Early Alzheimer's Disease Progression Detection using Multi-subnetworks of the Brain

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Abstract: Alzheimer's disease is neurodegenerative disorder believed to affect 24.3 million people worldwide. Proposed MRI based disease progression markers have shown ability to perform the classification between the Alzheimer's Disease (AD), Mild Cognitive Impariment (MCI) and Normal Cognitive (NC) subjects. We exploited two approaches, first one is to use single sub-network volume as a feature, second to use a network of most discriminative sub-networks. Multi-feature approach showed improvement by 4.5% in AD/NC classification case, and 1.5 % in MCI/NC case. Study was summarized for 48 AD, 119 MCI and 66 NC subjects.

1 INTRODUCTION

People hit by Alzheimer's disease (AD) live in average around 8 years, but there are cases of surviving up to 20 years. As for now there is no cure for the Alzheimer disease, but a large number of new compounds are constantly being developed to modify the flow of disease or to slow down its progression. Since AD-related brain atrophy is irreversible, its early detection is extremely important. This allows clinicians to introduce new treatment as early as possible.

Currently diagnosis of Alzheimer relies largely on medical documentation. There is no single test which could show whether the subject already is struck by Alzheimer's disease. Therefore, a list of mental assignments is performed (Mini-Mental State Examination, Clinical Dementia Rating, Clock Drawing Test, Hachinski Ischemic Score) and a complete test of the medical history of the subject and his family members is done. The earliest brain changes leading to development of AD may begin up to 20 years before the external symptoms appear. Therefore, we have chosen MRI as a source for early AD progression markers. Such decision is motivated by a fact that MRI is widely accessible, with standard protocols across different vendors. Therefore, we believe that MRI scan will be an integral part of the annual health check routine, at least for elderly subjects. In such case, a huge amount of data would overwhelm a single physician. Therefore, automatic and physician friendly computer analysis is urgently needed.

In this study we employed the data of 233 subjects from ADNI database, to assess the automatic classification between the Alzheimer's disease (AD) patients, mild cognitive impairment (MCI) and normal cognitive (NC) subjects. We treat these groups as two separate problems, AD versus NC, and MCI versus NC classification. Since according to in 6 years 80 % of the MCI subjects are expected to develop dementia, we found it useless to try discriminate between MCI converters and non-converters. Rather we treat MCI itself as an early stage of Alzheimer's disease.

We present a novel early AD detection technique based on the multiple (9 regions, 1 fig.) sub-network volume descriptors extracted from the brain. This approach improves results compared to one's based on the single region of interest by 1.5-4.5 depending on the stage of subject. Other novelty of this paper proposed a new sub-network volume. Due to difficulty to perform precise automatic segmentation between the

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hippocampus and amygdala, we propose to integrate these two volumes.

2 BACKGROUND

All the automatic classification MRI based methods can be roughly divided into 3 big groups, depending on the type of features used to perform the classification: direct approach or probability maps for three tissue classes (white matter (WM); gray matter (GM) and celebro spinal fluid (CSF)); atlas based approach, when atlas based segmentation is followed by extraction of volumes of interest; or single region of interest analysis.

2.1 Direct Approach

In direct approach all the brain region voxels are used as an input data. To align the subjects data is smoothed (8 mm kernel is usually used) and registered with template. To diminish the data size, often downsampling by averaging is used (Vemuri et al., 2008). Moreover, each voxel is assigned to one of 3 anatomical classes (WM, GM or CSF). (Vemuri et al., 2008) reports his algorithm obtained sensitivity of 88% and specificity of 86% for AD versus MCI subjects discrimination with linear-SVM. Moreover authors added age and gender to the feature vector improving results up to sensitivity 88% and specificity 90%. (Kloppel et al., 2008) in his study proposed two different approaches. One is based on extracted hippocampal volume, while the other one uses similar approach to (Vemuri et al., 2008), but this time no downsampling of input data is reported. The accuracy of classification is 87.5% (sensitivity 95.0%, specificity 80.0%). There was no significant improvement in performance if non-linear kernels were used compared to linear-SVM (Kloppel et al., 2008). Similar approach was taken by (Fan et al., 2008). The difference is after the registration with template, regional volumetric maps (so called RAVENS maps) were created (Goldszal et al., 1998). Results of classification via leave-one-out cross validation method were 94.3% for AD vs NC, 81.8% for MCI vs NC and 74.3% for MCI vs AD (Fan et al., 2008). (Davatzikos et al.,) using the brain watershed-based clustering method and other techniques described in (Goldszal et al., 1998) tries to distinguish between the MCI and NC subjects using only cross-sectional data. Applying leave-one-out procedure with SVM non-linear classifier for the 30 subjects he receives accuracy of 90%.

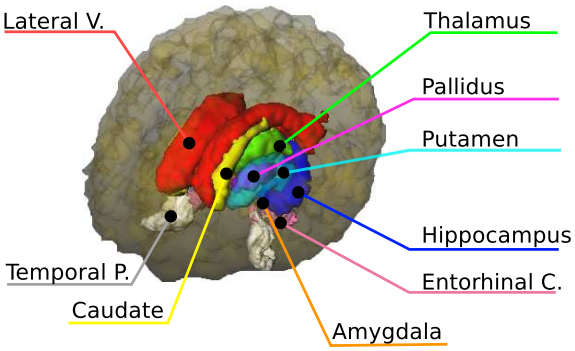


Figure 1: Analyzed brain sub-networks.

2.2 Atlas based Approach

Atlas based segmentation is common technique parcel brain into non-overlapping, anatomical regions. An unseen image is registered with labeled atlas and labels are transposed onto the unseen subject's volume. (Magnin et al., 2009) in his study after registering brains with MNI152 template parceled them into 90 regions of interest (ROI). The white matter for 34 most significant sub-networks was selected and modeled by Gaussian distribution. SVM with radial basis function was used for classification. (Magnin et al., 2009) claims specificity 96.6%, sensitivity 91.5%. (Desikan et al., 2009) after atlas registration, selected entorhinal cortex thickness, hippocampal volume and supra-marginal gyrus thickness as disease progression markers. Authors report specificity of 91% and sensitivity of 90% for the cohort based on the ADNI database when he tried to separate the MCI and NC subjects, and ideal results for the AD vs NC classification. (Kloppel et al., 2008) after performing atlas registration, uses only the region cropped from volume around hippocampus region ($12 \times 16 \times 12$ mm) to classify between the AD vs NC, which results with sensitivity 75.8%, specificity 91.2%.

2.3 Volume of Interest Analysis

Methods of this group are closely related to the atlas based approach. In most of cases atlas registration is used to segment the desired subnetwork from the other brain tissues. The difference is, that in subnetwork of interest approach whole classification procedure is dependent upon the features extracted from one region solely, rather than on network of different regions. Moreover, the registration step is often used only as an initialization step for more complex algorithm. Most authors rely on subnetwork of hippocampus solely. Nevertheless, according to (Braak and Braak, 1997) there is an evidence that early AD pathology may start in entorhinal cortex and only then

progress to hippocampus.

Labor intensive methods involving manual region delineation of hippocampus and entorhinal cortex were performed by (Pennanen et al., 2004), (Juottonen et al., 1998) and (Du et al., 2001). For AD/NC classification accuracy was in range from 86-91 % if hippocampus was used and 82-83 % if entorhinal cortex volume was as an input. In MCI/NC case accuracies were 60-70 % for hippocampus and 66 % for entorhinal cortex volume. Important conclusion was that incorporating few subnetworks together can improve overall results, for example in AD case if both sub-network volumes were incorporated accuracy improved by +3 % (Du et al., 2001).

(Fan et al., 2008) in the second part of his study used the volume of hippocampus (left and right) against the entorhinal cortex (left and right) after normalization by intra-cranial volume. The received accuracy using linear-SVM and leave-one-out cross validation was 82.0% for AD vs NC 76.0% for MCI/NC, and AD/MCI 58.3% respectively. (Chupin et al., 2009) proposed fully automatic approach based on anatomical priors for the hippocampus region extraction. Leave-one-out approach was used for testing. This method proved to be accurate in 76-80 % in NC/AD classification case. (Lotjonen et al., 2011) proposes to perform the automatic hippocampus extraction based on multi-atlas segmentation framework, adding the partial volume effect correction (Tohka et al., 2004). The basic idea is to register non-rigidly the unseen data with a template and to select the most similar atlas compared to the registered unseen data. Tissue class having the highest probability in voxel is chosen as feature for final segmentation. Simplest linear classifier was used with accuracy 75.0 % in AD/NC case.

(Gerardin et al., 2009) uses hippocampus segmentation method provided by (Chupin et al., 2009) as a first step, followed by hippocampus shape description by spherical harmonics coefficients. It is a mathematical approach to represent surfaces with spherical topology, which can be seen as 3D Fourier series expansion (Gerardin et al., 2009). The best combination of parameters gave sensitivity 96 % and specificity of 92 % in AD vs NC classification. MCI vs NC case best result was sensitivity 83 %, specificity 84 %. Results were validated for only 23 AD and 23 MCI subjects.

3 SUBJECTS

We studied and analyzed data of 48 patients with AD (25 males, 23 females, age$\pm$standard-deviation (SD)=76.6 ± 6.3, Mini Mental State Examination (MMSE)$\pm$(SD)=23.5 ± 1.9), 119 subjects with MCI (79 males, 40 females, age$\pm$(SD)=75.1 ± 7.4, (MMSE)$\pm$(SD)=27.2 ± 1.6) and 66 NC subjects (40 males, 26 females, age$\pm$(SD)=76.3 ± 4.6, (MMSE)$\pm$(SD)=29.2 ± 0.9) recruited for ADNI study. Provided MMSE scores correspond the first screening at the hospital. Detailed subject list with ID for ADNI database can be found at `http://pages.cs.wisc.edu/~hinrichs/`. All the subjects were followed up for two years, therefore data was collected during the first visit and the same procedures repeated in two years.

ADNI eligibility criteria in detail are described at `http://www.adni-info.org`. Briefly the subjects are 55-90 years old, if they have a memory complains. Have to be fluent in Spanish or English, accompanying person has to be present. Specific psychoactive medications are excluded (Fennema-Notestine et al., 2009). In this study all the ADNI subjects will be divided into 3 groups, based on criteria as follows:

- Normal Cognitive (NC) - Mini-Mental State Examination (MMSE) scores between 24 and 30 (maximal), CDR of 0 (3 maximal), non-depressed, no memory complains.
- Mild Cognitive Impairment (MCI) - MMSE scores between 24 and 30, memory complaint, preferably corroborated by an informant, objective memory loss measured by a education adjusted scores on Wenchsler Memory Scale Logical Memory, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living.
- Alzheimer's Disease Subject (AD) - MMSE scores between 20 and 26, CDR 0.5 or 1, memory complaint.

4 METHODS

Volumetric measures were created in 7 subcortical regions: hippocampus, amygdala, caudate, thalamus, pallidus, putamen, and two brain ventrical networks, namely lateral and 3rd ventricle. In addition, two gray matter structures temporal pole and entorhinal cortex. All together 10 different brain regions were investigated. Automatic 3D whole-brain segmentation process was based on publicly available **FreeSurfer** software package.

All experiments were performed using the stable release v5.1.0 with a HP Z800 workstation (parameters: 94.6 GB of RAM memory, 64-bit Intel® Xeon® Six-Core Processor X5670 with a processing

speed 2.93 GHz, 12 MB cache). During all the experiments Ubuntu 11.10, 64-bit operating system was used. The average processing time for one subject was 12 hours. After automatic processing was finished all the subjects were checked manually for the artifacts and segmentation errors.

Before we can measure individual volumes for the different subcortical structures we should decide "how to normalize brain size variability among different subjects?". According to our measurements registering all the brains with a MNI152 template (a 9 degrees of freedom affine transformation was used; transformation matrix was calculated using **FreeSurfer** software) gave better results, than structure normalization by cortical area. By better we mean, that differences between the subject groups in first case were larger compared to normalization by cortical volume, leading to better AUC scores.

We analyzed two approaches. First, each extracted sub-network volume was used solely as an input feature. Each sub-network was described by 3 features:

- $V^{SN}_{M_{00}}, mm^3$ – structure volume at the base line visit (month M_{00}), for the structure name SN.
- $V^{SN}_{M_{24}}, mm^3$ – structure volume after 24 months had passed from the base line visit, for the structure name SN
- $V^{SN}_{\Delta_{24}}, \%$ – structure volume change in 24 month. This criteria was added to have one dimensionless descriptor for the each volume.

Moreover, we propose one new sub-network. Hippocampus and amygdala are close to indistinguishable using only the intensity information available in MRI (Fischl et al., 2002). Therefore, automatic software performs the segmentation based on the spatial information provided by the atlas and local spacial relationship, such as "posterior amygdala is frequently superior to anterior hippocampus, but never inferior to it" (Fischl et al., 2002). Therefore, we propose to integrate these volumes, since they are neighbors and the border between them is hard to define. We call our new marker HA or hippocampus+amygdala.

Each feature was checked for its suitability to be employed for the automatic classification. This was done by evaluating the AUC for each feature, together with Fisher score (equation 1), due to it's close relation with LDA. The main advantage of AUC over the Fisher score is that it provides a non-parametric representation of the diagnostic accuracy of the feature. Moreover, features from completely different sources or studies can be compared to each other by computing

$$F = \frac{S_B}{S_W}. \quad (1)$$

Here, in a 2 class case, S_B presents the so called *between class scatter* of the original feature vectors:

$$S_B = \mu_1 - \mu_2. \quad (2)$$

μ_i - is the mean for each class i, while S_W presents *within class scatter*:

$$S_W = {\sigma_1}^2 + {\sigma_2}^2. \quad (3)$$

where, σ_i - is a measure of variability in each class i.

At the first stage, we performed classification using each feature separately. Then we tested a new, multi-volume based approach. It utilizes a group of the subnetwork based features, rather than on any single feature. The vector was constructed by sorting the features according their Fisher score in descending fashion, similar to:

$$\vec{V} = [V^{Hp}_{M00}, V^{Hp}_{M24}, \Delta^{Hp}_{24}, V^{Am}_{M00}, ..., \Delta^{LastVolume}_{24}], \quad (4)$$

where, Hp stands for the hippocampus and Am for amygdala.

Starting with a single feature, with each subsequent iteration we included extra feature as an input to the classificator. Since we used 9 subnetworks (amygdala and hippocampus were integrated) in our study and 3 descriptors per each volume in the final iteration there was 27 features used as an input data.

5 RESULTS

The best discriminative abilities have volumes of the hippocampus (AUC = 0.86), amygdala (AUC = 0.85) and entorhinal cortex (AUC = 0.80) in both AD and MCI cases (fig. 2) indicating that disease mostly progresses in medial temporal lobe and it's subnetworks.

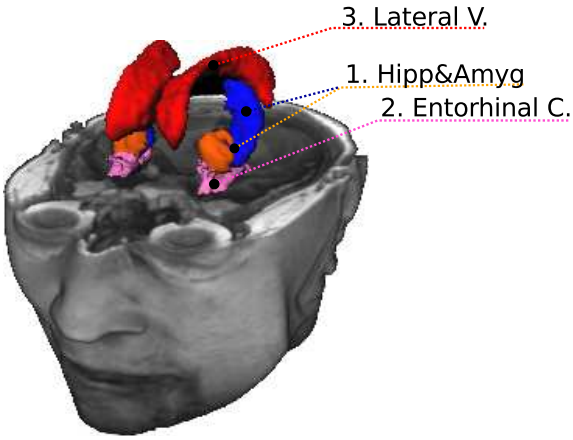


Figure 2: The most discriminative regions in AD and MCI cases: 1) Hippocampus and Amygdala; 2) Entorhinal Cortex; 3) Lateral Ventricle (only in AD case, in MCI case substituted by pallidus).

Table 1: AUC scores for investigated structures ($V_{M_{00}}$ and $V_{M_{24}}$ are given in mm^3, and $V_{\Delta_{24}}$ in % from $V_{M_{00}}$) in AD/NC case.

Feature Name	$V_{M_{00}}$	$V_{M_{24}}$	$V_{\Delta_{24}}$
Hipp.+Amyg.	0.88	0.94	0.81
Hippocampus	0.86	0.92	0.82
Amygdala	0.85	0.91	0.70
Entorhinal Cortex	0.80	0.92	0.78
Lateral Ventricle	0.68	0.76	0.61
Putamen	0.60	0.75	0.71
Caudate	0.57	0.47	0.60
Thalamus	0.57	0.70	0.61
Temporal Pole	0.56	0.71	0.74
3rd Ventricle	0.51	0.58	0.53
Pallidus	0.50	0.62	0.61

Table 2: AUC scores for investigated structures ($V_{M_{00}}$ and $V_{M_{24}}$ are given in mm^3, and $V_{\Delta_{24}}$ in % from $V_{M_{00}}$) in MCI/NC case.

Feature Name	$V_{M_{00}}$	$V_{M_{24}}$	$V_{\Delta_{24}}$
Hipp.+Amyg.	0.71	0.74	0.67
Hippocampus	0.71	0.74	0.66
Amygdala	0.68	0.70	0.62
Entorhinal Cortex	0.64	0.69	0.59
Pallidus	0.62	0.59	0.51
Thalamus	0.61	0.61	0.53
Putamen	0.59	0.60	0.57
Temporal Pole	0.56	0.58	0.55
Caudate	0.55	0.52	0.53
Lateral Ventricle	0.54	0.56	0.57
3rd Ventricle	0.53	0.54	0.51

The results for the AUC scores are presented in tables 1 for AD/NC case and 2 for MCI/NC case. Also figure 3 presents all 3 ROC curves for the AD/NC case. In both cases the best discriminative ability had been shown by integrated hippocampus and amygdala volume. Therefore, for our classification task instead of separate amygdala and hippocampus volumes, we will use the integrated one. Second remark would be, that the discriminative strength increases as time passes. It's due to fact, that in AD (same as MCI) the subject's brain deteriorates faster compared to a NC subject. Thus, differences between structures become bigger in two years. Therefore, they have more discriminative power.

Finally, the last remark would be, that in both AD and MCI cases, the cross-sectional differences $V_{M_{00}}$ and $V_{M_{24}}$, show better AUC scores, compared to the longitudinal changes in volume, presented by $V_{\Delta_{24}}$. This indicates, that incubating period for the disease is long. Therefore, volume change in 2 years is weaker compared to ones, happened before the subject has been included to the study. The other way around, it can happen that some NC subjects are on a way to develop dementia, and the shrinkage of some brain subnetworks just started recently. Therefore, while the absolute volumes of the subnetworks are still relatively large, they start to shrink with intensity comparable to the MCI or AD groups, so we shouldn't rely on the volume changes solely.

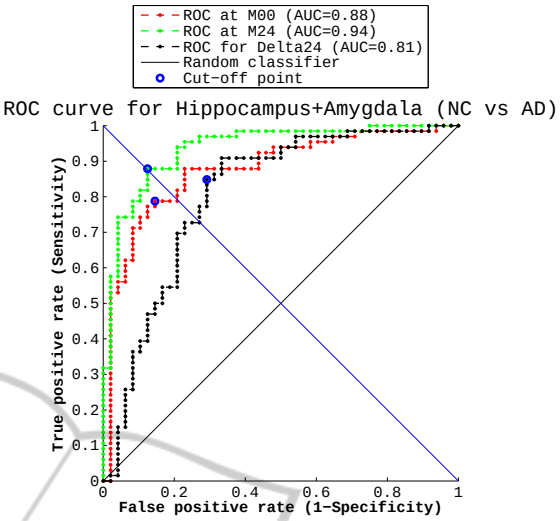


Figure 3: ROC curve in AD/NC case for the best MRI data based feature – Hippocampus+Amygdala. $V_{M_{00}}$ – red line, $V_{M_{24}}$ – blue line, $V_{\Delta_{24}}$ – black line.

5.1 Classification

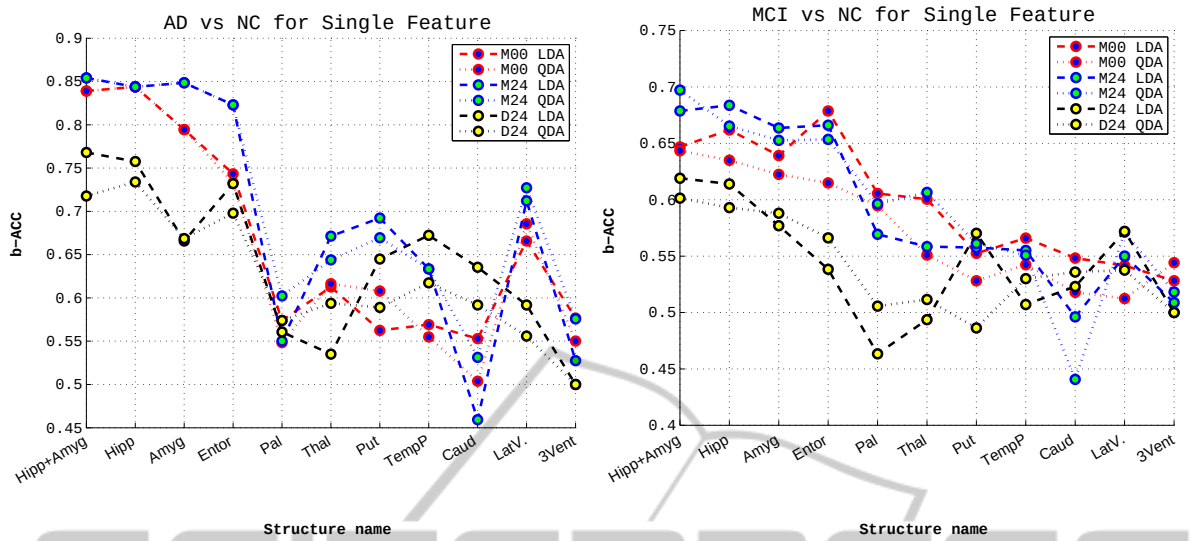
To evaluate automatic classification results we used Linear Discriminant Analysis (LDA) and Quadratic Discriminant Analysis (QDA). These methods maximize ratio of between-class variance to the within-class variance in any particular data set and guarantees maximal separability. These classificators in contrast to Support Vector Machines (SVM) are parameter free. Therefore it is easy to interpret results. Leave-one-out was used as a cross-validation strategy.

The accuracy in the figures 4(a), 4(b), 5(a) and 5(b) is presented by means of balanced Accuracy ($b-ACC$) in y-axis, which represents the averaged sensitivity and specificity value:

$$b-ACC = \frac{1}{2}\text{SEN} + \frac{1}{2}\text{SPE}, \qquad (5)$$

here, SEN - sensitivity, SPE - specificity.

Single Feature, AD vs NC. The results of cross validation are presented in figure 4(a). None of the single features is able to perform ideal classification. The best MRI based marker performance was obtained by hippocampus at M_{00} with $b-ACC = 84.4\%$, while integrated hippocampus and amygdala volumes



(a) (b)

Figure 4: Accuracy for LDA (dashed line) and QDA (dotted line) in Single-Feature case, for $V_{M_{00}}$ - red, $V_{M_{24}}$ - blue, $V_{\Delta_{24}}$ - black lines in (a) AD/NC (b) MCI/NC cases.

were right behind, with $b-ACC = 83.9\%$ at M_{00}. But at M_{24} best $b-ACC$ belongs already to hippocampus+amygdala with $b-ACC = 85.4\%$ (SEN = 80.3%, SPE = 87.5%), while hippocampus solely scores $b-ACC = 84.4\%$. Generally speaking most of MRI based features improved as time passed, except for caudate and 3rd ventricle. While the relative change $V_{\Delta_{24}}$ shows better results only in the case of the temporal pole, possibly indicating that the subnetwork is involved in the disease at a later stages. Moreover, in the most cases LDA showed better classification results than QDA.

Single Feature, MCI vs NC. The same procedure was repeated for the MCI vs NC subjects. The $b-ACC$ results are summarized in the figure 4(b). The best discriminative ability at $V_{M_{00}}$ is shown by entorhinal cortex with $b-ACC = 67.9\%$, followed by hippocampus (66.2%) and hippocampus and amygdala combined volumes (64.7%). While after two years, the best discriminative abilities shift to hippocampus+amygdala (69.7% with QDA classificator), followed by hippocampus (68.4%) and amygdala (66.4%), while entorhinal cortex declines to 66.7%. Relative changes based features presented results were worse compared to the absolute volume data, except for putamen and lateral ventricle, but in both cases results were close to random.

Multi-feature, AD vs NC. The second approach was to combine the strongest markers together. First we use training set, to sort features in descending order, according to their Fisher score. The 7 most discriminative features in AD/NC were:

$$\vec{V} = [V^{HA}_{M_{24}}, V^{Ent}_{M_{24}}, V^{HA}_{M_{00}}, V^{Ent}_{M_{00}}, V^{Ent}_{\Delta_{24}}, V^{HA}_{\Delta_{24}}, V^{Lat}_{M_{24}}]. \quad (6)$$

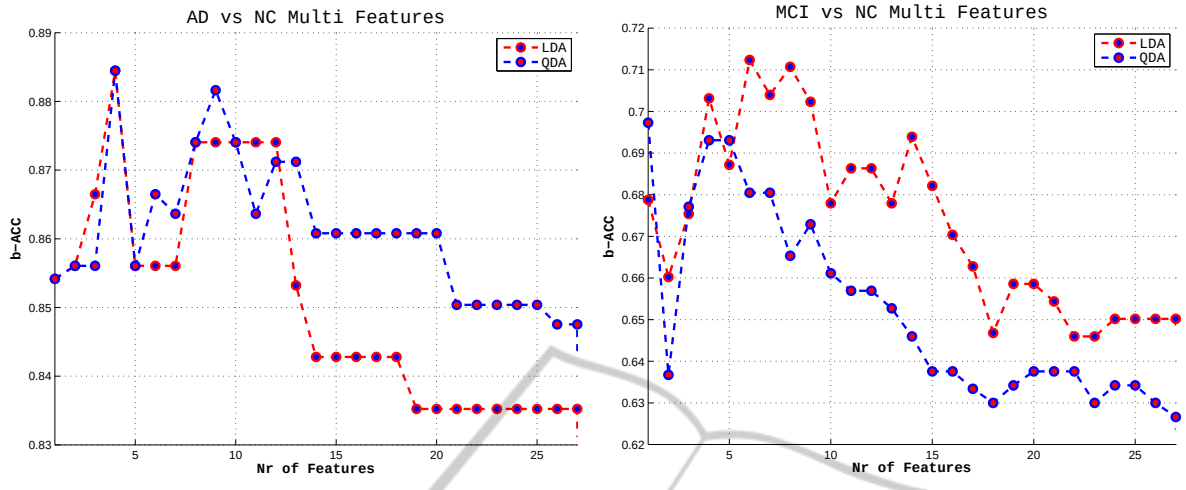
Starting from the most important feature, we include less important ones in each iteration. So, if

Table 3: Five best features, represented by Sensitivity and Specificity values with LDA classifier for investigated features in AD/NC case (**HA** - hippocampus+amygdala, **Hp** - hippocampus, **Am** - amygdala, **EC** - entorhinal cortex, **LV** - lateral venricle).

Name	$V_{M_{00}}$		$V_{M_{24}}$		$V_{\Delta_{24}}$	
	SEN	SPE	SEN	SPE	SEN	SPE
HA	80.3	87.5	83.3	87.5	84.8	68.8
Hp	83.3	85.4	83.3	85.4	84.8	66.7
Am	81.8	77.1	86.4	83.3	72.7	60.4
EC	75.8	72.9	83.3	81.2	81.8	64.6
LV	72.7	60.4	75.8	66.7	62.1	56.2

Table 4: Five best features represented by their Sensitivity and Specificity values with LDA classifier for investigated features in MCI/NC case (**HA** - hippocampus+amygdala, **Hp** - hippocampus, **Am** - amygdala, **EC** - entorhinal cortex, **Pl** - pallidus).

Name	M_{00}		M_{24}		$V_{\Delta_{24}}$	
	SEN	SPE	SEN	SPE	SEN	SPE
HA	69.7	59.7	72.7	63.0	66.7	57.1
Hp	72.7	59.7	71.2	65.5	68.2	54.6
Am	68.2	59.7	69.7	63.0	59.1	56.3
EC	72.7	63.0	65.2	68.1	60.6	47.1
Pl	60.6	60.5	57.6	56.3	43.9	48.7



(a) (b)

Figure 5: Accuracy for LDA (red) and QDA (blue) in Multi-Feature case (a) AD/NC (b) MCI/NC cases.

in first iteration we use one feature, namely hippocampus $V^{HA}_{M_{24}}$ and the result is exactly the same as if single feature would be used. Next iteration we add entorhinal cortex, and the feature vector becomes $[V^{HA}_{M_{24}}, V^{Ent}_{M_{24}}]$, this is continued until all the features are included. Using 9 volumes (volumes of hippocampus and amygdala were combined together), we have 27 features. Results for the full feature vector are presented in figure 5(a) for AD/NC case and 5(b) for MCI/NC case.

The best obtained accuracy was, when first 3 features were used, and is equal to $b-ACC = 88.5\%$ (SEN=87.9%, SPE=89.1%). Results obtained by the multi-approach are better than based on single feature approach by 4.5%.

Multi-feature, AD vs MCI. The best accuracy was 71.2% (SEN = 72.7%, SPE = 69.8%) when 6 features were used (LDA). 7 most discriminative features were:

$$\vec{V} = [V^{HA}_{M_{24}}, V^{HA}_{M_{00}}, V^{EC}_{M_{24}}, V^{HA}_{\Delta_{24}}, V^{Ent}_{M_{00}}, V^{Tl}_{M_{24}}, V^{Tl}_{M_{00}}]. \quad (7)$$

5 from the 6 strongest features in MCI case belong, to hippocampus, amygdala and entorhinal cortex regions. This confirms one more time that disease starts it's progression in the sub-networks of medial temporal lobe.

Compared with single feature case, where the best accuracy score was from 69.7 % for $V^{HA}_{M_{24}}$, result improved by 1.5% and became 71.2%.

6 CONCLUSIONS

1. We propose the integrated marker, consisting of hippocampus and amygdala volumes improves the AUC for M_{00} and M_{24}. Proposed marker improves ROC curve compared to hippocampus or amygdala volumes separately in both AD ($AUC_{M_{00}}$ = 0.88, $AUC_{M_{24}}$ = 0.94, $AUC_{\Delta 24}$ = 0.81) and MCI ($AUC_{M_{00}}$ = 0.71, $AUC_{M_{24}}$ = 0.74, $AUC_{\Delta 24}$ = 0.67) cases.
2. The best score for a single feature was obtained when hippocampus+amygdala marker was used with $b-ACC = 85.4\%$ (SEN = 80.3%, SPE = 87.5%) in AD and 67.9% (SEN = 72.7%, SPE = 63.0%) in MCI case.
3. Multi-Feature approach gives the classification results improvement by 4.5% compared to the single feature case for AD/NC classification. The best result was 88.5% (SEN = 87.9%, SPE = 89.1%) when 3 features were used. In MCI case using our approach we improved accuracy by 1.5% and is equal to $b-ACC = 71.2\%$ (SEN= 72.7%, SPE = 69.8%) when 6 features were used. In both AD/NC and MCI/NC cases QDA didn't show any significant advantage over LDA.

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