European Journal of Radiology 82 (2013) 1525–1530

Contents lists available at SciVerse ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Segmentation and volumetric analysis of the caudate nucleus in Alzheimer's disease

Sudevan Jiji[a], Karavallil Achuthan Smitha[b], Arun Kumar Gupta[c], Vellara Pappukutty Mahadevan Pillai[a], Ramapurath S. Jayasree[d,*]

[a] Department of Optoelectronics, University of Kerala, Kariavattom, Trivandrum 695581, Kerala, India
[b] Department of Imaging Sciences and Interventional Radiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695012, Kerala, India
[c] Department of Neuroimaging and Interventional Radiology, National Institute of Mental Health and Neuro Sciences, Bangalore, India
[d] Biophotonics and Imaging Lab, Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695012, Kerala, India

ARTICLE INFO

Article history:
Received 4 February 2013
Received in revised form 15 March 2013
Accepted 21 March 2013

Keywords:
Alzheimer's disease
Caudate nucleus
Image segmentation
Caudate volume

ABSTRACT

Objectives: A quantitative volumetric analysis of caudate nucleus can provide valuable information in early diagnosis and prognosis of patients with Alzheimer's diseases (AD). Purpose of the study is to estimate the volume of segmented caudate nucleus from MR images and to correlate the variation in the segmented volume with respect to the total brain volume. We have also tried to evaluate the caudate nucleus atrophy with the age related atrophy of white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) in a group of Alzheimer's disease patients.
Methods: 3D fast low angle shot (3D FLASH) brain MR images of 15 AD patients, 15 normal volunteers and 15 patients who had normally diagnosed MR images were included in the study. Brain tissue and caudate nuclei were segmented using the statistical parametric mapping package and a semi-automatic tool, respectively and the volumes were estimated. Volume of segmented caudate nucleus is correlated with respect to the total brain volume. Further, the caudate nucleus atrophy is estimated with the age related atrophy of WM, GM and CSF in a group of AD patients.
Results: Significant reduction in the caudate volume of AD patients was observed compared to that of the normal volunteers. Statistical analysis also showed significant variation in the volume of GM and CSF of AD patients. Among the patients who had normal appearing brain, 33% showed significant changes in the caudate volume. We hypothesize that these changes can be considered as an indication of early AD.
Conclusion: The method of volumetric analysis of brain structures is simple and effective way of early diagnosis of neurological disorders like Alzheimer's disease. We have illustrated this with the observed changes in the volume of caudate nucleus in a group of patients. A detailed study with more subjects will be useful in correlating these results for early diagnosis of AD.
© 2013 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

MR volumetric measurements of subcortical structures have recently gained importance in Alzheimer's disease, schizophrenia and epilepsy [1–6]. AD represents the most common degenerative neurological disorder of late life. It is associated with progressive cerebral atrophy, which can be revealed using magnetic resonance imaging (MRI). Advanced MRI techniques in conjunction with structural volumetric MRI measures show great promise in understanding and quantifying the progression of AD [7–10]. However, very few reports are available which characterizes changes in the volume of caudate nucleus (CN) and correlates the CN atrophy and the severity of AD [11]. Neuropathological studies suggest that the striatum, including the CN is a site of tangle and plaque pathology [12]. There is renewed interest in the role of the CN in cognition with increasing recognition that cortico–striato–thalamic loops are involved in cognitive processes, particularly, in attention and executive function, as well as in movement disorders [13,14]. Atrophy of the CN may be an important target as it plays a vital role in forming associations to acquire explicit memories and in motor learning,

Abbreviations: GM, grey matter; WM, white matter; CSF, cerebrospinal fluid; AD, Alzheimer's disease; CN, caudate nucleus; VBM, voxel based morphometry.

* Corresponding author at: Biophotonics and Imaging Laboratory, Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Poojappura, Trivandrum 695012, Kerala, India. Tel.: +91 0471 2520273; fax: +91 0471 2341814.
E-mail addresses: jijiaiswaryap@gmail.com (S. Jiji), mithamahesh@gmail.com (K.A. Smitha), gupta209@gmail.com (A.K. Gupta), vpmpillai9@gmail.com (V.P.M. Pillai), jayashreemenon@gmail.com, jayasree@sctimst.ac.in (R.S. Jayasree).

0720-048X/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejrad.2013.03.012

which are important factors in the search for AD biomarkers in the brain.

CN atrophy in AD has been reported earlier and has been explained in view of the demonstrated involvement of striatal nuclei by neuro-fibrillary changes [15–17]. Barber and colleagues have reported 9–14% reduction in the volume of CN [1]. Further evidence that the CN is abnormal in AD is reported by Bartzokis and Tishler showing an increase in iron load comparable to that of Huntington's disease [18]. Another group claims that no correlations were found between the volumes of CN and any neuropsychological score [14]. Except the recently reported work by Madsen et al., all available reports relate to cases of AD at an advanced stage which can be easily identified on the structural imaging [19]. The correlation with total brain volume has not been considered in any of the report. Strongly reduced putamen and thalamus in AD is reported by de Jong et al. [20].

Medical image segmentation has gained wide acceptance for visualizing structures of the human brain as well as for performing different volumetric analysis of brain structures. The review by Ma et al. summarizes the different algorithms used in medical image segmentation and their characteristics and the advantages and disadvantages of each type as illustrated in the segmentation of the pelvic cavity [21]. Many methods including manual, semi-automatic and fully automatic have been established for brain structure segmentation from MRI. Of these methods, manual segmentation is tedious, requires tough training and in most cases the results are not reproducible. Fully automatic methods require no training and are reproducible to a great extent for the same data. But has the disadvantage that this method does not allow for human intervention which is badly needed in many situations. Considering these factors, semi-automatic methods are considered as the preferred type of medical image segmentation [22]. In this study, we propose to estimate the CN volume and its relative variation with respect to the total brain volume of AD patients using a semi automatic segmentation tool. An equal number of controls and another group of patients who had undergone MRI studies for various reasons, but found to have no intracranial lesions, were also included in the study. The third group was included to see the feasibility of demonstrating any changes in the CN, WM, GM or CSF volume in patients with visibly normal MRI. We have employed an efficient and reliable semi automatic technique, based on the 3D active contour segmentation method. Considering the reliability and reproducibility of the results, we have preferred a semi-automatic method of segmentation for the present study. The currently adopted method has been validated previously with manual segmentation by highly trained raters. They have demonstrated excellent reliability of the tool for efficient three dimensional segmentation [23].

2. Materials and methods

2.1. Study groups

In this study, subjects were categorized based on a combination of medical history, clinical and radiological examinations. All patients were recruited in the outpatient division of Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India. Routine assessments were carried out in all including: standard history, laboratory examination, physical and neurological examinations.

Group I included 15 patients (9 men and 6 women in the age group of 57–73 years) who had been diagnosed as AD patients using standard criteria with diagnosis reinforced by other tests.

Group II included 15 patients (age 49–72 years, 8 men and 7 women) who had undergone MRI scan of brain to rule out various intracranial lesions but have diagnosed to have no major clinical neurological problems. The MR images of these patients demonstrated no visible abnormal changes from normal brain conditions. These patients who have presented with one or more of the symptoms like headache and seizure were examined for clinical diagnosis using MRI scan of the brain. Special care has been taken to correlate the clinical history of these patients and made sure that none of them reported to have AD at any stage.

Group III included 15 normal volunteers who were randomly selected from among our staff and bystanders. They never had any history of neurological deficit and were in the age group of 28–65 years.

2.2. MRI acquisition

MRI studies were performed on a 1.5 T Magnetom Avanto Tim MRI scanner (Siemens, Erlangen, Germany). Images from 3D FLASH pulse sequence (TE = 4.94 ms, TR = 11 ms) with matrix size 240×256 and field of view of 200 mm $\times$ 230 mm, slice thickness of 1.5 mm and in plane isotropic voxel size of 1 mm^2 were used for this study. The DICOM format images were transformed to Analyze format using MRI convert software (Lewis Center for Neuroimaging, University of Oregon).

2.3. Total brain volume and intracranial volume

GM, WM and CSF were segmented using the statistical parametric mapping (SPM5 – The Wellcome Trust Centre for Neuroimaging, UK). The SPM software is a suite of Matlab (The Math Works, Natick, MA, USA) functions, scripts and data files, with some externally compiled C routines. Voxel based morphometry (VBM) involves a voxel-wise comparison of the local concentration of GM, WM and CSF between two subjects. Here, the procedure involves spatially normalizing the images and smoothing. Inter individual variation in gyral anatomy is taken care and more normally distributed data is rendered for subsequent voxel wise analyses [24]. Voxel-wise parametric statistical tests were then performed to compare the smoothed images from different groups. The volumes of the segmented tissues were calculated using a program developed in-house which run on Matlab.

2.4. Segmentation and volumetric analysis of caudate nucleus

The T1 weighted images were analyzed using the ITK-SnAP 1.6 software. The segmentation of CN was performed as described by Yushkevich et al. [23]. This software displays structural images simultaneously in three different planes and allows manual segmentation of 3D medical images in standard ACPC alignment. In this study, the left and right CN were traced and segmented using the semiautomatic method. Briefly, caudates were manually segmented by an expert rater trained and established for its reliability allowing visualization in all three planes and image stored as 3D binary masks. The caudate was initially viewed sagittally as an outline to the ventral portion of the ventricles, thereby allowing the rater to understand the parameters of the caudate. The rater outlined the drawing of the caudate medially, and noted it would take the form of having a head and tail. The striatum is illustrated in the coronal view which was further taken by the rater as parameters of the caudate. Then the rater identifies the beginnings of the caudate, proceeds medially to laterally from each ventricle. Thus the rater first traces the head of the caudate in the axial view and proceeding laterally traces the tail as well. Tracing proceeded laterally for 15–20 slices until no head or tail portions of the extending caudate were visible. Once the tracing of the caudate in the axial views were completed for one hemisphere, the coronal and sagittal views were used to confirm the 2D axial tracings. Any overlooked

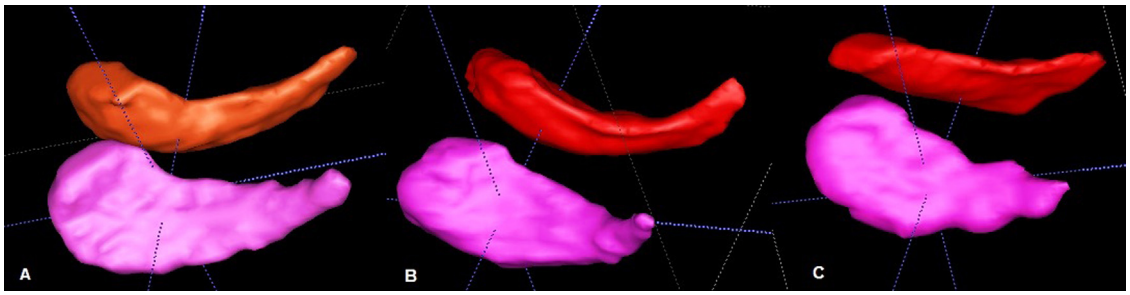

Fig. 1. Segmented left (red) and right (magenta) caudate of (A) normal brain, (B) normal appearing brain and (C) Alzheimer's disease.

caudate anatomy was taken care at this stage. Integrating all 2D tracings the rater had traced in each slice, a 3D image is compiled. Final result of the performed tracings is checked in the 3D image and any abnormalities present in the 3D image will revert back the rater to correct the tracing or to start tracing again. Standardized measurement of the volume of the left and right CN (in mm) was also estimated using the same software. The reproducibility of the results was confirmed by the segmentation and volume analysis done independently by a different user.

2.5. Statistical analysis

The variation in the head size was taken into consideration by performing the statistical analysis on the relative brain volume and not on the absolute brain volume. This step will give a relative volume of CN irrespective of the size of the head considered in this study which is very important during the comparison of CN size among the subjects. The atrophy level variations among the three different groups were evaluated statistically using Student's *t*-test, as it is the most sensitive test for interval data. Statistical values where ever $p < 0.05$ were considered as significant. The difference between the means of WM, GM, CSF, left and right caudate volumes separately, the total caudate volume and total brain volume of the independent groups were calculated and analyzed using the one way analysis of variance (ANOVA) using the Statistical Package for Social Sciences software (SPSS 15.0.1 Inc., Chicago, IL, USA). The relative caudate volume with respect to the total brain volume was also calculated in individual cases.

3. Results

Images showing the segmented caudate is shown in Fig. 1. Anatomical images along with the segmented CN are given in Fig. 2. Fig. 3 shows the images of segmented GM, WM and CSF of the three

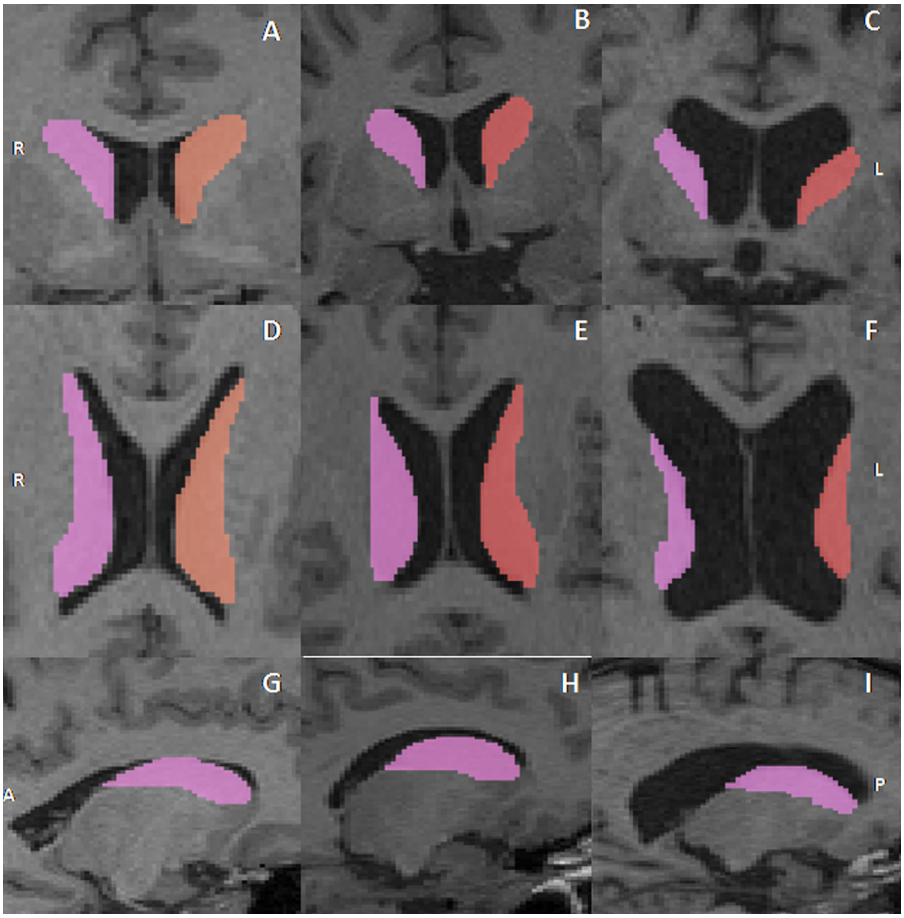

Fig. 2. Segmented left and right caudate in coronal, axial and sagittal view of normal brain (A, D, and G), normal appearing brain (B, E, and H) and Alzheimer's disease (C, F, and I).

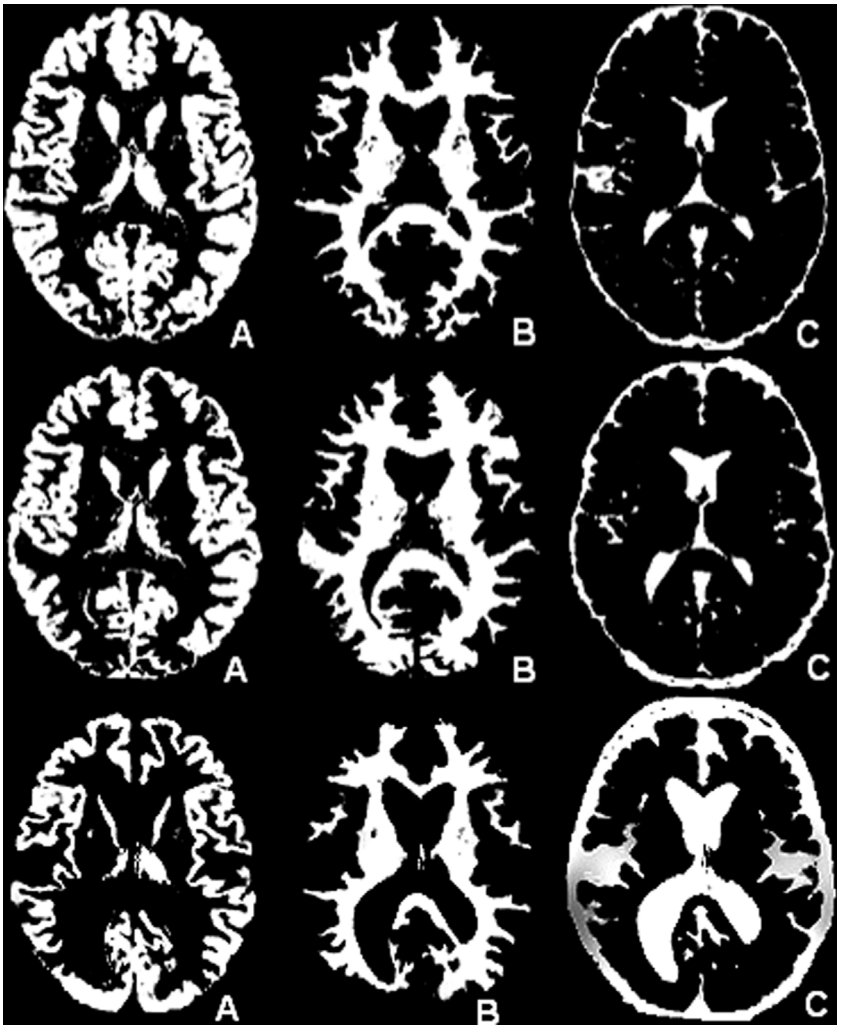

Fig. 3. Segmented axial view of gray matter, white matter, cerebrospinal fluid in normal brain (1st row, A–C), normal appearing brain (2nd row, D–F) and Alzheimer's disease (3rd row, G–I).

different groups. Estimated volumes in all the cases are given in Table 1. The variation in the CN, GM, WM and CSF volume and the relative volume of CN with respect to the total brain volume compared to the control group are given in Table 2 as the Fisher F and p values.

A significant difference in the total average volume of CN was observed between AD patients and normal volunteers ($p < 0.05$). But no significant difference was observed between patients with normal appearing brain and normal volunteers ($p < 0.072$). Out of the 15 AD patients studied, two (13%) had no reduction in caudate volume. From 15 patients who had normal appearing brain on MR images, five (33%) had significant reduction in caudate volume compared to the control group. These cases were given special attention and the clinical diagnosis was checked again for the reconfirmation of AD in the 2 patients in the first case and the absence of any visible brain abnormality in the 5 cases in the second case. The age of these 5 patients in the later group ranged between 49 and 58 years with an average of 52.2 years. Four of them were females and one male.

The variation in the average volume of right and left CN of AD, normal appearing brain and normal groups is shown in Fig. 4. Reduction in the volume of CN was observed on both sides in few

Table 1
The estimated volume of the caudate nuclei and total brain volume in various groups and their statistical variations. The deviations from the mean value are given in parentheses.

	Controls	Normal appearing	AD
WMV (ml)	457.77(74.19)	460.52(97.64)	438.90(48.97)
GMV (ml)	680.65(84.08)	671.54(93.48)	550.95(100.87)
CSFV (ml)	336.00(134.41)	353.36(125.29)	632.04(90.75)
Total brain volume (ml)	1473.48(196.21)	1481.42(203.89)	1622.74(139.4)
Right CN volume (ml)	4.10(0.47)	3.61(0.61)	2.58(0.52)
Relative volume (%)	0.28(0.03)	0.24(0.05)	0.16(0.04)
Left CN volume (ml)	4.12(0.42)	3.91(0.59)	2.97(0.55)
Relative volume (%)	0.28(0.03)	0.26(0.05)	0.18(0.04)
Total CN volume (ml)	7.76(0.87)	7.51(1.19)	5.56(0.99)
Relative volume (%)	0.53(0.03)	0.51(0.05)	0.34(0.04)

Table 2
Change in volume with respect to the control group as given by the Fisher value and *p* value.

	Normal appearing		AD	
	F-value	*p* value	*F*-value	*p* value
WMV	0.007	0.932	0.676	0.418
GMV	0.079	0.781	14.635	0.001
CSFV	0.134	0.717	49.988	0.00
Total brain volume	0.012	0.914	5.772	0.023
Right CN volume	6.226	0.019	70.382	0.00
Relative volume (%)	7.059	0.013	86.400	0.00
Left CN volume	1.302	0.264	41.462	0.00
Relative volume	1.765	0.195	60.00	0.00
Total CN volume	3.499	0.072	42.051	0.00
Relative volume	1.626	0.213	174.736	0.00

AD patients. It is interesting to note that in majority of AD patients (87%), the reduction is observed more on the right CN than on the left. This is true for the normal appearing brain also. A volume reduction of 37% and 28% was observed for the right and left caudate of AD, respectively whereas in the case of normal appearing brain it was 12% and 5%, respectively, compared to the average values of normal group. It is observed that the difference between the left CN volume of normal volunteers and patients with normal appearing brain was not significant ($p < 0.264$), whereas the difference between the right caudate of these two groups was significant ($p < 0.019$).

There is a significant variation in the volumes GM and CSF among the three groups. When the GM volume was reduced in both normal appearing brain (non significant) and AD patients (significant), the CSF volume was found to increase in both cases. This variation again was significant in the case of AD patients, the average change being as high as 48%. Corresponding changes were also observed in the total brain volume (Table 1 and Fig. 5). The changes observed in the WM volume were not significant in both the groups when compared to the normal one. Variation with respect to the gender was also taken into consideration and no significant variation of the caudate volume was observed between the males and females in the AD and normal appearing group.

4. Discussion

The present study used a semi-automatic segmentation with active contour method for the segmentation and volume calculation of CN and a VBM method for the segmentation and volume calculation of the intracranial brain structures. CN atrophy in AD has been recently reported by Madsen et al. by considering the 3D profile of caudate atrophy using a surface mapping approach using fully automatic method [19]. They have adopted a method where a central curve was calculated through the longitudinal axis of each caudate and the radial distance to each point in a 3D surface mesh was used as a localized measure of atrophy. Using the fully automatic method, they have analyzed the absolute volume of CN and has compared with controls. The volume of CN relative to the total brain volume has not been considered. In our study we have chosen a semi automatic segmentation method so that manual intervention is possible wherever necessary. This is very important as in many cases there can be over segmentation or under segmentation of the CN when an automatic method is adopted. A fully automatic diagnostic imaging test for attention-deficit hyperactivity disorder (ADHD) diagnosis assistance based on previously found evidences of caudate nucleus volumetric abnormalities was reported by Igual et al. [25]. They have split the segmentation methods into different steps for external and internal segmentation of caudate based on machine learning techniques. In an earlier study by the same group, a new fully automatic method of segmenting the caudate nucleus which combines an atlas-based segmentation strategy with the graph cut energy-minimization framework was also reported [26]. In both studies it is stated that the results are comparable to gold-standard segmentations of caudate nucleus in pediatric ADHD cases. From the present study involving semi automatic technique of segmentation, it is clear that the total caudate volume differs significantly and substantially (ranging from 51.5% to 14.6% of control caudate volumes) for AD patients. In most of the AD patients, both cerebral hemispheres showed significant change in the volume. The CN structure was significantly reduced and the estimated volumes of CN were also found to be reduced. Out of 15 AD patients, two had no atrophy in caudate volume and no visual structural difference on MR images. In 5 AD patients atrophy was observed on both the left and right CN and in the rest, either the left or the right CN showed atrophy. The average volume of the left caudate nucleus was found to be more than the average volume of right CN in all the groups studied. This result is in accordance with the finding of Castellanos et al. [27]. On an average, there was no detectable volume reduction of CN in patients with normal appearing brain as compared to normal volunteers. However, our present study shows some interesting findings regarding five of the patients who had been diagnosed clinically as normal. Reduced caudate volume was observed for these five patients compared to

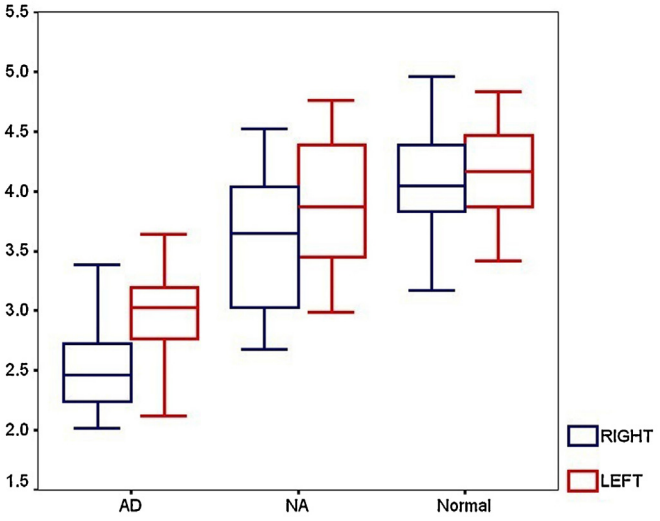

Fig. 4. Average volume of left and right caudate in Alzheimer's disease, normal appearing brain and normal brain.

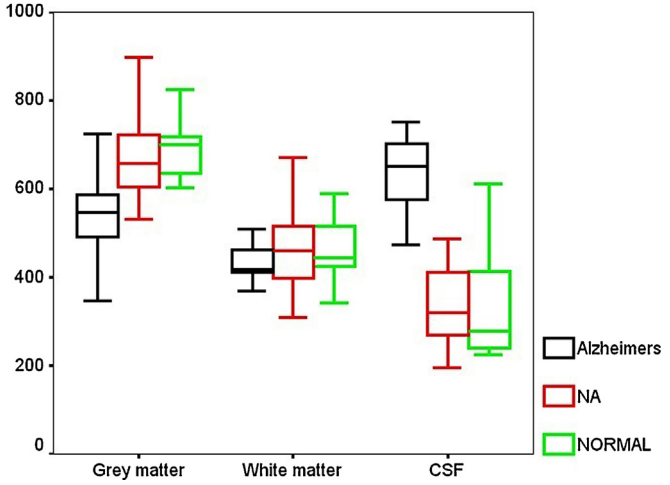

Fig. 5. Variation in the volume of GM, WM and CSF among the three different groups.

normal volunteers. This is reflected in the significant reduction in volume of the right CN and corresponding relative volume (%) of normal appearing brain group compared to normal volunteers as is seen from Table 2. We consider these findings as very important as there were no visible changes on the MR images of these patients and hence these findings may be considered as variation of the normal structure which could not be demonstrated on the MR images. Since these subjects were patients and not normal volunteers who had undergone MRI scan to rule out any intracranial lesions, and failed to pick up any abnormality in the scan, these and similar cases needs to be considered for further investigation, especially when MR imaging fails. These patients are being regularly followed up for any manifestation on the symptoms related to early stage AD. Likewise, the study may be considered as a torch light in many of the cases where the actual diagnosis becomes difficult or negative on imaging. Moreover, 5 out of 15 patients is not a small group to be neglected for the observed changes. Hence, from this preliminary study, we feel that the method of volumetric analysis can be considered as simple but effective way of early stage diagnosis of neurological disorders like AD.

Another major observation of this study is the significant reduction in the gray matter volume of AD patients as is clear from Table 1. This is in favor of the results of Rombouts et al., who also have reported a decrease of gray matter in Alzheimer's disease, but mainly in the head of caudate, hippocampus and insula [16]. There is a significant increase in the CSF volume of AD patients compared to the normal. The CSF volume was found to be almost doubled in AD compared to control. The increase in the CSF volume in AD condition is well understood and hence the result is as expected. The variation in the CN and CSF volume was also shown to have similar progression in the normal appearing brain as in the case of AD though not significant in majority of the cases. Volume estimation of sub cortical regional structures along with the neuropsychological examinations can limit the interpretations at least for the early memory changes that can classify patients with early stage of AD. To our knowledge, no reports are available for the estimation of the brain volume structures from the MR images for measuring the severity of AD and also for predicting early stage disease based on the results from the data of a group of patients with normal appearing brain. The insignificant atrophy observed in the patients who had no neurological challenges, as observed in the present study needs further consideration. Whether this is an indication of early stage AD is to be looked into. Further study in this direction with more number of patients is expected to give better results and would throw more light on this topic.

Acknowledgements

We acknowledge the developers of the software ITK-SNAP, Penn Image Computing and Science Laboratory (PICSL) of the Department of Radiology at the University of Pennsylvania for providing the software.

References

[1] Barber R, McKeith I, Ballard C, O'Brien J. Volumetric MRI study of the caudate nucleus in patients with dementia with Lewy bodies, Alzheimer's disease, and vascular dementia. Journal of Neurology, Neurosurgery and Psychiatry 2002;72(3):406–7.

[2] Almeida OP, Burton EJ, McKeith I, Gholkar A, Burn D, O'Brien JT. MRI study of caudate nucleus volume in Parkinson's disease with and without dementia with Lewy bodies and Alzheimer's disease. Dementia and Geriatric Cognitive Disorders 2003;16(2):57–63.

[3] Gur RE, Maany V, Mozley PD, Swanson C, Bilker W, Gur RC. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. American Journal of Psychiatry 1998;155(12):1711–7.

[4] Lang DJ, Kopala LC, Vandorpe RA, et al. An MRI study of basal ganglia volumes in first-episode schizophrenia patients treated with risperidone. American Journal of Psychiatry 2001;158(4):625–31.

[5] DeCarli C, Hatta J, Fazilat S, Gaillard WD, Theodore WH. Extratemporal atrophy in patients with complex partial seizures of left temporal origin. Annals of Neurology 1998;43(1):41–5.

[6] Dreifuss S, Vingerhoets FJ, Lazeyras F, et al. Volumetric measurements of subcortical nuclei in patients with temporal lobe epilepsy. Neurology 2001;57(9):1636–41.

[7] Kantarci K, Jack Jr CR, Xu YC, et al. Mild cognitive impairment and Alzheimer disease: regional diffusivity of water. Radiology 2001;219(1):101–7.

[8] Kantarci K, Petersen RC, Boeve BF, et al. DWI predicts future progression to Alzheimer disease in amnestic mild cognitive impairment. Neurology 2005;64(5):902–4.

[9] Muller MJ, Greverus D, Dellani PR, et al. Functional implications of hippocampal volume and diffusivity in mild cognitive impairment. Neuroimage 2005;28(4):1033–42.

[10] Rose SE, McMahon KL, Janke AL, et al. Diffusion indices on magnetic resonance imaging and neuropsychological performance in amnestic mild cognitive impairment. Journal of Neurology, Neurosurgery and Psychiatry 2006;77(10):1122–8.

[11] Bruen PD, McGeown WJ, Shanks MF, Venneri A. Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. Brain 2008;131(Pt 9):2455–63.

[12] Wolf DS, Gearing M, Snowdon DA, Mori H, Markesbery WR, Mirra SS. Progression of regional neuropathology in Alzheimer disease and normal elderly: findings from the Nun study. Alzheimer Disease and Associated Disorders 1999;13(4):226–31.

[13] Bruck A, Portin R, Lindell A, et al. Positron emission tomography shows that impaired frontal lobe functioning in Parkinson's disease is related to dopaminergic hypofunction in the caudate nucleus. Neuroscience Letters 2001;311(2):81–4.

[14] Deweer B, Lehericy S, Pillon B, et al. Memory disorders in probable Alzheimer's disease: the role of hippocampal atrophy as shown with MRI. Journal of Neurology, Neurosurgery, and Psychiatry 1995;58(5):590–7.

[15] Baron JC, Chetelat G, Desgranges B, et al. In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. Neuroimage 2001;14(2):298–309.

[16] Rombouts SA, Barkhof F, Witter MP, Scheltens P. Unbiased whole-brain analysis of gray matter loss in Alzheimer's disease. Neuroscience Letters 2000;285(3):231–3.

[17] Braak H, Braak E. Alzheimer's disease: striatal amyloid deposits and neurofibrillary changes. Journal of Neuropathology and Experimental Neurology 1990;49(3):215–24.

[18] Bartzokis G, Tishler TA. MRI evaluation of basal ganglia ferritin iron and neurotoxicity in Alzheimer's and Huntingon's disease. Cellular and Molecular Biology (Noisy-le-Grand, France) 2000;46(4):821–33.

[19] Madsen SK, Ho AJ, Hua X, et al. 3D maps localize caudate nucleus atrophy in 400 Alzheimer's disease, mild cognitive impairment, and healthy elderly subjects. Neurobiology of Aging 2010;31(8):1312–25.

[20] de Jong LW, van der Hiele K, Veer IM, et al. Strongly reduced volumes of putamen and thalamus in Alzheimer's disease: an MRI study. Brain 2008;131(Pt 12):3277–85.

[21] Ma Z, Tavares JMRS, Jorge RN, Mascarenhas T. A review of algorithms for medical image segmentation and their applications to the female pelvic cavity. Computer Methods in Biomechanics and Biomedical Engineering 2010;13(2):235–46.

[22] Hu YJ, Grossberg MD, Mageras GS. Semiautomatic medical image segmentation with adaptive local statistics in conditional random fields framework. In: 30th annual international conference of the IEEE engineering in medicine and biology society. 2008. p. 3099–102.

[23] Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage 2006;31(3):1116–28.

[24] Liu RS, Lemieux L, Bell GS, et al. Progressive neocortical damage in epilepsy. Annals of Neurology 2003;53(3):312–24.

[25] Igual L, Soliva JC, Escalera S, Gimeno R, Vilarroya O, Radeva P. Automatic brain caudate nuclei segmentation and classification in diagnostic of attention-deficit/hyperactivity disorder. Computerized Medical Imaging and Graphics 2012;36(8):591–600.

[26] Igual L, Soliva JC, Hernandez-Vela A, et al. A fully-automatic caudate nucleus segmentation of brain MRI: application in volumetric analysis of pediatric attention-deficit/hyperactivity disorder. BioMedical Engineering OnLine 2011;10, 105.

[27] Castellanos FX, Lee PP, Sharp W, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. Journal of the American Medical Association 2002;288(14):1740–8.