Diffusion Tensor Imaging retrieval for Alzheimer's disease diagnosis

CONFERENCE PAPER · JUNE 2014

DOI: 10.1109/CBMI.2014.6849831

5 AUTHORS, INCLUDING:

Olfa Ben Ahmed
Université Bordeaux 1
8 PUBLICATIONS **9** CITATIONS
SEE PROFILE

Jenny Benois-Pineau
Université Bordeaux 1
190 PUBLICATIONS **706** CITATIONS
SEE PROFILE

Chokri Ben Amar
University of Sfax
197 PUBLICATIONS **598** CITATIONS
SEE PROFILE

Diffusion Tensor Imaging retrieval for Alzheimer's disease diagnosis

Olfa Ben Ahmed*, Jenny Benois-Pineau*, Michèle Allard †, Gwénaëlle Catheline† and Chokri Ben Amar‡
*Laboratoire Bordelais de Recherche en Informatique, University of Bordeaux , France
Email: olfa.ben-ahmed, jenny.benois@labri.fr
†The Aquitaine Institute for Cognitive and Integrative Neuroscience, University of Bordeaux, France
† CNRS, INCIA, UMR 5287 Talence, France
Email: michelle.allard,gwenaelle.catheline@ch-bordeaux.fr
‡Research Groups on intelligent machines (ReGIM), University of Sfax, Tunisia
Email: chokri.benamar@ieee.org

***Abstract*—Content-Based Visual Information Retrieval (CBVIR) methods applieds to Magnetic Resonance Imaging (MRI) are penetrating the universe of IT tools for clinical decision support. A clinician can take profit from retrieving subjects' scans with similar patterns. The CBVIR approach has been used since recently for Alzheimer's disease (AD) diagnosis. The most explored imaging modality in this context is the structural MRI. The Diffusion Tensor Imaging (DTI) is a relatively recent technique and CBVIR approaches have not yet been developed on it. The combination of several MRI modalities improves the performances of CBVIR methods, but first of all it is necessary to explore the ability of DTI modality to give a correct answer alone. The present work is amongst the earliest attempts to use visual features as in a generic CBVIR, on this modality for AD research. The proposed approach is based on the comparison of visual features extracted from the hippocampal area. We use the Circular Harmonic Functions (CHFs) to describe the content of the Diffusion Tensor-derived map: Mean Diffusivity (MD). This study was first accomplished with a subset of participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset and then with the DTI scans of a French epidemiological study: "Bordeaux-3City". The obtained results are encouraging and open interesting perspectives.**

I. Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease characterized by alterations in brain structures and by memory disorders. Effective and early diagnisis may significantly reduce the prevalence and the impact of Alzheimer's disease [1]. In recent years, there has been growing interest in using neuroimaging techniques to track brain changes related to AD. Structural Magnetic Resonance Imaging (MRI) has, for a long time, been the most used modality to detect regional neurodegeneration in AD studies. Most investigations using structural MRI have focus on measuring atrophy of some Regions of Interest (ROI) known to be affected by AD i.e. the hippocampus and the entorhinal cortex [2] [3]. Despite effectiveness of structural MRI in detecting macro structural loss for AD diagnosis [2] [4] [5] [6], micro-structural changes remain invisible in anatomical scans. They can be delineated in other MRI modalities such as DTI.

Diffusion Tensor Imaging (DTI) is a recent MRI technique based on motion of water molecules in brain tissues [7]. The principle of DTI is to interpret the water diffusion in the brain as MR signal loss. A neurodegeneration is accompanied by a loss of barriers that restrict motion of water molecules. For diagnostic tasks, two DTI derived maps are used: Mean Diffusivity (MD) and Fractional Anisotropy (FA). MD represents the magnitude of water diffusion and the FA reflects the degree of anisotropy [7]. In case of Alzheimer's disease DTI-derived maps can in vivo quantify the neurodegeneration and the structural alteration of the hippocamups [8] [9] which is the most affected region. In fact, elevated MD and reduced FA in hippocampal areas might be highly indicative of hippocampal atrophy [10]. In [9], the authors showed that values of MD and FA maps in the hippocampus were more sensitive than the hippocampal volume to discriminate AD subjects from those with Mild Cognitive Impariment(MCI) and Normal Control(NC).

Recently, several Computer-Aided Diagnosis (CAD) methods have been proposed to support clinical individual decision making via visual and quantitative analysis of brain structures. Content-Based Visual Information Retrieval-CBVIR is a promising solution for CAD as it provides a clinician with similar cases with similar pathological areas to facilitate his/her decision. A general CBVIR approach consists in content description with visual features and similarity matching in a designed retrieval framework. Here the adequate choice of visual features to be used for content description plays an important role. In the literature, several approaches have been already proposed to describe structural MRI content using local features such as LBP [11], SIFT [12], and CHFs [13], [14]

In our previous works we showed the effectiveness of content-based structural MRI retrieval for AD diagnosis [13] [14]. Nevertheless, the general consensus of multimedia community today is that the fusion of different modalities/ channels is definitely the way to increase performance of retrieval methods. Furthermore, numerous DTI studies for Alzheimer's disease demonstrated that the use of DTI voxel values together with structural MRI voxel values improves classification accuracies [15] [16] [17]. This motivate us to adopt the idea of combining informations derived from both SMRI and DTI in a CBVIR framework. Nevertheless, before designing a fusion scheme in an early, intermediate, or late fusion family of approaches [18], it is mandatory to assess the performance of an individual modality. Today we have a good understanding of scores we can get from SMRI modality only [13]. In the

978-1-4799-3990-9/14/$31.00

present paper we explore DTI as a single modality in a CBVIR framework.

Visual features extraction from DTI-derived maps is a challenging problem since this modality does not contain any anatomical information about the brain structure. Thus, in this work we aim to test the ability of visual features to highlight anatomical structures in DTI. To our best knowledge, there is no previous work trying to investigate visual feature extraction techniques to capture structural information within DTI for AD diagnosis.

Hence, we propose a content-based image retrieval approach for distinguishing between subjects with and without AD from DTI-derived map (MD). We compare different descriptors: the CHFs, used in our previous works [13], and SIFT descriptors [19]. Features are extracted from the most involved area: hippocampus. For this study we use a subset of well-known Alzheimer's Disease Neuroimaging Initiative (ADNI) database [1], then we apply the method to the "Bordeaux-3City" cohort [20]. The rest of paper is organized as flows. Section 2 presents our method. The experiments and results are reported in section 3. Finally, section 4 concludes the work and outlines its perspectives.

II. Methods

A. Visual interpretation of DTI-derived maps

Mean Diffusivity (MD) and Fractional Anisotropy (FA) maps are quantitative gray-scale images that provide information about pathways and the integrity of a brain structure. Both of those maps encode each pixel by an intensity value. Here, image intensities are related to the motion and the direction of water molecules in a brain tissue. Figure 1 shows an example of the MD and the FA maps of healthy and AD individuals respectively. In general, as it is shown in figure 1(a) displayng an MD map, image intensity represents the quantitative value of the diffusion coefficient of the brain tissue at each point in the imaged plane. Due to the free motion of water molecules, the diffusion in ventricles is faster and the MD map is brighter. In white and grey matter regions, the diffusion is slower and the MD pixels are darker. In the FA map (figure 1(b)), white pixels correspond to high values of fractional anisotropy (FA) and dark pixels correspond to low values of FA.

Referring to the domain knowledge, when a brain is affected by Alzheimer's disease, its hippocampus ROI undergoes a cells' degeneration. Water molecules become less hindered because of the loss of barriers for diffusion motion. The faster diffusion of water on the affected hippocampal area results in brighter pixels on the MD maps (see an example in figure 1(c)). Hence, from MD maps, it is possible to extract features and build patterns to distinguish between an affected or a healthy hippocampus for AD diagnosis. The use of FA maps is a more complex problem and we do not address it in the present work.

B. Global framework

The proposed global framework as illustrated in Figure 2 consists of three main steps: image preprocessing, visual features extraction and finally, image retrieval.

[1] http://adni.loni.usc.edu

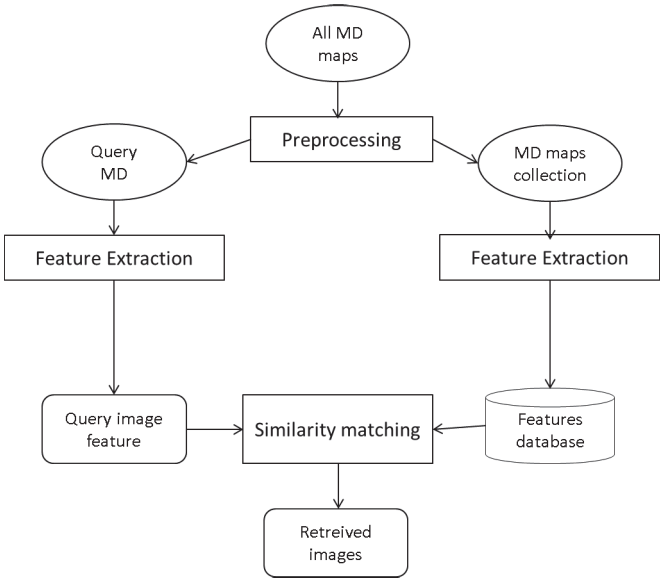

Fig. 2. Diagram of the proposed content-based MD maps retrieval framework

Since in this work, we aim to extract visual features related to the hippocampus alterations from the MD map, we need to locate this ROI on the MD maps. Thus, we perform a coregistration of DTI MD map to anatomical images (SMRI). We follow here [17] [16] where coregistation was used to extract regional values of DTI parameters in some specific areas. Moreover, because of the strong variability between individual scans and brain anatomies, before features extraction step, DTI data have to be normalized. This is done by several steps described in next section. It is to note that all performed transformations are affine in order to not deform the pattern of the features.

1) Preprocessing: For each subject, preprocessing of DTI included corrections for eddy currents and head motion, skull stripping with the Brain Extraction Tool (BET) and fitting of diffusion tensors to the data with DTIfit module of the Software Library FSL [2]. Fitting step allows the generation of the MD and FA maps.

In this work, we retain only the MD maps. All MD image preprocessing steps were performed using Statistical Parametric Mapping (SPM8, Welcome Department of Imaging Neuroscience, London, UK;)[3] running on MATLAB (MathWorks, Sherborn,MA, USA).

The MD images were realigned first using "Realignment" module of SPM8. The purpose here is to adjust movement between slices of DTI-derived maps. Then MD images were affinely co-registered to the corresponding anatomical scans using the registration method of SPM8 with a normalized mutual information approach. Indeed, co-registration consists in superimposing DTI-derived maps (MD images) on the subject's corresponding anatomical scan. This helps to overlay MD values onto an individual's own anatomy. Anatomical scans were then normalized onto the T1 template in MNI (Montreal Neurological Institute) brain template [21] using the

[2] http://www.fmrib.ox.ac.uk/fsl
[3] http://www.fil.ion.ucl.ac.uk/spm

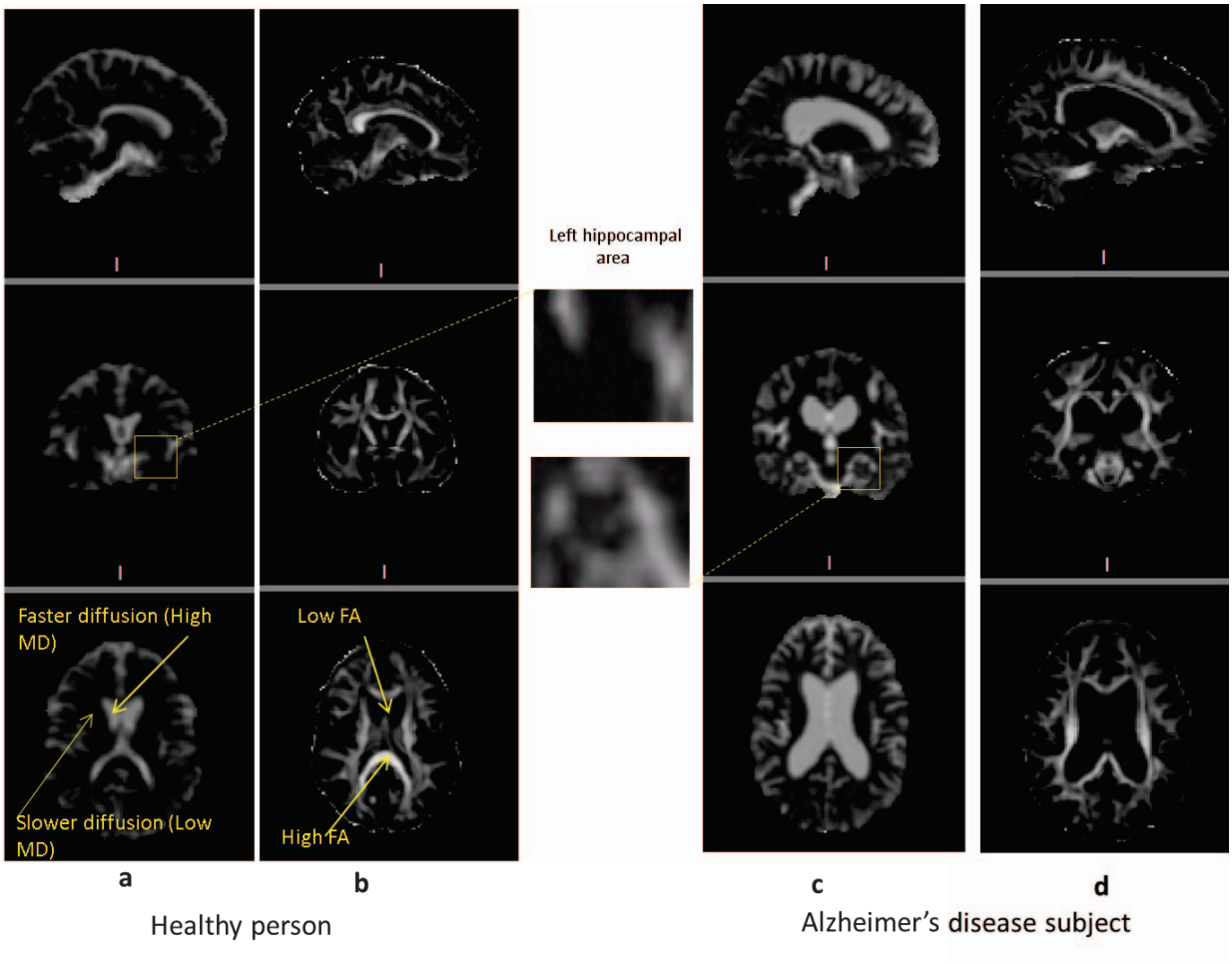

Fig. 1. Example Mean Diffusivity (a,c) and Fractional Anisotropy (b,d) maps of (from left to right) a healthy and AD persons. Image are token from the ADNI dataset.

VBM8 toolbox [4] implemented in SPM8. The resulting transformation parameters were applied to the corresponding co-registered MD maps. Hence the MD values were superimposed onto anatomical structures. Finally, the spatially normalized MD maps were smoothed with a Gaussian filter using teh smoothing module of SPM to improve signal to noise ratio.

2) Features Extraction: The hippocampus ROI was extracted from an anatomical scan using the Automated Anatomical Labeling Atlas (AAL) [22]. A binary mask of the hippocampus was thus obtained in a scan. Although AAL was designed for normal brain, we can use it for AD patient, as extracted hypothetically "normal" ROI will contain the anomalies of the latter. This will yield a variability of image description between NC and AD subjects. The hippocampal region of interest in MD map was obtained by superimposing the binary hippocampus mask from anatomical scans to MD image. Then, hippocampus features were computed on MD map by the development of the MD image signal on the basis of Circular Harmonic Functions (CHF). Indeed, CHF coefficients extracted from the parcel are different and depend on the signal presented in the ROI (atrophy or not). In this manner, we capture the variation of MD maps.

[4]http://dbm.neuro.uni-jena.de/vbm8/)

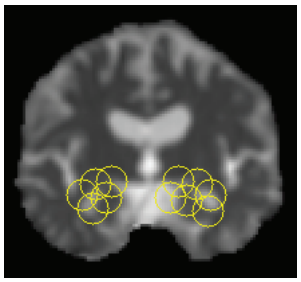

Fig. 3. CHF features detection

The CHF decomposition of a signal is performed on a 2D patch. We use a regular sampling of the MP into patches, we can possibly center them each pixel or use a grid sampling step. This strategy is called a "Dense Sampling". Thus the final feature vector consists of CHF coefficients computed on the hippocampal ROI on MD map.

Figure 3 shows an example of keypoint detection on a coronal projection from a MD map of an ADNI subject. Now, to justify the choice of the signal decomposition basis we briefly remind the definition of CHF functions.

Circular Harmonic Functions (CHF): Gauss-Laguerre Harmonic Functions are complex-valued radial profile multiplied by complex exponent:

$$\Psi(r,\theta;\sigma) = \Psi_n^{|\alpha|}(\frac{r^2}{\sigma})e^{i\alpha\theta} \quad (1)$$

Their radial profiles are Laguerre functions:

$$\Psi_n^{|\alpha|}(x) = \frac{1}{\sqrt{n!\Gamma(n+\alpha+1)}} x^{\frac{\alpha}{2}} e^{\frac{-x}{2}} L_n^{\alpha}(x) \quad (2)$$

where $n = 0, 1, ...; \alpha \pm 1, \pm 2...$ and $L_n^{\alpha}(x)$ are Laguerre polynomials. r, θ are polar coordinates, σ is a scale parameter and Γ is a gamma function.

$$L_n^{\alpha}(x) = (-1)^n x^{-\alpha} \exp^x \frac{d}{dx^n}(x^{n+\alpha}e^{-x}) \quad (3)$$

LG-CHF is complete orthogonal set of functions on the real plane. Thus, the image $I(x, y)$ can be expanded in the analysis point x_0 , y_0 for fixed scale σ in Cartesian system. The coefficients of the partial expansion of local neighborhood of x_0 , y_0 (patch) can be used as a feature descriptor. The advantages of these features are such that they capture both the direction and smooth variations of image signal. Note that MD images are even more blurry than anatomical scans for which the CHF features showed good results in our previous work [13]. They allow for capturing slow signal variations. Their drawback is in a rather slow convergence, hence a sufficient number of coefficients has to be retained for image description. The number of coefficients retained defines the dimensionality of the descriptor. The reasonable dimensionality of 150 coefficients (see [13] [14]) was used in the present work. Hence the dimension of the descriptor is comparable with that one of conventional SIFT. More Mathematical details about the CHF descriptors can be found in [23] [24].

3) MD maps retrieval: Brain scans are aligned and can be compared slice by slice since the features are extracted in a 2D space. The retrieval consists in comparing hippocampal ROIs in MD maps. Similar regions are expected to have similar features. Since the images are aligned, we used a one-to-one region similarity computation scheme, scans are compared slice by slice. As features were computed using the dense sampling strategy (dense placement of features), the number of features and their coordinates are the same for all images. We compare them by using the simple distance metric as described in equation 4.

$$d_n = \sqrt{\sum_{s=1}^{S}\sum_{i=1}^{I^s} \left\| f_i^{*s} - f_{n,i}^s \right\|^2} \quad (4)$$

Here n is the index of a MD map in the database, $f_{n,i}^s$ are features inside a given slice s, (we denote the features of the query scan by f_i^{*s}), S is the total number of slices containing the 3D ROI in query image, I^s is the number of features in a slice s The similarity of a query MD map to n^{th} map is $Sim_1(n) = 1/(d_n+1)$. Lower distance means better similarity.

In a second experiment, we tested the BOF approach [19] inside each scan. The approach consists in finding for every feature f_i^* from one image the best matching feature from other image $f_{n,i}^s$. We used, as similarity measure, the formula given in equation 5 to measure similarities across images. This presents the number of matching descriptors, Indeed, the descriptors are matching when the distance between descriptors $f_i^*, f_{n,i}^s$ is lower than a threshold T. The threshold was found experimentally and its value for these experiments was fixed as 0.4. Note that in our previous work, we used quantized features accordingly to a visual dictionary in a Bag-of-Visual-Words Paradigm [14]. Nevertheless before we can use this paradigm, it is necessary to asses the performance of our description in th original space, what we have done in the present work.

$$Sim_2(n) = \sum_{s=1}^{S}\sum_{i=1}^{I^{s*}} \begin{cases} 1, & \min_{j=1...I^s} \left\| f_i^* - f_{n,j}^s \right\| < T \\ 0, & otherwise \end{cases} \quad (5)$$

III. Experiments and results

In this section we describe the datasets used in our experiments and report the results of the proposed method.

A. Material

The experiments were conducted on two different datasets:

we first selected a subset of DTI images and their corresponding MRI scans from the ADNI database. The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a 60 million, 5- year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimers disease. The ADNI recently added diffusion tensor imaging (DTI), among several other new imaging modalities, in an effort to identify sensitive biomarkers of Alzheimer's disease. In this paper, we use only the MD maps. Resolution of MD maps used is 110x110x110 with a voxel size of 2x2x2 mm^3. We selected 25 AD and 32 NC subjects.

Then, we also validated our method on subset of a real cohort: the 10-year follow-up of a population-based cohort "Bordeaux-3City" [20]. We have only 7 DTI scans of AD and 21 NC subjects. The resolution of DTI scans is 224x224, with 60 slices, and with a voxel of size 2x 2x 2 mm^3.

Table 1 and Table 2 present a summary of the demographic characteristics of the studied subjects (including the number, age, gender and MMSE (Mini Mental State Examination) scale of the subjects).

TABLE I. DEMOGRAPHIC DESCRIPTION OF THE ADNI STUDIED POPULATION. VALUES ARE DENOTED AS MEAN ± STANDARD DEVIATION

Diagnosis	Number	Age	Gender (M/F)	MMSE
AD	25	77.3 ± 4.1	10/15	22.6± 0.3
NC	32	74 ± 3.31	12/20	28.71± 1

TABLE II. DEMOGRAPHIC DESCRIPTION OF "BORDEAUX-3CITY". VALUES ARE DENOTED AS MEAN ± STANDARD DEVIATION

Diagnosis	Number	Age	Gender (M/F)	MMSE
AD	7	85.2 ± 3	2/5	25.57 ± 2.44
NC	21	82.7 ± 4.5	9/12	27 ± 1

B. Experiments

In our testing procedure, we assess the performance of the method in terms of the "precision at N" metric used in information retrieval. Here the proportion of correct matches of classes between the query image and the N returned images is computed. Then a mean precision at N is computed for all query trials.

The retrieval approach has been tested on the MD images. Using this test we analyze the raw performance of the proposed descriptor-based technique. In Figure 4 and Figure 5, the percent of correct classes in N most relevant images is shown both with Sim_1, we call it "1-to-1" and Sim_2, called "BoF" measures.

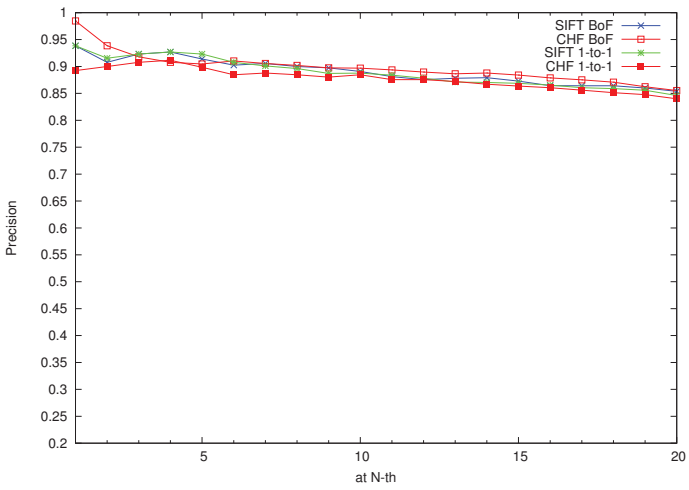

Fig. 4. Retrieval results for CHF and SIFT descriptors : ADNI subset

C. Results

The precision at N^{th} of CHF descriptor using the BOF scheme is in the worst case of 89.69% as illustrated in Figure 4. No significant difference is identified between BOF approach or one-to-one correspondence except the precision at 1. One can see that the precision at 1 is the best with the BOF of CHFs compared to conventional SIFT features.

The Figure 5 illustrates the result on "Bordeaux-3City". For example, the precision value at 4^{th} for CHF descriptor with BOF retrieval approach is about 83%. We can see from Figure 4 and Figure 5 that both CHF and SIFT descriptors give high retrieval results. These descriptors thus prove to be suitable for capturing the DTI image content.

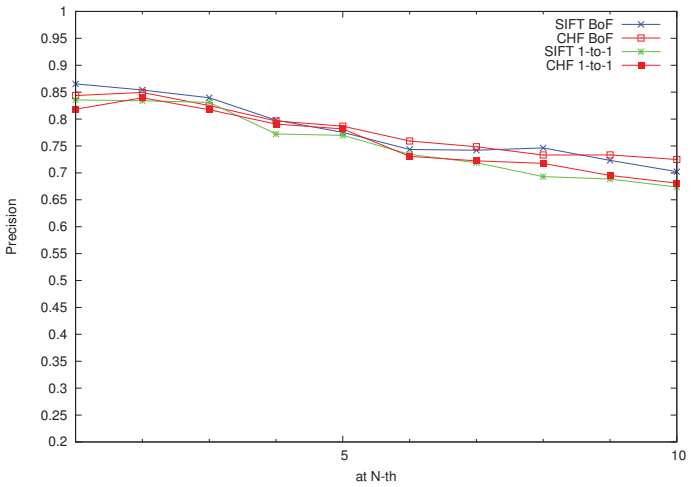

Fig. 5. Retrieval results for CHF and SIFT descriptors : Bordeaux-3City

IV. CONCLUSION

Hence, in this paper we applied a classical CBVIR approach on the DTI MD maps to evaluate the performance of this scheme on the recent MRI modality. This scheme has not yet allowed us to compare our results with voxel-based approaches which use classification framework. Our work can be considered just as a first step for this or as a proof of concept of CBVIR for DTI modality. Despite the tests were conducted on a small (for cohort population reasons) test set, the results obtained are promising. Alone this modality shows rather high scores in a realistic situation of a small cohort. Furthermore, our approach, which do not require a precise segmentation of ROI, performs well not only on SMRI, what we showed in our previous work, but also on more challenging modality such as DTI MD maps. In the perspective of this work we will proceed with fusion of different modalities in a global classification framework.

REFERENCES

[1] R. Brookmeyer, E. Johnson, K. Ziegler-Graham, and H. M. Arrighi, "Forecasting the global burden of Alzheimer's disease," *Alzheimer's and Dementia*, vol. 3, no. 3, pp. 186 – 191, 2007.

[2] E. Gérardin, G. Chételat, M. Chupin, R. Cuingnet, B. Desgranges, H.-S. Kim, M. Niethammer, B. Dubois, S. Lehéricy, L. Garnero, F. Eustache, and O. Colliot, "Multidimensional classification of hippocampal shape features discriminates Alzheimer's disease and mild cognitive impairment from normal aging." *NeuroImage*, vol. 47, no. 4, pp. 1476–86, 2009.

[3] M. Chupin, A. Hammers, and al, "Automatic segmentation of the hippocampus and the amygdala driven by hybrid constraints: Method and validation." *NeuroImage*, vol. 46, no. 3, pp. 749–761, 2009.

[4] R. Cuingnet, E. Gérardin, J. Tessieras, G. Auzias, S. Lehericy, M. O. Habert, M. Chupin, H. Benali, and O. Colliot, "Automatic classification of patients with Alzheimer's disease from structural MRI: A comparison of ten methods using the ADNI database." *NeuroImage*, vol. 56, no. 2, pp. 766–781, 2011.

[5] M. Chupin, E. Gérardin, R. Cuingnet, C. Boutet, L. Lemieux, S. Lehéricy, H. Benali, L. Garnero, O. Colliot, and Alzheimer's Disease Neuroimaging Initiative, "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.

[6] B. Gutman, Y. W. J. Morra, A. Toga, and P. Thompson, "Disease classification with hippocampal shape invariants," *Hippocampus*, vol. 19, pp. 572–578, 2009.

[7] D. L. Bihan, "Looking into the functional architecture of the brain with diffusion MRI," *Nature Reviews. Neuroscience*, vol. 4, pp. 469–80, jun 2003.

[8] T. den Heijer, F. van der Lijn, and al, "Structural and diffusion MRI measures of the hippocampus and memory performance," *NeuroImage*, vol. 63, no. 4, pp. 1782–1789, 2012.

[9] H. Müller and T. M. Deserno, "Content-based medical image retrieval," in *Biomedical Image Processing - Methods and Applications*. Springer, 2011.

[10] M. Mielke, N. Kozauer, K. Chan, M. George, and al, "Regionally-specific diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease," *NeuroImage*, vol. 46, no. 1, pp. 47 – 55, 2009.

[11] M. Agarwal and J. Mostafa, "Image retrieval for Alzheimer disease detection," in *Proceedings of the First MICCAI international conference on Medical Content-Based Retrieval for Clinical Decision Support*, ser. MCBR-CDS'09. Berlin, Heidelberg: Springer-Verlag, 2010, pp. 49–60.

[12] M. R. Daliri, "Automated diagnosis of Alzheimer disease using the scale-invariant feature transforms in magnetic resonance images," *J. Med. Syst.*, vol. 36, no. 2, pp. 995–1000, 2012.

[13] O. Ben Ahmed, J. Benois-Pineau, C. Ben Amar, M. Allard, and G. Catheline, "Early Alzheimer disease detection with bag-of-visual-words and hybrid fusion on structural MRI," in *Content-Based Multimedia Indexing (CBMI), 2013 11th International Workshop on*, 2013, pp. 79–83.

[14] M. Mizotin, J. Benois-Pineau, M. Allard, and G. Catheline, "Feature-based brain MRI retrieval for Alzheimer disease diagnosis," in *19th IEEE International Conference on Image Processing (ICIP)*, 2012, pp. 1241–1244.

[15] M. Dyrba, M. Ewers, M. Wegrzyn, I. Kilimann, C. Plant, and al, "Combining DTI and MRI for the automated detection of Alzheimer's disease using a large european multicenter dataset," in *Multimodal Brain Image Analysis*, ser. Lecture Notes in Computer Science, vol. 7509. Nice, France: Springer Berlin / Heidelberg, oct 2012, pp. 18–28.

[16] L. Mesrob, M. Sarazin, V. Hahn-Barma, and al, "DTI and structural MRI classification in Alzheimer's disease," *Advances in Molecular Imaging*, vol. 2, pp. 12 – 20, 2012.

[17] A. Cherubini, P. Pran, I. Spoletini, M. D. Paola, F. D. Iulio, and al, "Combined volumetry and DTI in subcortical structures of mild cognitive impairment and Alzheimer's disease patients," *Journal of Alzheimer's Disease*, vol. 19, no. 4, pp. 47 – 55, 2010.

[18] J. Pinquier, S. Karaman, L. Letoupin, P. Guyot, R. Mgret, J. Benois-Pineau, Y. Gastel, and J.-F. Dartigues, "Strategies for multiple feature fusion with hierarchical HMM: Application to activity recognition from wearable audiovisual sensors." in *ICPR*. IEEE, 2012, pp. 3192–3195.

[19] D. G. Lowe, "Distinctive image features from scale-invariant keypoints," *Int. J. Comput. Vision*, vol. 60, no. 2, pp. 91–110, Nov. 2004.

[20] A. Pelletier, O. Periot, B. Dilharreguy, B. Hiba, M. Bordessoules, K. Prs, H. Amieva, J.-F. Dartigues, M. Allard, and G. Catheline, "Structural hippocampal network alterations during healthy aging: A multi-modal mri study," *Frontiers in Aging Neuroscience*, vol. 5, p. 84, 2013.

[21] G. B. Frisoni, C. Testa, F. Sabattoli, A. Beltramello, H. Soininen, and M. P. Laakso, "Structural correlates of early and late onset alzheimer's disease: voxel based morphometric study," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 76, no. 1, pp. 112–114, 2005.

[22] N. Tzourio-Mazoyer, B. Landeau, D. Papathanassiou, F. Crivello, O. Etard, N. Delcroix, B. Mazoyer, and M. Joliot, "Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain," *NeuroImage*, vol. 15, no. 1, pp. 273 – 289, 2002.

[23] L. Sorgi, N. Cimminiello, and A. Neri, "Keypoints selection in the gauss laguerre transformed domain." in *BMVC*, M. J. Chantler, R. B. Fisher, and E. Trucco, Eds. British Machine Vision Association, 2006, pp. 539–547.

[24] D. V. Sorokin, M. M. Mizotin, and A. S. Krylov, "Gauss-laguerre keypoints extraction using fast hermite projection method," in *Proceedings of the 8th international conference on Image analysis and recognition - Volume Part I*, ser. ICIAR'11. Berlin, Heidelberg: Springer-Verlag, 2011, pp. 284–293.