The elusive nature of APOE ε4 in mid-adulthood: understanding the cognitive profile

Article (Supplemental Material)

Lancaster, Claire, Tabet, Naji and Rusted, Jennifer (2017) The elusive nature of APOE ε4 in mid-adulthood: understanding the cognitive profile. Journal of International Neuropsychological Society, 23 (3). pp. 239-253. ISSN 1355-6177

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http://sro.sussex.ac.uk
Table 1. Overview of cross-sectional studies investigating APOE genotype differences in mid-adulthood.

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<th>First Author (year)</th>
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<th>Age: mean (range)</th>
<th>Gender (% M)</th>
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<th>Cognitive domains</th>
<th>Neuropsychological tasks</th>
<th>Zygosity</th>
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<td>74% Caucasian, 26% other.</td>
<td>G, EM, EA, PS</td>
<td>MMSE, Word recognition task (individual, paired association), Size judgement span, Spatial recall, Listening span, n-back; Letter same-different (PS), Pattern same-different (PS)</td>
<td>ε4- vs. ε4+ (ε3/ε3, vs. ε3/ε4, ε4/ε4)</td>
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<td>DWR, DSS, VF</td>
<td>1. ε2+ vs. ε3 vs. ε4 He vs. ε4 Ho (ε2/ε2; ε2/ε3 vs. ε3/ε3 vs. ε2/ε4, ε3/ε4 vs. ε4/ε4) 2. ε4- vs. ε4+</td>
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<td>56 (49-69)</td>
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<td>AVLT, WAIS DS, WAIS Mental arithmetic, COWAT, WAIS Similarities, BNT, CFT, WAIS Block design</td>
<td>ε4- vs. ε4+ (ε3/ε3, vs. ε3/ε4, ε4/ε4)</td>
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<td>42 (-)</td>
<td>44</td>
<td>-</td>
<td>G, EA</td>
<td>MMSE, n-back</td>
<td>ε4- vs. ε4 He (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε3/ε4)</td>
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<td>Gender</td>
<td>Ethnicity</td>
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<td>Verbal learning, Verbal delayed recall, Figure delayed recall, DS (forward, backward), Recurring word test</td>
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<td>54 (44-65)</td>
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<td>AVLT, TMT-A &amp; B, DS</td>
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<td>59 (50+)</td>
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<td>59 (41-85)</td>
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<td>EA</td>
<td>Cued letter discrimination task, Spatial WM task, Attention/WM task</td>
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<td>92% Caucasian</td>
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<td>WAIS Logical memory, VF, Mill Hill Vocabulary scale, DSS</td>
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<tr>
<td>Panizzon (2014)</td>
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<td>56 (51-60)</td>
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<td></td>
<td>89.7% Caucasian</td>
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<td>CVLT, WMS Story recall, WMS Figure recall</td>
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**APOE: the cognitive profile in mid-adulthood**
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<th>Test/Measures</th>
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<td>72% Caucasian, 19% Afro-American, 9% Other</td>
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<td>G</td>
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<td>59 (-)</td>
<td>37</td>
<td>EM, EA</td>
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<tr>
<td>Velichkovsky (2015)</td>
<td>35</td>
<td>50 (-)</td>
<td>26</td>
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<td>Xu (2009)</td>
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<td>59 (50-65)</td>
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<td></td>
<td>43</td>
<td>58 (50-65)</td>
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<td>EM, EA, L, VF</td>
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APOE: the cognitive profile in mid-adulthood
Abbreviations: Domains: Global (G), Memory (M), Executive abilities (EA), Verbal Fluency (VF), Language (L), Visuospatial processing (VS), Processing Speed (PS), Tasks: Mini-mental State Examination (MMSE), Wide Range Achievement Test (WRAT), Delayed Word Recall (DWR), Brief Visuospatial Memory test (BVMT), Rey's Auditory verbal learning task (AVLT), Californian verbal learning test (CVLT), Digit span (DS), Paced Auditory Serial Attention task (PASAT), Prospective memory (PM), Rapid Visual Information Processing task (RVIP), Trails-making test (TMT), Wisconsin Card Sort task (WCST), Complex figure test (CFT), Controlled oral association task (COWAT), Boston Naming Task (BNT), Digit-symbol Substitution (DSS). Zygosity: Heterozyous (He), Homozygous (Ho)

Table 2. Average effect size per study organised by cognitive domain, where a positive effect size represents better performance by the ε4+ group

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<th>Domain</th>
<th>Authors (year)</th>
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<th>ε4-</th>
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<td>Goveas (2013)</td>
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Table 3. A summary of findings for the meta-analysis within each cognitive domain.

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<th>ε4- (n)</th>
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<th>95% CI</th>
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<td>2315</td>
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<td>-.01, .18</td>
<td>5.2</td>
</tr>
<tr>
<td>Memory</td>
<td>19</td>
<td>7702</td>
<td>15814</td>
<td>-0.01</td>
<td>-0.04, 0.02</td>
<td>17.40</td>
</tr>
<tr>
<td>EA</td>
<td>12</td>
<td>2045</td>
<td>3615</td>
<td>-0.03</td>
<td>-.10, .03</td>
<td>8.60</td>
</tr>
<tr>
<td>VF</td>
<td>10</td>
<td>6869</td>
<td>13909</td>
<td>0.02</td>
<td>-.02, .06</td>
<td>8.17</td>
</tr>
<tr>
<td>Language</td>
<td>8</td>
<td>4797</td>
<td>10732</td>
<td>0</td>
<td>-.07, .07</td>
<td>6.81</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>5</td>
<td>399</td>
<td>505</td>
<td>-0.01</td>
<td>-.14, .12</td>
<td>2.78</td>
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<tr>
<td>PS</td>
<td>7</td>
<td>6931</td>
<td>14791</td>
<td>-0.01</td>
<td>-.04, .02</td>
<td>7.15</td>
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</tbody>
</table>

Table 4. A summary of longitudinal studies investigating APOE differences in mid-adulthood

<table>
<thead>
<tr>
<th>First Author (year)</th>
<th>n</th>
<th>Age: M (range)</th>
<th>Gender (% M)</th>
<th>Ethnicity</th>
<th>Cognitive domain</th>
<th>Neuropsychological tasks</th>
<th>Follow-up</th>
<th>Attrition</th>
<th>Genotype comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blair (2005)</td>
<td>6810</td>
<td>56 (45-64)</td>
<td>51</td>
<td>6202 Caucasian</td>
<td>M, EA, VF</td>
<td>DWR, DSS, VF</td>
<td>6 yrs (2-yr intervals)</td>
<td>24%</td>
<td>1. ε2+ vs. ε3 vs. ε4 He vs. ε4 Ho (ε2/ε2; ε2/ε3 vs. ε3/ε3 vs. ε2/ε4, ε3/ε4 vs. ε4/ε4) 2. ε4- vs. ε4+</td>
</tr>
<tr>
<td>Caselli (2009)</td>
<td>815</td>
<td>60 (21-97)</td>
<td>31</td>
<td>85% Caucasian, 12 % Latino, 3%</td>
<td>G, M, VF, VS</td>
<td>MMSE, AVLT, COWAT, JLO</td>
<td>5 yrs (1-2 yr intervals)</td>
<td>-</td>
<td>ε4- vs. ε4+ (ε3/ε3, vs. ε3/ε4, ε4/ε4)</td>
</tr>
</tbody>
</table>
APOE: the cognitive profile in mid-adulthood

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Age (Range)</th>
<th>Gender</th>
<th>Zygosity</th>
<th>Tasks and Measurements</th>
<th>Follow-up</th>
<th>Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caselli (2011)</td>
<td>621</td>
<td>57 (21-97)</td>
<td>30</td>
<td>Homozygous</td>
<td>AVLT, COWAT, PASAT, DSS, WCST, Iowa Gambling task</td>
<td>6.3 yrs (2-yr intervals)</td>
<td>ε4- vs. ε4+ (ε3/ε3, vs. ε3/ε4, ε4/ε4)</td>
</tr>
<tr>
<td>Greenwood et al (2005b)</td>
<td>139</td>
<td>60 (33-85)</td>
<td>31</td>
<td>Homozygous</td>
<td>WMS-G, WMS-D, Cued Visual Search task, MMSE, WAIS logical memory, WAIS letter-number sequencing, Delayed match-sample task</td>
<td>3 yrs (1-yr intervals)</td>
<td>ε4- vs. ε4 Ho vs. ε4 Ho (ε2/ε2, ε2/ε3, ε3/ε3 vs. ε2/ε4, ε3/ε4 vs. ε4/ε4)</td>
</tr>
<tr>
<td>Jochemsen (2012)</td>
<td>188</td>
<td>57 (27-79)</td>
<td>80</td>
<td>Homozygous</td>
<td>RAVLT, ROCF, Elevator task, Brixton spatial task, MMSE, VF, Delayed recall, Recognition</td>
<td>3.8 yrs</td>
<td>44%</td>
</tr>
<tr>
<td>Kozauer (2008)</td>
<td>492</td>
<td>53 (18-65)</td>
<td>-</td>
<td>Homozygous</td>
<td>MMSE, Immediate recall, Delayed recall, Recognition</td>
<td>22 yrs (3 follow-ups)</td>
<td>-</td>
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<tr>
<td>Schultz (2008)</td>
<td>626</td>
<td>55 (50-59)</td>
<td>100</td>
<td>Homozygous</td>
<td>AFQT</td>
<td>35 yrs</td>
<td>-</td>
</tr>
<tr>
<td>Zhao (2005)</td>
<td>1128</td>
<td>- (40-49)</td>
<td>77</td>
<td>European descent</td>
<td>Verbal memory, AH4-1, MHV, VF (letter, category)</td>
<td>6 yrs</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2601</td>
<td>- (50-59)</td>
<td>74</td>
<td>European descent</td>
<td></td>
<td>6 yrs</td>
<td>-</td>
</tr>
</tbody>
</table>

**Abbreviations:** Domain- Global (G), Memory (M), Executive ability (EA), Verbal Fluency (VF), Language (L) Visuospatial (VS). Tasks-Mini-Mental State Examination (MMSE), Weschler Adult Intelligence Scale (WAIS), Weschler Memory Scale (WMS), Delayed Word Recall (DWR), Rey's Auditory Verbal Learning Task (AVLT), Controlled Oral Association Task (COWAT), Digit-symbol Substitution (DSS), Paced auditory serial attention task (PASAT), Wisconsin Card-sort task (WCST), Armed Forces Qualification task (AFQT), Rey-Osterrich Complex figure (ROCF), Judgement of Line Orientation (JLO), Mill Hill Vocabulary test (MHV). Zygosity: Heterozygous (He), Homozygous (Ho).