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▶ **To cite this version:**

Nicolas Guizard, Vladimir Fonov, Bérengère Aubert-Broche, Daniel García-Lorenzo, Pierrick Coupé, et al.. Robust individual template pipeline for longitudinal MR images. MICCAI 2012 Workshop on Novel Biomarkers for Alzheimer's Disease and Related Disorders, Oct 2012, France. pp.231, 2012. <hal-00740708>

HAL Id: hal-00740708
https://hal.archives-ouvertes.fr/hal-00740708

Submitted on 11 Oct 2012

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Robust individual template pipeline processing for longitudinal MR images

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Abstract. Longitudinal measures of brain volume are powerful tools to assess the anatomical changes underlying on-going neurodegenerative processes. In different neurological disorders, such as in multiple sclerosis, Alzheimer's disease and Parkinson's disease, the neurodegenerative aspect may result in subtle anatomical brain changes before the appearance of clinical symptoms. Large longitudinal brain imaging datasets are now accessible to investigate such structural changes over time and to evaluate their use as biomarkers of prodromal disease. However, manual segmentation is long and tedious and although automatic methods exist, they are often performed in a cross-sectional manner where each visit is analysed independently. With such analysis methods, bias, error and longitudinal noise may be introduced. MR scanner noise and physiological effects can also introduce additional variability. Therefore, we developed a specific pipeline for longitudinal brain image analysis. To avoid any bias, an individual subject template is created and used as a reference within the pipeline. Then, the pair-wise deformation fields of each visit to the individual template are used to estimate the variation between individual time-points.

1 Introduction

Longitudinal measures of brain volumetry are powerful tools to assess the anatomical changes underlying on-going neurodegenerative processes. In different neurological disorders, such as multiple sclerosis (MS), Alzheimer's disease (AD) and Parkinson's disease (PD), brain atrophy has been shown to be a good surrogate marker of disease progression [1-3]. Magnetic resonance imaging (MRI) can provide reproducible 3D structural images of the brain, which can be used to assess its integrity. Furthermore, the emergence of freely available longitudinal MRI databases, (e.g., ADNI [4], OASIS [5]) provide the necessary data to develop and test new methods and investigate the longitudinal structural changes of healthy and pathological brains.

MRI-based neuro-anatomical studies are often performed in a cross-sectional manner where each time-point is evaluated independently. Typically, brain morphometry comparison can be done by matching paired images (template-to-

subject or subject-to-subject), where the deformation field is used to map atlas regions for ROI analysis, or for voxel-wise comparisons of anatomical changes such as deformation-based morphometry (DBM), or by segmenting anatomical structures from each individual visit independently. However, in the context of longitudinal datasets, the robust estimation of anatomical changes is still challenging [6].

Different approaches have been proposed to overcome the complexity of anatomical longitudinal data image analysis. In the context of clinical evaluation over a few years where anatomical changes are small and continuous, the use of 3D individual template targets have been proposed to perform non-linear registration [7]. Indeed, to compare anatomical differences, 3D population templates have proven their importance for different applications such as mapping (function, structure, vasculature, etc) [8], volume estimation [9] and group comparisons [10]. While different techniques exist to create unbiased population templates for cross-sectional studies [11-12], few of these techniques have applied for the creation of an individual subject 3D template. Reuter et al. created a 3D template for longitudinal analysis by computing the median of the rigidly registered subject images [7].

In this article, we propose a method to create an unbiased individual template from non-linear registration of the subject's visits. The method is evaluated using segmentations of the brain: lateral ventricles and hippocampi obtained by non-linear matching of the individual template to a population-specific template (i.e., an AD template), followed by a non-local patch-based segmentation technique. Inspired by the non-local means technique proposed by Buades et al. [13], the non-local patch-based segmentation uses the redundancy of similar regions from different subjects to identify and label corresponding local structure. This segmentation approach is inspired by the work of Coupe *et al.* [14], Eskildsen *et al*. [15] and Fonov *et al* [16].

2 Method

The pipeline developed in the context of longitudinal MRI segmentation consists of two parts (**Fig. 1**). In summary, the first steps of the pipeline are performed cross-sectionally (CS) or independently for each of the subject visits. Then the pre-processed data goes through a subject-specific pipeline which considers the subject visits as an ensemble to generate the unbiased individual template for the subject *i* first using linear registration to build a subject-specific linear template (SL) and then using non-linear registration to build a subject-specific non-linear template (SNL). The method is detailed in the following sections.

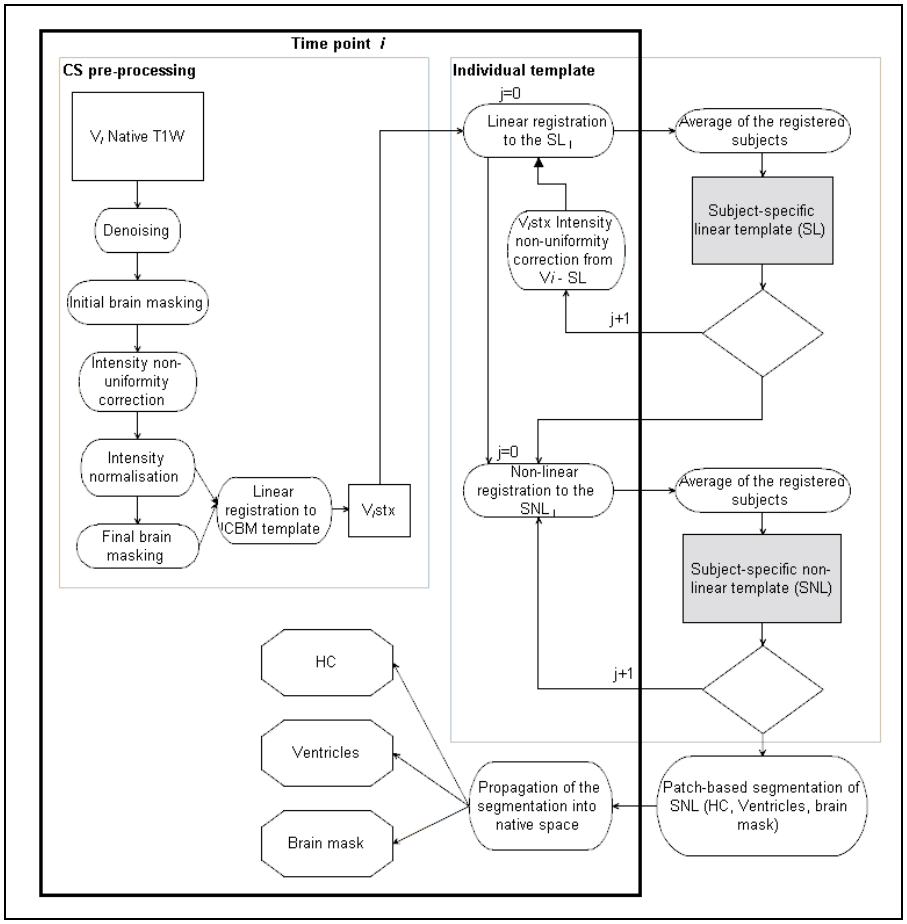

Fig. 1. Longitudinal pipeline. The different steps performed on each subject visits are represented in the left part of the diagram, where the processes in the left small square represents the cross-sectional (CS) part of the pipeline. The subject template creation (linear and non-linear) is represented in the right side of the figure.

2.1 Cross-sectional pre-processing

MRI denoising: to improve the performance of the pipeline, the redundancy of the image is used to remove the noise introduce during the MRI acquisition. The standard deviation of the MRI Rician noise is estimated automatically following [17]

Intensity non-uniformity correction and normalization: a non-parametric estimation of the slow varying non-uniformity field corrects the intensity inhomogeneity produce by scanner radio-frequency coil variations [18]. In addition, linear histogram matching is performed between each subject and a reference image (AD template) to normalize the image intensities between subjects/scans to a range between 0.0 and 100.0.

Stereotaxic space: to correct for variation in head position and orientation but to preserve the subject head size, an initial linear rigid registration (translation and rotation) is computed to bring each subject into the ICBM152 template stereotaxic space [19].

2.2 Subject specific pipeline

Individual template creation: The subject-specific template is based on the work of Guimond *et al.* and Fonov *et al.* [11-12, 20]. The template is created in two steps, first using linear registration and second, using non-linear registration:

- For each subject *i*, and each visit *j*, a hierarchical nine-parameter linear registration, based on an intensity cross-correlation similarity measure, is performed between the volume $V_{i,j}stx$ and the current linear template SL_i [19] and the first visit is used an initial target.
- Removal of the average transformation $\overline{T_i}$ for each subject transformation ($T_{i,j}$) to remove bias ($Tc_{i,j} = T_{i,j} \times \overline{T_i}^{-1}$).
- The new individual template is obtained by averaging each visit with their respective corrected transformations ($Tc_{i,j}$).
- To improve the inter-visit intensity inhomogeneity, at each iteration we compute the residual inhomogeneity field [18] of the difference image between the resampled visit and the subject template.

After creation of SL_i, the subject-specific linear template, the non-linear subject-specific template SNL_i is computed with a similar approach, but using non-linear registration, ANIMAL [9] (**Fig. 1**). The template SL_i is used as the target for the first iteration and the details of the hierarchical schedule is summarized in Table 1.

Iteration	*Step size (mm)*	*Blurring kernel (mm)*	*Neighbourhood size (mm)*	Local iterations
1-2	32	16	96	20
3-4	16	8	48	20
5-6	8	4	24	20
7-8	4	2	12	10
8-12	2	1	6	10

Table 1. ANIMAL non-linear registration schedule. For each iterations, we define a step size as the distance between control nodes for the free-form deformation recovered. The blurring kernel is the size of the full-width-half-maximum of the Gaussian kernel used to blur the source and target data. The local correlation which define the local similarity is estimated in the neighboorhood of diameter equals to the neighboorhood size parameter.

Template segmentation and propagation: The longitudinal pipeline applies the proposed methods of patch-based segmentation proposed initially by Coupé *et al.* [14] for hippocampus. then proposed for ventricles by Fonov *et al.* [16] and the whole brain by Eskildsen *et al.* [15]. In summery, based on the similarity of each patch of the SNL_i and its surrounding patches, to all patches of the library in a certain search volume, a label is attributed to the considered voxel. Experts manually segmented the different regions considered, however different cohorts were chosen therefore each segmentation is performed independently.

Once the SNL_i template is segmented, the non-linear deformations for each visit used to create the subject-specific template are then applied to transform the segmentations to each visit $V_{i,j}$ for the subject (**Fig. 2**).

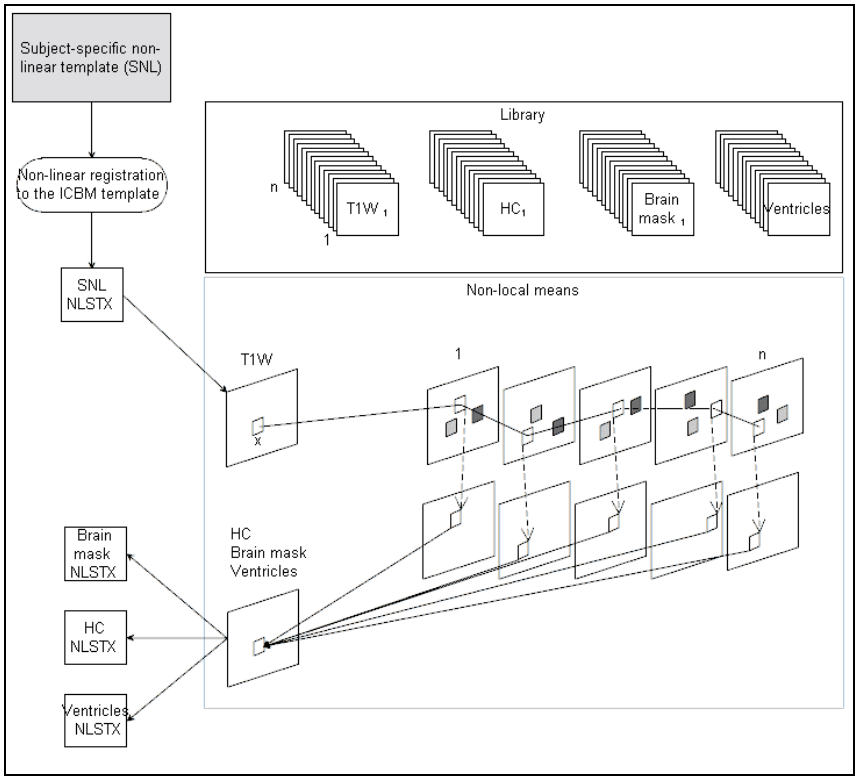

Fig. 2. Lateral ventricles, hippocampi and brain patch-based segmentation. The subject non-linear template is warpped into the ICBM template space to perform a non-local segmentation of the lateral ventricles, hippocampi and brain. The patch-based approach consists in finding the most similar voxels in a given neighbourhood of the T1W image library and then fuses the corresponding labels to create the segmentation of the different structures.

2.3 Data

The NIBAD challenge longitudinal data consists of T1W images (1.5x0.9375, 0.9375mm^3, 1.5T MRI scanner) of 46 patients with AD and 23 age-match controls scanned at 0, 2, 6, 12, 26, 38 and 52 weeks.

3 Results

Without a gold standard provided for the NIBAD challenge, it is impossible to measure the accuracy and precision of the proposed pipeline. However, the patch-based technique for anatomical region segmentation has been shown to yield good results compare to the state of the art. Figure 3 is a random selection of 5 subject non-linear templates with their corresponding brain, ventricles and hippocampi mask before propagation to the subject visits.

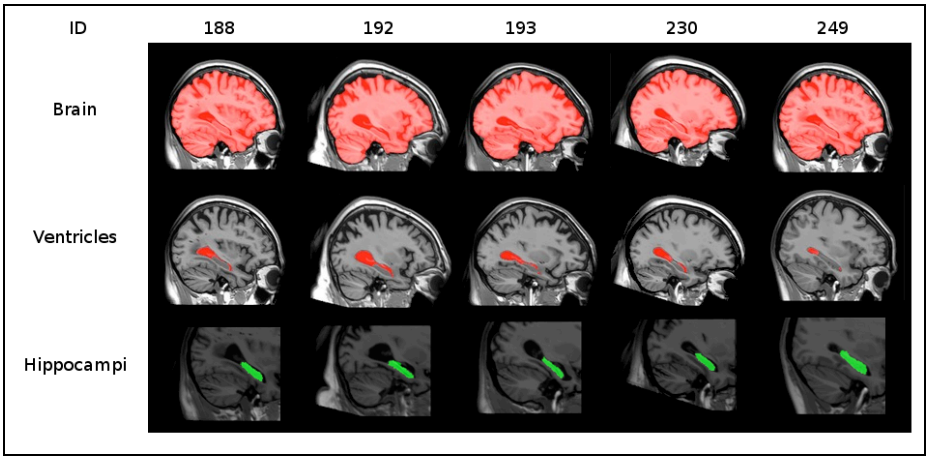

Fig. 3. Individual non-linear template brain, ventricles and hippocampi segmentation for subjects 188, 192, 193, 230 and 249.

4 Discussion and conclusion

The proposed pipeline with individual template creation in the context of longitudinal analysis provides accurate segmentation of brain, ventricles and hippocampi. Despite the lack of temporal information, the pipeline treats the ensemble of subjects first independently before creating a robust individual 3D template for segmentation, and therefore avoiding non-symmetric and/or non-transitive errors.

The patch-based technique for segmentation presents the advantage of being accurate and also it can produce multiple segmentations at once, if the pre-labeled library used as references contains more than one labeled structure. While the segmentation library used here has been created from different cohorts of subjects (e.g., ADNI,

ICBM, etc…), visual quality control of the NIBAD challenge data confirmed the accuracy of the segmentations.

In conclusion, our pipeline fulfills the requirements for the NIBAD challenge by providing brain, ventricles and hippocampi volumes and atrophies. All the longitudinal data completed the pipeline, including subjects with less conventional head positioning and poor quality acquisitions. If temporal information was provide, more sophisticated longitudinal regularization could improve the results by correcting for physiological, scanner physical variability, motion artifacts.

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