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

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Objective: The aim of this study was to validate computed tomography (CT)–based longitudinal markers of the progression of Alzheimer disease (AD).

Materials and Methods: We retrospectively studied 33 AD patients and 39 nondemented patients with other neurological illnesses (non-AD) having 4 to 12 CT examinations of the head, with over a mean (SD) of 3.9 (1.7) years. At each time point, we applied an automatic software to measure whole brain, cerebrospinal fluid, and intracranial space volumes. Longitudinal measures were then related to disease status and time since the first scan using hierarchical models.

Results: Absolute brain volume loss accelerated for non-AD patients by 0.86 mL/y^2 (95% confidence interval [CI], 0.64–1.08 mL/y^2) and 1.5× faster, that is, 1.32 mL/y^2 (95% CI, 1.09–1.56 mL/y^2) for AD patients ($P = 0.006$). In terms of brain volume normalized to intracranial space, the acceleration in atrophy rate for non-AD patients was 0.0578%/y^2 (95% CI, 0.0389%/y^2 to 0.0767%/y^2), again 1.5× faster, that is, 0.0919%/y^2 (95% CI, 0.0716%/y^2 to 0.1122%/y^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.

Conclusions: 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.

Key Words: Alzheimer disease, brain atrophy, longitudinal studies, computed tomography

(*J Comput Assist Tomogr* 2016;40: 827–832)

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Received for publication January 19, 2016; accepted March 1, 2016.

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Supplemental digital contents are available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jcat.org).

Supported by the US Department of Veteran Affairs, Office of Research and Development, Clinical Studies Section merit grant (1I01CX000887-01A1); NIBIB Biomedical Technology Resource Center (NIH P41 EB017183) to NYU Center for Advanced Imaging Innovation and Research (www.cai2r.net); and Steven and Alexandra Cohen Veterans Center for Post-Traumatic Stress and Traumatic Brain Injury.

The authors declare no conflict of interest.

NYU and VA medical centers have submitted a provisional patent for the technology described in this paper on behalf of authors A.B.Z., H.R., A.M., and U.S.

Author contributions: U.S. and H.R. conceived the study, obtained funding, and supervised its conduct. H.R., A.B.Z., A.M., J.B., and U.S. designed the study. A.B.Z. and H.R. did the literature search. A.M. and H.R. developed the algorithm to image process CT scans. A.B.Z. and U.S. selected the patients. A.B.Z. and N.S. collected the data. A.B.Z., H.R., and A.M. performed image processing. Statistical analysis was done by A.B.Z. and J.B. U.S., A.B.Z., H.R., and J.B. interpreted the results of statistical analysis. A.B.Z. and H.R. created the figures. All authors participated in the preparation of manuscript.

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

DOI: 10.1097/RCT.0000000000000435

Underlying clinical progressions in Alzheimer 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 are important goals. The most frequently studied in vivo marker for AD progression is brain atrophy rate derived from serial magnetic resonance imaging (MRI). Numerous cross-sectional studies report the average brain volume loss in AD to be several times greater than ~0.5%/y rate in nondemented 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 because they help gauge brain insult and its response to treatment.[7–9]

As early as 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 examination (<half of the cost of MRI), approximately 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 used 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 with age-matched nondemented elderly.

We used a data mining approach by selecting from image archives of a Veterans Affairs (VA) hospital system all CT examinations relevant to our hypothesis. There are 2 useful aspects of this approach: (1) patients with neurologic illnesses other than neurodegenerative diseases were not excluded, and (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 AD.

MATERIALS AND METHODS

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

Patient Selection

The local VA database was searched for digital CT head or brain examinations 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 3 subsequent CT scans, (2) serial scans extended over at less than 1 year, or (3) they were diagnosed with hydrocephalus or any other neurodegenerative disease other than AD. Patients were deemed to have AD if they met the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association criteria for probable AD[12] 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 examinations available for AD patients and 245 examinations 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 mA; field of view, 20–25 cm; yielding in-plane resolution, 0.39–0.468 mm; soft tissue reconstruction kernel FC64 (377 examinations for 61 patients, 27 with AD) or FC67 (59 examinations for 11 patients, 6 with AD); matrix size, 512 × 512; 28–35 slices (10th and 90th percentile) (range, 24–368; 16 studies with > 100 slices [161–368 slices] and 4 studies with 24–26 slices); and axial slice thickness, 4.6–5 mm (10th and 90th percentile) (range, 0.45–5.00 mm).

Preprocessing of CT Scans

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 used in the highest number of examinations 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 of −500 to +125 in Hounsfield units. This excludes bone and air. Then, on the remaining soft tissue, 3-dimensional morphologic erosion of 6-mm radius is performed that disconnects the extracranial soft tissue from the interior of the cranial cavity. Afterwards, the largest connected component is retained that results in the exclusion of extracranial soft tissue. Finally, constrained morphologic dilation is performed on the retained component resulting in the recovery of all ICS voxels. The cerebrospinal fluid (CSF) volume was then separated from the brain tissue by labeling all ICS voxels with attenuation values within the fluid range, that is, below 16 HU as CSF. The ICS voxels not classified as CSF were labeled as brain tissue. The threshold of 16 HU was selected by a multimodality CT/MRI optimization study using T2-weighted images as the criterion 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. Because 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 and CSF-V as well as 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). Figures 1 and 2 were constructed using SAS version 9.4 (SAS Institute, Cary, NC).

Reliability of Volumetry on CT Scan

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 2-way intraclass correlation coefficient (ICC) for absolute agreement for ICS-V′. To avoid missing values, ICC was computed for the first 4 CT examinations 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 the first scan) were allowed to vary between individuals. Because 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 3 shows a typical segmentation result. Table S-1, http://links.lww.com/RCT/A49 in supplemental file shows the distribution of mini mental state examination scores at the last examination. The indications for CT scans are given in Table S-2, http://links.lww.com/RCT/A49. Indications for which scans were positive are listed in Table S-3, http://links.lww.com/RCT/A49 (AD patients) and Table S-4, http://links.lww.com/RCT/A49 (control patients). The descriptive statistics are given in Table 1. As expected in a VA clinic, patients were males. We analyzed

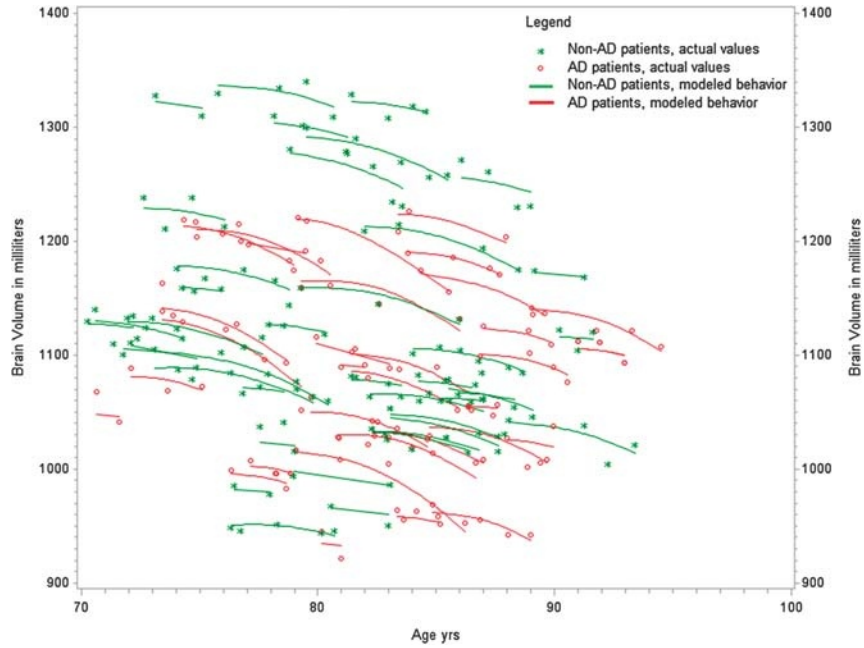

FIGURE 1. Longitudinal changes in brain volume for 72 individual patients. Alzheimer patients (n = 33) are shown in red; age-matched non-AD patients (n = 39) are in green. The lines plot the hierarchical model fitted to the CT data (see text for details). Note accelerated volume loss in most patients diagnosed with AD. Also note a significant overlap in baseline brain volumes across the 2 groups of patients.

between 4 and 12 CT examinations per subject (mean [SD], 6.06 [2.3]). The mean (SD) age at the time of initial CT scan was 80 (5.45) years (range, 70–91 years). The mean (SD) duration of follow-up was 3.9 (1.75) years (range, 1.02–8.69 years).

Longitudinal Changes in Brain Volumes

Figure 1 and Table 2 show changes in absolute brain volumes for AD and non-AD patients. The segmentation analyses

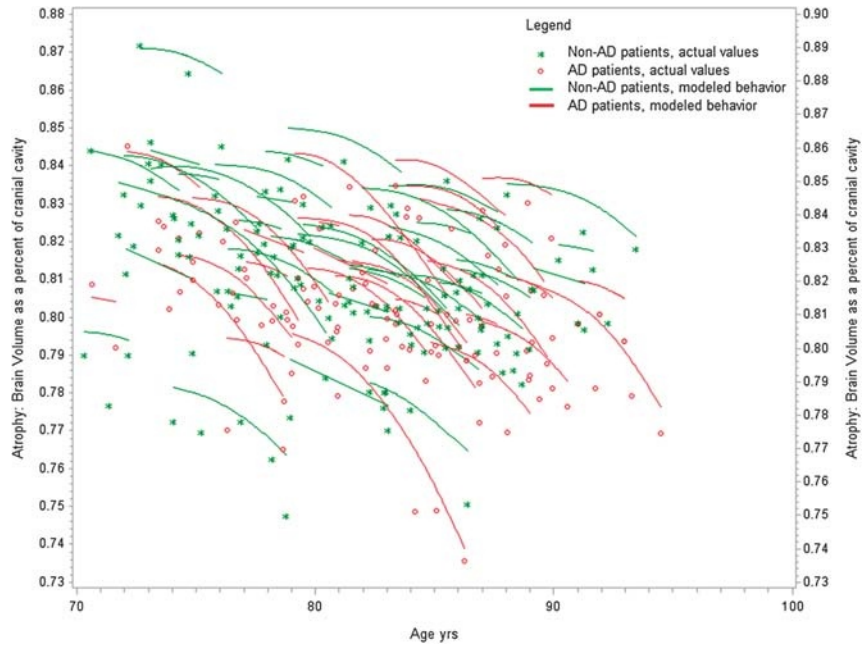

FIGURE 2. Plot of data from Figure 1 but with brain volume expressed as percent of cranial cavity. Alzheimer patients are shown in red; controls are in green. CT scans within 1 year (as determined by patient age) were combined to create the figure. Lines show volumes predicted by model fitted to the data using both fixed and random effects, as discussed in the text.

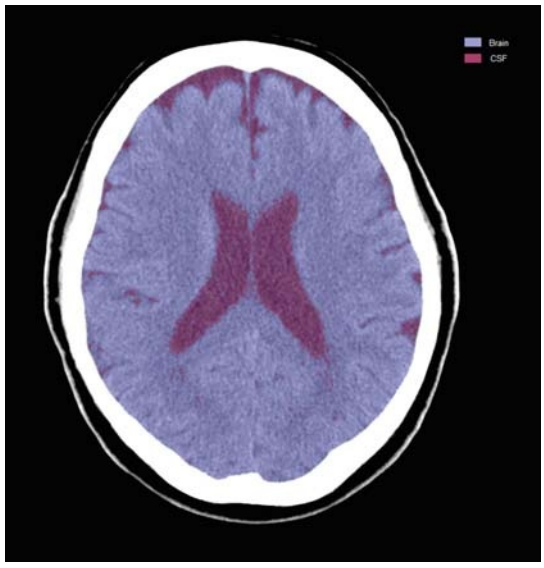

FIGURE 3. Segmentation results on a representative CT slice: the brain tissue is shown in light blue and the CSF containing regions are in dark red. The intracranial cavity is the sum of CSF and the brain volumes.

demonstrate significant acceleration of brain volume loss in both groups. In non-AD group, the quadratic term was 0.86 mL/y^2 ($P < 0.001$; 95% confidence interval [CI], 0.64–1.08); it was 1.32 mL/y^2 or approximately 50% larger (95% CI, 1.09–1.56) for AD group (intergroup $P = 0.006$).

Changes in Brain Volumes Adjusted for Head Size

Figure 2 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%/y^2 (95% CI, 0.0389–0.0767; $P < 0.001$) for non-AD patients. It was over 50% larger, 0.0919%/y^2 (95% CI, 0.0716–0.1122; intergroup $P = 0.017$) 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 years,[14] small differences in acceleration led to a difference of 1.4% between 2 groups at the end of 5 years.

Intraclass correlation coefficient for ICS-V′ was 0.996 with a 95% CI 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 seventh 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 mild cognitive impairment patients or sporadic AD patients (see Jack et al[19] for acceleration of atrophy rate and Leung et al[18] for stable model). Here we report significant quadratic terms, indicating acceleration of brain atrophy rates within both AD and non-AD elderly. Intergroup 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[19] reported the rate of acceleration in brain volume loss for the patients aged 79 years on average, while they converted from mild cognitive impairment to AD, to be 5.3 mL (95% CI, 3.3–7.4) over a mean duration of 4.7 years in their piecewise linear mixed model. Their data are in agreement with our estimate of the quadratic term (1.32 mL/y^2). Chan et al[6] found the acceleration in atrophy to be 0.32%/y^2 in normalized whole brain volumes (95% CI, 0.15–0.50) in their cohort of familial AD. This is approximately 3 times larger than our estimate of 0.09%/y^2 (95% CI, 0.07–0.11), consistent with common observation of familial AD progressing faster than sporadic AD.[20] Of note, CI for acceleration is much tighter (approximately 10 times smaller) in our study versus that in the study of Chan et al, suggesting greater precision of volumetry estimated from CT than from MRI scans. This may be due to decreased motion artifacts with CT versus MRI resulting from faster acquisition times for the former versus the latter. The detection of a small but significant accelerated volume loss in nondemented 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 carry out. 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 ICC 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

TABLE 1. Descriptive Statistics by Groups

	Baseline Age, y		Follow-up, y		Whole Brain Volume (BR′; mL)		Normalized Whole Brain Volume (nBV′; Percentage of Cranial Cavity)		Brain Radiodensity (BR′; HU)	
Parameter	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
SD	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

Parameter	Average Slope (Random Effect)	Quadratic Term (Fixed Effect)	Quadratic Term, 95% CI
BV′, AD patients	−0.15 mL/y	-1.32 mL/y^2	-1.56 to -1.09 mL/y^2
BV′, Non-AD patients	−0.20 mL/y	-0.86 mL/y^2	-1.08 to -0.64 mL/y^2
nBV′, AD patients	−0.011%/y	-0.092%/y^2	-0.112%/y^2 to -0.072%/y^2
nBV′, Non-AD patients	−0.016%/y	-0.058%/y^2	-0.077%/y^2 to -0.039%/y^2

Values were presented in milliliters and as a percentage of intracranial space.

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

Alzheimer disease 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 nonoperator-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 data sets. 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% to

TABLE 3. Projected Atrophy Compared, Starting at the Age of 60 Years, for Acceleration of 0.09% Versus 0.06%

	Acceleration of 0.09%, AD Group			Acceleration of 0.06%, Non-AD Group		
Age, y	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
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

Minor differences in acceleration translate to huge differences in brain volumes.

20%.[23] Computed tomography–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 to 90 years. 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 years.
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. In addition, 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 used 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/y^2 for absolute brain volumes, indicating a potential for atrophy on CT scan to serve as a reliable outcome measure for clinical trials.

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