**Introduction**

- The APOE e4 allele is a well-established genetic risk factor for sporadic Alzheimer’s disease (AD).
- e4 carriers (e4+) have a 4-fold increased risk of developing AD relative to non-e4 carriers (e4-).
- e4+ also affects healthy ageing: e4+ show greater declines in cognitive performance with age (Caselli et al., 2009).
- Studies have also looked for brain activation differences in e4+, at young adulthood.
- Functional imaging (fMRI) studies have shown that young adult e4+ activate their medial temporal lobe (MTL) more strongly. The MTL supports memory formation. e4+ show greater MTL activity, during both memory tasks and other tasks which shouldn’t activate the MTL at all (Trachtenberg et al., 2012; Rusted et al., 2013).
- Could young adult e4+ be ‘working’ their brains harder, which leads to problems later in life?
- Could this mean they are exerting greater cognitive ‘effort’ (although performance tends to be similar)?

**Aims**

- To show MTL overactivity in young adult e4+ during a memory task.
- To measure pupil diameter as an index of ‘cognitive effort’.

**Methods and task**

- Task completed in brain scanner (fMRI, 1.5T) while eyetracker measured pupil diameter.
- ‘Acquisition’ phase: 100 words presented serially; (1 sec/word); make button press to profession words (8/100).
- ‘Surprise ‘recall’ phase (35 min delay): 100 ‘old’ words plus 80 ‘new’ words; button press for old/new decision.
- Contrast brain activation patterns at acquisition for words subsequently remembered/forgotten.

**Participants**

- 26 e4- and 28 e4+ recruited (age 18-28)
- All participants performed with high accuracy at acquisition (95%).
- Exclude participants who scored <50% on ‘old words’ (7 e4+, 7 e4-)

**Results**

- Recall performance: no genotype differences (see Table 2).
- fMRI: Compare brain activity to words later remembered (R) vs. forgotten (F).
- Activation in all participants in temporal lobe (adjacent to MTL, see Fig. 1a).
- Only e4+ showed greater activity to remembered words within MTL (Fig. 1b).
- Pupillometry: e4+ fail to show the normal increase in pupil diameter to remembered words.
- How does this relate to brain activity? Examine correlation patterns between pupillometry and fMRI data.
- Common patterns between e4+ and e4- in visual areas (Fig. 2a), differential patterns in parietal lobe (Fig. 2b)

**Discussion**

- In line with previous findings, e4+ showed greater MTL activity to remembered items in a memory task.
- Pupillometry measures showed an unusual pattern in e4+ with no link between cognitive effort and recall.
- In e4+, enhanced MTL activity was observed, but e4+ did not show the normal pattern of downregulation in precuneus (usually indicating deactivation of the default mode network).
- This activation pattern is reminiscent of that seen in the early stages of MCI, thought to reflect inefficient cognitive processing, and predictive of subsequent cognitive decline.

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**Table 1. Volunteer characteristics**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Gender</th>
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<tbody>
<tr>
<td>e4- (n=26)</td>
<td>20.9 ± 1.90</td>
<td>M/F</td>
</tr>
<tr>
<td>e4+ (n=28)</td>
<td>20.9 ± 2.59</td>
<td>M/F</td>
</tr>
<tr>
<td>t-statistic</td>
<td>0.44, ns</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Performance during recall phase (% correct)**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>e4-</td>
<td>61 ± 10</td>
<td>75 ± 12</td>
</tr>
<tr>
<td>e4+</td>
<td>60 ± 11</td>
<td>76 ± 11</td>
</tr>
</tbody>
</table>

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