Quantitative Evaluation of Automated Skull-Stripping Methods Applied to Contemporary and Legacy Images: Effects of Diagnosis, Bias Correction, and Slice Location

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ABSTRACT

Performance of automated methods to isolate brain from non-brain tissues in magnetic resonance (MR) structural images may be influenced by MR signal inhomogeneities, type of MR image set, regional anatomy, and age and diagnosis of subjects studied. The present study compared the performance of four methods, Brain Extraction Tool (BET, Smith 2002); 3dIntracranial (Ward 1999, in AFNI); a Hybrid Watershed algorithm (HWA, Segonne et al. 2004, in FreeSurfer); and Brain Surface Extractor (BSE, Sandor and Leahy 1997; Shattuck et al. 2001), to manually stripped images. The methods were applied to un-corrected and bias-corrected datasets; Legacy and Contemporary T1-weighted image sets; and four diagnostic groups (depressed, Alzheimer's, young and elderly control). To provide a criterion for outcome assessment, two experts manually stripped six sagittal sections for each dataset in locations where brain and non-brain tissue are difficult to distinguish. Methods were compared on Jaccard similarity coefficients, Hausdorff distances, and an Expectation-Maximization algorithm. Methods tended to perform better on contemporary datasets; bias correction did not significantly improve method performance. Mesial sections were most difficult for all methods. Although AD image sets were most difficult to strip, HWA and BSE were more robust across diagnostic groups compared with 3dIntracranial and BET. With respect to specificity, BSE tended to perform best across all groups, whereas HWA was more sensitive than other methods. The results of this study may direct users towards a method appropriate to their T1-weighted datasets and improve the efficiency of processing for large, multi-site neuroimaging studies.

INTRODUCTION

Quantitative morphometric studies of magnetic resonance (MR) images often require a preliminary step to isolate brain from extracranial or "non-brain" tissues. This preliminary step, commonly referred to as "skull-stripping," facilitates image processing such as surface rendering, cortical flattening, image registration, de-identification, and tissue segmentation. To be feasible for large-scale, multi-site studies, such as the projects supported by the Biomedical Informatics Research Network (BIRN), skull-stripping methods should be accurate and relatively automated. Numerous automated skull-stripping methods have been proposed (e.g., Dale et al. 1999; Hahn and Peitgen 2000; Sandor and Leahy 1997; Segonne et al. 2004; Shattuck et al. 2001; Smith 2002; Ward 1999) and are widely used. However, the performance of these methods, which rely on signal intensity and signal contrast, may be influenced by numerous factors including MR signal inhomogeneities, type of MR image set, gradient performance, stability of system electronics, and extent of neurodegeneration in the subjects studied (Smith 2002). Sub-optimal outcomes of automated processing often require manual adjustment of method parameters and/or manual editing to create a suitable skull-stripped volume. Manual adjustment increases processing time and the level of required expertise, and potentially introduces inaccuracies or inconsistencies. There is a clear need to better understand the factors that influence the performance of various automated skull-stripping methods. The results of such studies may direct users towards a method appropriate to their particular datasets and improve the efficiency of processing for large, multi-site neuroimaging studies.

In addition to manual approaches, the primary bases for skull-stripping include intensity threshold, morphology, watershed, surface-modeling, and hybrid methods (e.g., Dale et al. 1999; Hahn and Peitgen 2000; Sandor and Leahy 1997; Segonne et al. 2004; Shattuck et al. 2001;

Smith 2002; Ward 1999). Although perhaps the most accurate, manual methods require significant time for completion, particularly on high-resolution volumes that often contain more than 120 slices. Furthermore, rigorous training is crucial to develop reliable standards that reduce the subjectivity of decisions. Depending on whether a study collects single contrast images or images with varying contrast, threshold methods define minimum and maximum values along one or more axes representing voxel intensities for univariate or multivariate histograms (e.g., DeCarli et al. 1992). Morphology or region-based methods rely on connectivity between regions, such as similar intensity values, and often are used with intensity thresholding methods (e.g., 3dIntracranial, Ward 1999; in AFNI, Cox 1996). Other approaches combine morphological methods with edge detection (e.g., Brain Surface Extractor, Sandor and Leahy 1997; Shattuck et al. 2001). Although watershed algorithms use image intensities, they operate under the assumption of white matter connectivity (e.g., Hahn and Peitgen 2000). Watershed algorithms try to find a local optimum of the intensity gradient for pre-flooding of the defined basins to segment the image into brain and non-brain components. That is, the volume is separated into regions connected in 3D space, and basins are filled up to a pre-set height. Surface-model-based methods, in contrast, incorporate shape information through modeling the brain surface with a smoothed deformed template (e.g., Dale et al. 1999; Brain Extraction Tool Smith 2002). A recent Hybrid Watershed method (HWA, Segonne et al. 2004; in FreeSurfer, Dale et al. 1999; Fischl and Dale 2000; Fischl et al. 1999) incorporated the watershed techniques of Hahn and Peitgen (2000) with surface-based methods of Dale et al. (1999). The resulting HWA method relies on white matter connectivity to build an initial estimate of the brain volume and applies a parametric deformable surface model, integrating geometric constraints and statistical atlas information, to locate the brain boundary.

A few previous studies of available automated skull-stripping methods have employed quantitative error rate analyses to compare the potential advantages and disadvantages of each approach (Boesen et al. 2004; Lee et al. 2003; Segonne et al. 2004; Smith 2002). In a careful evaluation of automated skull-stripping methods, Smith (2002) reviewed various approaches, introduced the Brain Extraction Tool (BET), and examined the automated performance of BET and two commonly available methods relative to manually skull-stripped volumes. The automated performance of BET (v. 1.1) was compared to the performance of a modified version of AFNI's 3dIntracranial (Ward 1999; in AFNI v. 2.29, Cox 1996) and Brain Surface Extractor (BSE v. 2.09, Sandor and Leahy 1997; Shattuck et al. 2001). The test data was acquired across many scanners and included primarily T1-weighted images as well as some T2 and PD-weighted image sets.. Analysis of a percent error measure revealed that BET produced significantly fewer errors relative to the modified AFNI and BSE methods across all dataset types and within only the T1-weighted datasets, although the difference was smaller in the latter comparison. Relative to the hand-segmented volumes, BET tended to produce a slightly smaller and more smoothed volume. Smith (2002) also examined the effect of systematically varying software parameters for each dataset. The findings suggested that all three methods performed similarly well under individually optimized conditions, particularly for T1-weighted images. The optimal parameters selected, however, did not reveal any consistent within-sequence values that might be automatically applied; thus, BET was judged the most robust and successfully automated application examined when global parameters were used. The author (Smith 2002) suggested that performance of these automated methods might be improved with pre-processing, such as the correction of field inhomogeneities, although most bias correction algorithms require datasets be skull-stripped prior to their application.

Subsequently, Lee et al. (2003) reported an evaluation of BET, BSE, and ANALYZE 4.0 as well as the authors' local Region Growing Tool (RG) relative to manual skull-stripping. BET and BSE were applied in an automated fashion whereas ANALYZE and RG required manual interaction. All methods were tested on the T1-weighted Montreal Neurological Institute's BrainWeb phantom at different levels of noise and on T1-weighted human datasets from the Internet Brain Segmentation Repository. Similarity indices that incorporated both false positive and false negative rates suggested no difference between methods for the small set of phantom data, although BSE excluded some brain tissue. Examination of the human data revealed that RG was more similar to the manual criterion than were the other three methods. The segmentation error rates suggested that BET included more non-brain tissue, whereas BSE and ANALYZE both removed some brain tissue. The authors suggested that the automated processing results were somewhat inaccurate, but that a two-step processing procedure utilizing both the semi-automated and automated methods may be useful.

Two more recent studies have examined skull-stripping performance with slightly different approaches. Boesen et al.(2004) examined the performance of BET (v. 1, Smith 2002), BSE (v. 2.99, Sandor and Leahy 1997; Shattuck et al. 2001), SPM (2b), and the Minneapolis Consensus Strip (MCS; intensity based thresholding and the use of BSE). Parameters for BET and BSE were examined in two ways 1) optimized parameters based on three training volumes and then applied in an automated fashion, and 2) subject-specific parameter settings based on an exhaustive review of all parameter combinations, selecting the outcome that produced the least misclassified tissue. Two sets of T1-weighted volumes were stripped and compared to manually stripped volumes. Results suggested that MCS and, in some cases, BSE tended to outperform the other methods, although MCS was least affected by site-related differences. Although MCS

requires more user interaction, the authors suggest that such a hybrid method may improve performance.

Finally, a relatively new hybrid approach, Hybrid Watershed (HWA, Segonne et al. 2004) has been compared to the performance of four skull-stripping methods: FreeSurfer's original method (Dale et al., 1999); BET (Smith 2002); a watershed algorithm (Hahn and Peitgen, 2000); and BSE (Shattuck et al., 2001). Forty-three T1-weighted images from two sites were used, and automated performance was compared to manually skull-stripped volumes. HWA produced the highest similarity coefficients for both datasets, BSE performed second best on the higher quality dataset, whereas BET often included additional non-brain tissue. In an evaluation of the risk reflecting a higher cost related to removing brain tissue than to adding non-brain tissue, HWA typically included all brain tissue and found the pial surface in most datasets.

Although these studies launched the quantitative evaluation of skull-stripping methods, important questions need to be answered before automated skull-stripping methods can be faithfully used in large-scale image analysis. First, little published research has focused on the impact of subject variables, such as age and diagnosis, on the accuracy of skull-stripping routines. Yet both aging and common neurodegenerative diseases, such as Alzheimer's disease (AD), reduce image contrast and adversely homogenize histograms, create partial volume effects, and obscure edges. Second, although Smith (2002) suggested that bias correction of MR signal inhomogeneities might improve results of automated skull-stripping programs, to the best of our knowledge, no studies have directly compared skull-stripping of bias corrected and uncorrected images. Third, large-scale image sets frequently contain legacy images collected over many years. Legacy image sets often include images of varying quality as gradients, software and electronic components of MR systems change over time. Little has been published

regarding how results of skull-stripping of legacy images compares with results from more homogenous, contemporary image sets. Fourth, previous skull-stripping studies have not evaluated the impact of local anatomy on skull-stripping results. Yet, in our experience, separation of skull from brain can be especially difficult in some regions, such as the anterior or posterior fossa, where subtle gradations of white matter, gray matter, soft tissue, and bone occur in proximity. Finally, most previous studies used one metric to measure the accuracy of skull-stripping methods. Multidimensional metrics of performance, such as those presented in this paper, may provide a better description of performance comparisons, as they can measure several aspects of similarity (Hand et al. 2001).

In the present study we investigated the effects of age and diagnosis, bias correction, type of image set (Legacy vs. Contemporary), and local anatomy (Slice location) on the performance of four automated skull-stripping methods. We predicted that MR brain images obtained from older individuals and those obtained from patients with AD would be less accurately skull-stripped than images from other groups. We expected that bias correction would improve the performance of 3dIntracranial due to its reliance on fitting the intensity histogram, whereas other methods also might be improved to varying extents. We also predicted less accurate skull-stripping of legacy images, where data are less likely to meet contemporary quality standards for image acquisition. And finally, given the difficulties distinguishing posterior fossa soft tissue from adjacent brain, we hypothesized that mesial brain slices, which include large posterior fossa regions and voxels including both partially-volumed tissue and CSF, would be less accurately skull-stripped than other regions. This assessment of local anatomical effects of skull-stripping, rather than examining the whole brain volume, is particularly relevant for subsequent morphometric studies of these regions of interest.

The methods studied herein – 3dIntracranial (Ward 1999; in AFNI, Cox 1996), BET (Smith 2002), HWA (Segonne et al. 2004; in FreeSurfer, Dale et al. 1999; Fischl and Dale 2000; Fischl et al. 1999), and BSE (Sandor and Leahy 1997; Shattuck et al. 2001) – encompass most of the commonly used algorithms for skull-stripping. We evaluated the most current software versions with expert input from developers to select the appropriate parameters for automated application. To provide a reasonable criterion, or "gold standard," for outcome assessment, two experts manually skull-stripped six sagittal sections in standard locations for all datasets. These manual outcomes were compared to automated outcomes with the Jaccard similarity index (JSC; Jaccard 1912; Zou et al. 2004a; Zou et al. 2004b), which expresses the overlap between automated and manual skull-stripping for each slice, and the Hausdorff distance measure (Huttenlocher et al. 1993), which examines the degree of mismatch between the contours of two image sets, providing information on shape differences. Then, all methods, including manual skull-stripping, were compared with an Expectation-Maximization algorithm (EM; Warfield et al. 2004; Zou et al. 2004b), which provides both sensitivity and specificity information.

MATERIALS AND METHODS

MR Image Sets: Data collected using two common structural gradient-echo (SPGR) T1-weighted pulse sequences were examined. All datasets were collected on a GE 1.5T magnet at the VA San Diego Healthcare System MRI Facility that was subject to regular hardware and software upgrades over time. *Legacy Datasets* were collected over four years in the mid to late 1990s (June of 1994 and July of 1998): TR=24ms, TE=5ms, NEX=2, flip angle=45 degrees, field of view of 24cm, and contiguous 1.2 mm sections (sagittal acquisition). *Contemporary Datasets* were collected between May of 2002 and April of 2003*:* TR=20 ms, TE=6ms, NEX=1, flip angle=30 degrees, field of view of 25cm, and contiguous 1.5 mm sections (sagittal

acquisition). Of the 32 datasets examined, 16 were *Legacy*, and 16 were *Contemporary* (Table I). The University of California, San Diego institutional review board approved all procedures, and written informed consent was obtained from all subjects.

INSERT TABLE I ABOUT HERE

Diagnostic Groups: For each MR Image set of 16 datasets, four different diagnostic groups were represented, including depressed (DEPR), Alzheimer's (AD), young (YNC) and elderly normal controls (ENC), with four subjects from each group (Table I). The YNC and DEPR groups were similar on age and education, as were the ENC and AD groups. Each diagnostic group from Legacy and Contemporary datasets were similar on age and gender, and the AD groups were also matched on disease stage as measured with the Mini-Mental State Examination (MMSE, Folstein et al. 1975).

Bias Correction: To correct image bias we employed the Non-parametric Non-uniform intensity Normalization method (N3, Sled et al. 1998), which uses a locally adaptive bias correction algorithm. This method was chosen for its applicability to un-skull-stripped image sets and for its excellent performance compared with other bias correction methods (Arnold et al. 2001). All 32 datasets were studied with and without prior bias correction with N3.

Manual Skull-Stripping: Two anatomists manually skull-stripped six sagittal slices from each raw MR image set to provide a criterion, or "gold standard," against which to judge the automated skull-stripping outcomes. Both anatomists (CPC and SM) were experienced neuroimaging experts with training in neuroscience and neuroanatomy. Both anatomists, in collaboration with a trained neuroanatomist (CFN), completed four sample datasets not included

in the present study to formalize a set of criteria for skull-stripping. If anatomists were unable to definitively classify tissue as brain or non-brain, they were instructed to conservatively include this tissue. Anatomists were provided with all orthogonal views, which provided them with better spatial information to make their decisions. Comparisons of the two anatomists manually skull-stripped datasets are examined in the Results section. Six sagittal slices were selected to assess skull-stripping on mid-sagittal slices and on lateral slices passing through the anterior medial temporal, anterior inferior frontal, posterior cerebellar regions, and posterior occipital regions (Figure 1). Brain and non-brain tissues in these regions are often difficult to distinguish on T1-weighted images, particularly in the posterior fossa (Figure 1, Slices 4-6A) and anterior temporal lobe (Figure 1, Slices 4-6B). The mid-line sections, in addition to including the posterior fossa, often contain cerebrospinal fluid that may be difficult to distinguish from partially-volumed adjacent cortex (Figure 1, Slice 4C and 4D).

INSERT FIGURE 1 ABOUT HERE

***Automated methods and parameter selection*:** For each method except 3dIntracranial (the developer choose not to participate), developers of the automated methods were provided with two sample datasets, one young, healthy control from the Legacy image set and one from the Contemporary image set. We asked developers to suggest the most appropriate parameters for the *automated* application of their software using the image sets provided. These values were used for all analyses in this study. The selected parameters and the computational processing times are defined within each method description below. The elapsed average processing time per dataset is based on the use of a Dell Pentium Xeon 2.2 or 2.4 GHz with 512 MB RAM.

1. 3dIntracranial (3dIntra, Ward 1999); in AFNI v. 2.29 (Cox 1996). 3dIntra, included in the Analysis of Functional NeuroImage (AFNI) library, involves several steps. First a three-compartment Gaussian model is fit to the intensity histogram. A downhill simplex method is used to estimate means, standard deviations, and weights of presumed gray matter, white matter, and background compartments. From these estimated values, a probability density function (PDF) is derived to set upper and lower signal intensity bounds as a first step to identify brain voxels. Upper and lower bounds are set to exclude non-brain voxels. Next a connected brain region within each axial slice is identified by finding the complement of the largest non-brain region within that slice, under the constraint that the area of connected brain becomes smaller as the segmentation moves from the center of the brain. The union of such connected brain regions is formed as this slice-by-slice segmentation is repeated for sagittal and coronal slices. Next a 3D envelope based on local averaging smoothes brain edges. Finally, brain voxels with few brain voxel-neighbors are excluded from brain, whereas holes with many brain-voxel-neighbors are included. 3dIntracranial is integrated in the extensive library of AFNI image analysis tools, and its public source code is freely available at http://afni.nimh.nih.gov/afni/. The 3dIntracranial parameters utilized in the present study were the default parameters, described as follows: minimum voxel intensity limit = internal probability density function (PDF) estimate for lower bound; maximum voxel intensity limit = internal PDF estimate for upper bound; minimum voxel connectivity to enter m=4; maximum voxel connectivity to leave n=2; and spatial smoothing of segmentation mask.

2. Brain Extraction Tool - Version 1.2 (BET, Smith 2002). BET employs a deformable model to fit the brain's surface using a set of "locally adaptive model forces." This method estimates the minimum and maximum intensity values for the brain image, a "centre of gravity"

of the head image, and head size based on a spherical equivalent, and subsequently initializes the triangular tessellation of the sphere's (head's) surface. BET v. 1.2 is freely available in the FMRIB FSL Software Library (http://www.fmrib.ox.ac.uk/fsl/). The developer recommended the default parameters for automated processing of both the legacy and contemporary images. The parameters utilized in the application herein are the default parameters, described as follows: fractional intensity threshold = 0.5; vertical gradient in fractional intensity threshold = 0.

3. Hybrid Watershed Algorithm - Version 1.21 (HWA, Segonne et al. 2004); in FreeSurfer (Dale et al. 1999; Fischl and Dale 2000; Fischl et al. 1999). This HWA method is a hybrid of a watershed algorithm (Hahn and Peitgen 2000) and a deformable surface model (Dale et al. 1999) that was designed to be conservatively sensitive to the inclusion of brain tissue. In general, watershed algorithms segment images into connected components, using local optima of image intensity gradients. HWA uses a watershed algorithm that is solely based on image intensities; the algorithm, which operates under the assumption of the connectivity of white matter, segments the image into brain and non-brain components. A deformable surface-model is then applied to locate the boundary of the brain in the image. A final option under development will incorporate an atlas-based analysis to verify the correctness of the resulting surface, modify it if important structures have been removed, and locate the best-estimate boundary of the brain in the image. In HWA v. 1.21, the atlas-based option was not finalized, resulting in a considerably better performance without the atlas-based option. Therefore, the present study examined HWA without the atlas option. HWA v. 1.21 is freely available as a component of the FreeSurfer software package at http://surfer.nmr.mgh.harvard.edu/. HWA developers recommended the default parameters for automated processing of both legacy and contemporary images. The parameters utilized in this study are the hard-coded default

parameters of HWA without the atlas option.

4. Brain Surface Extractor –Version 3.3 (BSE, Sandor and Leahy 1997; Shattuck et al. 2001). BSE, designed to fit the surface of all CNS regions, including the spinal cord, uses a sequence of anisotropic diffusion filtering, Marr-Hildreth edge detection, and morphological processing to segment the brain within whole head MRI. In MRI of the brain, the boundary between the brain and the skull will produce a contour in the Marr-Hildreth edge detection result. Additional gradients in the image may otherwise act as decoys for automated methods; for this reason, BSE uses anisotropic diffusion filtering (Perona and Malik 1990). This is a spatially adaptive edge-preserving filtering technique that smoothes small image gradients while preserving larger variations that correspond to strong edges in the image. Because of noise in the image and actual anatomic connections such as optic tracts, the brain contour that BSE generates may not separate the brain from the rest of the head. BSE breaks remaining connections between the brain and the other tissues in the head using a morphological erosion operation. After identifying the brain using a connected component operation, BSE applies a corresponding dilation operation to undo the effects of the erosion. As a final step, BSE applies a morphological closing operation that fills small pits and holes that may occur in the brain surface. BSE v. 3.3 is freely available for download from the BrainSuite website, http://neuroimage.usc.edu/brainsuite/. The developers recommended the following parameters for automated processing of both legacy and contemporary image sets: anisotropic filter = 5 iterations with 5.0 diffusion constant; edge detector kernel = 0.8 sigma. These parameters were utilized in this study.

Statistical Analyses: Data analytic methods included the following: 1) the comparison of two manual anatomists' performance using the Jaccard similarity coefficient (JSC) to measure

degree of correspondence, or overlap, for each image slice; 2) detailed qualitative review of all outcomes; 3) the comparison of each manually skull-stripped outcome (the criterion) to the outcome of each automated method using the JSC to measure the degree of correspondence for each slice (Jaccard 1912; Zou et al. 2004a; Zou et al. 2004b); 4) a similar comparison of methods with the Hausdorff distance measure (Huttenlocher et al. 1993) to examine the degree of mismatch between the contours (or shape) of two image sets; and 5) the comparison of the sensitivity and specificity of all methods (including both manual sets) derived from an Expectation-Maximization (EM) algorithm (STAPLE, Warfield et al. 2004; Zou et al. 2004b), which provides a maximum likelihood estimate of the underlying brain prototype inferred from the results of all skull-stripping methods .

Jaccard Similarity Comparison: The JSC is formulated as

$$JSC(A,B) = (A \cap B) / (\mathrm{A} \cup \mathrm{B})$$

where A is the area of brain region of the manually skull-stripped image slice (criterion) and B is the area of brain region of the corresponding image slice skull stripped using the compared skull-stripping tool (Jaccard 1912; Zou et al. 2004a; Zou et al. 2004b). A JSC of 1.0 represents complete overlap or agreement, whereas an index of 0.0 represents no overlap. At both extremes, this JSC is similar to the Dice similarity coefficient, which is a simple transform. First, the JSC was employed to describe the overall level of similarity between the two manual outcomes by expressing the overlap between each pair of slices. Second, the results of the four automated skull-stripping tools (with and without bias correction) were compared to the manually stripped slices.

Hausdorff Distance Image Comparison: We applied Hausdorff distance measures (Huttenlocher et al. 1993) to examine the degree of mismatch between the contours of two image

sets (A and B). This measure reflects the distance of the point in A that is farthest from any point of B and vice versa. Given two finite point sets $A = \{a_1, \ldots, a_p\}$ and $B = \{b_1, \ldots, b_q\}$, where A and B are sets of points on the contour of a skull-stripped brain slice. The Hausdorff distance is defined as:

$$H(A,B) = \max(h(A,B), h(B,A))$$

The directed Hausdorff distance from A to B $h(A,B)$ is defined as:

$$h(A,B) = \max_{a \in A} \min_{b \in B} \| a - b \|$$

Here the norm is L_2 or Euclidian norm, where h(A,B) and h(B,A) are asymmetrical distances.

Since Hausdorff distance measures the extent to which each point of a particular image point set lies near some point of another image point set, it can be used to determine the degree of resemblance between two objects superimposed on one another. For the Hausdorff distance d, every point of A must be within a distance d of some point of B and vice versa. The maximum displacement for the Hausdorff measure is calculated for each image comparison, A and B. For example, in Figure 4 (right panels), the distance from each point on the yellow contour (A: manual strip) to each point on the red contour (B: automated strip) is calculated. In our estimation of the Hausdorff distance, we adjusted the calculations to exclude outliers; if only a very few points are far from average, these extreme distances would not meaningfully represent common method performance. That is, the distance measure would not be representative of the common features resulting from automated application. In the present application of the Hausdorff measure, the algorithm first orders the boundary points distances (in ascending order). The 25th and 75th percentiles are then estimated for image A and B and the interquartile range (IQR) for image A and B is estimated. The IQR is equal to the boundary point distance at the 75th percentile less the boundary point distance at the 25th percentile. The present comparison

utilized the upper inner fence as defined by the boundary point distance at the 75th percentile plus 1.5*IQR (Tukey 1977). This fence is used as a more robust normal outlier boundary than maximum distance in Hausdorff calculations yielding a modified Hausdorff measure likely to be less sensitive to measurement error.

Expectation-Maximization (EM) Comparison: Warfield et al. (2004) has developed an EM algorithm, named STAPLE, for computing a probabilistic estimate of the ground-truth segmentation from a group of expert segmentations, and a simultaneous measure of the quality of each expert. As we applied their algorithm, this measure is a maximum likelihood estimate of the underlying agreement *among all* of the skull-stripping methods (two manual plus four automated both with and without bias correction). The underlying agreement is represented by an unobserved or hidden skull-stripped prototype that divides all voxels into brain or non-brain sets, a hidden, binary ground truth segmentation.

The iterative log likelihood maximization algorithm estimates specificity and sensitivity parameters given *a priori* probabilities of hidden binary ground truth segmentation and initial estimates of specificity and sensitivity. The sensitivity of an expert j expressed as a proportion p_j, where ($\{p_j\} \in [0,1]$), is the relative frequency of an expert decision that a voxel belongs to the brain region when the ground truth for that voxel also indicates the same decision. The specificity of an expert j expressed as a proportion q_j, where ($\{q_j\} \in [0,1]$), is the relative frequency of an expert decision that a voxel does not belong to the brain region when the ground truth for that voxel also indicates the same decision. The *a priori* probabilities for all the voxels for each slice of each subject tested are set to 0.5, indicating no initial knowledge about ground truth. The initial estimates for sensitivity and specificity are all set to 0.9. The termination criterion for convergence set the root mean square error to < 0.005.

Statistical Summary: We employed mixed model analyses with the conventional alpha level of 0.05 for a significant statistical effect. Partial eta-squared (η^2) values are provided as an estimate of effect size. Between-subjects effects were examined for Image Set (Legacy, Contemporary) and Diagnostic Group (YNC, ENC, DEPR, and AD). Univariate within-subjects repeated measures effects were examined for Slice (Slices 1 through 6 as in Figure 1), Bias Correction (with and without N3 correction), and Method (3dIntra, BET, BSE, and HWA). These univariate analyses employed the Huynh-Feldt correction since sphericity could not be assumed; logarithmic transforms of the same data produced similar findings. Both within and between group post-hoc analyses contrasted pairs of each condition in sequence. For example, post-hoc analyses of Diagnostic Group included three comparisons: YNC vs. DEPR, DEPR vs. ENC, ENC vs. AD. To analyze agreement between raters we performed a Slice by Image Set by Diagnostic Group mixed design analysis of variance using the JSC as the dependent variable. Investigation of the influence of study variables on the correspondence of each automated method with each manual outcome comparison required a Method by Bias Correction by Slice by Image Set by Diagnostic Group mixed design analysis of variance with the JSC and the modified Hausdorff measure analyzed as separate dependent variables. The latter ANOVA design also was used to investigate the influence of study variables on EM-derived sensitivity and specificity. EM analyses reported herein included all four automated methods and the two manual outcomes.

RESULTS

Statistical Comparison of Two Manually Stripped Outcomes. When the two anatomists' manually stripped sections were compared, the grand mean JSC averaged across slices was .938 (SE=.002). There were significant main effects of Slice ($F(4.5, 108.5)=18.5$,

p<.001, partial η^2=.44) and Diagnostic Group (F(3,24)=7.2, p=.001, partial η^2=.47). Neither the effect of Image Set nor any interactions reached significance (all p>.05; all partial η^2<.13). Post-hoc, within-subjects contrasts suggested that the similarity coefficient was lowest for the two mid-line sagittal sections (Figure 1, Slices 3-4) relative to the four lateral sections; these mid-line sections were most variable between anatomists. As predicted, contrasts for Diagnostic Group suggested that the similarity coefficients were lower for ENC and AD groups relative to the YNC and DEPR subjects (F(3,24)=7.2, p=.001, partial η^2=.47). Specifically, the coefficients for the YNC and DEPR groups did not differ (p>.05) and neither did the ENC and AD groups (p>.05). The similarity coefficients for the DEPR and ENC groups, however, were significantly different (p=.001). In summary, the brain contours drawn by anatomists agreed less in the two mesial slices and for data from the older diagnostic groups. These conditions that were more difficult for manual skull-stripping may also prove difficult for the automated methods.

Qualitative Evaluation of All Outcomes. Qualitative review of all individual results revealed that the outcomes differed in 1) the amount of cerebrospinal fluid (CSF) included in the stripped volume; 2) the type of non-brain remaining in the stripped volume; and 3) the regions and extent of brain tissue loss in the stripped volume. All methods included internal (e.g., ventricular) CSF in the resulting volume, which would allow future processing to evaluate ventricular volume. HWA consistently included external CSF in the space between brain tissue and the external dura (subarachnoid space; HWA in Figure 2).

INSERT FIGURE 2 ABOUT HERE

The type and extent of non-brain tissue remaining in the stripped volumes varied across

methods, and the most common results are described here (Figures 2, 3, and 4). All methods tended to leave some non-brain tissue in the posterior fossa (Figure 2). As intended by developers, BSE volumes consistently include the spinal cord (Figure 2). BET tended to leave muscle and other tissue in the mid-neck region (Figure 2-4). On some occasions, non-brain included in 3dIntra results was found in similar areas, although to a lesser extent. HWA volumes consistently included surrounding subarachnoid space and non-brain dura (Figures 2-4), occasionally including tissue around the eyes (Figure 2), although HWA consistently removed non-brain tissues in the neck regions.

The region and extent of brain tissue loss in stripped volumes also varied across methods (Figures 3-4). HWA was sensitive to retaining brain volume. On one occasion, however, the cerebellar volume was reduced. In general, the anterior frontal cortex, anterior temporal cortex, posterior occipital cortex, and cerebellar areas were common locations for loss of cortical voxels in other methods (3dIntra, BET, and BSE). Most cortical loss on stripped volumes of the Contemporary datasets tended to be a thin layer of brain voxels in these areas, with BSE seeming to result in the least amount of tissue loss. In the Legacy datasets, however, the loss of brain tissue was more severe in some cases for these methods.

INSERT FIGURE 3 ABOUT HERE

INSERT FIGURE 4 ABOUT HERE

Statistical Comparisons of Automated Methods. The average elapsed processing time for performing automated applications per dataset was calculated for each automated method

based on the performance across all 32 datasets. 3dIntracranial required less than one minute (53.9s; sd=10.5), BET required less than four minutes (223.1s; sd=60.0), HWA required less than 8 minutes (473.6s; sd=127.8), and BSE required on the order of fifteen seconds (14.2s; sd=0.8).

The effects of each condition (Image Set, Slice, Bias Correction, and Diagnostic Group) are described separately, followed by a description of the Method effects and interactions. Statistical results for significant findings are reported for JSC (Table II), Hausdorff distance (Table III), and EM Sensitivity and Specificity (Table IV). JSC and Hausdorff distance analyses were completed for each anatomist separately. Findings were similar for both anatomists unless otherwise reported; the representative findings for Anatomist 1 (CC) were reported herein for simplicity. EM analyses represent the inclusion of all four automated methods and the two manual outcomes. All results described emphasize the comparison of methods.

INSERT TABLE II ABOUT HERE

INSERT TABLE III ABOUT HERE

Image Set: There were no significant differences of JSC or Hausdorff distance between the Image Sets studied (Legacy vs. Contemporary) when the contour of either rater was used as the ground truth (Anatomist 1: JSC partial η^2=.03, Hausdorff partial η^2=.12; Anatomist 2: JSC partial η^2=.01, Hausdorff partial η^2=.10). Thus, the correspondence of each anatomist's brain contour to the contours produced by the four automated skull-stripping programs was similar for the two Image Sets. EM analyses, however, revealed a significant effect of Image Set for Sensitivity (Table IV); the effect did not reach significance for Specificity ($F(1,24) = 3.5$, p =

.074, partial η^2 = .13). The Contemporary data resulted in greater sensitivity (mean=.960, SE=.009) relative to the legacy data (mean=.926, SE=.009). Interactions between Image Set and other conditions are described below.

INSERT TABLE IV ABOUT HERE

Slice (Regional Anatomy): Significant main effects of Slice were found across all measures (Tables 2-4). The effects of Slice were similar to those found in the comparison of the two anatomists' manual skull-stripping results; that is, in general the two midline slices (Figure 1, Slices 3-4) had lower similarity coefficients and higher distance measures relative to the more lateral slices. Slice significantly interacted with Image Set for JSC (Table II) and measures of Sensitivity and Specificity yielded by the EM algorithm (Table IV). Mesial slices from Legacy data were least similar to the criterion dataset, whereas mesial (Figure 1, Slices 3-4) and most lateral (Figure 1, Slices 1 and 6) slices from Contemporary data were least similar. Specificity was best moving from mesial to lateral slices, particularly for the Contemporary data.

Bias Correction: There was no significant main effect of bias correction for any of the measures (all partial $\eta^2 < .05$), and no interactions with bias correction reached significance. Although there were some individual cases that qualitatively appeared to benefit from bias correction, this effect was not significant over any condition.

Diagnostic Group: The main effect of Diagnostic Group reached significance for all measures (Tables 2-4). Planned contrasts supported the hypothesis that all measures were significantly poorer for the AD group relative to all other groups. The YNC and DEPR groups did not differ significantly, and, unexpectedly, neither did the DEPR and ENC groups. The JSC for Anatomist 2 resulted in a significant Diagnostic Group by Slice by Image Set interaction

(Table II), although this interaction did not reach significance for Anatomist 1 (F(14.8, 118.2)=1.5, p=.12, partial η^2 =.16). This 3-way interaction is difficult to interpret, but it appears to suggest that the Contemporary data may result in better performance for the mesial slices for the older Diagnostic Groups. Diagnostic Group did not significantly interact with Image Set, Slice, or Bias Correction for any other measures. Interactions involving Method are examined below.

Automated Methods: Direct evaluation of the four automated skull-stripping methods (Table V) revealed consistent differences for JSC (Table II; analyses compared automated performance to manual method) and EM Sensitivity (Table IV; analyses included all automated and manual methods) measures (but not EM Specificity or Hausdorff indices). Post-hoc JSC contrasts for Method indicated that 3dIntra and BET did not differ significantly and neither did BSE and HWA. BET and BSE, however, were significantly different (p=.003). That is, BSE and HWA produced higher similarity measures than 3dIntra and BET for both anatomists (Table V). With respect to Sensitivity, 3dIntra, BET, and BSE did not differ significantly, whereas HWA was significantly more sensitive than BSE (p<.001). Thus, HWA was significantly more sensitive than all other automated methods (Table V).

INSERT TABLE V ABOUT HERE

For the measure of Sensitivity, Method significantly interacted with Image Set (Table IV). The performance of BET was greatly affected by Image Set; BET was least sensitive on the Legacy data with respect to all other methods, but performed better with the Contemporary data. No significant interactions were observed between Image Set and automated Method for other measures. The non-significant interaction of Image Set with Method accounted for less than 6%

of the observed variation of JSC or Hausdorff distance.

There were significant Method by Slice interactions for the JSC (Table II) and EM Sensitivity (Table IV). In general, BSE and HWA performed relatively similarly across slices with the mesial slices least similar; 3dIntra and BET, both with lower overall similarity coefficients, performed differently across slices. 3dIntra performed most poorly on Slice 1 with an otherwise similar pattern to BSE and HWA. BET, in contrast, performed best on Slice 1 and then at a slightly lower level across Slices 2-6. With respect to Sensitivity, HWA performed consistently high across all slices. Although less sensitive, BSE was also fairly consistent across slices with the exception of poor performance on Slice 1. 3dIntra also was least sensitive on Slice 1. BET was least sensitive for the two mesial slices (Slices 3 and 4).

For the JSC, the Method by Slice by Image Set interaction was significant for Anatomist 2 (Table II), although this interaction did not reach significance for Anatomist 1 (p=.11, partial η^2 =.08). This 3-way interaction, however, was also significant for EM Sensitivity (Table IV).

Of considerable interest, the effect of Diagnostic Group on JSC and Hausdorff distance varied by automated skull-stripping method for both anatomists (Figures 5 and 6; Tables 2 and 3). For EM Specificity, although there was no significant main effect of Method (partial η^2 =.039; Table V), there was a significant interaction between Method and Diagnostic Group (Table IV; Figure 7). EM Sensitivity, in contrast, did not significantly interact with Diagnostic Group, although the main effects of Diagnostic Group and Method were both significant (Table IV; Figure 8). Of critical interest, the post-hoc analyses of the interactions between Method and Diagnostic Group revealed that when compared with BSE and HWA, 3dIntra had significantly lower similarity and larger distance coefficients for the AD data, and BET had lower similarity and larger distance coefficients for the ENC and AD data (Figures 5 and 6). Thus BSE and

HWA were more effective at finding the brain contour for the AD group, the most challenging group to skull strip. However, 3dIntra was most effective for young normal controls. With respect to EM Specificity (Figure 7), 3dIntra demonstrated significantly worse performance in AD relative to other groups, and BSE tended to perform best across all diagnostic groups (Figure 7). In summary, the HWA algorithm most successfully retained "true" brain tissue even within the AD group (Table V; Figure 8), whereas BSE resulted in the best specificity across all conditions (Figure 7).

INSERT FIGURE 5 ABOUT HERE

INSERT FIGURE 6 ABOUT HERE

INSERT FIGURE 7 ABOUT HERE

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DISCUSSION

This collaborative study provides guidance to end-users and developers of automated skull-stripping applications and demonstrates a quantitative analysis path for the evaluation of morphometric analysis tools. The investigation examined the effects of bias correction, image set, slice location, and diagnostic group on automated skull-stripping performance. Bias correction of field inhomogeneities through the use of N3 (Sled et al. 1998) did not significantly improve performance of skull-stripping methods. Given that some individual cases of these 1.5T data did improve with prior bias correction, bias correction on data from higher-field strength

magnets may have a more significant effect. Performance was, in general, better on the Contemporary data relative to the Legacy data with respect to sensitivity, perhaps due to improved image contrast. As predicted, mesial brain slices proved the most challenging to skull-strip. These slices included posterior fossa tissue that is often difficult to distinguish from adjacent brain tissue, as well as voxels containing partially volumed tissues and CSF (Figures 2-4). Across all of our performance measures, images from the Alzheimer's disease (AD) group proved the most difficult to skull strip.

In general, HWA (Segonne et al. 2004) and BSE (v 3.3, Sandor and Leahy 1997; Shattuck et al. 2001) were more robust across all study conditions relative to 3dIntracranial (Ward 1999) and BET (Smith 2002), although the interactions between Method and other conditions warrant further discussion. It should be noted that BSE's final outcome purposefully aims to fit the brain surface and includes the spinal cord as part of the CNS, whereas HWA aims to conservatively bound the pial surface. Consistent with a recent study (Segonne et al. 2004), HWA was significantly more sensitive than other methods, resulting in a conservative strip that rarely removed any brain tissue. HWA preserved much of the subarachnoid space, which might allow the estimation of cranial vault volume to be incorporated into statistical analyses controlling for individual differences in head size. However, as with all methods' results, the final outcome would likely benefit from additional editing due to the extent of remaining non-brain tissue. BSE, in contrast, was more specific, although some brain voxels tended to be removed, and the final outcomes include some of the same posterior non-brain regions as in HWA although to a lesser extent.

The significant interaction between Method and Diagnostic Group supported the robust, general application of HWA and BSE relative to 3dIntracranial and BET. However, for the

Young Control (YNC) group, 3dIntracranial produced results that were the most similar to the criterion dataset and tended to be the most specific. As measured by inclusion of non-brain tissue (false positives) and exclusion of brain tissue (false negatives), 3dIntracranial performed poorly on the data from the AD group, suggesting that 3dIntracranial may be an appropriate tool particularly for younger populations. BET also performed less well for both the ENC and AD data, including neck regions of non-brain tissue, as in a recent study (Boesen et al. 2004), and removing some anterior and posterior cortical tissue. BSE and HWA, in contrast, were less affected by diagnostic group, despite lower similarity coefficients on the YNC data relative to 3dIntracranial. In short, 3dIntracranial performed extremely well when working with young subject data, however, in the study of older subjects, BSE and HWA appeared more promising. The HWA algorithm demonstrated the highest sensitivity, most successfully retaining brain tissue even within the AD group, and BSE demonstrated the best specificity in the older groups.

The performance of BSE relative to BET was not easily predictable based on previous studies of automated application of these methods (Boesen et al. 2004; Lee et al. 2003; Smith 2002). Although Lee et al. (2003) and Smith (2002) reported that BET performed better than BSE, Segonne et al. (2004) suggested that BSE may provide superior results. Boesen et al.'s (2004) findings suggested that the relative performance of BET and BSE may be influenced by image quality. The present study differed from previous work in that we employed a more recent version of the BSE software (v. 3.3), the parameters employed were determined by the expert developers, and anisotropic filtering was included in the BSE path of the present study, a processing step not always included in other studies (e.g., Smith 2002).

Our study focused only on T1-weighted image sets and was limited to rectangular k-space trajectories. Method performance on other types of image sets may be quite different. As

with 3dIntracranial and BSE, BET has the ability to strip other types of image sets and might perform especially well on T2- or proton-density-weighted image sets not examined herein (Smith 2002). Our preliminary work suggests that there are significant challenges to the application of these methods to spiral trajectories. In addition, the findings reported here are limited to the specific groups studied. Given our findings in AD, the characteristics of the AD data that influenced the performance of these automated methods should be investigated further, and these algorithms tested on other neurodegenerative groups. Finally, this study provides no information about region-growing algorithms and other hybrid approaches, which performed well in previous studies of skull-stripping methods (e.g., Boesen et al. 2004; Lee et al. 2003).

The comprehensive analysis path employed in the present study provides several quantitative measures that may be useful to future studies of image processing. The initial JSC analyses (Jaccard 1912; Zou et al. 2004a; Zou et al. 2004b) are similar to previously employed statistics. These provided general information on the amount of overlap between two outcomes, although there was no specific information as to the sensitivity, specificity, or shape differences that may be additionally informative. Our estimation of the Hausdorff distance measure (Huttenlocher et al. 1993) provided information on shape differences between outcomes, although in the present study the results were similar to the Jaccard findings. When this measure is small, the shapes are similar and almost exactly overlap. When this measure increases, the shapes may be quite dissimilar, despite overlap. Most important to the present work, the use of the Expectation-Maximization (EM) algorithm (Warfield et al. 2004; Zou et al. 2004b) provided both sensitivity and specificity indices for the methods examined, including the manual outcomes, relative to the overall ground truth. This additional information was critical to informing differences between BSE, a more specific method, and HWA, a more sensitive

method, both of which performed similarly well across diagnostic groups on the other similarity measures.

CONCLUSIONS

Evidence suggests that HWA may remove substantial non-brain tissue from the difficult face and neck regions, carefully preserving the brain, although the outcome often would benefit from further stripping of other non-brain regions; BSE, in contrast, more clearly reaches the surface of the brain, although, in some cases, some brain tissue may be removed. 3dIntracranial and BET often left large non-brain regions and/or removed some brain regions, particularly in the older populations. Based on the present findings, further investigations may pursue a skull-stripping approach that combines methods, either sequentially or in parallel. For example, HWA simplifies the problem of stripping away non-brain while proving to be quite sensitive, and following the application of HWA with BSE may improve the specificity of the final result. Another approach presented recently (Rex et al. 2003) pursued the possibility of combining methods within a single meta-algorithm to optimize results. Again, the present study aimed to examine the automated performance of available skull-stripping methods only on T1-weighted image sets. All methods examined in the present study permit users to manually optimize parameters, which may improve performance over values employed herein. These parameter choices may vary depending on the region of interest to the investigators, as some regions may be more susceptible to tissue loss with some methods. Furthermore, BSE, BET, and 3dIntracranial are applicable to some other types of image sets (e.g., T2-weighted) and thus might be significantly advantageous under such circumstances. We hope this study will guide end-users towards a method appropriate to their datasets, improve efficiency of processing for large, multi-site neuroimaging studies, and provide insight to the developers for future work.

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Table I. Dataset information.

Diagnostic Group	**Image Set**	**Age** (mean, sd)	**Gender**	**MMSE** (mean, sd)
Young Controls	Legacy	35.5 (13.5) *range* 25-54	2F/2M	*N/A*
	Contemporary	33.0 (15.1) *range* 21-54	2F/2M	*N/A*
Elderly Controls	Legacy	75.0 (2.2) *range* 72-77	2F/2M	*N/A*
	Contemporary	74.5 (1.7) *range* 72-76	2F/2M	*N/A*
Unipolar Depressed	Legacy	40.5 (13.3) *range* 28-56	3F/1M	*N/A*
	Contemporary	40.8 (10.8) *range* 21-54	3F/1M	*N/A*
Alzheimer's Disease	Legacy	76.0 (2.7) *range* 72-78	2F/2M	23.0 (2.7) *range* 21-27
	Contemporary	75.5 (1.7) *range* 72-78	1F/3M	23.2 (2.5) *range* 22-27

N/A = not available

Table II. Statistically significant main effects and interactions for Jaccard similarity coefficient (JSC) analyses. Automated methods were compared to manually stripped slices for each anatomist. Gray-shaded findings were significant for only one anatomist.

Anatomist 1	***F***	***p***	**partial η^2**
Slice	$F(4.9, 118.2) = 12.2$	<.001****	.34
Slice by Image Set	$F(4.9, 118.2)=9.2$	<.001****	.28
Diagnostic Group	$F(3,24) = 7.9$	.001***	.50
Method	$F(3,72) = 3.4$	.023*	.12
Method by Slice	$F(4.3, 103.2) = 8.1$	<.001****	.25
Method by Diagnostic Group	$F(9,72) = 2.8$	.007**	.26
Anatomist 2			
Slice	$F(4.8, 114.0) = 13.3$	<.001****	.36
Slice by Image Set	$F(4.8, 114.0)=11.8$	<.001****	.33
Diagnostic Group	$F(3,24) = 8.6$	<.001****	.52
Diagnostic Group by Slice by Image Set	$F(14.3, 114.0)=2.1$	.017*	.21
Method	$F(3,72) = 3.3$	.026*	.12
Method by Slice	$F(4.5, 107.1) = 8.0$	<.001****	.25
Method by Slice by Image Set	$F(4.5, 107.1)=2.8$	.023*	.11
Method by Diagnostic Group	$F(9,72) = 3.0$	.004***	.27

**** p<.001; *** p<.005, ** p<.01; * p<.05

Table III. Statistically significant main effects and interactions for Hausdorff distance analyses. Automated methods were compared to the manually stripped slices for each anatomist.

Anatomist 1	***F***	***p***	**partial η^2**
Slice	$F(4.1,98.4) = 23.0$	<.001****	.49
Diagnostic Group	$F(3,24) = 4.8$	.010*	.37
Method by Diagnostic Group	$F(9.0,72.0) = 2.1$	.037*	.21
Anatomist 2			
Slice	$F(3.9,93.2) = 24.1$	<.001****	.50
Diagnostic Group	$F(3,24) = 4.8$	.009**	.38
Method by Diagnostic Group	$F(9.0,72.0) = 2.1$	.037*	.21

**** $p<.001$; *** $p<.005$, ** $p<.01$; * $p<.05$

Table IV. Statistically significant main effects and interactions for EM analyses of Sensitivity and Specificity. All methods, including manual stripping, were treated similarly.

Sensitivity	***F***	***p***	**partial η^2**
Slice	$F(3.1,73.7) = 5.4$	.002***	.18
Image Set	$F(1,24) = 8.3$	.008**	.26
Slice by Image Set	$F(3.1, 73.7)=6.3$	.001***	.21
Diagnostic Group	$F(3,24) = 5.1$	.007***	.39
Method	$F(2.6,63.0) = 12.1$	<.001****	.33
Method by Image Set	$F(2.6, 63.0)=5.0$	.005**	.17
Method by Slice	$F(3.3, 78.1)=4.3$	.006**	.15
Method by Image Set by Slice	$F(3.3, 78.1)=2.9$	.04*	.11
Specificity	***F***	***p***	**partial η^2**
Slice	$F(3.5,83.7) = 40.1$	<.001****	.63
Slice by Image Set	$F(3.5, 83.7)=3.3$	.018*	.12
Diagnostic Group	$F(3,24) = 3.3$	.036*	.30
Method by Slice	$F(6.6, 159.1)=10.7$	<.001****	.31
Method by Diagnostic Group	$F(8.1,64.5) = 2.6$	.017*	.24
Method by Diagnostic Group by Slice	$F(20.0, 159.1) = 1.7$	.032*	.18

**** $p<.001$; *** $p<.005$, ** $p<.01$; * $p<.05$

Table V. Mean (standard error) coefficients for Jaccard similarity (JSC) and Hausdorff distance for each Method as they relate to the manually stripped slices, and Expectation-Maximization (EM) estimates of Sensitivity and Specificity. Each mean represents method performance averaged across all other conditions. Data from both Anatomists is presented where relevant. Main effect of method was significant for JSC and EM Sensitivity.

		3dIntra	**BET**	**BSE**	**HWA**
Jaccard Similarity (JSC)	Anatomist 1	.802 (.029)	.787 (.014)	.863 (.019)	.855 (.015)
	Anatomist 2	.809 (.027)	.796 (.014)	.865 (.019)	.865 (.015)
Hausdorff Distance	Anatomist 1	26.2 (5.4)	23.1 (2.4)	20.5 (5.2)	14.7 (2.8)
	Anatomist 2	24.6 (5.3)	22.2 (2.4)	19.9 (5.2)	14.6 (2.8)
Expectation - Maximization (EM)	**Sensitivity**	.914 (.015)	.925 (.015)	.937 (.005)	.996 (.001)
	Specificity	.953 (.017)	.964 (.003)	.975 (.010)	.951 (.008)

FIGURE LEGENDS:

Figure 1. Standard location of the six sagittal, manually stripped slices as demonstrated on a coronal image. The six sagittal slices represent the criterion dataset; three slices from each hemisphere in symmetrical locations passing through regions that are difficult to skull-strip. Slices are numbered for reference. Three sample images are presented in the sagittal plane. Letters represent difficult regions as referenced in the text.

Figure 2. Examples of automatically stripped volumes of a bias corrected, Contemporary YNC dataset. Sagittal sections are taken near the midline to represent extent of CSF and non-brain tissue included in the resulting volumes.

Figure 3. Examples of automatically stripped volumes of a bias corrected, Legacy YNC dataset. Sagittal sections are lateral to the midline and represent the extent of brain tissue retained or excluded from the resulting volumes.

Figure 4. Examples of outcomes for a bias corrected, Contemporary ENC dataset. Each pair of figures includes solid color overlays on the stripped image (LEFT) and the contours of these shapes (RIGHT). *LEFT* Yellow = regions included in the manual but not in the automatic outcome. Blue = regions included in the automatic but not in the manual outcome. *RIGHT* Yellow = contour of manually-stripped dataset, Red = contour of automatically stripped dataset.

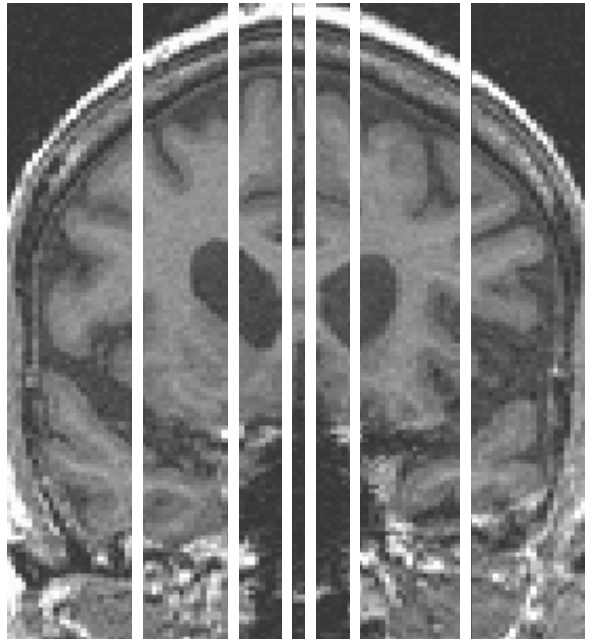
Figure 5. Mean (std. error bars) Jaccard similarity coefficient (JSC) for Diagnostic Group by Method relative to the manually stripped slices from Anatomist 1. Mean JSC for the two manual raters (0.938) is represented by the horizontal dashed black line.

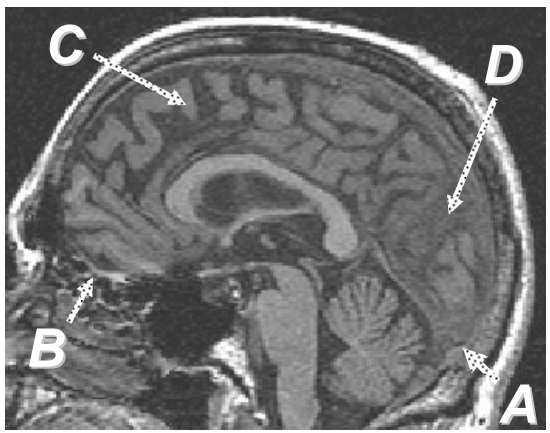
Figure 6. Mean (std. error bars) Hausdorff distance for Diagnostic Group by Method relative to the manually stripped slices from Anatomist 1. Mean Hausdorff distance for the two

manual raters (5.5) is represented by the horizontal dashed black line.

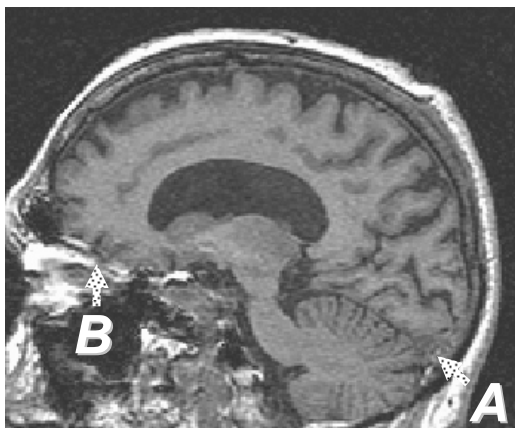
Figure 7. Mean Specificity from the Expectation-Maximization (EM) analysis by Diagnostic Group for each Method.

Figure 8. Mean Sensitivity from the Expectation-Maximization (EM) analysis by Diagnostic Group for each Method.

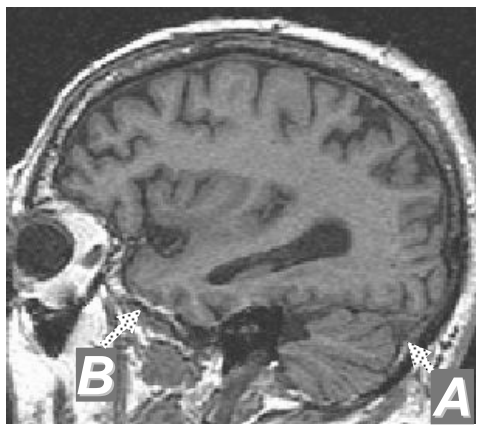




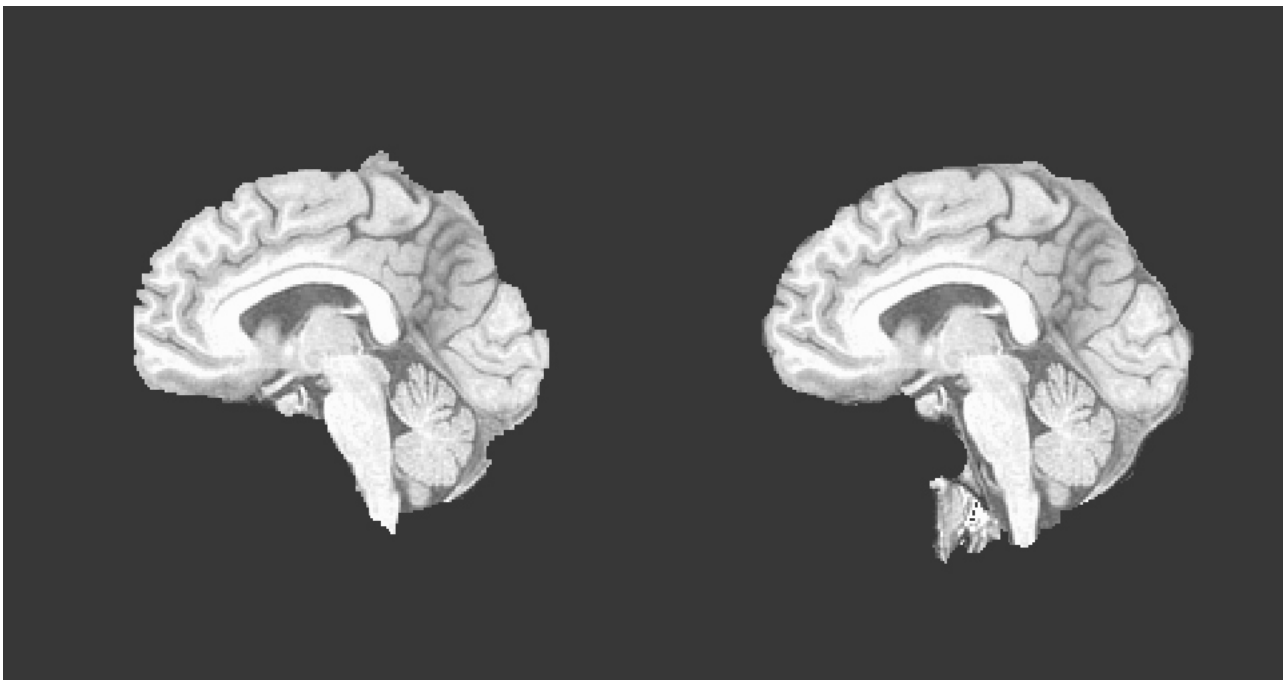
Slice 4



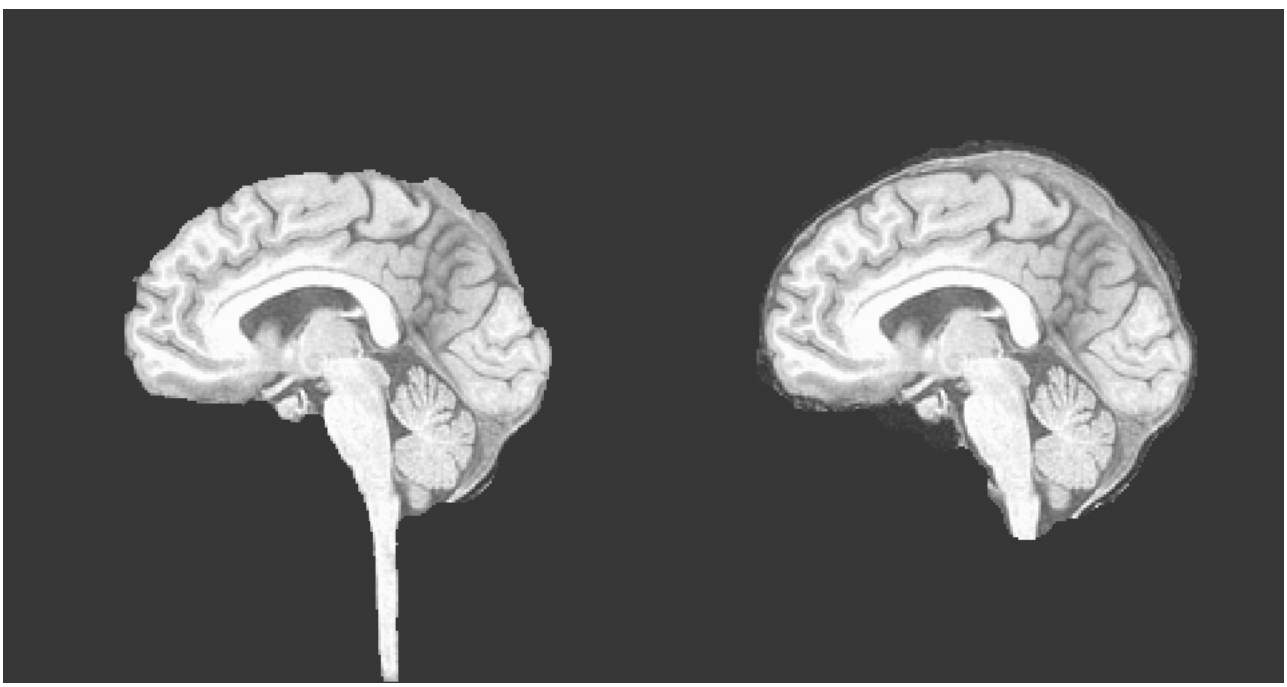
Slice 5



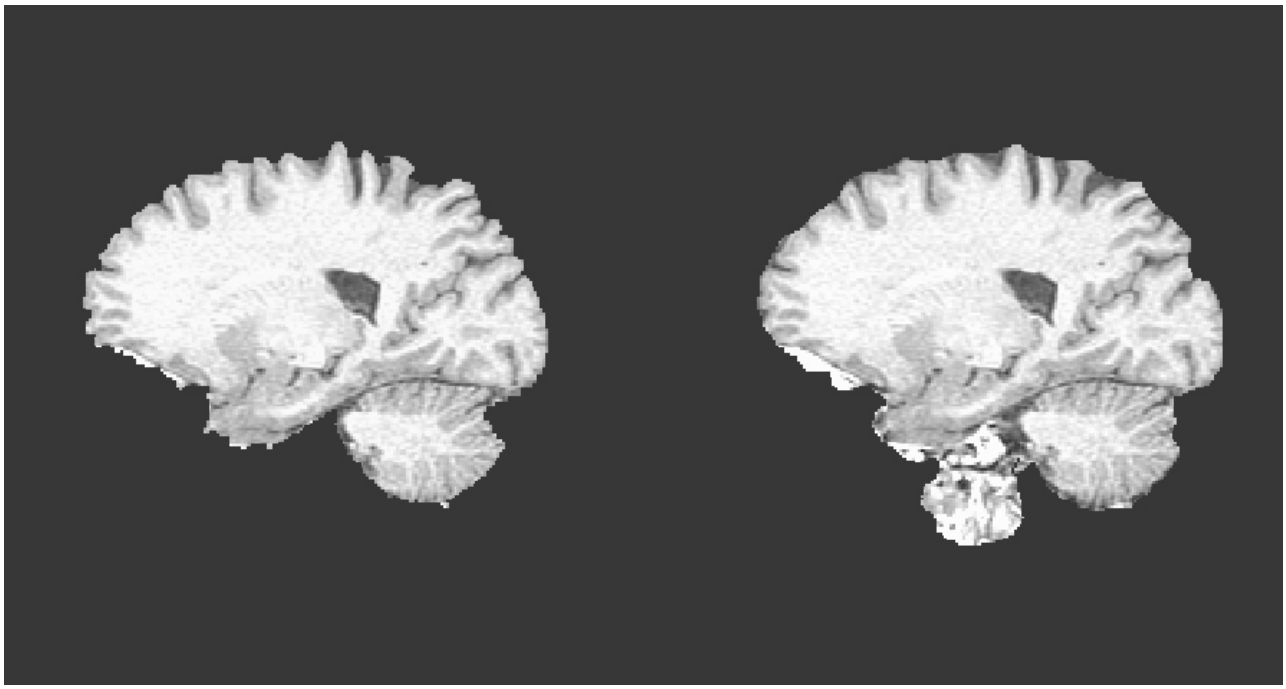
Slice 6



3dIntra BET



BSE HWA



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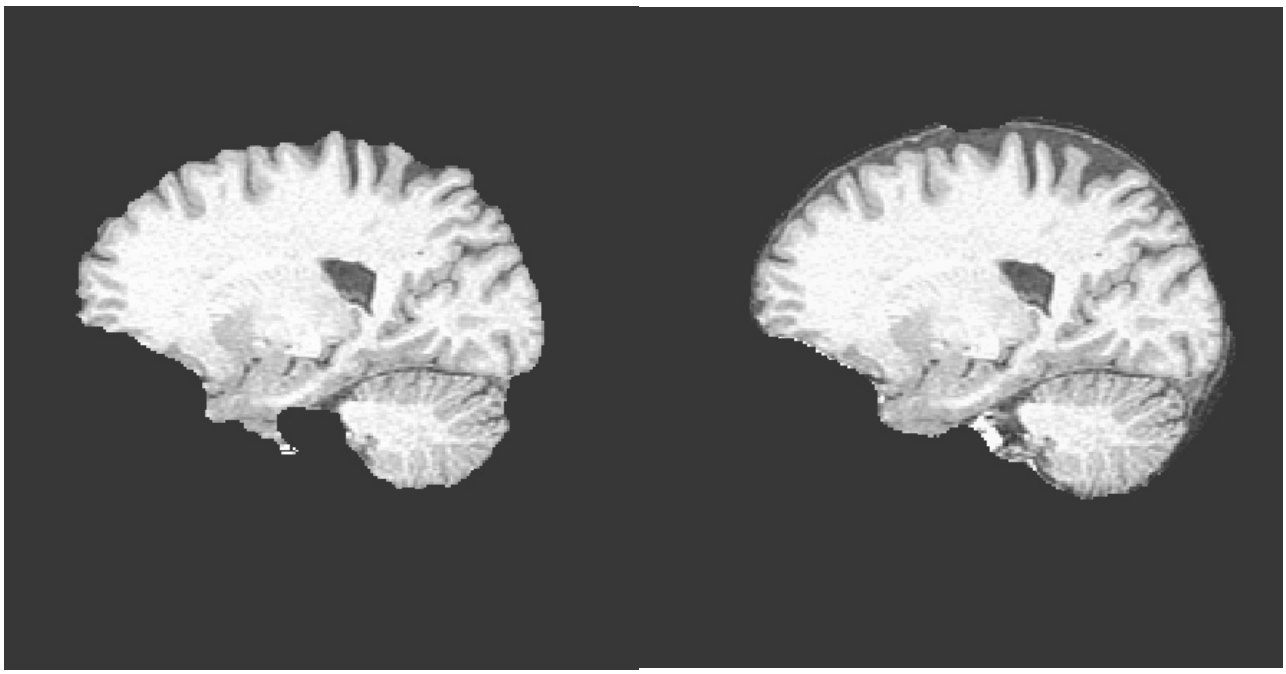
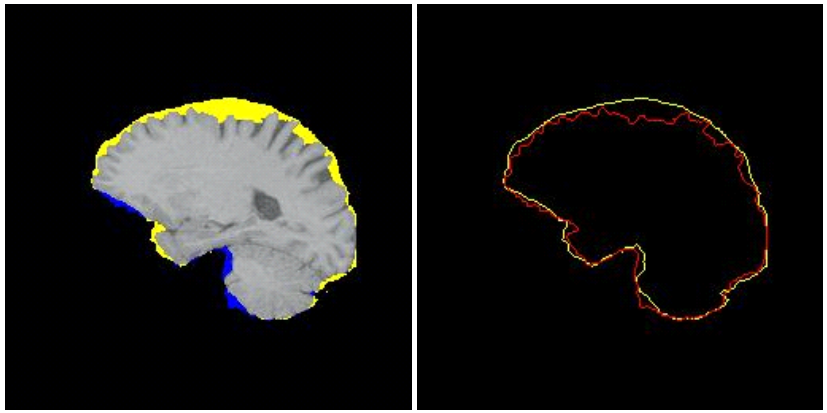


BSE HWA



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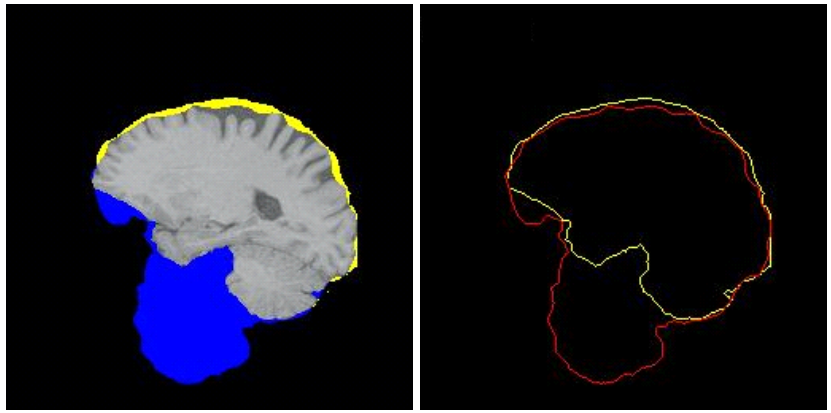
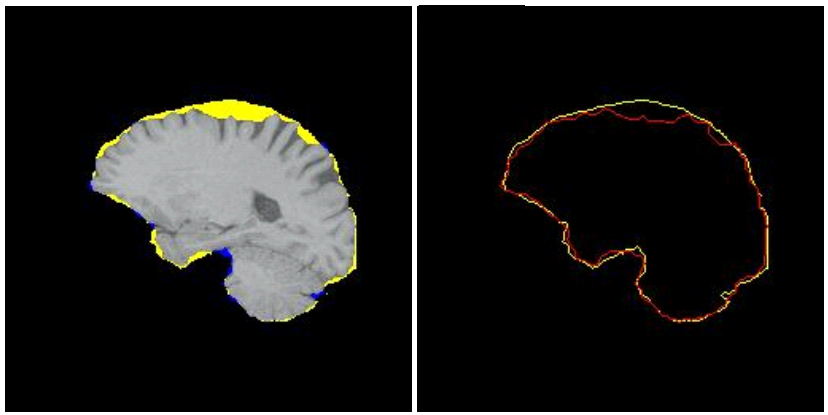
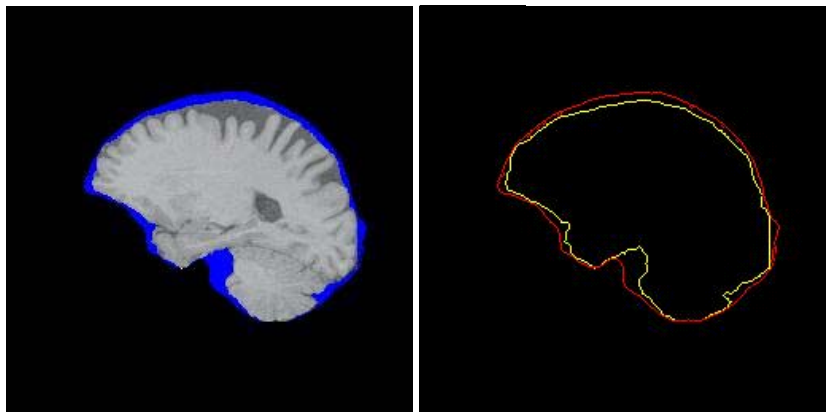


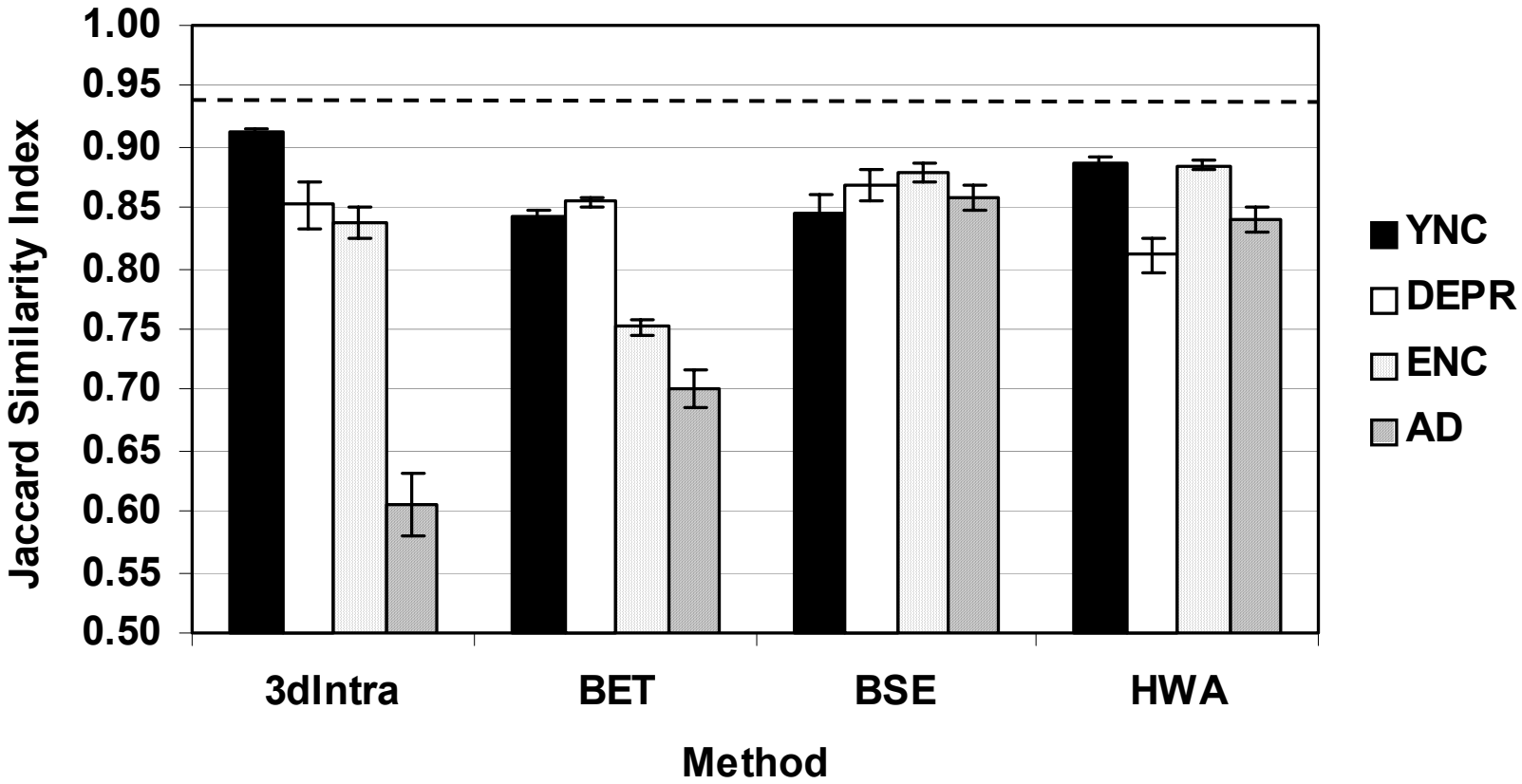
BET

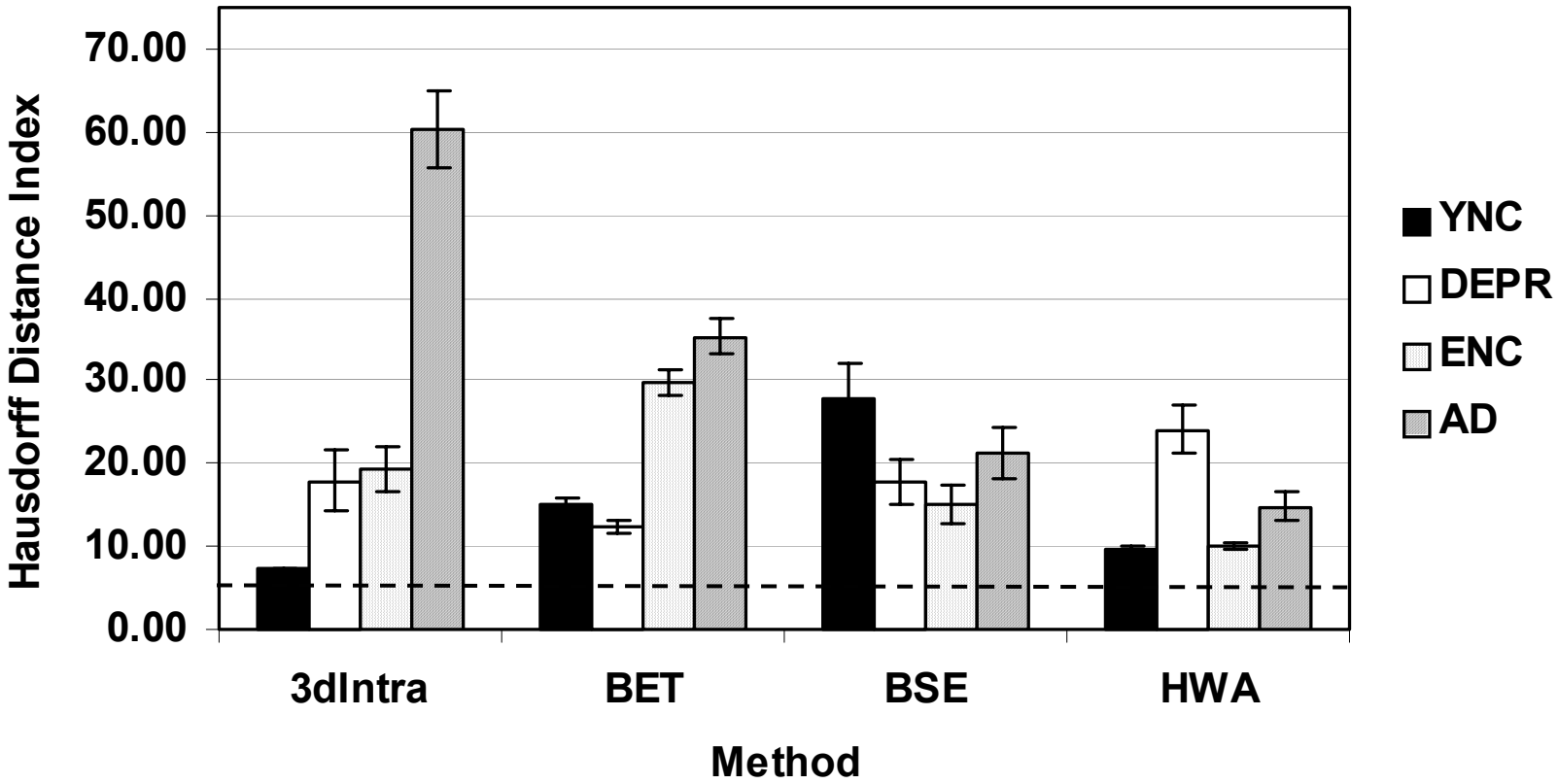


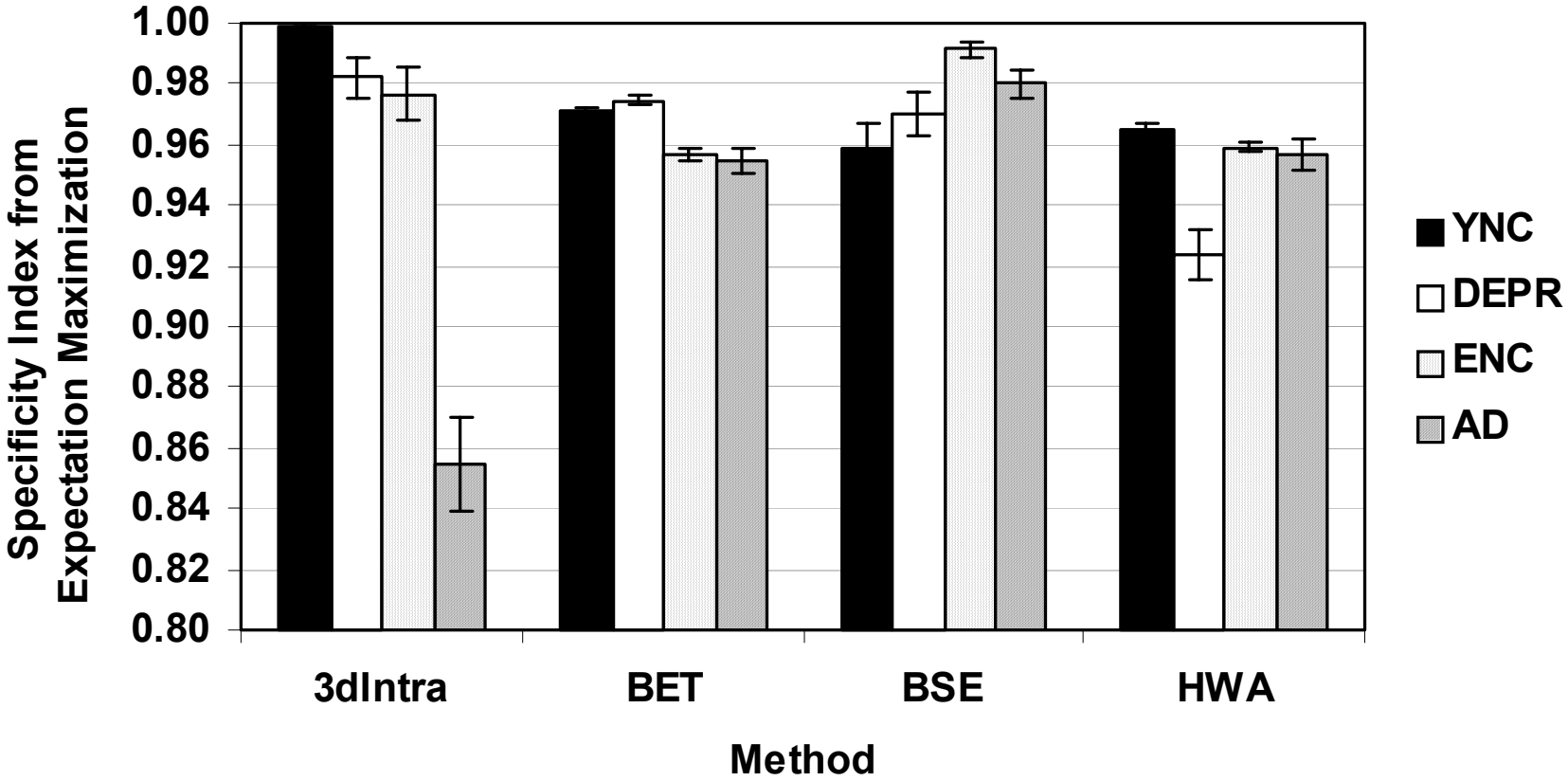
BSE

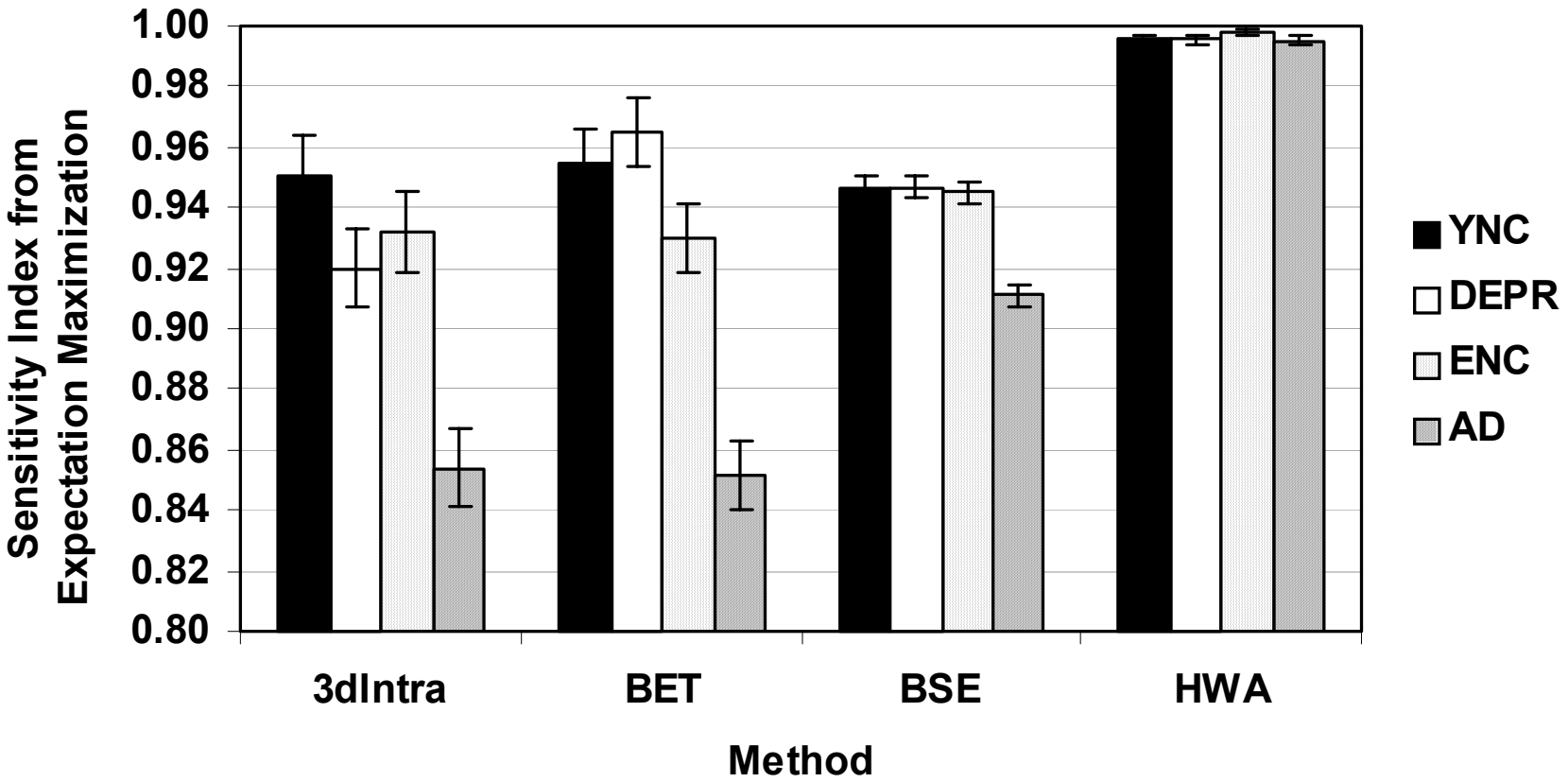


HWA


1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
Jaccard Similarity Index
3dIntra
BET
BSE
HWA
Method
YNC
DEPR
ENC
AD


Hausdorff Distance Index
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
3dIntra
BET
BSE
HWA
Method
YNC
DEPR
ENC
AD


Specificity Index from Expectation Maximization
1.00
0.98
0.96
0.94
0.92
0.90
0.88
0.86
0.84
0.82
0.80
3dIntra
BET
BSE
HWA
Method
YNC
DEPR
ENC
AD


Sensitivity Index from Expectation Maximization
1.00
0.98
0.96
0.94
0.92
0.90
0.88
0.86
0.84
0.82
0.80
3dIntra
BET
BSE
HWA
Method
YNC
DEPR
ENC
AD