An overview of quantitative Magnetic Resonance Imaging analysis studies in the assessment of Alzheimer's disease

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Abstract— **Medical image analysis and visualization, can contribute in quantitative and qualitative analysis of Magnetic Resonance Imaging (MRI) towards an earlier diagnosis of Alzheimer's disease (AD). Moreover, the early detection of Mild Cognitive Impairment (MCI) has recently attracted a lot of attention. The main objective of this paper is to present a survey of recent key papers focused on the classification of MCI and AD and the prediction of conversion from MCI to AD using volume, shape and texture analysis. The most frequent anatomical features used in the assessment of AD, is the hippocampus, the cortex and the local concentration of grey matter. Shape analysis can identify the signs of early hippocampal atrophy, whereas volume analysis evaluates the structure as a whole. Shape analysis seems to be a more accurate technique both in classification of patients and in prognostic prediction. Compared to volume, shape and voxel based morphometry (VBM) techniques, texture analysis can be used to identify the microstructural changes before the larger-scale morphological characteristics which are detected by the other aforementioned techniques. We concluded that quantitative MRI measurements can be used as an in vivo surrogate for the classification of patients and furthermore, for the tracking the Alzheimer's disease progression.**

Keywords— **Alzheimer's disease; Mild Cognitive Impairment; quantitative MRI; temporal lobe; hippocampus; brain volume; prediction; classification.**

I. Introduction

Mild Cognitive Impairment (MCI) represents a transitional period between normal ageing and clinical probable Alzheimer's disease (AD) [1]. Nowadays, the diagnosis of AD is based on Mini Mental State examination (MMSE) such as the criteria documented in the Diagnostic and Statistical Manual of Mental Disorders based on the revised recommendations of the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders working group [2]. However, by the time a patient is diagnosed with AD using the standard clinical assessment, the brain tissue has already undergone widespread and irreversible synaptic loss [3]. AD is indicated by inevitable and insidious progression of atrophy which initially affects the Medial Temporal Lobe (MTL) of the brain [4], a region of the brain which includes anatomically related structures that are essential for declarative memory [5]. The regions affected earlier by AD are the entorhinal cortex, followed by hippocampus, amygdala (see Fig. 1) and parahippocampal gyrus, a grey cortical region that surrounds hippocampus. With disease progression, these regions lose neuronal tissue with consequent brain atrophy [6].

There is a pressing need to identify the early signs of the disease using *in vivo* techniques, apart from the MMSE tests. In order to identify the MCI stage, suitable biomarkers need to be used. A biomarker is a biochemical or anatomical factor which can provide quantitative measurements of the pathophysiologic processes of a disease [2] thus, many researchers have been using neuroimaging to evaluate this possibility. The Alzheimer's disease Neuroimaging Initiative (ADNI) [7] is a multicenter collaborative effort created in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations. It is an open source database where a huge collection of Positron Emission Tomography (PET) and MRI images are available online. Apart from imaging data, other biological markers such as cerebrospinal fluid (CSF) of more than 2000 participants including AD patients, MCI subjects and elderly controls are available online. This paper focuses on studies derived mainly from the ADNI database, and more specifically on the studies where quantitative MRI analysis was used for the assessment of the disease.

Structural MRI is a non-invasive imaging modality that provides high resolution images of the brain in any plane. The high tissue contrast images provided by 3D T1-weighted acquisitions enables accurate structural neuroimaging analysis which can be used as a possible biomarker for both the assessment of the disease and the prediction of conversion from MCI to AD [8]. Furthermore, because MRI does not use any ionizing radiation it is a suitable technique for longitudinal studies, which are necessary in the investigation of AD. It has been proved by many volumetric and shape and thickness analysis studies [9]–[13] that structural MRI based software tools allow the visualization of macroscopic tissue changes, and thus can help on the detection of neuronal loss in the initial stages of the disease. Features related to texture may have the potential to detect earlier and more subtle changes in neural tissue than other volumetric or shape analysis techniques [14].

This paper also provides a very brief review of the most widely referenced medical image analysis techniques used

in the assessment of AD. It focuses on selected studies published in the last decade, investigating the prediction of conversion from MCI to AD and the classification of MCI patients, using only structural MRI imaging and specifically volume, shape and texture analysis techniques. The results of the various ADNI studies might not be directly comparable; however, the data used are from the same database.

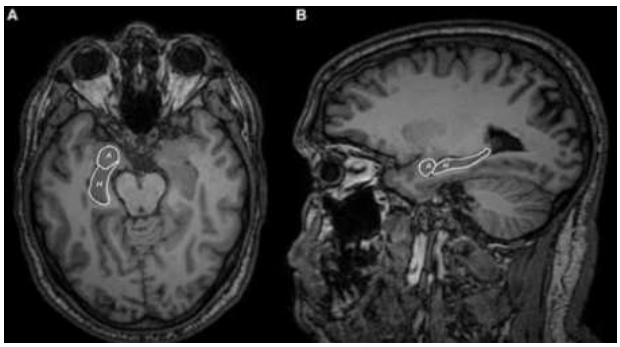

Fig. 1 Axial (A), sagittal (B) MRI views of hippocampus (H) and amygdala (A) segmentation [15]. Brain regions that are affected earlier by AD

II. Quantitative MRI studies based on volume and shape characteristics

Table 1 and Table 2 tabulate quantitative MRI studies covering volume, shape and texture analysis for brain atrophy classification and prediction from MCI to AD, respectively. In each table the following data are presented: study, subjects, follow-up duration, region of interest (ROI) investigated, data type, classifier, accuracy, sensitivity and specificity.

II.A Classification of MCI and AD studies: One of the most common areas affected, at the very early stage of the disease, is the hippocampus [16], [17]. Several studies [5], [9], have used volume measurements and confirmed that hippocampus atrophy as seen in structural MRI can constitute a useful diagnostic biomarker. Chupin *et al.*, 2009 [10] used automated segmentation techniques in order to calculate hippocampal volume in an attempt to differentiate normal controls (NC), MCI and AD subjects. In their study, they achieved an overall classification accuracy of 64%, showing that global hippocampal volume evaluation may not be a very accurate measure, mainly due to the fact that hippocampal volume is as variable in young as in older adults, thus this may have implications on the final results [18]. Desikan *et al.*, [19] carried out automated structural measurements of entorhinal cortex and supramarginal gyrus thickness. In conjunction with hippocampal volume, they classified MCI from AD patients with high accuracy. Gerardin et al. [20] used hippocampal shape features instead of volume analysis. Shape analysis methods can be used to reveal atrophy on local and non-global areas of the hippocampus, and according to the authors, the classification accuracy was superior to studies that used volume analysis. Specifically, they obtained a classification rate of 94%, with a sensitivity of 96% and a specificity of 92% for AD vs controls, and for MCI vs controls an accuracy of 83%, sensitivity 83% and specificity 84%. Kloppel *et al.*, [21] used SVM for the classification of patients (from 3 different groups) by using two different types of analysis: in the first model they used data from the whole brain and on the second they used data from an ROI within the hippocampus. Their results were comparable with other techniques which restrict their analysis only to medial temporal lobe structures. However, shape analysis used in [20] resulted in a better classification accuracy for both AD vs NC and MCI vs NC.

Table 1: Quantitative MRI studies in the classification of MCI and AD patients

Volume and shape analysis								
Study	Subjects	ROI	Data type	Classification method	Classification	Acc.	Se.	Sp.
Chupin *et al.*, 2009 [10]	210 MCI	Hippocampus & amygdala	Volume	Bootstrapping	NC vs AD NC vs MCI NC vs MCIc MCIc vs MCInc	76% 61% 71% 64%	75% 61% 67% 60%	77% 61% 72% 65%
Desikan *et al.*, 2009 [19]	49 NC, 48 MCI 94 NC, 57 MCI	Entorhinal cortex & supramarginal gyrus	Volume & Thickness	Logistic regression model	MCI	AUC: 0.91 AUC: 0.95	74% 90%	94% 91%
Gerardin *et al.*, 2009 **[20]**	23 NC, 23 MCI, 25 AD	Hippocampus	Shape	SVM	NC vs AD NC vs MCI	94% 83%	96% 83%	92% 84%
Kloppel et al., 2008 **[21]**	20 NC, 20 AD	Grey matter	Thickness	SVM	NC vs AD NC vs mAD mAD vs FTLD	95% 81.1% 89.2%	95% 60.6% 94.7%	95% 93.0% 83.3%
Texture analysis								
Zhang *et al.*, 2012 **[22]**	17 NC, 17 AD	Hippocampus & entorhinal cortex	3D texture	Non-linear ANN	NC vs AD	64.3% - 96.4%	-	-
Simoes *et al.*, 2012 **[23]**	15 NC, 15 MCI	Grey matter	Texture maps	SVM	NC vs MCI	87%	85%	95%

GLOSSARY: ROI: Region of interest; Acc: accuracy; Se: sensitivity; Sp: specificity; MCIc: MCI converters; MCInc: MCI non converters; SVM: support vector machine; AUC: area under curve; NC: Normal controls; ANN: Artificial neural network; mAD: mild AD; FTLD: frontotemporal lobar degeneration.

II.B Prediction of conversion from MCI to AD studies: Many studies have been investigating the prediction of conversion from MCI to AD (see Table 2). In a recent study, Costafreda *et al.,* [24] used a fully automated procedure to extract 3D hippocampal shape morphology in order to predict conversion from MCI to AD. Their predicting model had an accuracy of 80% (sensitivity 77%, and specificity 80%) which was competitive with other predictive models which used non automated measurements. In their prediction model, only hippocampus was used, which interestingly achieved a predictive performance comparable or superior to those employing a multi-region or whole brain approach [14],[15]. In [25], the authors used VBM analysis to evaluate the volume of white matter (WM) and grey matter (GM) of 103 MCI patients which they followed up for 15 months in order to predict which individuals will convert to AD. They evaluated their results via cross-validation and achieved an accuracy of 81.5% which is the one of best results published. Plant *et al.,* 2010 [17] in order to predict the conversion from MCI to AD from atrophic changes across the brain, they used 3 different classifiers including Support vector machine (SVM), Bayes statistics, and Voting Feature Intervals (VFI). When the anterior cingulate gyrus and orbitofrontal cortex was included in their measurements, they obtained their best predictive accuracy which was 75%. Bakkour *et al.,* [27] applied measures on cortical thickness of nine ROI's to test the predictive performance of this model. Among the other ROI's, MTL, cortical thickness had the best peak performance, predicting conversion to mild AD with 83% sensitivity and 65% specificity. Querbes *et al.,* [28] used mean cortical thickness within 22 ROI's and they obtained an accuracy of 73% and a sensitivity of 75% by applying their Normalized Thickness Index (NTI) on subjects from the ADNI database. In a very similar study [13], cortical thickness was measured, and based on the results, it was noticed that atrophy patterns differ with the disease progression, thus by learning these differences, the prediction accuracies can be improved.

The aforementioned ROI and whole brain studies successfully discriminated the individuals who converted from MCI to AD. The study by Desikan *et al.,* [29] attempted to predict the time to progress from MCI to AD. They used automated MRI-based software tools to apply measurements of medial temporal cortex thickness and volume on 64 ROI's among the two hemispheres of 324 MCI patients. Furthermore, they compared their results with CSF samples and PET measures and interestingly, their results revealed that structural MRI could better predict the disease progression rather than CSF biomarkers and metabolic changes detected rom PET. In a very similar study by Vemuri *et al.,* [30] where structural MRI and CSF biomarkers on 399 subjects were used, the results were similar to the study in [29] as it was found that MRI could predict with higher accuracy the time to conversion from amnestic MCI to AD, compared to CSF biomarkers.

III. Quantitative MRI studies based on texture analysis

Texture analysis, is a less frequently used compared to volume and shape analysis. The information provided by texture analysis cannot be visible through volume and shape properties [23] thus, texture analysis techniques may have the advantage of detecting earlier, subtle changes [31]. There exist different methods for texture analysis: (i) structural methods, (ii) statistical based methods, (iii) model based methods and (vi) transform based methods [32]. Quite frequently, the features are extracted from the grey level co-occurrence matrix (GLCM) methods which computes how often pair of pixels with specific values occur in an image [33].

III.A Classification of MCI and AD studies: In [22], Zhang *et al.,* used 3D texture features to identify normal controls from AD patients. They used over 100 texture features which were extracted from spherical ROIs placed within the area of the hippocampus and the entorhinal cortex, using image histograms, gradients, co-occurrence matrices and Run Length matrices (RLM). However, the classification accuracy of the method varied significantly, from 64.3% to 96.4%, depending on the chosen ROI. Not many studies applied texture analysis on MCI patients. One such study was that of Oliveira *et al.,* [34] where texture analysis was carried out only in the thalamus and corpus callosum of the brain. Because of the small number of subjects (17 MCI, 16 mild AD patients and 16 NC) the segmentation of corpus callosum and the thalamus was carried out manually and 44 texture parameters were extracted. The analysis was carried out separately for the two types of ROI's (and not on the whole brain) using the MaZda program [35]. According to the authors that method was more reliable than other techniques, where they analyze the brain texture as a homogenous structure. The aim of their study was to classify normal aging subjects from MCI and AD patients. In a similar study [36], where only corpus callosum was evaluated using 3D texture analysis on AD, MCI and normal controls, it was found that the 3D texture features had significance differences between the 3 groups of subjects. Because microstructural changes on the brain tissue start to develop years before the larger- scale alterations, Simoes *et al.,* [23] used a whole-brain voxel-wise approach by applying local statistical texture maps for the classification of MCI patients from NC. In order to classify the two groups they used SVMs and they obtained a mean accuracy of 87%, with a sensitivity at 85% and a specificity at 95%. However, the number of samples used in the study was very small as they used only 15 NC and 15 MCI patients.

III.B Prediction of conversion from MCI to AD studies: One of the few recent studies that carried out texture analysis to predict MCI to AD progression was that of Martinez Torteya *et al.,* [37]. In their study, they used Magnetization-Prepared Rapid Acquisition with Gradient Echo (MP-RAGE) images from the ADNI database and they include

six features, one related to genotyping, three related to image signal distribution and two related to texture features. In order to apply ROI's for every image, they used it's corresponding segmentation mask provided by [38]. For each ROI they used 9 texture-related features together with 13 morphological features and 28 signal distribution related features. They presented an MCI to AD progression biomarker which yielded a mean blind accuracy of 0.79.

IV. Magnetic resonance spectroscopy and diffusion tensor imaging in the assessment of MCI and AD

Magnetic Resonance Spectroscopy (MRS) is a non-invasive technique, which can be used to measure metabolites [39]. The concentration of N-acetyl aspartate (NAA) in cortical tissue has been associated with neuronal density and consequently, with AD patients [40]. MRS was used previously [43] in order to test its ability in the distinction of normal older subjects and AD patients. However, the results were variable and dependent on the anatomic region analysed. MRS it was found to be ineffective in clinical practice [43].

Diffusion tensor imaging (DTI) is another non-invasive MRI technique which studies the orientation and integrity of WM tracts by measuring the diffusion of water molecule in neural tissue [44]. DTI studies have been used to detect the levels of Fractional Anisotropy (FA) of water molecules in order to detect changes of white matter in AD. FA was found to be decreased in specific regions of the brain in AD and MCI patients compared to controls [45].

However, both MRS and DTI techniques are beyond the scope of this paper. Furthermore, thay are not included in the National Institute on Aging and Alzheimer's Association criteria for preclinical, MCI, and AD [46].

Table 2: Quantitative MRI studies in the prediction of conversion from MCI to AD

Study	Subjects	Follow-up (months)	ROI	Data type	Converters/ total MCI	Classification method	Acc.	Se.	Sp.
Volume and shape analysis									
Costafreda *et al.*, 2011 **[24]**	71 AD, 103 MCI 88 NC	0-12	Hippocampus	Shape	22/103	nSVM	80%	77%	80%
Misra *et al.*, 2009 **[25]**	103 MCI	0-36	Whole brain	VBM - Grey & White matter	27/103	nSVM	81.5%	-	-
Plant *et al.*, 2010 **[26]**	32 AD, 24 MCI 18 NC	0-30	Whole brain	VBM - Grey matter	9/24	VFI	75%	56%	87%
Bakkour *et al.*, 2009 **[27]**	49 QAD	0-30	Cortex	Thickness	20/49	ROC	-	83%	65%
Querbes et al 2009 **[28]**	130 AD 122 MCI 130 NC	0-24	Cortex	Thickness	77 /122	LDA	73%	75%	69%
Desikan *et al.*, 2010 **[29]**	324 MCI	0-36	Neocortex	Volume and Thickness	TC: 60/162 VC: 58/162	Factor analysis	AUC:0.82 AUC:0.84	74% 87%	84% 66%
Texture analysis									
Martinez-Torteya *et al.*, 2010	62 MCI	0-24	Whole brain	Signal and texture	-	Risk analysis	AUC: 0.79	-	-

GLOSSARY: ROI: Region of interest; Acc: accuracy; Se: sensitivity; Sp: specificity; QAD: questionable AD dementia; ROC: receiver operating characteristic; LDA: linear discriminant analysis; nSVM: non Support Vector Machine; VFI: voting feature interval; TC: Testing cohort; VC: Validation cohort; AUC: area under curve; NC: Normal controls.

V. Concluding remarks

The challenge for modern neuroimaging is to help in the early diagnosis of Alzheimer's disease and structural MRI is one of the biomarkers that could be selected in the assessment of early AD. Quantitative structural MRI is sensitive to the neurodegeneration that occurs in mild AD as it reveals the atrophy of the structures within the MTL, thus it can be used as a diagnostic marker in the MCI stage.

In this paper, the techniques compared can be grouped into three categories. In the first category volume analysis techniques are being used, and mainly on the hippocampus. The second category, is based on VBM analysis measurements on the cortical surface and specifically on the cortical thickness. The methods of the third category included features extracted from texture analysis. All the studies used automatic classification methods and most of them discriminate with high accuracy the normal from AD subjects. However, their sensitivity appears to be lower for the classification of MCI subjects. Perhaps, if additional data from other biomarkers such as CSF or PET can be combined with quantitative MRI, the accuracy could improve. Similar results were observed when morphometric pattern analysis was used in order to predict the prognostic conversion from MCI to AD as the results of shape analysis, were more accurate than volumetric measures.

The main finding of this study can be summarized as follows:

1. MRI could predict with higher accuracy the time to conversion from amnestic MCI to AD, compared to CSF biomarkers [29], [30].
2. Global hippocampal volume may not be the most accurate technique for the prediction of conversion from MCI to AD and for the classification of MCI patients. Shape analysis appears to be a more sensitive measure than volume analysis for the assessment of AD [20], [24].
3. Texture analysis is not currently used in clinical practice, and there is a lack of research in the assessment of AD~~,~~ using this technique. However, it has a very important role in image analysis research and may develop into a useful clinical imaging tool [22].
4. The majority of literature in the assessment of AD using medical image analysis is evaluated on images which have been acquired with 1.5 Tesla MRI systems. The analysis needs to be applied on images from 3.0 Tesla MRIs in order to investigate if both structure and texture features perform differently.
5. As the structures vulnerable to AD have been identified and used for the prediction of conversion from MCI to AD, further investigations is required in order to evaluate if the same structures can be used to predict the onset of cognitive impairment.

Conflict of interest

"The authors declare that they have no conflict of interest

References

[1] R. C. Petersen, "Mild cognitive impairment as a diagnostic entity," *J. Intern. Med.*, vol. 256, no. 3, pp. 183–194, Sep. 2004.

[2] B. Dubois, H. H. Feldman, C. Jacova, S. T. Dekosky, P. Barberger-Gateau, J. Cummings, A. Delacourte, D. Galasko, S. Gauthier, G. Jicha, K. Meguro, J. O'brien, F. Pasquier, P. Robert, M. Rossor, S. Salloway, Y. Stern, P. J. Visser, and P. Scheltens, "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria," *Lancet Neurol.*, vol. 6, no. 8, pp. 734–746, Aug. 2007.

[3] C. R. Jack, D. S. Knopman, W. J. Jagust, L. M. Shaw, P. S. Aisen, M. W. Weiner, R. C. Petersen, and J. Q. Trojanowski, "Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade," *Lancet Neurol.*, vol. 9, no. 1, pp. 119–128, Jan. 2010.

[4] R. I. Scahill, J. M. Schott, J. M. Stevens, M. N. Rossor, and N. C. Fox, "Mapping the evolution of regional atrophy in Alzheimer's disease: Unbiased analysis of fluid-registered serial MRI," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 99, no. 7, pp. 4703–4707, Apr. 2002.

[5] L. R. Squire, C. E. L. Stark, and R. E. Clark, "The medial temporal lobe," *Annu. Rev. Neurosci.*, vol. 27, pp. 279–306, 2004.

[6] J. L. Cummings and G. Cole, "Alzheimer disease," *JAMA*, vol. 287, no. 18, pp. 2335–2338, May 2002.

[7] C. R. Jack, M. A. Bernstein, N. C. Fox, P. Thompson, G. Alexander, D. Harvey, B. Borowski, P. J. Britson, J. L. Whitwell, C. Ward, A. M. Dale, J. P. Felmlee, J. L. Gunter, D. L. G. Hill, R. Killiany, N. Schuff, S. Fox-Bosetti, C. Lin, C. Studholme, C. S. DeCarli, Gunnar Krueger, H. A. Ward, G. J. Metzger, K. T. Scott, R. Mallozzi, D. Blezek, J. Levy, J. P. Debbins, A. S. Fleisher, M. Albert, R. Green, G. Bartzokis, G. Glover, J. Mugler, and M. W. Weiner, "The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods," *J. Magn. Reson. Imaging*, vol. 27, no. 4, pp. 685–691, Apr. 2008.

[8] K. Ritchie and S. Lovestone, "The dementias," *Lancet Lond. Engl.*, vol. 360, no. 9347, pp. 1759–1766, Nov. 2002.

[9] O. Colliot, G. Chételat, M. Chupin, B. Desgranges, B. Magnin, H. Benali, B. Dubois, L. Garnero, F. Eustache, and S. Lehéricy, "Discrimination between Alzheimer Disease, Mild Cognitive Impairment, and Normal Aging by Using Automated Segmentation of the Hippocampus," *Radiology*, vol. 248, no. 1, pp. 194–201, Jul. 2008.

[10] M. Chupin, E. Gérardin, R. Cuingnet, C. Boutet, L. Lemieux, S. Lehéricy, H. Benali, L. Garnero, and O. Colliot, "Fully Automatic Hippocampus Segmentation and Classification in Alzheimer's Disease and Mild Cognitive Impairment Applied on Data from ADNI," *Hippocampus*, vol. 19, no. 6, pp. 579–587, Jun. 2009.

[11] J. M. Lötjönen, R. Wolz, J. R. Koikkalainen, L. Thurfjell, G. Waldemar, H. Soininen, and D. Rueckert, "Fast and robust multi-atlas segmentation of brain magnetic resonance images," *NeuroImage*, vol. 49, no. 3, pp. 2352–2365, Feb. 2010.

[12] K. K. Leung, J. Barnes, M. Modat, G. R. Ridgway, J. W. Bartlett, N. C. Fox, and S. Ourselin, "Brain MAPS: an automated, accurate and robust brain extraction technique using a template library," *NeuroImage*, vol. 55, no. 3, pp. 1091–1108, Apr. 2011.

[13] S. F. Eskildsen, P. Coupé, D. García-Lorenzo, V. Fonov, J. C. Pruessner, and D. L. Collins, "Prediction of Alzheimer's disease in subjects with mild cognitive impairment from the ADNI cohort using patterns of cortical thinning," *NeuroImage*, vol. 65, pp. 511–521, Jan. 2013.

[14] D. Salat, S. Lee, A. van der Kouwe, D. Greve, B. Fischl, and H. Rosas, "Age-Associated Alterations in Cortical Gray and White Matter Signal Intensity and Gray to White Matter Contrast," *NeuroImage*, vol. 48, no. 1, pp. 21–28, Oct. 2009.

[15] A. Arrigo, E. Mormina, G. P. Anastasi, M. Gaeta, A. Calamuneri, A. Quartarone, S. De Salvo, D. Bruschetta, G. Rizzo, F. Trimarchi, and D. Milardi, "Constrained spherical deconvolution analysis of the limbic network in human, with emphasis on a direct cerebello-limbic pathway," *Front. Hum. Neurosci.*, vol. 8, p. 987, 2014.

[16] H. Braak and E. Braak, "Staging of Alzheimer's disease-related neurofibrillary changes," *Neurobiol. Aging*, vol. 16, no. 3, pp. 271–278; discussion 278–284, Jun. 1995.

[17] A. Delacourte, J. P. David, N. Sergeant, L. Buée, A. Wattez, P. Vermersch, F. Ghozali, C. Fallet-Bianco, F. Pasquier, F. Lebert, H. Petit, and C. Di Menza, "The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease," *Neurology*, vol. 52, no. 6, pp. 1158–1165, Apr. 1999.

[18] S. J. Lupien, A. Evans, C. Lord, J. Miles, M. Pruessner, B. Pike, and J. C. Pruessner, "Hippocampal volume is as variable in young as in older adults: implications for the notion of hippocampal atrophy in humans," *NeuroImage*, vol. 34, no. 2, pp. 479–485, Jan. 2007.

[19] R. S. Desikan, H. J. Cabral, C. P. Hess, W. P. Dillon, C. M. Glastonbury, M. W. Weiner, N. J. Schmansky, D. N. Greve, D. H. Salat, R. L. Buckner, B. Fischl, and A. D. N. Initiative, "Automated MRI measures identify individuals with mild cognitive impairment and Alzheimer's disease," *Brain*, vol. 132, no. 8, pp. 2048–2057, Aug. 2009.

[20] E. Gerardin, G. Chételat, M. Chupin, R. Cuingnet, B. Desgranges, H.-S. Kim, M. Niethammer, B. Dubois, S. Lehéricy, L. Garnero, F. Eustache, O. Colliot, and Alzheimer's Disease Neuroimaging Initiative, "Multidimensional classification of hippocampal shape features discriminates Alzheimer's disease and mild cognitive impairment from normal aging," *NeuroImage*, vol. 47, no. 4, pp. 1476–1486, Oct. 2009.

[21] S. Klöppel, C. M. Stonnington, C. Chu, B. Draganski, R. I. Scahill, J. D. Rohrer, N. C. Fox, C. R. Jack, J. Ashburner, and R. S. J. Frackowiak, "Automatic classification of MR scans in Alzheimer's disease," *Brain*, vol. 131, no. 3, pp. 681–689, Mar. 2008.

[22] J. Zhang, C. Yu, G. Jiang, W. Liu, and L. Tong, "3D texture analysis on MRI images of Alzheimer's disease," *Brain Imaging Behav.*, vol. 6, no. 1, pp. 61–69, Mar. 2012.

[23] R. Simoes, C. Slump, and A. van Cappellen van Walsum, "Using local texture maps of brain MR images to detect Mild Cognitive Impairment," in *2012 21st International Conference on Pattern Recognition (ICPR)*, 2012, pp. 153–156.

[24] S. G. Costafreda, I. D. Dinov, Z. Tu, Y. Shi, C.-Y. Liu, I. Kloszewska, P. Mecocci, H. Soininen, M. Tsolaki, B. Vellas, L.-O. Wahlund, C. Spenger, A. W. Toga, S. Lovestone, and A. Simmons, "Automated hippocampal shape analysis predicts the onset of dementia in mild cognitive impairment," *NeuroImage*, vol. 56, no. 1, pp. 212–219, May 2011.

[25] C. Misra, Y. Fan, and C. Davatzikos, "Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: Results from ADNI," *NeuroImage*, vol. 44, no. 4, pp. 1415–1422, Feb. 2009.

[26] C. Plant, S. J. Teipel, A. Oswald, C. Böhm, T. Meindl, J. Mourao-Miranda, A. W. Bokde, H. Hampel, and M. Ewers, "Automated detection of brain atrophy patterns based on MRI for the prediction of Alzheimer's disease," *Neuroimage*, vol. 50, no. 1, pp. 162–174, Mar. 2010.

[27] A. Bakkour, J. C. Morris, and B. C. Dickerson, "The cortical signature of prodromal AD," *Neurology*, vol. 72, no. 12, pp. 1048–1055, Mar. 2009.

[28] O. Querbes, F. Aubry, J. Pariente, J.-A. Lotterie, J.-F. Démonet, V. Duret, M. Puel, I. Berry, J.-C. Fort, and P. Celsis, "Early diagnosis of Alzheimer's disease using cortical thickness: impact of cognitive reserve," *Brain*, vol. 132, no. 8, pp. 2036–2047, Aug. 2009.

[29] R. S. Desikan, H. J. Cabral, F. Settecase, C. P. Hess, W. P. Dillon, C. M. Glastonbury, M. W. Weiner, N. J. Schmansky, D. H. Salat, and B. Fischl, "Automated MRI measures predict progression to Alzheimer's disease," *Neurobiol. Aging*, vol. 31, no. 8, pp. 1364–1374, Aug. 2010.

[30] P. Vemuri, H. J. Wiste, S. D. Weigand, L. M. Shaw, J. Q. Trojanowski, M. W. Weiner, D. S. Knopman, R. C. Petersen, and C. R. Jack, "MRI and CSF biomarkers in normal, MCI, and AD subjects," *Neurology*, vol. 73, no. 4, pp. 294–301, Jul. 2009.

[31] G. Castellano, L. Bonilha, L. M. Li, and F. Cendes, "Texture analysis of medical images," *Clin. Radiol.*, vol. 59, no. 12, pp. 1061–1069, Dec. 2004.

[32] A. Materka, "Texture analysis methodologies for magnetic resonance imaging," *Dialogues Clin. Neurosci.*, vol. 6, no. 2, pp. 243–250, Jun. 2004.

[33] R. M. Haralick, K. Shanmugam, and I. Dinstein, "Textural Features for Image Classification," *IEEE Trans. Syst. Man Cybern.*, vol. SMC-3, no. 6, pp. 610–621, Nov. 1973.

[34] M. S. de Oliveira, M. L. F. Balthazar, A. D'Abreu, C. L. Yasuda, B. P. Damasceno, F. Cendes, and G. Castellano, "MR imaging texture analysis of the corpus callosum and thalamus in amnestic mild cognitive impairment and mild Alzheimer disease," *AJNR Am. J. Neuroradiol.*, vol. 32, no. 1, pp. 60–66, Jan. 2011.

[35] P. M. Szczypiński, M. Strzelecki, A. Materka, and A. Klepaczko, "MaZda--a software package for image texture analysis," *Comput. Methods Programs Biomed.*, vol. 94, no. 1, pp. 66–76, Apr. 2009.

[36] X. W. Wei Fang Liu, "3D Texture Analysis of Corpus Caliosum Based on MR Images Inpatients with Alzheimer's Disease and Mild Cognitive Impairment," *Appl. Mech. Mater.*, vol. 533, pp. 415–420, 2014.

[37] A. Martinez-Torteya, J. Rodriguez-Rojas, J. M. Celaya-Padilla, J. I. Galván-Tejada, V. Treviño, and J. Tamez-Peña, "Magnetization-prepared rapid acquisition with gradient echo magnetic resonance imaging signal and texture features for the prediction of mild cognitive impairment to Alzheimer's disease progression," *J. Med. Imaging*, vol. 1, no. 3, pp. 031005–031005, 2014.

[38] R. A. Heckemann, S. Keihaninejad, P. Aljabar, K. R. Gray, C. Nielsen, D. Rueckert, J. V. Hajnal, and A. Hammers, "Automatic morphometry in Alzheimer's disease and mild cognitive impairment," *Neuroimage*, vol. 56, no. 4–2, pp. 2024–2037, Jun. 2011.

[39] J. Graff-Radford and K. Kantarci, "Magnetic resonance spectroscopy in Alzheimer's disease," *Neuropsychiatr. Dis. Treat.*, vol. 9, pp. 687–696, 2013.

[40] L. L. Cheng, K. Newell, A. E. Mallory, B. T. Hyman, and R. G. Gonzalez, "Quantification of neurons in Alzheimer and control brains with ex vivo high resolution magic angle spinning proton magnetic resonance spectroscopy and stereology," *Magn. Reson. Imaging*, vol. 20, no. 7, pp. 527–533, Sep. 2002.

[41] A. Fernández, J. M. García-Segura, T. Ortiz, J. Montoya, F. Maestú, P. Gil-Gregorio, P. Campo, and J. Viaño, "Proton magnetic resonance spectroscopy and magnetoencephalographic estimation of delta dipole density: a combination of techniques that may contribute to the diagnosis of Alzheimer's disease," *Dement. Geriatr. Cogn. Disord.*, vol. 20, no. 2–3, pp. 169–177, 2005.

[42] X. Zhu, N. Schuff, J. Kornak, B. Soher, K. Yaffe, J. H. Kramer, F. Ezekiel, B. L. Miller, W. J. Jagust, and M. W. Weiner, "Effects of Alzheimer disease on fronto-parietal brain N-acetyl aspartate and myo-inositol using magnetic resonance spectroscopic imaging," *Alzheimer Dis. Assoc. Disord.*, vol. 20, no. 2, pp. 77–85, Jun. 2006.

[43] K. Kantarci, "Proton MRS in Mild Cognitive Impairment," *J. Magn. Reson. Imaging JMRI*, vol. 37, no. 4, pp. 770–777, Apr. 2013.

[44] D. Le Bihan, "Looking into the functional architecture of the brain with diffusion MRI," *Nat. Rev. Neurosci.*, vol. 4, no. 6, pp. 469–480, Jun. 2003.

[45] C. E. Sexton, U. G. Kalu, N. Filippini, C. E. Mackay, and K. P. Ebmeier, "A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease," *Neurobiol. Aging*, vol. 32, no. 12, pp. 2322.e5–18, Dec. 2011.

[46] G. M. McKhann, D. S. Knopman, H. Chertkow, B. T. Hyman, C. R. Jack, C. H. Kawas, W. E. Klunk, W. J. Koroshetz, J. J. Manly, R. Mayeux, R. C. Mohs, J. C. Morris, M. N. Rossor, P. Scheltens, M. C. Carrillo, B. Thies, S. Weintraub, and C. H. Phelps, "The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimers Dement. J. Alzheimers Assoc.*, vol. 7, no. 3, pp. 263–269, May 2011.