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An MRI Study on Volumetric Changes in the Brain of Female Adolescents with Autism

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Abstract

This study attempts to identify regional differences in brain volume between the known brain disorders to detect autism with an integrated approach that uses several image-processing techniques. Neuroimages from 5 autistic 17 years old female patients and 10 female control (17 ± 1 years old), were used. These images were from dual-echo, fast spin echo slices (1,5 mm^3 thickness) that were acquired through Magnetic Resonance Image (MRI) scanners. The slices were segmented into gray matter and white matter. Several image-processing techniques such as global thresholding, adaptive thresholding and k-means algorithm were used to calculate the volumetric data of the brain tissue. The results are analyzed with independent sample of t-tests to compare the outcome for the autistic subjects with control group. Previous structural neuroimaging studies were reviewed; these studies were integrated to obtain results that detect gray matter, white matter, and whole brain volumes. The literature suggests that there are different results for each age group of autistic people. The results show that there is no significant volumetric growth in whole brain between control group and autistic female adolescents; but larger white matter volume was determined in 17 years old female autistic adolescents.

Keywords: Autism, Thresholding algorithms, K-means, Volumetric measurements, Gray level distribution.

Otizmli Kadın Ergenlerin Beyinlerindeki Volumetrik Değişimler Üzerine Yapılmış Bir MR Çalışması

Özet

Bu çalışma bazı görüntü işleme tekniklerini bir arada kullanan bir yaklaşımla bilinen beyin hastalıklarından biri olan Otizm hastalığını beyin hacmindeki bölgesel farklılıklardan tespit etmeyi hedeflemektedir. Görüntüler, 17 yaşında 5 otistik kadın ergen hastadan ve 10 kişiden oluşan kadın sağlıklı kontrol grubundan (17 ± 1 yaşında) oluşmaktadır. Bu görüntüler 1,5 mm^3 çift eko, hızlı spin eko kesitlerden oluşup Manyetik Rezonans Görüntü tarayıcılarından elde edilmiştir. Kesitler gri cevher ve beyaz cevher olarak ayrılmıştır. Global eşikleme, adaptif eşikleme gibi bazı görüntü işleme teknikleri ve k-means algoritması beyin dokusuna ait volumetrik veriyi hesaplamak için birlikte kullanılmıştır. Bağımsız iki grup olan otistik ve kontrol grubu arasındaki farkı karşılaştırmak için istatistiksel t-testi metodu ile analizi yapılmıştır. Önceden yapılmış olan yapısal nörolojik görüntüleme çalışmaları gözden geçirilmiş; bu çalışmalar gri cevher, beyaz cevher ve tüm beyin volumlerini ortaya çıkarmada

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kullanılmıştır. Literatür, otistik insanlar arasında her bir yaş grubu için farklı sonuçlar olduğunu göstermektedir.

Sonuçlar kontrol grubu ve otistik kadın ergenler arasında tüm beyin hacminde önemli bir büyüklük farkının var olmadığını, fakat 17 yaşında kadın ergenlerde daha büyük beyaz cevher hacminin saptandığını göstermektedir.

Anahtar Kelimeler: Otizm, Eşikleme algoritmaları, K-means, Volum hesaplamaları, Gri seviye dağılım

1. INTRODUCTION

Autism is a neuropsychiatric disorder that begins in the early period of childhood and lasts throughout life [1]. This brain disorder causes delays in cognitive development of the affected individual, results in communicative difficulties, abnormal behavior, and deficient social reciprocity.

Recent developments in the recognition of autism show that this disorder may be a result of familial and environmental factors. It is also known that some anomalies such as mental deficiency, epileptic disorders and abnormalities observed in electroencephalographic (EEG) abnormalities may accompany. Genetic studies and studies performed in the field of brain anatomy, physiology, histology and brain functions have proved that this complex syndrome is a neuro biological disorder [2]. Despite the vast literature about the topic, understanding the mechanisms underlying autism and still challenges researchers discover the changes in cerebral function in autism.

Since identification of autism by Leo Kanner in 1943 [3], several functional and structural imaging studies have been done regarding neuro-anatomical disorders. Neuroimaging studies provide important pathways towards the description of both the neuroanatomy and the pathophysiology of autism. In previous volumetric MRI studies, an increase in volume was detected in certain brain sub-regions and in the brain as a whole, but the distribution of this volume increase to the cerebral white matter, gray matter, and subcortical regions of the brain may vary [2]. Examination of the amygdala region shows a trend towards an increased volume in children but not in adolescents [4].

No significant differences with respect to gender have been detected for the total brain volume. However, the head differences in circumference in adolescents and adults have been detected [5]. White matter is composed of nerve fibers that support the communication between brain cells. It is still unknown whether an increase in white matter causes developmental disorders or abnormal behavior. Recent studies show that there are irregular connections in certain regions of the brain of autistic patients and less frequent connections between other regions [2]. For this reason, even though autistics are sensitive to details, they fluster in intuitive perception.

Genetic factors play a significant role in cerebral disorders [5]. During the first years of life of babies with autism, the brain exhibits abnormal growth, and so babies live in chaos. The chaos may be the result of excessive production of cells that carry nerve impulses in white matter. A significant increase in brain volume has been reported more often with autistic children between the ages of 2 and 4 years old [6, 7] compared to autistic adolescents and adults [8, 9]. Therefore, it is hypothesized that cerebral enlargement is faster in the early stages of children with autism spectrum disorder (ASD) [10, 11]. Some studies indicate that the disproportional growth and enlargement of the left-side gray matter continue in adolescence and adulthood with autism [12]. Recent studies with children between the ages of 2 and 4 years reveal that volume increase occur in gray matter, white matter, and several other brain regions in ASD; however, the volume increase may disappear after the children become teenagers [5, 8]. Detailed anatomical studies require an automated voxel-based technique with

nonparametric structure that would be more effective and sensitive. Considering the difficulties to obtain standard image intensity information [13] for all image series, a semi-automated technique has been preferred. Moreover, statistical parametric mapping of gray and white matter has been used for a non-parametric brain mapping approach [14-15].

The objective of this study is to develop an image processing method which detects autism in an effective and simple way. Image processing and clustering methods were used for brain segmentation, volumetric thickness measurements and calculations of volume ratios with thresholding techniques and k-means clustering algorithm.

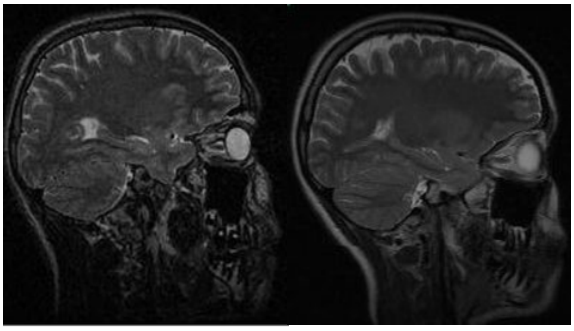
2. MATERIALS AND METHODS

2.1. Materials

The study focused on five 17 years old autistic adolescent females, because autism is seen less frequently in females than in male, and the adolescence in 17 years old is also a time for developing social and mental skills which is important for cognitive development. Utilizing appropriate clinical criteria, considering neurological history together with physical examination, the subjects were distinguished from persons who were under the effect of other neurological developmental disorders, such as Asperger syndrome, childhood disintegrative disorder, Rett syndrome and pervasive developmental disorder (PDD) [16]. Control subjects were 17 ± 1 years old adolescent females with no personal or family history of neurological disorders or psychiatric illnesses.

2.2. Image Acquisition

All MRI scans were obtained on a 1.5T GE HDx Signa MRI scanner (GE Healthcare, Milwaukee, WI, USA) using the Digital Imaging and Communications in Medicine (DICOM) that contains both a header and 3D image data. 3D Fast spin echo (FSE) imaging sequence sagittal series (repetition time (TR) = 4000 ms; echo time (TE) = 105 ms; flip angle = 90˚) of 1,5 mm^3 slice



(a)Autistic Subject (b) Control Subject

Figure 1. Example of a visual comparison of slices with control subject and autistic subject-17 years old (Sag 3D FSE)

thickness were used. FSE pulse sequence used for each slice because each slice has same processing stream. The sagittal slices of control subjects are consisted of different numbers of a contiguous 512x384 matrix. In order to extract the volumetric size of brain, white matter and gray matters, the sagittal slice dimensions for each control and autistic groups were reconstructed from 512 x 384 to 256 x 256 matrixes.

2.3. Methods

The approach utilized is a MR-based method to determine the abnormalities and boundaries of white matter, gray matter and whole brain, associated with autism spectrum disorder. In this approach, we focus first on the segmentation of the MR-image to distinguish the brain mass from the other tissues such as skull, scalp and cerebrospinal fluid (CSF), then on the computation of the brain volume based on 3D renderings. The latter involves extracting the volumes of white matter and gray matter, determining their densities and their volume ratio. The last step utilizes the k-means method [17] to cluster the specified regions in the brain. Finally, the whole brain and regional brain volumes of gray and white matter for control and autistic groups are comparatively analyzed. The procedures were evaluated on all autistic and

control subjects. The MRI scan data were explored for the properties of anatomical volumes of 3D renderings to obtain segmented volumes. The intensity-based tissue classification [18] method of MR images, which consists of histogram thresholding techniques [19], was applied to segment the brain into gray and white matter regions.

A semiautomated thresholding technique was supported with automated global thresholding and manual threshold values were used to extract background and cerebrospinal fluid. An investigating histogram for each neuroimaging set and a variety of test values were used to choose the best threshold values. For reasonably effective thresholding results, test values were operated for each voxel, and a comparison was made between the obtained resulting image and original image. The significant resulting slices were chosen from a 3D data set and superimposed on the original image.

The eight steps involved in the procedure are illustrated in Figure 2. In the image loading step, images were combined into a 3D matrix, and the multiple files selection feature was used to produce whole-volume data for each subject for image analysis. The next step focused on exploring the 3D data. The purpose of this step was to consider the images that were relevant to the general interest of the subject. In this stage, the 3D histograms were preferred in order to reconstruct 2D slices in grayscale. For the pre-processing step, global and adaptive thresholding techniques were used, depending on the general characteristics of 3D image data background. The next step in preprocessing was partial extraction of low positions such as cerebrospinal fluid using some manual thresholding values.

In this study, partitioned image histograms with a single global threshold, t that separates image from background was used. The t value is chosen automatically using the following algorithm:

An initial random threshold t is chosen
To extract background, the image is segmented into object and background; two sets are obtained:

$$g1 = \{f(m, n) : f(m, n) > t\,(\text{object pixels})\}$$
$$g1 = \{f(m,n) : f(m,n) \le t\,(\text{background pixels})\}$$

(f (m,n) is the gray level of point (m,n))

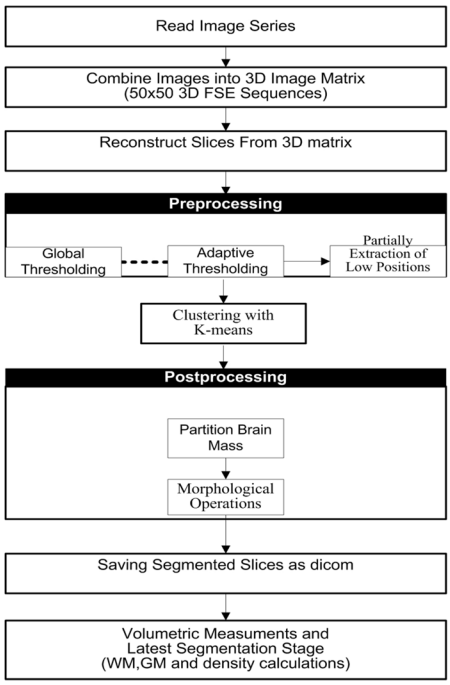


Figure 2. Flow chart of the study

The average of each set is computed;

m1 = average value of g1
m2 = average value of g2

A new threshold is created that is the average of m1 and m2:

$$t' = (m1 + m2)/2$$

Repeats Step 2 through 4 until t converges to t' .
By exploring the valleys from the histograms, two values for high and low positions were determined. After extracting these portions, k-means was used for clustering and obtaining brain mass. Acquired segmented slices were considered key images, and their neighboring slices could be segmented simply by propagating their information using the k-means algorithm [17]. This iterative algorithm involves redefined cluster numbers and calculates

the cluster centers using gray level differences. It is similar to the expectation-maximization algorithm for mixtures of Gaussian model in that both attempt to find the centers of natural clusters in data.

The objective was to minimize the total intra-cluster variance, or the squared error function, so the following equation was used

$$V = \sum_{i=1}^{k} \sum_{j=1}^{n} \left\| x_j - \mu_i \right\|^2 \quad (1)$$

where $\left\| x_j - \mu_i \right\|^2$ is a chosen measure of distance between a data point x_j and the cluster center μi which is an indicator of the distance of the n data points from their respective cluster centers, and k is a positive cluster center number. For a two - stage segmentation, it was decided to have 3 cluster numbers for two steps.

Then grouping was made by minimizing the sum of squares of distances between data and the corresponding cluster centroid [20]. After the isolation, the brain images from non-brain tissue pixels were restored and the dilation process was executed.

The post-processing step focused on cleaning small wisps of soft tissue from the image. Therefore, an erosion operation was used with a structuring element with a 7x7 pixels neighborhood from which the brain mass was obtained.

To return the brain to its original mass, which was reduced previously through the erosion, a dilation operation was used again with the structuring element in a 7x7 pixel neighborhood. To determine the connected regions, all brain regions were labelled to the boundaries. The segmented slices were saved and given standard parameters such as pixel spacing and slice thickness. These slices were then combined again into a 3D matrix and with k-means, 3D portions for white matter, gray matter and background was determined. The final step of the procedure involved morphological operations such as dilation and erosion. Mathematical morphology is a non-linear theory and technique for processing of the geometrical shape of the spatial image data structures [12].

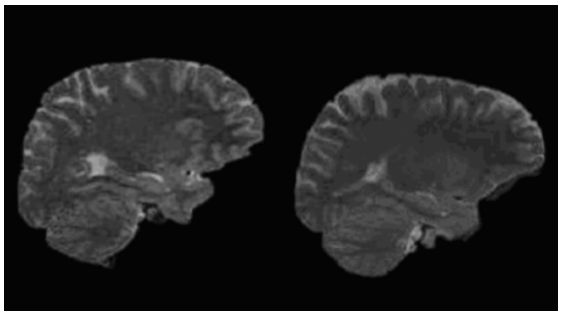
Dilation (D (A,B)) and Erosion (E (A,B)), based on Minkowski algebra and defined as Erosion-

$$E(A,B) = A\Theta(-B) = \bigcup_{\beta \in B} (A - \beta)$$
$$-B = \{-\beta \mid \beta \in B\} \quad (2)$$

Dilation- $D(A,B) = A \oplus B$

$$= \bigcup_{\beta \in B} (A + \beta) \quad (3)$$

If set A or B is evaluated as an image, A may be considered the original image and B may be considered the structuring element. So dilation, in general, causes objects in the image to grow in size; erosion causes objects to shrink. 7x7 structuring element was used for both erosion and dilation. Resultant brain mass image results are given in Figure 3.



(a) (b)

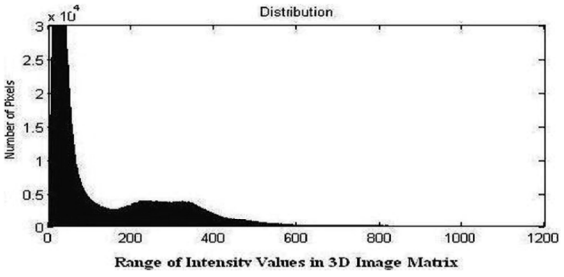
Figure 3. (a) brain mass of autistic subject (b) brain mass of control subject

3. RESULTS

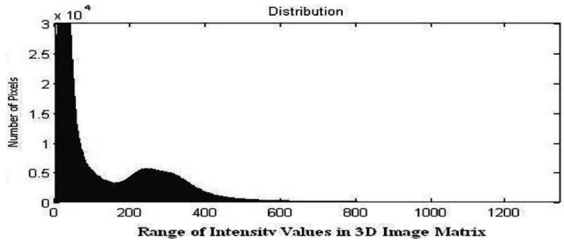
In this structural brain imaging study, some factors affect the reliability. All the samples belong to homogeneous images, same gender and the same

age range parameters, and correspondingly have the standard type of neurological disorder (autism only). In structural studies that evaluate volume differences, volumetric values do not provide direct information about the functionality of its white and gray matter.

When obtaining volume values of the brain images, the results from first step to the final stage were visualized to control the change in the images. Figure 4 shows histogram distributions of raw image data that are given in Figure 1.



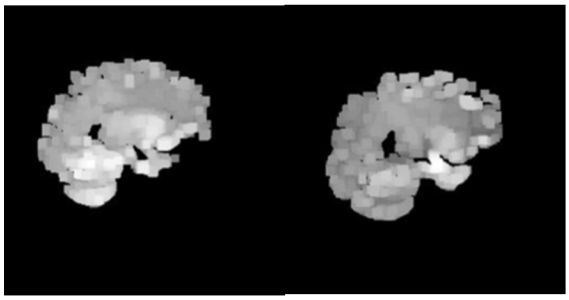
(a)



(b)

Figure 4. Distributions of 3D sample images illustrated in Figure 1. (a) The histogram of 3D image of autistic subject, (b) The histogram of 3D image of control subject image.

With these parameters, autistic and control groups were compared according to white matter. However, gray matter and total brain volume were extracted in order to test whether brain enlargement would continue for adolescents in the age group of 17 years old or not. Valley points can be seen according to histogram from Figure 4. There is a little increase in gray matter area for the autistic group and though the volume difference is small, it may be seen that it is caused from soft tissue largeness.



(a) (b)

Figure 5. The segmented image results of Figure 1.

Moreover, to test the results, independent sample t-tests analysis was used for white matter, gray matter and whole brain volume of patients. There was no significant difference ($p = 0,65$) figured for total brain volume between the control group and autistic subjects, and volume values of subjects in each group were shown in Table 1.

Table 1. Volume comparisons between autistic and control group

Values of volume(mL)		
Brain Region	Mean ± SD	***p* value for *t*-test**
WM		0,18
Autism	1 ± 39,2	
Control	144,1 ± 31,1	
GM		0,76
Autism	1,137 ± 35,6	
Control	1,120.9 ± 110,5	
Total brain		0,65
Autism	1,291.9 ± 78,00	
Control	1,265 ± 89,20	

4. DISCUSSION

The gray matter fraction for autistic subjects was 0,88 and gray matter fraction for control subjects was 0,89. Both the gray and white matter volumes were proportioned to whole brain volume. For the gray matter fraction, gray volume to brain volume proportion and for the white matter fraction white volume to brain volume proportion were calculated by using these image-processing techniques. The white matter fraction mean for autistic subjects was 0,12 and the value for control subjects was 0,11.

With respect to the gray matter, autistic subjects did not differ from control subjects with an admissible t-test result (p=0,76). However, the white matter volume was significantly larger in autistic subjects. The white matter volume mean for autistic subjects was 154,9 and for control subjects it was 144,1. A smaller ratio of white matter to gray matter was observed in autistic subjects compared to control subjects.

Previous MRI studies support the theory that brain volume enlarges in children with autism disorder but starts to disappear as they enter adulthood [5, 21]. The results which were obtained in this study support this hypothesis. Convergence in the brain volume at this age between the autistic group and the control subjects was determined.

This study suggests that this convergence is due to a decrease in brain volume in the adolescents with autism and growth in brain volume in control subjects. This decrease in brain volume in the adolescents with autism may demonstrate that the present difference would vanish in time. A slight difference in the size of in the autistic group whole brain was observed through our findings.

5. CONCLUSION

The presented method speeds up the evaluation process by eliminating manual data handling, reduces material costs and is reasonably effective for the diagnosis of autism in female patients. Another point is that this study demonstrates that although the number of patients in this study was not large, MRI has the potential to be a highly sensivitive measure capabile of detecting brain volume in autistic patients.

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