Published in final edited form as:

J Comput Assist Tomogr. 2016 ; 40(5): 827–832. doi:10.1097/RCT.0000000000000435.

Accelerated Brain Atrophy on Serial Computed Tomography: Potential Marker of the Progression of Alzheimer's Disease

Abdullah Bin Zahid, MD [Research scientist],

Dept. of Neurosurgery, New York University Langone Medical Center, 550 1st Ave, New York, NY, 10016; Dept. of Surgery, VA Harbor Healthcare System, Manhattan Campus, 423 E 23rd St., New York, NY, 10010

Artem Mikheev, MS [Senior application programmer],

Dept. of Radiology, Center for Biomedical Imaging, NYU Langone Medical Center 660 1st Ave, New York, NY, 10016

Neha Srivatsa [Undergraduate student],

New York University, 70 Washington Square South, New York, NY, 10012

James Babb, PhD [Professor],

Dept. of Radiology, Center for Biomedical Imaging, NYU Langone Medical Center 660 1st Ave, New York, NY, 10016

Uzma Samadani, MD, PhD [Assistant Professor], and

Dept. of Neurosurgery, New York University Langone Medical Center, 550 1st Ave, New York, NY, 10016; Dept. of Surgery, VA Harbor Healthcare System, Manhattan Campus, 423 E 23rd St., New York, NY, 10010; Steven and Alexandra Cohen Veterans Center for Post-Traumatic Stress and Traumatic Brain Injury, 550 1st Ave, New York, NY, 10016

Henry Rusinek, PhD [Professor]

Dept. of Radiology, Center for Biomedical Imaging, NYU Langone Medical Center 660 1st Ave, New York, NY, 10016

Abstract

Objective—To validate CT-based longitudinal markers of the progression of Alzheimer's disease (AD).

¹Abdullah Bin Zahid, Dept. of Surgery, VA Harbor Healthcare System, Manhattan Campus, 423 E 23rd Street, New York, NY, 10010, USA, Abdullah.binzahid@va.gov.

¹Present address: Abdullah Bin Zahid, MD, Minneapolis Veteran Affairs Medical Center, 1 Veteran's Drive, Building 49, Room A-100, Minneapolis, MN 55417, U.S.A., 1 (612) 467-4580

Author Contributions: US and HR conceived the study, obtained funding and supervised its conduct. HR, AB, AM, JB and US designed the study. AB and HR did the literature search. AM and HR developed the algorithm to image process CT scans. AB and US selected the patients. AB and NS collected the data. AB, HR and AM performed image processing. Statistical analysis was done by AB and JB. US, AB, HR and JB interpreted the results of statistical analysis. AB and HR created the figures. All authors participated in the preparation of manuscript.

Conflict of Interests: We declare that we have no conflicts of interest.

Additional Information: The software used for image processing is available for free to researchers and can be downloaded here. <https://wp.nyu.edu/firevoxel/downloads/>

Materials and Methods—We retrospectively studied 33 AD patients and 39 non-demented patients with other neurological illnesses (Non-AD) having 4–12 CT exams of the head, over 3.9 ± 1.7 years. At each time point we applied an automatic software to measure whole brain, CSF, and intracranial space (ICS) volumes. Longitudinal measures were then related to disease status and time since first scan using hierarchical models.

Results—Absolute brain volume loss accelerated for non-AD patients by 0.86 ml/yr^2 (95% C.I. 0.64 to 1.08 ml/yr^2) and $1.5\times$ faster, i.e. 1.32 ml/yr^2 (95% C.I. 1.09 to 1.56 ml/yr^2) for AD patients ($p=0.006$). In terms of brain volume normalized to ICS, the acceleration in atrophy rate for non-AD patients was $0.0578\%/yr^2$ (95% C.I. $0.0389\%/yr^2$ to $0.0767\%/yr^2$) again, $1.5\times$ faster, i.e. $0.0919\%/yr^2$ (95% C.I. $0.0716\%/yr^2$ to $0.1122\%/yr^2$) for AD patients ($p=0.017$). This translates to an increase in atrophy rate from 0.5% to 1.4% in AD versus to 1.1% in non-AD group after 10 years.

Conclusion—Brain volumetry on CT reliably detected accelerated volume loss in AD and significantly lower acceleration factor in age-matched non-AD patients, leading to the possibility of its use to monitor the progression of cognitive decline and dementia.

Keywords

Alzheimer's disease; Brain atrophy; Longitudinal studies; Computed tomography head; Computer assisted image analysis; Biomarkers; Quantitative image analysis; Image Segmentation

Introduction

Underlying clinical progression in Alzheimer's disease (AD) are neuropathologic changes that follow a pattern of spreading atrophy throughout the brain, starting in the medial temporal lobe.¹ With the prospect of disease-modifying therapies, early detection and accurate monitoring of such progression is an important goal. The most frequently studied in vivo marker for AD progression is brain atrophy rate derived from serial MRI. Numerous cross-sectional studies report the average brain volume loss in AD to be several times greater than $\sim 0.5\%/year$ rate in non-demented elderly.²⁻⁵ Accelerated within-subject brain volume loss has also been reported.⁶

Serial imaging allows specific assessment of progression, as the patient serves as his or her own reference baseline. In addition to AD, assessments of brain atrophy rates are also of importance in hydrocephalus, traumatic injury, and multiple sclerosis, since they help gauge brain insult and its response to treatment.⁷⁻⁹

As early as in the 1980s, serial computed tomography (CT) imaging studies showed abnormally large ventricular and sulcal enlargement in AD patients. Later, after the advent of MRI, the emphasis was placed on calculation of atrophy using MRI, given the better soft tissue contrast. Whereas there are only a few published studies of brain atrophy at CT^{10,11}, modern CT has many advantages over MRI, including lower cost of both the imaging system and patient exam, ($<1/2$ of the cost of MRI), about 100 times faster speed of acquisition (fewer motion artifacts), availability, higher spatial resolution, and fewer limitations related to claustrophobia and the presence of ferromagnetic material in the body. The disadvantages of CT include lower contrast/noise and exposure of the patient to ionized

radiation. While radiation exposure is of concern, the risk/benefit equation is age- and organ-dependent, favoring the use of CT to study brain atrophy in the elderly.

In this work we test the hypothesis that clinical 5 mm-section CT can be successfully employed in longitudinal studies of brain atrophy using fully automated processing (unlike interactive approach in previously published studies).^{10,11} We also test the ability of CT and automatic volumetry to detect faster brain shrinkage in AD patients compared to age-matched non-demented elderly.

We used a data mining approach by selecting from image archives of a VA hospital system all CT exams relevant to our hypothesis. Two useful aspects of this approach are: 1) patients with neurologic illnesses other than neurodegenerative diseases were not excluded; 2) volume measurements for scanner miscalibrations were retrospectively adjusted – both reflecting the real life situations making the study setting realistic. With these aspects built into study design, we have attempted to validate CT-based longitudinal markers to monitor the progression of Alzheimer's disease.

Materials and Methods

Institutional review board approval was obtained for this study and the requirement for informed consent was waived.

Patient selection

The local Veterans Affairs database was searched for digital CT head or brain exams performed from 2004 to 2014. Of all patients with an index CT scan of the head during this period, patients were excluded if: 1) they had less than three subsequent CT scans; 2) serial scans extended over at less than 1 year or 3) were diagnosed with hydrocephalus or any other neurodegenerative disease other than AD. Patients were deemed to have AD if they met the NINCDS–ADRDA criteria for probable AD¹² as determined by the treating physician. Review of medical records identified 33 such patients. Of the remaining patients with similar longitudinal imaging history but free of any neurodegenerative diseases and hydrocephalus, review of medical records yielded 39 age matched controls. Hence, a total of 72 patients, 33 in AD category and 39 in non-AD (control) category were selected, with 191 exams available for AD patients and 245 exams for non-AD group.

CT protocol

All CT scans were obtained on Toshiba Aquilion 16 or Aquilion 64 helical scanners (Toshiba Medical Systems, Tustin, CA). Acquisition parameters were as follows: peak tube voltage 120 kVp, x-ray tube current 150–300 mAs, field of view 20–25 cm yielding in-plane resolution 0.390–0.468 mm, soft-tissue reconstruction kernel FC64 (377 exams for 61 patients, 27 with AD) or FC67 (59 exams for 11 patients, 6 with AD), matrix size 512×512, 28–35 slices (10th and 90th percentile) (Range: 24 to 368; 16 studies with > 100 slices [161 to 368 slices] and four studies with 24 to 26 slices), and axial-slice thickness 4.6–5 mm (10th and 90th percentile) (Range: 0.45 to 5.00 mm).

Preprocessing of CT scans

In order to eliminate variability that results from the use of different CT reconstruction methods (kernels), for each subject we selected images computed with the kernel that was employed in the highest number of exams for this subject.

Image analysis technique

Total intracranial and total brain volumes were assessed using locally developed fully automated software, with no operator intervention. In the first step, intracranial space (ICS) was segmented. For ICS the algorithm selects voxels with CT attenuation in the range $[-500, +125]$ Hounsfield units (Hu). This excludes bone and air. Then, on the remaining soft tissue, 3D morphologic erosion of 6 mm radius is performed that disconnects the extra-cranial soft tissue from the interior of the cranial cavity. Afterwards the largest connected component is retained that results in the exclusion of extra-cranial soft tissue. Finally, constrained morphologic dilation is performed on the retained component resulting in the recovery of all intracranial space voxels. The CSF volume was then separated from the brain tissue by labelling all ICS voxels with attenuation values within the fluid range, i.e. below 16 Hu as CSF. The ICS voxels not classified as CSF were labelled as brain tissue. The threshold of 16 Hu was selected by a multimodality CT/MRI optimization study using T2-weighted images as the gold standard for estimating CSF volume.¹³ CSF masks included the entire ventricular and sulcal space. No coregistration techniques or other normalization techniques were used. All volumes reflected absolute measurements in milliliters. All attenuation values were expressed in Hu.

Compensation for lack of CT calibration

Multiple factors (detector drift, x-ray tube current) affect calibration of linear attenuation of water used as reference signal in CT. Since our scanners were not calibrated daily against a phantom, and our image processing technique in part was dependent on thresholding, this led to the noise in the volume measurements. Our correction is based on the premise that instrument miscalibration can be inferred from variability in average radiodensity of intracranial cavity μ_{ICC} among CT scans. This was suggested by a strong, constant linear relationship between BV & CSF-V and μ_{ICC} over the whole range of values studied that is otherwise not expected. Hence we corrected for noise by linearly regressing BV and CSF-V against average intracranial radiodensity. This yielded adjusted whole brain volume (BV') and adjusted CSF volume (CSF-V'). The adjusted ICS volume (ICS-V') was defined as the sum of adjusted CSF-V' and BV'. Notice adjusted ICS volume was calculated in the last step, after measuring BV' and CSF-V'. The normalized brain volume (nBV') was defined as $BV' / ICS-V'$. Only adjusted volumes (BV', ICS-V' and nBV') were used in further statistical modeling. The output from the software was visually inspected for any gross segmentation errors.

Statistical analysis

All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS version 21, IBM Corporation, Armonk, NY, USA). Figure 2 and Figure 3 were constructed using SAS version 9.4 (SAS Institute, Carry, NC, USA).

Reliability of volumetry on CT scan

In order to estimate reliability of volumetry on CT scans acquired over time, we used the fact that for each patient intracranial cavity size remains constant in adults. Hence, we calculated two-way intraclass correlation coefficient (ICC) for absolute agreement for ICS-V'. To avoid missing values, ICC was computed for the first four CT exams only.

Estimation of acceleration in brain parenchyma atrophy rate

To analyze time series data with unequal follow up duration and correlated error terms, separate multilevel mixed (hierarchical) models were developed for BV' and nBV' using SPSS Mixed procedure. The models related the target measurements to group membership and its interaction with follow-up time (quadratic term only) as fixed effects. Intercept and slope (linear term, time since first scan) were allowed to vary between individuals. Since both groups had comorbidities such as cerebrovascular accidents, head trauma or cerebral edema that might affect the linear term, we allowed only the quadratic term to be a fixed effect for our cohort. Both models were constructed using restricted maximum likelihood estimation.

Results

Figure 1 shows a typical segmentation result. Table S-1 in supplemental file shows the distribution of MMSE scores at the last exam. The indications for CT scans are given in table S-2. Indications for which scans were positive are listed in table S-3 (AD patients) and table S-4 (control patients). The descriptive statistics are given in Table 1. As expected in a VA clinic, patients were males. We analyzed between 4 and 12 CT exams per subject (Mean 6.06, S.D. 2.3). The mean age at the time of initial CT scan was 80 yrs (S.D. 5.45, Range 70 to 91). The mean duration of follow up was 3.9 yrs (S.D. 1.75, Range 1.02 to 8.69).

Longitudinal changes in brain volumes

Figure 2 and Table 2 show changes in absolute brain volumes for AD and non-AD patients. The segmentation analyses demonstrate significant acceleration of brain volume loss in both groups. In non-AD group, the quadratic term was 0.86 ml/yr² (p-value < 0.001; 95% C.I. 0.64 to 1.08), it was 1.32 ml/yr² or about 50% larger (95% C.I. 1.09 to 1.56) for AD group (intergroup p-value = 0.006).

Changes in brain volumes adjusted for head size

Figure 3 and Table 2 show changes in brain volumes after dividing by the volume of intracranial cavity. Again, there was a significant acceleration of atrophy for both AD and non-AD patients. The acceleration was 0.0578%/yr² (95% C.I. 0.0389 to 0.0767; p-value < 0.001) for non-AD patients. It was over 50% larger, 0.0919%/yr² (95% C.I. 0.0716 to 0.1122; intergroup p-value = 0.017) for AD patients.

Comparison of acceleration factors

Table 3 compares the acceleration factor of 0.09% with 0.06%. Starting with an initial atrophy rate of 0.5% at the age of 60 yrs,¹⁴ small differences in acceleration led to a difference of 1.4% between two groups at the end of 5 yrs.

Intraclass correlation coefficient (ICC) for ICS-V' was 0.996 with a 95% C.I. ranging from 0.994 to 0.997.

Discussion

Comparison with MRI studies

Multiple cross-sectional MRI and pathology studies suggest that brain atrophy rates accelerate after the 7th decade, even for cognitively normal individuals.¹⁵⁻¹⁷ Unfortunately, there are no longitudinal imaging studies to demonstrate such acceleration, most likely due to the limited precision of current methodology.^{18,19} There is conflicting evidence regarding whether or not whole brain atrophy accelerates in MCI patients or sporadic AD patients (see Jack et al 2008 for acceleration of atrophy rate,¹⁹ and Leung et al 2013 for stable model¹⁸). Here we report significant quadratic terms, indicating acceleration of brain atrophy rates within both AD and non-AD elderly. Inter group comparison indicates that acceleration is significantly greater in AD patients versus non-AD patients. Our results hold for both absolute brain volumes and brain volumes normalized to ICS. Jack et al. reported the rate of acceleration in brain volume loss for the patients 79 yr old on average, while they converted from mild cognitive impairment to AD, to be 5.3 ml (95% C.I. 3.3 to 7.4) over a mean duration of 4.7 yrs in their piecewise linear mixed model.¹⁹ Their data are in agreement with our estimate of the quadratic term (1.32 ml/yr²). Chan et al⁶ found the acceleration in atrophy to be 0.32%/year² in normalized whole brain volumes (95% C.I. 0.15–0.50) in their cohort of familial AD. This is about three times larger than our estimate of 0.09%/yr² (95% C.I. 0.07 – 0.11), consistent with common observation of familial AD progressing faster than sporadic AD.²⁰ Of note, C.I. for acceleration is much tighter (about ten times smaller) in our study versus Chan et al., suggesting greater precision of volumetry estimated from CT than from MR images. This may be due to decreased motion artifacts with CT versus MRI resulting from faster acquisition times for the former versus latter. The detection of a small but significant accelerated volume loss in non-demented elderly discussed herein, might be important for the design of AD clinical treatment trials, as neglecting accelerated atrophy in normal elderly may lead to underestimation of drug effect. In addition, these seemingly small acceleration factors translate into huge differences in volume losses over time (Table 3). Very long cohort studies following patients for a quarter century are expensive and difficult to carryout. Demonstration of a small decrease in acceleration factor over a short period for a therapy will mean compounding clinical benefit over time.

Reliability of intracranial size volume on CT scan has not been previously reported. Reliability can be estimated given the assumption of no skull changes in advanced aging. Our finding of intraclass correlation coefficient of 0.996 is in agreement with MRI literature.²¹

Interpretation of statistical models

Our longitudinal models to detect acceleration used both linear and quadratic terms. The linear terms (Table 2), entered as the random effects, revealed higher linear atrophy rate (in the presence of acceleration factor) in non-AD patients versus AD patients. This result may imply 1) stroke and other neurological illness caused acute loss of brain tissue without any increase in long-term loss of brain parenchyma in non-AD group, or 2) neurodegeneration in non-AD patients follows predominantly linear patterns, whereas in AD the pattern is mostly quadratic (accelerated changes) that reflect progressive territory, or the spread of atrophy from medial temporal to cortical brain regions.¹⁴

Clinical relevance

AD and non-AD patients in this study were male military veterans. While representing a select group, they are representative of a large segment of the population. The inclusion of confounding illnesses among the non-AD group makes the study especially relevant.²² When confirmed by other studies validating CT volumetry tool in a cohort with confounding neurological illnesses, our methodology may enable new cost-effective applications in clinical practice and clinical trials.

The study inspires the use of a non-operator dependent modality coupled with fully automated image processing. This not only results in objective data and saves the cost and personnel time, but also enables analyzing very large datasets. In addition, shorter acquisition time (reducing discomfort and potential for head motion artifacts), and virtually no contraindications make CT modality much more suited than MRI to elderly population. The prevalence of MRI claustrophobia is estimated to be 4 – 20%.²³ CT based biomarkers for the progression of AD can help overcome these limitations.

Limitations of the study:

1. The age distribution of population being studied was 70-90. It would be of interest to generalize our finding to younger patients and female subjects. However, AD is relatively rare in people younger than 70.
2. Strict CT quality control was not possible in this retrospective study. Future prospective studies based on instrument calibration and uniform protocol will likely provide us with better precision.
3. Statistical modeling was performed using slope in individual level (random) effects only, to accommodate the abrupt changes in brain volumes due to confounding neurological illnesses.
4. CT scan exposes patients to ionizing radiation. However, modern scanners significantly reduce radiation exposure. Also, radiation exposure is of greatest concern in young individuals, as reproductive organs are significantly more radiosensitive than the brain.

Summary

This first CT-based longitudinal brain volumetry study suggests that CT based potential biomarkers can be employed to monitor the progression and treatment of AD. Accelerated within subject atrophy, not previously shown for cognitively normal elderly was demonstrated here, along with significant 1.5× greater acceleration for AD patients. Confidence intervals for the quadratic term were within 0.4 ml/yr² for absolute brain volumes, indicating a potential for atrophy on CT scan to serve as a reliable outcome measure for clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge funding from United States Department of Veteran Affairs, Office of Research and Development, Clinical Studies section Merit Grant (1I01CX000887-01A1) and from NIBIB Biomedical Technology Resource Center (NIH P41 EB017183) to NYU Center for Advanced Imaging Innovation and Research (www.cai2r.net). US is also partially supported by the Steven and Alexandra Cohen Veterans Center for Post-Traumatic Stress and Traumatic Brain Injury.

Sources of support:

1. United States Department of Veteran Affairs, Office of Research and Development, Clinical Studies section Merit Grant (1I01CX000887-01A1)
2. NIBIB Biomedical Technology Resource Center (NIH P41 EB017183) to NYU Center for Advanced Imaging Innovation and Research (www.cai2r.net)
3. Steven and Alexandra Cohen Veterans Center for Post-Traumatic Stress and Traumatic Brain Injury

References

1. de Leon MJ, George AE, Stylopoulos LA, et al. Early marker for Alzheimer's disease: the atrophic hippocampus. *Lancet*. 1989; 2(8664):672–3. [PubMed: 2570916]
2. 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(4):591–600. [PubMed: 14981176]
3. Resnick SM, Pham DL, Kraut MA, et al. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J Neurosci*. 2003; 23(8):3295–301. [PubMed: 12716936]
4. Thompson PM, Hayashi KM, de Zubicaray G, et al. Dynamics of gray matter loss in Alzheimer's disease. *J Neurosci*. 2003; 23(3):994–1005. [PubMed: 12574429]
5. Wang D, Doddrell DM. MR image-based measurement of rates of change in volumes of brain structures. Part I: method and validation. *Magn Reson Imaging*. 2002; 20(1):27–40. [PubMed: 11973027]
6. Chan D, Janssen JC, Whitwell JL, et al. Change in rates of cerebral atrophy over time in early-onset Alzheimer's disease: longitudinal MRI study. *Lancet*. 2003; 362(9390):1121–2. [PubMed: 14550701]
7. Frank RA, Galasko D, Hampel H, et al. Biological markers for therapeutic trials in Alzheimer's disease. Proceedings of the biological markers working group; NIA initiative on neuroimaging in Alzheimer's disease. *Neurobiol Aging*. 2003; 24(4):521–36. [PubMed: 12714109]
8. Gunter JL, Shiung MM, Manduca A, Jack CR Jr. Methodological considerations for measuring rates of brain atrophy. *J Magn Reson Imaging*. 2003; 18(1):16–24. [PubMed: 12815635]

9. Mikheev A, Nevsky G, Govindan S, et al. Fully automatic segmentation of the brain from T1-weighted MRI using Bridge Burner algorithm. *J Magn Reson Imaging*. 2008; 27(6):1235–41. [PubMed: 18504741]
10. Zhang Y, Londos E, Minthon L, et al. Usefulness of computed tomography linear measurements in diagnosing Alzheimer's disease. *Acta Radiol*. 2008; 49(1):91–7. [PubMed: 18210318]
11. Rossi R, Joachim C, Smith AD, Frisoni GB. The CT-based radial width of the temporal horn: pathological validation in AD without cerebrovascular disease. *Int J Geriatr Psychiatry*. 2004; 19(6):570–4. [PubMed: 15211538]
12. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7(3): 263–9. [PubMed: 21514250]
13. Bin Zahid, A.; Mikheev, A.; Yang, AI., et al. Calculation of brain atrophy using computed tomography and a new atrophy measurement tool. In: Ourselin, S.; Styner, MA., editors. *Proc. SPIE 9413, Medical Imaging 2015: Image Processing*, 94132S; February 21 2015; Orlando, FL.
14. Rusinek H, Endo Y, De Santi S, et al. Atrophy rate in medial temporal lobe during progression of Alzheimer disease. *Neurology*. 2004; 63(12):2354–9. [PubMed: 15623699]
15. Dekaban AS. Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. *Ann Neurol*. 1978; 4(4):345–56. [PubMed: 727739]
16. Scallan RI, Frost C, Jenkins R, et al. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Arch Neurol*. 2003; 60(7):989–94. [PubMed: 12873856]
17. Courchesne E, Chisum HJ, Townsend J, et al. Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology*. 2000; 216(3):672–82. [PubMed: 10966694]
18. Leung KK, Bartlett JW, Barnes J, et al. Cerebral atrophy in mild cognitive impairment and Alzheimer disease: rates and acceleration. *Neurology*. 2013; 80(7):648–54. [PubMed: 23303849]
19. Jack CR Jr, Weigand SD, Shiung MM, et al. Atrophy rates accelerate in amnesic mild cognitive impairment. *Neurology*. 2008; 70(19 Pt 2):1740–52. [PubMed: 18032747]
20. Swearer JM, O'Donnell BF, Ingram SM, Drachman DA. Rate of progression in familial Alzheimer's disease. *J Geriatr Psychiatry Neurol*. 1996; 9(1):22–5. [PubMed: 8679059]
21. Nugent AC, Luckenbaugh DA, Wood SE, et al. Automated subcortical segmentation using FIRST: test-retest reliability, interscanner reliability, and comparison to manual segmentation. *Hum Brain Mapp*. 2013; 34(9):2313–29. [PubMed: 22815187]
22. Ganguli M, Lee CW, Hughes T, et al. Who wants a free brain scan? Assessing and correcting for recruitment biases in a population-based sMRI pilot study. *Brain Imaging Behav*. 2015; 9(2):204–12. [PubMed: 24573773]
23. McIsaac HK, Thordarson DS, Shafran R, et al. Claustrophobia and the magnetic resonance imaging procedure. *J Behav Med*. 1998; 21:255–268. [PubMed: 9642571]

Figure 1. Segmentation results on a representative CT slice: the brain tissue is shown in light blue and the CSF containing regions are in dark red. The intracranial cavity is the sum of CSF and the brain volumes.

Figure 2.

Longitudinal changes in brain volume for 72 individual patients. Alzheimer patients (N=33) are shown in red, age-matched non-AD patients (N=39) are in green. The lines plot the hierarchical model fitted to the CT data (see text for details). Note accelerated volume loss in most patients diagnosed with AD. Also note a significant overlap in baseline brain volumes across the two groups of patients.

Figure 3.

Plot of data from Figure 2, but with brain volume expressed as percent of cranial cavity. Alzheimer patients are shown in red, controls are in green. CT scans within one year (as determined by patient age) were combined to create the figure. Lines show volumes predicted by model fitted to the data using both fixed and random effects, as discussed in text.

Table 1
Descriptive statistics by groups

Parameter	Baseline Age (yrs)		Follow up (yrs)		Whole brain volume (BR' ; ml)		Normalized whole brain volume (nBV' ; percentage of cranial cavity)		Brain Radiodensity (BR' ; Hounsfield units)	
	AD	non-AD	AD	non-AD	AD	non-AD	AD	non-AD	AD	non-AD
Mean	81.08	79.31	3.95	3.87	1078.12	1117.06	80.82	81.81	30.774	30.484
Median	80.74	79.29	4.54	3.70	1083.00	1101.40	81.00	81.72	30.762	30.447
Std. Dev.	5.37	5.45	1.78	1.75	80.73	98.36	2.24	2.37	0.690	0.662
Range	20.37	19.97	6.21	7.20	317.73	399.33	12.48	15.61	4.373	4.834

Table 2
Rate of loss of brain volume, in milliliters and as a percentage of intracranial space

Parameter	Average slope (random effect)	Quadratic term (fixed effect)	Quadratic term, 95% confidence intervals
BV', AD patients	-0.15 ml/yr	-1.32 ml/yr ²	-1.56 ml/yr ² to -1.09 ml/yr ²
BV', Non-AD patients	-0.20 ml/yr	-0.86 ml/yr ²	-1.08 ml/yr ² to -0.64 ml/yr ²
nBV', AD patients	-0.011 %/yr	-0.092%/yr ²	-0.112%/yr ² to -0.072%/yr ²
nBV', Non-AD patients	-0.016 %/yr	-0.058%/yr ²	-0.077%/yr ² to -0.039%/yr ²

Table 3

Projected atrophy compared, starting at the age of 60, for acceleration of 0.09% versus 0.06%. Minor differences in acceleration translate to huge differences in brain volumes.

Age	Acceleration of 0.09% - AD group			Acceleration of 0.06% - non-AD group		
	annual atrophy rate	brain volume (ml)	brain lost (ml)	annual atrophy rate	brain volume (ml)	brain lost (ml)
60	0.50%	1000.0	5.0	0.50%	1000.0	5.0
61	0.59%	995.0	5.9	0.56%	995.0	5.6
62	0.68%	989.1	6.8	0.62%	989.4	6.2
63	0.77%	982.3	7.6	0.68%	983.2	6.7
64	0.86%	974.7	8.4	0.74%	976.5	7.3
65	0.95%	966.3	9.3	0.80%	969.2	7.8
66	1.04%	957.0	10.0	0.86%	961.4	8.3
67	1.13%	947.0	10.8	0.92%	953.1	8.8
68	1.22%	936.1	11.6	0.98%	944.2	9.3
69	1.31%	924.6	12.3	1.04%	934.9	9.8
70	1.40%	912.3	12.9	1.10%	925.1	10.3
71	1.49%	899.4	13.6	1.16%	914.8	10.7
72	1.58%	885.8	14.2	1.22%	904.1	11.2
73	1.67%	871.6	14.8	1.28%	892.9	11.6
74	1.76%	856.8	15.3	1.34%	881.3	12.0
75	1.85%	841.4	15.9	1.40%	869.4	12.3
76	1.94%	825.6	16.3	1.46%	857.0	12.7
77	2.03%	809.3	16.8	1.52%	844.3	13.0
78	2.12%	792.5	17.2	1.58%	831.3	13.3
79	2.21%	775.4	17.5	1.64%	818.0	13.6
80	2.30%	757.8	17.8	1.70%	804.3	13.9
81	2.39%	740.0	18.1	1.76%	790.4	14.2
82	2.48%	721.9	18.4	1.82%	776.3	14.4
83	2.57%	703.5	18.6	1.88%	761.9	14.6
84	2.66%	685.0	18.7	1.94%	747.3	14.8

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Age	Acceleration of 0.09% - AD group			Acceleration of 0.06% - non-AD group		
	annual atrophy rate	brain volume (ml)	brain lost (ml)	annual atrophy rate	brain volume (ml)	brain lost (ml)
85	2.75%	666.3	18.8	2.00%	732.5	14.9
86	2.84%	647.4	18.9	2.06%	717.6	15.1
87	2.93%	628.5	19.0	2.12%	702.5	15.2