Title
Regional distribution of white matter changes in Alzheimer's disease

Permalink
https://escholarship.org/uc/item/1gs9w3w0

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Publication Date
2004-07-01

DOI
10.1016/S0197-4580(04)81243-0

Peer reviewed
A COVARIANCE RESTING PET PATTERN THAT DISCRIMINATES BETWEEN HEALTHY ELDERLY AND EARLY AD PATIENTS CORRELATES WITH FUNCTIONAL AND COGNITIVE SEVERITY IN SUBJECTS WITH COGNITIVE IMPAIRMENT BUT NO DEMENTIA

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Background: Multivariate techniques capture a different dimension of the imaging data (covariance among brain regions) than voxel-based or ROI analyses, but have rarely been used to in detecting AD. Objective(s): We sought to identify a single covariance pattern of relative rest blood flow that would help in discriminating between AD patients and elderly controls, and would display meaningful associations with cognitive performance measures in subjects with minimal to mild cognitive impairment (CI) but not dementia. Methods: Non-quantitative H215O PET scans during rest were acquired in 16 probable AD subjects selected for mild severity (modified Mini Mental Status examination [mMMS] 46-57; sd 5.1) and 23 CI subjects (mMMS 54-57; sd 2.6) (broadly defined, including subjects with CDR = 0 and CDR = 0.5). AD-Control discrimination was attempted (i) voxel-wise comparisons, (ii) ROI analyses and (iii) multivariate voxel-wise regional covariance analysis. The covariance analysis derived pattern was then prospectively applied to the CI subjects. Results: There were no significant mean flow differences in either voxel-wise or ROI analyses. However, the multivariate analyses identified a covariance pattern whose mean expression was significantly higher in the AD patients as compared to controls (p = 0.03) (sensitivity 76-94%; specificity 63-81%). Sites of increased concomitant flow included insula, cuneus, pulvinar, lingual, fusiform, superior occipital and parahippocampal gyri, whereas decreased concomitant flow was found in cingulate, inferior parietal lobule, middle and inferior frontal, supramarginal and precentral gyri. When prospectively applied to the CI subjects, the covariance pattern discriminated well between subjects with CDR = 0 and CDR = 0.5 (p = 0.009). Expression of this pattern correlated inversely with Selective Reminding Test total recall (r = −0.401, p = 0.002), delayed recall (r = −0.351, p = 0.008) and mMMS scores (r = −0.401, p = 0.002) in all 3 groups combined, and in the CI group alone. Conclusions: Multivariate techniques may be of use in early AD diagnosis even when univariate methods fail. They also provide a sensitive tool for differentiating subjects with CI into those with higher and lower functional and cognitive abilities, and perhaps into those with greater probability of subsequent conversion to AD.
Conclusions: AD participants had disproportionately less temporal WM, whereas deep WM was relatively spared. These preliminary regional findings lend support to the theory that the breakdown in AD is related to the pattern of myelination, although the findings related to abnormal WM changes are less clear. Future studies will examine the relationship of such structural changes to other measures of WM integrity and to the progression of AD. Support: NIH/NIA P50 AG05131, AG12674, & AG04085, DVA Medical Research Service

Table 1. Percent difference in median volume (md) of AD relative to NC group [(1 - ADmd/NCmd) x 100]

<table>
<thead>
<tr>
<th>Region</th>
<th>WM Volume (%)</th>
<th>Abnormal WM Volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cerebrum</td>
<td>-10.9</td>
<td>+48.1</td>
</tr>
<tr>
<td>Frontal Lobe</td>
<td>-12.0</td>
<td>+71.4</td>
</tr>
<tr>
<td>Parietal Lobe</td>
<td>-6.6</td>
<td>+52.2</td>
</tr>
<tr>
<td>Occipital Lobe</td>
<td>-8.6</td>
<td>+60.5</td>
</tr>
<tr>
<td>Temporal Lobe</td>
<td>-16.0</td>
<td>+16.4</td>
</tr>
<tr>
<td>Deep Region</td>
<td>-3.2</td>
<td>+25.5</td>
</tr>
</tbody>
</table>

Conclusions: AD patients had disproportionately less temporal WM, whereas deep WM was relatively spared. These preliminary regional findings lend support to the theory that the breakdown in AD is related to the pattern of myelination, although the findings related to abnormal WM changes are less clear. Future studies will examine the relationship of such structural changes to other measures of WM integrity and to the progression of AD. Support: NIH/NIA P50 AG05131, AG12674, & AG04085, DVA Medical Research Service

P3-092  TEMPORAL LOBE GRAY MATTER REDUCTIONS IN ALZHEIMER’S DISEASE USING VOLUME-BASED MORMHPOMETRY

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Background: Voxel-based morphometry (VBM) may afford a more rapid and extensive survey of structural abnormalities in Alzheimer’s disease than manually drawn region of interest analysis. Objective(s): To examine the relationship of grey matter atrophy to other measures of WM integrity and to the progression of AD. Results: The AD patients showed grey matter reduction in the anterior temporal cortex and the amygdala/anterior hippocampal region bilaterally. Conclusions: These results confirm previous findings of temporal lobe atrophic changes in AD.

P3-094  PREDICTING COGNITIVE DECLINE WITH BASELINE HIPPOCAMPAL VOLUME AND RATE OF HIPPOCAMPAL ATROPHY

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Background: Because the hippocampus, a central structure for normal memory function, is an early site of Alzheimer’s disease (AD), hippocampal volume at baseline or rate of volume change may predict subsequent cognitive decline. Objective(s): To determine the extent to which hippocampal baseline volume or atrophy rate are related to cognitive decline in cognitively normal (CN) and mild cognitively impaired (MCI) subjects. Methods: Seventy-one CN and 39 MCI subjects were studied longitudinally with interscan period of 2.6 ± 1.2 years. CN subjects had cognitive dementia rating (CDR) scores of zero. MCI subjects had CDR of 0.5. Eleven CN and 12 MCI subjects, whose CDR scores increased at the time of their second MRI, were classified as cognitive decliners. Thirteen CN and 19 MCI had subcortical lacunes at first MRI. Hippocampal volume was measured on T1-weighted MRI. Logistic regression and receiver operator characteristics (ROC) were used to predict cognitive decline. Results: Decliners had smaller hippocampal volumes at baseline (F(1,100) = 14.5, p < 0.001) than non-decliners, after accounting for group, presence of subcortical lacunes, age, and sex. Furthermore, decliners had higher rates of hippocampal atrophy (F(1,100) = 46.9, p < 0.001) than non-decliners, after accounting for group, presence of subcortical lacunes, age and sex. As expected, high rates of hippocampal atrophy were inversely correlated with small baseline volumes (r = -0.48, p < 0.001). Using baseline volume yielded a 79% overall classification and an area under ROC curve of 0.70 between decliner and non-decliner. Using atrophy rate yielded an 82% overall classification and an area under ROC curve of 0.82 between decliner and non-decliner. Furthermore, atrophy rate was significantly better (p < 0.001) than baseline volume in differentiating between decliner and non-decliner. Conclusions: Although atrophy rate and baseline volume of hippocampus are correlated, atrophy rate is better than baseline volume in predicting cognitive decline.

P3-095  AGE-DEPENDENT CHANGES IN REGIONAL BRAIN VOLUME AND CEREBRAL BLOOD VOLUME IN WHITE MATTER OF THE CANINE BRAIN MEASURED USING DYNAMIC SUSCEPTIBILITY CONTRAST MRI

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Background: White matter abnormalities, common in dementia and normal aging, are associated with impaired learning, memory, and speed of