Volumetric Analysis of Regional Atrophy for the Differential Diagnosis of AD and FTD

Tinu Varghese
Department of EIE
Noorul Islam University
Kumaracoil, Thuckalay, TN

Sheela Kumari R
Department of Neurology
Sree Chitra Tirunal Institute For Medical Science and Technology, Trivandrum,Kerala

P.S Mathuranath, MD,DM
Department of Neurology
Sree Chitra Tirunal Institute For Medical Science and Technology, Trivandrum,Kerala

ABSTRACT

The aim of this study was to characterize the patterns of brain atrophy in Alzheimer's disease (AD) patients compared to FTD patients and healthy controls. This study assesses the brain gray matter (GM) and ROI abnormalities jointly to reveal differences in abnormal MRI patterns between the diseases. Hippocampal, amygdala and cingulate gyrus volume was measured by Magnetic Resonance Imaging in patients with AD (n=25), FTD (n=10) and in healthy control subjects (n= 20) The neuropsychological assessment was used to stratify subjects according to cognitive functions VBM was performed to characterize the voxel wise analysis of neuro anatomic changes that occur in AD and FTD based on 3D flash spoiled gradient sequence using standard parameters. Our findings suggest that the magnitude of amygdale atrophy is comparable to that of the hippocampus in the earliest clinical stages of AD and FTD. The severity of dementia increased associated with decreasing hippocampal volume. Measurement of hippocampal and amgdalar regions may facilitate differentiation between dementia subtypes. In this study, there was no evidence that cingulate regional atrophy is specifically associated with early-onset AD and FTD

Keywords

Alzheimer's disease, Frontotemporal Dementia, Voxel Based Morphometry, Mini Mental State Examination.

1. INTRODUCTION

Dementia is a chronic syndrome, characterized by a progressive, global deterioration in intellect including memory, learning, orientation language, comprehension and judgment due to disease of the brain [1] Different types of dementia are associated with particular types of brain cell damage in particular regions of the brain. In 2010 dementia India reports estimated that over 3.7 million people are affected by dementia in our country. Alzheimer's disease (AD) is the commonest type of dementia. It is a progressive and irreversible disease. It usually occurs after the age of 65. Neurofibrillary tangles and amyloid plaques are the histopathological hallmark of AD and are associated with neuronal loss and brain volume reductions[2]. The concept of MCI is a midway between normal aging and very early AD. It provides a window for intervention in the preclinical stage of dementia and thereby for possible prevention of dementia[3]. MR imaging technique must be consistently differentiates AD from normal aging in individual scans[4].

In Alzheimer's disease hippocampus is the center of learning and memory in the brain, and the brain cells in this region are often the first to be damaged. That's why memory loss is often one of the earliest symptoms of Alzheimer's disease[4]. Doctors diagnose Alzheimer's and other types of dementia based on a careful medical history, a physical examination, laboratory tests, and the characteristic changes in thinking, day-to-day function and behavior associated with each type. In some situations doctors can't easily determine the exact type of dementia because the symptoms and brain changes of different dementias can overlap. [5-7].

Frontotemporal dementia (FTD) is a group of disorders caused by progressive cell degeneration in the brain's frontal and temporal lobes. FTD was once considered rare, but it's now thought to account for up to 20 to 50 percent of all dementia cases. People usually develop FTD in their 50s or early 60s, making the disorder relatively more common in this younger age group[8].FTD into three main categories, they are Behavioral variant frontotemporal dementia (bvFTD), Primary progressive aphasia (PPA) and FTD movement disorders. Magnetic resonance imaging (MRI) often plays a key role in diagnosis because it can detect shrinkage in the brain's frontal and temporal lobes, which is a hallmark of FTD [9-10].

In the present study, we used voxel-based morphometry (VBM) of MRI data to assess GM changes and regional abnormalities associated with patients groups compared with the control groups[11].This technique has been successfully and reliably used to determine correlations between atrophy in specific areas and symptoms in patients with AD and FTD[12]. Early diagnosis allows a person to get the maximum benefit from available treatments and provides time to plan for the future. This study identifies the neuropsychological and behavioral profiles of Alzheimer's disease and frontotemporal dementia and to determine the regional brain damage through MRI analysis. In the present study examined the size of the amygdala, hippocampus and cingulate region in AD and FTD patients in order to determine the relationship between the cognitive impairment and the amount of atrophy in each region.

1.1 Comparison between AD and FTD

Age have important role in the diagnosis and prognosis of dementia.AD is the commonest type of dementia among people age 65 and older. It grows with increasing age. In people with FTD are diagnosed in their 50s and early 60s. Only about 10 percent are diagnosed after age 70.Memory loss tend to be a more well known symptom in early AD than in early FTD[13].. In the advanced stage of FTD often causes memory loss as well as more characteristic effects on behavior and language. bvFTD is the most common form of FTD, Behavior changes are the first noticeable symptoms in bvFTD. Behavior changes are also common as Alzheimer's progresses, but they tend to occur later in the disease. Problems with spatial orientation symptoms is more common

in Alzheimer's than in FTD. In AD people may have some trouble in thinking of the right word or remembering names, they tend to have less difficulty making sense when they speak, understanding the speech of others, or reading than those with FTD[14-15] .Hallucinations and delusions These are relatively common as Alzheimer's progresses, but relatively uncommon in FTD

2. METHODS

2.1 Subjects

All Participants in this study were selected in the Sree Chitra Tirunal Institute for Medical Science and Technology (SCTIMST), Trivandrum, Kerala dementia clinic. This study was accomplished with 55 total participants. 25 early AD patients 10 FTD patients and 20 age-similar controls were recruited for possible inclusion in the study. From the database, we included participants 55 years of age or more and education ≥ 7 years. The Exclusion Criteria of Patients who had previously taken cholinesterase inhibitors and/or memantine, b) Patients with uncontrolled hypertension and cardiac disease c) History of epilepsy, stroke, head-injury with loss of consciousness

Table 1: General Demographic details of all study groups

	AD	FTD	NC
Number of patients	25	10	20
Age	67.1±5.9	62±6.2	60±3.3
Education	14.7±3.8	13.3±3.3	15.7±2.2
Sex(M/F)	15/10	7/3	10/10
MMSE	22.2±5.5	22.6±9.5	28.5±0.5

The subjects were underwent clinical examination, detailed neuropsychological and neuroimaging evaluation. Research diagnoses of AD and FTD were made using NINCDS ADRDA criteria . There were no significant differences between the groups for education, gender, MMSE score of dementia subjects.

The proposed study was approved by Institutional Ethics Committee of Sree Chitra Tirunal Institute for Medical Sciences and Technology

2.2 Neuropsychological Assessment

Cognitive function was evaluated in all study groups using the ACE and Mini Mental State Examination (MMSE).Subjects were stratified according MMSE score. Normal controls (>28), Mild dementia (24-27), Moderate dementia (19-23) and severe dementia (<18)

2.3 Image Acquisition and Processing

Whole brain MRI scans were obtained on Siemens Magnetom-Avanto SQ engine, 1.5T MR Scanner. Whole brain volume was acquired by the 3D flash spoiled gradient echo sequence using standard parameters.TR=11msec, TE=4.95, flip angle=150, slice thickness=1mm, matrix=256x256, 112 Sagital plane images were made to cover the whole brain.

The images were post processed in the fully equipped Brain mapping unit of Cognitive and Behavior Neurology Section (CBNS). The VBM analysis was performed in the MATLAB 7.1 platform with Statistical Parametric Mapping (SPM5) software.

2.4 Voxel Based Morphometry (VBM)

VBM analysis will be performed using SPM software (Wellcome department of Imaging Neuroscience, London, URL: www.fil.ion.ucl.ac.uk). Volumetric MRI has been considered to be an appropriate aid in characterizing the neuro degenerative dementias. Structural neuroimaging studies in FTD have revealed prominent atrophy of the frontal lobes and anterior temporal lobes. . VBM studies in AD have confirmed significant greymatter changes in medial and temporal regions [16] . The medial temporal lobe volumes do not distinguish FTD from AD..VBM involves a Voxel-wise statistical comparison of gray matter intensity between two groups of subjects.. It automatically quantifies the tissue changes. Meanwhile, segmentation algorithms were introduced to the tissue classification procedure. A good segmentation algorithm will help the clinicians for the 3-D visualization; surgical planning and early disease recognition especially in the disease dementia. Initially the 3D MR images were normalized into a standard stereotactic space [17]. Hence the images were registered into T1 MRI template, provided by MNI. After normalization images were segmented into GM, WM and CSF[18-19].. It has several advantages over traditional ROI-based hand-drawn morphometry, which typically involves drawing around a region of interest on a number of slices and uses Cavalieri principle for volume calculation.

VBM has three main potential advantages over label based methods: (a) removal of operator bias in ROI drawings (local bias), (b) quantification of subtle features easily missed by operator inspection, and (c) assessment of global structural changes in brain, unrestricted by the selection of specific ROIs (global bias).

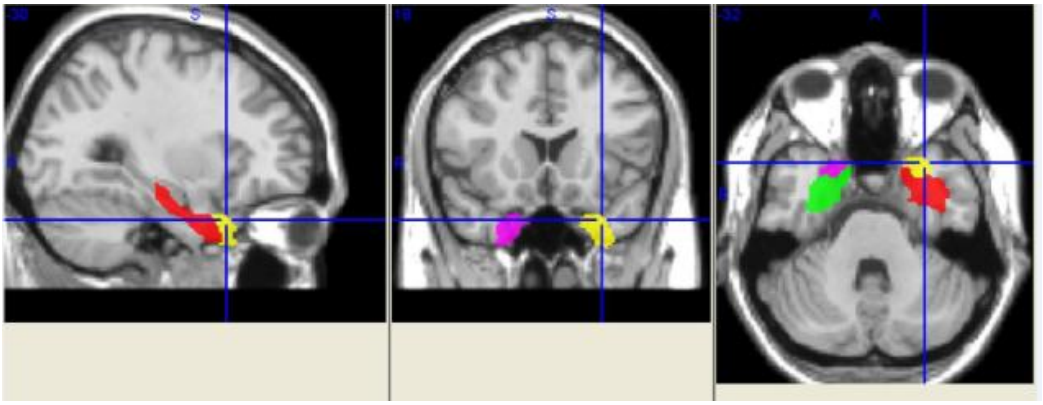


Fig: 1 Hippocampus and Amygdala in control group

2.5 Statistical Analysis

All statistical analysis were performed using SPSS-PC+V.10 software for windows. One way ANOVA was used for comparison of GM and regional volume.

3. RESULTS

The study population comprised 55 patients (25 with AD,10 with FTD and 20 control subjects. There were no significant between group difference in age and education. In AD, compared with all other group the mean MMSE rate were significantly lower. Hippocampal volume smaller than controls in all the study groups.

3.1 GM volume across diagnosis

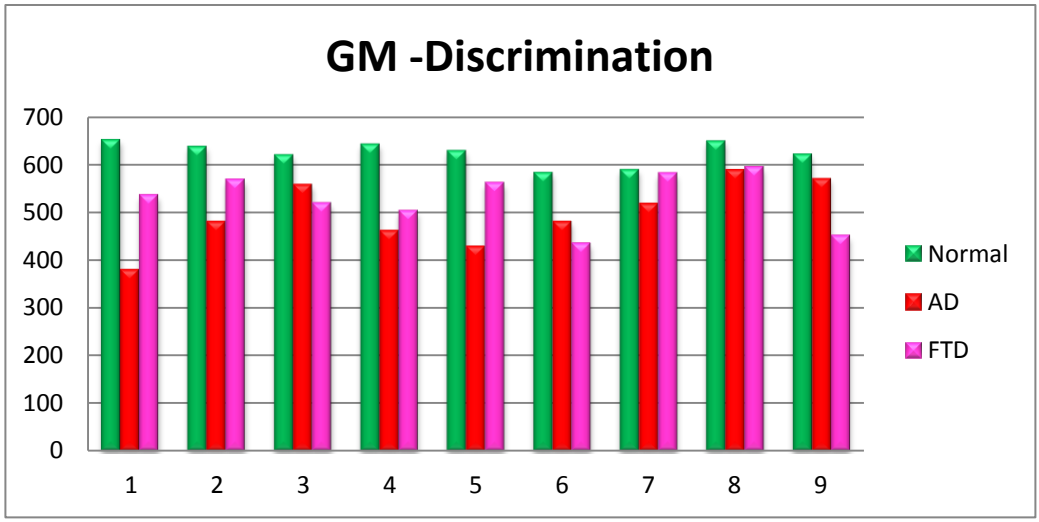


Fig: 2 GM volume for the discrimination of the study groups

3.2 Hippocampal Volume across diagnosis

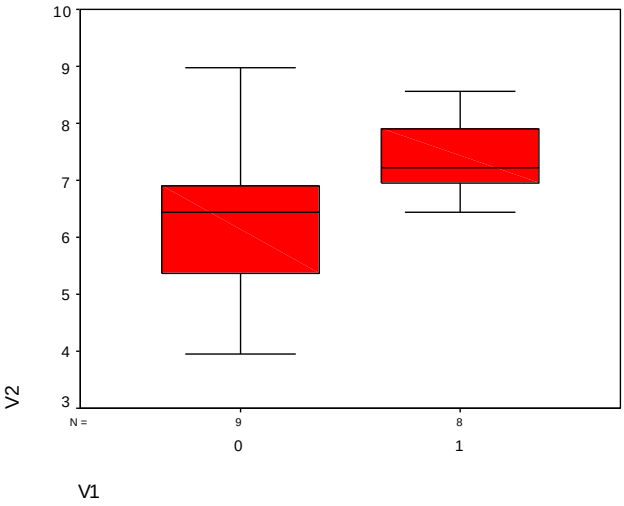


Fig: 3 FTD Vs AD Hippocampal volumes.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	5.524	1	5.524	3.516	.080
Within Groups	23.570	15	1.571		
Total	29.094	16			

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	5.429	1	5.429	6.759	.020
Within Groups	12.049	15	.803		
Total	17.479	16			

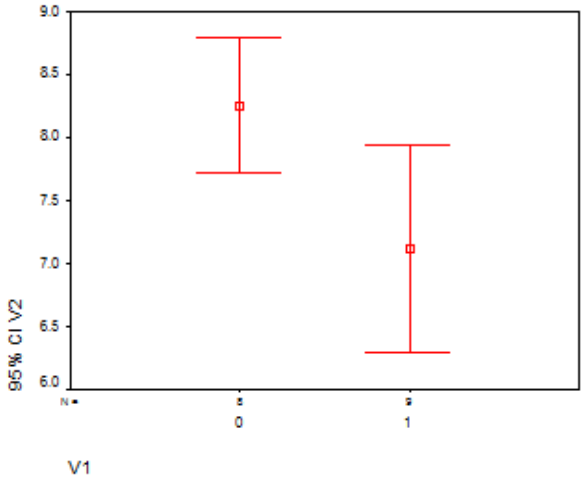
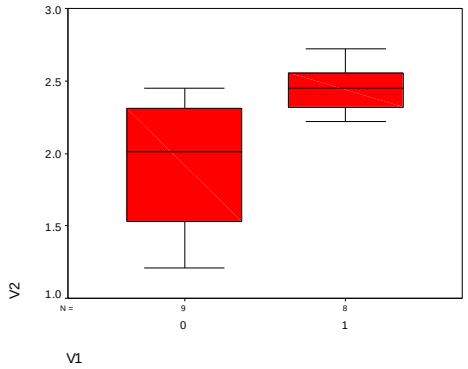


Fig: 4 NCI Vs AD Hippocampal volumes

Table 1: NCI Vs FTD Hippocampal volume

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	16.828	1	16.828	10.944	.005
Within Groups	23.064	15	1.538		
Total	39.893	16			

3.3 Amygdala volume across diagnosis

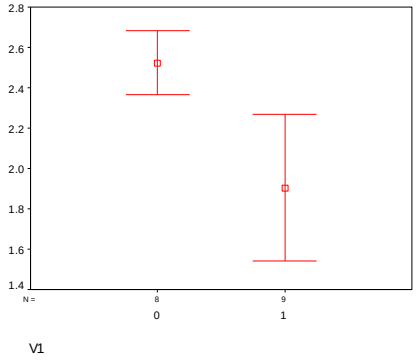


	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1.254	1	1.254	9.485	.008
Within Groups	1.983	15	.132		
Total	3.237	16			

Fig: 5 FTD Vs AD amygdala volume.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.105	1	.105	1.700	.212
Within Groups	.922	15	6.149		
Total	1.027	16			

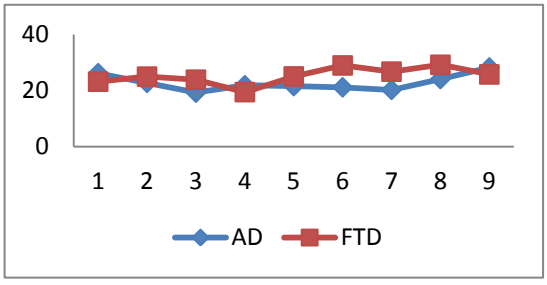
Fig: 6 NCI Vs AD amygdala volumes



	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1.630	1	1.630	11.962	.004
Within Groups	2.044	15	.136		
Total	3.674	16			

Fig: 7 NCI Vs FTD amygdala volumes

3.4 Cingulate volume across diagnosis



	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1.251	1	1.251	.068	.798
Within Groups	277.086	15	18.472		
Total	278.337	16			

Fig: 8 AD VS FTD cingulate volume

4. DISCUSSIONS

In this study we investigated regional differences in the distribution of pathology between FTD and AD using information from VBM imaging modalities. Our primary aim was to identify disease specific brain regions that distinguish AD from FTD and normal aging on a group as well as an individual basis .In this study we are able to assess GM volume loss and regional brain volumetric evaluations of each study group.

This study examined the relationship between regional volume especially the amygdala, hippocampus and the cingulate regions and cognitive impairment in patients with AD, FTD and control subjects using an MRI based voxel Based Morphometric method. MRI based regional volume analysis has been widely used for the non invasive diagnosis of different types of dementia. Measurement of amygdala and hippocampal volume may be used to differentiate AD from FTD and from healthy subjects.in this study have found no significant difference in hippocampal volume between AD and FTD but has to shown to be severe atrophy in the hippocampus compared to the healthy controls .

In the resent study, the measurement of the hippocampus revealed a progressive reduction in volume from control

subjects and FTD .That means hippocampal atrophy was more prominent and may be used to differentiate patients with AD than in controls and other dementia subtypes.

This study have some limitations . The small size of the study cohort mean that it was not possible to analyze the relationship between the amygdala and hippocampal volume for the discrimination of AD and FTD.

5. CONCLUSION

In summary, our findings suggest that measurement of amgdalar and hippocampal volume may help in the discrimination of AD and FTD. Both the hippocampus and amygdala are atrophic in AD and FTD compared to the healthy controls . The extent and pattern of atrophy of the hippocampus is virtually similar in both of the dementias. In this study, there was no evidence that cingulate regional atrophy is specifically associated with AD and FTD.

6. Acknowledgements

The authors like to express their thanks to Noorul Islam University and Sree Chitra Tirunal Institute for Medical Science and Technology, Trivandrum for their support and encouragement during this work

7. REFERENCES

[1] Alistair Burns., Michael, Zaudig. “Mild cognitive impairment in older people”. Lancet. 360: 1963-65(2002).

[2] Richard, J.P., Anne, M.F., David, M.H. “Multimodal Technique for diagnosis and prognosis of AD”. Nature. 461(2009).

[3] Mathuranath, P.S., Mathew R. “Role of subjective memory complaints in defing MCI”. Neurobiology of Aging. 25: 74-79(2004).

[4] Rahul, S Desikan., Howard, J.C. “Automated MRI measures identify individuals with MCI and AD”. Brain. 132: 2048-2057(2009).

[5] D.P Devanand, Liu J, Hao X, Pradhaban G, Peterson BS. “MRI hippocampal and entorhinal cortex mapping in predicting conversion to AD”, Neuroimage, 60, pp. 1622-1629.(2012)

[6] Barbro, robertson. ,Monica, Nordstorm., Helle,Wijk.I”nvestigating poor insight in AD: A survey research approaches”. Dementia. 6:44-61(2007)

[7] Gary, W.S., Thomsun, P.M., Colegm..Current and future uses of neurimaging for cognitively impaired patients. Neurology.79 (2008)

[8] Graff-Radford NR, Woodruff BK.Frontotemporal dementia. Semin Neurol 27(1):48-57(2007)

[9] Perry RJ, Graham A, Williams G, Rosen H, Erzinclioglu S, Weiner M, et al. Patterns of frontal lobe atrophy in frontotemporal dementia: a volumetric MRI study. Dement Geriatr Cogn Disord 2006;22(4):278-87

[10] Keith A. Josephs, MST, MD. “Frontotemporal Dementia and Related Disorders: Deciphering the Enigma”. Ann Neurol. 64:4–14(2008)

[11] Jennifer L.Whitewell. “VBM: An automated technique for assessing structural changes in the brain”, Journal of Neuroscience, 29,pp. 9661-9664(2009)

[12] Ashburner J, Karl J. Friston." Voxel based Morphometry -The methods. Neuroimage, 11, pp. 805–821 (2000)

[13] Stéphane P. Poulin , Rebecca Dautoff , John C. Morris,Lisa Feldman Barrett , Bradford C. Dickerson. “Amygdala atrophy is prominent in early Alzheimer's disease and relates to

[14] symptom severity”, Psychiatry Research: Neuroimaging. 194 : 7–13(2011)

[15] G. Zamboni, MD, E.D. Huey, MD, F. Krueger, PhD, P.F. Nichelli, MD,J. Grafman, PhD.” Apathy and disinhibition in frontotemporal dementia”. Neurology.71:736–742(2008)

[16] G. D. Rabinovici, MD, W. W. Seeley, MD, E. J. Kim, MD, M. L. Gorno-Tempini, et al . “Distinct MRI Atrophy Patterns in Autopsy-Proven Alzheimer’s Disease and Frontotemporal Lobar Degeneration”. Am J Alzheimers Dis Other Demen. 22(6): 474–488(2007)

[17] Grossman M, McMillan C, Moore P, et al. What’s in a name: voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer’s disease, frontotemporal dementia and corticobasal degeneration. Brain 2004;127:628–649.

[18] Michael PL, Devita. C, James CG, Grossman. M. Using Voxel-Based Morphometry to Examine Atrophy-Behavior Correlates in Alzheimer's Disease and Frontotemporal Dementia. In: Medical Image Computing and Computer-Assisted Intervention. . Springer Berlin / Heidelberg; 2002. p. 770-776.

[19] Den Heijer, T., Geerlings, M.I., Hoebeek, F.E., Hofman, A., Koudstaal, P.J., Breteler, M.M.,. Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people. Archives of General Psychiatry 63, 57–62(2006)

[20] Andrea Mechelli, Cathy J. Price, Karl J. Friston, John Ashburner. “Voxel-Based Morphometry of the Human Brain: Methods and Applications, Current Medical Imaging Reviews, 2005, 1, 1-9 (2005)