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CONSTRUCTION AND EVALUATION OF A QUANTITATIVE ARTERIAL SPIN LABELING BRAIN PERFUSION TEMPLATE AT 3T

Jan Petr[1−3]*, Jean-Christophe Ferré*[1−5]*, Elise Bannier*[5]*, Hélène Raoult*[4]*,*
Jean-Yves Gauvrit[1−5]*, Christian Barillot*[1−3,5]

[1]INRIA, VisAGeS Project-Team, F-35042 Rennes, France
[2] INSERM, U746, F-35042 Rennes, France
[3] University of Rennes I, CNRS, UMR 6074, IRISA, F-35042 Rennes, France
[4] Neuroradiology Dept., University Hospital of Rennes, F-35043 Rennes, France
[5] Neurinfo Platform, University Hospital of Rennes, F-35043 Rennes, France

ABSTRACT

Arterial spin labeling (ASL) allows non-invasive imaging and quantification of brain perfusion by magnetically labeling blood in the brain-feeding arteries. ASL has been used to study cerebrovascular diseases, brain tumors and neurodegenerative disorders as well as for functional imaging. The use of a perfusion template could be of great interest to study inter-subject regional variation of perfusion and to perform automatic detection of individual perfusion abnormalities. However, low spatial resolution and partial volume effects (PVE) issues inherent to ASL acquisitions remain to be solved. The purpose of this study is to enhance the template quality by using DARTEL non-rigid registration and by correcting for PVE. PICORE-Q2TIPS ASL datasets were acquired on 25 healthy volunteers at 3T. Four methods of creating the template were evaluated using leave-one-out cross correlation. Subsequently, these methods were applied to hyper-perfusion detection on functional ASL data of 8 healthy volunteers and compared with the standard generalized linear model (GLM) activation detection.

***Index Terms*—** arterial spin labeling, MRI, partial volume, functional MRI, atlases

1. INTRODUCTION

ASL is a completely non-invasive MRI method that measures brain perfusion by magnetically labeling blood in brain-feeding arteries. The labeled blood goes through the vascular system reaching the imaged slice where it exchanges with the tissue contributing to tissue magnetization. A standard echo-planar imaging (EPI) dataset (labeled image) is acquired at time *TI* (inversion time) after the labeling. A second EPI acquisition (control image) is repeated without any labeling RF pulse. The difference between labeled and control images reflects tissue perfusion [1].

Being non-invasive, ASL is especially well adapted for repetitive acquisitions and for studies on healthy volunteers [1]. The drawback of ASL is its low signal to noise ratio. The difference between labeled and control images generally lies between 1% and 2% of the control image magnitude. A single control/label subtraction is therefore not sufficient to assess perfusion and around 20 to 40 pairs of images usually need to be acquired to obtain reasonable signal-to-noise-ratio (SNR). At 1.5T, the random noise affects reproducibility of measurements more than within-subject variability [2]. The situation is improved using 32-channel coil at 3T. Nevertheless in order to obtain sufficient SNR in a practical acquisition time, the resolution in ASL images is kept low with pixel sizes between 3×3 and 4×4mm^2 and slice thickness between 5 and 8mm. Besides, ASL signal comes mainly from the gray matter tissue (GM). White matter (WM) perfusion is on average 3 times smaller than GM perfusion.The images are therefore severely affected by partial volume effects (PVE).

These low spatial resolution and partial volume effects are the main issues when creating a multi-subject template. The purpose of this study is three-fold:

- First, to assess the ability of DARTEL registration [3] to improve template quality as compared to standard SPM normalization to the ICBM template;
- Second, to evaluate the use of a partial volume correction algorithm to separate GM and WM contributions to perfusion by using the T1 GM/WM segmentation [4] and thus increase perfusion image resolution;
- Third, show a possible application for the template by detecting zones of hyper-perfusion.

The results are evaluated using leave-one-out cross-correlation to measure the difference between the perfusion image and its approximation using the template. The hyper-perfusion detection using the template is then tested on 8 additional functional ASL scans of healthy volunteers and compared with the standard GLM model.

2. METHODS

2.1. Image acquisition

Twenty five healthy volunteers gave written informed consent to be enrolled in this study (11 males, 14 females, mean age 31.6±8.3, median age 29, age range: 23–53). Data acquisitions were performed on a 3T whole-body MRI scanner

(Magnetom Verio, Siemens, Erlangen, Germany) using a 32-channel head coil. An anatomical 3D T1-weighted scan was performed using the following sequence parameters: field of view $256 \times 256\text{mm}^2$, acquisition matrix 256×256, 160 sagittal slabs, voxel size $1 \times 1 \times 1\text{mm}^3$, TR/TE 1900/2.98ms, flip angle 9° in an acquisition time of 4min 26s.

Multi-slice PASL acquisitions were performed using a PICORE Q2TIPS sequence. Nine slices were acquired with a 7mm slice thickness and an inter-slice gap of 0.7mm. The third slice was aligned with the AC-PC plane. The PICORE labeling slab of 100mm was positioned 29.5mm below the lowest imaged slice. Sixty one labeled and control images were acquired in an interleaved fashion using a single EPI sequence, with a $192 \times 192\text{mm}^2$ FOV, 64×64 acquisition matrix, $3 \times 3 \times 7\text{mm}^3$ voxel size, a TR/TE of 3000/25ms and a flip angle of 90°. Crusher gradients were used to reduce intravascular signal with speed exceeding 4cm/s [5]. Q2TIPS saturation pulse (700ms onset time, 800ms duration) was used to define the duration of the label in order for the quantification to be less sensitive to variations of blood arrival time over the whole brain [6]. The inversion time (TI) between the labeling pulse and the beginning of the readout was 1700ms for all subjects. The acquisition time was 3min 6s.

The sequence parameters for the functional ASL were similar to the ones described above, apart from the number of slices (8) and the TE (18ms). Using a block-design experiment, seven alternating 30s-phases of rest and right hand motor tasks were recorded. The first 3 images accounting for signal stabilization were discarded in the processing. The acquisition lasted 7min 12s to acquire 143 control and labeled images.

2.2. Preprocessing

Image processing was performed using MATLAB (MathWorks,Natick, MA) and the SPM8 Toolbox [7]. Motion correction of the control and labeled images was performed to compensate for unintentional subject movements using a six-parameter 3D rigid registration. All control and labeled images were aligned to the first control image using a sum-of-square-differences cost function. The mean control image was then co-registered with the T1-weighted image of the same subject by the means of a 3D rigid-body registration with normalized mutual-information cost function and NEWUOA optimization [8]. The inhomogeneity bias in the T1 images was corrected and the images were segmented to GM, WM and cerebro-spinal fluid (CSF) regions. The GM and WM partial-volume percentages for each pixel of the ASL images were calculated using this high-resolution tissue segmentation.

2.3. Perfusion quantification

A standard kinetic model [9] was used to quantify the perfusion from the measured data. The values of perfusion f in $ml/g\,min$ are given by

$$f = 3\frac{\lambda\,\Delta\,M\,e^{TI/T_{1a}}}{M_{T0}\,TI_w} \quad (1)$$

where λ is the blood brain partition coefficient ($\lambda = 0.98$), ΔM is the measured mean control-label subtraction in each pixel, T_{1a} is the T_1 of blood ($T_{1a} = 1664$ms), TI_w is the width of the bolus ($TI_w = 700$ms), TI is the inversion time ($TI = 1700$ms), and M_{T0} is the control-image value [10].

2.4. Spatial normalization

The GM/WM segmentation of each T1 image was used to align the T1 images to the ICBM-152 template [11] using the standard spatial normalization from the SPM8 toolbox [7]. There are several registration methods available all providing high precision results. Since our goal was not to compare them, we chose DARTEL registration for its convenient and public-available implementation. DARTEL registration was used to further increase the precision of the inter-subject co-registration [3]. This method takes all the segmented T1 images and aligns them to their mean GM/WM image. Then it iteratively recreates the GM/WM template and realigns the image of each subject to the template. The joint ASL/T1 and T1/template transformation was used to spatially normalize all the ASL images.

2.5. Partial volume correction

The measured value of perfusion $\Delta M(r)$ in pixel r is assumed equal to [4]

$$\Delta M(r) = P_{GM}(r)\Delta M_{GM}(r) + P_{WM}(r)\Delta M_{WM}(r), \quad (2)$$

where P_{GM} and P_{WM} are volume fractions of GM and WM; and ΔM_{GM} and ΔM_{WM} are the values of tissue-specific perfusion.

According to Asllani et al [4], the real tissue perfusion ΔM_{GM} and ΔM_{WM} can be assumed constant on a 3×3 pixel neighborhood. The perfusion values in each pixel are obtained by solving a system of 9 linear equations in the least-square sense. The partial volume corrected values obtained for GM and WM perfusion are then combined with the high-resolution segmentation yielding high-resolution perfusion maps. The drawback of this method is that the perfusion maps Δ_{GM}, Δ_{WM} are inherently smoothed by a 3×3 average filter. To overcome this limitation we used the method [12] that solves the Eq. 2 while minimizing the total variation of ΔM_{GM} and ΔM_{WM}.

2.6. Template evaluation framework

Four methods of template construction were evaluated. The templates were created as a mean of the 25 perfusion images after pre-processing, spatial normalization and partial volume correction:

- Template 1: perfusion images were spatially normalized to the ICBM template;

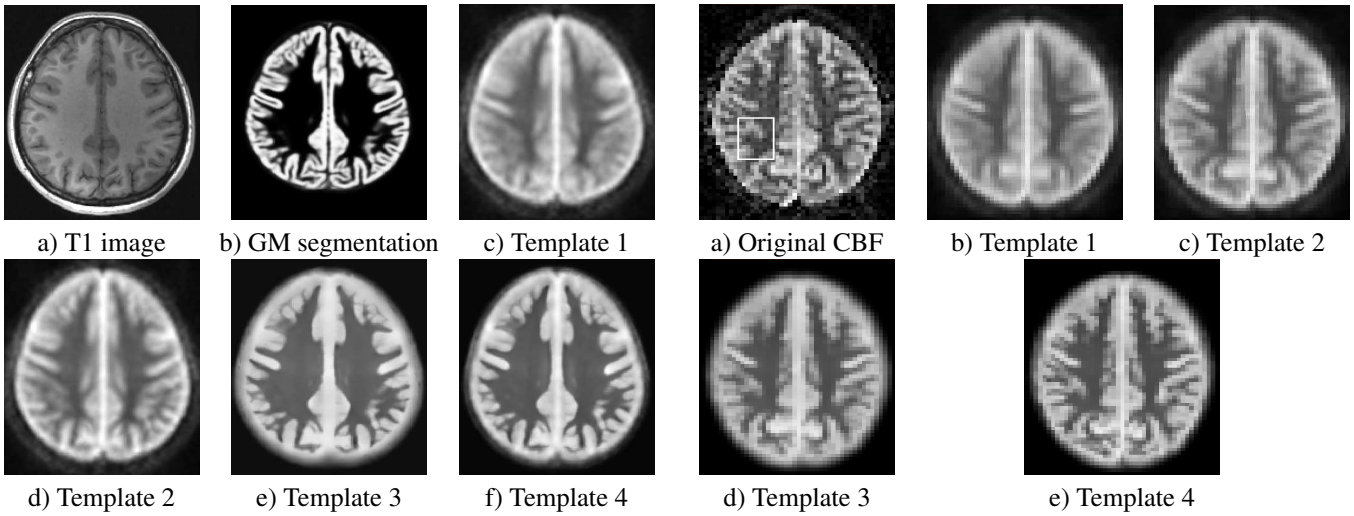


Fig. 1. *a)* T1 image of the first subject. *b)* Mean GM segmentation of all subjects. *c) – f)* Perfusion templates 1-4. The GM structures are distinctly blurred in *d)* and especially in *c)*. They appear more clearly in *e)* and *f)*. In *c)* and *d)*, there are several artifacts in the posterior part of the brain that are not apparent on the anatomical images. They were propagated by interpolation from the adjacent slices. The partial volume correction methods remove these artifacts as can be seen in *e)* and *f)*.

Fig. 2. *a)* Perfusion image of the first subject. *b)-e)* Templates 1-4 co-registered with the image *a)* and subsampled to the same resolution. In the first two templates, we can observe structures that are not in *a)* (marked by the white box in *a)*). These artifacts are caused by the low resolution of the ASL images and propagation of structures from adjacent slices by interpolation.

- Template 2: perfusion images were spatially normalized to the DARTEL template;
- Template 3: DARTEL normalization and simple partial volume correction [4];
- Template 4: DARTEL normalization and partial volume correction using total variation [12].

The values in each perfusion image were normalized by dividing by the mean perfusion in pixels with GM partial volume exceeding 70%. To assess the quality of the four templates they were inversely transformed to align them with the perfusion image of each subject. For each subject, the corresponding perfusion image was excluded from the template and only the 24 remaining subjects were used. The mean squared difference between the template and the perfusion image was calculated.

2.7. Functional ASL processing

The SPM software [7] was used to detect task related activated areas using the standard GLM model with convolution with the canonical HRF and statistical significance $p < 0.001$. Regions corresponding to primary motor and supplementary motor cortex were manually selected. For each subject, the activated ASL images were created by averaging only those images acquired during the phases of activity. This average activated image was aligned with the perfusion template and hyper-perfused areas were extracted by comparison with the template ($p < 0.001$). The same method was applied to assess the zones of hyper-perfusion on the set of 25 volunteers.

3. RESULTS

The qualitative comparison of the templates (Figure 1) shows blurred structures in the first template. The registration is improved by using the DARTEL registration with template 2. However there is still significant spatial blurring due to the interpolation of the low resolution ASL data. The partial volume correction compensates for this as shown on templates 3 and 4, where regions with different perfusion are much better delimited. The Figure 2 shows the low-resolution perfusion images of the first subject and the corresponding approximation using the template. Slight improvement of the GM structures is visible when using PVE correction with the total variation [12] over the standard correction [4]. Confirming qualitative observations, mean template SNR are 12.3 dB, 13.6 dB, 13.9 dB and 14.4 dB for template 1 to 4 respectively, as shown on Figure 3. The ratio of false detection of hyper-perfusion using the template measured on the 25 resting subjects was below 1% for all four templates. The group results with functional ASL show that the comparison enables to detect for templates 1 to 4, respectively 81.6%, 84.4%, 86.4%, 87% of the ground-truth primary motor cortex region obtained by standard GLM analysis. Percentages for the supplementary motor cortex were respectively 74.4%, 76.2%, 80.3% and 79.9%. In one subject, the supplementary motor cortex was not detected using the GLM model and this datasets was not taken into account (see Figure 4).

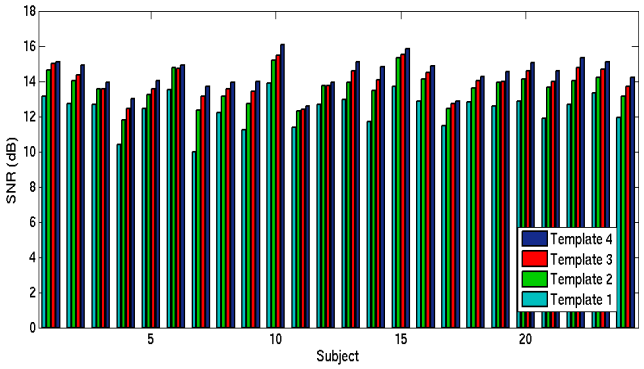


Fig. 3. Template/individual subject difference in SNR.

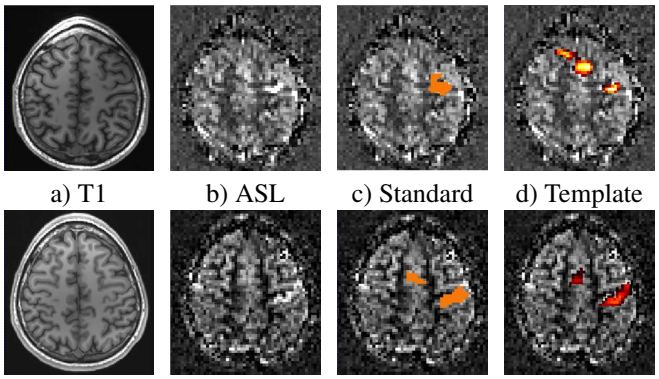


Fig. 4. Functional results for two subjects. *a)* Corresponding T1 slice; *b)* ASL image; *c)* activated regions obtained using standard GLM model; *d)* Hyper-perfusion regions detected with the use of the template. Notice that the supplementary motor cortex of the second subject is not detected in *c)*, however, it is clearly visible in *d)*.

4. DISCUSSION AND CONCLUSIONS

This study demonstrates how non-rigid registration and partial volume correction can be used to improve the quality of a brain perfusion template. We have shown that using prior knowledge on the perfusion spatial distribution does increase both visual quality and template precision. The use of a template on the functional ASL data proves that DARTEL registration and partial volume correction increase the ratio of hyper-perfusion zones detected. There are two hypothesis why the standard functional analysis produces slightly larger activation regions. First, the SPM method smooths the data with FWHM 6mm Gaussian kernel which can possibly enlarge the detected zones. Although it should be noted that recent developments in fMRI enable the analysis of spatially unsmoothed data. Secondly, the data analyzed using SPM contains both resting and activated phases where only the activated phase was compared to the template. Future work will focus on further increasing the quality of the perfusion template by using a more sophisticated method for intensity normalization.

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