ABSTRACT

Objective: To determine the ability of clinically available volumetric MRI (vMRI) and CSF biomarkers, alone or in combination with a quantitative learning measure, to predict conversion to Alzheimer disease (AD) in patients with mild cognitive impairment (MCI).

Methods: We stratified 192 MCI participants into positive and negative risk groups on the basis of 1) degree of learning impairment on the Rey Auditory Verbal Learning Test; 2) medial temporal atrophy, quantified from Food and Drug Administration–approved software for automated vMRI analysis; and 3) CSF biomarker levels. We also stratified participants based on combinations of risk factors. We computed Cox proportional hazards models, controlling for age, to assess 3-year risk of converting to AD as a function of risk group and used Kaplan-Meier analyses to determine median survival times.

Results: When risk factors were examined separately, individuals testing positive showed significantly higher risk of converting to AD than individuals testing negative (hazard ratios [HR] 1.8–4.1). The joint presence of any 2 risk factors substantially increased risk, with the combination of greater learning impairment and increased atrophy associated with highest risk (HR 29.0): 85% of patients with both risk factors converted to AD within 3 years, vs 5% of those with neither. The presence of medial temporal atrophy was associated with shortest median dementia-free survival (15 months).

Conclusions: Incorporating quantitative assessment of learning ability along with vMRI or CSF biomarkers in the clinical workup of MCI can provide critical information on risk of imminent conversion to AD.

GLOSSARY

AD = Alzheimer disease; ADNI = Alzheimer’s Disease Neuroimaging Initiative; AVLT = Auditory Rey Verbal Learning Test; CDR = Clinical Dementia Rating; FDA = Food and Drug Administration; HC = healthy control; HOC = hippocampal occupancy; HR = hazard ratio; ILV = inferior lateral ventricle; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association; vMRI = volumetric MRI.

Amnestic mild cognitive impairment (MCI) is associated with an increased but variable rate of progression to Alzheimer disease (AD). Severity of cognitive impairment, abnormal CSF biomarker levels, and atrophy on volumetric MRI (vMRI) each predict conversion to AD.1–8 Combinations of these measures improve outcome prediction.1,5,7,9–12

Neuropsychological assessment is often used to diagnose MCI13 but CSF and vMRI measures are not included in routine clinical workup of patients with MCI. These measures may be used to rule out other causes of dementia, such as cerebral infections and inflammatory disorders in the case of CSF,14,15 or subdural hematoma and cerebrovascular pathology in the case of MRI,16 but neither measure is currently used to support a diagnosis of early AD.

Methodologic barriers have prevented implementation of vMRI in clinical practice17; however, large-scale studies, such as the Alzheimer’s Disease Neuroimaging Initiative (ADNI) and...
clinical trials incorporating vMRI as outcome measures, have assisted in overcoming these barriers.\(^{18-20}\) Commercially available, Food and Drug Administration (FDA)–approved medical device image analysis software now exists for fully automated vMRI (NeuroQuant, CorTechs Labs., Inc., La Jolla, CA). Integration of clinical practice has been described.\(^{17}\) Commercial CSF analysis services also exist that can indicate whether CSF biomarkers levels are consistent with AD (e.g., Athena Diagnostics, Worcester, MA).

The purpose of this study is to demonstrate the ability of these clinically available biomarkers, alone or in conjunction with neuropsychological assessment, to predict progression to dementia in patients with MCI.

**METHODS**  
**ADNI.** Data used in the preparation of this article were obtained from the ADNI database (http://www.loni.ucla.edu/ADNI). ADNI was launched in 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. ADNI’s primary goal is to determine the best set of biomarkers for early detection and tracking of AD.

ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations. Subjects have been recruited from over 50 sites across the United States and Canada. ADNI has recruited 230 healthy controls (HCs), 399 patients with amnestic MCI, and 193 with mild AD (for up-to-date information, see www.adni-info.org).

**Participants.** ADNI eligibility criteria have been described.\(^9\) Briefly, subjects are 55–90 years old, with a study partner able to provide independent evaluation of functioning. HCs have Mini-Mental State Examination (MMSE) scores between 24 and 30, and a Clinical Dementia Rating (CDR) of 0. Subjects with MCI have MMSE scores between 24 and 30, subjective memory complaint, objective memory loss measured by education-adjusted scores on Wechsler Memory Scale Logical Memory II, CDR of 0.5, preserved activities of daily living, and absence of dementia. Subjects with AD have MMSE scores between 20 and 26, CDR of 0.5 or 1.0, and meet National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD.\(^{18}\) All participants underwent MRI at 1.5 T, approximately half underwent lumbar puncture.

Data collected and processed between August 26, 2005, and October 14, 2010, were analyzed, including 215 HCs and 192 mild AD. The HC group excluded 11 individuals who converted to MCI or AD over the course of the study. MCI participants were limited to 192 subjects with valid baseline Auditory Rey Verbal Learning (AVLT) measures and MRI and CSF data. Table 1 shows demographic and clinical characteristics of the subjects with MCI, separated into those who remained stable over the 3-year follow-up and those who converted to dementia.

**Standard protocol approvals, registrations, and patient consents.** The research protocol was approved by each local institutional review board and written informed consent was obtained from each participant or participant’s guardian.

**Procedures.** **MRI acquisition and analyses.** We downloaded raw baseline DICOM MRI data from the public ADNI Web site (http://www.loni.ucla.edu/ADNI/Data/index.shtml) and performed fully automated volumetric segmentation with the NeuroQuant software package, as previously described.\(^{21-23}\) Briefly, images are corrected for gradient nonlinearity and B1 field inhomogeneity, followed by automated segmentation and labeling of 10 subcortical structures, including the hippocampus and the inferior lateral ventricle (ILV), using a probabilistic brain atlas designed specifically to represent the aged population. We visually inspected segmentation results and those with errors (9 out of 822) were discarded. Volumes obtained using NeuroQuant have been validated against computer-assisted manual segmentations, and this software has received FDA approval for clinical use.\(^{21}\)

We computed a hippocampal occupancy (HOC) score as an estimate of medial temporal lobe atrophy. The HOC was computed as the ratio of hippocampal volume to the sum of the hippocampus and ILV volumes in each hemisphere separately. Right and left HOC scores were averaged then normalized for age and sex.

The HOC is a measure of ex vacuo dilation, indicating expansion of the ILV as a function of brain tissue loss. This measure may aid in differentiation of individuals with congenitally small hippocampi from those with small hippocampi due to a degenerative disorder. We compared the predictive ability of the HOC score with the more commonly used measure of hippocampal volume, corrected for intracranial volume and normalized for age and sex.\(^{13}\)

**CSF acquisition and analysis.** CSF sample acquisition and analysis methods have been described.\(^{24}\) T-tau, p-tau, and \(\beta\)-amyloid\(_{1-42}\) (\(\beta\)\()_{1-42}\) levels were determined using the

<table>
<thead>
<tr>
<th>Table 1 Clinical and demographic data of patients with MCI who converted to AD over the 3-year follow-up and those who remained stable</th>
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</thead>
<tbody>
<tr>
<td><strong>Stable</strong></td>
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<tr>
<td><strong>Male, n (%)</strong></td>
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<tr>
<td><strong>Age, y</strong></td>
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<td><strong>Education, y</strong></td>
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<td><strong>APOE e4 positive, n (%)</strong></td>
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<td><strong>MMSE</strong></td>
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<td><strong>CDR-SB</strong></td>
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<td><strong>ADAS-Cog</strong></td>
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<td><strong>AVLT-Sum</strong></td>
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<td><strong>HC/ICV</strong></td>
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<td><strong>HOC</strong></td>
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<tr>
<td><strong>CSF A(\beta)_{1-42} pg/mL</strong></td>
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<td><strong>CSF T-tau, pg/mL</strong></td>
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<td><strong>CSF P-tau, pg/mL</strong></td>
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Abbreviations: AD = Alzheimer disease; ADAS-Cog = Alzheimer’s Disease Assessment Scale, cognitive subscale; AVLT-Sum = sum of the 5 learning trials on the Auditory Rey Verbal Learning Test; CDR-SB = Clinical Dementia Rating scale, sum of boxes score; HC/ICV = hippocampal volume as percent of intracranial volume; HOC = hippocampal occupancy score, ratio of hippocampal volume to hippocampal volume plus volume of the inferior lateral ventricle; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination.
Table 2  Hazard ratios, from Cox proportional hazard models, controlling for age, as a function of risk factor group

<table>
<thead>
<tr>
<th>Risk factor combination</th>
<th>No. (%)</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Negative atrophy, negative AVLT</td>
<td>38 (20)</td>
<td></td>
</tr>
<tr>
<td>Negative atrophy, positive AVLT</td>
<td>68 (35)</td>
<td>9.7 (2.31–41.04)</td>
</tr>
<tr>
<td>Positive atrophy, negative AVLT</td>
<td>20 (10)</td>
<td>12.3 (2.67–57.2)</td>
</tr>
<tr>
<td>Positive atrophy, positive AVLT</td>
<td>66 (35)</td>
<td>29.0 (7.0–120.03)</td>
</tr>
<tr>
<td>Negative CSF, negative AVLT</td>
<td>27 (14)</td>
<td></td>
</tr>
<tr>
<td>Negative CSF, positive AVLT</td>
<td>31 (16)</td>
<td>4.4 (0.92–20.2)</td>
</tr>
<tr>
<td>Positive CSF, negative AVLT</td>
<td>31 (16)</td>
<td>4.5 (0.94–21.0)</td>
</tr>
<tr>
<td>Positive CSF, positive AVLT</td>
<td>103 (54)</td>
<td>13.8 (3.38–57.6)</td>
</tr>
<tr>
<td>Atrophy and tau/Aβ1–42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative atrophy, negative CSF</td>
<td>38 (20)</td>
<td></td>
</tr>
<tr>
<td>Negative atrophy, positive CSF</td>
<td>68 (35)</td>
<td>4.1 (1.4–11.9)</td>
</tr>
<tr>
<td>Positive atrophy, negative CSF</td>
<td>20 (10)</td>
<td>4.5 (1.3–15.8)</td>
</tr>
<tr>
<td>Positive atrophy, positive CSF</td>
<td>66 (35)</td>
<td>13.8 (5.0–38.5)</td>
</tr>
</tbody>
</table>

Abbreviations: AVLT = Auditory Rey Verbal Learning Test; CI = confidence interval; HC = healthy control; HOC = hippocampal occupancy; HR = hazard ratio; ICV = intracranial volume. *HRs are expressed relative to the negative risk group for each risk factor alone. No. positive = number of subjects (%) testing positive when each risk factor was examined alone. For the analysis of combinations of risk factors, HRs are expressed relative to the group testing negative on both factors. Number (%) of subjects in each of the 4 categories defined by the combination of each 2 sets of risk factors is shown.

b \( p \leq 0.001 \)

c \( p < 0.01 \)

d \( p = 0.06 \)

e \( p = 0.01 \)

RESULTS  Mean conversion-free follow-up time was 29 months (SD 11.6). Figure 1 shows survival curves from the Cox proportional hazards models for the full MCI group and for subjects with MCI separated into negative and positive risk groups based on AVLT, CSF, and atrophy measures. The top portion of table 2 reports the HRs for each risk factor when used alone. Individuals with MCI testing positive for each factor showed significantly greater hazard of converting to AD than those testing negative. Since the discriminative and predictive accuracy of the HOC score exceeded that of the standard hippocampal volume measure, we used the HOC score as the atrophy biomarker in combined risk factor analyses. Similarly, since the T-tau/Aβ1–42 ratio showed the best discriminative and predictive ability of all CSF measures, combined risk factor analyses used this ratio as the CSF biomarker. Since Aβ biomarkers are of great interest as early indicators of AD pathology, we evaluated combinations of CSF Aβ1–42 with AVLT and atrophy risk and present the results in figure e-2 and table e-2.

Figure 2 shows survival curves for risk groups defined by the combination of risk factors. Combining information from any 2 risk categories dramatically improved risk discrimination (table 2, lower portion). The combination of AVLT and medial temporal atrophy provided the best predictive ability. Individuals testing negative for severe learning impairment and for atrophy were at very low risk of converting to AD: 95% of these patients remained stable through the 3-year follow-up period. In contrast, individuals with both atrophy and learning impairment were at very high risk of converting to AD: only 15% were free of dementia at 3 years. Almost

multiplex xMAP Luminex platform (Luminex Crop, Austin, TX) with the INNO-BIA AlzBio3 kit (Innogenetics, Ghent, Belgium). CSF data are often analyzed commercially using ELISA techniques. Although absolute concentrations differ between Luminex and ELISA methods, measures are highly correlated and provide equivalent diagnostic accuracy for AD.28–30

Risk stratification. In separate analyses, we divided MCI participants into positive and negative risk groups using published threshold values for the AVLT learning score, defined as the sum of correctly recalled words on the 5 list-learning trials,7 and for CSF measures.23 For atrophy measures, we used linear discriminant analysis to determine the age- and sex-corrected value that maximized accuracy of discriminating AD from HC data. Table 2 shows threshold values for all measures; figure e-1 on the Neurology® Web site at www.neurology.org shows receiver operator characteristic curves and table e-1 reports areas under the curve for all measures.

We also stratified MCI participants based on paired combinations of AVLT, vMRI, and CSF risk factors, and on the presence or absence of all 3 risk factors. Statistical analyses. Using the SPSS software package (version 15.0, SPSS, Inc., Chicago, IL), we performed Cox proportional hazard analyses, correcting for age, to assess risk of converting to AD. We used Kaplan-Meier survival analysis to determine median dementia-free survival time. Time to event is the difference (in months) between the baseline visit and the halfway point between the last visit at which the patient was diagnosed with MCI and the first visit at which the patient was diagnosed with AD. Conversion to AD was determined according to NINCDS-ADRDA criteria.
half the sample was discordant for these 2 measures. These individuals were also at elevated risk of conversion, although risk was not as high as when both factors were present: approximately 50% of these patients remained free of dementia at 3 years.

We also created groups based on concordant negative (n = 18) or positive risk for all 3 factors (n = 55). None of the individuals in the concordant negative-risk group converted to AD whereas more than 85% of those who tested positive on all 3 mea-

![Survival curves for the full mild cognitive impairment (MCI) cohort, and for negative and positive risk groups defined according to learning performance (Auditory Rey Verbal Learning Test [AVLT]), CSF T-tau, Aβ_{1–42}, and the tau/Aβ_{1–42} ratio, as well as for medial temporal atrophy determined from the hippocampal occupancy score (HOC). Cox proportional hazard models controlled for age. The x-axis shows months to conversion to AD; the y-axis shows proportion of subjects who have not converted to Alzheimer disease. High risk is shown in red, low risk in blue.](image-url)
Sures had converted to AD within 3 years (figure 2). Since there were no converters in the low-risk group, we could not compute a HR.

Figure 3 shows median survival times for the high-risk group for each risk category. Median survival time was significantly shorter (as determined by the nonoverlapping error bars) for those at risk due to atrophy, alone (15.5 months) or in combination with other factors (15.0 months), than for those at risk from any other measure or combination of measures (range 20.5–28.5 months).

To determine whether random-censoring differed by risk group, we examined censoring as a function of AVLT risk. A total of 43 cases were random-censored (i.e., they did not complete all study visits and were classified as MCI at the last available visit). Most of these patients were at high risk (n = 30; $\chi^2 = 5.13; p = 0.024$). Length of follow-up did not significantly differ: $15.3 \pm 9.2$ vs $20.5 \pm 10.6$ months for the high- vs low-risk groups ($F_{1,41} = 2.6; p = 0.11$).

**DISCUSSION** Clinically available behavioral, CSF, and vMRI biomarkers each predict risk of conversion to AD in MCI, but combinations of these measures substantially improve prediction. We found that severity of learning impairment assessed with the AVLT predicted increased risk of conversion to AD, with a HR similar to that reported in a study of a smaller subset of ADNI participants. Abnormal CSF biomarkers levels were also predictive of conversion to AD, with HRs equivalent to those in a prior study of all ADNI MCI participants with CSF data. Importantly, we also found that medial temporal atrophy quantified with commercially available vMRI analysis software predicted conversion to AD with larger HRs than those reported in
studies of ADNI data that used research vMRI analysis tools.5,7,10

Because diagnosis of AD and MCI are based, in part, on severity of cognitive dysfunction, use of neuropsychological test performance as a predictor is circular. However, MCI is associated with a range of severity. The more severe the cognitive impairment, the more likely the patient is to decline to dementia. While we used the AVLT in our models as a “predictor,” it might be better conceptualized as a measure of severity within the MCI category.

Recently updated guidelines for diagnosis of MCI in research studies incorporate vMRI and CSF biomarkers.30 The goal of biomarker characterization is to increase certainty that a person diagnosed with MCI has or does not have underlying AD pathophysiology. Besides providing etiologic specificity, studies such as ours and many others show that patients with MCI with AD biomarkers are more likely to decline to dementia within a few years than patients without AD biomarkers. Thus, assessment of etiology also provides important prognostic information.

Our results showed that combining AVLT performance with CSF or vMRI biomarkers substantially improved risk prediction, consistent with prior findings demonstrating the complementary nature of behavioral, CSF, and MRI measures.5,7,9,10,12,31 We found that the combination of impaired learning ability and medial temporal atrophy was associated with the greatest risk of developing dementia. Further, we found that the presence of medial temporal lobe atrophy, when considered alone or in combination with other factors, was associated with the most rapid rate of conversion, with median survival times of approximately 15 months. Individuals at risk due to severity of learning impairment or abnormal CSF biomarkers showed a less rapid course of decline, with median survival times of 20 to 28 months. This is consistent with the previously suggested dynamic cascade of AD pathology, in which atrophy is the pathologic event that immediately precedes, and underlies, functional decline to dementia.32

In contrast to the immediacy of medial temporal atrophy to functional decline, much research suggests that Aβ pathology develops years or decades prior to cognitive symptoms.29,32–34 Aβ pathology is observed in a substantial number (20%–40%) of cognitively healthy elderly individuals35 (including 38% of ADNI’s healthy controls24). It is not clear whether these individuals will eventually develop AD. Evidence suggests that some healthy elderly who test positive for Aβ pathology are at risk for cognitive decline.29,33,36 When Aβ pathology occurs with memory impairment, however, it is associated with significantly higher risk of converting to AD.10

Using evidence of Aβ pathology from CSF measures or Pittsburgh compound B amyloid imaging, a recent study reported equivalent HRs for hippocampal atrophy and Aβ biomarkers when subjects with MCI were separated into those with highest and lowest quartile scores.10 Further, the study reported that patients with MCI testing positive for Aβ pathology were more likely to convert to AD when hippocampal atrophy was present. The current results are consistent with this, but also show that absence of Aβ

Figure 3 Median survival times for those testing positive on each risk factor or combination of risk factors

Median survival time (in months) reflects the last time at which 50% of the subjects in the group retained the MCI diagnosis. AVLT = Auditory Rey Verbal Learning Test.
pathology in MCI does not imply a benign clinical course. Individuals in the current study with normal $A_\beta_{1–42}$ levels but with medial temporal atrophy (figure e-2) showed almost as high risk of converting to dementia as individuals testing positive for both factors (HR 9.8 vs 14.3; see table e-2). Although caution in interpretation is warranted by the few subjects in this subgroup ($n = 14$), these results might reflect a lack of sensitivity of CSF $A_\beta_{1–42}$ to the oligomeric form of $A_\beta$, which has been shown to be synaptotoxic. Alternatively, dementia in these patients may be due to causes other than AD. In any case, these results suggest that patients with medial temporal atrophy require close monitoring of functional status over time, regardless of $A_\beta$ status.

Presently, CSF measures are not routinely included in clinical evaluation of suspected AD in the United States, although such measures are routinely used in some European countries. Multisite studies have demonstrated significant variability in CSF measures across laboratories, but have also shown that uniform collection, handling, and analysis methods can reduce variability, enabling meaningful clinical interpretation. Further efforts are underway to allow standardization of measures across international centers.

Structural MRIs may be included in the clinical workup, but typical scanning protocols are not conducive to automated volumetry. However, obtaining suitable scans in clinical practice requires minor, easily implemented changes in the imaging protocol: ADNI-compatible 3-dimensional T1-weighted scans take about 7 minutes to acquire. These scans can then be analyzed, using fully automated procedures followed by qualitative review by an imaging expert or trained technician, to obtain volumes for various brain structures implicated in AD, including hippocampus, ventricles, and whole brain volume, relative to sex- and age-matched normative values.

The improved predictive prognostic information available from combined use of these measures argues strongly for their inclusion in the clinical investigation of suspected AD. Evidence of negative CSF or negative atrophy risk factors, with relatively intact learning ability, may allow a clinician to offer reassurance to patients with MCI that the likelihood of progressing to AD in the near term is small. Approximately 95% of patients with MCI in this study who tested negative for learning and atrophy risk factors and 92% of those testing negative for learning and CSF risk factors remained dementia-free after 3 years. When all 3 risk factors were negative, none of the individuals with MCI converted to AD. However, the very few subjects in this group warrants caution in generalizing these findings beyond the present study.

In contrast, a more aggressive course of treatment and care planning would be called for when either atrophy or CSF risk factors are present. When both occur in the presence of learning impairment, risk of AD within 3 years is close to 90%. Although no disease-altering treatments are yet available for AD, information on increased risk of imminent clinical decline would enable clinicians to better anticipate potential problems in management of other chronic conditions and would enable patients and their families to better plan for the future. If disease-modifying therapies become available, accurate early diagnosis will be essential for risk:benefit assessments in treatment decisions since these therapies may be associated with risk of significant adverse effects. Accurate, early detection of prodromal AD would then enable patients to be treated at the earliest possible stage to preserve cognitive abilities without exposing individuals unlikely to progress to AD to undue risk.

One limitation of this study is the loss of some subjects with MCI to follow-up, which may have resulted in a conservative bias in estimate of conversion rates: individuals who dropped out of the study were more likely to fall into the high-risk group based on the learning measure than into the low-risk group, and several may have converted to AD within the timeframe of the follow-up without our knowledge. Other important limitations include lack of histopathologic verification of AD and the highly selected amnestic MCI population. MCI participants within ADNI were carefully selected to include individuals with documented memory impairment and to exclude those whose impairment could arise from other potential causes. Thus the MCI population studied here is not representative of the general clinical population. There is a strong need to gain more experience with currently available clinical tools for aiding in the prediction of AD in the clinical setting, so that if disease-modifying treatments become available, these techniques will have been validated on typical clinical populations and be ready for routine use.

**AUTHOR CONTRIBUTIONS**

Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI or provided data but did not participate in analysis or writing of this report. Dr. Heister: statistical analyses, data interpretation, drafted manuscript. Dr. Brewer: data interpretation, manuscript revision for intellectual content. Dr. Magda: morphometric analysis, manuscript revision for intellectual content. Dr. Blennow: data interpretation, manuscript revision for intellectual content. Dr. McEvoy: study conception and design, statistical analyses, data interpretation, manuscript revision for intellectual content.
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board for Elan Corporation; serves as Special Issue Editor for the
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cal effort is spent conducting quantitative segmental volume reporting
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REFERENCES


