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Comparisons between Global and Focal Brain Atrophy Rates in Normal Aging and Alzheimer Disease:

Boundary Shift Integral versus Tracing of the Entorhinal Cortex and Hippocampus

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Abstract

The objectives of this study were to (1) compare atrophy rates associated with normal aging and Alzheimer disease (AD) using the semi-automated Boundary Shift Integral (BSI) method and manual tracing of the entorhinal cortex (ERC) and hippocampus and (2) calculate power of BSI vs. ERC and hippocampal volume changes for clinical trials in AD. We quantified whole brain and ventricular BSI atrophy rates and ERC and hippocampal atrophy rates from longitudinal MRI data in 20 AD patients and 22 age-matched healthy controls. All methods revealed significant brain atrophy in controls and AD patients. AD patients had approximately 2.5 times greater whole brain BSI atrophy rates and more than 5 times greater ERC and hippocampal atrophy rates than controls. ERC and hippocampal atrophy rates were higher in both groups than whole brain BSI atrophy rates, but lower than ventricular BSI atrophy rates. Effect size and power calculations suggest that ERC and hippocampal measurements may be more sensitive than ventricular or whole brain BSI for detecting AD progression and the potential effects of disease modifying agents. Logistic regression analysis revealed that combined rates of ERC and ventricular BSI were the best explanatory variables for classifying AD from controls.

Keywords

dementia; Boundary Shift Integral; serial MRI; longitudinal; normal aging; Alzheimer disease

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Alzheimer disease (AD) is a neurodegenerative disorder that involves the accumulation of neuritic plaques and neurofibrillary tangles in certain regions of the brain.[1] AD neuropathology is thought to begin in the transentorhinal cortex and Entorhinal cortex (ERC), progresses to the hippocampus, and finally spreads throughout the limbic system and neocortex.[2] Numerous investigators have used magnetic resonance imaging (MRI) as a surrogate marker for tracking the neuronal changes that underlie the clinical manifestations of AD. These neuroimaging studies have reported significant volumetric differences in the ERC, hippocampus, and neocortex of AD patients relative to healthy control subjects.[3–13] However, because large between-individual variations exist in the normal morphology of these brain structures, it has been difficult to accurately identify AD pathology with a single MRI measurement. In this respect, longitudinal MRI studies may be more sensitive to AD pathology than single cross-sectional MRI studies because each subject serves as his or her own control.

Several longitudinal MRI studies have reported significant differences between AD patients and controls. Using manual tracing of serial MRI, Jack and colleagues have reported greater rates of hippocampal and temporal horn atrophy in AD patients relative to controls.[14] This group has also found significant correlations between rates of hippocampal atrophy and clinical status.[15] Using manual tracing of the ERC, we have reported greater annual ERC volume loss in AD patients than control subjects.[16] More recently, we compared those ERC data to hippocampal volume data quantified with a semi-automated tracing technique. These results revealed that AD patients had greater ERC than hippocampal atrophy rates.[17] Using a regional brain boundary shift analysis to measure medial temporal lobe (MTL) atrophy, Rusinek and colleagues[18] showed that increased MTL atrophy rates appear to predict future memory decline in healthy elderly individuals. Using the Boundary Shift Integral (BSI) method to measure longitudinal whole brain tissue loss, Fox and colleagues have demonstrated substantially greater atrophy in AD patients than cognitively normal subjects.[19–22] Using a semiautomated method of measuring volume change from serial MRIs, Gunter and colleagues[23] have found that ventricular measures of volume change show greater separation between cognitively normal subjects and AD patients than whole brain measures of volume change.

Although several studies have noted significant differences in the rates of brain atrophy in AD patients and controls using serial MRIs, the majority of these studies used different methods on different patient populations. This has made it difficult to compare the power of the different methods for measuring longitudinal changes in brain structure. Nevertheless, the BSI method appears to have at least two practical advantages over manual and semi-automated tracing techniques, which can be time-consuming and potentially susceptible to operator bias. First, BSI is fully automated once tissue masks have been identified. Second, BSI does not require regions of interest to be hand-selected for measurements of longitudinal volume changes. Although this means that BSI does not use the characteristic pattern of regional atrophy in AD (instead, it detects changes in the boundaries between brain tissue and cerebrospinal fluid over time), BSI affords the ability to identify, in an unbiased manner, brain regions with progressive tissue loss.

We have previously compared the annual rates of ERC atrophy, determined by manual tracing, hippocampal atrophy, determined by a semi-automated non-linear atlas warping method,[24] and whole brain atrophy, determined by BSI, on a small sample of subjects.[10] Although all three methods examined in that study revealed greater atrophy rates in demented patients relative to controls, no single method proved to be more sensitive than the others for detecting group differences in longitudinal change. In the present study, we reexamine this issue with a larger subject sample. Specifically, the goals of this study are to: (1) implement the BSI method as previously published by Freeborough and Fox[22] and to validate and calibrate this method for use with our data; (2) use the BSI method to measure rates of cortical atrophy in AD patients

and control subjects; and (3) compare the power of BSI-determined rates of cortical atrophy with our previously published rates of ERC and hippocampal atrophy for detecting group differences in longitudinal change. We tested the hypothesis that elderly control subjects and AD patients both have BSI measurements of whole brain atrophy that are greater than zero. Because reports in the literature suggest that AD pathology begins in and causes focal damage to the ERC and hippocampus, we also tested the hypothesis that rates of ERC and hippocampal volume change are greater than BSI measurements of whole brain atrophy in AD subjects.

METHODS

Subjects

Table 1 summarizes the demographic information of 20 AD patients and 22 control subjects. Subjects were recruited through advertisements or were referred by memory clinics in the greater San Francisco Bay Area. All subjects were evaluated at Alzheimer centers at the University of California at San Francisco or Davis with a previously described battery of standard neuropsychological tests.[16] Subjects also underwent at least two MRI scans. The mean interscan interval was 2.0 ± 0.7 years in the control group and 1.8 ± 0.7 years in the AD group. The rates of hippocampal and ERC atrophy in these subjects have been reported in an earlier publication.[17] However, due to excessive motion artifact, data from 3 control subjects in the previous study were excluded from analyses in the present study.

Image Acquisition

MRI data were obtained on a 1.5-T Siemens Vision System (Siemens, Inc., Iselin, NJ), using a standard quadrature head coil. Structural MRI data were acquired using a double spin-echo sequence (DSE) with TR/TE1/TE2 (repetition and echo times) = 2,500/20/80-millisecond timing, 1.00 × 1.25 mm^2 in-plane resolution, and about 50 contiguous 3.00-mm-thick axial slices oriented along the optic nerve as seen from a midsection sagittal scout MRI. In addition, a volumetric magnetization-prepared rapid gradient echo (MPRAGE) sequence was acquired with TR/TE/TI = 10/7/300-millisecond timing, 15° flip angle, 1.00 × 1.00 mm^2 in-plane resolution, and approximately 1.40-mm-thick coronal partitions and oriented orthogonal to the image planes of DSE. An experienced rater (A.T.D.) performed manual editing of the ERC using T1-weighted images from MPRAGE. Boundaries of the ERC were defined using the protocol described by Insausti et al[4] Boundaries of the hippocampus were defined using the SNT semi-automated atlas based measurement described in previous publications.[24–25] Rater reliability values, expressed as a coefficient of variation, were 2.4% for ERC measurements and 2.6% for hippocampal measurements, as previously reported.[17]

BSI Method

Our application of the BSI method is largely the same as that previously described by Peter Freeborough and Nick Fox.[22] Briefly, this involved (1) Linear registration of two T1 images using AIR V3.08,[26] (2) Image calibration by dividing each pixel intensity by a mean value selected from a sample of gray and white matter in that image, (3) Windowing of each calibrated image so that values below a minimum (I1) or above a maximum (I2) percentage cutoff are set to the minimum or maximum value, and (4) Creation of a subtraction image in which the windowed image (resulting from step 3) of the later scan is subtracted from the windowed image of the earlier scan. Subsequently, each pixel is multiplied by a scaling factor, defined as (1/(I2-I1)). This scaling factor adjusts for the size of the intensity window (I2-I1). On this subtraction image, intensities range from +1.0 (i.e., a full pixel of tissue loss) to − 1.0 (i.e., a full pixel of tissue gain). 5) Boundary regions are identified and change is summed throughout the boundary region on the subtraction image. The boundary region is defined as the logical ‘‘OR’’ of the tissue masks (expanded by one pixel) with the logical ‘‘AND’’ of those masks (reduced by one pixel) removed as a final step.

Our implementation of the BSI method differed from that described by Freeborough and Fox in two aspects: First, we used a nonparametric algorithm for bias field corrections, know as N3[27] to correct image non-uniformity prior to creating the subtraction image. Second, we identified cortical and ventricular regions of the brain based on existing tissue classifications and intracranial vault (ICV) definitions generated from multiple datasets previously analyzed in our laboratory.[9] This method of identifying cortical and ventricular regions has several advantages. It results in BSI region-of-interest masks that are separated into cortical and ventricular regions. It is more likely to exclude areas of white matter (WM) disease that are not immediately adjacent to the ventricle. Finally, it has the potential to reduce the confounding effects of WM disease on BSI measurements of tissue loss.

The BSI method is most effective when calibrated to data characteristics that are specific to the MRI sequences applied. Thus, the primary goal of calibration is to identify optimal values for I1 and I2, the lower and upper intensity fractions of the subtraction image windowed in the analysis.

BSI Calibration – Affine data

In the present study, we use two criteria for identifying an ideal set of calibration values. Because simulated data suggest that BSI has a tendency to underestimate actual tissue loss, we sought calibration values that would result in large measurements of change. We also sought calibration values that would result in minimum error when applied to images with known change or images with multiple measurements of the same change. To produce a series of known volume changes, we applied affine transformations to T1-weighted images. The apparent tissue change generated with the affine transformations varied from 6% tissue loss to 6% tissue gain in increments of 0.5%. Next, we applied BSI to unmodified images acquired at the first timepoint and affine-modified images acquired at the later timepoint. Resulting measurements of tissue loss or gain were then corrected for the actual change measured in each image pair when no affine transformation was applied. Table 2 shows the results of this analysis applied to five different calibration values for 2 different subjects. The table displays the summed percentage of simulated change measured with BSI.

BSI Calibration – Multiple time point data

We assessed the reproducibility of our BSI measurement with data from 15 subjects with 3 or 4 serial scans. In each case, we calculated BSI values for scans acquired at the first and second timepoints, the second and third timepoints, etc. (i.e., short interval BSIs). We also calculated BSI values for scans acquired at the first and last timepoints (i.e., long interval BSI). We define the difference between long interval BSI and the sum of the short interval BSIs as the ‘‘calibration error’’. Errors in reproducibility, the average of the absolute value of the ‘‘calibration error’’ for the 15 test cases, are reported in Table 3. The absolute value is used so that the error in each case is counted fully regardless of sign. Calibration values of I1 = 40, I2 = 90 resulted in the smallest reproducibility error in our test dataset. We also report the average signed error in Table 3. This is the sum of the ‘‘calibration errors’’ with the sign preserved. A large negative signed error indicates that the calibration values resulted in a bias toward measuring a smaller percentage of tissue loss as the total amount of loss increased. Because of this bias, the sum of the short interval BSIs will be greater than the long interval BSI. Our analyses indicate that calibration values of I1 = 40, I2 = 90 and I1 = 45, I2 = 95 result in the smallest signed error. Finally, we directly compared the sum of the short interval BSIs with the long interval BSI using a 2-tailed *t* test. This analysis revealed that the signed error was not significant for calibration values of I1 = 40, I2 = 90 but was significant for smaller values.

Analysis of the affine data suggested that calibration values of I1 = 35, I2 = 85 and I1 = 40, I2 = 90 provide a measurement of change that is closest to the actual simulated change values.

Analysis of the multiple timepoint data suggested that calibration values of I1 = 40, I2 = 90 and I1 = 45, I2 = 95 provide the smallest reproducibility errors and the smallest bias tied to size-of-change. Based on these data, we selected calibration values of I1 = 40, I2 = 90 for all subsequent BSI analysis in this study.

RESULTS

Table 4 summarizes measurements of whole brain atrophy determined by ventricular, cortical, and total BSI. The annual rates of ERC and hippocampal atrophy, reported previously[17] are also shown in this table. Both control subjects and AD patients had BSI measurements of whole brain atrophy that were greater than zero ($P < 0.01$). Relative to controls, AD patients had greater cortical ($P < 0.05$), ventricular ($P < 0.01$), and total ($P < 0.01$) BSI measurements of brain atrophy. AD patients also had greater rates of ERC and hippocampal atrophy ($P < 0.01$) than controls, as previously reported.[17] In AD patients, all measurements of tissue atrophy were significantly different from each other ($P \leq 0.05$, 2-tailed, paired). In controls, ventricular ($P \leq 0.05$, 2-tailed, paired) and cortical ($P < 0.01$, 2-tailed, paired) BSI measurements were different from all other measurements of tissue atrophy; however, total BSI measurements were different only from ERC atrophy rates ($P < 0.05$, 2-tailed, paired). No other atrophy measurements in the control group were significantly different from each other. Among the different BSI measurements, ventricular BSI had the largest and cortical BSI had the smallest effect size. However, hippocampal and ERC atrophy rates both had larger effect sizes than BSI for detecting differences between AD patients and elderly controls.

In clinical trials that measure cerebral atrophy as a marker of disease progression, it is important to have sufficient power to detect a treatment effect. Therefore, we estimated the sample sizes necessary for using annualized rates of ventricular, cortical, and total BSI measurements of brain atrophy and ERC and hippocampal atrophy. The results of the sample size calculations are summarized in Table 5. This table can be interpreted as follows: For a drug with an anticipated ability to reduce the rate of cerebral atrophy by 20% over 1 year, 88 patients will be needed in each arm if hippocampal atrophy is used, 99 patients if ventricular BSI atrophy is used, 109 patients if ERC atrophy is used, 204 patients if total BSI atrophy is used, and 356 patients if cortical BSI atrophy is used.

Finally, we used logistic regression to explore the best explanatory variables for classifying AD patients from controls. We applied the analysis to additive combinations of annualized ventricular BSI percentage, annualized ERC percentage loss, and annualized hippocampal percentage loss using the following criteria to search for the optimal additive combination: The first variable included explained the most variance, the next variable included explained the most variance not explained by the first variable etc. until a variable was reached that did not explain significant extra variance. Results indicate that the optimal combination of measurements was annualized percentage ERC loss plus annualized ventricular BSI percentage. Annualized ERC loss alone explained 62% of the variation ($P < 0.001$) while annualized ventricular BSI percentage explained an additional 12% of the variance ($P < 0.01$). Although annualized hippocampal percentage loss explained only 0.09% ($P = 0.82$) of the added variance, rates of hippocampal and ERC atrophy are highly correlated. Therefore, it would be expected that annualized hippocampal loss plus ventricular BSI would provide similar discriminatory power as annualized ERC loss plus annualized ventricular BSI.

DISCUSSION

In this study, we implemented the BSI method as described by Freeborough and Fox[22] and found it to be valid and reliable. Using this method, we found that (1) control subjects and AD patients both had significant rates of brain tissue loss, (2) AD patients had higher rates of tissue

loss than controls, (3) rates of ERC and hippocampal atrophy were significantly higher than the rates of BSI-measured whole brain atrophy, (4) rates of ERC and hippocampal atrophy were lower and less variable than rates of BSI-measured ventricular atrophy, (5) rates of ERC and hippocampal atrophy had greater statistical power to detect treatment effects than whole brain BSI, (6) rates of ERC and ventricular BSI combined were the best explanatory variables for classifying AD from controls.

The primary goals of this study were to (1) implement the BSI method as described by Freeborough and Fox,[22] (2) validate this technique for use with our data using affine transformations, and (3) model atrophy and test reproducibility of the BSI method by using serial scans of the same subject. Use of affine transformations to simulate tissue loss had several limitations. First, this method did not allow us to take into account the contrast changes that occur due to subvoxel tissue shifts. Second, affine transformations ignored the resolution blurring due to the finite width of the modulation transfer function of MRI. These limitations may partially explain the marked under-estimation of simulated change by the BSI method. Nonetheless, affine simulation allowed us to measure the validity of the BSI method against a known standard. We next examined the reproducibility of the BSI method with our dataset by analyzing MRI data from subjects with 3 or 4 serial scans. With the calibration values selected for this study, we found no significant differences between BSI measurements obtained from scans acquired closest to each other in time (i.e., summed small measured change) and BSI measurements obtained from scans acquired farther apart in time (i.e., single larger measured change). Because analysis of the three and four timepoint data incorporates and compounds all sources of measurement error (e.g., MRI instrument noise, biologic noise, and variability in the application of the BSI method), this finding suggests that the BSI method is highly robust. These results further suggest that the proportion of tissue loss captured by BSI is not biased with respect to the size of that loss. In summary, our calibration of the BSI method with affine transformations and serial scans demonstrated that we were able to successfully measure known quantities of tissue loss in a consistent manner with this technique and that this technique was highly reliable in our hands.

When we applied the BSI method to clinical MRI data, we found that control subjects and AD patients both had BSI measurements of whole brain atrophy that were greater than zero. Moreover, ventricular, total, and cortical BSI measurements were all able to detect larger rates of whole brain atrophy in AD patients compared with control subjects. AD patients also exhibited greater rates of hippocampal and ERC atrophy than controls, replicating our previous findings.[16] All the different methods of quantifying tissue atrophy (i.e., BSI, hippocampal, and ERC atrophy rates) were significantly different from each other in AD patients. However, in control subjects, only ventricular and cortical BSI measurements were different from the other methods of quantifying tissue atrophy. Total BSI measurements were different from only from ERC atrophy rates in controls. A comparison of effect sizes of the different BSI measurements revealed that ventricular BSI had the largest and cortical BSI had the smallest effect size. This is consistent with findings reported in a recent paper by Gunter and colleagues that compared different techniques for measuring brain atrophy rates from serial MRIs.[23] Using the separation in atrophy rate between cognitively normal elderly subjects and AD patients as the standard, Gunter et al found greater separation between clinical groups with ventricular than whole brain measures. However, in the present study, hippocampal and ERC atrophy rates both had larger effect sizes than BSI for detecting differences between AD patients and controls.

The second objective of this study was to compare different methods of measuring atrophy rates in the same subjects to determine the method most sensitive to group differences in longitudinal change. Our analyses revealed that measurements of percent hippocampal loss over time had the largest effect, followed by percent ERC loss, percent ventricular BSI, percent

whole brain BSI, and finally percent cortical BSI. Our sample size calculations revealed that hippocampal volume measurements required the smallest sample to measure a given treatment effect, followed by ventricular BSI, ERC, total BSI, and cortical BSI.

Our sample size calculations for detecting a 50% reduction in hippocampal volume are similar to those reported by Jack and colleagues[28] in a publication where they followed a large group of AD patients, utilizing hippocampal volume as the primary MR measure of disease progression, in a therapeutic trial of milameline. More recently, this group has compared different methods of measuring rates of brain atrophy from serial MRIs by examining annualized changes in the volumes of the hippocampus, ERC, whole brain and ventricle.[6] While our sample size calculations for detecting a 50% difference are also similar to values reported by Jack and colleagues,[6] our calculations for 25% differences differed in the sample size required for hippocampal volume and whole brain measures. However, it is doubtful that these differences, likely the result of measurement error and sample differences, are statistically distinguishable.

In summary, the effect size and power calculations of the present study suggest that longitudinal measurements of ERC and hippocampal atrophy may be more sensitive to AD pathology and to potential disease modifying agents than BSI measurements of whole brain atrophy. This is consistent with reports that AD pathology begins in and causes focal damage to the ERC and hippocampus. Thus, longitudinal measurements of hippocampal and ERC atrophy, as well as BSI measures of ventricular atrophy, may be better surrogate markers than BSI measures of global atrophy for forthcoming trials in AD.

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TABLE 1

Subject Demographic and Clinical Information

	Controls	AD Patients
N	22	20
Male:female ratio	13:9	8:12
Age (years)	76.7 ± 8.1	75.3 ± 7.2
Education (years)	15.6 ± 3.7	15.2 ± 2.0
Inter-scan interval (years)	2.0 ± 0.7	1.8 ± 0.7
Timepoint 1 MMSE	29.1 ± 1.1	22.4 ± 5.9
Timepoint 2 MMSE	29.5 ± 2.2	19.8 ± 7.0
Timepoint 1 CDR	0.1 ± 0.1	0.9 ± 0.5
Timepoint 2 CDR	0.2 ± 0.2	1.1 ± 0.6

TABLE 2

Summed Percentage of BSI-Measured Simulated Change With Different Calibration Values

	I1 = 25, I2 = 75	I1 = 30, I2 = 80	I1 = 35, I2 = 85	I1 = 40, I2 = 90	I1 = 45, I2 = 95
Subject 1	0.633 ± 0.034	0.674 ± 0.028	0.694 ± 0.024	0.685 ± 0.025	0.647 ± 0.030
Subject 2	0.534 ± 0.047	0.576 ± 0.037	0.600 ± 0.030	0.599 ± 0.030	0.573 ± 0.037

Note: Affine-induced change was ± 6% in increments of 0.5%.

TABLE 3

BSI Calibration Values With Multiple Timepoint Data

	I1 = 25, I2 = 75	**I1 = 30, I2 = 80**	**I1 = 35, I2 = 85**	**I1 = 40, I2 = 90**	**I1 = 45, I2 = 95**
Average tissue loss (cc)	26.99	30.53	33.06	34.16	33.86
Errors in reproducibility (cc)*	2.3 ± 1.2	1.8 ± 1.1	1.2 ± 0.9	0.7 ± 0.6	0.8 ± 0.5
Averaged signed error (cc)	− 2.3	− 1.8	− 1.1	− 0.4	0.3
Difference between summed short and long intervals†	< 0.01	< 0.01	< 0.01	0.10	0.23

*absolute value of the summed short intervals minus the long interval.

†*p*-value from 2-tailed *t*-test.

TABLE 4

Amount and Effect Size of BSI, ERC and Hippocampus Tissue Loss, MMSE and CDR Change in AD Patients and Controls

	Ventricular BSI	Cortical BSI	Total BSI	ERC Volume	Hippocampal Volume	MMSE Change	CDR Change
AD patients	10.97 ± 4.74	0.67 ± 0.55	1.28 ± 0.80	7.13 ± 3.24	5.92 ± 2.42	1.88 ± 2.67	0.10 ± 0.19
Controls	3.34 ± 3.77†	0.38 ± 0.31*	0.49 ± 0.39†	1.33 ± 1.96†	0.90 ± 1.79†	− 0.29 ± 1.47†	0.04 ± 0.11
Effect size	1.8	0.6	1.3	2.2	2.4	1.0	0.4

Ventricular, cortical, and total BSI volumes: annualized percentage tissue loss/year; normalized to timepoint 1 tissue volume.

ERC and hippocampal volumes: annualized percentage tissue loss/year.

MMSE Change: TP1-TP2/inter-test interval; positive value represents cognitive decline.

CDR Change: TP2-TP1/inter-test interval; positive value represents cognitive decline.

* $p < 0.05$,

† $p < 0.01$ Controls vs AD, 2-tailed *t*-test with heterogeneous distributions.

TABLE 5

Sample Sizes Required for Pharmaceutical Study

Treatment Effect Magnitude	Ventricular BSI	Cortical BSI	Total BSI	ERC Volume	Hippocampal Volume
10%	393	1422	816	435	351
20%	99	356	204	109	88
25%	63	228	204	70	57
30%	44	158	91	49	39
40%	25	89	51	28	22
50%	16	57	33	18	15

90% power to detect change with a confidence of $p = 0.05$, 2-tailed analysis.