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ASAP (Automatic Software for ASL Processing): A toolbox for processing Arterial Spin Labeling images

Virginia Mato Abad [a,*], Pablo García-Polo [b], Owen O'Daly [c], Juan Antonio Hernández-Tamames [a], Fernando Zelaya [c]

[a] Laboratorio de Análisis de Imagen Médica y Biometría (LAIMBIO), Universidad Rey Juan Carlos, Mostoles, Madrid, Spain
[b] M+Visión Advanced Fellowship, Medical Imaging Laboratory, Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain
[c] Department of Neuroimaging, Institute of Psychiatry, King's College London, London, United Kingdom

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ABSTRACT

The method of Arterial Spin Labeling (ASL) has experienced a significant rise in its application to functional imaging, since it is the only technique capable of measuring blood perfusion in a truly non-invasive manner. Currently, there are no commercial packages for processing ASL data and there is no recognized standard for normalizing ASL data to a common frame of reference. This work describes a new Automated Software for ASL Processing (ASAP) that can automatically process several ASL datasets. ASAP includes functions for all stages of image pre-processing: quantification, skull-stripping, co-registration, partial volume correction and normalization. To assess the applicability and validity of the toolbox, this work shows its application in the study of hypoperfusion in a sample of healthy subjects at risk of progressing to Alzheimer's disease. ASAP requires limited user intervention, minimizing the possibility of random and systematic errors, and produces cerebral blood flow maps that are ready for statistical group analysis. The software is easy to operate and results in excellent quality of spatial normalization. The results found in this evaluation study are consistent with previous studies that find decreased perfusion in Alzheimer's patients in similar regions and demonstrate the applicability of ASAP.

1. Introduction

Arterial Spin Labeling (ASL) has become a popular magnetic resonance technique for imaging brain function. It is entirely non-invasive and capable of quantitatively determining regional blood perfusion; providing therefore a significant advantage over contrast agent based methods like ^{15}O enriched H_2O Positron Emission Tomography (PET) or Gadolinium-based Dynamic Susceptibility Contrast Magnetic Resonance Imaging (DSC-MRI). The basic principle of ASL is to employ arterial blood water itself as contrast agent to measure perfusion. For cerebral blood flow (CBF) this is obtained by tagging a bolus of arterial blood in the region of the carotid arteries. The magnetization of inflowing blood water protons is inverted in that region by means of an external radiofrequency pulse, which is applied either as a short pulse (10–20 ms) or as a continuous or pseudo-continuous burst of radiofrequency (1–2 s) in the presence of a gradient. After a period of time (post-labeling delay), blood labeled with inverted signal is delivered to the entire brain through the smaller arteries and capillaries. This labeled arterial blood signal gives rise to a reduction in the image intensity when compared to a non-labeled (control) image. The control and labeled images are subtracted to generate a 'perfusion weighted' image. The intensity of each voxel will reflect the amount of arterial blood delivered in the inversion time; and through the use of a suitable model, the difference image is transformed to a map of CBF in conventional physiological units of ml blood/100 g tissue/min.

The availability of ASL as a routine method for assessment of basal CBF data has provided the possibility to examine brain physiology and generate a marker to probe functional differences between groups. ASL is increasingly used in clinical studies of cerebral perfusion and has shown its validity in measuring perfusion changes in several neurodegenerative diseases including Alzheimer's disease (AD) [1,2]; as well as in psychiatric studies [3], pharmacology [4] and pain [5]. However, to perform this type of analysis, multiple image processing steps are required: quantification, registration, normalization to a standard space, partial volume correction, etc.

Partial volume effects (PVE) are a consequence of limited spatial resolution in imaging and especially in ASL, where the low signal-to-noise (SNR) ratio leads to the need to employ larger voxels. In an effort to increase SNR, tissue specific saturation pulses are applied to the volume of interest to suppress the static tissue signal. This is known as 'background

* Corresponding author at: Universidad Rey Juan Carlos, Departamental II, Despacho 157, Campus de Móstoles, C/Tulipán s/n, 28933, Móstoles, Madrid, Spain. Tel.: +34 914888522.
E-mail address: virginia.mato@urjc.es (V. Mato Abad).

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suppression' and it is now used extensively in ASL [6]. Nevertheless, the change in the received signal due to blood water proton relaxation remains very small, such that voxels are typically of the order of 3 × 3 × 6 mm, generating the need to employ some form of PVE correction as each voxel is likely to contain signal mixing from different tissue types. Normal gray matter (GM) perfusion values are around 60 ml/100 g/min while white matter (WM) values are significantly lower (20 ml/100 g/min) [7]. Due to the relative insensitivity of ASL in white matter, the prime interest when using this technique is the study of pure GM perfusion. However, in voxels containing (for example) 50% GM and 50% WM, the CBF values could be underestimated by up to one-third. PVE is of paramount importance in the study of neurodegenerative diseases where GM atrophy significantly affects CBF quantification and therefore the comparison of patient data with control populations.

The absence of a standard approach for data processing has been partly driven by the fact that several ASL methodologies have evolved independently [8]. Therefore, there is no recognized standard for normalizing ASL data to a common frame of reference. This lack of a harmonized processing pipeline contributes to the potential discrepancies in studies of brain perfusion across different laboratories [9].

A number of packages, such as BASIL [10] and ASLTbx [11] provide a set of functions for pre-processing of ASL data and they both are free for academic use. BASIL consists of a collection of tools from the Functional Software Library (FSL) suite [12] that aid in the quantification and subsequent spatial processing of CBF images acquired with ASL. BASIL is based on Bayesian inference principles and was originally developed for ASL data acquired with several post-labeling delays (known as 'multi-TI' data). ASLTbx is a MATLAB [13] and SPM [14] based toolkit for processing ASL data, which requires basic MATLAB script programming.

These packages typically perform a step-by-step and subject-by-subject processing and require a large amount of manual operation. To date, a toolbox supporting a fully automated processing of raw ASL data, with minimum user intervention that can be used for effective comparison of group data, is not yet available.

In this article, we describe the development, implementation and test of an ASL processing toolbox (ASAP) that can automatically process several ASL datasets, from their raw image format to a spatially normalized, smoothed (if desired) version, with minimal user intervention. Ease of operation has been facilitated by a graphical user interface (GUI) whose operation is entirely intuitive. After the user sets the input/output and processing parameters using the GUI, the toolbox fully executes all processing steps for datasets of any number of subjects and results in data ready for second level statistical analysis. The data can be written in a variety of formats to facilitate its inclusion in several software packages for group analysis. The toolbox also has a facility to display the spatially normalized data in a manner that facilitates quality control by the user.

To assess the applicability and validity of the toolbox, we demonstrate its use in the study of hypoperfusion in a sample of healthy subjects at risk of progressing to Alzheimer's disease (AD).

2. Methods

2.1. Toolbox processing procedures

ASAP has been developed in MATLAB with the goal of simplifying the process of quantification and pre-processing of ASL studies. It includes functions like CBF quantification, skull stripping, co-registration, partial volume correction and normalization. Different processing strategies have been made available depending on user requirements:

(1) System requirements: ASAP is written in MATLAB under a Unix system (Linux or Mac OS) but it is not entirely a stand-alone utility. It accesses both FSL software and SPM libraries, which are two of the most widely available image processing platforms for MRI. These are invoked by the toolbox and are transparent to the user, but they must be installed independently by each user and added to the MATLAB path (including the FSLDIR environment variable). The software works equally well with earlier version of SPM or with the latest release (SPM-12).

(2) Input data: The ASL input data can be the raw difference image (control image − labeled image) or the perfusion image (CBF map). Regardless of the input or the ASL modality used, computation of the CBF map is made according to the formula proposed in the recent article "Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications" published by Alsop et al. [15]. For subsequent spatial co-registration and normalization, the user is able to choose between providing a high-resolution T1-weighted or T2-weighted structural scan. DICOM, NIfTI or ANALYZE formats are accepted.

(3) Resolution: The user can select between two different execution methods regarding the resolution of the images: the low-resolution native space of ASL or up-sampling the ASL images to the structural image high-resolution grid, typically of the order of 1 × 1 × 1 mm voxel size (acquisition matrix of 288 × 288 or 512 × 512 voxels with full brain coverage). The up-sampling is made by means of the spatial interpolation 'Nearest Neighbour', which preserves the gray values of the original voxel and ensures the consistency of CBF values. After the spatial normalization, the ASL voxel size is 2 × 2 × 2 mm, the resolution of the MNI template.

(4) Cerebral blood flow quantification: Due to the fact that most multi-TI ASL sequences are currently only available as experimental or prototype versions, the toolbox only includes CBF quantification for single inversion time data. In that case, the ASL difference image should be provided as input. The CBF quantification map is calculated using the formula currently recommended method [15]. In addition to the difference image, a reference proton density image and the postlabeling delay time employed are also required.

(5) Partial volume correction (PVC): ASAP provides the option of PVC of the ASL data. In its current version, two different methods are provided: (1) the method described by Asllani [16] and (2) a method based on a previous approached developed for PET that assumes perfusion of WM is globally 40% of that of GM for correction of resting CBF [17]. Although the later is a more simplistic approach and has been largely superseded by the methods introduced by Asllani and Chappell, this method (hereafter referred to as the PET correction) is available in our toolbox because it has been applied historically in earlier ASL studies [18–20]. Asllani's algorithm is based on linear regression and represents the voxel intensity as a weighted sum of pure tissue contribution, where the weighting coefficients are the tissue's fractional volume in the voxel. This algorithm is able to estimate the CBF for gray matter and white matter independently. The PET correction assumed that all contributions to perfusion are from brain tissue and that cerebrospinal fluid has no contribution. In that case, ASL intensities are corrected according to the following equation:

$$I_{corr} = I_{uncorr} / (P_{GM} + 0.4^{*} P_{WM})$$