Automated Analytical Determination of CNS Atrophy: A Comparative Study of an MR Image Subtraction Method (ISM) with Common Segmentation Algorithms

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Abstract

The purpose of this work was to develop an automated method to determine CNS atrophy. Two volumetric analysis algorithms, the Image Subtraction Method (ISM) and the Single Histogram Image Method (SHIM), were developed and evaluated. The two programs were tested using a computerized phantom MRI brain image and clinical MRI data. The ISM and SHIM were evaluated against six multi-modality algorithms and eight single-modality image segmentation algorithms to determine which algorithms had the most accuracy and reproducibility in volume determination of CSF and brain matter. The results of the phantom study showed that ISM was the most accurate algorithm to measure CSF and brain matter: 20.08% systematic error in CSF volume determinations; 1.5% overestimation of GM and WM areas. The clinical data study also showed that the ISM algorithm gave the most consistent results for the analysis compared to the neuroradiological interpretations, and the manually determined volumes. The reproducibility and reliability of the ISM algorithm show its potential for quantitative diagnosis of CNS atrophies.

1. Introduction

Magnetic Resonance Imaging (MRI) has become a standard tool to evaluate and determine anatomical and pathological changes in the human brain. Studies have shown that some neuropathological disorders affect the cerebral spinal fluid (CSF) and brain volumes. For example, the human immune-virus (HIV) infection produces ventricular atrophy and a decrease in white matter (WM) volume (1). Hydrocephalus disorders in children increase CSF and decrease WM(2). Atrophy is commonly associated with Alzheimer's disease(3). Neuroradiologists, in standard clinical practice, visually evaluate central nervous system (CNS) atrophy. In general, four categories of atrophy are used: normal, mild, moderate, and severe atrophy. Comparative studies and subtle changes can be difficult to assess by visual interpretation. A diagnostic method, which could measure the volume of CSF, WM and gray matter (GM) in a rapid and reliable manner, could be of clinical importance for evaluating progressive disease.

Many segmentation algorithms have been developed with different degrees of accuracy, reproducibility and speed(2-8). Clarke et al (7) compared three types of pattern recognition approaches of parametric, nonparametric and nonstatistical methods to segment MR brain images. They found that the *K Nearest Neighbor* (*KNN*) and the *Artificial Neural Network* (*ANN*) had comparable segmentation results while the *Maximum Likelihood Method* (*MLM*) suffers from intensive noise. Jackson et al (8) used the *Parzen Window* method to determine CSF volumes and evaluate the accuracy and reproducibility of this technique for normal human brains.

Some algorithms need operator interaction and supervision of a trained investigator or medical expert but inter-operator variability of supervised algorithms can significantly affect outcome. In a clinical practice, where patient numbers are high and the rapid reporting of results is a necessity, manual segmentation or operator supervised segmentation are not practical or feasible. However, a methodology, which could rapidly process and segment different tissue types of the brain, could lead to quantitative grading of atrophy.

The *Image Subtraction Method* (*ISM*) is a non-statistical technique, which does not require any user intervention. The *Single Histogram Image Method* (*SHIM*) is a histogram-based approach for segmentation of MR brain images together with *2D Entropy* (15) and *Moment Preserving* (16) methods. *KNN* (10), *Gaussian Clustering* (12), *Parzen Window* (11) and *ANN* (12,13) were the supervised algorithms evaluated in this study. The purpose of this study was to evaluate two new volumetric analysis algorithms (*ISM* and *SHIM*) against the common algorithms used for volumetric determinations from MRI images.

KNN, Gaussian Clustering, Parzen Window, Artificial Neural Network, Chain Method (14) *and ISODATA* (14), can be run in both the multi-modality and single modality operation. *2D Entropy* and *Moment Preserving* algorithms are single modality approaches.

2. Materials and Methods

Software: *ISM* and *SHIM* algorithms were programmed in C language and run on a SunOS 4.1 workstation and the other algorithms run on an SGI running IRIX 6.1. ANALYZE software (12) was used to select the region of interest of each tissue type for the training set and to perform clustering for *KNN*, *Gaussian*, *Parzen Window* and *ANN*, as well as *ISODATA* and *Chain Method*.

ISM: The *ISM* is based on subtraction T1 from T2 weighted image. However, dynamic ranges of signal intensities in T1 and T2 images are different depending on MRI receiver gain settings, voxel size and signal to noise ratio (SNR). Therefore, scaling of signal intensities was performed in the range of zero to one; zero representing the lowest signal intensity and one representing the highest signal intensity of the brain region. Only the isolated brain pixels were scaled so that the outlying pixels, e.g. dura or eyeballs, did not affect the results. These regions, especially in T1 images, had the highest signal intensities and therefore had to be removed prior to scaling. The CSF regions can be separated from WM and GM if the following criteria is met: $I_2(x,y)>I_1(x,y)$ where $I_2(x,y)$ and $I_1(x,y)$ are the scaled intensities of T2 and T1 at the location of (x,y).

SHIM: The *SHIM* algorithm is based on histogram of a T2 weighted image. The histogram was smoothed by an averaging filter width of seven, which produced a more stable outcome. Brain matter (WM and GM) is assumed to be normally distributed with a mean (μ) and standard deviation (σ). The mean (μ) is the first peak in the smoothed T2 histogram and standard deviation of the peak is calculated using the full width at half maximum (FWHM), σ = FWHM/2.35. The CSF threshold was selected as $\mu + k\sigma$ The constant k was calculated for 11 slices from two patients which the CSF thresholds were manually selected. The average of the 11 k values (k= 3.5) was used for the study.

Evaluation: Evaluation of brain image segmentation algorithms is a difficult task due to factors such as the complexity of the brain, MRI signal to noise, slice thickness, resolution and RF coil uniformity. Qualitative assessment of any algorithm based solely on visual assessment could not produce a quantitative comparative study. Therefore, we evaluated all algorithms using two independent tests. The first, a computer generated brain phantom (5) based on routine clinical MR images, was chosen because the exact pixel volume of WM, GM, and CSF pixels could be known prior to testing the algorithms. The programs performances were then re-tested using standard clinical MR images with different degrees of age-related atrophy determined by board certified neuroradiologists.

Phantom Study: The brain phantom images were generated by using brain tissue templates. The templates are the anatomical structures of the brain produced from clinical data, and model WM, GM and CSF for each slice of a normal brain. One advantage of using is that the topology of each tissue type remains realistic. Our assumption was that preserving topology of brain regions would be important for clinically referable results. Extra-ventricular CSF regions are more affected by partial volume averaging than other regions since they consist of smaller areas and have longer boundaries with WM and GM. The extra-ventricular CSF has a larger perimeter-to-area ratio (in 3D analysis area-to-volume ratio) which causes more partial volume averaging effects and thus greater inaccuracy in final results.

Each brain image template consisted of 10 slices spaced 0.5 mm apart with an image matrix size of 512x512. The brain phantom was modeled by assigning each tissue type with a mean intensity for a corresponding region of a clinical image and adding gaussian noise. The gaussian noise was estimated by measuring the variance of a region of interest in the clinical images. The means and variances used in our study to generate T2 weighted phantom, were 270 and 2500 arbitrary units for WM regions, 363 and 6400 for GM regions, and 1000 and 8400 for CSF regions and the means and variances to generate T1 weighted phantom, were 415 and 2500 arbitrary units for WM regions, 325 and 3600 for GM regions, and 140 and 1000 for CSF regions. The 10 template slices were averaged to simulate partial volume averaging effects in Z direction. Changing the image resolution from 512x512 to 256x256 simulated partial volume averaging in x and y directions. By using these methods, we were able to generate T1 and T2 brain phantom images and test the accuracy of the algorithms by knowing *a priori* the exact volumes of the phantom CSF, GM and WM pixels. Examples of the phantom images used in this study are shown in Figure 1.

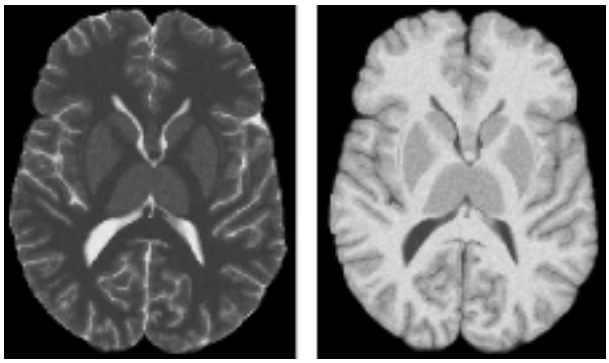

Figure 1. (a) T2-weighted computer generated phantom image. (b) T1-weighted computer generated phantom image comprising ten 0.5mm slices. The individual images were obtained by averaging the ten slices to create partial volume effects with known CSF, GM and WM pixels.

Clinical Data Study: Standard clinical T1 (TE/TR 11/500), dual spin echo (TE/TR 30/85/2500) or fast spin echo T2 (TE/TR/ETL 85/3000/8) images were obtained using a General Electric Signa 1.5T clinical system. The field of view was 22cm with pixel resolution of 256x256. Slice thickness was 5 mm with either 2.5 mm or 0 mm inter-slice spacing.

Pre-Processing: Background noise and dura were removed from the images using the T2 weighted images and the connected components algorithm (9). In this process, a background noise threshold was manually selected for each slice to generate a binary image. The connected component algorithm iteratively assigns labels to all non-zero pixels and finds the single largest connected object and rejects all others. The largest connected object is the brain region. This process uses T2 weighted images, since in the T1 images, extra-ventricular CSF and bone both have low signal intensities, and CSF regions could be incorrectly removed as part of the background noise or extra-meningeal tissues. We found this initial step to be important for pixel classification since the dura region has a similar intensity range as CSF, especially in FSE/T2 image sets. The connected component step also provides an outline of the brain perimeter, which can be used for T1 image analysis if there is no patient motion between the acquisitions of the MRI series.

The performance of all multi-modality segmentation algorithms was assessed with MR data from four clinical cases with different degrees of atrophy. These clinical images were from patients 33-87 years old with normal, mild, moderate and severe clinical atrophies, as determined by board certified neuroradiologists. Each data set consisted of six slices through the midbrain and encompassing the lateral ventricles. The CSF volumes of four clinical data sets were manually determined by selecting the CSF threshold for each clinical case after pre-processing the image slices. The signal intensity of the pixels higher than a threshold corresponding to the smallest determinable CSF pixels, were considered as CSF. The manual selection of CSF thresholds is subjective, especially in tissue interface areas. Some factors that affect manual segmentation are: display resolution, image contrast, and degree of expertise. To best approximate the true CSF volume and account for possible user variability, the CSF threshold was selected with radiological supervision. The CSF volume in each clinical case was then calculated by averaging three CSF volumes obtained by thresholds of 3% higher and lower than the original selected threshold. The results of manual segmentation are shown in Table 1.

Atrophy	Ave. CSF Threshold	Ave. % CSF	Ave. % BM	Standard Deviation
Normal	580	10.52	89.48	0.99
Mild	580	15.99	84.01	1.38
Moderate	760	20.65	79.35	1.33
Severe	565	27.47	72.53	1.62

Table 1: Clinical Study (Manual Segmentation)

In both phantom and clinical studies, the supervised algorithms, *Parzen Window*, *KNN*, *ANN* and *Gaussian*, were trained with the same training sets selected from the 5^{th} slice of each data set. These training sets were used to segment the whole volume. Representative clinical axial T2 images in the areas of the ventricles are shown, after connected component processing, in Figure 2.

3. Results

Phantom Study: The phantom results of the multi-modality algorithms are summarized in Table 2. Comparing the seven algorithms, the smallest percent error of calculated CSF was obtained by our *ISM* algorithm. The *ISM* algorithm gave the volume of 9.54cc CSF for the phantom image when the true CSF volume

was 7.945cc, or an overestimation of 20.08%. The total brain matter (GM + WM) was calculated to be 95.90cc by the *ISM* algorithm or an overestimation of 1.5%. The next best result was obtained using the *ISODATA* algorithm (9.88cc CSF, 24.35%). The *ISM* and *ANN* methods overestimated the total gray and white matter volume (95.90cc and 94.79cc vs. 94.48cc). All other methods underestimated the total brain matter. The *Parzen Window* and *Chain Method* underestimated the total volume of the phantom, while the other algorithms overestimated the total volume by 0.5-2.9%.

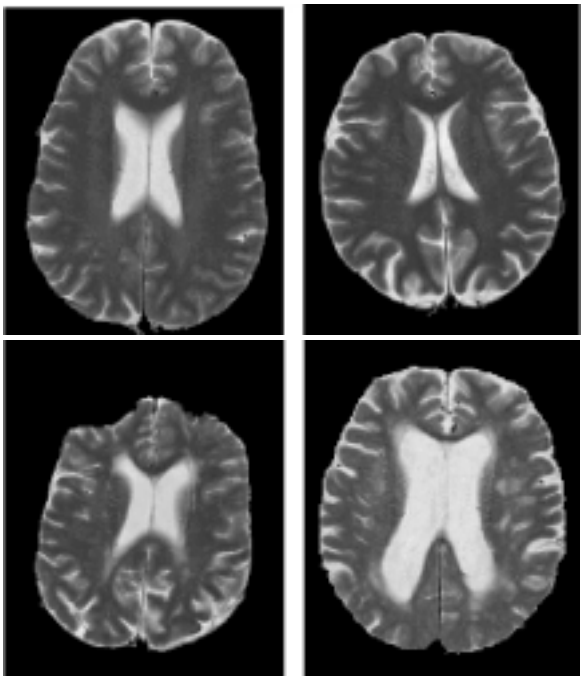

Figure 2. Representative clinical MR T2 images of individuals with neuroradiologically determined (a) normal brain, 49 y.o. female, (b) mild atrophy, 33 y.o. male (c) moderate atrophy, 87 y.o. female and (d) severe atrophy, 83 y.o. male.

The results of the single-modality algorithms are summarized in Table 3. The most accurate method for estimating CSF of the phantom was *ISODATA*. There was virtually no error in the *ISODATA* CSF determination (7.94cc CSF). However *ISODATA* overestimated the GM-WM volume by 1.85%. *ANN* gave the second best result for calculating CSF volume (10.39cc, a 30.77% overestimation) and the best results for total gray and white matter volume (94.40cc, a 0.09% underestimation). As in the majority of single-modality and multi-modality algorithms, there was an overestimation of total CSF, GM and WM. This overestimation is from multiple counting of pixels with mixed characteristics of white matter, gray matter and CSF.

Table 2. Phantom Results (Multi-Modality)

Algorithm	CSF(cc) V=7.94	%Err	GM(cc) V=49.80	%Err	WM(cc) V=44.68	%Err
ISM	9.54	20.08%	95.90#	1.50%	-	-
ISODATA	9.88	24.35%	93.07#	1.49%	-	-
ANN	10.53	32.53%	58.00	16.46%	36.79	17.66%
PARZEN	13.42	68.92%	54.98	10.40%	36.05	19.32%
KNN	16.12	102.89%	53.16	6.75%	35.37	20.84%
CHAIN	17.44	119.51%	84.85#	10.19%	-	-
GAUSSIA	17.80	124.04%	61.39	23.27%	26.13	41.51%

Table 3. Phantom Results (Single-Modality)

Algorithm	CSF(cc) V=7.94	%Err	GM(cc) V=49.80	%Err	WM(cc) V=44.68	%Err
ISODATA	7.94	0.01%	96.33#	1.85%	-	-
ANN	10.39	30.77%	57.19	1.48%	37.21	16.72%
PARZEN	10.60	33.42%	55.42	11.29%	38.52	13.79%
SHIM	11.50	44.75%	93.16#	1.40%	-	-
KNN	12.93	62.74%	55.16	10.76%	36.74	17.77%
ENTROPY	15.66	97.11%	89.00#	5.80%	-	-
CHAIN	19.24	142.17%	85.07#	9.96%	-	-
GAUSSIAN MOMENT	23.01 60.55*	189.61% 4.86%	44.53 -	10.58% -	37.84 44.10	15.31% 1.30%

GM and WM could not be separated. * CSF and GM could not be separate

Clinical MRI Data Study: The percentage CSF volume manually determined from the MRI images of four patients, with normal, mild, moderate and severe atrophies as determined by board certified neuroradiologists, were 10.52% (0.99) , 15.99% (1.38), 20.65% (1.33) and 27.47% (1.62) respectively (Table 1).

The volumetric results for the clinical studies obtained from multi-modality analysis are shown in Table 4. The *ISM* algorithm gave the most consistent results among seven multi-modality segmentation algorithms for the percent CSF volume of 13.30%, 19.82%, 22.00% and 34.71%, respectively for normal, mild, moderate and severe atrophies.

Two unsupervised algorithms of *ISODATA* and *Chain Method* did not yield consistent results. The *Chain Method* measured 25.21% CSF for the mild atrophy,

significantly higher than 24.33% CSF for the severe case. *ISODATA* gave consistent results for moderate and severe atrophies but measured a smaller percent CSF for mild atrophy (11.14%) than the normal case (13.97%). *Parzen window*, *Gaussian* and *KNN* suffered from a high percentage of unclassified pixels. The unclassified pixels were mostly extra-ventricular CSF and GM which could not be separated. This problem was partially due to interslice variation and use of the same training sets in one slice to segment the whole volume. In addition, choosing training set for GM is difficult because of small and disperse anatomical structures.

The results of the clinical studies from single-modality algorithms are shown in Table 5. Among single-modality algorithms, *2D Entropy* had the most consistent result. However, significant over estimation of the percent CSF, based on the manual segmentation, (normal 17.27%, mild 22.26%, moderate 26.54 and severe 37.80%) appeared to make this algorithm problematic. The supervised algorithms, such as *ANN*, *KNN*, *Parzen* and *Gaussian* gave very similar results to multi-modality analysis for CSF classification even though they did not use the additional information of T1 weighted image modality. *KNN*, *Parzen* and *ANN* measured about the same percent CSF for normal, mild and moderate atrophies. The *SHIM* algorithm overestimated percent CSF volume (18.89%) for the normal case and underestimated for severe atrophy (24.37% CSF). This algorithm also measured percent CSF for the moderate atrophy case 22.85%, slightly lower than mild atrophy 23.34%.

4. Discussion

The difficulty with assessing segmentation algorithms is that in-vivo results are impossible to verify. One cannot determine the CSF volume in a patient directly. CT and MR image can give accurate estimations of ventricular atrophy, but determination of an accurate volume is dependent on the algorithm used in the image analysis. The algorithms used in this study gave varied results.

For any multi-modality algorithm, registration of images is crucial for accurate segmentation. Registration is necessary prior to segmentation if there is any movement of the patient's head during the MRI scan.

The subtraction of normalized T1 from normalized T2 weighted images resulted in separation of CSF regions from the brain matter. Our phantom and clinical studies showed that the *ISM* algorithm could indeed segment CSF regions with a high degree of accuracy, reproducibility and speed. This algorithm measured the CSF volume of the phantom images with 20.08% error, the lowest among multi-modality algorithms and the second lowest among single-modality algorithms. Reproducibility of the results for CSF volume measurements in clinical cases, which have different degrees of atrophy, could be achieved by using *ISM*. WM and GM however could not be separated by this method. Although *ISM* segmented part of the *falx cerebri* as CSF (See Figure 3), this structure does not comprise a large volume. The volumes calculated by *ISM* compared to the manually segmented images were within the 20% systematic error as determined by the phantom study. It must be kept in mind that a 20% error in CSF determination represents a result of 10cc +/- 2cc CSF volume. Combined with the measurement of total GM and WM, which has a lower systematic error of 1.5%, a scale of atrophy based on brain volumes is attainable.

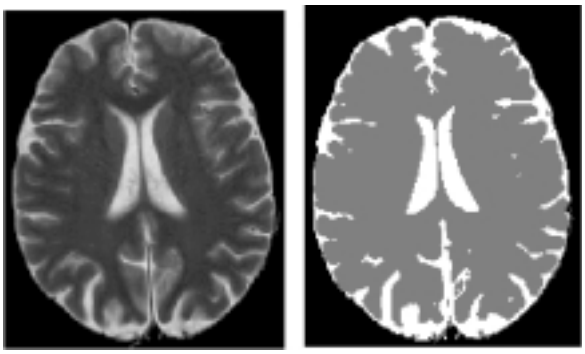

Figure 3. (a) T2-weighted image of mild atrophy after dura and background were removed. (b) Segmented image by the *ISM* algorithm.

T2 phantom and clinical images were used to test SHIM algorithm. The result showed 44.75% inaccuracy for CSF volume measurement in the phantom study. The variation of mean and standard deviation of the brain matter peaks in T2-weighted image histograms for different atrophies is one of the sources of inaccuracy in CSF volume measurement. The severe atrophy has the smallest percent brain matter, even though the peak is the highest. This is because the CSF regions made up a significant percent of the brain volume and therefore the partial volume averaging had the least effects on the brain matter. In addition, the assumption of Gaussian

distribution for brain matter with the mean and standard deviation of m and s might be acceptable for the severe atrophy case, but not for normal, mild and moderate atrophies. Overestimation of CSF for the normal case and underestimation of CSF for the sever atrophy case are believed to be due to slight variations of constant k from slice to slice and patient to patient. Any variation in k was disregarded to gain full automation. The result of the SHIM segmentation on the mild atrophy case is shown in Figure 4a. The variation of k from slice to slice can be partially resolved by using the histogram of the whole volume instead of each slice.

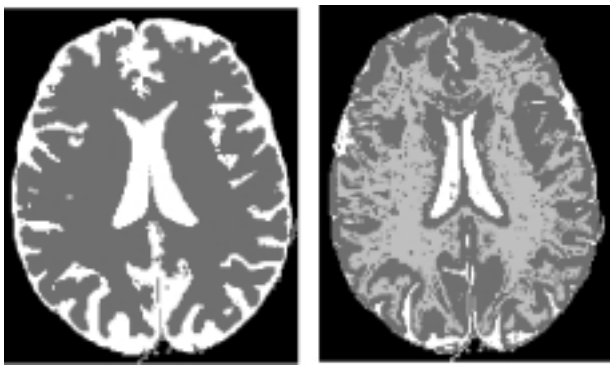

Figure 4. Segmented images of the mild atrophy data by (a) SHIM algorithm (b) single-modality Gaussian algorithm

Summary: As Tables 4 and 5 show only *ISM*, among the multi-modality algorithms, gave reasonable increases in CSF as a function of clinical atrophy as determined by neuroradiological interpretation. The *Entropy* method gave the most consistent results for the single-modality methods. Although the absolute quantitation is not possible *in vivo*, the consistency of the *ISM* results as well as the determined systematic error of this method from the phantom study show that it is a promising method with reasonable, and acceptable systematic errors. Although the CSF volumes determined by the automated algorithm are higher than the manually segmented images, a 20% overestimation of the areas determined by manual segmentation, are similar to the *ISM* results, and demonstrate a consistent increase in CSF volume with progression in atrophy (Table 6).

4. Conclusions

The results of our study indicate that the *Image Subtraction Method* gave rapid, reproducible results for both the phantom and clinical image sets. Comparing both the *ISM* and *SHIM* methods with six multi-modality and eight single modality segmentation algorithms, we have found that there is no method for CSF volume determinations without systematic errors and limitations. In a clinical setting, we believe considerations such as automation and rapidity of data analysis are important. Expert systems, such as *KNN* and *Parzen*, which require a trained technician or medical expert to supervise and run the algorithms, are not practical for routine patient care. Furthermore, the volumetric results from the supervised algorithms are subject to errors from the signal-to-noise variations in the areas chosen as the training pixels. These factors make the results of expert systems difficult to reproduce, even for trained personnel.

Table 6. Final Comparative Results

Atrophy	Ave. %CSF Manual	Ave. %CSF + 20%	%CSF by ISM	%CSF by Entropy
Normal	10.52	12.62	13.30	17.27
Mild	15.99	19.19	19.82	22.26
Moderate	20.65	24.78	22.00	26.54
Severe	27.47	32.96	34.71	37.80

It has been our goal to develop a rapid and reliable methodology to determine the percentage of CSF and total white and gray matter for clinical evaluation of progressive atrophy disease, such as HIV and Alzheimer's disease. At present neuroradiologists use a relative scale of normal, mild, moderate and severe atrophy. Inter-reader variability and clinical experience can affect image interpretation. Clearly, a reproducible automated or semi-automated system, with known systematic errors, would give a more reproducible and consistent clinical evaluation for progressive degenerative brain diseases, independent of observer variability. We believe that a semi-quantitative atrophy scale is now possible and that disease related atrophy may be distinguished from "age-related" atrophy as often reported in clinical studies. Because of the rapid analysis of image information obtainable by *ISM*, and the reasonable and reproducible errors in estimating brain volumes, we are pursuing this methodology in further studies.

Table 4. Clinical Study (Multi-Modality)

Algorithm	Normal % CSF	Mild % CSF	Moderate % CSF	Severe % CSF	Normal % GM	Mild % GM	Moderate % GM	Severe % GM	Normal % WM	Mild % WM	Moderate % WM	Severe % WM
ISM	13.30	19.82	22.00	34.71	86.70#	80.18#	78.00#	65.29#	-	-	-	-
ISODATA	13.97	11.14	20.15	21.75	86.03#	88.46#	79.85#	76.97#	-	-	-	-
ANN	12.75	10.83	7.33	21.89	30.85	44.55	43.71	20.11	56.40	44.62	48.96	58.01
PARZEN	7.76	7.24	9.10	19.72	34.92	42.22	32.75	21.01	51.76	46.35	49.76	55.43
KNN	7.04	7.46	7.31	20.06	27.73	37.49	28.62	18.12	56.92	47.87	50.03	56.37
CHAIN	13.32	25.21	15.09	24.33	21.79	38.34	24.71	16.09	61.45	34.49	55.33	57.00
GAUSSIAN	5.43	7.66	5.04	18.08	30.29	44.19	29.50	20.97	52.04	42.92	47.02	53.48

Table 5. Clinical Study (Single-Modality)

Algorithm	Normal % CSF	Mild % CSF	Moderate % CSF	Severe % CSF	Normal % GM	Mild % GM	Moderate % GM	Severe % GM	Normal % WM	Mild % WM	Moderate % WM	Severe % WM
ISODATA	13.84	30.16	15.33	29.24	86.16#	69.84#	84.67#	70.76#	-	-	-	-
PARZEN	6.83	7.35	8.66	18.96	32.13	42.11	27.14	17.08	61.04	50.54	63.24	64.26
SHIM	18.89	23.34	22.85	24.37	81.11#	76.66#	77.15#	75.63#	-	-	-	-
KNN	6.78	7.21	7.33	18.88	25.63	42.27	23.82	15.62	67.59	50.52	64.96	65.35
ENTROPY	17.27	22.26	26.54	37.80	82.73#	77.74#	73.46#	58.18#	-	-	-	-
CHAIN	9.98	9.59	11.87	23.89	26.85	19.64	21.81	20.96	63.17	70.77	67.76	55.15
AUSSIAN	7.03	7.01	2.36	16.80	14.17	59.21	97.64#	22.40	75.67	33.78	-	60.79
ANN	8.31	8.30	7.31	18.62	30.66	41.16	22.38	15.95	61.03	50.54	70.31	65.43
MOMENT	64.82*	59.19*	63.78*	65.28*	-	-	-	-	35.18	40.81	36.22	34.72

GM and WM could not be separated. * CSF and GM could not be separated.

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