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### ► To cite this version:

Andreas Kodewitz, Vincent Vigneron, Christophe Montagne, Sylvie Lelandais. Where to search for Alzheimer's disease related changes in PET scans?. Colloque national Recherche en Imagerie et Technologies pour la Santé (RITS 2011), Apr 2011, Rennes, France. (elec. proc). hal-00762932

**HAL Id: hal-00762932**

**<https://hal.science/hal-00762932v1>**

Submitted on 1 Feb 2014

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# WHERE TO SEARCH FOR ALZHEIMER'S DISEASE RELATED CHANGES IN PET SCANS?

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## ABSTRACT

The development of non-invasive techniques for the early diagnosis of Alzheimer's disease are of high importance facing the growing number of affected persons and the immense cost to our society caused by dementia. Computer based analysis of FDG-PET scans might become a possibility to make early diagnosis more efficient. Temporal lobe is the main location of medical findings. We have clues that in PET images the parietal lobe contains more information about Alzheimer's disease. We used a probabilistic brain atlas to include prior information about the localization of changes in the human brain, classified Alzheimer's disease versus normal control group and got better classification rates focusing on parietal lobe.

*Index Terms*— Alzheimer's disease, PET, brain atlas

## 1. INTRODUCTION

In 2010 there are 35.6 million people estimated to be affected by dementia. With the growth of the elder population, this number is expected to raise to about 115 million by 2050, while there is no reliable early diagnosis method and effective treatment at hand. The most common cause of dementia is Alzheimer's disease (AD). Dementias do not only affect the patient himself, but also his social environment. In many cases, relatives cannot handle daily life without external help. Hence, dementias also charge health care systems with huge amounts of money (estimated to 604 billion US dollars in 2010).

With positron emission tomography (PET) nuclear medicine provides a non-invasive, three-dimensional functional imaging method that measures the metabolism in the brain. By analysis of those images it is possible to discover abnormalities, even before anatomic or structural alterations can be observed by other imaging techniques. However, discriminating age-related changes which are often seen in healthy aged people from changes caused by AD is still a challenging task

that demands a high expertise. A definite diagnosis of AD is only possible post-mortem.

The American Alzheimer's disease neuroimaging initiative (ADNI) collects data of patients affected by AD, mild cognitive impairment (MCI) and normal control group (NC) [1]. It is engaged in the development of early diagnosis and treatment of dementias, especially AD. This includes diagnosis based on mental state exams (e.g. mini mental state exam (MMSE)), biomarkers, MRI and PET scans. With a collection of PET scans, acquired with the tracer 18F fluorodeoxyglucose, of more than 200 AD patients, 200 controls and 400 MCI patients, the ADNI database provides a fairly large data set for investigations.

Recent publications analysing this type of images where using empirical matrix factorization (e.g. PCA) [2], projection to the subspace spanned by the mean intensity image for each class [3] and methods based on covariance analysis of voxels [4], respectively of 116 anatomical volumes of interest (AVOI) [5] to classify AD versus NC.

This methods, besides the last one, process the whole amount of voxels in the PET scans without using prior information, hoping the discriminant information to emerge. In this methods the feature vector is designed in a multi-dimensional Hilbert space using the components of highest variance. In the contrary we defend that the information is sparse distributed - *hidden*, but some prior knowledge about its position is available. In the experimental protocol we will present a method how to discover it.

## 2. MATERIALS

The 18F-FDG PET data from 404 ADNI participants, acquired with Siemens, General Electric and Philips PET scanners, were collected from the web site of the Laboratory on NeuroImaging (LONI, University of California, Los Angeles) [1]. After revision of meta information, in particular confirmation of diagnosis in at least one follow-up examination, we selected the baseline scans of 84 normal control group (NC) patients and 82 early stage AD patients for analysis. The AD set in particular contains only patients with a clinical dementia rating (CDR) of 1 or 0.5 and a mini mental state exam (MMSE) score of 20 or more (mean MMSE:  $24 \pm 2$ ). Patients

This project is partly founded by a grant from BFHZ/CCUFB organization (München).

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with CDR 2 that were present in a data set we used before are now excluded. CDR and MMSE are clinical tests to determine whether a person is demented or not. The two groups are age matched.

We registered the selected with the Matlab SPM toolbox to the included PET brain template to achieve voxel-to-voxel comparability between all scans. The intensity normalization was kept as proposed by the preprocessed data provided by the database (normalization to a average voxel intensity of 1). After preprocessing, the images have a bounding box of  $91 \times 109 \times 91$  voxels, the amount of voxels that is covered by the brain is about 180.000.

### 3. EXPERIMENTAL PROTOCOL

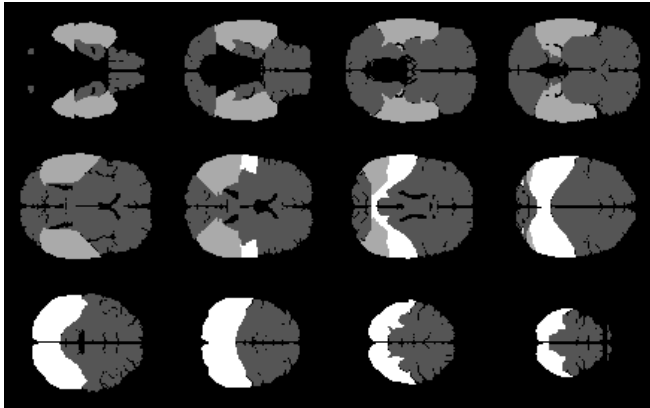
In a former publication we presented a method for the classification of AD patients based on non-negative matrix factorization (NMF) of whole slices [6]. This method is rather global and we were treating a huge amount of data. To reduce the data and focus the analysis to the most important region we developed a method that uses prior knowledge about Alzheimer’s disease, i.e. histopathologic findings of medical doctors and their procedure of PET image analysis for the diagnosis of Alzheimer’s disease.

#### 3.1. Creation of the probabilistic brain atlas

The definite diagnosis is based on the post-mortem observation of intracellular neurofibrillary tangles (NFT),  $\beta$ -amyloid deposition in the form of extracellular senile plaques and blood vessel deposits, synapse dysfunction and loss. NFT deposition originates in the medial temporal lobes and then begin to cluster in the adjacent inferior temporal and posterior cingulate cortex in mild AD, and finally spread to the parieto-temporal and prefrontal association cortices. Medical doctors use this information in their analysis of PET scans. They search for abnormal variations in the brain metabolism and do their diagnosis based on the location of the changes. So are changes in the temporal and parietal lobe indicators for AD disease, changes in other regions can be indicators for other diseases like fronto temporal dementia or depression.

With the Matlab toolbox WFU PickAtlas [7], using the Talairach deamon by Lancaster et al. [8], it is even for non-specialists possible to select AVOIs in the brain by knowing the name of a certain area, e.g. the name of the lobe or Brodman area and create a indexed mask for this AVOIs.

We used these prerequisites to create a probabilistic map that roughly represents the probabilities for AD to manifest in a certain region of the brain (see fig. 1). That means we assign to each voxel in a grid of same size than our brain scans a probability for the occurrence of Alzheimer’s disease. The probabilistic atlas we created is kept as simple as possible. It distinguishes only four zones: outside the brain, temporal lobe, parietal lobe and the rest of the brain. We assign to the



**Fig. 1.** Brain template with indexed intensities for parietal lobe (white), temporal lobe (light gray), the rest of the brain matter (dark gray) and the areas outside of the brain (black). Those indices are replaced by heuristically chosen probability values.

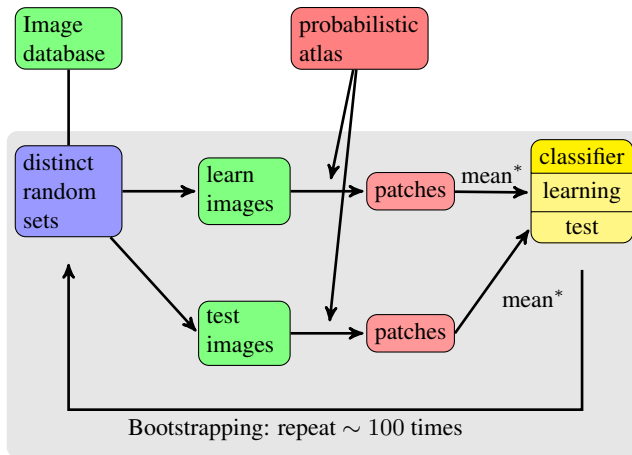
different zones the probabilities: AVOIs (parietal and temporal lobe)  $0.1 \leq P \leq 1$ , the rest of the brain  $P = 0.1$  and everything outside the brain  $P = 0$ . This probabilistic map is used to select small regions, 2D or 3D patches, for the analysis. By varying the assigned probability values it is possible to focus the patch selection to a desired degree to a certain region.

#### 3.2. Patch selection by the probabilistic atlas

To obtain random locations of patches distributed by the probabilities assigned to the different brain regions by the probabilistic brain atlas we created it is sufficient to draw  $(x, y, z)$ -coordinates at random and accept them with the probability assigned to the voxel in our brain atlas. This is repeated until the desired amount of patches is reached. This method is widely known as a Monte Carlo method. The voxels that are to analyse are selected around the random created center, so it is possible to consider 2D- as well as 3D-patches. The amount of voxels to analyse is the number of patches  $n$  times the size of the patch  $S$ . With  $S = 5 \times 5 \times 1$  voxels and  $n = 100$  patches the amount of voxels to be analysed reduces to 2500. That means we will *just* analyse about 1% of the data.

#### 3.3. Classification and Evaluation

As features we considered the mean intensity and the intensity variance of the patches selected by the probabilistic method described before. As the mean provided the better classification results and costs less computation time we chose to feed the classifier with the means of the patches as feature. As classifiers used random forest (RF) classifier and a support vector machine (SVM). The SVM creates a hyperplane in multi-



**Fig. 2.** Schematic of our resampling and feature calculation method; \* the mean intensity of each single patch is calculated.

dimensional feature space to separate the classes whereas the RF classifier is based of classification and regression trees (CARTs).

For the evaluation of the classifier we chose a bootstrap method. With this method it is possible to rate the quality of the classification independent from the specific images that are used to train and test the classifier. We used distinct sets for training and testing of the classifier with a size of 40 images for training and 25 images for the test. Images for training and testing where 100 times simultaneously re-sampled. With this method it is possible to rate the quality of the classification. The method is more robust in cases of unbalanced and biased data sets.

#### 4. CONCLUSION

First results showed that the use of the information contained in the parietal lobe increase the classification rate of more than 6,5%.

Focusing the analysis of PET images to the temporal lobe only excludes important information that can be find in the parietal lobe. Regions that are outside temporal and parietal lobe contain also a certain amount of discriminating information. This information can be included in a patch based analysis by selecting the patches by a probabilistic atlas, like we proposed it, instead of using masks. For a high performant classification the mean of the patches lacs in specificity.

#### 5. ACKNOWLEDGEMENTS

Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database ([www.loni.ucla.edu/ADNI](http://www.loni.ucla.edu/ADNI)). As such, the investiga-

tors within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. ADNI investigators include (complete listing available at [http://www.loni.ucla.edu/ADNI/Collaboration/ADNI\\_Manuscript\\_Citations.pdf](http://www.loni.ucla.edu/ADNI/Collaboration/ADNI_Manuscript_Citations.pdf)).

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