Multistructure Brain Registration Using Multimodal Neuroimaging for the Detection of Alzheimer's Disease

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***Abstract*— Alzheimer's Disease (AD) is an irreversible neuro degenerative brain disorder. The progression of AD can be traced from Magnetic Resonance Images (MRI) and Positron Emission Tomography (PET) images. The cortical features can be well extracted from MR images while PET images clearly resolve the subcortical structures of brain. The registration approach used in this paper is a multistructure registration approach. The multistructure registration approach eliminates the problem of partial voluming and information loss. The segmentation of white matter and gray matter tissues traces the amount of tissue loss associated with AD. The multistructure registration of PET and MR images allows loading information in to a central space. By adopting multimodal neuroimaging the correlation between the modalities is exploited for the study. The registration procedure is based on the fluid kinematic model of the brain volume. This preserves the underlying topology and anatomy while constraining the transformation to be smooth. In this paper a novel framework for the early detection of AD using multimodal neuroimaging is proposed. The differentiation of AD from Mild Cognitive Impairment (MCI) was also studied.**

***Index Terms*— Alzheimer's Disease, Multistructure, registration, fluid model, MRI, PET**

I. INTRODUCTION

As per the census about 10.3% of the total population in the world is suffering with Alzheimer's Disease. Alzheimer's Disease is mainly characterized by the gradual loss of memory. The memory loss is due to the missing links of white matter and gray matter tissues of brain. The main road block in the diagnosis of AD is due to the lack of efficient techniques for representing the neuro imaging biomarkers. The AD progression is mainly characterized by the atrophy of the hippocampus of the brain and deposition of neuro fibrillary tangles. The rate of loss of memory can be identified from the deterioration of the white matter and gray matter tissues. The early syndromes include decline of memory and improper cognitive functions. Precise diagnosis is not possible in AD since evaluation of mental status is difficult when consciousness is impaired. Also it is necessary to differentiate AD from other neural disorders such as dementia and Mild Cognitive Impairment (MCI). Some MCI subjects can be get converted into AD cases. Hence it is important to control the risk factors before irreversible brain damages take place.

Christensen.et.al represented the brain structure as a deformable template for accommodating the local shape variability [1]. This method relies on a smooth velocity vector transformation. The template is basically an electronic or anatomic atlas in which individual anatomic variations are incorporated by deforming the template. Later a two dimensional to three dimensional volumetric transformation was proposed [2]. But this method was not suitable for anatomies with different topologies since it does not permit normal variations across disparate anatomical structures. Fischel.et.al gave prime importance to cortical surface based analysis since cortex constitutes major portion of the brain and has a highly folded geometry [3]. In this approach the reconstruction procedure was sub divided in to many sub tasks.

Later Fischel.et.al proposed an automatic neuro anatomic labeling procedure [4] by providing a label for each voxel in the MR image depending upon the probabilistic information associated. But the problem of differentiating multiple gray matters was not solved. The method adopted by Pohl.et.al [5] used a statistical approach combining registration of the atlas with segmented MR images. It was an integrated segmentation and registration approach utilizing Bayesian framework. Such voxel based classification approaches explicitly model image artifacts for segmenting large data sets. But the accuracy was limited depending upon the segmentation of indistinct boundaries of MR images. The automated segmentation was initiated using Freesurfer software [6]. The large deformation diffeomorphic metrics (LDDMM) improves the accuracy and reliability. The LDDMM is calculated for a particular Region of Interest (ROI). A Large Deformation Diffeomorphic method of registration was put forwarded by Khan.et.al [7]

Mild Cognitive Impairment (MCI) is considered as a primary stage of AD since it has clinical interest. MCI patients have a large risk of AD. Hence it is necessary to detect each stage of AD progression. Previous works for AD diagnosis was mainly based on machine learning methods. These methods were aided by the volume [8] and cerebral metabolic rate [9] calculated from the MR images. The other techniques adopted were Support Vector Machine (SVM) [10] and Bayesian methods [11]. These methods have better performance in binary classification and are not suitable for multiclass diagnosis. Another problem encountered is the representation

of original biomarkers. The dimensionality reduction causes the loss of information regarding the fine structure while mapping in to new feature space. The multimodal neuro imaging utilizes the synergy available within the modalities. The multiple biomarkers used in this paper are MRI and PET images. This study is based on the automated segmentation of multiple structures and mapping the subject in to a target template using diffeomorphic registration. The procedure is to extract morphometric features which can define the anatomical variation within or across a group. The structure specific information is used to initialize and constrain registration for improved accuracy and robustness.

II. PROPOSED METHOD

The previous works described in this paper require large computational resources and are time consuming. Also those works cannot provide precise information regarding stage wise progression of AD and its early detection. To overcome such limitations a novel framework for detecting AD using multimodal neuroimaging is proposed in this paper. The MR brain images can well depict the cortical surface features without distortion. But MR image based registration fail to distinguish the sub cortical fine features precisely. PET images preserve the fine detailed structures in the subcortical surface. Hence this paper incorporates both PET and MR images for detecting AD. By segmenting the neuro biomarker images the loss of white matter and gray matter tissues can be clearly traced. The registration approach used in this paper is multistructure registration which relies on a large deformation diffeomorphic algorithm. This helped to preserve the topological as well as anatomical properties of the underlying brain image. The block diagram of the proposed method is shown in Fig. 1.

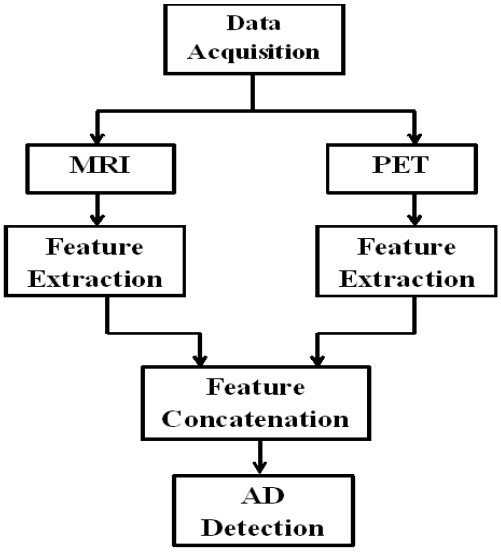


Fig. 1. Proposed block diagram

A. Data Acquisition

In this study MRI and PET are the chosen modalities. The data base is chosen from Alzheimer's Disease Neuro Imaging (ADNI) available at http://www.adni.loni.ulca.edu. ADNI consist of biomarkers such as MRI, PET and Cerebro Spinal Fluid (CSF) data with neuro psychological assessments for the early detection of MCI and AD. We obtained 469 MR images of subjects in different age and gender groups. The subjects were in the age group ranging from 54 to 90 years. The structure and anatomy of the brain varies in accordance with the age and gender. Out of these 19 images were excluded due to incomplete data. Also 450 PET images were collected for the study. The data set contained normal subjects as well as subjects with MCI and AD. The data acquisition procedure consists of further processing as shown in Fig. 2. The images were converted in to gray scale and resized to 256 x 256 for simplification. The obtained raw data were preprocessed using a Gaussian filter of variance 0.2 for removing the biological artifacts and electromagnetic interferences. The artifacts occur due to misalignment of head. Such artifacts were predominant in MR images rather than PET images. Hence skull stripped MR images were used.

B. Segmentation

From the preprocessed images both gray matter and white matter tissues were segmented. The loss of white matter and gray matter tissues represent the loss of memory. The segmentation procedure adopted was K- means clustering. The intensities of median white matter and gray matter tissues were calculated to aid the segmentation. There occurs severe atrophy of hippocampus and amygdala during AD. Such severe tissue loss is not predominant in the case of MCI subjects. The partial voluming effect during segmentation is avoided since separate channels are provided for gray matter and white matter segmentation. The nature of missing links of gray matter and white matter tissues helps to differentiate AD and MCI from normal ageing dementia.

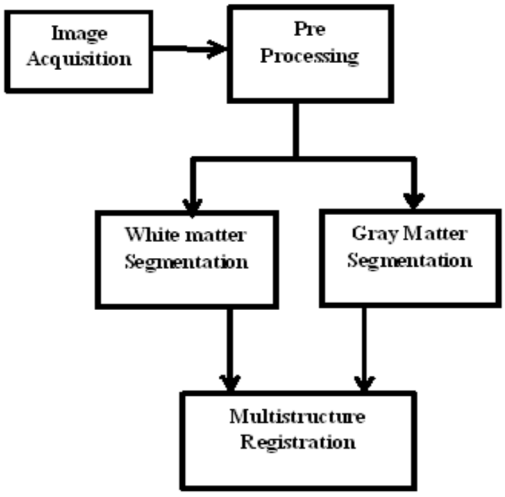


Fig. 2. Preprocessing of raw data

C. Multistructure Diffeomorphic Registration

The segmented images are to be registered. The registration method used in this paper is large deformation diffeomorphic algorithm based multistructure registration. The algorithm has its foundation from the fluid kinematic model of brain. For registering the image the energy function associated with a Hilbert space has to be reduced. The subject template has to be matched to the target template. The amount of deformation required is obtained from the amount of body force applied for the transformation and the viscosity parameter. The transformation applied is one to one, smooth and invertible. Subjects that were structurally similar to the central template required only a small amount of deformation. But structurally dissimilar subjects required larger amount of deformation. The fluid model used in this paper is Navier Stokes fluid model. Let I_a^{MR} be the template image and I_b^{MR} be the subject image. Assume $I_a^{Seg,i}$ and $I_b^{Seg,i}$,i € [1,….N] are the N segmented images of I_a^{MR} and I_b^{MR} respectively. The diffeomorphic transformation of I_a and I_b is given by ϕ: $\Omega \rightarrow \Omega$ such that $I_a \circ \phi^{-1} \approx I_b$. This transformation ϕ is a time-dependent velocity vector field, $v_t \in V,\ t \in [0, 1]$, where V is a Hilbert space of smooth vector fields on Ω. The energy functional for intensity-based MRI registration is

$$E(v)=\int_0^1 \| v_t\|^2 vdt+\Lambda^{MR}\| I_a^{MR} \circ \Phi_{1,0}-I_b^{MR} \|^2_{(L^2)} \quad (1)$$

$$E(v)=\int_0^1 \| v_t\|^2 vdt+ \Lambda^{MR} \| I_a^{MR} \circ \Phi_{1,0}-I_b^{MR} \|^2_{(L^2)}+ \sum_{i=1}^{N} \Lambda^{seg,i} \| I_a^{Seg,i} \circ \Phi_{1,0} - I_b^{Seg,i} \|^2_{L^2} \quad (2)$$

Here $\Lambda^{seg,i}$ specifies the role of each segment in the overall registration. In this method equal weights were assigned for each segment. $\Lambda^{MR}=\Lambda^{seg,i}$, i=1, 2…….N. The body force for MR image [1] is given by

$$C(T(\overrightarrow{x}),S\vec{u}\,(\vec{x},t)) = \frac{\alpha}{2}\int \left|T\left(\vec{x}-\vec{u}\,(\vec{x},t)\right)-(\vec{x})\right|^2 d\vec{x} \quad (3)$$

where α is a constant. For Magnetic Resonance imaging this appears to be reasonably appropriate. But for Positron Emission Tomography (PET) Poisson models are more appropriate. Taking the variation of the cost function with respect to the displacement field yields the body force as

$$\vec{b}[\vec{x},\vec{u}\,(\vec{x},t)]=\alpha(T[\vec{x}-\vec{u}\,(\vec{x},t)]-S(\vec{x}))\,\nabla T|\vec{x}-\vec{u}\,(\vec{x},t) \quad (4)$$

The transformation preserves the cortical and subcortical features without loss of information.

D. Feature Extraction

From the registered image salient features are extracted from the Region of Interest (ROI). The features such as volume of white matter and gray matter, intensities and texture of the tissues and edges were extracted. From the PET images the average Cerebral Metabolic Rate of Glucose (CMRGlc) was extracted. After extracting the features from each modality they were compared so that we can distinguish normal, MCI and AD subjects. The features were normalized to values between 0 and 1 for easier manipulation and comparison. The method exploits the synergy between the two different modalities effectively. Also the Gray Level Co-occurrence Matrix (GLCM) was obtained from the registered images. This matrix provides information about the correlation, covariance and mutual information contained in the registered images.

III. RESULTS AND DISCUSSIONS

The MR and PET images of normal, MCI and AD subjects from ADNI database were preprocessed, segmented and registered. From the registered image salient features were extracted for the detection of AD. Also AD subjects were differentiated from MCI subjects based on the extracted features. The processing of normal and AD MR images is shown in Fig .3. The PET image processing of normal, MCI and AD subjects is depicted in Fig. 4. Skull stripped images were used for processing to avoid the problem of false anatomy. The cortical and subcortical structures are distinguished by sharp boundaries. The difference in the amount of tissue loss in the AD and MCI subjects can be resolved in this method. From the segmented images the progression and stage of AD can be identified as shown in Fig.5.

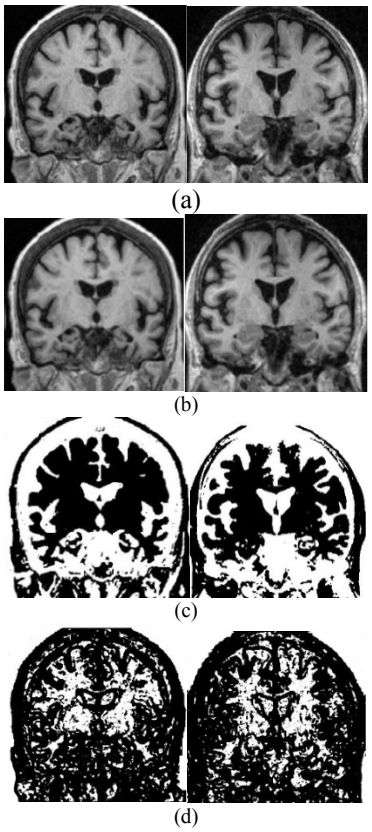
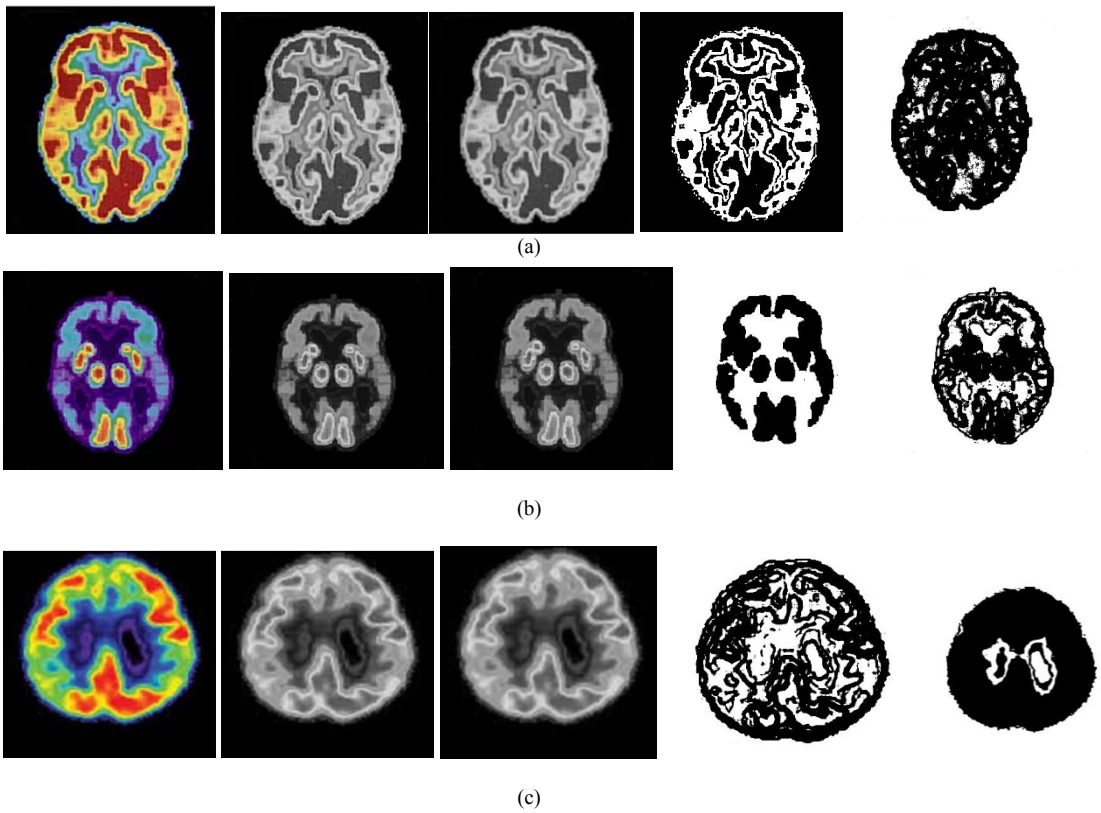


Fig. 3. MR image processing of normal and AD subjects. First column represents MRI of normal subject and second column represents MRI of AD subject. (a) Original MR images. (b) Filtered images. (c) Segmented gray matter. (d) Segmented white matter



(a)

(b)

(c)

Fig. 4. PET image processing. (a) Normal subject. (b) AD subject. (c) MCI subject. First column represents the original PET images. Second column represents the gray scale images; third column is the filtered images. Fourth and fifth column represents the segmented gray matter and white matter respectively.

(a) (b) (c)

Fig. 5. Stage wise progression of AD. (a) Early AD. (b) Mild AD. (c) Severe AD

It is clear from Fig. 3 and Fig. 4 that the loss of gray matter tissues characterizes AD. But in the case of MCI severe damages are seen in white matter tissues. This implies that AD patients will experience missing links between memory cells while MCI patients experience loss of memory cells. Hence there occurs a greater chance of MCI patients to get converted in to AD. The progression of AD can be mainly differentiated in to three stages namely early AD, mild AD and severe AD depending upon the severity of gray matter loss. From Fig. 5 the gradual loss of gray matter tissue in each stage can be identified. In the early stage of AD there occurs only an indistinguishable atrophy of the hippocampus. But as the disease get worsens the rate of atrophy increases. It is clear that there occurs severe tissue loss in the final stage of AD. Hence there will be severe loss of memory as the disease progresses.

The registered image using multistructure registration procedure is shown in Fig. 6. The subject is to be mapped to this target template so that the required amount of deformation can be identified. The registered image serves as the reference template. A comparison of different transformations relative to the speed of performance is charted in Table I. Since affine transformation is faster it has been chosen for the registration method in this paper. Also affine transformation incorporates the volumetric transformations such as scaling, rotation and shearing to preserve the topological properties. The accuracy of the different modalities and demography of the results obtained are quantified in Tables I and II respectively. The features of MR and PET images were adaptively fused to obtain more accurate results. Also such an approach helped to distinguish between normal, AD and MCI subjects.

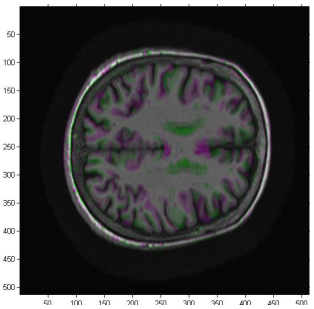


Fig. 6. Registered image

TABLE I. COMPARISON OF TRANSFORMS

Transform Type	Time elapsed (in seconds)
Group wise	761.816
Affine	176.2585
Translation	838.991
Rigid	980.9649

TABLE II. ACCURACY OF DIFFERENT MODALITIES

Number of samples	MRI only	PET only	Multimodal
100	84.32%	91%	93.25%
200	84.51%	91.32%	94.56%
300	86%	92.22%	95.79%
450	87.67%	92.41%	96.4%

TABLE III. DEMOGRAPHY OF SUBJECTS OBTAINED FROM MULTIMODAL NEUROIMAGING

Category	Normal	AD	MCI
Normal	133	166	151
Gender(Male/female)	54/69	68/88	72/70
Age	56 to 71	65 to 92	61 to 80

From Table II it is clear that as the number of samples increases the accuracy attained also increases. The accuracy of PET neuroimaging is more than that of MRI. The proposed method in this paper provides an accuracy of 87.67% for the MR images and 92.41% for the PET images. This difference in accuracy may be due to the loss of finer details of subcortical structures in MR images. Also it can be noticed that the multimodal fused method gives a better accuracy when compared to individual neuroimaging modalities. The accuracy of the fused method was 96.4%. Hence this method was found to be superior over the previous methods discussed in this paper. By observing the demographic statistics of the different subjects used for the study it can be seen that female subjects have a greater probability of AD than male subjects. The reason of such a chance may be due to the structural and anatomical variations of human brain depending upon the gender. The volume of brain is larger for males than females. As per the statistics, AD and MCI is found to be predominant after the age of 65. This implies that AD and MCI strikes older adults.

Since the multistructure registration approach was used the fine anatomical details have well distinguished boundaries. The hippocampus region can be well identified using this technique and hence a precise determination of tissue loss can be made. In other methods described the hippocampus region is not resolvable due to inaccurate segmentation. The segmented images were registered using a deformation diffeomorphic algorithm by using an affine transformation. A moving and fixed target was randomly selected to perform the transformation. The moving target was deformed to match the fixed target and a registered brain image was obtained. From the registered image the subjects were classified as normal, MCI and AD subjects for efficient diagnosis. The level of hippocampal atrophy varies in normal, MCI and AD subjects. AD subjects have greater atrophy of hippocampus compared to MCI subjects. The MCI patients do not have much atrophy of hippocampus. Also it is seen that the AD patients have greater loss of gray matter tissue when compared to MCI subjects as shown in Fig. 4. As shown in Fig. 5 the brain volume shrinks significantly as the Alzheimer's Disease become widespread. From the experimental results we found that the proposed technique in this paper is a robust and precise method.

IV. CONCLUSION

The proposed method uses multistructure registration using multimodal neuroimaging for the detection of AD. The multimodal approach is adopted by incorporating both MRI and PET modalities. This novel framework can distinguish AD from MCI subjects. By adopting multimodal approach the correlation available within and across the neuroimaging modalities was exploited. Thus we can differentiate AD from other brain disorders. The three stages of progression of AD namely early AD, mild AD and severe AD were identified from the segmented gray matter tissues of brain. A demography based study was also performed to identify the nature of disease based on gender and age. The multimodal neuroimaging and multistructure brain registration together provides a better performance and a robust technique for detecting Alzheimer's Disease.

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