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# Patch-Based Super-Resolution of Arterial Spin Labeling Magnetic Resonance Images

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## Abstract

Arterial spin labeling is a magnetic resonance perfusion imaging technique that, while providing results comparable to methods currently considered as more standard concerning the quantification of the cerebral blood flow, is subject to limitations related to its low signal-to-noise ratio and low resolution. In this work, we investigate the relevance of using a non-local patch-based super-resolution method driven by a high resolution structural image to increase the level of details in arterial spin labeling images. This method is evaluated by comparison with other image dimension increasing techniques on a simulated dataset, on images of healthy subjects and on images of subjects diagnosed with brain tumors, who had a dynamic susceptibility contrast acquisition. The influence of an increase of ASL images resolution on partial volume effects is also investigated in this work.

*Keywords:* MRI, Arterial Spin Labeling, Super-Resolution, Denoising, Partial Volume Effects

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## 1. Introduction

2 Cerebral perfusion corresponds to the delivery of nutrients and oxygen to  
3 brain tissues. Its assessment is important for clinicians, as it has been shown  
4 that abnormal perfusion patterns are often the causes or consequences of  
5 pathologies [1].

6 Arterial spin labeling (ASL) is a non-invasive magnetic resonance (MR) imag-  
7 ing technique that quantitatively evaluates this perfusion. Radio frequency

8 inversion pulses are applied to the blood water protons flowing through the  
9 neck of the imaged subject. After a certain amount of time left for these  
10 labeled protons to reach the brain, called the post-labeling delay (PLD), an  
11 image is acquired, which is called the labeled image. The difference between  
12 this image and a control image, acquired without the labeling step, is propor-  
13 tional to brain perfusion. The cerebral blood flow (CBF) can be quantified  
14 from this perfusion image [4, 5]. Recommendations regarding ASL image ac-  
15 quisitions have been formulated by a consortium in the ASL "white paper"  
16 [6].

17 While very promising in some aspects, ASL is, however, still subject to a  
18 number of limitations. Indeed, fast acquisition techniques such as echo plan-  
19 nar imaging (EPI) are required to image the dynamic process of the labeled  
20 protons circulation, which generate low resolution and low signal-to-noise  
21 ratio (SNR) images. For that reason, multiple label and control pairs are  
22 usually acquired and averaged. However, this makes ASL subject to new  
23 potential corruptions, such as movement artifacts and the introduction of  
24 outlier intensity values. Moreover, small subject motion and the low resolu-  
25 tion of the images involve the introduction of partial volume effects (PVE),  
26 meaning that perfusion of different tissues contribute to the perfusion signal  
27 observed in a single image voxel.

28 Several post-processing algorithms have been proposed to deal with these  
29 limitations. Particularly, denoising methods are successfully applied to deal  
30 with artifacts and outliers in ASL images [7, 8, 9, 10]. PVE correction al-  
31 gorithms have also been proposed and investigated in [11, 12, 13]. These  
32 methods have in common to be applied at the resolution of the acquired  
33 images. While attenuating the effect of the previously listed corruptions,  
34 they do not allow to increase the level of details in images. However, this  
35 aspect could be of great interest, the thickness of grey matter (GM) being  
36 often inferior to the size of the ASL images voxel size. In clinical conditions,  
37 acquiring ASL images at higher resolutions is a challenging task, since this  
38 would imply a decrease in SNR, or increase the acquisition time.

39 Various methods have been proposed in order to increase the resolution of  
40 MR images facing similar low resolution properties, such as T2-weighted and  
41 diffusion images, as a post-processing step. Interpolation methods can be  
42 applied to MR images (trilinear interpolation, B-splines), unfortunately re-  
43 sulting in blurred images. To overcome this aspect, super-resolution (SR)  
44 approaches allow to reconstruct high frequency information from low reso-  
45 lution data. Some of these methods are based on multiple low resolution

46 acquisitions, therefore requiring specific acquisition protocols, which can be  
 47 time consuming [14]. Recently, [15, 16, 17] have adapted and extended non-  
 48 local patch-based SR approaches that are independent of the acquisition  
 49 process to the MRI domain. The main idea consists in using self similarities  
 50 in the images to perform reconstructions at higher resolutions [18]. These  
 51 methods can be applied to data commonly acquired in clinical conditions,  
 52 such as T2-weighted or diffusion weighted images, thus preventing any in-  
 53 crease in the acquisition time. A first application of this kind of method  
 54 to pseudo-continuous ASL (pCASL) images has been proposed in [19]. The  
 55 main limitation of these methods is that they require clean low resolution  
 56 data as inputs, which means that denoising algorithms must first carefully  
 57 be applied to the images prior to SR reconstruction.

58 In this paper, we propose a novel method to increase the resolution of ASL  
 59 images, which deals with the presence of noise. This non-local patch-based  
 60 SR reconstruction approach is based on the assumption of appearing simi-  
 61 larities between neighborhoods in the image that is reconstructed and a high  
 62 resolution (HR) structural image, generally acquired in imaging protocols.  
 63 This aspect allows to increase the resolution of ASL images without extend-  
 64 ing the acquisition time. The proposed method is evaluated on a simulated  
 65 dataset and images of healthy subjects in order to investigate its capacity to  
 66 reconstruct images close to HR ASL references. As DSC is commonly con-  
 67 sidered as a reference perfusion imaging technique, we investigate the ability  
 68 of our method to generate images closer to the DSC quantitative maps on  
 69 images acquired on subjects diagnosed with brain tumors. In addition, we  
 70 investigate the influence of a recovery of HR details on PVE.

71 The material and methods are presented in section 2, results regarding com-  
 72 parisons between generated images and reference HR ASL or DSC maps in  
 73 section 3, an evaluation of the influence of the SR reconstruction on PVE in  
 74 section 4 and a discussion of these aspects in section 5.

## 75 2. Materials and Methods

### 76 2.1. Summary of existing similarity-based SR methods

77 The objective of super-resolution methods is to recover an unknown high  
 78 resolution (HR) image  $x$  from a low resolution acquired one  $y$ . The following  
 79 model explicit the relation between both images :

$$y = Mx + \eta, \tag{1}$$

80 with  $M$  a matrix representing subsampling, blurring and geometric transfor-  
 81 mations, and  $\eta$  representing some additive noise [18, 15, 16, 17]. An optimiza-  
 82 tion problem of the following form would correspond to a common approach  
 83 to recover the unknown image  $x$ :

$$\tilde{X} = \arg \min_x \{ \|y - Mx\|_2^2 + \gamma\Phi(x) \}, \quad (2)$$

84 where  $\Phi$  is a regularization term necessary to solve this ill-posed mini-  
 85 mization problem and  $\gamma$  a positive parameter.

86 As shown in [16] and [17], an iterative reconstruction-correction procedure  
 87 can be adopted in order to reconstruct  $x$ , which allows to avoid problems  
 88 such as local minima or parameters initialization linked to this ill-posed op-  
 89 timization problem. This procedure consists in two steps, corresponding to  
 90 a reconstruction and a subsampling consistency constraint.

91 The reconstruction is based on the assumption that locations in a HR ac-  
 92 quired structural image and the SR reconstructed one should share anatomi-  
 93 cal properties, and that the structural image could therefore be used to drive  
 94 the reconstruction process. This assumption leads to the choice of non-local  
 95 regularization approaches, such as in [16] and [17].

96 The subsampling consistency imposes the constraint of a strict equality be-  
 97 tween the downsampled version of the SR reconstructed image and the orig-  
 98 inal low resolution image  $y$ , which is made possible by formulating strong  
 99 assumptions about the  $M$  matrix composition. However, this constraint im-  
 100 plies the need for well denoised low resolution images for the method to be  
 101 consistent. Therefore, Coupé et al. [17] proposed to apply a Rician-adapted  
 102 denoising filter on diffusion images before solving the optimization problem.  
 103 In the case of low signal-to-noise ratio ASL images, different noise patterns  
 104 can be introduced regarding the scanners, sequences or settings chosen to  
 105 perform the acquisition. The use of parameters that could not be the most  
 106 appropriate ones in the filtering step, could have important consequences  
 107 regarding the quality of the final reconstructed image. This is the reason  
 108 why we introduce a reconstruction driven by a HR structural image, while  
 109 denoising the SR reconstructed image at the same time.

## 110 *2.2. A new SR method for ASL images*

111 The main objective of this work is to assess the relevance of using a HR  
 112 anatomical image to increase the resolution of ASL images. This assumption  
 113 of shared anatomical properties between structural and ASL images comes

114 from the fact that gray matter and white matter are the two tissues that  
 115 contribute to the brain ASL signal, with their own perfusion characteristics  
 116 (e.g. CBF and arterial arrival time) [11, 12, 13]. Following a similar idea  
 117 than [15], [16] and [17], we propose a non-local patch-based method, while  
 118 introducing a novel denoising strategy.

119 Because of the use of non-local patch-based approaches, both in the denois-  
 120 ing and SR methods previously described [17], we propose to combine them  
 121 in a unique SR image reconstruction process. A third order B-splines in-  
 122 terpolation is first applied to the low resolution image in order to increase  
 123 its dimension to the desired one. This initialization is followed by iterations  
 124 between a non-local patch-based regularization and a fidelity term assuring  
 125 the global intensities mean consistency between the initial low resolution im-  
 126 age and the reconstructed one. This fidelity term differs from the one in use  
 127 in the works presented in the previous section [16,17], in the sense that it  
 128 involves a global image mean consistency, and not a subsampling consistency  
 129 at the voxel level, therefore allowing a denoising of the reconstructed image.  
 130 In the regularization term, correspondences between voxels' neighborhoods  
 131 are assessed both in the reconstructed image and the structural one:

$$X_i^{t+1} = \frac{1}{Z_i} \sum_{j \in V_i} X_j^t \exp - \left( \frac{\|N(X_{i,S}) - N(X_{j,S})\|_2^2}{\beta_S \sigma_{i,S}^2} + \frac{\|N(X_i^t) - N(X_j^t)\|_2^2}{\beta \sigma_i^2} \right), \quad (3)$$

132 where  $X_i^t$  is the intensity of voxel  $i$  in the image  $X^t$  corresponding to iteration  
 133  $t$ ,  $X_S$  the structural image,  $N(X_i)$  and  $N(X_{i,S})$  patches selected around voxel  
 134  $i$  in the ASL and structural images respectively,  $\sigma_i^2$  and  $\sigma_{i,S}^2$  the empirical local  
 135 variances,  $V_i$  the correspondence search volume around voxel  $i$ ,  $Z_i$  a scaling  
 136 parameter controlling that the sum of the weights is equal to 1, and  $\beta$  and  
 137  $\beta_S$  two scalars adjusting the importance of the terms related to the ASL  
 138 and structural images. The exponential weights, including an evaluation  
 139 of the simultaneous similarity of voxel neighborhoods in the structural HR  
 140 and reconstructed images, enable an increase in the level of details in the  
 141 ASL image, while preserving features that are only visible in this image.  
 142 Indeed, if neighborhoods are similar on two voxel locations in both images,  
 143 the contribution in the regularization will be important. In the contrary, if  
 144 a feature is only visible in one of the images, the weight will have a lower  
 145 value, and have a reduced contribution in this process.  
 146 The global low resolution mean value consistency corresponds to an additive

147 offset equal to the difference between the mean image value of  $X^t$  and the  
 148 mean of the low resolution image  $Y$ , respectively  $\mu(X)$  and  $\mu(Y)$ :

$$X^{t'} = X^t + (\mu(Y) - \mu(X^t)). \quad (4)$$

149 Iterations between these two steps are performed until no significant differ-  
 150 ence between consecutive reconstructed images can be observed, which can  
 151 be written as follows:

$$\frac{|X^{t-1} - X^{t-2}|}{|X^t - X^{t-1}|} < \tau. \quad (5)$$

152 As in [17], a coarse to fine approach is proposed where the weights  $\beta$  and  $\beta_S$   
 153 are decreased at each iteration of the process, leading to  $[\beta, \beta/2, \beta/4, \dots]$  and  
 154  $[\beta_S, \beta_S/2, \beta_S/4, \dots]$  respectively.

### 155 2.3. Validation framework

#### 156 2.3.1. Simulated dataset

157 In order to evaluate the proposed method in a controlled environment,  
 158 we constructed a simulated set of 9 CBF maps. This dataset was built  
 159 from structural (MP2RAGE UNI, [20]) images acquired at a resolution of  
 160  $1 \times 1 \times 1 \text{ mm}^3$  with a 3T Siemens Verio scanner and a 32-channel head-coil.  
 161 Fixed CBF values were considered for gray matter (GM) and white matter  
 162 (WM), equal to 70 and 25 ml/100g/min respectively [21]. These values were  
 163 affected to the probability maps obtained by means of the SPM12 segmen-  
 164 tation algorithm [22], leading to the application of the following equation:

$$\text{cbf}_i = p_{GM,i} \cdot 70 + p_{WM,i} \cdot 25, \quad (6)$$

165 with  $\text{cbf}_i$  the simulated CBF value at voxel  $i$ , and  $p_{GM,i}$  and  $p_{WM,i}$  the respec-  
 166 tive PV probability values for GM and WM provided by the segmentation  
 167 at the same voxel location.

168 These HR simulated CBF maps were then downsampled to a resolution of  
 169  $2 \times 2 \times 2 \text{ mm}^3$  by applying a gaussian blurring before downscaling by a factor  
 170 of 2 in the 3 directions. The downsampled images were then reconstructed  
 171 at the original resolution using different methods: nearest neighbor inter-  
 172 polation, trilinear interpolation, 3rd order B-splines interpolation and the  
 173 proposed SR reconstruction method.

174 The root mean square errors (RMSE) between the original HR simulated

175 CBF maps and the reconstructed images were calculated in order to evalu-  
 176 ate the ability of each method to provide reconstructed images close to this  
 177 reference. As ASL images acquired in clinical conditions are usually affected  
 178 by noise, commonly considered as gaussian in CBF maps due to the aver-  
 179 aging of multiple label-control pairs, we also studied the behavior of each of  
 180 these methods as a function of the amount of noise. Downsampled images  
 181 affected by gaussian noise with standard errors corresponding to 3 to 14% of  
 182 the GM CBF value were reconstructed at the original resolution in order to  
 183 evaluate this behavior. Figure 1 illustrates these images generation and the  
 184 processing steps.

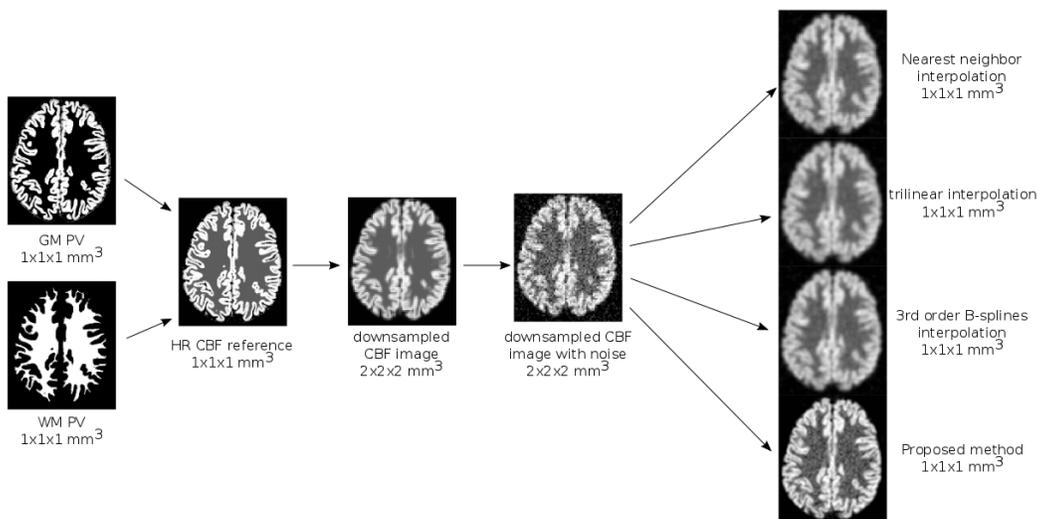


Figure 1: Pipeline describing the generation of the simulated dataset and the different reconstruction methods to be compared, applied to the downscaled and noise corrupted images.

### 185 2.3.2. Healthy controls

186 The SR reconstruction method was also evaluated on images acquired  
 187 on 4 healthy subjects (3 females, 1 male, age =  $34 \pm 6$  years). For each of  
 188 these volunteers, images were acquired on a 3T Siemens Verio scanner with  
 189 a 32-channel head-coil. The structural image consisted in a MP2RAGE UNI  
 190 (resolution:  $1 \times 1 \times 1$  mm<sup>3</sup>). pCASL (resolution:  $3.5 \times 3.5 \times 5$  mm<sup>3</sup>, interslice  
 191 gap: 1 mm, 30 control-label pairs repetitions, PLD: 1800 ms, labeling dura-  
 192 tion (LD): 1800 ms, 20 slices [23]) and M0 (resolution:  $3.5 \times 3.5 \times 5$  mm<sup>3</sup>, inter-

193 slice gap: 1 mm, 5 repetitions, 20 slices) images were acquired as the low reso-  
 194 lution data used to generate the CBF maps to be reconstructed by increasing  
 195 their dimensions by a factor of 2 in each direction. HR pCASL images were  
 196 also acquired for the evaluation purpose (resolution:  $1.75 \times 1.75 \times 2.5 \text{ mm}^3$ ,  
 197 interslice gap: 0.5 mm, 100 control-label pairs repetitions, PLD: 1800 ms,  
 198 LD: 1800 ms, 20 slices), as well as HR M0 (resolution:  $1.75 \times 1.75 \times 2.5 \text{ mm}^3$ ,  
 199 interslice gap: 0.5 mm, 10 repetitions, 20 slices). Image SNR being propor-  
 200 tional to voxel volume, 100 repetitions were acquired in order to generate the  
 201 HR pCASL images. While not entirely compensating for the SNR decrease  
 202 in comparison with the 30 repetitions low resolution acquisitions, this repe-  
 203 tition number was chosen as a compromise between scan time (10 minutes),  
 204 risk of subjects motion and SNR.  
 205 CBF maps were obtained by applying the general kinetic model for pCASL  
 206 acquisitions [4]:

$$CBF = \frac{6000 \cdot \lambda \cdot \Delta M \cdot \exp(\frac{PLD}{T_{1,blood}})}{2 \cdot \alpha \cdot T_{1,blood} \cdot M0 \cdot (1 - \exp(-\frac{LD}{T_{1,blood}}))}, \quad (7)$$

207 with  $\lambda$  the blood/brain partition coefficient ( $\lambda : 0.9$ ),  $\alpha$  the labeling efficiency  
 208 ( $\alpha : 0.85$ ),  $\Delta M$  the control-label difference, and  $T_{1,blood}$  the blood  $T_1$  relax-  
 209 ation time ( $T_{1,blood} : 1650 \text{ ms}$ ).

210 As in the case of the simulated data, RMSE values between the reconstructed  
 211 images generated by the different methods and the HR pCASL CBF map,  
 212 considered as the reference, were calculated.

### 213 2.3.3. Correlation with DSC

214 As mentioned in the introduction, Dynamic Susceptibility Contrast (DSC)  
 215 imaging is often considered as a standard perfusion MR imaging technique.  
 216 A contrast agent, usually gadolinium-based, is injected to the subject and  
 217 the induced susceptibility effects are imaged via T2\*-weighted acquisitions.  
 218 In clinical conditions, this technique enables acquisitions at a higher reso-  
 219 lution than ASL scans. Therefore, we studied the correlation between low  
 220 resolution CBF maps obtained from pulsed ASL (PASL) images, the same  
 221 images after an increase of the dimensions by a factor of 2 in each direction  
 222 with different interpolation methods and the HR DSC CBF images.

223 The dataset contains images of 10 patients diagnosed with brain tumors  
 224 (3 females, 7 males, age =  $63 \pm 13$  years). Images were acquired on a 3T  
 225 Siemens Verio scanner with a 32-channel head-coil. A 3D T1w sequence (res-

226 olution:  $1 \times 1 \times 1 \text{ mm}^3$ ) was acquired, as well as a PICORE Q2TIPS PASL  
 227 sequence with crushers (EPI readout, TR: 3000 ms, TE: 18 ms, FOV:  $192 \times$   
 228  $192 \text{ mm}^2$ , flip angle:  $90^\circ$ , in plane resolution:  $3 \times 3 \text{ mm}^2$ , slice thick-  
 229 ness: 7 mm, interslice gap: 0.7 mm, inversion time ( $TI$ ): 1700 ms, bolus width  
 230 ( $TI_1$ ): 700 ms, 30 control-label repetitions) and a DSC sequence (GRE EPI  
 231 readout, TR: 1500 ms, TE: 300 ms, FOV:  $230 \times 230 \text{ mm}^2$ , flip angle:  $90^\circ$ , in  
 232 plane resolution:  $1.8 \times 1.8 \text{ mm}^2$ , slice thickness: 4 mm, interslice gap: 1.2 mm).  
 233 The CBF maps were generated from the DSC images by use of the method  
 234 proposed by Østergaard et al. [24]. The general kinetic model for PASL  
 235 acquisitions was applied to the ASL scans [4]:

$$CBF = \frac{6000 \cdot \lambda \cdot \Delta M \cdot \exp\left(\frac{TI}{T_{1,blood}}\right)}{2 \cdot \alpha \cdot TI_1 \cdot M_0}, \quad (8)$$

236 The other parameters are the same as in (7), except  $\alpha : 0.98$ . Assuming that  
 237 ASL and DSC CBF estimations are linearly correlated, as stated in Warmuth  
 238 et al. [25], the Pearson correlation coefficients were calculated between the  
 239 low resolution ASL CBF and the registered HR DSC CBF maps, and the SR  
 240 reconstructed ASL CBF and DSC CBF maps.

#### 241 *2.4. Implementation details*

242 An in-house image processing pipeline based on Python, Cython, Nipype [26]  
 243 and SPM12 functions was used to conduct the experiments. Considering re-  
 244 sults presented in [17] and our own experiments, the patch size was chosen  
 245 equal to  $3 \times 3 \times 3$  voxels in the non-local patched-based regularization, and  
 246 the search volume to  $7 \times 7 \times 7$  voxels. In order to obtain an equivalent contri-  
 247 bution of the ASL and structural related terms in the reconstruction process,  
 248  $\beta$  and  $\beta_S$  were chosen to be equal. Tests and quantitative evaluations with  
 249 different values on the simulated dataset and the healthy subjects images  
 250 conducted to the selection of  $\beta = \beta_S = 0.5$ . Therefore, all results presented  
 251 in the following sections have been obtained by use of these parameters.

## 252 **3. Results**

### 253 *3.1. Simulated dataset*

254 Images corresponding to reconstructions of a low resolution CBF map  
 255 corrupted by gaussian noise with a standard deviation equal to 9% of the  
 256 GM CBF value, which we qualitatively suppose being a close example to

257 effective low resolution acquired images, are displayed in Figure 2. The im-  
 258 ages generated by use of interpolation techniques (nearest neighbor, trilinear  
 259 and 3rd order B-spline interpolations) appear flattened, compared to the SR  
 260 reconstructed map, which enables to recover sharp structures and edges. Ta-  
 261 ble 1 confirms these observations, with lower mean RMSE values (in bold)  
 262 calculated between the simulated reference images and the SR reconstructed  
 263 ones than between the references and the interpolated images. In addition,  
 264 the evolution of these RMSE values indicates that the more the standard  
 265 deviation of noise increases, the closer to the reference the reconstructed im-  
 266 age is in comparison with the interpolated images. This result is associated  
 267 with the capability of the proposed method to denoise the images. Table 2  
 268 provides information about the p-values obtained by applying paired t-tests  
 269 between the RMSE values obtained from the proposed reconstructions and  
 270 the other interpolation methods. Significant differences between the pro-  
 271 posed reconstruction method and the interpolation techniques are found for  
 272 levels of noise superior to 6% of the GM CBF value.

Noise std	<b>3</b>	<b>6</b>	<b>9</b>	<b>11</b>	<b>14</b>
Nearest neighbor	14.82 ± 0.82	15.3 ± 0.78	16.31 ± 0.80	17.72 ± 0.97	19.98 ± 1.43
Trilinear	14.80 ± 0.91	14.93 ± 0.90	15.22 ± 0.89	15.66 ± 0.86	16.38 ± 0.94
B-splines	14.01 ± 0.89	14.35 ± 0.86	15.08 ± 0.83	16.12 ± 0.85	17.78 ± 1.19
Proposed method	<b>13.92</b> ± 1.05	<b>14.05</b> ± 1.04	<b>14.34</b> ± 1.01	<b>14.79</b> ± 0.99	<b>15.56</b> ± 1.08

Table 1: Means and standard deviations of the 9 RMSE values calculated between the reference HR image and the images reconstructed with nearest neighbor interpolation, trilinear interpolation, 3rd order B-splines interpolation and the proposed SR reconstruction method, with increasing levels of noise. Standard deviations of noise are expressed as percentage of the GM CBF value.

### 273 3.2. Healthy controls

274 Figures 3, and 4 present the images obtained from one of the 4 volunteers.  
 275 Sagittal slices are shown, notably to insist on the influence of the methods on  
 276 the staircase effect related to the particularly low initial resolution in the slice  
 277 acquisition direction (5mm + 1mm gap). This effect is strongly corrected by  
 278 the proposed SR reconstruction method. The RMSE values are reported in  
 279 table 3, the proposed method providing images closer to the HR references  
 280 than common interpolation techniques for three of the four subjects.

Noise std	3	6	9	11	14
Nearest neighbor	$3.9 \times 10^{-4}$	$4.5 \times 10^{-5}$	$2.8 \times 10^{-6}$	$1.4 \times 10^{-6}$	$4.3 \times 10^{-7}$
Trilinear	$3.2 \times 10^{-4}$	$2.8 \times 10^{-4}$	$2.6 \times 10^{-4}$	$2.8 \times 10^{-4}$	$3.1 \times 10^{-4}$
B-splines	$5.4 \times 10^{-1}$	$6.1 \times 10^{-2}$	$6.6 \times 10^{-4}$	$2.0 \times 10^{-5}$	$2.7 \times 10^{-6}$

Table 2: P-values obtained by application of paired t-tests between the RMSE values obtained after the proposed reconstruction and by nearest neighbor interpolation, trilinear interpolation and 3rd order B-splines interpolation, with increasing levels of noise. Standard deviations of noise are expressed as percentage of the GM CBF value.

Method	Subject 1	Subject 2	Subject 3	Subject 4
Nearest neighbor	28.16	26.83	32.19	24.23
Trilinear	26.93	24.80	30.15	22.58
3rd order B-splines	<b>26.34</b>	25.04	29.68	22.49
Proposed method	26.44	<b>24.49</b>	<b>29.12</b>	<b>22.20</b>

Table 3: RMSE values calculated between the HR acquired reference image and the images generated by nearest neighbor interpolation, trilinear interpolation, 3rd order B-splines interpolation and the proposed SR reconstruction method, for each of the 4 healthy subjects (lower RMSE value in bold for each subject).

### 281 3.3. Comparison with DSC

282 Figure 5 reports, for each of the subjects, the values of the Pearson correlation coefficients obtained between the reference DSC CBF images and  
283 the low resolution acquired ASL CBF maps, their interpolations by trilinear  
284 and 3rd order B-splines and the images generated with the proposed SR re-  
285 construction method. For each subject, the reconstructed image was more  
286 correlated to the DSC reference than the others. The significance of the dif-  
287 ferences was assessed by applying a Fisher transformation to the correlation  
288 coefficients. The p-values obtained after this transformation indicate a sig-  
289 nificant difference between the correlation coefficients distributions. Indeed,  
290 a paired t-test between the correlation values obtained for the proposed re-  
291 constructions and the low resolution acquisitions provided a p-value equal to  
292  $1.4 \times 10^{-4}$ ,  $p = 8 \times 10^{-5}$  by comparison with the trilinear interpolation, and  
293  $p = 3.33 \times 10^{-4}$  by comparison with the 3rd order B-splines. Figure 6 dis-  
294 plays the DSC CBF images, low resolution ASL CBF maps and CBF maps  
295 reconstructed with our method for two of the patients.  
296

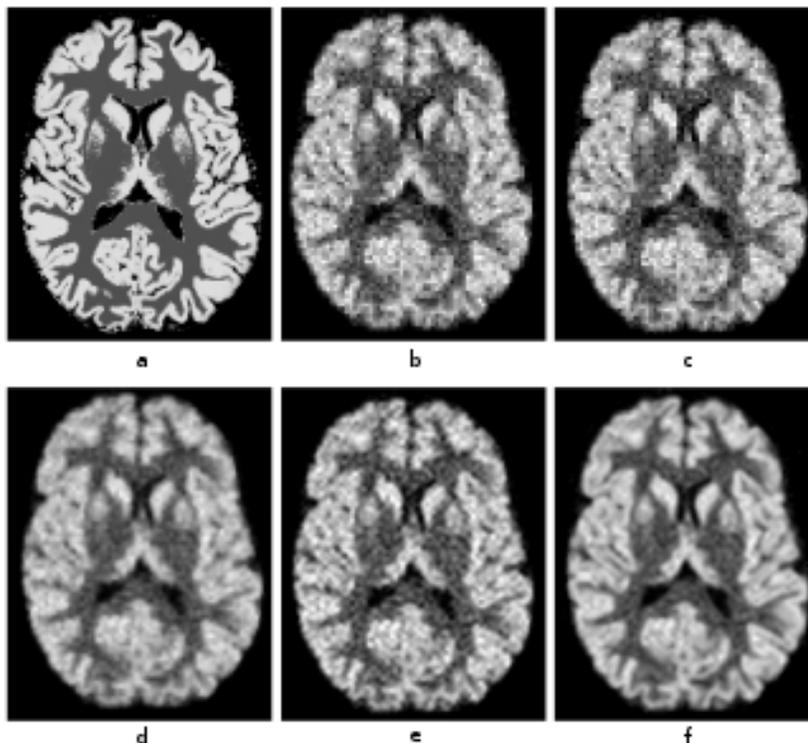


Figure 2: Simulated dataset: comparison of a) a HR reference image and b) the corresponding low resolution downsampled image corrupted by noise with  $\text{std}=9\%$  of the GM CBF value, c) nearest neighbor interpolation, d) trilinear interpolation, e) 3rd order B-splines interpolation, and f) proposed SR reconstruction.

## 297 4. Comparison with Partial Volume Correction methods

### 298 4.1. Method

299 Typical low resolution ASL acquisitions lead to well known PVE in ASL  
 300 images, sometimes unfortunately preventing clinicians to interpret MRI ob-  
 301 servations such as reduced CBF values in regions of interest. Indeed, they  
 302 could be the consequences of an effective reduced perfusion, a thinner GM  
 303 or small subject motion. Because of the fact that the method described in  
 304 this paper enables the recovery of high frequency details that are not visible  
 305 in low resolution acquisitions, we propose to evaluate the influence of this  
 306 recovery on a potential reduction of PVE. This is of particular interest, since  
 307 the PVE correction methods that are currently the most commonly applied  
 308 to ASL images correct CBF values at the voxel level, thus not providing

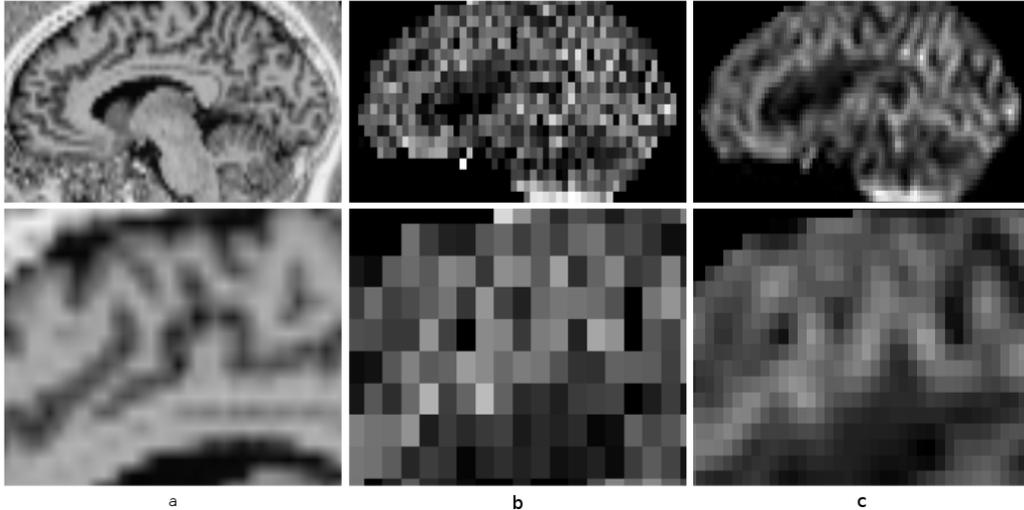


Figure 3: Sagittal slices of a) a structural image, b) the corresponding CBF map from the low resolution ASL acquisition, and c) the proposed SR reconstruction.

309 better detailed images. Moreover, the method that we present in this work  
 310 is only dependent on the registration of a HR structural image on an inter-  
 311 polated ASL one, while classical PVE correction methods require the use of  
 312 tissue PV estimates. These PV estimate maps are provided by segmentation  
 313 algorithms, and are therefore subject to potential additional errors.  
 314 In order to compare the impact of these algorithms on PVE, a simulation  
 315 was conducted from the same 9 structural images as presented in 2.3.1, in  
 316 which we aimed at having the most possible information about intensity val-  
 317 ues. In order to construct these 9 HR ASL images in which we knew the  
 318 exact voxel constitution and associated values, images containing 100% GM  
 319 or WM voxels were created, by thresholding the PV estimates generated by  
 320 the SPM12 segmentation algorithm. Perfusion maps were generated by af-  
 321 fecting  $\Delta M$  values of 10 for GM and 1.5 for WM, with additional sinusoidal  
 322 variations of 20% amplitude to make them more realistic, and evaluate the  
 323 capability of the tested algorithms to preserve spatial variations and details  
 324 [29]. The same process was used to create M0 images, with values of 1350  
 325 and 1000 in GM and WM respectively. These HR perfusion and M0 maps  
 326 were downsampled by averaging  $2 \times 2 \times 2$  voxel cubes, therefore reducing the  
 327 size of the images and adding PVE, while knowing the exact brain tissue mix-  
 328 ture of these new low resolution voxels. Different amount of gaussian noise

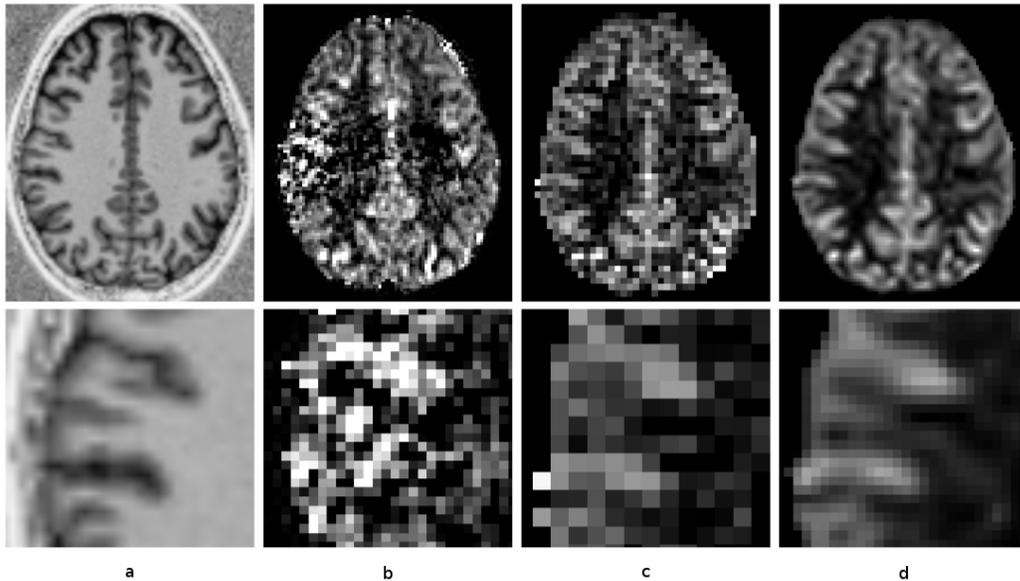


Figure 4: Axial slices of a) a structural image, b) the corresponding CBF maps from the HR and c) low resolution ASL acquisitions, and d) the proposed SR reconstructed image.

329 (SNR=5,10) were added to these images in order to evaluate the influence of  
 330 noise on PVE correction. The general kinetic model for pCASL acquisitions  
 331 was then applied to obtain the corresponding CBF maps ( $\lambda : 0.9$ ,  $\alpha : 0.85$ ,  
 332  $T_{1,blood}$ : 1650 ms, LD: 1800 ms, PLD: 1800 ms).

333 The effect of the proposed algorithm on PVE was evaluated by analyzing its  
 334 ability to recover the effective GM contribution in the CBF values observed  
 335 in each voxel, in comparison with the linear regression method, which is one  
 336 of the standard PVE correction technique applied to ASL images [11].

337 Our proposed SR method provides high resolution CBF maps unlike the lin-  
 338 ear regression method, which produces two PV maps at the initial resolution.  
 339 This is the reason why our SR CBF maps have been downsampled, in order  
 340 to be able to compare the two results. The GM contributions in the CBF  
 341 maps obtained by applying the general kinetic model to the HR perfusion  
 342 and M0 images, without noise, were considered as the references to which  
 343 the generated images had to be compared. Figure 7 illustrates the pipeline  
 344 that corresponds to the above-mentioned operations.

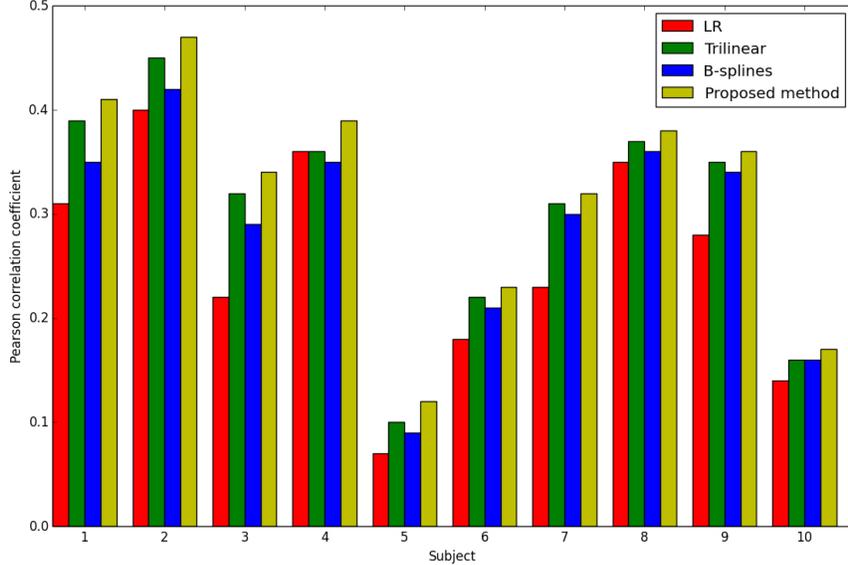


Figure 5: Pearson correlation coefficient between the reference DSC CBF maps and low resolution CBF images, the same images after trilinear interpolation, 3rd order B-splines interpolation and the proposed SR reconstruction method. These coefficients are presented for each of the 10 subjects.

#### 345 4.2. Results

346 Contrary to differences in the produced GM contribution maps reported  
 347 in Zhao et al. [29], between an application of the linear regression to the calcu-  
 348 lated CBF map and to perfusion and M0 images before the CBF calculation,  
 349 our method did not show such significant differences while testing for the  
 350 influence of this effect. Figure 8 presents the GM contributions to the CBF  
 351 values in a reference image, their recovery by application of the linear regres-  
 352 sion method to the low resolution CBF map, by applying the same method  
 353 to perfusion and M0 images before CBF calculation, and after increasing  
 354 the CBF image dimensions with our method. Figure 9 shows the difference  
 355 images obtained after the subtraction of each of the produced images listed  
 356 above and the corresponding reference. An important aspect illustrated in  
 357 these difference images is the fact, already stated in [11, 12, 13, 29], that the  
 358 linear regression method implies a smoothing of the GM contributions. On  
 359 the contrary, the sinusoidal variations are retained in the image originating

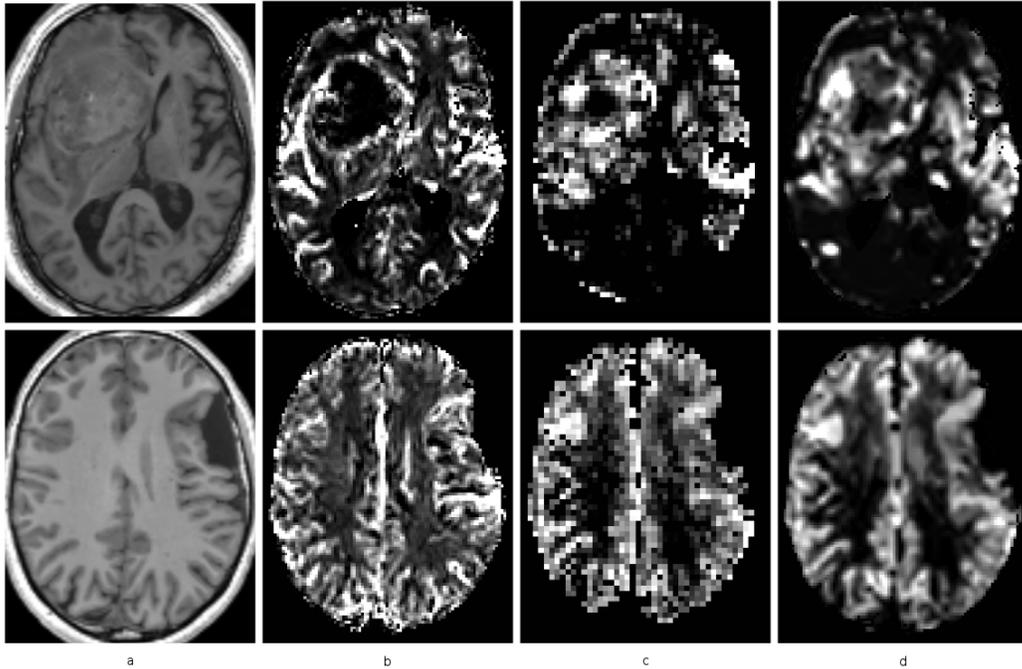


Figure 6: a) structural image, b) DSC CBF image, c) low resolution ASL CBF image and d) SR reconstructed ASL CBF map. The two lines correspond to images of two different subjects.

360 from the proposed algorithm.  
 361 Table 4 presents the evolution of the mean RMSE values calculated between  
 362 the generated GM contribution images and their references as a function of  
 363 noise (SNR=inf, 10, 5). In practice, both applications of the linear regression  
 364 method to the CBF maps or to the perfusion and M0 images are commonly  
 365 accepted [29]. Since the mean RMSE values obtained by applying our method  
 366 to CBF maps are bounded by the mean RMSE provided by these two linear  
 367 regressions, we can presume that our method reduces the influence of PVE.  
 368 Moreover, the linear regression method is based on the use of information  
 369 provided by PV estimates, which makes it dependent upon the chosen seg-  
 370 mentation algorithm and sensitive to potential segmentation errors. On the  
 371 contrary, our SR reconstruction method is independent of any segmentation  
 372 algorithm. In order to investigate the influence of these segmentation cor-  
 373 ruptions on the GM contribution maps resulting from the application of the  
 374 linear regression, we simulated variations in the segmented PV estimates by

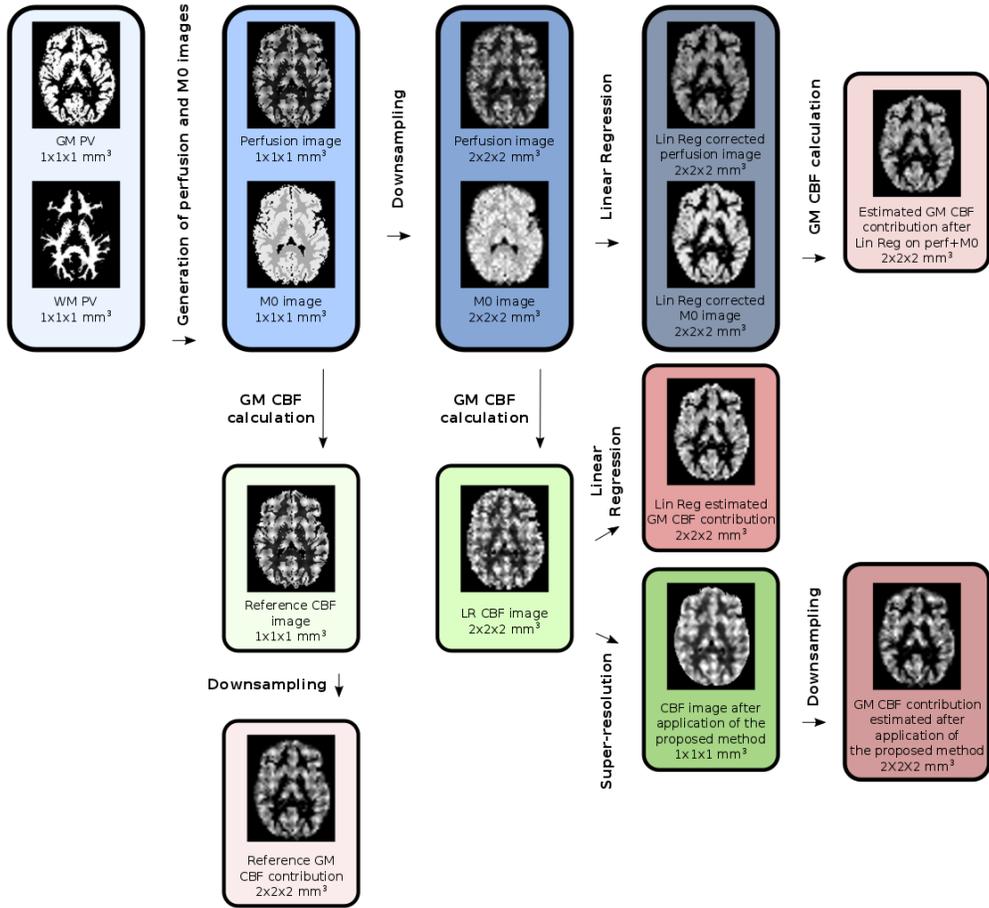


Figure 7: Pipeline describing the operations applied to each of the 9 images of the simulated dataset and the GM contribution assessment maps to be compared.

375 introducing gaussian noise or by applying an opening and closing morphological  
 376 operation to these PV maps. Tables 5 and 6 show a significant increase in  
 377 the mean RMSE values when the PV estimates are modified. These results  
 378 indicate that the property of the SR reconstruction to be independent of the  
 379 use of PV estimates could be of great interest to avoid potential errors due  
 380 to segmentation corruption.

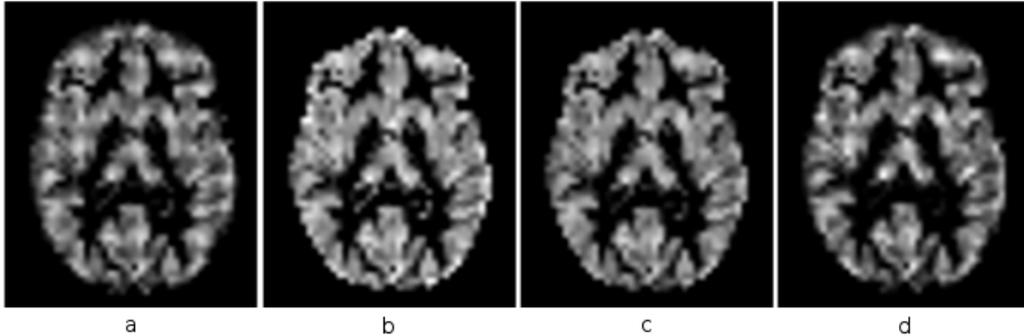


Figure 8: Comparison of gray matter cerebral blood flow contribution maps: a) GM contribution maps from the reference image, b) linear regression applied to the low resolution CBF image, c) linear regression applied to the low resolution perfusion and M0 images, and d) proposed SR method applied to the LR CBF image (SNR=5).

Method	SNR=inf	SNR=10	SNR=5
Lin Reg on CBF	$6.41 \pm 0.74$	$6.54 \pm 0.75$	$7.05 \pm 0.75$
Lin Reg on Perf & M0	$4.39 \pm 0.17$	$4.52 \pm 0.17$	$4.90 \pm 0.17$
SR on CBF	$5.66 \pm 0.11$	$5.94 \pm 0.13$	$6.77 \pm 0.14$

Table 4: Mean RMSE values between the reference GM CBF contribution images and the images obtained after linear regression (Lin Reg) on the low resolution (LR) CBF image, Lin Reg on the perfusion and M0 images, and the proposed SR method applied to the LR CBF images.

Method	SNR=inf	SNR=10	SNR=5
Lin Reg on CBF	$7.46 \pm 0.60$	$7.65 \pm 0.59$	$8.09 \pm 0.62$
Lin Reg on Perf & M0	$5.84 \pm 0.23$	$5.97 \pm 0.24$	$6.24 \pm 0.22$
SR on CBF	$5.66 \pm 0.11$	$5.94 \pm 0.13$	$6.77 \pm 0.14$

Table 5: Mean RMSE values between the reference GM CBF contribution images and the images obtained after linear regression (Lin Reg) on the low resolution(LR) CBF image and on the perfusion and M0 images, with noise added to the PV estimates needed by the Lin Reg method, and the proposed SR method applied to the LR CBF images.

## 381 5. Discussion

382 In this work, we have presented and investigated different properties of a  
 383 SR reconstruction method dedicated to ASL images. This method enables to  
 384 increase the level of details, while providing a denoising of the reconstructed  
 385 images. It is based on the assumptions of an appearing accordance between

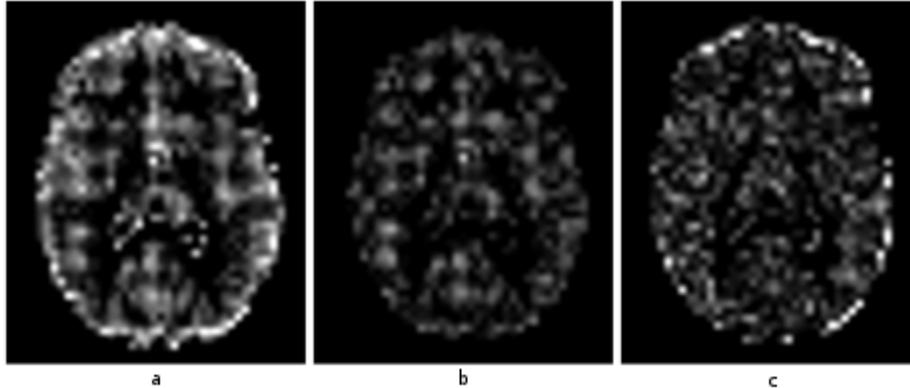


Figure 9: Comparison of gray matter cerebral blood flow contribution maps: a) difference images obtained by subtraction of the reference GM contribution map from the images obtained by applying the linear regression (Lin Reg) to the low resolution (LR) CBF image, b) the linear regression to the LR perfusion and M0 images, and c) the proposed SR method to the LR CBF image (SNR=5).

Method	SNR=inf	SNR=10	SNR=5
Lin Reg on CBF	$11.68 \pm 0.70$	$11.78 \pm 0.70$	$12.10 \pm 0.75$
Lin Reg on Perf & M0	$11.19 \pm 0.50$	$11.23 \pm 0.49$	$11.42 \pm 0.51$
SR on CBF	$5.66 \pm 0.11$	$5.94 \pm 0.13$	$6.77 \pm 0.14$

Table 6: Mean RMSE values between the reference GM CBF contribution images and the images obtained after linear regression (Lin Reg) on the low resolution (LR) CBF image and on the perfusion and M0 images, with an opening+closing operation added to the PV estimates needed by the Lin Reg method, and the proposed SR method applied to the LR CBF images.

386 neighborhoods in the image to be reconstructed and a classically acquired  
 387 HR anatomical image, and that distant neighborhoods could serve as a learn-  
 388 ing database in the reconstruction process.

389 On a simulated dataset, we have shown that our method provides images  
 390 closer to references than common interpolation techniques. The fact that  
 391 this result could be obtained with different levels of noise added to the im-  
 392 ages to be reconstructed is an indication of the ability of the proposed method  
 393 to denoise the reconstructed images.

394 Experiments on low resolution data acquired on healthy subjects confirmed  
 395 these findings on 3 over 4 subjects. The main limitation of this study is  
 396 nonetheless the relevance of the definition of the HR ASL images as refer-

397 ences, because of their low SNR. In order to maintain the scan time rea-  
398asonable and avoid subject motions that would almost certainly happen after  
39910 minutes of continuous scanning, 100 control-label repetitions have been  
400acquired to generate the high resolution ASL images. This number is cer-  
401tainly still not sufficient to obtain an appropriate image quality, which could  
402explain the fact that a better RMSE value was obtained by applying a 3<sup>rd</sup>  
403order B-spline interpolation for the first subject. This limitation is precisely  
404the reason why we chose to conduct the two other studies, meaning with a  
405simulated dataset and the comparison with DSC images.

406The study based on images of patients diagnosed with brain tumors revealed  
407a significantly increased correlation between DSC and images reconstructed  
408with our method, supporting the capability of the proposed method to re-  
409cover details by driving the reconstruction of ASL images with a high res-  
410olution structural one. The *TI* value chosen to acquire these PASL data  
411was possibly a little short for subjects 5, 6 and 10, which could explain the  
412reduced correlation values obtained for these three subjects.

413We showed that our method associates an increase in the level of details with  
414a reduction of the partial volume effect in ASL images. The main advantage  
415of this SR reconstruction in comparison with the linear regression partial  
416volume correction method is to preserve spatial signal fluctuations, which  
417are smoothed by the latter.

418The method proposed in this paper only depends on the accurate registration  
419of a HR structural image on the initially interpolated ASL image to be recon-  
420structed. Indeed, experiments revealed that the initial interpolation method  
421selected in order to increase the dimension of the image to reconstruct does  
422not have a significant influence on the generated image, and denoising is  
423performed jointly with the details recovery process. This aspect makes our  
424method an appropriate tool to increase the quality and the fidelity of ASL  
425images, and particularly CBF maps, with respect to effective physiological  
426processes. Another promising aspect is its faculty to recover well detailed  
427ASL images from standard clinical acquisition protocols, therefore not in-  
428creasing the acquisition time and patient discomfort. We believe that such a  
429post-processing procedure could help clinicians to establish even more accu-  
430rate diagnosis, by reducing interrogations concerning the reasons of reduced  
431perfusion values and being able to distinguish GM thickness reduction or an  
432effective perfusion reduction for example.

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