Brain Changes in Asymptomatic Individuals with Autosomal-dominant Alzheimer's Disease

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Continuum of Alzheimer’s disease

Adapted from Sperling et al., 2011
Autosomal dominant AD (ADAD): A unique opportunity to examine early AD-related changes in cognitively-normal individuals.

Presenilin-1 (PSEN-1) mutation carriers develop early-onset AD with near 100% certainty.

The Colombian kindred has a median age of mild cognitive impairment (MCI) at 44 years (95% CI +/- 2 years), and dementia at 49 years (95% CI +/- 2 years).

Clinical, cognitive and biomarker similarities between ADAD and late-onset Sporadic AD.
Are there changes in the brain of mutation carriers years before the onset of AD symptoms?
What are the earliest brain changes associated with the predisposition to Alzheimer’s disease?
Learning of face-name associations

ERP biomarkers

ABnormalities in ERP correlates of recognition

Picture recognition memory

FMRI biomarkers

Hyperactivation of MTL regions

Novel picture encoding

MRI biomarkers

Cortical thinning in the AD-signature

Brain morphology in AD-signature regions

ERP biomarkers

Abnormalities in ERP correlates of recognition

Studies

AD biomarkers

Novel picture encoding

Brain morphology in AD-signature regions

Hyperactivation of MTL regions

Picture recognition memory
Is brain hyperactivity one of the earliest signs of AD-related neurodegeneration?
Hippocampal Hyperactivation

Statistical Parametric Maps (SPMs) for the comparison PSEN1 mutation carriers versus controls for the contrast novel face-name pairs versus repeated face-name pairs. Color bar represents $t$-statistic values for all activated voxels within the anatomical mask.

Quiroz et al. (2010) Annals of Neurology
Younger group of carriers (18-25 years)

Carriers had greater right hippocampal and parahippocampal activation, and less precuneus and posterior cingulate deactivation.

Figure 2. Reduced %BOLD suppression during face/name associated encoding in young pre-symptomatic E280A mutation carriers vs non-carriers (p=0.013).

Reiman, Quiroz et al. (2012), Lancet Neurology
Children/Adolescents (9-18 years)

Carriers had less parietal deactivation (Novel>Familiar)
Biomarker abnormalities in preclinical PSEN1 E280A carriers

Fleisher et al, 2012; 2015
Objective:

To characterize the relationship between amyloid burden and tau accumulation in the brains of PSEN1 E280A mutation carriers and non-carriers from the Colombian kindred with autosomal dominant AD.

Hypotheses being tested:

- Abnormal levels of tau will be evident in the brains of asymptomatic PSEN1 mutation carriers.
- Amyloid- beta deposition will precede tau tangle formation both within and beyond the medial temporal lobe.
19 members of the Colombian kindred with *PSEN1* mutation traveled to Boston (USA) for tau PET using [F18] AV1451 and amyloid PET using [11C] PIB. Ten mutation carriers aged 28-44, and 9 non-carriers were included.

<table>
<thead>
<tr>
<th></th>
<th>MCI (n=2) (individual values)</th>
<th>Asymptomatic Carriers (n=8)</th>
<th>Noncarriers (n=9)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean (SD)</td>
<td>43, 44</td>
<td>33 (5)</td>
<td>38 (11)</td>
<td>0.28</td>
</tr>
<tr>
<td>Education</td>
<td>5, 11</td>
<td>9 (4)</td>
<td>11 (3)</td>
<td>0.13</td>
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<tr>
<td>MMSE</td>
<td>18, 26</td>
<td>28 (1.4)</td>
<td>29 (0.5)</td>
<td>0.23</td>
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<tr>
<td>CERAD Word List:</td>
<td></td>
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<tr>
<td>Immediate Learning</td>
<td>8, 11</td>
<td>19 (5)</td>
<td>22 (4)</td>
<td>0.18</td>
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<tr>
<td>Delayed Recall</td>
<td>2, 7</td>
<td>7 (2)</td>
<td>8 (1)</td>
<td>0.21</td>
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<tr>
<td>Semantic Fluency (Animals)</td>
<td>14, 25</td>
<td>22 (6)</td>
<td>21 (4)</td>
<td>0.78</td>
</tr>
</tbody>
</table>
Aβ pathology measured with mean cortical 11C PiB for *PSEN1* mutation carriers > controls
[18F] AV1451 binding for PSEN1 carriers and controls
Conclusions:

Limitations:
Next Steps

- Characterize the relationship between tau deposition, decreased cognitive function, and neurodegenerative changes in preclinical ADAD.

- Compare the ability of tau biomarker measurements to predict subsequent cognitive decline in mutation carriers.

- Longitudinal study of tau biomarkers in preclinical ADAD.

- Compare findings from ADAD studies to preclinical late-onset AD (Harvard Aging Brain Study)
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PSEN1
Colombian families

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