Object pattern separation performance in Alzheimer’s patients links compromised hippocampal neurogenesis to APOE4 status and CSF Aβ42

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BACKGROUND & OBJECTIVES

65 Mild to Moderate Alzheimer’s disease patients (DSM-IV)’
Mean age 76.6 years SD 7.5
Patients were on stable, continuous treatment with acetylcholinesterase inhibitors (fixed dose for at least two months)
Patients were excluded if treated with memantine, lithium, warfarin, or recently started (2-months) CNS active substances (e.g. anti-depressants and neuroleptics)
Patients were APOE genotyped
CSF Aβ42 and Phosphorylated-tau and Total-tau were measured

METHODS

■ 65 Mild to Moderate Alzheimer’s disease patients (DSM-IV)
■ Mean age 76.6 years SD 7.5
■ Patients were on stable, continuous treatment with acetylcholinesterase inhibitors (fixed dose for at least two months)
■ Patients were excluded if treated with memantine, lithium, warfarin, or recently started (2 months) CNS active substances (e.g. anti-depressants and neuroleptics)
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RESULTS

Aβ42 & EPISODE MEMORY When correlations were run in all AD patients, the strongest relationships were for higher levels of Aβ42 to be associated with superior accuracy and speed in rejecting the closely similar pictures; therefore linking Aβ42 to this non-invasive biomarker of DG activity and potentially neurogenesis

<table>
<thead>
<tr>
<th>Object Pattern Separation Task</th>
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<th>p</th>
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<tbody>
<tr>
<td>Ability to reject closely similar pictures</td>
<td>0.31</td>
<td>0.011</td>
</tr>
<tr>
<td>Speed of rejection of closely similar pictures</td>
<td>-0.39</td>
<td>0.002</td>
</tr>
<tr>
<td>Ability to correctly indentify original pictures</td>
<td>0.13</td>
<td>0.315</td>
</tr>
<tr>
<td>Speed of identification of original pictures</td>
<td>-0.3</td>
<td>0.017</td>
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</tbody>
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Word Recognition Task

| Ability to reject novel words | 0.15 | 0.237 |
| Speed of rejection of novel words | -0.22 | 0.074 |
| Ability to correctly indentify original words | 0.08 | 0.507 |
| Speed of identification of closely similar words | -0.21 | 0.094 |

DISCUSSION & CONCLUSIONS

■ In man neurogenesis occurs in two major brain areas, one being the hippocampal dentate gyrus (DG), which is also a region heavily involved in pattern separation
■ DG activity can be monitored in man by measuring the ability to make different discriminations in object pattern separation (OPS) tasks
■ Preclinical work has associated APOE e4 status & declining levels of Aβ42 with reduced dentate gyrus (DG) activity & disrupted neurogenesis
■ This study employed a OPS validated task and this analysis identified:
  » CSF Aβ42 levels to be related to difficult OPS in AD patients
  » e4 homozygotes to show a selective decline on the ability to make difficult OPS
■ This finding is consistent with preclinical work and suggests that therapies designed to reduce brain levels of beta amyloid may promote neurogenesis
■ This task which takes less than 4 minutes can thus serve as a proof of principle as well as being an outcome measure for such therapies

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