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Detection of Alzheimer's Disease Using Multitracer Positron Emission Tomography Imaging

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A B S T R A C T

Alzheimer's disease is characterized by impaired glucose metabolism and demonstration of amyloid plaques. Individual positron emission tomography tracers may reveal specific signs of pathology that is not readily apparent on inspection of another one. Combination of multitracer positron emission tomography imaging yields promising results. In this paper, 57 Alzheimer's disease neuroimaging initiative subjects that had FDG and PiB-positron emission tomography neuroimaging scans at the same time were used for development of proposed multitracer classification method. The subject's brain image was automatically parcelled into 48 pre-defined regions of interest. Then, 96 features were extracted for each subject. The principal features weere extracted using principal component analysis, then they were combined based on intersection strategy. Finally, a support vector machine was adopted to evaluate the classification accuracy. Combination of two tracers with positron emission tomography scan yielded a higher diagnostic accuracy in Alzheimer's disease compared to individual tracer and other combination methods.

1. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia [1-3]. It is a progressive neurodegenerative disorder that impairs memory, cognitive function, thinking, behavior and language [4, 5]. It has been reported that 35.6 million people worldwide are suffering from dementia and this number will increase to 65.7 million by 2030 [6, 7]. There is still no cure for the disease but early detection of AD is a prerequisite for early treatment [8].

The neuroimaging is an approach increasingly used for accurate clinical diagnosis of AD [9, 10]. There are two main categories of neuroimaging: structural neuroimaging (e.g. magnetic resonance imaging (MRI)) and functional neuroimaging (e.g. positron emission tomography (PET)) [10]. Although the brain atrophy measured using MRI in patient at prodromal stage of the AD (mild cognitive impairment (MCI)) is similar to those in normal elderly people, PET has the ability to display very mild symptoms such as amyloid plaques and impaired glucose metabolism, which are signed

with AD [11, 12]. Therefore, extracting the features from brain regions using PET neuroimaging can provide useful hallmarks for discriminant normal control (NC) from AD (or MCI). Brain glucose metabolism and amyloid plaques are measured by 18F-fluorodeoxy (FDG) and 11C Pittsburgh Compound-B (PiB) tracers with PET scans, respectively [10, 13]. Nevertheless, PET neuroimaging provides specific information about subjects with and without AD. In this paper, multitracer PiB and FDG-PET neuroimaging that has been acquired at the same time are combined. These can provide valuable information, including amyloid plaque and glucose metabolism. The problem of classification in case of multiple feature space obtained from different sources is combinations of individual classifiers or combination of feature spaces [14]. The aim of combination of feature spaces is to obtain highly accurate classifiers by combining individual feature space. As the most common way, all features derived from different data sources, i.e. modalities, are concatenated into a larger feature space. Other ways for combination feature spaces can be grouped into two basic categories: 1) ad hoc methods [15], and kernel combination methods [16, 17].

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TABLE 1. Demographic characteristics of the studied population (from the ADNI database).

Group	Number	Gender (M/F)	Age Mean ± SD	Age Range	MMSE Mean ± SD	MMSE Range
NC	19	11/8	78.8±5.5	71-87	28.5±1.5	24-30
MCI	20	15/5	76.6±8.0	61-90	26.1±2.8	20-30
AD	18	11/7	73.6±8.6	55-88	20.2±4.2	12-26

MRI, FDG-PET and also CSF modalities were combined based on multi-kernel combination for both AD and MCI classifications [18]. The proposed method was operated within support vector machine (SVM) learning classifier. However, in this paper an approach for combing feature spaces derived from FDG and PIB-PET modalities has been proposed and compared with multi-kernel SVM method used in [18].

2. SUBJECTS

Data used in this research were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI). In this study, 57 subjects, including 18 AD patients, 20 MCI patients, and 19 normal controls (NC) were collected from the ADNI public database (LONI, University of California, http://www.loni.ucla.edu/ADNI/Data). All patients and healthy subjects (subjects were manually found between all ADNI databases) had [11C] PIB-PET and [18F] FDG-PET imaging. A detailed description of PET protocol and acquisition can be found at "www.adni-info.org". The demographic characteristics of the subjects used in this study have been summarized in Table 1.

3. METHOD

3. 1. Preprocessing   All PET images have been preprocessed with SPM8 [19] (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, www.fil.ion.ucl.ac.uk/spm) and was performed in MATLAB 7.10.0 (MathWorks Inc., Sherborn, MA). Preprocessing was performed in the following steps:

- **Normalization**   This step includes registration and normalization into a standardized coordinate system. The goal of normalization is to register images from different participants into a rough template image. Normalization was performed to ensure that the voxels in different images refer to the same anatomical positions in the brain [20].

Each individual subject's FDG-PET was automatically spatially normalized to the PET Montreal Neurological Imaging (MNI) template (http://www.bic.mni.mcgill.ca) through 12-parameters affine model [21] using the SPM8 software with the default settings. PiB-PET images were also normalized to the template generated by averaging all normal control images. After the normalization step, the dimensions of the obtained images were re-sampled to a voxel spacing of 2 mm3 and size 91×109×91 voxels.

- **Smoothing**   Smoothing is used to reduce the high frequency noise and increase the signal-to-noise ratio of the hemodynamic effect. Smoothing was performed using a Gaussian kernel with full-width of half-maximum (FWHM) of 8 mm.

3. 2. Features   In this study, features were obtained by voxel grouping using a labeled atlas. Atlas-based approach used for PET images is similar to method used in [18]. After pre-processing, the subject's brain image was automatically parcellated into 48 pre-defined regions of interest (ROI). The anatomical regions were constructed based on the Harvard-Oxford probabilistic atlas that distributed with FMRIB Software Library (FSL: http://www.fmrib.ox.ac.uk/fsl/fslview/atlas-descriptions.html). The Harvard-Oxford atlas includes 48 regions.

Feature used in this study was obtained using averaging all voxels intensity of each ROI region. Previously, Zhang in [18] combined MRI and FDG-PET modalities as a multimodal classification of Alzheimer's disease. For each MRI and FDG-PET image, they extracted 93 features from 93 automatically labeled ROIs [22] by calculating the average intensity of each ROI region. Unlike [18], used 93 ROIs, that developed by Kabani at the MNI [22], we parcellated images into 48 ROIs based on the Harvard-Oxford atlas.

3. 3. Feature selection/extraction: PCA   Principal component analysis (PCA) is one of the most effective methods in data compression and pattern recognition. The aim of PCA is to reduce the dimension of the data. PCA is used to omit redundant data for feature selection and feature extraction. Since PCA works in linear domain, it is used in linear applications, such as, signal processing, image processing, system and control theory and communication.
PCA depends on eigenvector method designed to model linear variations in large dimensional data. PCA performs dimension reduction by projecting the original n-dimensional data to k-dimensional (k<<n) linear subspace [23].

3. 4. Support Vector Machine   Support Vector Machine (SVM) creates an optimal hyper plane using binary labeled training data by maximizing the margin

between two classes [24]. Once the model has been trained, the measures of the diagnostic accuracy can be carried out with the test set. A detailed description of SVM algorithms can be found in [25-27]. The idea behind SVMs is to map the input patterns into a high-dimensional feature space through a suitable kernel function. The mapping is done in order to make the classification problem simpler in the high-dimensional feature space [28]. In this paper, the SVM classifier was implemented using libsvm toolbox available at http://www.csie.ntu.edu.tw/cjlin/libsvm in MATLAB 7.10.0 (MathWorks Inc., Sherborn, MA).

The reason of wide application of SVM in AD domain is that SVM often performs more efficiently than other classifiers [2, 29, 30].

3. 4. Proposed Method   The proposed approach in this research involves two major steps: training step; learning the useful information, and testing step. Firstly, some subjects were used for training step. Training was achieved by means of the leave-one-out method, a technique that iteratively holds out one subject for test [31]. After the optimum parameters were obtained with the remaining subjects, in the test step, each new subject that was left out was assigned to its appropriate class.

In order to combine information derived from different images there are several ways in machine learning research. The most common way is to combine all features derived from different modalities into a longer feature vector [32]. Additionally, several researchers [18, 33, 34] provide an alternative way by using a kernel combination to integrate different modalities for AD study. More detailed description for multi-kernel approach used in SVM can be found in [18]. In order to evaluate the proposed method, two methods proposed in [32] and [18] were implemented and compared with proposed method.

In this paper, a new approach for combination of the feature spaces derived from different neuroimaging scans, is proposed. First, the principal features are selected from two tracer image scans using PCA. Combining features that have been chosen in first step can achieve premier features, e.g. ROIs, of two tracers. In order to combine the features chosen from individual PET tracer image, there are two different methods, union and intersection.

Intersection method selects the repeated features selected in two of the PET tracer image by PCA. On the other hand, the results of union combination method are based on all features that have been selected by each of the two PET tracer images. Therefore, features extracted from each individual tracer image are combined and evaluated agaist the classification accuracy in discriminate NC and AD (or MCI). It is based on premier features selected by intersection combination method.

4. RESULTS

In order to compare the performance of FDG-PET and PiB-PET images in AD, we perform experiments (1) using only each individual modality, FDG-PET and PiB-PET modalities, (2) combining features using multi-kernel and concatenation methods, and finally (3), using the proposed method. For posterior analysis, all subjects were arranged into two different groups, and the performance of our classification methods is tested in identification:
- NC vs. AD: NC subjects from AD patients,
- NC vs. MCI: NC subjects from MCI patients.

The classification results are summarized in Tables 2 and 3. As discussed in Section 3, all experiments were carried out by the leave-one-out cross-validation method. The classification results are described in terms of accuracy, sensitivity and specificity values, the most widely statistics used in diagnostic test. For analysis of PET tracers each image modality of each subject was first parcellated into 48 ROIs using the Harvard-Oxford atlas. Afterward, all 48 ROIs were used in order to create the feature set by averaging the intensity value of voxels in each ROI. Using single-modality, FDG-PET reached highest accuracy rates. FDG-PET distinguished NC from AD (MCI) patients with 88.89% (75%), 89.74% (78.95) and 89.19% (76.92) for sensitivity, specificity and accuracy, respectively. In order to compare multi-kernel SVM method and concatenation method for combining features obtained from different PET tracers, we implemented these two methods. Table 2 shows the performance of these two combination methods. In all groups, combining features using multi-kernel method reached highest accuracy rates. For NC vs. AD, the multi-kernel SVM and concatenation SVM methods reached the accuracy of 83.78% and 88.24%, respectively. For NC vs. MCI, multi-kernel method also reached higher accuracy (87.5%) than those based on the concatenation (76.92%). The results of this study show that the multi-kernel method achieved higher performance than concatenation methods in discriminanting between NC and AD (or MCI). The experimental results obtained in this research shows that considering the multi-kernel method is more accurate than concatenation method in combining different modalities. Moreover, multi-kernel method has advantages over combining different modalities [18]: 1) it provides a unified way to combine heterogeneous data when a different type of data cannot be directly concatenated, and 2) it offers more flexibility by using different weights on biomarkers of different modalities.

Multimodal imaging in AD has been previously studied by several researches [18, 24, 25]. As the most recent work, ([18]) evaluated MRI, FDG-PET and also CSF, and combination of these modalities based on multi-kernel combination for both AD classification and

TABLE 2. Classification results.

Methods	NC vs. AD (%)			NC vs. MCI (%)		
	Specificity	Sensitivity	Accuracy	Specificity	Sensitivity	Accuracy
(1) FDG-PET	78.947	88.888	83.78	78.95	65	71.79
(1) PIB-PET	68.42	77.78	72.97	68.42	85	76.92
(2) Concatenation Method	89.47	77.78	83.78	78.95	75	76.92
(2) Multi-Kernel Method	94.12	82.35	88.24	78.95	80	79.49
(3) Proposed Method	100	94.12	94.12	78.95	85	82.05

TABLE 3. Comparison between performances reported in [35] and this study.

Method		Subjects	Specificity (%)	Sensitivity (%)	Accuracy (%)
Zhang, D., et al [31]	NC vs. AD (%)	52 NC, 51 AD	93.3	93	93.2
	NC vs. MCI (%)	52 NC, 99 MCI	66.0	81.8	76.4
Proposed Method	NC vs. AD (%)	17 NC, 17 AD	100	94.12	94.12
	NC vs. MCI (%)	17 NC, 20 MCI	78.95	85	82.05

MCI classification. In this paper, we used a more significant feature selection/extraction method using PCA and combined features extracted from FDG-PET and PiB-PET image scans. Preliminary experimental results of individual modality as shown in proposed method for combination of FDG-PET and PIB-PET achieved higher accuracies compared to the approach reported in [18] (see Table 3). Performance rate reported in [18] for discriminanating between NC and MCI was 76.4% and our accuracy value is 82.05%.

5. CONCLUSION

In this research, we combined different neuroimaging modalities, FDG-PET and PiB-PET, in the same group of AD (and MCI) patients and normal controls. As individual neuroimaging technologies do not provide optimal information for the analysis pathology in AD, combining neuroimaging modalities could provide higher recognition rate in AD. Therefore, we evaluated individual PET images, and also combination of multitracer PET neuroimaging in AD. In order to evaluate the combinations of tracers with PET, we compared proposed method with concatenation and multi-kernel methods. This paper compares FDG-PET and PIB-PET modalities in order to discriminate NC from AD (or MCI). We proposed a novel method for combining these tracers with PET neuroimaging scan and we compared concatenation and multi-kernel methods.

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چکیده

بیماری آلزایمر بااختلال متابولیسم گلوکز ونمایش پلاک آمیلوئیدمشخص می‌شود. ردیاب‌های توموگرافی گسیل پوزیترون تکی ممکن است نشانه‌های خاص از پاتولوژی را نشان دهند که در بازرسی از نوع دیگر به راحتی آشکار نمی‌باشد.ترکیب پوزیترون تصویربرداری توموگرافی گسیل چند ردیاب، نتایج امیدوار کننده‌ای را به دست آورده است. در این مقاله از۷۵بیماری آلزایمرتصویربرداری عصبی از افرادی که FDGوPIB–پوزیترون تصویربرداری عصبی توموگرافی اسکن شده در یک زمان دارند برای توسعه روش طبقه بندی چند ردیاب پیشنهادی استفاده شده است. تصویر مغ زفردبه طور خودکار به ۴۸ناحیه از پیش تعریف شده مورد توجه تقسیم می‌شود. سپس ۹۶ ویژگی برای هر فرد استخراج می‌گردد. ویژگی‌های اصلی با استفاده ازتجزیه مولفه‌های اصلی(PCA) استخراج شده، سپس آنها براساس استراتژی تقاطع با هم ترکیب می‌شوند. درنهایت یک ماشین بردار پشتیبان (SVM)برای ارزیابی دقت کلاس‌بندی استفاده شده است. ترکیبی از دو ردیاب با اسکن توموگرافی گسیل پوزیترون منجر به دقت تشخیص بالاتری دربیماری آلزایمردر مقایسه باتک ردیاب وروش‌های ترکیبی دیگرمی‌شود.

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