<u>*Araştırma Makalesi*</u>

<u>*Research Article*</u>

Comparison Global Brain Volume Ratios on Alzheimer's Disease Using 3D T1 Weighted MR Images

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Abstract

Alzheimer's Disease is a cause of dementia that starts with the loss of cognitive functions. The degeneration that starts in memory-related areas in the brain spreads to other regions as the disease progresses. Volumetric losses occurring in the brain can be monitored with high resolution 3D T1-weighted magnetic resonance images. The interpretation of these images is carried out by radiologists in hospitals. However, since the voxel intensity transitions of the brain regions are not clear in magnetic resonance images, computer-aided numerical methods are needed. These methods can perform pre-processing, post-processing, segmentation and volume calculation on magnetic resonance images. In this study, gray matter, white matter, cerebrospinal fluid, total intracranial volume, parenchyma, and lateral ventricle global volumes were calculated for 70 Alzheimer Patients and 70 Normal Control 3D T1-weighted magnetic resonance images taken from Open Access Series of Imaging Studies database. SPM8 and MRIcro programs, ALVIN and VBM8 libraries were used. Since the numerical methods used are found in different programs and libraries, a model is proposed which combinations should be used. Volumetric results are relative due to the different head sizes in each person. Therefore, the problem of relativity should be eliminated by proportioning each volume value with another volume value. Twenty different metrics of the brain were obtained by summing and dividing the six global volume regions obtained in different combinations. Using these values, it was determined whether there was a statistically significant difference between two groups by independent samples t-test. The performance of the numerical methods and the statistical results of twenty metrics obtained from global brain volumes were discussed. After measurements and evaluations, it was observed that the ratio of cerebrospinal fluid volume to gray matter volume was an important marker in the differential diagnosis of the disease.

Keywords: Alzheimer, Volume, Ratios, SPM8, VBM8, MRI

3B T1 Ağırlıklı MR Görüntüleri Kullanarak Alzheimer Hastalığına İlişkin Global Beyin Hacim Oranlarının Karşılaştırılması

Öz

Alzheimer Hastalığı bilişsel fonksiyonların kaybı ile başlayan bir demans nedenidir. Beyinde hafıza ile ilgili bölgelerde başlayan dejenerasyon hastalık ilerledikçe diğer bölgelere yayılmaktadır. Beyinde meydana gelen hacimsel kayıplar yüksek çözünürlüklü 3B T1 ağırlıklı manyetik rezonans görüntüleri ile izlenebilmektedir. Bu görüntülerin yorumlanması hastanelerde radyologlar tarafından gerçekleştirilmektedir. Ancak manyetik rezonans görüntülerinde beyin bölgelerinin voksel intensite geçişleri net olmadığından bilgisayar destekli sayısal yöntemlere ihtiyaç duyulmaktadır. Bu yöntemler manyetik rezonans görüntüleri üzerinde önişleme, son işleme, segmentasyon ve hacim hesaplama yapabilmektedir. Bu çalışmada Open Access Series of Imaging Studies veri tabanından alınan 70 Alzheimer Hasta 70 Normal Kontrol 3B T1 ağırlıklı manyetik rezonans görüntüleri üzerinde bilgisayar destekli sayısal yöntemler kullanılarak gri madde, beyaz madde, beyin omurilik sıvısı, total beyin hacmi, parankima ve lateral ventrikül bölgelerinin hacimleri hesaplanmıştır. Çalışmada SPM8 ve MRIcro programları , ALVIN ve VBM8 kütüphaneleri kullanılmıştır. Kullanılan sayısal yöntemler farklı program ve kütüphaneler de bulundukları için hangi kombinasyonda kullanılmaları gerektiğini gösteren bir model

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önerilmiştir. Her insanda kafa büyüklüğünün farklı olmasından dolayı hacimsel sonuçlar göreceli olmaktadır. Bundan dolayı her bir hacim değeri başka bir hacim değeri ile oranlanarak görecelik problemi ortadan kaldırılmalıdır. Elde edilen altı global hacim bölgesinin farklı kombinasyonlarda toplanması ve bölünmesi ile beyne ait yirmi farklı metrik elde edilmiştir. Bu değerler kullanılarak bağımsız örneklem t-testi ile iki grup arasında istatistiksel olarak anlamlı bir farklılık olup olmadığı belirlenmiştir. Kullanılan sayısal yöntemlerin performansı ve global beyin hacimlerinden elde edilen yirmi metriğin istatistiksel sonuçları tartışılmıştır. Ölçümler ve değerlendirmelerden sonra beyin omurilik sıvısı hacminin gri madde hacmine oranının hastalığın ayırıcı tanısında önemli bir işaretçi olduğu gözlemlenmiştir.

Anahtar Kelimeler: Alzheimer, Hacim, Oran, SPM8, VBM8, MRI

1. Introduction

Alzheimer's Disease (AD) is a neurological disorder that starts with aging and forgetfulness. It is not known why the disease started and there is no cure to stop it. If it can be diagnosed at an early stage, there are some treatments that extend the patient's AD stage for some time (Dubois et al., 2016). Approximately 50-70% of the causes of dementia seen in the clinic are AD (Selekler, 2010). While the proportion of many common diseases is decreasing in the world, AD is increasing proportionally (Association, 2019). According to the Alzheimer's Association of Turkey, 600 thousand families in our country are struggling with AD (Derneği, 2020). AD begins with simple forgetfulness and volumetric losses occur in memory-related areas of the brain. These volume changes of the brain regions and their ratios to each other give information about the disease as a biomarker (Holland et al., 2009; Petropoulos, Sibbitt Jr, & Brooks, 1999; Schuff et al., 2009; Villarreal et al., 2002). These biomarkers are extremely important in terms of diagnosis of the disease, early phase identification, long-term follow-up (G. B. Frisoni, Fox, Jack, Scheltens, & Thompson, 2010; Vemuri & Jack, 2010). 3D Magnetic Resonance (MR) imaging is a high-resolution medical imaging technique that shows rigid changes in the brain (G. B. Frisoni et al., 2010; Vemuri & Jack, 2010). MR images consist of successive slices. Therefore, if a slice is being evaluated, the previous and next slice of that slice should also be evaluated together. 3D MR images are usually interpreted manually by radiologists. This interpretation gives specific information about the disease such as volumetric measurements, perimeters, segmentation, and the amount of atrophy. However, the results of the calculation of these variables may vary from experiment to experiment and give relative results. It is also time-consuming and capable of making mistakes (Keller & Roberts, 2009). Since the voxel intensity transition between brain regions is not very clear in MR images, computer-aided digital systems that measure and segment regions automatically instead of manual interpretations could be an effective solution. With the increasing of numerical methods, automatic brain analysis programs are continuously being developed. Linux based Freesurfer (Fischl, 2012) and FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012), MATLAB based Statistical Parametric Mapping (SPM) (Ashburner et al., 2008) are frequently used in the literature. These programs can perform pre-processing, post-processing and segmentation operations on images using powerful algorithms.

The brain consists of three basic areas: gray matter (GM), white matter (WM), cerebrospinal fluid (CSF). GM is a region where functional centers are located. WM is the region where neurons are located under GM. The CSF is a fluid that protects the brain from outside interventions. Since AD starts with forgetfulness, volumetric losses occur primarily in the memory-related regions. Atrophy occurs especially in the hippocampus, amygdala, limbic system and temporal lobe areas on GM (Petrella, Coleman, & Doraiswamy, 2003). It is stated that there are also some losses in the WM (Salat et al., 2009). As volumetric losses in GM and WM regions increase, the amount of CSF increases. The lateral ventricle (LV) in the middle of the brain enlarges, and this part is filled with CSF. As a result, GM, WM, CSF and LV volumes are the main global volume biomarkers for the disease. In this study, GM, WM, CSF and LV volume measurements were calculated by using packet programs on 3D T1-weighted Normal Control (NC) and AD MR images. 70 AD and 70 NC 3D T1-weighted MR images were taken from the Open Access Series of Imaging Studies (OASIS) database. MR images have been labeled with Clinical Dementia Rating (CDR) neuropsychological test. Using this test, some questions are asked to patients and their relatives. Thus, the stage of the disease is determined. CDR consists of five phases; CDR0 normal, CDR0.5 mild cognitive impairment, CDR1 early stage, CDR2 moderate stage, CDR3 heavy stage. There are data labeled between CDR0-CDR2 in the OASIS database. In Figure 1, a single slice of MR images labeled CDR0, CDR0.5, CDR1, CDR2 are given, respectively. As seen in Figure 1, as the stage progresses, the brain shrinks and volumetric losses increase (Öziç, 2018).
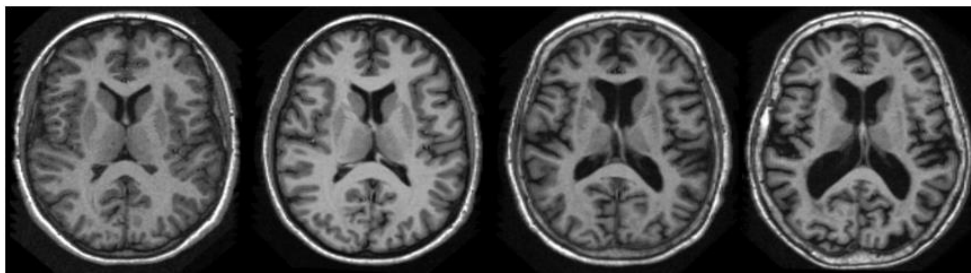

Figure 1: Single slice of MR images labeled CDR0, CDR0.5, CDR1, CDR2, respectively (Marcus et al., 2007)

MRIcro, SPM8, VBM8, ALVIN package programs were used in this study (Kempton et al., 2011; Kurth, Luders, & Gaser, 2010; MRIcro, 2020; Penny, Friston, Ashburner, Kiebel, & Nichols, 2011). ALVIN and VBM8 are an SPM8 plugin. MRICro is used for preprocessing and visualization. The programs used are not sufficient for volume calculation alone. The output of one program can be

the input of another program. Therefore, in this study, a model regarding the order in which package programs and libraries can be used is also proposed. For the analysis of AD disease, a total of twenty metrics were derived, with different combinations of six global volume regions: GM, WM, CSF, LV, Total Intracranial Volume (TIV (GM+WM+CSF)), and Parenchyma (GM+WM). The measured values were analyzed with independent samples t-test. It was evaluated whether the values were significant or not.

2. Material and Methods

2.1. Data Set

70 AD and 70 NC T1 weighted MR images were taken from the OASIS database. The OASIS database consists of MR images ranging in age from 18 to 96. The images are composed of young and old AD MR images. MR data are labeled with Mini Mental Status Test (MMSE) and Clinical Dementia Rating (CDR) neuropsychological tests. MMSE scoring ranges from 0-30, while CDR ranges from 0-3. The OASIS database contains only labeled CDR0-2. Therefore, images labeled CDR0 as NC, images labeled CDR0.5-2 were used as AD in this study. Since age 65 is a risk factor for AD, data above this age were taken from the database. Data set used and demographic distrubution are given in Table 1. There are MR images already pre-processed and registered to the Talairach axis in the database. However, these registered images do not represent actual volume values. Therefore, only the raw images prefixed with "OAS1_xxxx_MRy_mpr _ni_ anon_sbj_111" were taken. The necessary pre-processing on the raw images have been performed in the study. OASIS database imaging protocols are TE:4.0 msec, TR:9.7 msec, TI:20 msec, flip angle=10, 128 sagittal, 1.25 slice thickness without gap, pixel resolution 256x256 (1x1mm) and T1 weighted magnetization-prepared rapid gradient echo (MPRAGE) multiple high- resolution images via 1.5 T vision scanner (Siemens, Erlangen, Germany)(Marcus et al., 2007).

Table 1: Data set used in this study and demografic distrubution

NC						AD					
Age Gr.	**Numb.**	**M\F**	**Mean Age**	**Mean MMSE**	**CDR**	**Age Gr.**	**Numb.**	**M\F**	**Mean Age**	**Mean MMSE**	**CDR**
60s	9	3\6	68.00±1.11	28.77±1.64	0	**60s**	7	3\4	67.85± 1.21	23.42± 4.85	5\2\0
70s	32	8\24	73.37±2.44	29.15±0.91	0	**70s**	35	14\21	74.42±2.61	24.54±4.21	23\11\1
80s	22	6\16	83.40±3.27	28.77±1.26	0	**80s**	23	11\12	82.69± 2.61	24.47 ±4.06	16\6\1
90s	7	1\6	91.14±1.67	28.57±1.71	0	**90s**	5	2\3	92.00± 2.44	23.80±1.92	4\1\0
Total	70	18\52	77.61±7.48	28.92± 1.21	0	**Total**	70	30\40	77.74 ±6.66	24.35 ±4.05	48\20\2

2.2. Measurement of Global Brain Volumes

To make volume analysis in 3D raw MR images, some pre-processing techniques must be done. Firstly, images were converted from the sagittal axis to axial axis with MRIcro program. Because the template images in VBM8 and SPM8 programs are defined on the axial axis, this process must be done. With the *"Display"* option of SPM8 program, a reorientation process was performed to the Anterior Commissure (AC) point. This point is considered to be the center point of the brain (x, y, z = 0) (Talaraich & Tournoux, 1988). This process is called AC/Posterior Commissure (PC) line correction. Otherwise, the MATLAB program gives an error in the next steps. These data for the segmentation process were given to input of the VBM8 library. VBM8 library is an SPM8 plug-in that combines the preprocessing and segmentation stages of structural MR images. Using this plug-in, bias correction, denoising, normalization, and segmentation processes were performed automatically on the 3D structural MR images. The high-dimensional Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) method was chosen for normalization to the Montreal Neurological Institute (MNI) space. The DARTEL method was proposed by John Ashburner (Ashburner, 2007). This normalization method gives the best register among 14 different normalization algorithms (Klein et al., 2009). It also gives the best register between MR images taken with different protocols from different centers (Goto et al., 2013). The Modulation method was preferred for segmentation. Modulation operation is an option that maintains the volume in the native space before normalization (Mechelli, Price, Friston, & Ashburner, 2005). As a result of the processes, segments of GM, WM ,and CSF regions were obtained in Montreal Neurological Institue (MNI) space. Image volumes were calculated by using "get_totals.m" MATLAB script developed by Ged Ridgway (Ridgway, 2020). LV volume and segmentation were obtained with the ALVIN program over the modulated CSF images segmented with the SPM8 program (Kempton et al., 2011). The amount of TIV was calculated by summing up GM, WM and CSF volumes, and the Parenchyma (PRM) tissue volume was calculated by summing up GM and WM volumes. Thus, the volumes of six regions in total were calculated in milliliters (ml). In Figure 2, a flow diagram that performs pre-processings on raw 3D T1-weighted MR image of the subject numbered 430 from OASIS database and finding segmentation and volume values of GM, WM, CSF, LV, TIV, PRM regions are given. Three-dimensional models of four global brain regions are shown in Figure 3. In Figure 4, the borders of the GM, WM, CSF, PRM, TIV regions on the MR image and the LV region's borders on the modulated segmented GM are given.
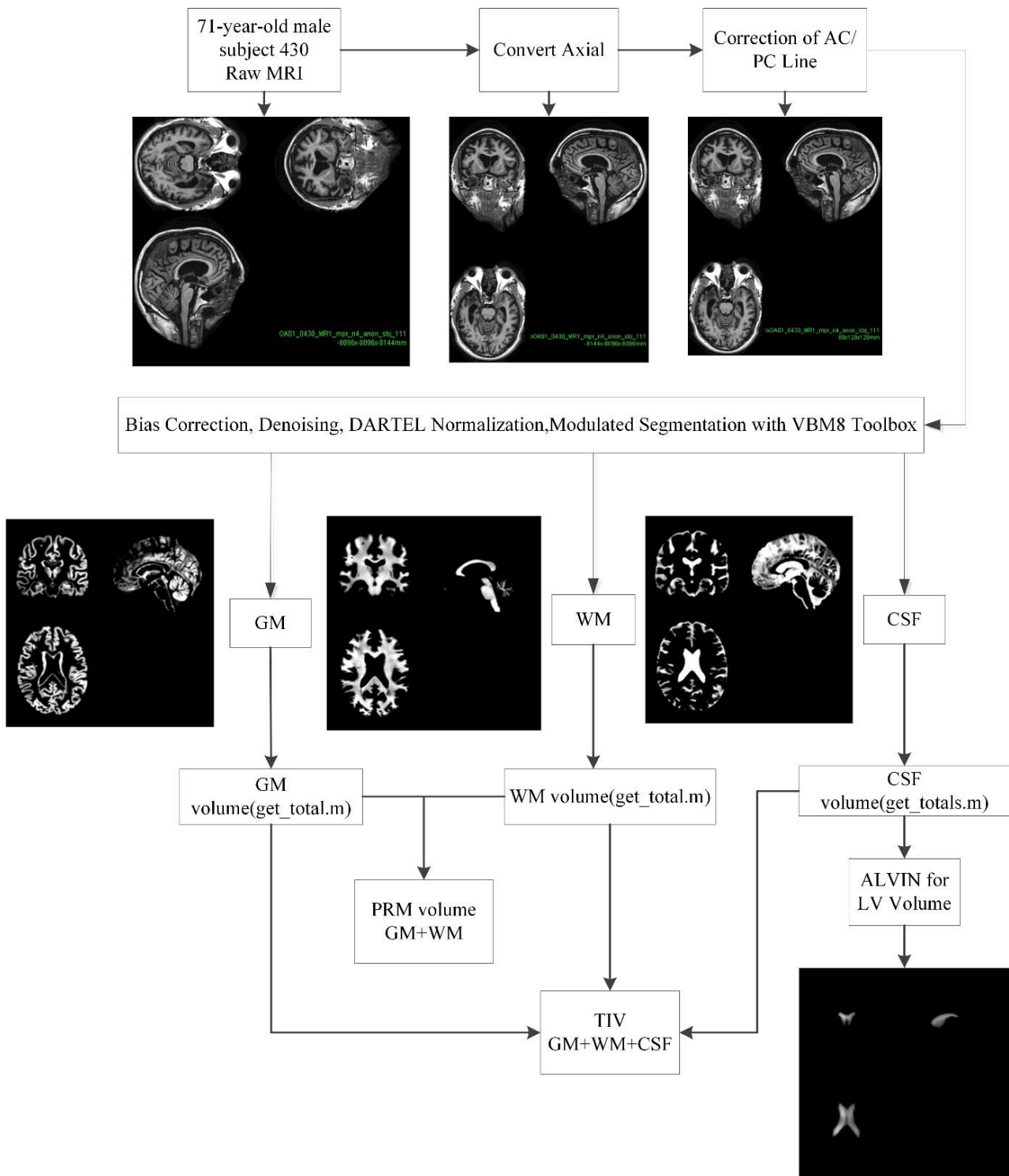
Figure 2. Flow diagram that performs pre-processings on raw 3D T1-weighted MR image of the subject numbered 430 from OASIS database and finding segmentation and volume values of GM, WM, CSF, LV, TIV, PRM regions (Öziç, 2018)
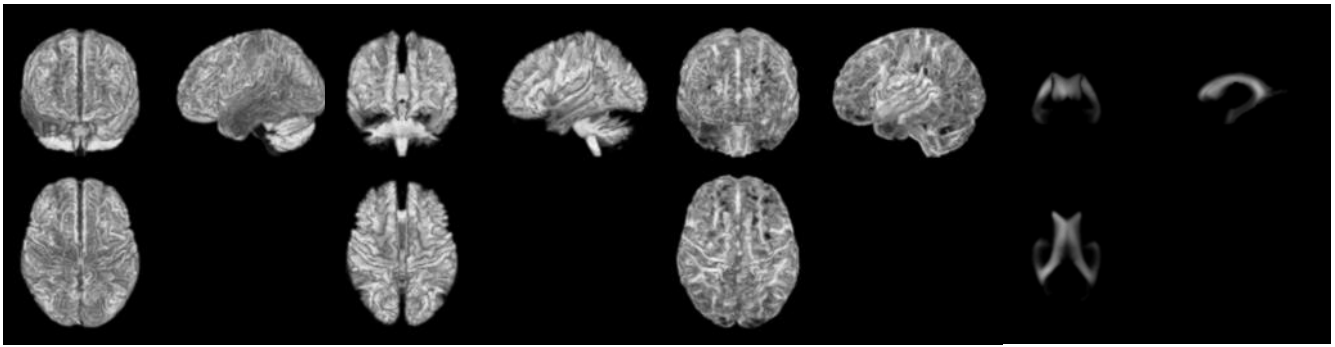
Figure 3. Three-dimensional models of four global brain regions (GM, WM, CSF, LV)
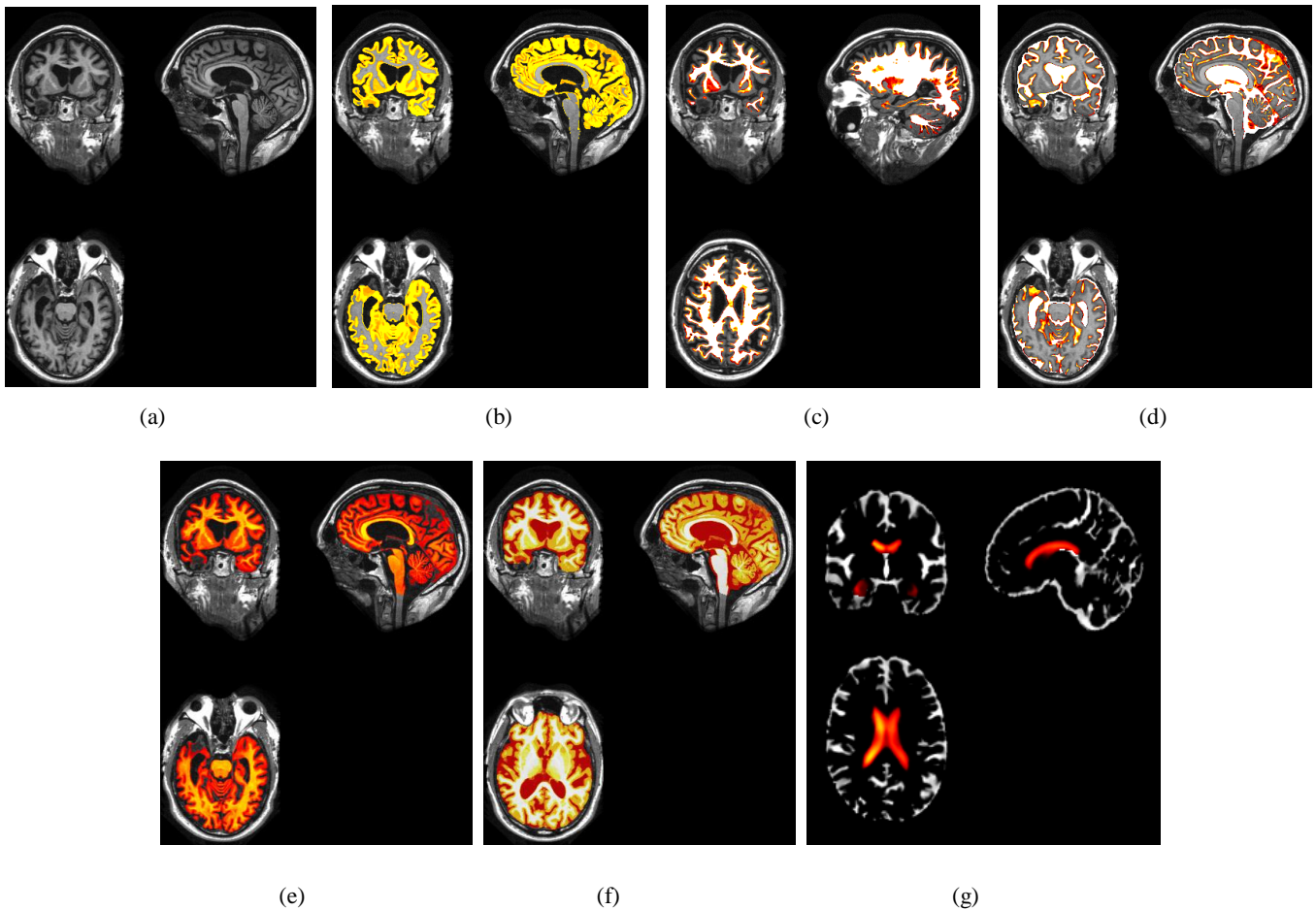

Figure 4. (a) Converted axial plane OASIS 430 raw MR image (b) GM borders on raw MR image (c) WM borders on raw MR image (d) CSF borders on raw MR image (e) Parenchyma borders on raw MR image (f) TIV borders on raw MR image (g) LV borders on modulated segmented GM

3. Research Results and Discussion

GM, WM, CSF, PRM, TIV, LV volumes were obtained by using the flow diagram in Figure 2 in each T1-weighted 3D MR image. With the volumes of the six regions obtained, twenty-six metrics were derived from different ratios and combinations. Mean and standard deviations of all metrics were calculated for AD and NC groups. Whether the values are significant between AD and NC was calculated by independent samples t-test. Mean, standard deviation and p significance value of the metrics are given in Table 2. The metrics were sorted in the table from the most significant to the most insignificant with respect to p value.

Table 2: Mean, standard deviation and p significance values of the metrics(Öziç, 2018)

	AD		NC		Stats
	Mean	Std	Mean	Std	p
CSF/GM	0.598	0.085	0.53	0.072	1,00E-06
(WM+CSF)/TIV	0.586	0.022	0.57	0.016	2,00E-06
GM/TIV	0.414	0.022	0.43	0.016	2,00E-06
(LV+CSF)/TIV	0.28	0.034	0.253	0.033	7,00E-06
CSF/TIV	0.246	0.025	0.227	0.024	9,00E-06
PRM/TIV	0.754	0.025	0.773	0.024	9,00E-06
CSF/ PRM	0.328	0.044	0.295	0.041	1,00E-05
CSF	337	47.97	305.3	40.49	4,00E-05
LV/GM	0.082	0.032	0.063	0.027	0.0002
WM/CSF	1.Nis	0.19	1.538	0.231	0.0002
LV/ PRM	0.045	0.017	0.035	0.015	0.0004
LV/TIV	0.034	0.012	0.027	0.011	0.0006
LV	46.44	19.77	36.01	15.58	0.0007
LV/WM	0.099	0.038	0.078	0.034	0.0009
(GM+LV)/TIV	0.447	0.019	0.456	0.013	0.0018
LV/CSF	0.135	0.044	0.115	0.041	0.0068
WM/GM	0.824	0.064	0.801	0.051	0.0149
GM/ PRM	0.549	0.019	0.556	0.016	0.018
WM/ PRM	0.451	0.019	0.444	0.016	0.018
GM	565.9	55.93	578	47.35	0.1706
(WM+LV)/TIV	0.374	0.018	0.37	0.017	0.2347
(GM+CSF)/TIV	0.66	0.017	0.656	0.018	0.2548
WM/TIV	0.34	0.017	0.344	0.018	0.2548
TIV	1369	132.9	1346	116	0.2861
PRM	1032	104.7	1041	96.57	0.5934
WM	466.2	55.73	463.2	53.19	0.7488

The most significant value in AD and NC volume comparison is found in CSF/GM. GM/TIV and (WM+CSF)/TIV demonstrate a high degree of statistical significance after CSF/GM. GM, (WM+LV)/TIV, (GM+CSF)/TIV, WM/TIV, WM, TIV, PRM values are statistically insignificant. Since AD begins with forgetfulness, initial volumetric differences occur in memory-related brain regions on GM. In the literature, there are studies showing that volumetric losses and differences occur in GM and WM using voxel-based morphometry (G. Frisoni et al., 2002; Guo et al., 2010). But in this study, GM, WM, Parenchyma volume values alone gave meaningless results. Even if volumetric loss occurs in these regions, the different head size of each person gives meaningless results in volume comparisons. To overcome this problem, it is usually used by normalizing the measurements to a value. Normalization is performed by dividing the measured value by TIV or GM. Another approach is the proportion of measured values to each other (Ge et al., 2002; Orellana et al., 2016; Youn & Hsiung, 2015). The aim of these approaches, even if the values measured in healthy people differ among themselves, their proportions to each other or global volumes will be similar. Therefore, patient-normal comparisons made using volume values will yield more objective results. Since there is the volumetric loss in GM and WM regions, CSF is filled to these regions. Since CSF increases too much, it shows a significant difference both alone and in TIV normalization. Significant differences were observed in LV volume alone and in TIV normalization as the LV region expands and the volume increase is very high (Bigler, 2015; Rababa'h, 2014). Since the skull does not shrink and the total brain volume does not change, it is an expected result that no significant difference TIV volume is observed. Since the PRM region is the sum of WM and GM, the change in this region significantly affected the statistical results in the combinations using PRM. As a result of the experiments, the normalization process to the TIV and Parenchyma regions mostly gives meaningful results. At the same time, the proportion of areas where volumetric loss is expected gives each other meaningful results. CSF/GM, (WM+CSF)/TIV, GM/TIV, (LV+CSF)/TIV, PRM/TIV, CSF/PRM, LV/ GM, WM/CSF, LV/PRM, LV/GM, WM/CSF, LV/PRM, LV/TIV, LV/WM, (GM+LV)/TIV, LV/CSF, WM/GM, GM/PRM, WM/PRM rates and normalization processes are the remarkable results of the study.

4. Conclusion

Volumetric differences measured for AD in 3D T1-weighted MR images have a biomarker feature for the disease. In this study, global volumetric calculations were made with a model developed in AD and NC MR images, the ratios of regions to each other and the results of normalization processes were evaluated statistically. In the literature, although values such as GM / WM, GM / TIV are generally used for comparison, in this study has been determined that the ratios of other regions in the brain may give statistically significant results. Therefore, different rates determined in the study can be used as a biomarker for the disease. The different head sizes of each person can give misleading results for the analysis of regions alone in volumetric analysis studies. In this study, misleading points are statistically revealed and discussed after volumetric measurements. CSF/GM ratio has been proven in the study that it is an important and powerful biomarker for the disease. Manual interpretation of 3D MR images is a laborious, user-prone, time-consuming process. Computer-aided numerical methods can give more accurate and faster measurement results practically. With the measurement method used in this study, global brain regions can be measured quickly. In the future, it is an expected development in the field of medicine that such numerical methods are analyzed through the MR device or server and directed to the doctors as a pre-diagnosis in the form of a report.

Kaynakça

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