Original Article

Multimodality Neuroimaging in Mild Cognitive Impairment: A Cross-sectional Comparison Study

R. Sheelakumari[1,2], Sankara P. Sarma[3], Chandrasekharan Kesavadas[2], Bejoy Thomas[2], Deepak Sasi[1], Lekha V. Sarath[1], Sunitha Justus[1], Mridula Mathew[1], Ramshekhar N. Menon[1]

Departments of [1]Neurology and [2]Imaging Sciences and Interventional Radiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, [3]Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India

Abstract

Background and Purpose: Mild cognitive impairment (MCI) is a focus of considerable research. The present study aimed to test the utility of a logistic regression-derived classifier, combining specific quantitative multimodal magnetic resonance imaging (MRI) data for the early objective phenotyping of MCI in the clinic, over structural MRI data. **Methods**: Thirty-three participants with cognitively stable amnestic MCI; 15 MCI converters to early Alzheimer's disease (AD; diseased controls) and 20 healthy controls underwent high-resolution T1-weighted volumetric MRI, diffusion tensor imaging (DTI), and proton magnetic resonance spectroscopy (^{1}H MR spectroscopy). The regional volumes were obtained from T1-weighted MRI. The fractional anisotropy and mean diffusivity maps were derived from DTI over multiple white matter regions. The ^{1}H MRS voxels were placed over posterior cingulate gyri, and N-acetyl aspartate (NAA)/creatine (Cr), choline (Cho)/Cr, myoinositol (mI/Cr), and NAA/mI ratios were obtained. A multimodal classifier comprising MR volumetry, DTI, and MRS was prepared. A cutoff point was arrived based on receiver operator characteristics analysis. Results were considered significant, if $P < 0.05$. **Results:** The most sensitive individual marker to discriminate MCI from controls was DTI (90.9%), with a specificity of 50%. For classifying MCI from AD, the best individual modality was DTI (72.7%), with a high specificity of 87.9%. The multimodal classifier approach for MCI control classification achieved an area under curve (AUC) (AUC = 0.89; $P < 0.001$), with 93.9% sensitivity and 70% specificity. The combined classifier for MCI-AD achieved a highest AUC (AUC = 0.93; $P < 0.001$), with 93% sensitivity and 85.6% specificity. **Conclusions:** The combined method of gray matter atrophy, white matter tract changes, and metabolite variation achieved a better performance at classifying MCI compared to the application of individual MRI biomarkers.

Keywords: Magnetic resonance imaging, mild cognitive impairment, multimodality, spectroscopy, tensor imaging, volumetry

Introduction

Alzheimer's disease (AD) is the most common form of dementia affecting elderly people and presents with decline in memory and cognition.[1] Hence, it is important to identify patients at high risk of AD in the prodromal stage known as mild cognitive impairment (MCI), which is considered as a continuum between normal aging and dementia. However, the annual conversion rate of MCI to AD has been found to be approximately 10%–15%, with longitudinal trends in cognitive performances fluctuating between relative stability over time to decline.[2,3] Stable amnestic MCI has certain structural volumetric signatures.[4]

Several modalities of biomarkers have been proven to be sensitive for diagnosis of AD and MCI due to AD including brain atrophy measured by magnetic resonance imaging (MRI),[4,5] hypometabolism measured by positron emission tomography (PET),[6] and quantification of specific proteins measured through cerebrospinal fluid (CSF).[7,8] However, the nonavailability of the ligand C11-Pittsburgh compound B (PiB) and CSF amyloid beta (Aβ) or tau analysis in many centers across the world renders importance to other novel imaging biomarkers. In this study, we have used a combination of structural MRI analysis methods

Access this article online

Quick Response Code:

Website: www.annalsofian.org

DOI: 10.4103/aian.AIAN_379_17

Address for correspondence: Dr. Ramshekhar N. Menon, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum - 695 011, Kerala, India.
E-mail: rsnmenon@yahoo.com

How to cite this article: Sheelakumari R, Sarma SP, Kesavadas C, Thomas B, Sasi D, Sarath LV, *et al*. Multimodality neuroimaging in mild cognitive impairment: A cross-sectional comparison study. Ann Indian Acad Neurol 2018;21:133-9.

using voxel-based morphometry (VBM), diffusion tensor imaging (DTI), and proton magnetic resonance spectroscopy (^{1}H MRS) to measure volumetric changes, diffusion anisotropy of water molecules, and ratio of metabolites, respectively, in cognitively stable amnestic MCI compared to converters to early AD and healthy controls. We hypothesize that multiple MRI markers of underlying neuronal dysfunction can help improve the ability to identify patients with MCI as a distinctive entity, rather than using a single MRI marker. Furthermore, in the absence of expensive established biomarkers for AD such as PiB-PET, CSF Amyloid beta (Aβ)-42:Aβ-40 and CSF tau analysis that are not available at most centers in the developing countries, the MRI markers could be useful in diagnosis.. We also evaluate the relative sensitivity and specificity of multimodal MRI markers to enable objective phenotyping in MCI diagnosed using a standard array of neuropsychological tests.

Methods

Subjects

The study was designed as a cross-sectional observational study from a prospectively maintained database at a Memory and Neurobehavioral Disorders Clinic of a tertiary care hospital situated in the South Indian state of Kerala. The study had the approval from the Institutional Ethics Committee of our institute. Sixty-eight participants were recruited into the current study. These included 20controls; 33 amnestic MCI and 15 AD patients. Healthy controls were required to have a Mini–Mental State Examination (MMSE) score between 28 and 30, a clinical dementia rating (CDR) score of 0 with formal education of >8 years and no history of subjective memory complaints, and with no major neurological/psychiatric disorders were included in the study. The early AD patients were selected from a cohort of converters from amnestic MCI according to standard NINCDS–ADRDA diagnostic criteria with CDR of <2, to serve as diseased controls.[9] The MCI patients were diagnosed according to modified Petersen's criteria[2] with CDR of ≤0.5 and MMSE score between 24 and 29. Longitudinal cognitive stability without progression to overt dementia was required for a minimum period of 2 years before inclusion into the study for the MCI patients. The participants underwent cognitive screening by the vernacular adaptation of Addenbrooke's Cognitive Examination battery (ACE) and other domain-specific neuropsychological tests as detailed previously.[10,11]

Magnetic resonance imaging data acquisition

Only participants who had undergone structural MRI, DTI, and spectroscopic data were included in the study. All MRI scans were acquired on a 1.5T Siemens Magnetom Avanto scanner. Structural MR images were acquired using a FLASH sequence with TR/TE = 11/4.95 ms, slice thickness = 1 mm, flip angle = 15°, matrix size = 256 × 256, and voxel size = 1 mm × 1 mm × 1 mm. For DTI, we used a single-shot spin-echo echo-planar sequence with diffusion gradients along 30 noncollinear directions with parameters TR/TE = 6000/88 ms, slice thickness = 3 mm with 1.5 mm gap averaged twice a b value of 0 and 1000 s/mm^2. We also performed ^{1}H MRS acquisitions using PRESS sequence with water suppression by means of CHESS sequence. The two-dimensional chemical shift (2D CSI) multivoxel sequence with a TR/TE = 1590/30 ms, NEX = 3, bandwidth = 10 kHz, and data points = 2048 was used for the examinations. ^{1}H MRS voxels of 1.6 cm × 1.6 cm × 2.5 cm were placed over the posterior cingulate gyri on the midsagittal slice covering posterior cingulate gyri and inferior precunei bilaterally [Supplementary Figure 1].

Image analysis

The volumetric structural data were processed using voxel-based morphometry (VBM 8) toolbox in SPM8 (statistical parametric mapping software, Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). First, the images were registered into the MNI space using high-dimensional DARTEL normalization algorithm. Then, the images were segmented into three different tissues: gray matter (GM), white matter (WM), and CSF [Figure 1]. After segmentation, the GM images were smoothed with a Gaussian kernel of 8 mm full width half maximum. The smoothed images were then multiplied with the binary masks of 11 region of interests (ROIs) bilaterally (including temporal

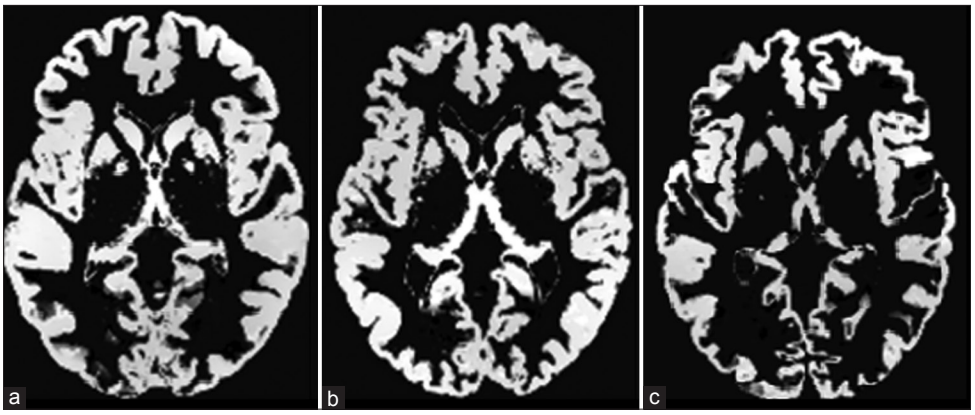

Figure 1: Segmented gray matter density maps in (a) controls (b) mild cognitive impairment and (c) Alzheimer's disease

neocortex, precuneus, and posterior cingulate) chosen priori from automated anatomic labeling atlas.[12] We computed the volume of each of the ROI region using MATLAB scripting. Postprocessing of DTI data was performed using a dedicated software package implemented in Siemens Leonardo workstation (Neuro 3D card). The system used an automatic correction of imaging distortions by scaling, de-skewing, and translational alignment of each of the image with the reference image (b = 0) to minimize the mismatch between the diffusion images and reference image. The offline tensor images and color maps were generated using the inbuilt "DTI task card." The anatomical images were overlaid on the DTI data and measured the fractional anisotropy (FA) and mean diffusivity (MD) at different locations using ROI-based analysis. The ROIs were placed on the specific anatomic locations by an experienced neuroradiologist (C. K) who was blinded to the clinical diagnosis. All data were analyzed by placing seven circular ROIs bilaterally with 5 mm pixels in temporal WM adjacent to temporal horn (TWM), genu and splenium of corpus callosum (CC), anterior and posterior subcortical WM (ASC and PSC), and anterior and posterior periventricular WM (APV and PPV) [Supplementary Figure 2]. The spectroscopic data were processed in the Leonardo workstation (Neuro3Dsoftware, Siemens) and the major peaks of N-acetyl aspartate (NAA), Creatine (Cr), Choline (Cho), and myoinositol (mI) were identified to evaluate the possible alterations in the posterior cingulate. Then, the ratios of NAA/Cr, Cho/Cr, mI/Cr, and NAA/mI were analyzed.

Statistical analysis

The demographic, neuropsychological, and radiological measures were compared across the three groups (MCI, AD, and NC) using univariate analysis of variance with *post hoc* Bonferroni correction. As there was significant age differences, age-adjusted comparisons were performed using general linear model. ROC curve analysis was carried out to classify MCI from controls and AD from MCI. For the ROC analysis, we used the mean GM density of the cortical regions, mean FA of the periventricular region, and mean metabolite ratios of NAA/mI and mI/Cr that differed in comparisons of MCI and controls and MCI and AD.

Furthermore, we computed a logistic regression that generated a probabilistic likelihood of MCI or AD diagnosis in each patient, and a score was derived as a linear combination of the regression coefficients and the imaging variables (T1-weighted MRI, DTI, and MRS). The obtained score was used to discriminate MCI from controls or AD. A cutoff point was arrived based on an ROC analysis. Results were considered significant, if $P < 0.05$.

Results

Demographic and neuropsychological results

Table 1 depicts demographics and neuropsychological test scores in patients and controls. The neuropsychological assessment results are listed in Table 1. Patients with MCI and AD were significantly impaired on ACE total, RAVLT total, and RAVLT recall after 20 min compared to controls. As neuropsychology test scores formed the objective basis for classification, the table is reflective of classification accuracy into each subgroup.

Gray matter density results

Patients with MCI had significantly reduced GM volume relative to controls in the right thalamus ($P = 0.02$) and posterior cingulate cortex (PCC; $P = 0.03$) [Supplementary Table 1]. Patients with AD compared to controls demonstrated significant volumetric differences in bilateral hippocampus ($P < 0.001$ for right and $P = 0.03$ for left), parahippocampus ($P = 0.03$ for right and $P = 0.04$ for left), and superior temporal gyrus ($P = 0.01$ for right and $P = 0.001$ for left), along

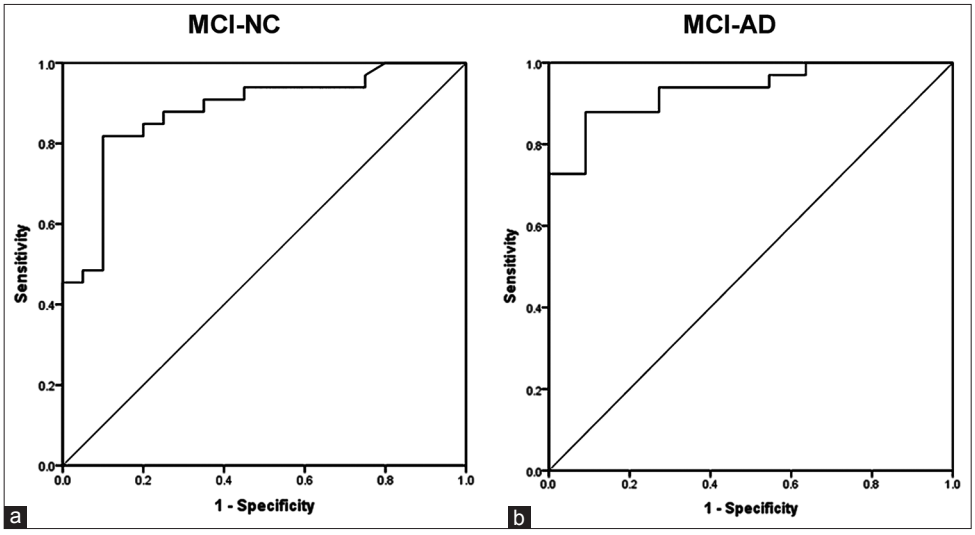

Figure 2: Receiver operator characteristic curves for classification of (a) mild cognitive impairment and controls and (b) mild cognitive impairment and Alzheimer's disease based on the optimal measure from each domain alone, and multimodal combination of gray matter density, fractional anisotropy, and metabolite ratios

with right amygdala (P = 0.002), thalamus (P = 0.02), and PCC (P = 0.006). A direct comparison between AD and MCI also revealed volume loss in hippocampus (P = 0.001 for right and P = 0.045 for left), inferior temporal gyrus (P = 0.004 for right and P = 0.026 for left), superior temporal pole (P = 0.001 for right and P = 0.03 for left) bilaterally, and right parahippocampus, middle temporal pole (P = 0.02), and superior temporal gyrus (P = 0.034) in AD.

Diffusion tensor imaging findings

Patients with MCI demonstrated significantly reduced FA in the left APV (P = 0.03) and increased MD in genu of CC (P = 0.04) relative to controls. Abbreviations elaborated in Supplementary Table 2. Patients with AD relative to controls had significantly reduced FA in bilateral APV (P = 0.014 for left and P = 0.007 for right) and splenium (P = 0.001), with a corresponding increase in MD values over bilateral APV (P = 0.02), left TWM genu (P = 0.007), and splenium (P < 0.001). A direct comparison of patients revealed significantly reduced FA in bilateral PPV (P = 0.001) and APV (P = 0.04 for left and P = 0.05 for right) as well as increased MD in bilateral APV (P = 0.02 for left and P = 0.04 for right), splenium (P = 0.03), and right hippocampus (0.048) in AD relative to MCI.

^{1}H MR spectroscopic findings

Patients with MCI have significantly lower NAA/mI (P = 0.005) and higher Cho/Cr (P = 0.045) ratios than controls [Supplementary Table 3]. Patients with AD showed significantly lower NAA/mI (P < 0.001) along with higher mI/Cr (P = 0.002) and Cho/Cr (P = 0.014) ratios. Comparison between patients with MCI and those with AD revealed significantly lower NAA/mI (P = 0.002) and higher mI/Cr (P < 0.001) in AD relative to MCI.

Multimodal classification based on T1-weighted magnetic resonance imaging, diffusion tensor imaging, and Proton magnetic resonance spectroscopy

We tested the performance of our multimodal classification method in the identification of MCI from AD and healthy controls. Table 2 summarizes the classification accuracy of our multimodal combination method, compared with individual modalities. ROC analysis revealed that the combined measurements of structural MRI, DTI, and ^{1}H MRS consistently achieve more accurate discrimination between MCI and controls and MCI and AD [Figure 2]. More specifically, for classifying MCI from healthy controls, our multimodal classifier achieved a significant area under the curve (AUC) (0.89, P < 0.001), with 93.9% sensitivity and 70% specificity. While considering an individual modality, the DTI provides the best classifier (AUC [0.798, P < 0.001]) with a sensitivity of 90.9% and specificity of 50%. On the other hand, for classifying MCI from AD, our multimodal classification method revealed the highest overall AUC (0.926, P < 0.001), with 93% sensitivity and 85.6% specificity. In addition, the best AUC (0.854,

Table 1: Comparison of demographic and neuropsychological measures between subjects

	NC	MCI	AD	Bonferroni corrected *P* value		
				MCI versus NC	AD versus NC	AD versus MCI
Demographic						
n	20	33	15			
Sex (male/female)	10/10	23/10	9/6	0.225	0.325	1.00
Mean age (mean±SD in years)	62.27±7.52	69.13±6.00	69.45±5.48	<0.001	0.011	1.00
Education (years)	12.80±3.68	11.29±3.25	12.85±3.64	0.95	0.253	0.08
Cognitive						
ACE	89.32±8.96	81.23±7.67	68.64±9.26	0.009	<0.001	<0.001
RAVLT cumulative learning score	52.80±8.12	37.89±10.1	25.36±7.15	<0.001	<0.001	<0.001
RAVLT 20 min recall score	12.29±1.76	6.54±3.49	2.00±1.73	<0.001	<0.001	<0.001

NC=Normal control, MCI=Mild cognitive impairment, AD=Alzheimer's disease, ACE=Addenbrooke's cognitive examination, RAVLT=Rey Auditory Verbal Learning Test, SD=Standard deviation

Table 2: Receiver operating characteristic results for the performance comparison of voxel-based morphometry, diffusion tensor imaging and proton magnetic resonance spectroscopy, and multimodal combination of these neuroimaging methods

	MCI versus controls			MCI versus AD		
Modality	AUC	Sensitivity (%)	Specificity (%)	AUC	Sensitivity (%)	Specificity (%)
T1 weighted MRI	0.775	78.8	70.0	0.829	90.9	60.6
DTI	0.798	90.9	50.0	0.854	72.7	87.9
^{1}H MRS	0.787	87.9	60.1	0.836	81.8	75.8
Multimodal	0.890	93.9	70.0	0.926	93	85.6

AUC=Area under the curve, DTI=Diffusion tensor imaging, ^{1}H MRS=Proton magnetic resonance spectroscopy, MCI=Mild cognitive impairment, MRI=Magnetic resonance imaging, AD=Alzheimer's disease

$P < 0.001$) on individual modality is obtained for DTI, with sensitivity of 72.7% and high specificity of 87.9%.

Logistic regression revealed that a combination of GM, WM, and ^{1}HMRS provides the best overall fit for predicting the diagnosis of MCI. Our best fit classifier included each variable from each modality with maximum AUC for classifying MCI. The score was derived from regression coefficient weighted sum of three modalities for predicting MCI from controls (7.0* [volume of PCC]-9.9* [MD value of Genu] +0.7* [NAA/mI value of PCC]) and MCI from AD (2.7* [volume of HP] +19* [FA value of PPVL] +1.2* [NAA/mI value of PCC]). The combined approach for MCI control classification achieved an AUC (AUC = 0.88; $P < 0.001$) [Figure 3a] with a cutoff score of 3.12, with 82% sensitivity and 90% specificity: 27 out of 33 MCI patients were correctly classified as MCI and 18 out 20 controls were correctly classified as controls. The combined classifier for MCI-AD achieved a highest AUC (AUC = 0.93; $P < 0.001$) [Figure 3b] with a cutoff score of 23.6, with 88% sensitivity and 91% specificity in which 30 out of 33 MCI patients were correctly classified as MCI and 13 out of 15 AD patients were correctly classified as AD.

Discussion

In this article, we have proposed a statistical classifier using logistic regression to discriminate patients with longitudinally stable amnestic MCI from healthy controls and AD. The diagnosis of AD and MCI in its initial stages is still challenging. Hence, predicting the risk of progression from MCI to AD is extremely relevant for future treatment trials. Although clinical and cognitive tests are used in practice, these are not able to identify the more subtle patterns of the disease process at an early stage, and clinical manifestations on neuropsychology are evident well into disease progression in prodromal dementia. Considering that around 10%–12% of MCI progress annually to overt dementia,[13] doubts have been raised regarding the existence of this entity as a notional one[14] and we attempted to study the morphometric and metabolic signatures of MCI that would aid in objective characterization of stability versus an "at risk" state in what is considered to be a prodromal dementia. This assumes significance in centers where specific biomarkers such as 11C-PiB PET, tau PET, and CSF biomarkers are not readily available.

Many existing studies have used structural MRI for measuring GM density (in the form of voxel maps),[15] volume/shape,[16,17] or cortical thickness. It is well known that multivoxel ^{1}H-MRS of the PCC is sensitive to the biochemical changes during the pathologic progression of AD before there is a significant loss of neuronal integrity commensurate to atrophy of the same region in MCI. Therefore, MRS has proven potential for predicting and monitoring different pathological stages in the course of AD.[18] Researchers have demonstrated that a combination of multiple biomarkers can improve the prognostic ability, but these have combined MRI, CSF, and PET analysis as opposed to multimodal MRI techniques alone.[17,19,20] Many studies have used only structural MRI and specifically, hippocampal volumetry to differentiate AD (or MCI) from controls.[21,22] The limited predefined ROIs considered in many studies constrain sampling of spatial–temporal pattern of structural and functional or metabolic abnormalities in their entirety, and we have tried to offset this limitation using whole-brain VBM and values from multiple areas of WM during DTI analysis. This is pertinent, especially in MCI, wherein accurate prediction of risk of conversion may not be tenable with MRI in isolation, especially in patients in whom hippocampal atrophy has not evolved,[14] and also because MCI/dementia is essentially clinically diagnosed. In addition, for AD classification, there are little differences among accuracy, sensitivity, and specificity for any multimodal classification method, considering the fact that the disease process has already been established, whereas, for MCI classification, the differences are relatively large, for example, a relatively large sensitivity, but low specificity, for each method.[16] This is reflected in our results as well as our study revealed an intermediate measurement in GM density, WM integrity, and metabolite ratio in MCI compared to controls and AD. The utility of a similar combination of MRI biomarkers including structural MRI, DTI, and ^{1}HMRS has not been reported previously from an Indian population.

Our findings on MCI control comparison in relation to PCC and thalamic atrophy are in line with a recent study.[23] However, in contrast to previous studies,[16,24] we could not

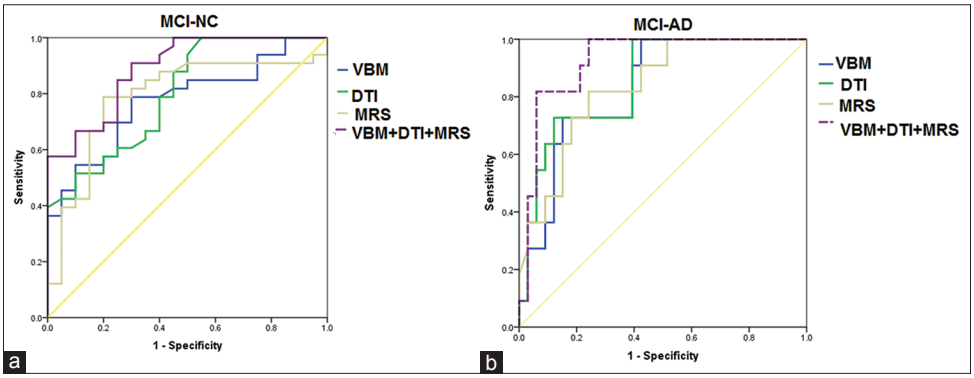

Figure 3: Receiver operator characteristic curves of combined classifiers for classification of (a) mild cognitive impairment from controls and (b) mild cognitive impairment from Alzheimer's disease

find any hippocampal atrophy in amnestic MCI compared to controls, possibly reflective of relative cognitive stability in our MCI. A longer period of follow-up is warranted to conclude on their evolution into multiple domain involvement versus early dementia. Regarding DTI, our observations corroborate with Chen *et al*.,[24] who described DTI changes in APV, PPV, and genu in MCI patients. The major pathological process contributing to reduced anisotropy in the cortical and subcortical WM tracts in AD and MCI may be either due to the presence of subclinical ischemic changes[25] or an increased susceptibility of oligodendrocytes to free radical and other metabolic damages.[26] In addition, there may be alterations in microvasculature, WM rarefaction with axonal damage, and gliosis[27] in brains of patients with AD favoring a mixed pathology beyond amyloid plaques and neurofibrillary tangles. Our finding of reduced posterior DTI indices of WM integrity in MCI and early AD mirrored the GM pathology in posterior brain regions relative to anterior regions.[28,29] The presence of significant regional brain WM anisotropy changes in both MCI and AD groups suggests that posterior regional anisotropy changes in normal-appearing WM of patients with MCI may play a role in the progression toward AD.[30] Furthermore, the anisotropy changes in the splenium of the CC might because of Wallerian degeneration seen in AD pathology.[31,32] The diffusivity changes in the genu of the corpous callosum (CC) in MCI patients might support the retrogenesis hypothesis, as the genu is known to myelinate much later than other WM regions.[33]

The MRS analysis revealed lower NAA/mI levels and higher Cho/Cr levels in the PCC in MCI. The metabolite NAA is a neuronal cell marker, and it can quantify neuronal loss or dysfunction, whereas myoinositol is a glial marker and its activation in MCI patients may be associated with glial activation and inflammation in the pathology of AD.[15]

Among the MRI biomarkers, the most sensitive measurement for discriminating MCI from control was DTI with high sensitivity and only moderate specificity. However, multimodal classifier using genu ADC values, posterior cingulate cortex volume, and NAA/mI MRS ratios produced a discernible improvement in diagnostic classification, with 82% sensitivity and 90% specificity. Considering the accuracy obtained with back classification of the MCI (30/33 correctly classified), it is evident that each modality (volumetry, DTI, and MRS) has its utility in achieving good combinational classification.

Expectedly, for discriminating MCI from AD, the volumetric findings in hippocampus, inferior temporal, and superior temporal pole as well as WM integrity in the periventricular areas showed high sensitivity. Furthermore, the neuronal markers of NAA/mI in the posterior cingulate region discriminated MCI from AD with sensitivity higher than DTI. The reduced NAA levels in AD have been well correlated with the presence of neuritic plaques and neurofibrillary tangles.[34] Moreover, these reductions in NAA/Cr and increases in mI/Cr ratios in the PCC have been demonstrated to be highly linked with the Braak neuropathological stages.[35] Previous findings indicated that NAA/mI ratio has enabled a highest sensitivity (82%–83%) and specificity (80%–95%) for the differentiation of AD from controls.[23,36] Our MRS findings in AD corroborate with another study which demonstrated correlation between reduction of regional glucose metabolism measured by [18F] FDG-PET and NAA/mI by MRS in the PCC of MCI, AD, and healthy controls.[37] A lower NAA/mI for the AD group compared to controls failed to reveal statistical significance in MCI group, unlike our results. Their findings suggest that brain glucose metabolism is a surrogate marker of synaptic activity[38] which should correlate with the measures of neuronal activity and density such as NAA/mI by MRS.

Overall, the utility of our combined classifier using hippocampal volume, FA of the posterior periventricular WM, and adjoining NAA/mI ratio is demonstrable on our back classification accuracy. The current study is limited by certain factors. First, the AD group sample size was small. We, however, primarily attempted to provide a classifier for MCI due to which the AD group served as a "diseased-control" cohort. Second, the other modalities such as CSF, PET, and APOE are not included in the model due to nonavailability of these tests at our center at the time of initiation of this study.

Conclusions

We have introduced a robust method to objectively classify MCI participants in comparison to early AD and cognitively normal healthy controls. We have proposed a new multimodal MRI measure combining cortical GM volume, FA, and MD at the voxel level and metabolite ratio at posterior cingulate region. The discrimination between MCI and AD patients reached a high sensitivity when relevant regions were selected. This result implies that multimodal analysis gives better results than unimodal analysis and hence may be a useful tool to assist in prognostication in MCI. Future studies utilizing our model for prediction on individual patients with stable and unstable MCI are required to gauge its utility over proven non-MRI biomarkers

Financial support and sponsorship

This work was supported by Research Grants from Kerala State Council for Science, Technology and Environment (19SRSHS/2011) and Cognitive Science Initiative, Department of Science and Technology, India (CSI/90/2012).

Conflicts of interest

There are no conflicts of interest.

References

1. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 2007;3:186-91.
2. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, *et al.* Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985-92.
3. Bruscoli M, Lovestone S. Is MCI really just early dementia? A systematic review of conversion studies. Int Psychogeriatr 2004;16:129-40.
4. McEvoy LK, Fennema-Notestine C, Roddey JC, Hagler DJ Jr.,

Holland D, Karow DS, *et al.* Alzheimer disease: Quantitative structural neuroimaging for detection and prediction of clinical and structural changes in mild cognitive impairment. Radiology 2009;251:195-205.
5. Du AT, Schuff N, Kramer JH, Rosen HJ, Gorno-Tempini ML, Rankin K, *et al.* Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. Brain 2007;130:1159-66.
6. De Santi S, de Leon MJ, Rusinek H, Convit A, Tarshish CY, Roche A, *et al.* Hippocampal formation glucose metabolism and volume losses in MCI and AD. Neurobiol Aging 2001;22:529-39.
7. Bouwman FH, Schoonenboom SN, van der Flier WM, van Elk EJ, Kok A, Barkhof F, *et al.* CSF biomarkers and medial temporal lobe atrophy predict dementia in mild cognitive impairment. Neurobiol Aging 2007;28:1070-4.
8. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, *et al.* Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 2009;65:403-13.
9. O'Bryant SE, Waring SC, Cullum CM, Hall J, Lacritz L, Massman PJ, *et al.* Staging dementia using clinical dementia rating scale sum of boxes scores: A Texas Alzheimer's research consortium study. Arch Neurol 2008;65:1091-5.
10. Mathuranath PS, Cherian JP, Mathew R, George A, Alexander A, Sarma SP, *et al.* Mini mental state examination and the Addenbrooke's cognitive examination: Effect of education and norms for a multicultural population. Neurol India 2007;55:106-10.
11. Menon R, Lekha V, Justus S, Sarma PS, Mathuranath P. A pilot study on utility of Malayalam version of Addenbrooke's cognitive examination in detection of amnestic mild cognitive impairment: A critical insight into utility of learning and recall measures. Ann Indian Acad Neurol 2014;17:420-5.
12. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002;15:273-89.
13. Petersen RC. Early diagnosis of Alzheimer's disease: Is MCI too late? Curr Alzheimer Res 2009;6:324-30.
14. Fan Y, Resnick SM, Wu X, Davatzikos C. Structural and functional biomarkers of prodromal Alzheimer's disease: A high-dimensional pattern classification study. Neuroimage 2008;41:277-85.
15. Gerardin E, Chételat G, Chupin M, Cuingnet R, Desgranges B, Kim HS, *et al.* Multidimensional classification of hippocampal shape features discriminates Alzheimer's disease and mild cognitive impairment from normal aging. Neuroimage 2009;47:1476-86.
16. Zhang D, Wang Y, Zhou L, Yuan H, Shen D; Alzheimer's Disease Neuroimaging Initiative. Multimodal classification of Alzheimer's disease and mild cognitive impairment. Neuroimage 2011;55:856-67.
17. Desikan RS, Cabral HJ, Hess CP, Dillon WP, Glastonbury CM, Weiner MW, *et al.* Automated MRI measures identify individuals with mild cognitive impairment and Alzheimer's disease. Brain 2009;132:2048-57.
18. Vemuri P, Wiste HJ, Weigand SD, Shaw LM, Trojanowski JQ, Weiner MW, *et al.* MRI and CSF biomarkers in normal, MCI, and AD subjects: Predicting future clinical change. Neurology 2009;73:294-301.
19. Walhovd KB, Fjell AM, Dale AM, McEvoy LK, Brewer J, Karow DS, *et al.* Multi-modal imaging predicts memory performance in normal aging and cognitive decline. Neurobiol Aging 2010;31:1107-21.
20. Bailly M, Destrieux C, Hommet C, Mondon K, Cottier JP, Beaufils E, *et al.* Precuneus and cingulate cortex atrophy and hypometabolism in patients with Alzheimer's disease and mild cognitive impairment: MRI and (18)F-FDG PET quantitative analysis using FreeSurfer. Biomed Res Int 2015;2015:583931.
21. Westman E, Simmons A, Zhang Y, Muehlboeck JS, Tunnard C, Liu Y, *et al.* Multivariate analysis of MRI data for Alzheimer's disease, mild cognitive impairment and healthy controls. Neuroimage 2011;54:1178-87.
22. Oliveira PP Jr., Nitrini R, Busatto G, Buchpiguel C, Sato JR, Amaro E Jr., *et al.* Use of SVM methods with surface-based cortical and volumetric subcortical measurements to detect Alzheimer's disease. J Alzheimers Dis 2010;19:1263-72.
23. Kantarci K, Xu Y, Shiung MM, O'Brien PC, Cha RH, Smith GE, *et al.* Comparative diagnostic utility of different MR modalities in mild cognitive impairment and Alzheimer's disease. Dement Geriatr Cogn Disord 2002;14:198-207.
24. Chen TF, Lin CC, Chen YF, Liu HM, Hua MS, Huang YC, *et al.* Diffusion tensor changes in patients with amnesic mild cognitive impairment and various dementias. Psychiatry Res 2009;173:15-21.
25. Kalaria RN. The role of cerebral ischemia in Alzheimer's disease. Neurobiol Aging 2000;21:321-30.
26. Bartzokis G. Age-related myelin breakdown: A developmental model of cognitive decline and Alzheimer's disease. Neurobiol Aging 2004;25:5-18.
27. Englund E. Neuropathology of white matter changes in Alzheimer's disease and vascular dementia. Dement Geriatr Cogn Disord 1998;9 Suppl 1:6-12.
28. Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cereb Cortex 1991;1:103-16.
29. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging 1995;16:271-8.
30. Wang Y, West JD, Flashman LA, Wishart HA, Santulli RB, Rabin LA, *et al.* Selective changes in white matter integrity in MCI and older adults with cognitive complaints. Biochim Biophys Acta 2012;1822:423-30.
31. Di Paola M, Di Iulio F, Cherubini A, Blundo C, Casini AR, Sancesario G, *et al.* When, where, and how the corpus callosum changes in MCI and AD: A multimodal MRI study. Neurology 2010;74:1136-42.
32. Alves GS, Oertel Knöchel V, Knöchel C, Carvalho AF, Pantel J, Engelhardt E, *et al.* Integrating retrogenesis theory to Alzheimer's disease pathology: Insight from DTI-TBSS investigation of the white matter microstructural integrity. Biomed Res Int 2015;2015:291658.
33. Aboitiz F, Scheibel AB, Fisher RS, Zaidel E. Fiber composition of the human corpus callosum. Brain Res 1992;598:143-53.
34. Klunk WE, Panchalingam K, Moossy J, McClure RJ, Pettegrew JW. N-acetyl-L-aspartate and other amino acid metabolites in Alzheimer's disease brain: A preliminary proton nuclear magnetic resonance study. Neurology 1992;42:1578-85.
35. Kantarci K, Knopman DS, Dickson DW, Parisi JE, Whitwell JL, Weigand SD, *et al.* Alzheimer disease: Postmortem neuropathologic correlates of antemortem 1H MR spectroscopy metabolite measurements. Radiology 2008;248:210-20.
36. Shonk TK, Moats RA, Gifford P, Michaelis T, Mandigo JC, Izumi J, *et al.* Probable Alzheimer disease: Diagnosis with proton MR spectroscopy. Radiology 1995;195:65-72.
37. Coutinho AM, Porto FH, Zampieri PF, Otaduy MC, Perroco TR, Oliveira MO, *et al.* Analysis of the posterior cingulate cortex with [18F] FDG-PET and Naa/mI in mild cognitive impairment and Alzheimer's disease: Correlations and differences between the two methods. Dement Neuropsychol 2015;9:385-93.
38. Jack CR Jr., Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, *et al.* Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12:207-16.