MRI measures of temporoparietal regions show differential rates of atrophy during prodromal AD


Neurology 2008;71:819-825 Published Online before print July 30, 2008
DOI 10.1212/01.wnl.0000320055.57329.34

This information is current as of July 30, 2008

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MRI measures of temporoparietal regions show differential rates of atrophy during prodromal AD

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ABSTRACT

Background: MRI studies have demonstrated differential rates of atrophy in the entorhinal cortex and hippocampus during the prodromal phase of Alzheimer disease (AD). The current study was designed to determine whether a broader set of temporoparietal regions show differential rates of atrophy during the evolution of AD.

Methods: Sixteen regions of interest (ROIs) were analyzed on MRI scans obtained at baseline and follow-up in 66 subjects comprising three groups: controls = individuals who were cognitively normal at both baseline and follow-up; nonconverters = subjects with mild cognitive impairment (MCI) at both baseline and follow-up; converters had MCI at baseline but had progressed to AD at follow-up.

Results: Annualized percent change was analyzed with multivariate analysis of variance (MANOVA), covaried for age. The MANOVA demonstrated an effect of group ($p < 0.004$). Post hoc comparisons demonstrated greater rates of atrophy for converters vs nonconverters for six ROIs: hippocampus, entorhinal cortex, temporal pole, middle temporal gyrus, fusiform gyrus, and inferior temporal gyrus. Converters showed differentially greater rates of atrophy than controls in five of the same ROIs (and inferior parietal lobule). Rates of change in clinical status were correlated with the atrophy rates in these regions. Comparisons between controls and nonconverters demonstrated no differences.

Conclusion: These results demonstrate that temporoparietal regions show differential rates of atrophy on MRI during prodromal Alzheimer disease (AD). MRI data correlate with measures of clinical severity and cognitive decline, suggesting the potential of these regions of interest as antemortem markers of prodromal AD.

Neurology® 2008;71:819–825

GLOSSARY

AD = Alzheimer disease; APC = annualized percent change; CDR-SB = Clinical Dementia Rating Sum of Boxes; CVLT = California Verbal Learning Test; MANOVA = multivariate analysis of variance; MCI = mild cognitive impairment; ROI = region of interest; SRT = Selective Reminding Test.

Longitudinal MRI studies have focused on volumetric changes primarily in the hippocampus and entorhinal cortex. Postmortem studies indicate that additional regions beyond hippocampus and entorhinal cortex are involved in the early phases of Alzheimer disease (AD). The few longitudinal studies examining temporoparietal changes in subjects with mild cognitive impairment (MCI) who progressed to AD found atrophy in inferior and middle temporal gyrus, posterior cingulate, and precuneus, and in medial temporal lobe and posterior cortical...
regions.\textsuperscript{7} Two studies have also demonstrated differential rates of atrophy between individuals without dementia with a dominant genetic mutation in comparison to controls in posterior cingulate, medial temporal lobe, neocortical temporoparietal regions,\textsuperscript{8} and precuneus.\textsuperscript{9}

In this study, we used analysis tools to conduct an assessment of temporoparietal gray matter regions in order to determine which regions demonstrate greater rates of atrophy among individuals destined to develop AD.

Measures of clinical severity and neuropsychological performance were available on the subjects, allowing us to examine the relationship between the atrophy rates and the rate of change in the clinical status. The clinical relevance of atrophy in the MRI measures was also examined by performing power calculations to determine the sample size needed for a clinical trial that used the three regions of interest (ROIs) with the largest effect size.

\textbf{METHODS} \textbf{Subjects.} A total of 66 individuals were examined. The subjects were chosen from the larger population of 339 subject as being the only ones who met the clinical criteria for this study and had two MRI scans that were acquired on a 1.5T GE scanner, obtained with an SPGR sequence. Subjects were originally recruited through the print media. The details of the screening procedures have been described elsewhere.\textsuperscript{10} All subjects provided informed consent prior to the initiation of the study, in accordance with the requirements of the Human Research Committee of Massachusetts General Hospital (Boston, MA).

The subjects were selected to fit into three groups based upon their clinical status at baseline and follow-up: (A) control (n = 19), cognitively normal at both baseline and follow-up; (B) nonconverter (n = 22), MCI at both baseline and follow-up; (C) converter (n = 25), MCI at baseline (2 were cognitively normal at baseline), but progressed to a diagnosis of probable AD on follow-up (table 1). Nonconverters and converters showed no difference (p > 0.05) in their baseline CDR-SB scores. A comparison of baseline age showed a difference between the groups (p < 0.05). No other demographic or genetic variables differed between the groups. Data from baseline scans for 18 of the subjects have been included in prior publications related to manual ROIs.\textsuperscript{11,12}

\textbf{Assessment of clinical severity.} The degree of clinical severity was evaluated by an annual semi-structured interview that generated both an overall Clinical Dementia Rating (CDR) rating the CDR Sum of Boxes (CDR-SB).\textsuperscript{13} The mental status evaluation included the Blessed Memory and Orientation Test,\textsuperscript{14} a set of similarities and differences, calculations, and a standardized language evaluation. Mean inter-rater reliability of the CDR rating was high (r = 0.99, p < 0.0001), as was the inter-rater reliability of the 6 CDR subcategories (r = 0.90).

Annually, a consensus diagnostic process determined 1) presence of sufficient impairment for a diagnosis of dementia, and if so, 2) whether the dementia was consistent with criteria for AD\textsuperscript{15} or another entity, e.g., frontotemporal dementia, vascular dementia.\textsuperscript{16,17} Diagnoses were based on clinical history, medical records, laboratory evaluation, and neuroimaging studies (presence of infarcts). Only subjects with a diagnosis of probable AD on follow-up were included in the converter group.

\textbf{Measures of clinical status.} Subjects were administered a neuropsychological battery.\textsuperscript{16} Three test scores from this battery were selected for analysis in the present study because they had previously been shown to be sensitive predictors of progression from MCI to AD.\textsuperscript{18} The three scores were total recall score on the California Verbal Learning Test (CVLT),\textsuperscript{19} free recall score on the Selective Reminding Test (SRT),\textsuperscript{20} and time to complete Trail Making Test B.\textsuperscript{21} Mean interval between acquisition of the MRI scan and the semi-structured interview was 4.7 months; mean interval between acquisition of the MRI scan and administration of the neuropsychological tests was 3.6 months.

\textbf{MRI acquisition.} MRI scans were obtained at baseline and were repeated, based on a priori criteria concerning progression in level of clinical severity (i.e., subjects who crossed specific

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Variable} & \textbf{Controls} & \textbf{Nonconverters} & \textbf{Converters} \\
\hline
\textbf{Sample size} & 19 & 22 & 25 \\
\textbf{Years of age} & 69.7 (3.7) & 70.1 (4.4) & 72.8 (4.7) \\
\textbf{Time between scans, y} & 3.0 (0.4) & 3.1 (0.7) & 4.5 (3.8) \\
\textbf{Years of education} & 15.8 (2.7) & 16.1 (2.1) & 14.9 (3.2) \\
\textbf{Percent female} & 63.2 & 59.1 & 64.0 \\
\textbf{MMSE} & 29.7 (0.6) & 29.4 (1.0) & 28.9 (1.3) \\
\textbf{MMSE time 2} & 29.7 (0.6) & 27.8 (2.3) & 27.8 (2.3) \\
\textbf{CDR-SB} & 0.00 (0.0) & 1.34 (0.6) & 1.48 (0.8) \\
\textbf{CDR-SB time 2} & 0.0 (0.0) & 1.8 (1.0) & 4.7 (0.6) \\
\textbf{Percent APOE-ε4} & 31.6 & 31.8 & 37.5 \\
\textbf{Total follow-up time, y} & 6.4 (4.3) & 8.8 (4.8) & 9.7 (4.2) \\
\hline
\end{tabular}
\caption{Descriptive statistical information for the subjects in the study, mean (SD)}
\end{table}

Descriptive statistics for the groups at baseline. MMSE = Mini-Mental State Examination; CDR-SB = Clinical Dementia Rating Sum of Boxes.
We focused on 14 ROIs: 1) hippocampus; 2) entorhinal cortex; 3) fusiform gyrus; 4) inferior parietal lobule; 5) inferior temporal gyrus; 6) middle temporal gyrus; 7) posterior cingulate cortex; 8) precuneus cortex; 9) parahippocampal gyrus; 10) superior parietal lobule; 11) superior temporal gyrus; 12) supramarginal gyrus; 13) amygdala; and 14) temporal pole.

The clinical relevance of these effect size calculations was evaluated by power calculations to determine the sample size needed for a theoretical clinical trial that used the three with the largest effect size. Sample size estimates needed to detect both a 25% and a 50% treatment effect were performed. All calculations incorporated the assumption that a clinical trial should have 90% power to detect a treatment effect, with a two-tailed 5% level of significance. Sample size estimates were recalculated to reflect a 10% loss to follow-up, and an additional 10% loss of MRI scans. Similar estimates were calculated for the CDR-Sum of Boxes and the Selective Reminding Test.

Correlation coefficients were used to examine the relationship between rates of atrophy in the ROIs and rates of change in the measures of clinical status for the subjects who were MCI at baseline. Spearman rank correlation coefficients were utilized. In order to account for multiple comparisons a $p$ value of $\leq 0.01$ was used for interpreting statistical significance.

**RESULTS** Table 2 presents the mean APC for each of the ROIs. The MANOVA revealed an effect of group ($F = 2.04$, $df = 32$, $p = 0.004$). Post hoc comparisons demonstrated that six ROIs were different between converters and nonconverters: hippocampus ($p < 0.001$), temporal pole ($p < 0.001$), entorhinal cortex ($p < 0.01$), fusiform gyrus ($p < 0.01$), middle temporal gyrus ($p < 0.01$), and inferior temporal gyrus ($p < 0.01$). Post hoc comparisons between converters and controls demonstrated that six ROIs were different, including hippocampus.
none of the 16 ROIs proved to be different in the comparisons between controls and nonconverters.

Table 3 shows the effect size calculations for each ROI with a significant APC, based on the post hoc comparisons (d values greater than 0.73 correspond to an effect size of $p < 0.05$). Between converters and controls, large effects were observed for hippocampus (d = 1.69), entorhinal cortex (d = 1.53), temporal pole (d = 1.51), fusiform gyrus (d = 1.01), and middle temporal gyrus (d = 1.00). Between converters and nonconverters, large effects were observed for hippocampus (d = 1.39), temporal pole (d = 1.17), middle temporal gyrus (d = 0.88), fusiform gyrus (d = 0.87), and entorhinal cortex (d = 0.84).

We calculated sample size estimates needed to detect 25% and 50% reduction for the ROIs that demonstrated the largest effect size for comparison of controls vs converters (i.e., entorhinal cortex, hip-

### Table 2

<table>
<thead>
<tr>
<th>Temporoparietal regions of interest</th>
<th>Controls (mean APC)</th>
<th>Nonconverters (mean APC)</th>
<th>Converters (mean APC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>-2.14 (1.40)</td>
<td>-2.11 (1.50)</td>
<td>-2.57 (2.36)</td>
</tr>
<tr>
<td>Banks superior temporal sulcus</td>
<td>-1.82 (1.03)</td>
<td>-2.22 (1.38)</td>
<td>-2.63 (2.32)</td>
</tr>
<tr>
<td>Entorhinal cortex</td>
<td>-0.68 (1.40)</td>
<td>-1.92 (2.12)</td>
<td>-3.93 (2.63)</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>-0.39 (1.05)</td>
<td>-0.51 (1.18)</td>
<td>-1.61 (1.34)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>-0.71 (0.88)</td>
<td>-1.13 (1.01)</td>
<td>-3.45 (2.12)</td>
</tr>
<tr>
<td>Inferior parietal lobule</td>
<td>-0.77 (1.19)</td>
<td>-1.09 (1.50)</td>
<td>-1.76 (1.50)</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>-1.02 (0.90)</td>
<td>-0.71 (0.86)</td>
<td>-1.67 (1.49)</td>
</tr>
<tr>
<td>Isthmus of cingulate cortex</td>
<td>-0.57 (1.40)</td>
<td>-0.16 (0.72)</td>
<td>-0.69 (1.22)</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>-0.78 (0.65)</td>
<td>-0.84 (1.03)</td>
<td>-2.12 (1.77)</td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>-0.41 (1.35)</td>
<td>-0.88 (2.31)</td>
<td>-1.57 (2.06)</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>-0.68 (1.28)</td>
<td>-0.72 (1.22)</td>
<td>-0.77 (1.45)</td>
</tr>
<tr>
<td>Precuneus cortex</td>
<td>-0.65 (1.09)</td>
<td>-0.87 (1.24)</td>
<td>-1.05 (1.16)</td>
</tr>
<tr>
<td>Superior parietal lobule</td>
<td>-0.31 (1.24)</td>
<td>-0.44 (1.06)</td>
<td>-0.86 (1.58)</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>-0.69 (0.77)</td>
<td>-0.82 (1.72)</td>
<td>-1.15 (1.21)</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>-0.67 (1.06)</td>
<td>-0.64 (1.01)</td>
<td>-1.31 (1.32)</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>-0.24 (1.32)</td>
<td>-0.82 (1.45)</td>
<td>-3.10 (2.23)</td>
</tr>
</tbody>
</table>

The symbols reflect the significant differences between the controls vs converters, and the converters vs nonconverters, which used age-adjusted data.

* `$p \leq 0.001$`

† Only different in comparison of converters vs controls.

‡ `$p \leq 0.01$`

§ `$p \leq 0.05$`

¶ Only different in comparison of converters vs nonconverters.

APC - annualized percent change.

(p < 0.001), entorhinal cortex ($p < 0.001$), temporal pole ($p < 0.001$), middle temporal gyrus ($p < 0.01$), fusiform gyrus ($p < 0.01$), and inferior parietal lobule ($p < 0.05$). None of the 16 ROIs proved to be different in the comparisons between controls and nonconverters.

Table 3 shows the effect size calculations for each ROI with a significant APC, based on the post hoc comparisons (d values greater than 0.73 correspond to an effect size of $p < 0.05$). Between converters and controls, large effects were observed for hippocampus (d = 1.69), entorhinal cortex (d = 1.53), temporal pole (d = 1.51), fusiform gyrus (d = 1.01), and middle temporal gyrus (d = 1.00). Between converters and nonconverters, large effects were observed for hippocampus (d = 1.39), temporal pole (d = 1.17), middle temporal gyrus (d = 0.88), fusiform gyrus (d = 0.87), and entorhinal cortex (d = 0.84).

We calculated sample size estimates needed to detect 25% and 50% reduction for the ROIs that demonstrated the largest effect size for comparison of controls vs converters (i.e., entorhinal cortex, hip-

### Table 3

<table>
<thead>
<tr>
<th>Temporoparietal regions of interest</th>
<th>Converters vs controls</th>
<th>Converters vs nonconverters</th>
<th>Controls vs nonconverters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entorhinal cortex</td>
<td>1.53*</td>
<td>0.84*</td>
<td>0.69</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>1.01*</td>
<td>0.87*</td>
<td>0.11</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>1.69*</td>
<td>1.39*</td>
<td>0.45</td>
</tr>
<tr>
<td>Inferior parietal lobule</td>
<td>0.73*</td>
<td>0.53</td>
<td>0.29</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>0.52</td>
<td>0.78*</td>
<td>0.35</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>1.00*</td>
<td>0.88*</td>
<td>0.07</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>1.51*</td>
<td>1.17*</td>
<td>0.42</td>
</tr>
</tbody>
</table>

* `$p \leq 0.001$`

† `$p \leq 0.01$`

‡ `$p \leq 0.05$`
DISCUSSION

Results show that specific temporal and parietal cortices have greater rates of atrophy in MCI subjects who progress to AD within 4–5 years than controls who remain cognitively normal and MCI subjects who do not progress to AD within this time frame. Three regions that were most discriminative were hippocampus, entorhinal cortex, and temporal pole. Of clinical interest, atrophy rates in these regions correlated with changes in clinical severity and declines in cognition. Utilizing the atrophy rate from a combined measure of these regions reduced the estimated sample size needed for a clinical trial in MCI.

The hippocampal APC had the largest effect size overall. The entorhinal cortex had a large effect size in comparison of controls vs converters. These findings corroborate reported progressive atrophy in these medial temporal regions in the evolution of AD.

These results emphasize the importance of other regions within the temporal and parietal lobes as antemortem markers of AD. In particular, atrophy within the temporal pole has not been previously reported. Additional regions as markers of AD include fusiform gyrus and middle temporal gyrus. Examination of other reports reveal that these regions were included within areas identified by comparing groups of converters and controls, using voxel-based morphometry or fluid registration methods.

The atrophy rates of controls and nonconverters in this study were not different from one another. Atrophy rates of nonconverters fell midway between those of controls and converters for most ROIs (table 2). We found that the effect size of the entorhinal cortex approached statistical significance in the comparison of controls and nonconverters indicating that more work needs to be done to better understand the differences between these groups.

A concern in this study pertains to the difference in baseline age between the groups. Since converters were older than the other groups at baseline, one possibility is that age could be a cause for the increased rates of atrophy observed. In order to investigate this possibility, a MANOVA, using intracranial-corrected volumes for each ROI at the baseline timepoint, with baseline age as a covariate and group as a between subjects variable, was conducted. This analysis showed that the hippocampus, entorhinal cortex, and temporal pole did not differ between the groups indicating that disease progression, not age, is the underlying factor.

The regions that did not differ between the groups in the prodromal phase of AD are also of interest. They include amygdala, banks of superior temporal sulcus, superior parietal lobule, superior

### Table 4

Sample size estimates needed per group to detect either 25% or 50% treatment effects using mean rates of atrophy in subjects with mild cognitive impairment (calculated with 90% power and an alpha level of 0.05 using unpaired two-tailed t-tests)

<table>
<thead>
<tr>
<th>Temporoparietal regions of interest</th>
<th>Based on atrophy rates alone</th>
<th>Additionally assuming 10% dropout rate</th>
<th>Additionally assuming 10% of scans are unusable for analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entorhinal cortex</td>
<td>251/63</td>
<td>276/69</td>
<td>303/76</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>252/63</td>
<td>277/69</td>
<td>305/76</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>410/101</td>
<td>451/111</td>
<td>496/122</td>
</tr>
<tr>
<td>Combined ROI (entorhinal cortex + hippocampus + temporal pole)</td>
<td>179/44</td>
<td>197/48</td>
<td>217/52</td>
</tr>
<tr>
<td>CDR-Sum of Boxes</td>
<td>467/117</td>
<td>514/129</td>
<td>565/142</td>
</tr>
<tr>
<td>Selective Reminding Test</td>
<td>1,156/290</td>
<td>1,272/319</td>
<td>1,399/351</td>
</tr>
</tbody>
</table>

Values are 25% treatment effect/50% treatment effect. ROI = region of interest; CDR = Clinical Dementia Rating.
Differential atrophy in three of these regions (precuneus, posterior and isthmus portions of cingulate cortex) has been reported in other studies. Differences between those studies and this one that may influence the outcome include clinical characteristics of subjects, size of groups, and image analysis techniques.

Differential atrophy within temporal lobe regions during prodromal AD reported here (i.e., entorhinal cortex, hippocampus, temporal pole, middle temporal gyrus, fusiform gyrus, and inferior temporal gyrus) are consistent with neurofibrillary changes reported in postmortem cases. Differential atrophy within parietal lobe regions (i.e., inferior parietal lobule) may be more related to both amyloid and tangle pathology. The preponderance of accelerated atrophy within temporal lobe regions may, in part, explain reports that neurofibrillary tangle number correlates better with cognitive performance than amyloid pathology. Correlations between atrophy rates in the three regions with the largest effect size (i.e., hippocampus, entorhinal cortex, and temporal pole) and change in the measures of clinical severity (i.e., CDR-SB) suggest the potential of using these MRI measures as surrogate markers of underlying disease. Correlations between changes in atrophy of hippocampus and changes in episodic memory (CVLT and the SRT) are consistent with the fact that declines in episodic memory are reported as predictors of progression.

The atrophy rates reported here correspond to previous reports. For entorhinal cortex and hippocampus, the APC for controls was less than 1% per year, and for converters 3–4% per year. This is comparable to rates reported by investigators using voxel-based morphometry techniques. It is slightly less than that reported by investigators who have outlined these regions manually. The sample size estimates presented here are greater than those in another study. This difference may be related to the nature of the subject population. For example, the mean MMSE score of the subjects in the other report was 26, whereas MMSE score of this sample was 29. This indicates that the subjects in the present study were more mildly impaired than those in the prior study. Differences in conversion rates across studies are likely the result of the same phenomenon. Taken together, the findings in this report represent a novel approach to the analysis of MRIs among cases of prodromal AD. The MRI data presented here correlate with measures of clinical severity and cognitive decline, and can feasibly be utilized in therapeutic trials of MCI, affirming the utility of this approach for identifying antemortem markers of prodromal AD. The results also suggest that a broader range of structural MRI measures than have previously been identified may be useful as surrogate markers for the evolution of neuropathology in AD.

ACKNOWLEDGMENT
The authors thank Dr. Mary Hyde for assistance with data analysis and Dr. Svetlana Egorova, Amanda Dow, and Marisa Trisciano for assistance with data management.

Received October 30, 2007. Accepted in final form May 5, 2008.

REFERENCES

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Neurology 2008;71:819-825 Published Online before print July 30, 2008
DOI 10.1212/01.wnl.0000320055.57329.34

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