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Neuropsychological and Volumetric Analysis Techniques Mapping Progressive Brain Structural Changes in Alzheimer's disease

Tinu Varghese[1, 2,] Sheela Kumari R[2], P.S Mathuranath[2], Neelima Renjith[2]

[1,2]Department of Electronics and Instrumentation, Noorul Islam University, Kumara coil, Thuckalay, Tamilnadu, India.

[1]Cognition and Behavioural Neurology Section, Department of Neurology, Sree Chitra Tirunal Institute for Medical Science and Technology, Trivandrum, India

Abstract—Alzheimer's disease (AD) is a complex progressive brain disorder. The concept of Mild Cognitive impairment (MCI) is considered as a subtle but measurable disorder that is greater than the normal aging controls. In this paper, we have explored the efficacy of neuropsychological and structural volumetric techniques changes of the human brain for the discrimination of MRI (Magnetic Resonance Imaging) of patients with AD and their age matched controls. Subjects consisted of 25 AD and 25 MCI patients and 20 age matched normal controls that underwent detailed neuropsychological and neuroimaging evaluation. The subjects who attended the memory clinic at SCTIMST were administered ACE, MMSE, RAVLT, Trail Making tests and also underwent MRI of brain and hippocampal volumes were obtained. When the neuropsychological performance of the three groups was compared it was seen that the AD performed significantly poorer than the MCI on 9 subcomponents in ACE and also on MMSE, RAVLT and Trail Making tests and the MCI had significant ($p < .01$) impairment on tests of memory compared to NCI. Volumetric analysis revealed a significantly lower hippocampus volume in AD (3.49+0.78ml) and MCI (5.97+0.93ml) compared to NCI (7.44+0.98). Patients with dementia of Alzheimer's type on comparison with Mild Cognitive Impairment have poor performance on tests of memory and greater hippocampal volume loss. Hippocampal volume is a determinant of memory function.

Index Terms— Alzheimer's disease, Mild Cognitive Impairment, No Cognitive Impairment, Magnetic Resonance Imaging. MMSE=Mini Mental State Examination; CDR = clinical dementia rating; MCI = mild cognitive impairment; ROI = Region of interest

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]. In 2010 dementia India reports estimated that over 3.7 million people are affected by dementia in our country. Dementia is not a part of aging and it is caused by variety of diseases. 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].

- *Tinu Varghese is currently pursuing PhD program in Noorul Islam university. Kumaracoil, Thuckalay TN. tinuannevarghese@gmail.com .*
- *Sheela Kumari , Mathuranath P.S, Neelima Rengith, Department of Neurology, CBNC,Sree Chitra Tirunal Institute For Medical Science and Technology*

It is characterized by atrophy in the hippocampus, temporal lobe and entorhinal cortex[4]. Hence these studies have largely focused on these regions of interest

2 Materials and Methods

2.1Samples and Recruitment

All Participants in this study were selected in the Sree Chitra Tirunal Institute for Medical Science and Technology (SCTIMST), Trivandrum, Kerala dementia clinic. Patients were selected with a clinical diagnosis of probable MCI according to the NINCDS/A-DRDA criteria. Subjects consisted of 25 AD and 25 MCI patients and 20 age matched normal controls that underwent clinical examination, detailed neuropsychological and neuroimaging evaluation. The patients ranged in age from 52 to 75 years and the average score of Mini Mental State (MMSE) was 23 ±3. 20 healthy volunteers group matched to patients on age and education and MMSE score of 28±2.

2.2 Neuropsychological Evaluation

The study subjects were administered the MMSE, CDR ACE, RAVLT, Semantic Battery and Trail Making test. The neuropsychological assessment was done at the hospital in a quiet room by a trained neurophysiologist [5-7]

2.3 MRI Acquisition and Pre-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 axial 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 images will be post-processed in the fully equipped brain mapping lab.The data will be analyzed using SPM5 software. VBM involves a Voxel-wise statistical comparison of gray matter intensity between two groups of subjects. VBM studies in AD have confirmed significant greymatter changes in medial and temporal regions [8]. 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 [9]. Hence the images were registered into T1 MRI template, provided by MNI. After normalization images were segmented into GM, WM and CSF. The VBM analysis was performed in the MATLAB 7.1 platform with Statistical Parametric Mapping (SPM5).

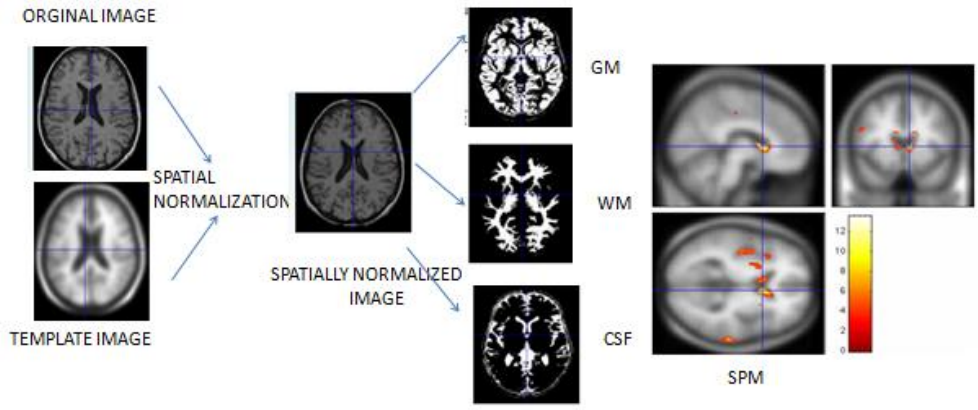


Fig 1: VBM –Pre-processing overview

2.4 Statistics

Comparison of the three groups on neuropsychological parameters was done using one-way ANOVA. Brain volumes were estimated using voxel based morphometry (VBM).VBM involves a voxel –wise statistical comparison of grey matter intensity between two groups of subjects ,were groups of images are normalized ,segmented ,smoothed and then compared using voxel wise statistical parametric tests. Group differences in normalized hippocampal volume between AD patients, MCI patients and healthy controls were assessed by using student t tests [10].

In the present study the AD patients were of mild severity on the CDR (≤1). The mean education of AD (11.07+3.99) was lower than MCI and NCI, while that of MCI (16.60+4.36) and NCI (17.71+3.90) were comparable. MCI (73.1+ 9.0) and AD(72.9 + 7.1) groups were comparable on age and NCI were younger (61+1.0).

Results indicate that on the ACE, MCI on comparison with NCI performed significantly poorer only in memory subtests. However AD on comparison to MCI showed impairment also on other sub tests.

3 Results and Discussions

In the present cross sectional study, we have focused on how AD evolves from MCI and MCI from AD from a neuropsychological and neuroradiological perspective

Table 1: MMSE scores in the Discrimination study

NCI VS MCI			
Test parameters	Mean ± SD		p value
	NCI	MCI	
Total	29.60 ±0.55	27.14 ± 2.67	1.000

MCI Vs AD			
Test parameters	Mean ± SD		p value
	MCI	AD	
Total	27.14 ± 2.67	20.42 ± 5.57	0.010*

Table 2: Results of ACE and WMS comparing scores of MCI and NCI

Test	Subtest	MCI (n = 25)	NCI (n = 20)	p value
		Mean ± SD	Mean ± SD	
Addenbrookes Cognitive Examination (ACE)	Recall	1.95 ± 0.91	2.64 ± 0.50	0.001
	Address Immediate Recall	15.0 ± 3.62	19.18 ± 1.72	0.000
	Address Delayed Recall	2.79 ± 1.62	6.09 ± 1.14	0.000
	ACE Total	83.53 ± 6.52	94.0 ± 3.26	0.000
Wechsler Memory Scale (WMS)	Story 1 Immediate recall	7.42 ± 4.45	12.55 ± 4.57	0.004
	Story 1 Delayed Recall	4.16 ± 3.55	10.36 ± 4.57	0.000
	Story 2 Immediate recall	5.32 ± 2.19	8.82 ± 2.89	0.001
	Story 2 Delayed Recall	3.74 ± 2.54	7.91 ± 2.59	0.000
	Drawing Immediate Recall	17.42 ± 6.29	26.91 ± 5.72	0.000
	Drawing Delayed Recall	8.53 ± 8.34	24.91 ± 7.03	0.000

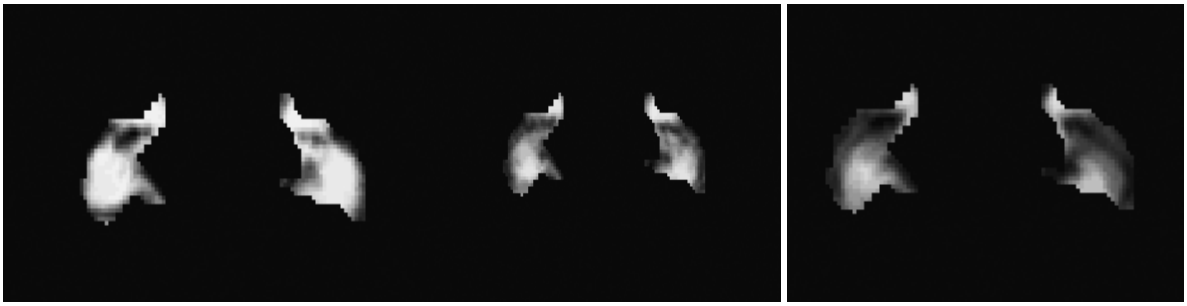
Table: 3 Results of RAVLT and Trail making comparing scores of MCI and NCI

Test	Subtest	MCI (*n* = 25) Mean ± SD	NCI (*n* = 20) Mean ± SD	p value
Rey Auditory Verbal Learning test (RAVLT)	Average Learning	6.52 ± 1.70	9.04 ± 1.44	0.000
	Immediate Recall	5.16 ± 2.81	9.82 ±2.40	0.000
	Delayed Recall	5.26 ± 2.84	9.55 ± 3.27	0.001
Trail Making Test	Trial A time	122.53 ± 5.061	27.96 ±46.51	0.000
	Trail B time	268.74 ± 15.06	56.05 ±90.84	0.000

On the MMSE, there was no significant difference between MCI and NCI, whereas, AD patients scored significantly lower than MCI. On Semantic Battery, MCI showed significant impairment in category fluency, while AD patients showed significant impairment in both category and letter fluency. On Trial Making test, MCI was not seen to differ from NCI. Comparison of AD with MCI showed significantly more errors for AD in both Trail A and B.

For Trail A, AD patients took more time to complete the task compared to MCI [11-13].

In hippocampal volume, MCI and AD had significant volume loss compared to NCI .In GM volume, AD had significant volume loss compared to the NCI group.



(a) **(b)** **(c)**

Fig 2: Total Hippocampal Volume (ml) in (a) NCI (7.44), (b) MCI (5.97) and (c) AD (3.49)

Table 4: Discrimination analysis of Hippocampus in

NCI Vs MCI

	Sum of Squares	Mean Square	F	Sig
Between Groups	9.158	9.158	6.350	.016
Within Groups	53.36	1.442		
Total	62.52			

MCI Vs AD

	Sum of Squares	Mean Square	F	sig
Between Groups	119.57	119.574	41.08	.000
Within Groups	165.88	2.910		
Total	285.46			

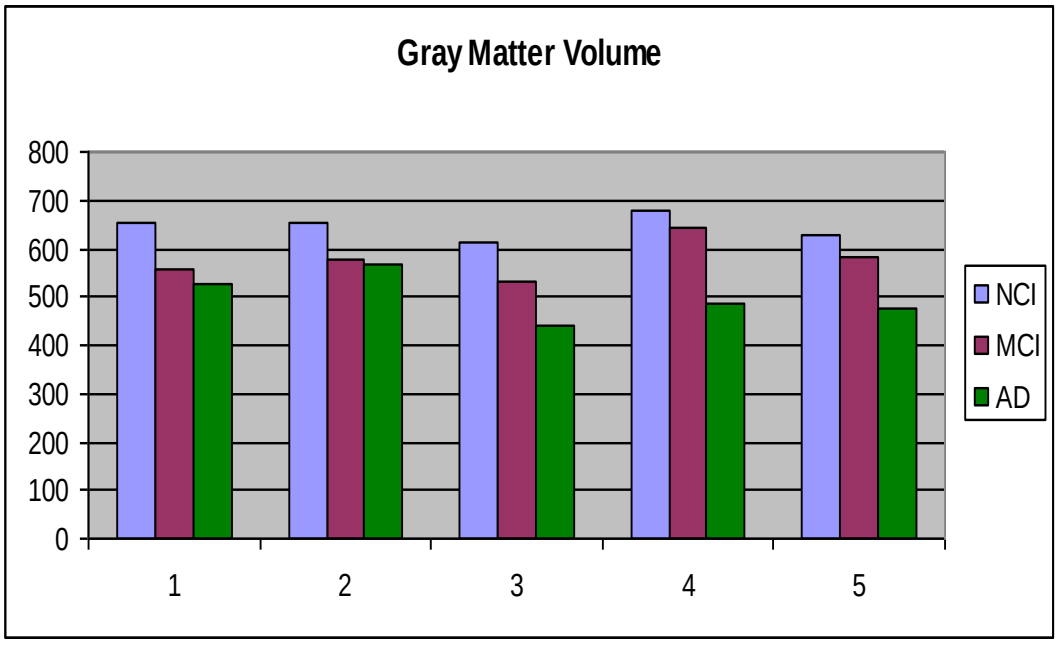


Fig 3: GM scores in the discrimination study

Our results show that, neuropsychologicaly the MCI when compared to NCI showed impairment only on tests involving memory but was comparable on all other cognitive tests. From MCI to AD it can be seen that in addition to worsening of memory, the impairment has spread to include other dimensions such as, naming component of language, visuo spatial and executive functions[14]

Neuroradiologically, the MCI patients were seen to have a greater hippocampal volume loss compared to NCI also significant volume loss in the transition stage of MCI to AD. This could be attributed to the inclusion of patients with mild AD in this study. From our results we find that tests such as ACE, MMSE, SB and Trail are able to pick up the transition from MCI to AD.

4 Conclusion

Our study showed that automated segmentation of the GM, Hippocampus and Neuropsychological evaluations individually classify Alzheimer's Desease,Mild Cognitive Impairment and control participants with a high degree of of accuracy. MCI subjects have impaired memory functions compared to NCI. By using normalized hippocampal volume of AD patients were correctly classified with respect to the control subjects. hippocampal volume is an indicator of future progression to AD. The method helped identify significant group differences in terms of hippocampal volume. Volumetric analyses of brain structures have become increasingly common for diagnostic purposes and for identifying disease progression. The assessment of medial temporal lobe (MTL) atrophy predicted progression of MCI and AD. From our neuropsychological results we find that tests such as ACE, MMSE, SB and Trail are able to pick up the transition from MCI to AD

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