NFI | 3.16 | 3.43 | -0.59 | 0.30 | 0.26 | 5.38 | -0.04 | 54.28 | 3 | **9.80E-12** |
| se | 0.10 | 0.16 | 0.26 | 0.03 | 0.05 | 0.18 | 0.47 | | | |
| NFD | 2.94 | 3.34 | -0.74 | 0.24 | 0.21 | 5.69 | -0.24 | 30.46 | 3 | **1.10E-06** |
| se | 0.11 | 0.19 | 0.28 | 0.02 | 0.05 | 0.19 | 0.60 | | | |
| PMI | 9.81 | 4.21 | 0.18 | 0.64 | -0.15 | 0.13 | 0.17 | 2.52 | 3 | 4.71E-01 |
| se | 0.42 | 0.59 | 0.17 | 0.13 | 0.21 | 0.20 | 0.24 | | | |
| PMD | 6.00 | 6.38 | -0.05 | 0.57 | 0.13 | 1.12 | 0.20 | 6.75 | 3 | *8.03E-02* |
| se | 0.36 | 0.48 | 0.24 | 0.03 | 0.07 | 0.18 | 0.15 | | | |
| CPS | 14.56 | 25.91 | -0.20 | 0.56 | 0.02 | 2.91 | 0.07 | 7.48 | 3 | *5.81E-02* |
| se | 0.41 | 0.56 | 0.61 | 0.01 | 0.01 | 0.11 | 0.10 | | | |
| ROTA | 6.74 | 128.38 | -0.66 | 0.36 | 0.03 | 1.11 | 0.20 | 1.06 | 3 | 7.87E-01 |
| se | 9.04 | 10.00 | 3.65 | 0.02 | 0.02 | 0.32 | 0.15 | | | |

**Figure 2. Nonlinear Growth Model (Gompertz): (A) SEM representation, (B) *APOE* ε4 effects from full model.** I = Performance at age 9; A = gain to upper Asymptote; D = years to acceleration (from 9 years); R = rate of approach to asymptote. Adjusted for *APOE* ε2, sex, study (CAP/LTS), practice and mode of administration.

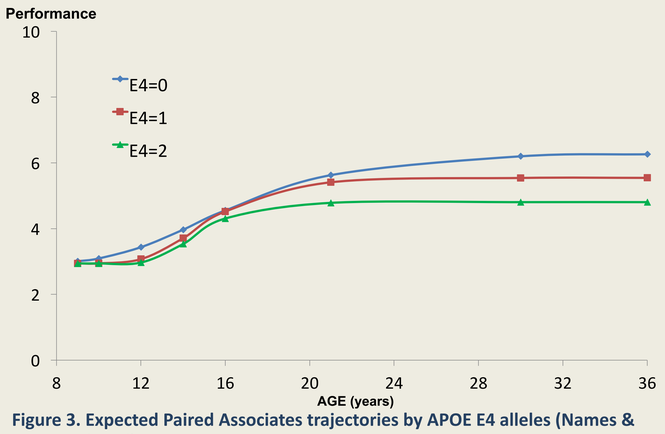



**Figure 3. Expected Paired Associates trajectories by APOE E4 alleles (Names & Faces, Delayed).**
E4 effect: $\Delta\chi2(3) = 30.46$, p = 1.10E-06. For each ε4 allele, a lower asymptote (p=.008) and faster rate of change to the asymptote (p=.000). Adjusted for APOE ε2, sex, study (CAP/LTS), practice and mode of administration.

## Discussion

*APOE* may be associated with lower general cognitive performance and some non-verbal and hippocampal-dependent memory abilities earlier than midlife.

- WAIS Full IQ scores show small detriments at age 16 per ε4 allele ($d = -.11$).
- Trajectory analyses suggested that *APOE* ε4 was associated with poorer memory performance on a paired associates task .

A recent large cross-sectional imaging and neuropsychological study of individuals aged 3 to 20 years suggested potential differences in brain and cognitive development (executive functioning, working memory) for those with *APOE* ε4 genotypes, but they did not find significant age**APOE* effects for an episodic memory task (reproduce sequence of pictures)[9]. Likewise, we found significant *APOE* associations for our paired associates task (Names & Faces), but not for picture memory. Paired associative learning deficits, particularly for names and faces, may present early in those eventually diagnosed with mild cognitive impairments and Alzheimer's disease[10].

Sensitivity of findings with the addition of more longitudinal participants, and with respect to model assumptions (e.g., comparing other sigmoidal growth models) will be further interrogated.

## Acknowledgements

NIH AG046938 [MPIs, Chandra A. Reynolds (Contact), Sally J. Wadsworth].
The content of this presentation is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## References

1. Barnett, J. H., Hachinski, V., Blackwell, A. D. (2013). Cognitive health begins at conception: addressing dementia as a lifelong and preventable condition. *BMC Medicine*, *11*, 246.
2. Liu S, Jones R, Glymour M. (2010). Implications of Lifecourse Epidemiology for Research on Determinants of Adult Disease. *Public Health Reviews*, 32, 489-511.
3. Dean DC, Iii, Jerskey BA, Chen K, et al. (2014). Brain differences in infants at differential genetic risk for late-onset Alzheimer disease: A cross-sectional imaging study. *JAMA Neurology*, *71*, 11-22.
4. Knickmeyer, R. C., Wang, J., Zhu, H., Geng, X., Woolson, S., Hamer, R. M., ... Gilmore, J. H. (2014). Common Variants in Psychiatric Risk Genes Predict Brain Structure at Birth. *Cerebral Cortex*, *24*, 1230-1246.
5. Chang, L., Douet, V., Bloss, C., Lee, K., Pritchett, A., Jernigan, T. L., ... & Amaral, D. G. (2016). Gray matter maturation and cognition in children with different APOE ε genotypes. *Neurology*, *87*, 585-594.
6. Ihle A, Bunce D, Kliegel M. (2012). APOE epsilon4 and cognitive function in early life: a meta-analysis. *Neuropsychology*, *26*, 267-77.
7. Grimm, K. J., Ram, N., & Estabrook, R. (2010). Nonlinear Structured Growth Mixture Models in Mplus and OpenMx, *Multivariate Behavioral Research*, *45* (6), 887 – 909.
8. Sterba, S. K. (2014). Fitting nonlinear latent growth curve models with individually varying time points. *Structural Equation Modeling, 21*(4), 630-647.
9. Chang, L., Douet, V., Bloss, C., Lee, K., Pritchett, A., Jernigan, T. L., ... & Amaral, D. G. (2016). Gray matter maturation and cognition in children with different APOE ε genotypes. *Neurology*, *87*, 585-594.
10. Amariglio, R. E., Frishe, K., Olson, L. E., Wadsworth, L. P., Lorius, N., Sperling, R. A., & Rentz, D. M. (2012). Validation of the Face Name Associative Memory Exam in Cognitively Normal Older Individuals. *Journal of Clinical and Experimental Neuropsychology*, *34*, 580–587.