Generating a set of templates in Magnetic Resonance neuroimages for the early diagnosis of Alzheimer's disease

A. Agrusti[1] , A. Carlà[2] , R. Cataldo[1 2] , I. De Mitri[3 2] , G. De Nunzio[1 2] , M. Favetta[3 2], M. Quarta[4 2], and the MAGIC-5 Collaboration [5]

[1]Dipartimento di Scienza dei Materiali, Università del Salento,Lecce, Italy

[2]Istituto Nazionale di Fisica Nucleare, Sezione di Lecce, Italy

[3]Dipartimento di Fisica, Università del Salento,Lecce, Italy

[4]Dipartimento di Matematica, Università del Salento, Lecce, Italy

[5]Universities and INFN units of Bari, Genova, Lecce, Napoli, Pisa, Torino

Introduction. Structural and functional neuroimaging methods offer the potential to provide a non-invasive tool to better understand neurodegenerative disease processes as well as to monitor progression in clinical studies. Magnetic Resonance Imaging (MRI) has been used in several *in vivo* anatomical studies of the brain [1], especially for the hippocampus, and plays an important role in the diagnosis of temporal lobe epilepsy, or degenerative diseases such as Alzheimer's dementia, and in the evaluation of their time evolution [2]. Anatomical reference images (templates) are becoming of vital importance for comparison of results, and to allow better identification of structures. They are primarily intended to serve as reference for spatial normalization usually required before studying human anatomical or functional variability. The fundamental shortcomings of using templates result from the inherent complexity of the problem. Thus a significant goal is to account for inter-subject variability of anatomy and function, in order to find templates that are representative of the population under investigation [3]. The MAGIC-5[1] group is an Italian collaboration involving many academic and clinical institutions in the field of Computer Aided Detection (CAD) software systems for the analysis of medical images, as a support for the early diagnosis of lung cancer and neurological pathologies, especially the Alzheimer's Disease (AD)[5]. Within this project we developed a rather simple procedure for generating a set of templates for the efficient extraction of the hippocampal region in Magnetic Resonance (MR) images of the brain.

Template generation procedure. Two hundreds MR brain T1-weighted images have been downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) web site (*http://www.loni.ucla.edu/ADNI/*) and were used for this study. The complete procedure goes through three main steps:

1. Histogram standardization, and Spatial Normalization to stereotactic space (ICBM152);

2. 'Exhaustive' extraction of the hippocampal regions (hereafter called hippocampal boxes, HBs) from all the images;

3. Template-set selection.

In step (1) we built a method for standardizing the intensity scale of brain MR images. As a consequence, similar intensities have similar tissue type, even among images coming from different sources. Then (step 2) we extracted the hippocampal regions from a large dataset of MR images (by iterated coregistration with an initial, manually defined by a doctor, hippocampal region). We finally addressed (step 3) template generation, choosing a small number k of them, by means of clustering methods, and building a set S_k of templates. An example of a set S_{10} (i.e. for k=10) of templates is given in Fig.1.

Minimizing the number of templates. The question arises, if a minimum k number of templates can be chosen, able to represent the whole population. For this purpose, a different MR image set was taken and its hippocampal regions HB_j were extracted both by the exhaustive procedure (giving HB_j^x) and using only the templates in sets S_k as the extraction tools, with k spanning from 3 to 20 and more (the result were boxes HB_j^k). We then defined a metric $D(HB_j^x, HB_j^k)$ based on the geometrical

[1]Medical Applications on a Grid Infrastructure Connection, http://www.magic5.unisalento.it

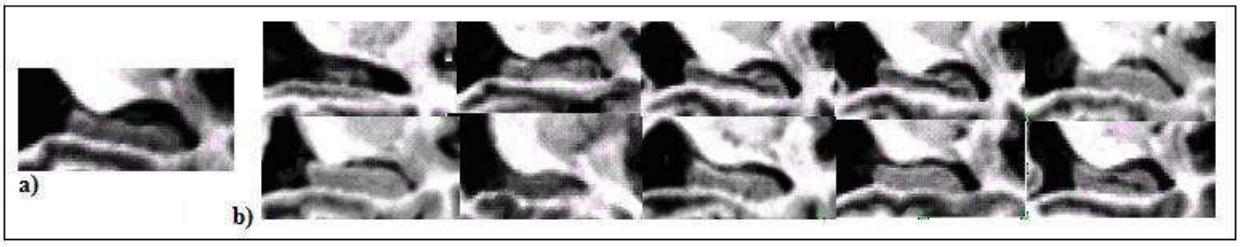

Figure 1. a) The initial hippocampal box (HB_0) from which the 'exhaustive' extraction started and b) Templates selected after clusterization for $k = 10$ (see text)

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position of the hippocampal regions, as follows:

$$D = \frac{1}{n}\sum_{j=1}^{n}\frac{1}{2}[dist(V_{j1}^x, V_{j1}^k) + dist(V_{j2}^x, V_{j2}^k)]$$

where V_{j1}^x and V_{j2}^x are two opposite vertices of the j-th (among n) HB extracted by the exhaustive procedure, V_{j1}^k and V_{j2}^k are the corresponding vertices for the j-th HB extracted by template set S_k, and *dist* is the Euclidean distance. The D parameter measures a mean distance of corresponding HB_s, extracted by the two alternative methods (exhaustive and template-driven). It is therefore a measurement of the accuracy of the template-driven procedure compared to the exaustive one (considered optimal). Fig.2 shows the D parameter versus k, for a dataset of 200 subjects with clinical conditions including normal subjects, and both Mild Cognitive Impairment (MCI) and AD cases. Two different clusterization methods (*k-means* and *hierarchical clustering*) are compared. We see that the D parameter is largely independent on the clusterization method. Moreover D(k) diminishes with increasing k, so we can chose a minimum k value, as a good compromise for describing the population variability, where D(k) becomes stable and 'sufficiently' low. This

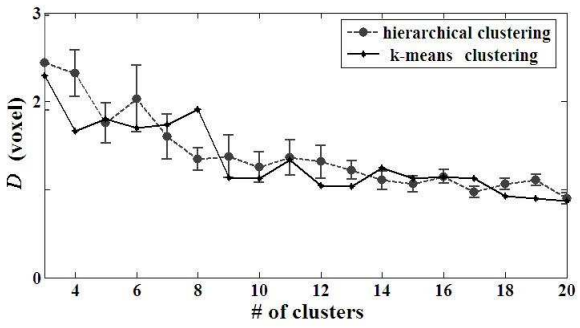

Figure 2. The D parameter versus the number k of clusters, for two different clusterization methods (hierarchical and k-means). The uncertainty on the value of D is shown for the hierarchical clustering only, as for the k-means method they are of the same order.

stability is generally achieved, for sample sizes of the order of hundreds, for k in the range 10 to 15. This gives an estimate of the minimum number of clusters able to describe the morphological variability of the whole sample for the extraction of the hippocampal region. The accuracy in extracting the regions depends only on the number of templates chosen to describe the population, which is lower for a population with homogeneous clinical conditions than with mixed degrees of neuropathology. We also checked that this procedure can be successfully applied to the extraction of other regions of interest in the brain. The results indicate that the inter-individual variability in the shapes of anatomical structures, as in the human brain, is captured by the template-set selection procedure: a promising approach to atlas generation.

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