Partial Volume Correction on ASL-MRI and Its Application on Alzheimer’s Disease Diagnosis*

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SUMMARY Arterial spin labeling (ASL) is a non-invasive magnetic resonance imaging (MRI) method that can provide direct and quantitative measurements of cerebral blood flow (CBF) of scanned patients. ASL can be utilized as an imaging modality to detect Alzheimer’s disease (AD), as brain atrophy of AD patients can be revealed by low CBF values in certain brain regions. However, partial volume effects (PVE), which is mainly caused by signal cross-contamination due to voxel heterogeneity and limited spatial resolution of ASL images, often prevents CBF in ASL from being precisely measured. In this study, a novel PVE correction method is proposed based on pixel-wise voxels in ASL images; it can well handle with the existing problems of blurring and loss of brain details in conventional PVE correction methods. Dozens of comparison experiments and statistical analysis also suggest that the proposed method is superior to other PVE correction methods in AD diagnosis based on real patients data.

key words: arterial spin labeling, magnetic resonance imaging, Alzheimer’s disease

1. Introduction

Alzheimer’s disease (AD), the most common form of dementia, is often diagnosed in patients over 65 years old and is generally regarded as one of the five most severe non-communicable diseases worldwide (i.e. others include cardiovascular disease, cancer, diabetes and chronic lung disease) by the WHO[1]. According to a population report published by the UN, there are already over 26.6M patients diagnosed with AD globally [2], and 1 in 85 worldwide people is predicted to suffer from AD by the year 2050 [3]. In China, the number of diagnosed AD patients by the year 2012 is nearly 10M, accounting for 1 in 18 of the whole population over 60 years old [4].

In order to diagnose patients with dementia, a variety of methods have been proposed and applied, including pathography analysis, cognitive examination, brain scanning. Pathography is helpful to shortlist curable symptoms of AD patients, who usually have other forms of diseases (e.g. stroke, heart disease, renal failure) simultaneously. Cognitive examination evaluates whether patients suffer from dementia through a series of tests based on their capabilities of short-memory, long-memory, cognition, execution, etc. Popular cognitive examinations include Mini-Mental State Examination (MMSE) [5] and Addenbrooke’s Cognitive Examination (ACE) [6]. However, the outcomes of those examinations are often far from being objective as patients’ education status could seriously bias examination results. Brain scanning is now widely acknowledged as an efficient and effective way in clinical diagnosis, and magnetic resonance imaging (MRI) is a powerful tool in contemporary dementia diagnosis. Compared with other widely adopted scanning tools such as Computed Tomography (CT) and Positron Emission Tomography (PET), MRI receives vast popularity globally as it is free of radiation exposure (regarding patients safety) and it becomes affordable to more and more patients. MRI can be generally categorized into structural MRI (sMRI) and functional MRI (fMRI), both of which have already been greatly adopted in dementia studies [7]–[9]. On the other hand, arterial spin labeling (ASL), which is an emerging MRI technique, has begun to attract increasing attention in the dementia domain in recent years [10], [11].

In this paper, the issue of diagnosing AD based on ASL-MRI images is addressed. The problem of partial volume effects (PVE) in ASL is emphasized, and a novel PVE correction method is proposed. ASL-MRI images after PVE correction via the introduced method are later utilized in AD diagnosis, and the superiority of the new correction method in AD diagnosis can be verified. The organization of this paper is as follows. In Sect. 2, principles of ASL and PVE are introduced. In Sect. 3, popular existing PVE correction methods are elaborated and their shortcomings are presented. A novel PVE correction method handling those existing problems is proposed. In Sect. 4, dozens of experiments are conducted. ASL-MRI images after applying the proposed PVE correction method as well as several conventional PVE correction methods are adopted with a number of supervised and unsupervised pattern recognition approaches in differentiating dementia progress stages based on data extracted from 360 real patients. In Sect. 5, the conclusion of this study is drawn.
2. Arterial Spin Labeling and Partial Volume Effects

ASL is an emerging fMRI technique. Compared with other conventional fMRI techniques such as BOLD, ASL requires no injection of external contrast enhancement agent on patients while being scanned. Thus, ASL becomes more favored nowadays regarding patients safety issues. An ASL-MRI image is often produced by two kinds of images: a label image and a control image. Their acquisition steps and examples are illustrated in Fig. 1. The yellow region (2 in Fig. 1-a) and the green region (4 in Fig. 1-b) denote the same region-of-interest (ROI) in which ASL-MRI images would reflect. The purple region (1 in Fig. 1-a) represents an area where water molecule of arterial blood is magnetically labeled via a 180 degree radio frequency (RF) inversion pulse. In other words, water molecule within the arterial blood is utilized as the “tracer” instead of injected contrast agent. Label images are taken when paramagnetic tracer flows into ROI and example label images are shown in Fig. 1-a. For control images, there is no RF inversion pulse in the same area (3 in Fig. 1-b) and control images are taken at the same ROI. After label and control images are acquired, ASL-MRI images are obtained using control images minus label images, and ASL signal on each voxel is also proportional towards the cerebral blood flow (CBF) on that voxel. An example of ASL-MRI images is illustrated in Fig. 1-c. The plotting scale unit of example images in Fig. 1 is [mL/(100g*min)]. Generally speaking, brain atrophy can be observed in certain brain regions of dementia patients, making CBF of those regions lower than that of ordinary people. Hence, ASL signal proportional towards CBF can be utilized as an indicator for dementia diagnosis.

In Fig. 1, it can also be observed that, the spatial resolution of ASL-MRI images is not high, and voxel heterogeneity as well as signal cross-contamination are serious in ASL-MRI images. Those problems will bring about partial volume effects (PVE) in ASL-MRI images. Generally speaking, PVE is defined as the loss of apparent activity in small objects because of the limited resolution of an imaging system. In ASL-MRI images, since the spatial resolution is not high, each voxel containing gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) is likely to be assigned underestimated ASL signal, resulting in lower CBF (i.e. loss of apparent activity). Therefore, in order to make ASL-MRI images usable in AD diagnosis, PVE should be corrected first.

3. A Novel PVE Correction Method

Recently, there are several research efforts proposed to correct PVE, and the linear regression-based method in [12] is among the most popular studies. The problem of PVE correction can be represented as follows. Provided a voxel $i$ in an ASL-MRI image, the control magnetization $M_C$ and label magnetization $M_L$ of voxel $i$ can be calculated as:
A regression matrix $P$ for PVE correction. After correction, the ASL signal of CSF tissue volume on voxel $i$ can be obtained from brain tissue segmentation in a preprocessing step on ASL-MRI images. MC could be obtained from brain tissue segmentation in a pre-processing step, and $\triangle M$ in Eq. (3)) and its calculated value (e.g., the right part of Eq. (3)) computed using unknowns $M_{GM}^C, M_{WM}^C$ and $M_{CSF}^C$ under specific constraints, So Eq. (3) can be formulated via the following two constrained optimization problems:

$$
\frac{\triangle M}{M_C} = \frac{M_C - M_L}{M_C} = \frac{P_{GM} \cdot \triangle M_{GM} + P_{WM} \cdot \triangle M_{WM}}{P_{GM} \cdot M_{GM}^C + P_{WM} \cdot M_{WM}^C + P_{CSF} \cdot M_{CSF}^C}
$$

In order to deal with the above problems in contemporary methods, a novel PVE correction method based on individual pixel-wise voxels is proposed. Equations (1) & (2) are first re-written as:

$$
\frac{\triangle M}{M_C} = \frac{M_C - M_L}{M_C} = \frac{P_{GM} \cdot \triangle M_{GM} + P_{WM} \cdot \triangle M_{WM}}{P_{GM} \cdot M_{GM}^C + P_{WM} \cdot M_{WM}^C + P_{CSF} \cdot M_{CSF}^C}
$$

where, $\triangle M$ represents the difference between control $M_C$ and label $M_t$ magnetization. The general purpose is to minimize the difference between observed value (e.g., $M_C$ and $\triangle M$ in Eq. (3)) and its calculated value (e.g., the right part of Eq. (3)) computed using unknowns $M_{GM}^C, M_{WM}^C$ and $M_{CSF}^C$ under specific constraints, So Eq. (3) can be formulated via the following two constrained optimization problems:

$$
\text{arg min}_{i=1}^N ||M_{C,i} - P_{GM} \cdot M_{GM}^C - P_{WM} \cdot M_{WM}^C - P_{CSF} \cdot M_{CSF}^C||^2
$$

s.t. $M_{CSF}^C \geq M_{GM}^C \geq M_{WM}^C$ (4)

$$
\text{arg min}_{i=1}^N ||\triangle M_t - P_{GM} \cdot \triangle M_{GM} - P_{WM} \cdot \triangle M_{WM}||^2
$$

s.t. $\frac{\triangle M_{GM}}{M_{GM}^C} \geq \frac{\triangle M_{WM}}{M_{WM}^C}$ (5)

where, $i$ denotes the $i^{th}$ ASL-MRI image obtained from a repeated scanning process (usually implemented in clinical diagnosis to enhance the SNR of ASL-MRI images); constraints in Eqs. (4) & (5) are based on clinical knowledge of brain tissues [13, 14]. Equations (4) & (5) are solved via methods of split-Bregman [15] and Lagrange multipliers. Detailed steps are illustrated in Table 1.

Table 1 is made up of two folds. The first one is to solve for control magnetization of different tissues (Outputs 1) via Steps 1 to 3. In each step, one unknown is separated from the rest via the split-Bregman method, and Lagrange multiplies $\lambda$ are incorporated to form a typical quadratic programming (QP) problem. To solve the QP problem in each step, an interior point method is applied. Iterations from
MRI images, and 23 ASL-MRI images of the same ROI are acquired consecutively for each patient to improve the SNR of ASL. Other acquisition parameters are: labeling duration = 1500 ms, post-labeling delay = 1500ms, TR/TE = 4000/9.1ms, voxel size = 3 × 3 × 5mm³. High-resolution MPRAGE images are also acquired for all patients. After image acquisition, motion correction was applied on raw ASL-MRI before the subtraction between control and label images. MPRAGE was segmented into GM/WM/CSF (probability maps are obtained therein) and registered onto ASL-MRI images via SPM8 software [16].

4. Experiments and Analysis

4.1 Data Description and Pre-Processing

In order to demonstrate the superiority of the newly proposed PVE correction method over other methods, real patient data obtained from an ongoing population study, which is currently conducted in Nanchang University and its affiliated hospitals, is utilized. Informed consent is obtained from all patients for research purpose. There are totally 360 patients in the current dataset, including 120 AD patients, 120 mild cognitive impairment (MCI) patients, and 120 no cognitive impairment (NCI) patients as normal control. The average age of patients is 70.56 ± 7.20 years. A SIEMENS 3T TIM Trio MR scanner is utilized to acquire their ASL-MRI images, and 23 ASL-MRI images of the same ROI are acquired consecutively for each patient to improve the SNR of ASL. Other acquisition parameters are: labeling duration = 1500 ms, post-labeling delay = 1500ms, TR/TE = 4000/9.1ms, voxel size = 3 × 3 × 5mm³. High-resolution MPRAGE images are also acquired for all patients. After image acquisition, motion correction was applied on raw ASL-MRI before the subtraction between control and label images. MPRAGE was segmented into GM/WM/CSF (probability maps are obtained therein) and registered onto ASL-MRI images via SPM8 software [16].

4.2 Experiments and Analysis on PVE Correction Using Multiple Patients Data of Single Resolution

As introduced in Sect. 2, ASL-MRI images suffering from PVE will likely to bring about under-estimated CBF results, hence more effective correction methods could improve under-estimated CBF results better. The newly proposed PVE correction method (denoted as “New”) is compared with contemporary regression-based method (denoted as “RB”) [12] regarding CBF calculated from corrected ASL-MRI images. Sizes of neighbors implemented in RB include 5 × 5, 9 × 9, and 15 × 15 (denoted as “RB-5”, “RB-9”, and “RB-15”, respectively). Figure 3 illustrates boxplots depicting statistical distribution of CBF obtained by different PVE methods based on overall patients data (i.e., left figure of 1st row), AD patients data (right of 1st row), MCI patients data (left of 2nd row) and NCI patients data (right of 2nd row). In each box, a red horizontal line across each box represents median of CBF obtained by one individual method, while upper and lower quartiles of CBF are depicted by blue lines above and below the median in each box. A vertical dashed line is drawn from the upper and lower quartiles to their most extreme data points, which are within a 1.5 inter-quartile range (IQR). Each data point beyond ends of...
Fig. 3 Boxplot of CBF obtained via different PVE correction methods on overall patients data (left of 1st row), AD patients data (right of 1st row), MCI patients data (left of 2nd row), and NCI patients data (right of 2nd row).

Table 2 Multiple comparison test of all methods on CBF results based on all patients data.

| Method I | Method II | CBF Mean Diff (I-II) | A 95% Conf Int of CBF Mean Diff |
|----------|-----------|----------------------|---------------------------------|
| New      | RB-5      | 7.4797               | [5.3766, 9.5827]                |
| New      | RB-9      | 4.3904               | [2.2873, 6.4935]                |
| New      | RB-15     | 2.5758               | [0.4727, 4.6789]                |

Table 3 Multiple comparison test of all methods on CBF results based on AD patients data.

| Method I | Method II | CBF Mean Diff (I-II) | A 95% Conf Int of CBF Mean Diff |
|----------|-----------|----------------------|---------------------------------|
| New      | RB-5      | 10.1406              | [3.4070, 16.8742]               |
| New      | RB-9      | 7.4409               | [0.7072, 14.1745]               |
| New      | RB-15     | 5.5938               | [-1.1398, 12.3274]              |

Table 4 Multiple comparison test of all methods on CBF results based on MCI patients data.

| Method I | Method II | CBF Mean Diff (I-II) | A 95% Conf Int of CBF Mean Diff |
|----------|-----------|----------------------|---------------------------------|
| New      | RB-5      | 7.7955               | [4.9419, 10.6491]               |
| New      | RB-9      | 4.6873               | [1.8337, 7.5409]                |
| New      | RB-15     | 2.8549               | [0.0013, 5.7085]                |

Table 5 Multiple comparison test of all methods on CBF results based on NCI patients data.

| Method I | Method II | CBF Mean Diff (I-II) | A 95% Conf Int of CBF Mean Diff |
|----------|-----------|----------------------|---------------------------------|
| New      | RB-5      | 6.2709               | [2.8536, 9.6882]                |
| New      | RB-9      | 3.0961               | [-0.3213, 6.5134]               |
| New      | RB-15     | 1.3157               | [-2.1016, 4.7331]               |

above tables provide two kinds of evaluation, one is a single-value estimation which is the CBF mean difference (using Method I minus Method II), the other is an interval estimation which implies an interval that the previous single-value estimation is likely to fall into (over 95% confidence). It can be noticed that, major entries in Tables 2 to 5 are positive, which is a strong indication that the newly proposed method can improve CBF better compared with other conventional methods. Although negative values exist in some
4.3 Experiments and Analysis on PVE Correction Using Single Patient Data of Multiple Resolutions

In this section, another series of experiments is conducted to demonstrate the superiority of the new voxel-wise PVE correction method using single patient data of multiple ASL resolutions. The motivation of experiments is described as follows. Since PVE in original ASL images is often inevitable because of their limited spatial resolution and severe signal cross-contamination, it is often hard to obtain absolutely “clean” ASL images totally without PVE as “golden standard” for evaluating PVE correction performance. However, it is also acknowledged that ASL images of lower spatial resolution (e.g. voxel size of $3\times3\times5\, mm^3$ in this section) will suffer from more severe PVE than ones of higher spatial resolution (e.g. voxel size of $2\times2\times5\, mm^3$ in this section), because voxel heterogeneity and signal cross-contamination in the former are obviously more serious. Thus, CBF as well as its corresponding ASL signal will become lower in ASL images of lower spatial resolution. Hence, a series of experiments are designed in this section to use ASL images of higher resolution as the pseudo-“golden standard” (in fact containing less PVE), and ASL images of lower resolution from the same patient as original images for PVE correction. Correction methods providing correction results as close as possible towards the pseudo-“golden standard” will become superior.

Figures 4 and 5 demonstrate two plots with comparisons of ASL signal $\frac{\Delta M_{GM}}{M_{GM}}$ in GM calculated from correction results using different PVE correction methods on one patient. Figure 4 is regarding a low resolution $3\times3\times5\, mm^3$ and a high resolution $2\times2\times5\, mm^3$ as the pseudo-“golden standard”, while Fig. 5 is regarding a much lower resolution $4\times4\times5\, mm^3$ and the same high resolution $2\times2\times5\, mm^3$ of the same patient. In each figure, the x-axis represents ASL signal of the high resolution, while the y-axis denotes ASL signal of the low resolution. Hence, a dot in each plot indicates a single voxel with its original ASL signal in high-resolution (revealed by its x-coordinate) and its corrected ASL signal in low-resolution (suggested by its y-coordinate). Different lines are generated in each plot to linearly fit correction results obtained by different compared correction methods, and their gradients can disclose which one is the closest towards the pseudo-“golden standard” (illustrated by a cyan line in each plot). It can be observed in Figs. 4 and 5 that, fitting lines produced by correction results via the new method is higher than the conventional regression-based method. Similar results can be observed in other 30 patients scanned using multiple ASL resolutions as well in our database. Thus, the superiority of the new PVE correction method can also be revealed by single patient data of multiple ASL resolutions.

4.4 Experiments on AD Diagnosis Using Corrected ASL Images

AD diagnosis capability based on PVE corrected results from Sect. 4.2 is further evaluated using several popular supervised/unsupervised pattern recognition tools. Mean $M_{GM}^C$ and mean $M_{GM}^L$ extracted from hippocampus, parahippocampal gyrus, putamen, and thalamus comprise 8-dimensional feature. Linear regression (LR), k-means clustering (K-means), support vector machine (SVM), and ranking SVM (rSVM) are incorporated as pattern recognition tools for dementia diagnosis using the above feature extracted from corrected ASL images obtained by different correction methods. The whole dataset is equally divided into 6 subsets, and a 6-fold cross validation strategy is utilized to conduct experiments. For supervised methods (i.e., LR, SVM, rSVM), 5 subsets are used for learning parameters within each supervised method (e.g. regression coefficients in LR, Gaussian width in RBF kernel of SVM and rSVM) and 1 subset is used for testing purpose in each fold. For unsupervised methods (i.e. K-means), testing is con-
duced directly. Statistical dementia diagnosis results based on corrected ASL-MRI images obtained by different correction methods are summarized in Table 6. It can be concluded that the newly proposed method can guarantee highest diagnosis precision in 3 out of 4 pattern recognition tools, which is superior to others.

5. Conclusions

A novel PVE correction method for ASL-MRI images is introduced for the first time in this paper. The newly proposed PVE correction method is different from other conventional PVE correction methods as: (1) multiple MRI slices repeated acquired within one MRI sequence are adopted for PVE correction for one patient, instead of one single MRI slice to be utilized in conventional PVE methods; (2) prior information from the perspective of medicine is incorporated as optimization constraints for PVE correction in our newly proposed method. The main contribution of this study resides in this newly proposed method, as well as demonstrating its superiority over compared methods in both PVE correction and the dementia diagnosis application. Future efforts will emphasize more sophisticated dementia diagnosis strategies on corrected ASL-MRI images using the introduced PVE correction approach.

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