Published in final edited form as:

Alzheimer Dis Assoc Disord. 2013 ; 27(2): 174–181. doi:10.1097/WAD.0b013e3182677b3d.

Ventricular atrophy and its clinical correlates in the imaging cohort from the ADCS MCI Donepezil/Vitamin E study

Liana G. Apostolova^{1,2}, Sona Babakchanian^{1,2}, Kristy S. Hwang^{1,2}, Amity E. Green³, Dimitar Zlatev⁴, Yi-Yu Chou⁵, Charlie DeCarli⁶, Clifford R. Jack Jr⁷, Ronald C. Petersen⁸, Paul S. Aisen⁹, Jeffrey L. Cummings¹⁰, Arthur W. Toga¹, and Paul M. Thompson^{1,2}

¹Departments of Neurology, University of California Los Angeles, Los Angeles, CA

²Laboratory of Neuro Imaging, University of California Los Angeles, Los Angeles, CA

³Monash University, Victoria, Australia

⁴Stanford University, Stanford, CA

⁵Center for Neuroscience and Regenerative Medicine, Bethesda, MD

⁶Department of Neurology and Center for Neuroscience, University of California, Davis, CA

⁷Department of Radiology, Mayo Clinic, Rochester, MN

⁸Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN

⁹Department of Neurosciences, University of California San Diego, San Diego, CA

¹⁰Lou Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, NV

Abstract

We analyzed the baseline and 3-year T1-weighted magnetic resonance imaging data of 110 amnesic mild cognitive impairment (MCI) participants with minimal hippocampal atrophy at baseline from the Alzheimer's Disease Cooperative Study group (ADCS) MCI Donepezil/Vitamin E trial. 46 subjects converted to AD (MCIC) while 64 remained stable (MCInc). We used the radial distance technique to examine the differences in lateral ventricle shape and size between MCIC and MCInc and the associations between ventricular enlargement and cognitive decline.

MCIC group had significantly larger frontal and right body/occipital horns relative to MCInc at baseline and significantly larger bilateral frontal, body/occipital and left temporal horns at follow-up. Global cognitive decline measured with ADAScog and MMSE and decline in activities of daily living (ADL) were associated with posterior lateral ventricle enlargement. Decline in ADAScog and ADL were associated with left temporal and decline in MMSE with right temporal horn enlargement. After correction for baseline hippocampal volume decline in ADL showed a significant association with right frontal horn enlargement. Executive decline was associated with right frontal and left temporal horn enlargement.

Keywords

Alzheimer's disease; AD; mild cognitive impairment; MCI; imaging; MRI; brain atrophy; ventricular enlargement

Ventriculomegaly is commonly observed in most neurodegenerative disorders and results from passive enlargement of the lateral, third and fourth ventricles as a result of brain parenchymal shrinkage. Ventricular expansion has received considerable attention in the Alzheimer's disease (AD) literature¹⁻³. Several studies have shown that AD subjects demonstrate both larger ventricles and faster rates of ventricular expansion over time, compared to groups of NC and MCI subjects^{1,4-8}. In healthy elderly subjects, ventricular volume^{1,2} and its rate of change³ are both associated with future cognitive decline to MCI and dementia. Ventricular enlargement correlates with cognitive decline^{4,7,9} and has been also shown to associate with cerebrospinal fluid levels of amyloid beta and ApoE4 genotype^{2,3}.

The 3-year long Alzheimer's Disease Cooperative Study (ADCS) studied the efficacy of Donepezil and vitamin E for delaying the progression of mild cognitive impairment (MCI) to AD in a double-blind randomized placebo-controlled fashion¹⁰. Neither agent influenced progression to AD. Yet the imaging data of the ADCS Donepezil/Vitamin E MCI trial has resulted in several important observations to date¹¹⁻¹⁴. Donepezil showed a trend-level significant effect on hippocampal atrophy rates¹⁴. Subjects with moderate to severe hippocampal involvement -visually graded by experts using the medial temporal atrophy rating scale – had double the risk for future conversion of MCI to AD¹². Recently a publication from our group documented the gradual progression of hippocampal atrophy from the subiculum and CA1 to the CA2-3 in the subset of MCI patients with none to mild hippocampal atrophy at baseline as classified in¹², providing for the first time a true *in vivo* dynamic map of the spread of hippocampal neurodegeneration in early AD¹¹.

Manual ventricular delineation is time consuming and tedious, and is unsuitable for studies with large sample sizes. Recent ventricular automated segmentation approaches have finally allowed us to better understand and track structural changes in the lateral ventricles as a diagnostic and prognostic AD biomarker^{3-6,15,16}. Our group recently showed that while AD and MCI have significantly larger lateral ventricles relative to cognitively normal elderly (NC) there was very little difference between MCI and AD subjects suggesting that the lateral ventricles are a viable early AD disease biomarker¹⁷. One group applied another automated ventricular extraction technique to a small sample of MCI subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and reported that MCI subjects who later converted to AD (MCIc) showed significantly greater rates of ventricular enlargement relative to those who remained stable (MCInc) over 6 months⁶.

In this study we analyzed the baseline and 3-year T1-weighted magnetic resonance imaging data of the 110 ADCS Donepezil/vitamin E MCI trial participants who had both a baseline and a month 36 scan and minimal hippocampal atrophy at baseline defined as medial temporal atrophy scale (MTA) score <2. Our goals were to apply advanced computational anatomy methods to examine and quantify the longitudinal ventricular changes in MCIc and MCInc and to examine the associations of progressive ventricular enlargement with cognitive and functional decline. We hypothesized that MCIc would show larger ventricles at baseline and in follow-up and faster ventricular expansion rates than MCInc. We also hypothesized that cognitive and functional decline will associate with progressive ventricular enlargement over time.

Subjects

The 69 North American sites of the ADCS MCI Donepezil/Vitamin E trial enrolled a total of 769 amnesic MCI subjects all of whom had insidious, gradually progressive memory decline, a Logical Memory delayed recall score at least 1.5 SD below an education-adjusted norm, a Clinical Dementia Rating (CDR) score of 0.5 and a Mini-Mental State Examination

(MMSE) score between 24 and 30. The demographic characteristics of the full sample are described elsewhere¹⁰. The primary outcome of the study was defined as conversion to possible or probable AD according to the National Institute of Neurologic and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) criteria¹⁸.

Twenty-four of the 69 sites opted to participate in the MRI arm of the study. Clinical trial subjects at these 24 sites were approached for participation in the MRI substudy; those who were willing to participate and had no contraindications to MRI were included. The final MRI sample consisted of 194 participants who received a baseline and a 3-year MRI scan, in addition to all standard clinical trial procedures. The MCIc group received an additional scan at the time of conversion to AD.

Of these 194 subjects, 110 subjects with minimal or no medial temporal atrophy based on visual assessment with the medial temporal atrophy (MTA) rating scale as previously described in¹² had baseline and follow-up scans of sufficient quality for our analyses. Minimal hippocampal atrophy, i.e., a rating of 1 on the MTA rating scale, is assigned when the structural changes in the medial temporal lobe structures are no more severe than those expected from aging alone¹⁹. 46 out of our 110 MCI subjects converted to possible or probable AD (MCIc) over the 3-year follow-up interval, while the remaining 64 did not (MCIinc).

MRI acquisition, preprocessing and analyses

All MRI data was acquired at 1.5T. Of the 24 sites, 14 used General Electric scanners, 9 Siemens and one Philips scanner. We analyzed the 3D coronal spoiled gradient echo (SPGR) or equivalent T1-weighted scan with minimum full-time echo, minimum repetition time, 124 partitions, 25 degree flip angle and 1.6 mm slice thickness. Each subject's T2-weighted scan was inspected for strokes or significant white matter hyperintensities at the main image repository site (Mayo Clinic, Rochester, MN). Only scans devoid of such abnormalities were shared with the University of California Los Angeles (UCLA) research team. All data were checked for quality and compliance with the imaging protocol as described elsewhere¹⁴.

The ADCS and the UCLA Institutional Review Board approved the analyses reported here. Baseline and follow-up images were each registered separately to the ICBM53 standardized brain template using a 9-parameter linear transformation²⁰ and subjected to intensity normalization²¹. We used our recently developed semi-automated ventricular segmentation approach, called multi-atlas fluid image alignment (MAFIA), which has been previously described⁵. Briefly, an experienced human rater (AEG, intra-rater reliability Cronbach's Alpha = 0.995) hand-traced the lateral ventricles of four subjects. These traces were converted into 3D parametric ventricular mesh models and were used as primers for segmenting the remainder of the dataset via fluid propagation over the ventricles of the rest of the subjects in the study. Using fluid registration, each primer was separately warped to match and thereby extract the shape of the lateral ventricle of each new subject's scan resulting in four lateral ventricle segmentations per subject. These four segmentations were then averaged (using 3D vector averaging of mesh surface points) to create one final ventricular model for each subject that most accurately captured individual anatomy. This substantially reduces segmentation errors that occur when only one atlas is used. The ventricular models were split up into frontal, inferior and body/occipital partitions. The medial core (a medial curve threading down the center of each partition) and the radial distance from the medial core to each ventricular surface point were computed.

Statistical analyses

We used two-tailed Student's *t*-test to compare the mean age, education and MMSE scores between MCIC vs. MCInc at baseline. A chi-squared test was used to compare sex, Apolipoprotein E4 (ApoE4) genotype and treatment arm distribution between the two groups.

We used multiple linear regression with ventricular radial distance as the outcome measure and diagnosis as the predictor variable for between-group comparisons at baseline and at follow-up. We also directly compared the rate of ventricular enlargement in MCIC vs. MCInc. Our longitudinal within-group assessments used the study time point (baseline vs. follow-up) as the predictor variable. The former reveals differences between groups at each time point and the latter assesses progressive ventricular enlargement in each group over time.

Next, we used linear regression with % change in ventricular radial distance between scanning time points as the dependent variable and the following global cognitive and functional measures as predictor variables - change in MMSE, change in Activities of Daily Living (ADL) score and change in AD Assessment scale cognitive subscale (ADAScog) score. After examining the pattern of associations we repeated these analyses while controlling for hippocampal atrophy over time (measured as % change in hippocampal volume), baseline frontal horn volume and total ventricular volume. Next we also investigated the associations between verbal memory decline (i.e., change on ADAScog delayed word recall), visuospatial decline (i.e., change on ADAScog constructional praxis score) and executive decline (i.e., change in Maze task total errors score) and ventricular enlargement. Our 3D statistical maps were further corrected for multiple comparisons using permutation tests at a predefined threshold of $p < 0.01$. Permutation analyses derive a single overall corrected *p*-value for each 3D statistical map based on the number of surface points surviving a particular *a priori* threshold. For more details on the permutation approach, please see ²². All analyses were repeated with ventricular volumes.

Results

MCIC and MCInc groups were well balanced with respect to age, sex, education and treatment arm. The MCIC group had a significantly higher proportion of ApoE4 carriers, significantly worse MMSE, total ADAScog, ADAS verbal memory, Maze errors and ADL scores, and hippocampal and right frontal horn volume at baseline, as well as significantly greater decline in MMSE, total ADAScog, ADAS verbal memory, ADAS construction and ADL score over time relative to the MCInc group (Table 1).

MCIC vs. MCInc comparisons at baseline and follow-up

At baseline, the MCIC group had significantly larger frontal (left $p_{\text{corrected}} = 0.012$, right $p_{\text{corrected}} = 0.008$) and trend-level larger right body/occipital horns ($p_{\text{corrected}} = 0.055$) relative to MCInc. Quantitatively, areas with significant between group differences showed up to 15% larger ventricular radial distance in MCIC relative to MCInc (Figure 1, *left panel*). The volumetric between-group differences at baseline were restricted to right frontal horn only ($p = 0.006$).

At 3-year follow-up, the frontal horn differences between MCIC and MCInc were even more pronounced (left $p_{\text{corrected}} = 0.0024$, right $p_{\text{corrected}} = 0.0015$, Figure 1, *right panel*) while posterior ventricular differences were now observed bilaterally (left body/occipital horn $p_{\text{corrected}} = 0.022$, right body/occipital horn $p_{\text{corrected}} = 0.006$). MCIC also showed significant right and trend-level left temporal horn enlargement relative to MCInc at follow-up (left

$p_{\text{corrected}} = 0.06$, right $p_{\text{corrected}} = 0.043$). The volumetric between-group comparisons at 3-year follow-up revealed larger right frontal ($p < 0.0001$) and left occipital horn ($p = 0.005$).

Within-group longitudinal analyses

Over the 3-year duration of the trial, the MCInc group experienced progressive enlargement of the body/occipital horns of the lateral ventricles (left $p_{\text{corrected}} = 0.032$, right $p_{\text{corrected}} = 0.048$; Figure 2, *left panel*) while the MCInc group failed to show significant ventricular enlargement over the 3-year period (Figure 2, *right panel*).

Figure 3 shows the average 3-year % change in ventricular radial distance in MCInc and MCInc (top left and right, resp) as well as the direct statistical comparison of the magnitude of ventricular enlargement in MCInc and MCInc over the course of the study (bottom). MCInc subjects showed significantly greater ventricular enlargement of the body/occipital horns bilaterally (left $p_{\text{corrected}} = 0.02$, right $p_{\text{corrected}} = 0.0055$) and the right frontal horn ($p_{\text{corrected}} = 0.031$) relative to MCInc. The volumetric comparisons failed to reveal any differences in % enlargement between the two groups.

Associations between cognitive and functional decline and ventricular enlargement

Changes in ADAScog and MMSE scores over the trial duration in the pooled sample showed significant or trend-level association with progressive ventricular enlargement of the temporal horns (ADAScog left $p_{\text{corrected}} = 0.038$, right $p_{\text{corrected}} = 0.056$; MMSE left $p_{\text{corrected}} = 0.2$, right $p_{\text{corrected}} = 0.026$) and body/occipital horns (ADAS cog left $p_{\text{corrected}} = 0.028$, right $p_{\text{corrected}} = 0.0022$; MMSE left $p_{\text{corrected}} = 0.024$, right $p_{\text{corrected}} = 0.015$; see Figure 4 and Table 2). After controlling for baseline frontal horn volume, total ventricular volume and hippocampal atrophy, ADAScog and MMSE association's pattern remained largely unchanged (Table 2, maps not shown).

Decline on ADAScog Delayed Word Recall showed significant association with enlargement of the left temporal ($p_{\text{corrected}} = 0.026$) and right body/occipital horn ($p_{\text{corrected}} = 0.0015$) in addition to a trend-level association with the left body/occipital horn ($p_{\text{corrected}} = 0.073$; Figure 4 and Table 2). After controlling for baseline frontal horn volume, total ventricular volume and hippocampal atrophy the pattern of associations remained largely unchanged (Table 2, maps not shown).

ADAScog Constructional Praxis decline showed significant bilateral associations with enlargement of the body/occipital horn (left $p_{\text{corrected}} = 0.0051$, right $p_{\text{corrected}} = 0.019$) and the right frontal horn ($p_{\text{corrected}} = 0.049$; Figure 4 and Table 2). After controlling for baseline frontal horn volume, total ventricular volume and hippocampal atrophy the pattern of these associations remained unchanged (Table 2, maps not shown).

Executive decline assessed with the Maze error score was associated with progressive enlargement of the right frontal ($p_{\text{corrected}} = 0.047$) and left temporal horns ($p_{\text{corrected}} = 0.036$; Figure 4 and Table 2). After controlling for baseline frontal horn volume, total ventricular volume and hippocampal atrophy the pattern of these associations remained unchanged (Table 2, maps not shown).

ADL decline was significantly associated with enlargement of the body/occipital horns bilaterally (left $p_{\text{corrected}} = 0.004$, right $p_{\text{corrected}} = 0.032$) and the left temporal horn ($p_{\text{corrected}} = 0.019$) as well as trend-level association with the frontal horn on the right ($p_{\text{corrected}} = 0.073$; see Figure 4 and Table 2). After controlling for hippocampal atrophy, the association between ADL decline and right frontal horn enlargement also became significant ($p_{\text{corrected}} = 0.044$). After controlling for baseline frontal horn or total ventricular volume

rendered the association with the right body/occipital horn trend-level and the association with the right frontal horn nonsignificant (Table 2, maps not shown).

All the above analyses were reran with % volumetric increase as the dependent variable and all cognitive measures as predictor variables first unadjusted and then also while adjusting for total ventricular, frontal horn volume or hippocampal volume at baseline. The results are provided in Supplementary Table 1. Overall volumetric regression models proved less powerful for detecting associations between the selected cognitive measures and ventricular change over time relative to ventricular radial distance.

Discussion

The most significant ventricular differences between MCIc and MCIInc with minimal hippocampal involvement at baseline and at follow-up were localized to the frontal horns. These differences suggest greater underlying frontal lobe atrophy in MCIc vs. MCIInc. The frontal lobes have been long recognized as the seat of executive control. Executive function –s one's ability to operate independently, solve problems, monitor and alter behavior to achieve a preselected task, is essential for independent living. Executive dysfunction is predictive of progression from MCI to AD²³ and manifests with impairments in activities of daily living. Thus it is not surprising that of all clinical and cognitive measures decline in activities of daily living and executive function measured by the Maze Task showed the strongest associations with progressive enlargement of the frontal regions of the lateral ventricles. These data as well as the observed posterior predominant associations of the visuospatial measure and the left temporal horn association of the verbal memory measure suggest a functionally relevant regionally specific pattern of lateral ventricular changes in AD.

Our data extends previous work of our and other groups. While several groups have reported greater lateral ventricular expansion in MCIc relative to MCIInc over time^{1, 6, 24}, these groups have not provided evidence for regionally specific clinically relevant pattern of involvement as we have here. Additionally all studies of ventricular changes in MCI to date have focused on the typical MCI subjects many of whom show pronounced hippocampal atrophy. Here our goal was to investigate for potentially useful predictor of clinical progression among MCI subjects who upon visual inspection do not show medial temporal atrophy greater than what one might expect to result from normal aging alone. Our findings suggest that in the absence of pronounced hippocampal involvement enlargement of the frontal horns of the lateral ventricle might become a useful predictive biomarker for future conversion from MCI to AD.

Strengths of our study include the selection of a large well-defined prospectively collected and exceptionally well-characterized longitudinal MCI sample, and the use of sensitive state-of-the-art ventricular analytic techniques. Clinical trials aim to enrol a 'clean' subject pool with a specific, tightly defined, clinical presentation, minimal co-morbidities, and carefully mandated allowable medication regimens. One limitation imposed by the clinical trial design stems from the fact that enrolled participants are frequently healthier than the general population; patients with multiple medical problems are excluded. As such, an epidemiologic dataset might be better poised to provide truly unbiased evidence about MCI and AD cognitive and functional decline and disease progression as manifested in structural brain changes. Nevertheless, developing biomarker tools in clinical trial populations is tremendously valuable as a biomarker validated in epidemiological studies may easily underperform in clinical trials due to the stringent refinement of the trial participants as mandated by the strict inclusion and exclusion criteria^{13, 25}. Another limitation of our study is the lack of definitive diagnosis. The latter requires postmortem histopathological

examination, which is not available on our participants. The inclusion of the MMSE in our analyses was not guided by its sensitivity and specificity for the MCI population but rather by the fact that this is one of the most commonly used global cognitive screens in the dementia literature and that it has been most exhaustively researched in the past. Finally, the imaging data analyzed here comes from a well-known clinical trial. As such our research participants were randomized to donepezil, vitamin E or placebo. Donepezil is an FDA approved therapy for AD and as such it could potentially have an effect on hippocampal atrophy. Although no treatment effect on any of the imaging measures including hippocampal atrophy was seen in the original analyses published by Jack et al in 2008¹⁴, a concern that donepezil or vitamin E could have a differential effect on ventricular enlargement and can thus affect our analyses remained. However, as demonstrated in Table 1 the proportion of MCIC and MCInc subjects in each treatment arm were nearly identical (i.e., 25% MCIC and 26% MCInc were assigned to donepezil, 32% MCIC and 31% MCInc were assigned to Vitamin E and 43% MCIC and 43% MCInc were assigned to placebo, ANOVA $p=0.98$). Such negligible and statistically insignificant differences are highly unlikely to have influenced our analyses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This study was generously supported by NIA U01 AG10483, NIA K23 AG026803 (jointly sponsored by NIA, AFAR, The John A. Hartford Foundation, The Atlantic Philanthropies, The Starr Foundation and an anonymous donor; to LGA), the Turken Foundation (to LGA); NIA AG16570 (to LGA, JLC and PMT); NIBIB EB01651, NLM LM05639, NCRR RR019771 (to PMT); and NIMH R01 MH071940, NCRR P41 RR013642 and NIH U54 RR021813 (to AWT).

The authors thank all research subjects for participating in this trial, all evaluating clinicians and staff members for data collection, and the ADCS group for their support.

References

1. Carmichael OT, Kuller LH, Lopez OL, et al. Ventricular volume and dementia progression in the Cardiovascular Health Study. *Neurobiol Aging*. 2007; 28:389–397. [PubMed: 16504345]
2. Chou YY, Lepore N, Saharan P, et al. Ventricular maps in 804 ADNI subjects: correlations with CSF biomarkers and clinical decline. *Neurobiol Aging*. 2010; 31:1386–1400. [PubMed: 20620663]
3. Jack CR Jr, Shiung MM, Gunter JL, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. *Neurology*. 2004; 62:591–600. [PubMed: 14981176]
4. Chou Y, Lepore N, Avedissian C, et al. Mapping correlations between ventricular expansion and CSF amyloid and tau biomarkers in 240 subjects with Alzheimer's disease, mild cognitive impairment and elderly controls. *Neuroimage*. 2009; 46:394–410. [PubMed: 19236926]
5. Chou YY, Lepore N, de Zubicaray GI, et al. Automated ventricular mapping with multi-atlas fluid image alignment reveals genetic effects in Alzheimer's disease. *Neuroimage*. 2008; 40:615–630. [PubMed: 18222096]
6. Nestor SM, Rupsingh R, Borrie M, et al. Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's disease neuroimaging initiative database. *Brain*. 2008; 131:2443–2454. [PubMed: 18669512]
7. Thompson PM, Hayashi KM, De Zubicaray GI, et al. Mapping hippocampal and ventricular change in Alzheimer disease. *Neuroimage*. 2004; 22:1754–1766. [PubMed: 15275931]
8. Driscoll I, Davatzikos C, An Y, et al. Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology*. 2009; 72:1906–1913. [PubMed: 19487648]
9. Josephs KA, Whitwell JL, Ahmed Z, et al. Beta-amyloid burden is not associated with rates of brain atrophy. *Ann Neurol*. 2008; 63:204–212. [PubMed: 17894374]

10. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005; 352:2379–2388. [PubMed: 15829527]
11. Apostolova LG, Thompson PM, Green AE, et al. 3D comparison of low, intermediate, and advanced hippocampal atrophy in MCI. *Hum Brain Mapp*. 2010; 31:786–797. [PubMed: 20143386]
12. DeCarli C, Frisoni GB, Clark CM, et al. Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. *Arch Neurol*. 2007; 64:108–115. [PubMed: 17210817]
13. Fleisher AS, Sun S, Taylor C, et al. Volumetric MRI vs clinical predictors of Alzheimer disease in mild cognitive impairment. *Neurology*. 2008; 70:191–199. [PubMed: 18195264]
14. Jack CR Jr, Petersen RC, Grundman M, et al. Longitudinal MRI findings from the vitamin E and donepezil treatment study for MCI. *Neurobiol Aging*. 2008; 29:1285–1295. [PubMed: 17452062]
15. Chou, Y.; Lepore, N.; Zubicaray, GI., et al. Automated 3D mapping and shape analysis of the lateral ventricles via fluid registration of multiple surface-based atlases. *Proc 4th IEEE International Symposium on Biomedical Imaging: From Nano to Macro*; 2007. p. 1288-1291.
16. Ferrarini L, Palm WM, Olofsen H, et al. Ventricular shape biomarkers for Alzheimer's disease in clinical MR images. *Magn Reson Med*. 2008; 59:260–267. [PubMed: 18228600]
17. Chou Y, Lepore N, Avedissian C, et al. Mapping correlations between ventricular expansion and CSF amyloid and tau biomarkers in 240 subjects with Alzheimer's disease, mild cognitive impairment and elderly controls. *Neuroimage*. 2008 submitted.
18. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34:939–944. [PubMed: 6610841]
19. Scheltens P, Launer LJ, Barkhof F, et al. Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. *J Neurol*. 1995; 242:557–560. [PubMed: 8551316]
20. Collins DL, Neelin P, Peters TM, et al. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr*. 1994; 18:192–205. [PubMed: 8126267]
21. Shattuck DW, Sandor-Leahy SR, Schaper KA, et al. Magnetic resonance image tissue classification using a partial volume model. *Neuroimage*. 2001; 13:856–876. [PubMed: 11304082]
22. Thompson PM, Apostolova LG. Computational anatomical methods as applied to ageing and dementia. *Br J Radiol*. 2007; 80(Spec No 2):S78–91. [PubMed: 18445748]
23. Chen P, Ratcliff G, Belle SH, et al. Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. *Neurology*. 2000; 55:1847–1853. [PubMed: 11134384]
24. Evans MC, Barnes J, Nielsen C, et al. Volume changes in Alzheimer's disease and mild cognitive impairment: cognitive associations. *Eur Radiol*. 20:674–682. [PubMed: 19760240]
25. Fox NC, Black RS, Gilman S, et al. Effects of Abeta immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease. *Neurology*. 2005; 64:1563–1572. [PubMed: 15883317]

Figure 1. Statistical (top) and percent difference (bottom) maps from the MCIc vs. MCInc baseline and follow-up comparisons. Regions in red or white in the statistical maps denote $p < 0.05$.

Figure 2. Statistical (top) and percent difference (bottom) maps from our within-group longitudinal analyses. Regions in red or white in the statistical maps denote $p < 0.05$.

Figure 3.

Average ventricular enlargement maps in MCIc (top left) and MCIinc (top right) over the course of the study (in %). The bottom maps show the statistical comparison of the magnitude of ventricular enlargement in each group over the course of the study. Regions in red or white in the statistical maps denote $p < 0.05$.

Figure 4. Statistical maps of the associations between global cognitive and functional decline and ventricular enlargement. Regions in red or white in the statistical maps denote $p < 0.05$

Table 1

Demographic and cognitive between-group comparisons (significant between-group differences defined as $p < 0.05$ appear in bold)

Variable	MCIf, n=46	MCInc, n=64	p-value
Age, yr	73.5 (6.9)	71.9 (6.3)	0.2
Education, yr	15.0 (3.5)	15.4 (2.8)	0.5
Sex, M:F	29:26	42:24	0.2
ApoE4+ subjects	42 (87.5%)	32 (50.8%)	<0.001
Treatment arm	Donepezil 25% Vitamin E 32% Placebo 43%	Donepezil 26% Vitamin E 31% Placebo 43%	p=0.98
MMSE at baseline	26.8 (1.6)	28.2 (1.6)	<0.0001
ADAScog baseline	13.1 (3.5)	9.1 (3.3)	<0.0001
ADL baseline	45.3 (4.1)	47.8 (3.0)	0.001
ADAS verb mem at baseline	4.3	2.43	<0.0001
ADAS construction at baseline	0.5	0.55	0.6
Maze errors at baseline	0.06	0.21	0.041
MMSE 3-year change	-5.2 (5.4)	0.11 (2.1)	<0.0001
ADAScog 3-year change	8.2 (8.6)	-0.03 (4.0)	<0.0001
ADL 3-year change	13.8 (11.0)	0.32 (3.7)	<0.0001
ADAS verb mem, 3-year change	1.5 (1.9)	0.19 (2.2)	0.002
ADAS construction, 3-year change	-0.56 (0.8)	0.02 (0.6)	<0.0001
Maze errors, 3-year change	-0.19 (0.8)	0.03 (0.3)	0.1
Baseline hippocampal volume (mm ³)	Left 3351 (484) Right 3200 (508)	Left 3524 (495) Right 3460 (530)	Left 0.056 Right 0.007
Baseline frontal horn volume (mm ³)	Left 12610 (1811) Right 14183 (3518)	Left 12441 (1680) Right 12510 (3129)	Left 0.6 Right 0.007
Baseline temporal horn volume (mm ³)	Left 760 (159) Right 1133 (222)	Left 726 (132) Right 1141 (173)	Left 0.2 Right 0.8
Baseline body/occipital horn volume (mm ³)	Left 6748 (2054) Right 7130 (1671)	Left 6172 (1783) Right 7043 (1842)	Left 0.1 Right 0.8

Table 2

Permutation-corrected p-values of the associations between change in ADAScog, MMSE and ADL and ventricular enlargement with and without controlling for baseline frontal horn volume and hippocampal atrophy (significant p-values defined as $p < 0.05$ appear in bold)

Measure	Ventricular subregion	Uncorrected		Controlling for baseline frontal horn volume		Controlling for whole ventricular volume		Controlling for hippocampal atrophy	
		Left	Right	Left	Right	Left	Right	Left	Right
ADAScog	Temporal horn	0.038	0.055	0.07	0.14	0.089	0.11	0.04	0.037
	Body/occipital horn	0.028	0.0022	0.027	0.0037	0.02	0.0036	0.031	0.035
	Frontal horn	0.32	0.56	0.25	0.54	0.19	0.53	0.34	0.46
MMSE	Temporal horn	0.2	0.026	0.31	0.039	0.41	0.039	0.18	0.019
	Body/occipital horn	0.024	0.015	0.02	0.024	0.014	0.024	0.023	0.019
	Frontal horn	0.417	0.53	0.14	0.56	0.1	0.59	0.18	0.44
ADL	Temporal horn	0.019	0.36	0.018	0.61	0.026	0.71	0.021	0.27
	Body/occipital horn	0.004	0.032	0.0042	0.056	0.0025	0.053	0.0036	0.041
	Frontal horn	0.15	0.073	0.13	0.22	0.13	0.23	0.12	0.044
ADAScog Verbal Memory	Temporal horn	0.026	0.16	0.051	0.21	0.06	0.22	0.024	0.14
	Body/occipital horn	0.073	0.0015	0.081	0.002	0.071	0.002	0.07	0.0021
	Frontal horn								
ADAScog Visuospatial	Temporal horn	0.41	0.27	0.32	0.29	0.32	0.30	0.45	0.3
	Body/occipital horn	0.19	0.67	0.23	0.61	0.21	0.57	0.18	0.69
	Frontal horn	0.005	0.019	0.0045	0.019	0.0053	0.018	0.0051	0.029
Maze errors	Temporal horn	0.2	0.049	0.21	0.044	0.21	0.046	0.21	0.035
	Body/occipital horn	0.036	0.23	0.038	0.47	0.037	0.33	0.035	0.24
	Frontal horn	0.61	0.18	0.6	0.21	0.6	0.21	0.6	0.18
		0.51	0.047	0.43	0.02	0.49	0.032	0.47	0.037