The Value of Hippocampal and Temporal Horn Volumes and Rates of Change in Predicting Future Conversion to AD

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Abstract: Hippocampal pathology occurs early in Alzheimer disease (AD), and atrophy, measured by volumes and volume changes, may predict which subjects will develop AD. Measures of the temporal horn (TH), which is situated adjacent to the hippocampus, may also indicate early changes in AD. Previous studies suggest that these metrics can predict conversion from amnestic mild cognitive impairment (MCI) to AD with conversion and volume change measured concurrently. However, the ability of these metrics to predict future conversion has not been investigated. We compared the abilities of hippocampal, TH, and global measures to predict future conversion from MCI to AD. TH, hippocampi, whole brain, and ventricles were measured using baseline and 12-month scans. Boundary shift integral was used to measure the rate of change. We investigated the prediction of conversion between 12 and 24 months in subjects classified as MCI from baseline to 12 months. All measures were predictive of future conversion. Local and global rates of change were similarly predictive of conversion. There was evidence that the TH expansion rate is more predictive than the hippocampal atrophy rate ($P = 0.023$) and that the TH expansion rate is more predictive than the TH volume ($P = 0.036$). Prodromal atrophy rates may be useful predictors of future conversion to sporadic AD from amnestic MCI.

Key Words: hippocampus, Alzheimer disease, atrophy, longitudinal studies, magnetic resonance imaging

(Alzheimer Dis Assoc Disord 2013;27:168–173)

Dementia is estimated to affect >80 million people worldwide by 2040.[1] The most common cause of dementia is Alzheimer disease (AD).[2] Confirmation of AD requires histopathologic examination of brain tissue, usually at postmortem. Brain atrophy can be measured at autopsy, with cortical volumes reported to be lower than controls,[3] and atrophy can be seen in vivo using magnetic resonance imaging (MRI). An early site of AD tau pathology is the hippocampus[4] and this is mirrored by increased hippocampal atrophy.[5,6] Because of the physical proximity of the temporal horn (TH) to the hippocampus, changes in TH structure may reflect those of the hippocampus. Indeed, the volumes of these 2 structures have been shown to correlate,[7] and AD subjects have significantly greater hippocampal and TH rates of change than controls.[8] After medial temporal tissue loss, generalized cortical atrophy occurs with corresponding increases in whole-brain volume losses.[9,10]

Identifying subjects who are likely to develop AD would allow potential disease-modifying treatments to be given before patients become severely impaired. Subjects with amnestic mild cognitive impairment (MCI) who have measurable memory deficits have an increased risk of converting to AD of around 12% per year compared with 1% to 2% for controls.[11] However, not all MCI subjects convert to AD and therefore predicting converters would be useful for the clinician and for the patient and their carers.

Hippocampal volume is predictive of conversion from MCI to AD.[5,12–16] However, cross-sectional volumes may have large intersubject variances that are unrelated to the disease, and not all studies have found differences in the hippocampal volume between converters and nonconverters.[17] Using the atrophy rate may reduce intersubject variance and provide a better prediction of future converters.

Studies suggest that the hippocampal atrophy rate can predict AD conversion.[15,18,19] However, these studies

calculated the atrophy rate within the time frame of conversion and thus assess only the concurrent conversion. Few studies have assessed TH expansion rates and AD conversion, but 1 study reported that TH expansion rates of presymptomatic subjects [before second clinical dementia rating (CDR) = 0.5] are higher in converters than in stable MCI.[13] It is therefore interesting to investigate the power of TH expansion rates to predict the prospective conversion of amnestic MCI subjects to AD, which may be useful in the recruitment of patients in clinical trials that target prodromal AD subjects.

Global measures such as whole brain and ventricles have reportedly higher rates of volume change in subjects who convert from MCI to AD than in nonconverters.[20,21] The brain parenchymal fraction (percentage of intracranial cavity occupied by brain tissue)[22] and the brain and ventricular rate of change[16] have been shown to predict the conversion from MCI to AD. However, 1 study found no difference in the baseline brain volume or atrophy rate between converters and nonconverters[23] and another showed that neither the whole-brain volume nor the atrophy rate was predictive of conversion from MCI to AD.[15]

Our aims were (1) to investigate whether hippocampal and TH rates of change can predict which amnestic MCI subjects will convert to AD in the future; (2) to assess whether local regions (hippocampi and THs) have a higher predictive value than less disease-specific global measures (whole brain and ventricles); and (3) to examine whether using rates of change yields a higher predictive value than cross-sectional volumes.

METHODS

Subjects

Subjects were a subset of the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. ADNI is a multicentre public/private-funded longitudinal study investigating adult subjects with AD, amnestic MCI, and normal cognition. Participants underwent baseline and periodic clinical and neuropsychometric assessments and serial MRI. Details are available at http://www.adni-info.org. Written informed consent was obtained, as approved by the Institutional Review Board, at each of the participating centers. ADNI inclusion and exclusion criteria are detailed elsewhere (http://adni.loni.ucla.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf).

Subjects included in the current study were classified as MCI at the time of their baseline visit and remained as MCI up to and including their 12-month visit. Subjects in the ADNI study were classified as MCI according to the Petersen criteria.[11] MCI subjects had an Mini Mental State Examination score of 24 to 30, a CDR of 0.5, and were amnestic. Subjects were included in the current study if they had 1.5 T scans available at the baseline and 12 months (n = 335), which were downloaded from the LONI website (http://www.loni.ucla.edu/ADNI). Patient diagnosis was recorded at 6-month intervals for 24 months. Seventy subjects were excluded because they did not have a stable diagnosis from baseline to 12 months. A further 39 subjects were excluded because of poor-quality scans (on the basis of the internal quality control). Subjects were classified as converters if they converted to AD between 12 months and 24 months and as stable if they did not convert by 24 months. Criteria for the diagnosis of AD were based on the

National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable AD. Subjects with AD had an MMSE of 20 to 26 and a CDR of 0.5 or 1. Subjects who converted but then withdrew from the study were not excluded from the analysis (n = 6), but stable subjects were included only if they were confirmed stable at or after 24 months. Twenty-eight subjects were excluded because they could not be confirmed as stable at 24 months. Of the remaining subjects, 1 was diagnosed with semantic dementia (but also classified as MCI from baseline to 24 months) and 1 had a diagnosis of shy dragger syndrome (and was classified as MCI until 24 months when they also had a diagnosis of AD) during the study period. These 2 subjects were not excluded from the study as they still had classifications of MCI or AD throughout the study period.

MRI Acquisition

Details can be found elsewhere (http://adni.loni.ucla.edu/wp-content/uploads/2008/11/mritrainingmanual-adn_a4b28.pdf).[24] T_1-weighted volumetric scans were acquired using 1.5 T Siemens Medical Solutions, Philips Medical Systems, or General Electric Healthcare units. Representative imaging parameters were repetition time = 2400 ms, inversion time = 1000 ms, echo time = 3.5 ms, flip angle = 8 degrees, field of view = 240 × 240 mm and 160 sagittal 1.2-mm–thick slices and a 192 × 192 matrix yielding a voxel resolution of 1.25 × 1.25 × 1.2 mm³, or 180 sagittal 1.2-mm–thick slices with a 256 × 256 matrix yielding a voxel resolution of 0.94 × 0.94 × 1.2 mm³. Images were corrected for distortion due to gradient nonlinearity,[25] image intensity nonuniformity (using N3[26] for all images and B1[27] where required), and scaling-corrected on the basis of phantom measures.[24]

Region Creation

Hippocampal and TH regions were created on baseline and 12-month scans after registration to a standard template using 6 degrees of freedom.[28] Hippocampal regions were generated using hippocampal multiatlas propagation and segmentation as described by Leung et al.[29] In brief, a template library was used to find the best-matched atlases for each individual hippocampus in the target image. The hippocampi in the top 8 atlases were nonlinearly registered and propagated to the target image. The 8 hippocampal segmentations were combined to produce a single consensus segmentation using the simultaneous truth and performance level estimation algorithm.[30]

TH, whole-brain, and ventricle regions were created using the MIDAS software.[31] For THs, a threshold of 60% mean brain intensity defined the brain-cerebrospinal fluid (CSF) boundary, with manual editing where required. The posterior boundary of the TH was the slice before which the atrium of the lateral ventricle joins the TH. THs were segmented by a single segmentor blinded to diagnosis and laterality. The TH segmentation time was around 5 minutes per scan. Intraclass correlation for the within-rater reliability for TH volume was > 0.99 for an independent group of 10 AD and 10 control subjects. Whole-brain and ventricular segmentation is detailed elsewhere.[31,32] Twelve-month whole-brain regions were generated by propagating baseline regions to the 12-month scans after nonrigid registration.[33] The within-rater and between-rater reliability

intraclass correlation for 11 segmentors was > 0.99 for 5 independent scans for brain and ventricle volumes.

The intracranial volume (TIV) was used as a measure of head size.[29] TIV was calculated from the summation of gray matter, white matter, and CSF volumes. Individual volumes were calculated by summing (over voxels) the values of probabilistic tissue segmentations produced using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) multiplied by the voxel volume.

Measuring Rates of Change

Rates of change were measured using the boundary shift integral (BSI),[34,35] which estimates volume change by summing intensity shifts of serial registered images in the boundary area of serial registered regions. Hippocampal BSI was calculated from registered baseline and 12-month scans using the baseline hippocampal regions and a double-intensity window approach[29] to capture changes across the CSF—hippocampal and the white matter—hippocampal borders. TH BSI was calculated using the baseline TH region and a single-intensity window to capture changes across the TH—brain border. Whole-brain and ventricle BSI were calculated using linearly registered baseline and 12-month scans using the whole-brain and ventricular regions.

Statistical Analyses

Analyses were performed using Stata version 10. Differences between stable subjects and converters for baseline characteristics of age, scan interval, and MMSE score were assessed using a 2-sample t test. Differences between stable subjects and converters for sex and APOE ϵ4 carriers were assessed using Fisher exact test.

Annualized hippocampal and whole-brain atrophy rates were calculated as a percentage of baseline change per year using a back-transformed arithmetic scale; TH and ventricular rates of expansion were calculated as milliliter change per year using an arithmetic scale. Cross-sectional hippocampal and TH volumes were measured on the 12-month scans in accordance with the literature,[5,12–16] which examines diagnostic changes occurring immediately after volume measurement. Differences in group means for cross-sectional volumes and rates of change were assessed using a 2-sample t test.

To quantify the predictive value of each measure, we estimated the area under the receiver operating characteristic curve (AUC)[36] and tested the null hypothesis that this equaled 0.5 using the Wilcoxon rank-sum test. An AUC value of 0.5 corresponds to no predictive value, whereas an AUC of 1 represents perfect discrimination between groups (converters and stable). The AUC is the probability that for a randomly chosen converter/stable pair, the converter has a higher (or more abnormal) value for the given measure than the stable subject. We calculated 95% confidence intervals for the AUCs and compared AUCs between measures using the Stata command roccomp, which uses the nonparametric method proposed by DeLong et al.[37] Logistic regression was used to assess whether TIV adjustment improved the prediction above that afforded by each measure by fitting the model with TIV and the measure as explanatory variables.

RESULTS

Subjects

The final cohort consisted of 137 stable and 61 converter subjects. Baseline characteristics for age, scan interval, sex, APOE ϵ4 status, and MMSE are shown in Table 1.

TABLE 1. Baseline Characteristics for Stable Subjects and Converters

	Stable	Converters	
n	137	61	**P**
Age	75.1 (6.7) [57.9, 88.0]	74.4 (7.5) [56.3, 87.8]	0.51
Scan interval (y)	1.08 (0.07) [0.96, 1.34]	1.08 (0.08) [0.97, 1.34]	0.79
Male	88 (64.2)	39 (63.9)	0.55
APOE ϵ4 carriers	63 (46.0)	45 (73.8)	< 0.001
MMSE	27.39 (1.65) [24, 30]	26.54 (1.62) [24, 30]	< 0.001

Mean (SD) [minimum, maximum], except sex and APOE ϵ4 carriers, which show the number (percentage).

Volumes and Rates

Group Statistics and Predictive Values

Table 2 shows baseline and 12-month volumes and rates of change for the hippocampus, TH, whole brain, and ventricle, and *P*-values (testing the null hypothesis of no difference between converters and stable). Table 3 shows AUCs, 95% confidence intervals, and *P*-values (testing the null hypothesis of no predictive value) for all measures. There was statistically significant evidence that each measure had some predictive value, with the estimated AUCs indicating a moderately strong predictive power.

Hippocampal and TH Rates of Change

Comparing the AUCs, there was evidence that the TH expansion rate had a greater predictive value than the hippocampal atrophy rate ($P = 0.023$).

Local and Global Rates of Change

There was no evidence that the hippocampal atrophy rate ($P = 0.24$) or the TH rate of change ($P = 0.21$) improved the prediction of conversion compared with the whole-brain atrophy rate. Similarly, there was no evidence that the predictive value of ventricular rates differed from that of the hippocampal ($P = 0.19$) or the TH ($P = 0.19$) rate of change.

Rates of Change and Cross-Sectional Volume

A logistic regression model incorporating the hippocampus volume and the TIV fit the data no better than the hippocampus volume alone ($P = 0.09$). TIV was, therefore, not used in subsequent hippocampal analyses. Comparing AUCs, there was no significant difference between the hippocampal volume and the hippocampal atrophy rate ($P = 0.90$).

A logistic regression model incorporating the TH volume and TIV did not fit the data any better than the TH volume alone ($P = 0.75$), and so TIV was not used in further TH statistical models. There was some evidence that the AUC of the TH rate of change was higher than that of the TH volume ($P = 0.036$).

DISCUSSION

We found evidence that the TH and the hippocampal rate of change were predictive of prospective conversion from MCI to AD in the following year. There was some evidence

TABLE 2. Mean (SD) Baseline and 12-month Raw Volumes and Rates of Change for Stable Subjects and Converters

	Stable	Converters	*P*
n	137	61	
Baseline volumes (mL)			
Hippocampus	4.61 (0.85)	4.31 (0.93)	0.030
TH	1.41 (1.18)	1.87 (1.40)	0.030
Whole brain	1065.7 (110.0)	1051.7 (132.2)	0.47
Ventricle	43.6 (23.2)	47.9 (24.3)	0.25
12 month volumes (mL)			
Hippocampus	4.46 (0.86)	4.08 (0.93)	0.0080
TH	1.59 (1.32)	2.22 (1.65)	0.0096
Whole brain	1055.0 (111.1)	1034.2 (128.3)	0.27
Ventricle	46.2 (24.4)	51.9 (25.4)	0.14
Rates of change			
Hippocampus (% baseline volume/y)	2.34 (2.22)	3.24 (2.49)	0.017
TH (mL/y)	0.144 (0.161)	0.282 (0.247)	< 0.001
Brain (% baseline volume/y)	0.84 (0.75)	1.26 (0.64)	< 0.001
Ventricle (mL/y)	2.11 (2.08)	3.63 (2.27)	< 0.001

P-values test the null hypothesis of no difference in the means between converters and stable subjects.
TH indicates temporal horn.

that the TH expansion rate had a greater predictive value than the hippocampal atrophy rate. Global rates of change (whole brain and ventricles) were predictive of future cognitive decline. However, there was no evidence of differences in the predictive ability of local and global rates of change. Comparing the predictive ability of atrophy rates and volumes suggested that the TH rate of change was a better predictor than the TH volume. The analogous comparison with hippocampi showed no evidence of a difference. To the authors' knowledge, this is the first paper to assess future conversion to AD in stable MCI patients using atrophy rate measurements of the hippocampus and TH.

Changes in brain and ventricular volume were predictive of future decline to AD, but we found no evidence that their predictive value was less than that of the volume changes in the hippocampus.[4] The absence of a predictive advantage for regions affected early in the disease such as the hippocampi may be because larger losses outside the temporal lobe are necessary before clinical conversion to AD. This explanation is also consistent with our finding that THs have a greater predictive ability than hippocampi as the TH are likely to reflect wider changes throughout the temporal lobe, and not just the hippocampus. Other studies have demonstrated atrophy spreading from the medial temporal lobe to other brain areas.[9,10] The current study used relatively impaired MCI subjects[38] who may be further along the disease process and may be past the point where atrophy is localized. To establish whether more localized changes occur earlier in the disease, early MCI subjects should be investigated, such as those being recruited in ADNI GO and ADNI 2 (http://adni.loni.ucla.edu/about/about-the-study/). It may be the case that changes in hippocampal atrophy rates that occur before conversion are smaller, relative to between-subject differences in rates, than for TH expansion rates. Alternatively, hippocampal atrophy rates may be measured with greater measurement error, which would lead to reduced predictive power.

Our finding that the TH expansion rate is a significant predictor of future conversion from MCI to AD is consistent with Erten-Lyons et al,[13] who found that the presymptomatic TH expansion rate was associated with stable and decliner MCI group membership. Similarly, our finding that the hippocampal atrophy rate was predictive of future decline is consistent with Henneman et al[15] and Wang et al.[18] However, these studies included subjects who converted to AD before their second scan, whereas our study included only subjects who converted after the second scan, thus assessing future, rather than concurrent, conversion.

Our finding that global rates of change were predictive of conversion is inconsistent with Henneman et al,[15] but consistent with Jack et al.[16] Differences between the studies' designs may explain this inconsistency. Henneman et al. used a lower strength scanner (1.0 T, compared with 1.5 T for Jack et al. and the present study), which may have contributed to a greater measurement error. Furthermore, Henneman et al. had fewer subjects (44 MCI, compared with 72 in Jack et al. and 198 in the present study), and consequently less power to detect an effect. We found little previous work on comparing the predictive ability of local and global measurements, although Jack et al[16] found that the cross-sectional hippocampal volume yielded complementary predictive information to whole-brain and ventricular rates of change. Although we found no difference in the predictive value of local and global measurements,

TABLE 3. AUC Representing the Value of the 12-month Rate of Change and Baseline Volumes in Predicting Subsequent Conversion, 95% Confidence Intervals, and *P*-values Testing the Null Hypothesis That the AUC Equals 0.5 for Each of the Measures

	AUC	95% Confidence Interval		*P*
		Lower	Upper	
Hippocampal atrophy rate	0.624	0.536	0.712	0.005
TH expansion rate	0.728	0.654	0.80	< 0.001
Brain atrophy rate	0.679	0.600	0.758	< 0.001
Ventricle expansion rate	0.687	0.609	0.766	< 0.001
Hippocampus volume	0.617	0.532	0.703	0.008
TH volume	0.655	0.576	0.733	< 0.001

AUC indicates area under the receiver operator curve; TH, temporal horn.

we only assessed these using rates of change, whereas Jack et al. used the volume for the local (hippocampal) measurement.

Our finding that the hippocampal volume was predictive of future decline is consistent with several studies.[5,12–16] Our finding that the TH baseline volume was also predictive is inconsistent with Erten-Lyons et al,[13] who found no difference between stable and decliner MCI groups. This discrepancy may arise from differences in group definitions; all subjects in Erten-Lyons et al. started as normal controls—stable MCI were subjects who were MCI by the end of the study, but did not progress to AD—whereas our stable subjects started with a diagnosis of MCI. Our subjects were also younger (stable mean 75.1 y, converters 74.4 compared with 85.7 and 87.7 for stable and decliners, respectively in Erten-Lyons et al.).

Our hippocampal atrophy rates were generally consistent with the literature. Our mean stable hippocampal atrophy rates (2.3%/y) were comparable to those reported previously, which ranged from 2.3% to 2.5% per year,[39,40] and our median hippocampal atrophy rates (2.1%/y) were reasonably similar to that of Jack et al,[20] who reported a median of 1.8% per year. Jack et al[39] and Archer et al[40] report mean hippocampal atrophy rates for declining MCI subjects of 3.7% and 3.6% per year, respectively; the analogous value from our converters was 3.2% per year. Likewise, Jack et al[20] reported a median value for hippocampal converters as 3.3% per year, which is comparable to 3.1% per year for our converters. Note that our converter group differs from these studies because we include only subjects converting after 1 year, whereas the other studies include any subjects converting from baseline.

We found only 1 study that reported TH expansion rates in MCI subjects. Erten-Lyons et al[13] reported a 3% per year TH expansion rate (estimated from a graph) for MCI stable subjects. Analogous rates for stable subjects in our study are 10.8% per year. As Erten-Lyons et al. stable MCI subjects started the study as controls and changed to an MCI status, the annualized rates of change may be expected to be lower than our study. Interestingly, the TH expansion rate of declining MCI subjects in the Erten-Lyons et al. paper is 17% per year, which is more comparable to the rates of our converters (17.4% per year).

A limitation of this study is that only a subset of the ADNI data set was used, mostly because we included good-quality scans only. Our results pertain to the prediction of imminent (in the next year) conversion. It is important to note that although the stable subjects have not yet converted to AD, they may still convert in the future. Further, we note that the findings of this study may be relevant only to amnestic MCI because subjects with other forms of MCI (nonamnestic MCI and multidomain MCI) were not included in the ADNI study. However, studies suggest that amnestic MCI subjects may represent a transitional zone from normal aging to AD[41,42]; it is therefore appropriate to focus on amnestic MCI in the current study to assess future conversion to AD. Finally, some subjects were excluded because their conversion status was unavailable. This may bias our results if these excluded subjects differ with respect to the value of the imaging measures in predicting conversion. Strengths of the study include its multisite nature, careful diagnosis at 6-month intervals, and examination of future diagnosis change in MCI subjects, which is more clinically relevant and useful than concurrent diagnosis change.

This study demonstrates that TH, hippocampus, whole-brain, and ventricular rates of change and TH and hippocampal volumes are predictive of future decline to AD from MCI using serial MRI. We found no evidence that regions susceptible to early change were more predictive of future decline than global measures. However, there was some evidence that the TH expansion rate had a greater predictive ability than the hippocampi atrophy rate. There was also some evidence that the TH expansion rate was a better predictor than the TH cross-sectional volume. In conclusion, prodromal atrophy rates may be useful predictors of future conversion to sporadic AD from MCI.

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