

# Robust, Accurate and Automated Normalization of 3D Arterial Spin Labeling Brain Images

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**Introduction:** Arterial spin labeling (ASL) has been proven a useful technique both in clinical and research applications<sup>1</sup>. To compare the 3D images obtained from different subjects, it is a critical first step to transform the patients' perfusion images to a common space, frequently referred to as spatial normalization. Perfusion images are of low SNR in nature because its signals are around 1% of the brain tissue signals and the images may have variable signal from tissues and vessels of the scalp. To obtain good alignment with the template in a common space, ASL scans often require manual preprocessing, such as cropping of vessels and stripping of scalp signal. Aside from consuming time, the manual preprocessing may also introduce large alignment errors between subjects depending on the experience of analysts, and therefore may compromise the statistical results. Here, we seek for fully automatic image normalization tools to reliably transform routinely acquired ASL images from a large cohort to a common space.

**Methods:** Perfusion image normalization techniques can be divided into two categories: direct normalization and indirect normalization (using other MRI images). Due to the popularity of voxel-based morphometry (VBM), T1-based image normalization has been studied extensively and improved significantly. Indirect normalization taking advantage of improved T1 normalization may have great potential to provide robust automatic perfusion normalization. Direct nonlinear normalization from perfusion images with limited SNR to template images with high SNR may compromise the normalization quality.

We tested the performance of an indirect normalization method together with the two direct normalization methods on 146 ASL images from an elderly cohort study. For indirect normalization, the T1 images were first segmented by the "new segment" algorithm in SPM8, which outputs gray matter images and other images in the original image space; the 3D perfusion images from the subject were then co-registered (coregistration in SPM8) to the gray matter images using only linear transformations; finally the coregistered images were normalized to the SPM8 standard space by applying the transformation parameters from the gray matter images of the subject to the gray matter template in standard space (normalization in SPM8). For direct normalization, the 3D perfusion images were directly normalized to the PET and gray matter templates for comparison. For each normalization method, a batch script was used to automatically register all the ASL images to the standard space in SPM8 by inputting only subjects' IDs from a file. All the normalized ASL images were averaged for each normalization method. The sharpness of the 3D mean ASL image, calculated as sum of all gradient norms divided by num of pixels, was used to compare the performance of each normalization method. The larger the sharpness is, the better the image alignment from the different subjects is.

The perfusion images were acquired as a part of the Successful Aging after elective surgery (SAGES) study to investigate the potential cerebral damage associated with post-surgical delirium<sup>2</sup>. 146 elderly patients over 70 years old scheduled for elective surgical procedures were scanned at baseline. Pseudo-continuous arterial spin labeling (PCASL)<sup>3</sup> was used for labeling with 3.5 s labeling and 1.5 s post-labeling delay. A 3D stack of spirals RARE sequence was used to acquire PCASL images with 4 mm isotropic resolution. T1 images were acquired with a 3D MDEFT sequence (resolution of  $1 \times 1 \times 1.4 \text{ mm}^3$ ).

**Results & Discussions:** T1 image segmentation was successfully performed in all subjects without any user intervention. The mean PCASL images from indirect normalization showed clearer details than those from direct normalizations (e.g. the location indicated by arrows in Fig. 1). The sharpness of the normalized 3D mean PCASL images was 40.74 from indirect normalization, a 142% of increase from direct normalization to gray matter template (sharpness: 16.86) and a 20% increase from direct normalization to PET template (sharpness: 34.10). For direct normalization to the gray matter template, the registered ASL images did not converge successfully for 2/3 of subjects (98 out of 146). The unsuccessfully registered images shrank to the base of the brain, contributing to excessive signal in the inferior slices of the mean ASL image (Fig 1a). For direct normalization to the PET template, ASL images with bright vessels on the scalp were misaligned because the bright vessels were mistaken for the edge of the brain (Fig 2a). For indirect normalization, all the ASL images co-registered to the individual subject gray matter image successfully. The use of affine only transformation, a more subject specific template, and a robust mutual information maximization algorithm contributed to the registration robustness. The PCASL images acquired with RARE sequence, free of image distortion, might be an important contributor to the reliable registration. The indirect normalization procedure could be applied with DARTEL or FreeSurfer registration tools to further improve the normalization accuracy of ASL images.

We have proposed a reliable automatic normalization method for transforming the ASL images to the standard space, and also generated an elderly ASL perfusion template. We tested the template by directly registering all 146 ASL images to it and the sharpness of the mean ASL images is 40.45, suggesting its capability of generating similar registration quality even compared to the indirect normalization. The elderly perfusion template can serve as a template for elderly perfusion studies having no high-resolution T1 images available.

**References:** 1. Detre et al, JMRI, 2011;54:2066-2078. 2. Schmitt et al. J Am Med Dir Assoc. 2012;13(9):818.e1-10. 3. Dai et al, Magn Reson Med 2008;60(6):1488-97.

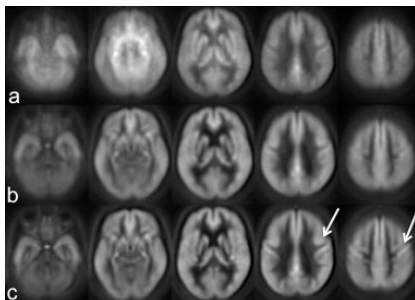


Fig. 1. Mean of the ASL images from 146 subjects in the SPM8 standard space registered using (a) direct registration to the gray matter template, (b) direct registration to the PET template, and (c) indirect registration using subjects' T1 weighted images. White arrows points to a couple of locations in (c) showing more ASL contrast than (a) and (b).

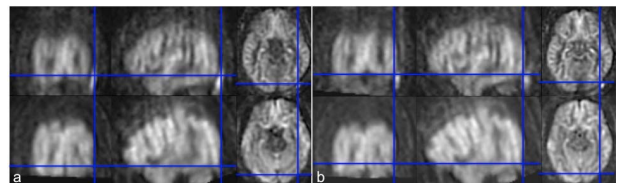


Fig. 2. ASL image alignment from a representative subject with bright vessel in skull (top) and a subject without bright vessels (bottom) using (a) direct registration to the PET template and (b) indirect registration.