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Generalized Regional Disorder-Sensitive-Weighting Scheme for 3D Neuroimaging Retrieval

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***Abstract*—3D functional neuroimaging is used in the diagnosis and management of neurological disorders. The efficient management and analysis of these large imaging datasets has prompted research in the field of content-based image retrieval. In this context, our generalized regional disorder-sensitive-weighting (DSW) scheme gives greater weight to brain regions affected by the diseases than regions that are relatively spared. We used two DSW matrices; one matrix is based on the occurrence maps that highlight abnormal functional regions; the other is based on the regional Fisher discriminant ratio. Our results suggest that our DSW matrices enhance neuroimaging data retrieval and provide a flexible weighting solution for the clinical analysis of different types of neurological disorders.**

I. Introduction

FUNCTIONAL neuroimaging, such as positron emission tomography (PET), plays an important role in the diagnosis and management of a variety of neurological disorders. Instrumentation advances have led to the introduction of PET-CT and, very recently, PET-MR scanners into clinical practice and with these advances there has been a marked increase in the size of the neuroimaging datasets. The efficient management and analysis of these large imaging datasets has prompted research in the field of content-based image retrieval (CBIR) with the anticipation of applications in computer aided diagnosis (CAD), education and clinical research.

There are a number of recent reports on neuroimaging data retrieval but accurate CBIR remains a challenging area [1-5]. Previous reports can be separated by the major features that the investigators used. Ramirez *et al* used statistical-based features [1-2]. Their studies focused on FDG (*[^{18}F]2-fluoro-deoxy-glucose*) PET in distinguishing Alzheimer's disease (AD) cases from normal controls using the support vector machine (SVM) for early AD detection and Gaussian mixture models (GMM) based multivariate approach for brain image classification [1, 2]. Wong *et al.* and Kim *et al.* used physiological features [3, 4]. Wong *et al.* built a neuro-informatics database system for temporal lobe epilepsy studies and used glucose consumption as the physiological feature [3]. Kim *et al.* proposed a retrieval system for dynamic PET brain images using volume of interest (VOI) based tissue time activity curves (TTAC) [4]. Batty *et al*. [5] designed a prototype system for semantic retrieval of brain PET images and they extracted visual texture features from a fixed region of interest (ROI) by Gabor filters [5]. Our group recently proposed a 3D retrieval approach based on physiological and visual features, *i.e.* cerebral metabolic rate of glucose consumption (CMRGlc) based parameters combined with texture features extracted by 3D gray level co-occurrence matrices (GLCM) algorithm [6]. Rather than use the whole brain data or fixed ROI-based data for all neurological disorders, we designed a set of disorder-oriented-masks (DOMs), each of which corresponded to a particular neurological disorder and included functional brain regions specific to that disorder's degenerative pattern. The DOMs reduced the retrieval of non-specific data from irrelevant regions.

The construction of DOMs, however, relied heavily on clinical expertise and an understanding of the underlying neuropathology [6]. In addition, the DOMs could not take into account the variability of abnormality in the affected regions due to progression of neurological disorders. In other words, DOMs treated all the disorder related regions equally. To understand this, we could consider the DOMs as a special binary weighting matrix, having 0 and 1 values only. If abnormalites in a particular region were associated with a particular neurological disease, then its weight was set to 1, otherwise its weight was set to 0.

Our aim with this work was to develop an objective and flexible weighting solution for different brain functional regions that was not dependent on clinical expertise for selecting the disorder associated regions and which could reflect the functional regions' sensitivity to the disorder's pathological changes quantitatively. Therefore, we proposed a generalized regional disorder-sensitive-weighting (DSW) scheme with two generalized DSW matrices for region-wise texture feature extraction. The proposed generalized DSW matrix based retrieval approach were compared to the DOM

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based and whole brain based retrieval approaches, and the validity of the proposed approach was tested on 141 clinical neurological FDG-PET studies.

II. METHODS

A. Functional Neuroimaging Data Pre-processing

The static FDG-PET images were acquired on a CTI ECAT 951R whole body PET scanner and the CMRGlc parameters were derived from these images with the autoradiographic (ARG) algorithm [7]. The CMRGlc images were then spatially normalized to the Montreal Neurological Institute (MNI) template by the SPM2 package [8]. The MNI-based Tzourio-Mazoyer atlas was used to define 116 functional regions. For simplicity, we used $\boldsymbol{R} = \{\boldsymbol{R_1}, \boldsymbol{R_2}, \ldots, \boldsymbol{R_n}\}$ instead of the full functional region names to represent the entire collection of brain functional regions ($\boldsymbol{R}$), where $\boldsymbol{n}$ in this study was 116, as defined by the Tzourio-Mazoyer atlas.

B. Occurrence Map based DSW Matrix

To describe the occurrences of the abnormal voxels appearing in a functional region, inspired by the probability map proposed by Hammers *et al.* [9], we designed an occurrence map (o-map) for constructing the DSW matrix. The o-map was constructed by summing the t-maps [6] of all cases diagnosed with a specific disorder. The t-maps were generated by comparison against all the normal controls used in this study (see section E). Setting a threshold (p-value < 0.05), t-map could capture the lesion areas within a 95% confidence interval. The voxel value in an o-map reflected the presence or absence of the abnormality. If the voxel value is 0, that means no abnormality was captured by any t-map for this voxel, therefore, that voxel is normal. If the voxel value is greater than 0, then at least one t-map has captured that voxel as abnormal. The fraction of the abnormal voxels, *i.e.*: voxels with values greater than 0, to the total number of voxels in a region showed the discriminant power of that region.

The ratio ($\boldsymbol{r_i}$) of the number of abnormal voxels in region $\boldsymbol{R_i}$ to the total number of voxels in $\boldsymbol{R_i}$ reflected the probability of $\boldsymbol{R_i}$ being abnormal for that disorder. We computed $\boldsymbol{r_i}$ for every $\boldsymbol{R_i}$, and then derived the weight for $\boldsymbol{R_i}$ as in (1):

$$w_i = \frac{r_i}{\sum_1^n r_i}, \sum_1^n w_i = 1 \cdot \qquad (1)$$

Combining all the $\boldsymbol{w_i}$, we generated the DSW matrix as $\boldsymbol{W_{DISORDER}} = \{\boldsymbol{w_1}, \boldsymbol{w_2}, \ldots, \boldsymbol{w_n}\}$. For each of the investigated disorders, we derived an o-map based DSW matrix.

C. Fisher Discriminant Ratio based DSW Matrix

For any functional region, we assumed that its intensity distribution for a disorder group could reflect the region's sensitive degree to that disorder's pathological changes when compared to same region's intensity distribution for the normal controls. We also assumed that such regional disorder sensitive degree to one disorder's pathological changes could be different from that for another. We thus designed another DSW matrix based on the Fisher discriminant ratios (FDR) [1] which could evaluate of the distribution difference between a disorder group and the normal control group. For each of the investigated disorders, we let $\boldsymbol{\mu_{i\_DISORDER}}$ and $\boldsymbol{\sigma_{i\_DISORDER}}$ denote the mean and standard deviation of the voxel values in $\boldsymbol{R_i}$, and $\boldsymbol{\mu_{i\_NC}}$ and $\boldsymbol{\sigma_{i\_NC}}$ for the normal controls, respectively. We then computed the $\boldsymbol{FDR_i}$ as in (2) to quantify the discriminant power of $\boldsymbol{R_i}$ for distinguishing a case in a disorder group from the normal controls:

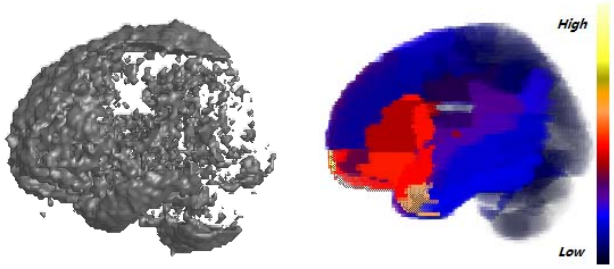
$$FDR_i = \frac{(\mu_{i\_DISORDER} - \mu_{i\_NC})^2}{\sigma_{i\_DISORDER}^{\ 2} + \sigma_{i\_NC}^{\ 2}} \cdot \qquad (2)$$

We calculated the $\boldsymbol{FDR_i}$ for each $\boldsymbol{R_i}$ and then define the weight for each $\boldsymbol{R_i}$ as in (3):

$$w_i = \frac{FDR_i}{\sum_1^n FDR_i}, \sum_1^n w_i = 1 \cdot \qquad (3)$$

As with the o-map based DSW matrix, we combined all the $\boldsymbol{w_i}$ to construct the FDR-based DSW matrix.

FDR and o-map based DSW matrices both try to identify abnormal regions using certain ratios instead of values with measurement units, but their weights were derived differently. An o-map based DSW matrix is based on the fraction of abnormal voxels ($p < 0.05$) within a region. In contrast, FDR is based on the difference in grey level (voxel value) distribution of a region compared to the distribution in the corresponding region for the normal population. Fig. 1 shows examples of the o-map and the FDR-labeled atlas for frontotemporal dementia (FTD).



(a) O-map (b) FDR labeled atlas

Fig. 1. Volume rendering of the o-map and the FDR labeled atlas for FTD.

D. Feature Extraction based on DSW Matrices

The 3D Gray Level Co-occurrence Matrix (GLCM) algorithm [11] was used to capture the texture features. Fig.2 shows the pseudo codes on how the features were extracted from individual regions and subsequently aggregated into one feature vector according to the DSW matrix.

For each functional region, 39 co-occurrences matrices were extracted in 13 directions and 1, 3, 5 depths, respectively. A 14-dimensional Haralick feature vector was computed from each of the 39 extracted co-occurrences matrices. Then a single feature vector was derived by averaging the 39 feature vectors to represent the region, *i.e.*:

$v_i = \{ v_{i,1}, v_{i,2}, v_{i,3}, \ldots, v_{i,m} \}^T$, where $m = 14$, $1 \le i \le 116$. For a whole brain image volume consisting of 116 functional regions, the feature vector matrix was defined as follows: $V = \{v_1, v_2, v_3, \ldots, v_n\}$, $n = 116$. Finally, we computed the dot product, Q, of the feature vector matrix, V, and the DSW matrix, $W_{DISORDER\_MATRIX}$, as in (4):

$$Q = V^T \bullet W_{DISORDER\_MATRIX}, \quad (4)$$

where Q was the final representation of the input image with the same dimension as v_i, and $W_{DISORDER\_MATRIX}$ was specified by the disorder name and DSW matrix type.

```
SET     distance depth (depth) = 1, 3, 5
SET     replacement direction (direction) = 13 angles
SET     feature vector matrix (V) = empty
SET     DSW matrix type (type) = 'o-map' or 'FDR'
SET     disorder name (disorder) = 'AD', 'FTD', 'DLBD'…
FOR     each region in the 3D CMRGlc image
    FOR   each depth in each direction
        EXTRACT    a co-occurrence (glcm)
        COMPUTE    a Haralick feature vector (haralick) for glcm
        ADD        haralick to a temporary regional feature vector list (v_list)
    END FOR
    COMPUTE   a regional feature (v_i) as the average of all haralicks in v_list
    ADD       v_i to V
END FOR
READ        DSW matrix (W) specified by type and disorder
COMPUTE     Q as dot product of V and W
RETURN      Q
```

Fig. 2. Pseudo codes for DSR weighting matrix based feature extraction.

E. Dataset and Evaluation

We tested the proposed generalized regional DSW scheme on a dataset which was comprised of 141 neurological FDG-PET studies acquired on a CTI ECAT 951R whole body PET scanner, at the Department of PET and Nuclear Medicine, Royal Prince Alfred Hospital, Sydney. The dataset contained 38 Alzheimer's disease (AD) cases, 6 Diffuse Lewy body disease (DLBD) cases, 36 frontotemporal dementia (FTD) cases and 12 indefinite AD/DLBD (suspicious AD or DLBD) cases, together with 18 normal cases and 31 other dementia cases.

The retrieval was conducted by the leave-one-out strategy on the whole dataset using query by example paradigm. The similarity was calculated by Euclidean distance on the normalized feature space [6]. Taking into consideration the overlap of the degenerative patterns of disorders, when we calculated the retrieval precision, we set the relevance score of any two different disorders to 0.25, except for the AD/DLBD cases, whose relevance score was 0.75 if the query image was either AD or DLBD, or vice versa.

To show how much a particular disorder's DSW matrix could enhance the retrieval of that particular disorder, we focused on the retrieval performance of one specific disorder group using that disorder's DSW matrices only. We compared the proposed DSW scheme to the whole brain based retrieval using the average precision of top 5 and top 3 retrieved results, respectively. The whole brain based retrieval referred to the retrieval based on the global features extracted from the whole brain volume with no DOM or generalized DSW matrices applied.

III. Results

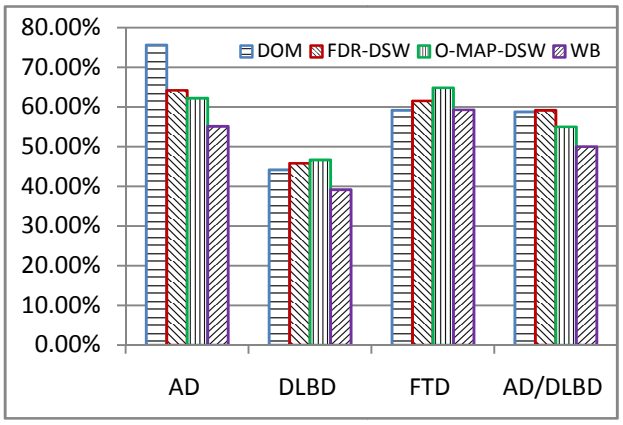


Fig. 3. Top 5 retrieval precision for four disorders using the DSR weighting scheme, compared to the whole brain based retrieval.

Fig. 3 shows the average precision of the top 5 retrieved results for four types of disorders, 'AD', 'DLBD', 'FTD' and 'AD/DLBD'. For all of these four disorders, the retrieval based on DSW scheme, including the DOM (DOM: 1^{st} bar), the FDR based DSW matrix (FDR-DSW: 2^{nd} bar) and the o-map based DSW matrix (O-MAP-DSW: 3^{rd} bar), yielded up to over 20% better results than the whole brain based retrieval (WB: 4^{th} bar). The largest increase resulting from DOM was 20.5% for AD cases. The largest increase by using FDR -DSW was 9.17% for AD/DLBD cases, and the largest increase by using O-MAP-DSW was 7.5% for DLBD cases.

When we compared the two generalized DSW matrices (FDR-DSW and O-MAP-DSW) with each other, we found that they had equivalent performance. FDR-DSW was slightly higher than O-MAP-DSW for DLBD and FTD cases, while O-MAP-DSW prevailed for the other two disorders. When we compared generalized DSW matrices to

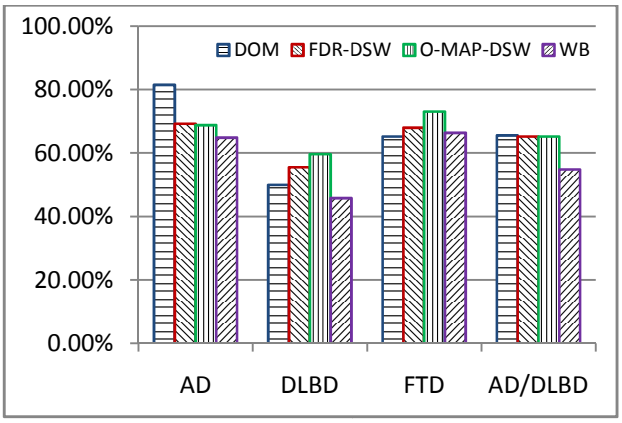


Fig. 4. Top 3 retrieval precision for four disorders using the DSR weighting scheme, compared to the whole brain based retrieval.

the special binary weighting matrix, DOM, we found that the generalized DSW matrices achieved higher average precision than DOM for most disorders. For 'DLBD' and 'FTD' cases, the O-MAP-DSW reached the highest precision; while for 'AD/DLBD' cases, the FDR-DSW had the best performance. The only exception was found in AD cases. The retrieval of AD cases by using DOM was unexpectedly better than the generalized DSW matrices. Fig. 4 shows the average precision of the top 3 retrieval results. Similar findings were discovered when we compared Fig. 4 to Fig. 3.

IV. Discussion

For all the investigated disorders, the DOM based retrieval achieved better results than the whole brain based retrieval. This was due to DOMs' superiority in capturing the pathological information, for the DOMs were constructed based on clinical expertise. However, DOM was not the optimum way for exploiting the pathological information contained in the functional regions, for it was not able to reflect the sensitivity level to a disorder's pathological changes in different functional regions. The generalized regional DSW scheme, on the other hand, could capture such senstivity information and measure the sensitive degree of different functional regions quantitatively. The generalized DSW matrices did not utterly retain or discard the functional regions like the DOMs, but assigned a weight to each functional region according to the information inherent in the data. In addition, the generalized DSW scheme combined the multilevel information, *i.e.*: the voxel-level information captured by the GLCM algorithm and the region-level information in the weighting matrices. Therefore, our proposed generalized DSW matrices performed better than the DOMs for most of the disorders.

One thing we should note was that the retrieval of AD cases using DOM was much better than using the generalized DSW matrices. This finding could be explained by AD's characteristics. AD was a special subtype of dementia, whose degenerative pattern spread out many functional regions of the brain. It is very difficult to find the differences between AD cases and normal controls at the early stage, or even at the mild stage. The dataset used in this study mixed the AD patients at different stages. As a result, the AD cases at early stage contributed little to the construction of o-map and diluted the significance of FDR, and they are unlikely to be retrieved by the search of a late AD study, and vice versa. In addition, some normal controls also made the biased retrieval of AD cases, because they exhibited a whole brain degenerative pattern, which was similar to some AD cases. Such normal cases were quite rare, only two in our database. By contrast, the DOM was based on clinical expertise and only focused on specific pattern of defect for late AD studies, hence would not be affected by these negative factors.

V. Conclusions and Future Work

In this study, we presented a generalized regional DSW scheme for 3D neuroimaging retrieval. This generalized functional-region-wise DSW scheme was evaluated using two weighting matrices. The first weighting matrix was based on the o-map and the other was based on the functional-regional-wise FDR. Both of the two generalized DSW matrices could enhance the retrieval of neurological images for all disorders investigated, and they also demonstrated the superiority over DOMs for most of the disorders. In conclusion, our proposed generalized regional DSW scheme provides a flexible weighting solution for the neurological disorder analysis, and unlike DOM, it does not require clinical knowledge of the disease pathology.

For the future work, we would extend this study by:

1) Improving the retrieval of AD cases and other progressive neurological disorders. We suggest that the patients should be grouped by their progression stage. As we do so, we could also extract useful information on distinguishing future patients at different stages.

2) Investigating more neurological disorders using our generalized functional-region-wise DSW scheme, *e.g.*: epilepsy and many other subtypes of dementia.

References

[1] J. Ramírez, J. M. Górriz, M. López, *et al.* "Early detection of the Alzheimer disease combining feature selection and kernel machines," *Advances in Neuro-Information Proc.*, Lecture Notes in Comp. Sci., 2009, pp. 410-417: Springer Berlin / Heidelberg.

[2] F. Segovia, J. M. Gorriz, J. Ramirez, *et al.*, "Classification of functional brain images using a GMM-based multi-variate approach," *Neuroscience Letters*, vol. 474, no. 1, 2010, pp. 58-62.

[3] S.T.C. Wong, K.S. Hoo, X. Cao, *et al.*, "A neuroinformatics database system for disease-oriented neuroimaging research," *Academic Radiology*, vol. 11, no. 3, 2004, pp. 345-358.

[4] J. Kim, W. Cai, D. Feng, *et al.*, "A new way for multi- dimensional medical data management: volume of interest (VOI)- based retrieval of medical images with visual and functional features," *IEEE Trans. on Info. Tech. in Biomed.* vol. 10, no. 3, 2006, pp.598-607.

[5] S. Batty, J. Clark, T. Fryer, *et al.*, "Prototype system for semantic retrieval of neurological PET images," *Proc. 2nd Int. Conf. on Med. Imaging and Info. (MIMI 2007)*, Beijing, Aug 14-16, 2007, LNCS 4987, pp. 179-188.

[6] S. Liu, W. Cai, L. Wen, *et al.*, "A robust volumetric feature extraction approach for 3D neuroimaging retrieval." *Proc. Eng. in Med. and Bio. Society (EMBC)*, 2010, pp. 5657-5660.

[7] G.D. Hutchins, J.E. Holden, R.A. Koeppe, *et al.*, "Alternative approach to single-scan estimation of cerebral glucose metabolic rate using glucose analogs with particular application to ischemia," *J. of Cerebral Blood Flow and Metab.*, vol. 4, 1984, pp. 35-40.

[8] R. S. J. Frackowiak, K. J. Friston, C. D. Frith, *et al.*, *Human Brain Function*. Amsterdam; Boston: Elsevier Academic Press, 2004.

[9] A. Hammers, R. Allom, M.J. Koepp, *et al.*, "Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe," *Human Brain Mapping*, vol. 19, is. 4, 2003, pp. 224-247.

[10] W. Cai, S. Liu, L. Wen, *et al.*, "3D neurological image retrieval with localized pathology-centric CMRGlc patterns." *Proc. 17th IEEE Int. Conf. on Image Proc. (ICIP),* 2010, pp. 3201-3204.

[11] S. Kurani, D.H. Xu, J. Furst, *et al.*, "Co-occurrence matrices for volumetric data," *Proc. 7th Int. Conf. on Computer Graphics and Imagine (CGIM)*, 2004, Hawaii.