High-throughput, Fully Automated Volumetry for Prediction of MMSE and CDR Decline in Mild Cognitive Impairment

Sanja Kovacevic, PhD,* Michael S. Raji, MD, PhD,**† and James B. Brewer, MD, PhD*† and the Alzheimer’s Disease Neuroimaging Initiative

Abstract: Medial temporal lobe (MTL) atrophy is associated with increased risk for conversion to Alzheimer disease, but manual tracing techniques and even semiautomated techniques for volumetric assessment are not practical in the clinical setting. In addition, most studies that examined MTL atrophy in Alzheimer disease have focused only on the hippocampus. It is unknown the extent to which volumes of amygdala and temporal horn of the lateral ventricle predict subsequent clinical decline. This study examined whether measures of hippocampus, amygdala, and temporal horn volume predict clinical decline over the following 6-month period in patients with mild cognitive impairment (MCI). Fully automated volume measurements were performed in 269 MCI patients. Baseline volumes of the hippocampus, amygdala, and temporal horn were evaluated as predictors of change in Mini-mental State Examination and Clinical Dementia Rating Sum of Boxes over a 6-month interval. Fully automated measurements of baseline hippocampus and amygdala volumes correlated with baseline delayed recall scores. Patients with smaller baseline volumes of the hippocampus and amygdala or larger baseline volumes of the temporal horn had more rapid subsequent clinical decline on Mini-mental State Examination and Clinical Dementia Rating Sum of Boxes. Fully automated and rapid measurement of segmental MTL volumes may help clinicians predict clinical decline in MCI patients.

Key Words: hippocampus, temporal horn, amygdala, atrophy, magnetic resonance imaging, memory, mild cognitive impairment, automated segmentation

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Mild cognitive impairment (MCI) is considered a transitional stage between normal aging and Alzheimer disease (AD), yet a certain proportion of patients do not seem to progress to AD, at least with the follow-up periods published thus far.1 Such patients are not likely to be appropriate for the treatments targeted to prevent or slow down degenerative processes specific for AD. Therefore, robust and objective measures are necessary to distinguish patients with MCI who will clinically decline, particularly those who exhibit rapid decline, from those who will remain stable.2 One such measure is atrophy of medial temporal lobe (MTL) structures.

Assessment of MTL atrophy has previously required input from skilled personnel and manual tracing of structures or editing of semiautomated segmentations, making such techniques impractical for the clinical setting. Advancements in automated volumetric segmentation have minimized the requirement for human intervention3 allowing fully automated quantitative analysis to be performed. Such fully automated techniques are faster, less subjective, and less expensive than manual or semiautomated techniques.4

In this study, fully automated volumetric methods were applied to the baseline magnetic resonance (MR) images from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) dataset of MCI patients (n = 269). The goal was to examine whether volumes of hippocampus, amygdala, and temporal horn of the lateral ventricle would predict clinical decline over the next 6-month interval. Although atrophy in hippocampal volume is a well-established predictor of conversion from MCI to AD, much less is known about the value of temporal horn of the lateral ventricle and amygdala volume predicting clinical decline, especially over a short time interval. We also investigated whether treatment with acetylcholinesterase inhibitors (AChE-I) would modify prediction of decline. We hypothesized that the baseline MTL volumes would predict rate of clinical decline over a 6-month interval.

METHODS

ADNI Protocol

Data used in the preparation of this article were obtained from the ADNI database (www.loni.ucla.edu/ADNI). The
ADNI was launched in the year 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations. The principle investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco. ADNI is the result of efforts of many coinvestigators from over 20 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90 years, to participate in the research—approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For up-to-date information see www.adni-info.org. The ADNI study has undergone institutional review board evaluation and approval at each participating site and informed consent was obtained from all participants in the study.

Participants

Enrolled patients were in good general health and had no MR scanning contraindications, had completed at least 6 years of education (or had a good work history sufficient to exclude mental retardation), and had adequate visual and auditory acuity to allow neuropsychologic testing. In addition, each patient had an informant who had a frequent contact with the patient and was able to provide an independent evaluation of functioning.

To be included in the ADNI study in the MCI category, patients were required to have Mini-mental State Examination (MMSE) scores between 23 and 30 (inclusive), a memory complaint, objective memory loss measured by education-adjusted scores on Wechsler Memory Scale-Revised (WMS-R) or a Clinical Dementia Rating (CDR) score of 0.5, absence of significant enough levels of impairment in other cognitive domains so that criteria for dementia are not met, largely preserved activities of daily living, and an absence of dementia. In addition, Geriatric Depression Scale (GDS) score < 6 and vascular etiology modified Hachinski score < 4 were required. Both subtypes of amnestic MCI, single domain and multiple domain, were enrolled in ADNI protocol, as both subtypes have a high rate of conversion to AD.

Exclusion criteria included any significant neurologic disease other than suspected incipient AD. Patients with screening/baseline MR scan with evidence of infection, large infarction, other focal lesions, or multiple lacunes or lacunes in a critical memory structure were excluded from the study. In addition, exclusion criteria were major depression or bipolar disorder within the past 1 year of baseline visit, history of schizophrenia, or history of alcohol or substance abuse.

Demographic characteristics of MCI subjects are presented in Table 1. ADNI is an ongoing project and longitudinal data are still being collected. The present study included all MCI patients from the ADNI dataset who included all MCI patients from the ADNI dataset who received 6-month follow-up clinical evaluations at the time of 2-year follow-up. For up-to-date information see www.adni-info.org. The ADNI study has undergone institutional review board evaluation and approval at each participating site and informed consent was obtained from all participants in the study.

Table 1. Demographic Characteristics of the MCI Cohort

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<th>Age (y)</th>
<th>Education (y)</th>
<th>Range</th>
<th>MMSE at baseline</th>
<th>Range</th>
<th>CDR SB at baseline</th>
<th>Range</th>
<th>HC volume (% WBV) at baseline</th>
<th>Range</th>
<th>AMG volume (% WBV) at baseline</th>
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<th>TH volume (% WBV) at baseline</th>
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<th>ΔMMSE in 6 mo</th>
<th>Range</th>
<th>ΔACDR SB in 6 mo</th>
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<td>154 (57%)</td>
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<td>15.7 ± 3.0</td>
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<td>26.9 ± 1.8</td>
<td>23, 30</td>
<td>1.5 ± 0.9</td>
<td>0.5, 4.5</td>
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Mean and SD are presented unless indicated otherwise. AChE-I indicates acetylcholinesterase inhibitors; AMG, amygdala; APOE, apolipoprotein E; CDR SB, Clinical Dementia Rating Sum of Boxes; HC, hippocampus; MCI, mild cognitive impairment; MMSE, Mini-mental State Examination; TH, temporal horn of the lateral ventricle; WBV, whole-brain volume.

Cognitive Assessment

A number of tests were given to the subjects. Of particular interest in this report were results from the MMSE and CDR, because these tests, especially MMSE, are widely used in clinical practice to assess global cognitive functioning. Although subjects participated in a detailed neuropsychologic testing, Logical Memory Test (Delayed Paragraph Recall) and Rey Auditory Verbal Learning Test (AVLT) were selected as memory tests especially relevant to atrophy of MTL structures. In addition, Clock Drawing Test Copy score was used to assess visuospatial abilities, Boston Naming Test was used to assess language abilities, and Trail Making Test difference score (B – A) was used to assess attention and executive function.

MR Image Analysis

For each subject, a volume of T1-weighted anatomic images obtained using various 1.5T scanner systems (Siemens, Philips, General Electric) was downloaded from the ADNI image depository at the Laboratory of Neuroimaging at the University of California, Los Angeles, CA. A detailed description of the sequences used on different participating sites with various scanner systems can be found on http://www.loni.ucla.edu/ADNI/Research/Cores/. Images from an MPRAE sequence were processed by the NeuroQuant software package (CorTechs Labs Inc, La Jolla, CA). This recently released software package provides a full volume segmentation of 10 subcortical brain regions in each hemisphere and reports volumes for each. This procedure was compared with manual segmentation and on the basis of those studies received Food and Drug Administration 510K approval for clinical use in measuring volumes of brain structures in MR images. The algorithm used by this software package includes (1) a quality checking step to determine that the MR imaging sequence...
RESULTS

Association of MR Imaging Volumes With Baseline Characteristics

Hippocampus, amygdala, and temporal horn volumes were correlated with age and neuropsychologic measures of memory (Table 2). Specifically, larger hippocampus and amygdala volumes correlated with higher baseline delayed recall memory scores. Correlations between hippocampus volume and AVLT learning and delayed recall and logical memory delayed recall were evident (r > 0.22, P < 0.001). Larger amygdala volumes correlated significantly with higher baseline AVLT delayed recall and logical memory delayed recall (r > 0.23, P < 0.001). In addition, larger temporal horn volumes correlated with lower AVLT learning and delayed recall (r < −0.20, P < 0.001). Controlling for age and education resulted in qualitatively similar correlation values. Hippocampus, amygdala, and
Association of MR Imaging Volumes With Longitudinal Change in MMSE and CDR SB Scores

Baseline hippocampus, amygdala, and temporal horn volumes correlated with change in MMSE and CDR SB scores over the following 6 months (Table 3). Smaller baseline hippocampus, smaller baseline amygdala, or larger baseline temporal horn volumes predicted greater subsequent decline in MMSE, indicating worsening global cognitive function, and predicted greater subsequent increase in the CDR SB, indicating a decline in cognition and activities of daily living. Although each MTL volume was analyzed as a continuous variable, Figure 2 graphically illustrates the results using quartiles on the basis of the volumes of each MTL structure. MMSE scores at the baseline and the 6-month follow-up were plotted for each quartile group. This plot demonstrates that, in general, patients with smaller hippocampus, smaller amygdala, or larger temporal horn show the greatest decline on the 6-month follow-up visit, as measured by MMSE and CDR SB.

Correlation between the baseline neuropsychologic measures of memory and subsequent clinical decline was even stronger (Table 3). Therefore, multiple regression analyses were performed to determine if automated measures of MTL atrophy provide independent predictive information beyond that of demographics and baseline clinical and neuropsychologic measures.

In the multiple regression analysis, adjusting for age and education, smaller baseline hippocampus volume was associated with greater decline on MMSE (β = 0.13, P = 0.048) and CDR SB (β = −0.17, P = 0.01). Smaller baseline amygdala volume was associated with greater decline on MMSE (β = 0.19, P = 0.003) and showed a trend toward association with CDR SB (β = −0.12, P = 0.07). Larger baseline temporal horn volume was associated with greater decline on MMSE (β = −0.12, P = 0.02) and CDR SB (β = 0.15, P = 0.03).

MTL volumes were associated with decline on MMSE and CDR SB (Table 4) after adjusting for age, education, APOE-e4 status, and the baseline clinical scores. Smaller baseline hippocampus volume was associated with greater decline on MMSE (β = 0.14, P = 0.04) and CDR SB (β = 0.14, P = 0.04) and showed a trend toward association with CDR SB (β = −0.12, P = 0.06, trend). Larger baseline temporal horn volume was associated with greater decline on MMSE (β = −0.20, P = 0.003) and CDR SB (β = 0.20, P = 0.005). Treatment status did not influence the ability of automated MTL measures to predict clinical decline as measured by MMSE and CDR SB scores.

When the model included baseline neuropsychologic measures of memory, baseline MTL volumes did not add significantly to prediction of clinical decline, partially owing to the high correlation between baseline MTL volumes and the memory scores.

**DISCUSSION**

Volume measurements of the MTL are associated with the rate of clinical decline in a large cohort of MCI patients. This study, using fully automated segmentation, demonstrates the novel finding that in addition to smaller baseline hippocampus, patients with smaller amygdala or larger
temporal horn declined more rapidly on 2 widely available clinical assessments of general cognitive and functional ability. Measures of MTL atrophy contributed to prediction beyond that provided by age, education, APOE-ε4 and baseline clinical scores. In addition to associations between hippocampal volume and baseline learning and delayed recall scores,25,26 measures of amygdala volume and temporal horn volume were also related to memory performance.

In this study, we used fully automated brain MR image segmentation to examine MTL volume in MCI patients, and identified an association between MTL volume and clinical decline within a 6-month interval. Previous studies using manual or semiautomated measures of segmental MTL volumes with longer follow-up times (1 y or more) have shown a significant association between rate of clinical decline and extent of MTL atrophy in elderly patients.27,28 AD is associated with early MTL atrophy,29 and prodromal AD may underlie the memory complaints of most, but not all, amnestic MCI patients.30,31 MCI patients with MTL atrophy may be more likely to have prodromal AD and a more rapid clinical decline. Furthermore, the extent of MTL atrophy may reflect disease severity, which also contributes to a rapid decline. Further studies with attention to long-term clinical course and pathologic findings will be essential to understanding the observed relationship between MTL atrophy in MCI patients and subsequent development of AD.

Both subtypes of amnestic MCI, single domain and multiple domain, are known to have a high rate of conversion to AD, and were studied in the ADNI cohort. As expected, a number of MCI patients (20 out of 269, 7%) converted to AD within the 6-month period examined at the time of this study. Interestingly, conversion rates from MCI to AD have been reported to be approximately 16% per year31,32 and our analysis of the 6-month ADNI data supports this finding. Prior studies have compared baseline MR image volumetry in patients who progress to AD versus those who do not.33–35 Such studies have suggested that MTL atrophy is associated with subsequent conversion to AD. The current study assessed whether MTL atrophy predicts rate of clinical decline, which may be associated with earlier conversion from MCI to AD. The results from this large multicenter sample of MCI patients are consistent with the findings reported in previous studies that typically used smaller samples and manual tracing or visual assessment techniques in evaluating hippocampal or entorhinal atrophy in prediction of conversion from MCI to AD.33–42

Few studies have evaluated amygdala atrophy and temporal horn enlargement in prediction of disease progression in MCI subjects.43–46 Neuropathologic studies have implicated involvement of amygdala in AD progression.47 However, findings from previous manual volumetric studies of amygdala have been inconsistent.48 In the current study, amygdala atrophy was a significant predictor of
TABLE 4. MTL Volumes Predict Decline on Clinical Tests After Adjustment for Age, Education, Baseline Clinical Scores, and APOE-ε4 Status in MCI Subjects

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AMG indicates amygdala; APOE, apolipoprotein E; CDR SB, Clinical Dementia Rating Sum of Boxes baseline score; HC, hippocampus; MCI, mild cognitive impairment; MMSE, Mini-mental State Examination baseline score; MTL, medial temporal lobe; TH, temporal horn of the lateral ventricle.

decline as measured by MMSE and CDR SB, and remained a significant predictor after adjustment for baseline clinical scores.

Fully automated temporal horn measurements were also significant predictors of decline as measured by MMSE and CDR SB even after accounting for age, education, and baseline clinical scores. Enlargement of the temporal horn of the lateral ventricle reflects atrophy of the hippocampus and atrophy of the surrounding tissue, and thus may gauge regional atrophy beyond the MTL. It remains to be seen whether such fully automated measures are able to predict clinical decline in patients with more severe disease, such as when the pathology of AD extends beyond MTL structures. Temporal horn measures may complement hippocampal measures in predicting cognitive decline in such a group of patients. The current results suggest that temporal horn measures may provide information that is supportive to hippocampal measures in predicting subsequent decline when a memory deficit is noted, but overall level of functional impairment is mild.

In this study, treatment with AChE-I was allowed, and 45% of subjects received treatment for the duration of the follow-up or longer. Given that modest treatment effects on behavioral performance have been reported in AChE-I trials, treatment status was included in the analysis to control for treatment effects on prediction of clinical decline. Treatment status was included in the analysis to control for treatment status in prediction of decline. It did not change qualitatively the association between MTL volumes and decline on MMSE and CDR SB. Beneficial effects of treatment could have been obscured in this study because selection of patients for treatment could have been biased toward more severe cases. In fact, the treated group had more MTL atrophy and lower baseline clinical and memory scores. However, the goal was not to study the treatment effects per se, but to control for them if they exist. It is important that future studies control for AChE-I medication effects as many MCI patients receive such treatment off label.

Some limitations of this study warrant mentioning. Owing to the brief follow-up period, the cohort included very few converters to clinical AD, and therefore, relating baseline volumetry to clinical conversion was not possible. In addition, the outcome measures, MMSE and CDR SB, widely used to define clinical decline, are relatively insensitive to clinical decline over a 6-month period. On the other hand, the more specialized neuropsychologic batteries used to assess memory in these patients are time consuming (approximately 3 h) and not available in all clinical settings. Though these measures have been shown to have a higher predictive value in relation to cognitive decline in some studies, the use of additional brain regions in the analysis may prove to be superior when compared with these specialized tests.

This study demonstrates that fully automated MTL volume measurement can be performed rapidly and without manual input, yielding measures that are consistent with manual tracing and that are associated with the rate of clinical decline in a large cohort of MCI patients. Association of baseline atrophy with rapid decline was noted even with the short follow-up time of 6 months. Quantitative and objective measures, such as these, may improve selection of patients appropriate for early intervention against AD, and will be especially valuable as new medications that target AD pathophysiology are developed. Given that MR imaging is widely available and is already performed on patients with cognitive impairment, fully automated methods for subregional volume assessment may provide additional clinically relevant information at little added cost. The findings of the current study suggest that this capability may help clinicians identify which MCI patients are at greatest risk for rapid clinical decline.

REFERENCES


