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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 scanned for 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

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 [2, 3]. Recommendations regarding ASL image ac-
15 quisitions have been formulated by a consortium in the ASL "white paper"
16 [4].

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, voxelwise estimations of perfusion related
25 parameters are corrupted by small subject motion and the low resolution of
26 the images, that involve the introduction of partial volume effects (PVE),
27 meaning that perfusion of different tissues contribute to the perfusion signal
28 observed in a single image voxel [5, 6, 7].

29 Several post-processing algorithms have been proposed to deal with these
30 limitations. Particularly, denoising methods are successfully applied to deal
31 with artifacts and outliers in ASL images [8, 9, 10, 11]. PVE correction algo-
32 rithms have also been proposed and investigated in [6, 7, 12]. These methods
33 have in common to be applied at the resolution of the acquired images. While
34 attenuating the effect of the previously listed corruptions, they do not allow
35 to increase the level of details in images. However, this aspect could be
36 of great interest, the thickness of grey matter (GM) being often inferior to
37 the size of the ASL images voxel size. In clinical conditions, acquiring ASL
38 images at higher resolutions is a challenging task, since this would imply a
39 decrease in SNR, or increase the acquisition time.

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

46 lution data. Some of these methods are based on multiple low resolution
47 acquisitions, therefore requiring specific acquisition protocols, which can be
48 time consuming [13]. Recently, [14, 15, 16] have adapted and extended non-
49 local patch-based SR approaches that are independent of the acquisition
50 process to the MRI domain. The main idea consists in using self similarities
51 in the images to perform reconstructions at higher resolutions [17]. These
52 methods can be applied to data commonly acquired in clinical conditions,
53 such as T2-weighted or diffusion weighted images, thus preventing any in-
54 crease in the acquisition time. A first application of this kind of method
55 to pseudo-continuous ASL (pCASL) images has been proposed in [18]. The
56 main limitation of these methods is that they require clean low resolution
57 data as inputs, which means that denoising algorithms must first carefully
58 be applied to the images prior to SR reconstruction.

59 In this paper, we propose a novel method to increase the resolution of ASL
60 images, which deals with the presence of noise. This non-local patch-based
61 SR reconstruction approach is based on the assumption of appearing sim-
62 ilarities between neighborhoods in the image that is reconstructed and a
63 high resolution (HR) structural image, generally acquired in imaging proto-
64 cols. This assumption of shared anatomical properties between structural
65 and ASL images comes from the fact that gray matter and white matter
66 are the two tissues that contribute to the brain ASL signal, with their own
67 perfusion characteristics (e.g. CBF and arterial arrival time) [6, 7, 12]. This
68 proposition allows to increase the resolution of ASL images without extend-
69 ing the acquisition time. The method is evaluated on a simulated dataset
70 and images of healthy subjects in order to investigate its capacity to recon-
71 struct images close to HR ASL references. As DSC is commonly considered
72 as a reference perfusion imaging technique, we investigate the ability of our
73 method to generate images closer to the DSC quantitative maps on images
74 acquired on subjects scanned for brain tumors. In addition, we investigate
75 the influence of a recovery of HR details on PVE.

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

80 2. Materials and Methods

81 2.1. Summary of existing similarity-based SR methods

82 The objective of super-resolution methods is to recover an unknown high
83 resolution (HR) image x from a low resolution acquired one y . The following
84 model explicits the relation between both images :

$$y = Mx + \eta, \quad (1)$$

85 with M a matrix representing subsampling, blurring and geometric transfor-
86 mations, and η representing some additive noise [17, 14, 15, 16]. An optimiza-
87 tion problem of the following form would correspond to a common approach
88 to recover the unknown image x :

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

89 where Φ is a regularization term necessary to solve this ill-posed mini-
90 mization problem and γ a positive parameter.

91 As shown in [15] and [16], an iterative reconstruction-correction procedure
92 can be adopted in order to reconstruct x , which allows to avoid problems
93 such as local minima or parameters initialization linked to this ill-posed op-
94 timization problem. This procedure consists in two steps, corresponding to
95 a reconstruction and a subsampling consistency constraint.

96 The reconstruction is based on the assumption that locations in a HR ac-
97 quired structural image and the SR reconstructed one should share anatomi-
98 cal properties, and that the structural image could therefore be used to drive
99 the reconstruction process. This assumption leads to the choice of non-local
100 regularization approaches, such as in [15] and [16].

101 The subsampling consistency imposes the constraint of a strict equality be-
102 tween the downsampled version of the SR reconstructed image and the origi-
103 nal low resolution image y , which is made possible by formulating strong
104 assumptions about the M matrix composition. However, this constraint im-
105 plies the need for well denoised low resolution images for the method to be
106 consistent. Therefore, Coupé et al. [16] proposed to apply a Rician-adapted
107 denoising filter on diffusion images before solving the optimization problem.
108 In the case of low signal-to-noise ratio ASL images, different noise patterns
109 can be introduced regarding the scanners, sequences or settings chosen to
110 perform the acquisition. The use of parameters that could not be the most
111 appropriate ones in the filtering step, could have important consequences

112 regarding the quality of the final reconstructed image. This is the reason
 113 why we introduce a reconstruction driven by a HR structural image, while
 114 denoising the SR reconstructed image at the same time.

115 *2.2. A new SR method for ASL images*

116 The main objective of this work is to assess the relevance of using a HR
 117 anatomical image to increase the resolution of ASL images. Following a sim-
 118 ilar idea than [14], [15] and [16], we propose a non-local patch-based method,
 119 while introducing a novel denoising strategy.

120 Because of the use of non-local patch-based approaches, both in the denois-
 121 ing and SR methods previously described [16], we propose to combine them
 122 in a unique SR image reconstruction process. A third order B-splines in-
 123 terpolation is first applied to the low resolution image in order to increase
 124 its dimension to the desired one. This initialization is followed by iterations
 125 between a non-local patch-based regularization and a fidelity term assuring
 126 the global intensities mean consistency between the initial low resolution im-
 127 age and the reconstructed one. This fidelity term differs from the one in use
 128 in the works presented in the previous section [15, 16], in the sense that it
 129 involves a global image mean consistency, and not a subsampling consistency
 130 at the voxel level, therefore allowing a denoising of the reconstructed image.
 131 In the regularization term, correspondences between voxels' neighborhoods
 132 are assessed both in the reconstructed image and the structural one:

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

133 where X_i^t is the intensity of voxel i in the image X^t corresponding to iteration
 134 t , X_S the structural image, $N(X_i)$ and $N(X_{i,S})$ patches selected around voxel
 135 i in the ASL and structural images respectively, σ_i^2 and $\sigma_{i,S}^2$ the empirical local
 136 variances, V_i the correspondence search volume around voxel i , Z_i a scaling
 137 parameter controlling that the sum of the weights is equal to 1, and β_{asl} and
 138 β_{struct} two scalars adjusting the importance of the terms related to the ASL
 139 and structural images. The exponential weights, including an evaluation
 140 of the simultaneous similarity of voxel neighborhoods in the structural HR
 141 and reconstructed images, enable an increase in the level of details in the
 142 ASL image, while preserving features that are only visible in this image.
 143 Indeed, if neighborhoods are similar on two voxel locations in both images,

144 the contribution in the regularization will be important. In the contrary, if
 145 a feature is only visible in one of the images, the weight will have a lower
 146 value, and have a reduced contribution in this process.
 147 The global low resolution mean value consistency corresponds to an additive
 148 offset equal to the difference between the mean image value of X^t and the
 149 mean of the low resolution image Y , respectively $\mu(X)$ and $\mu(Y)$:

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

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

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

153 As in [16], a coarse to fine approach is proposed where the weights β_{asl} and
 154 β_{struct} are decreased at each iteration of the process, leading to $[\beta_{asl}, \beta_{asl}/2, \beta_{asl}/4, \dots]$
 155 and $[\beta_{struct}, \beta_{struct}/2, \beta_{struct}/4, \dots]$ respectively.

156 2.3. Validation framework

157 2.3.1. Simulated dataset

158 In order to evaluate the proposed method in a controlled environment,
 159 we constructed a simulated set of 9 CBF maps. This dataset was built
 160 from structural (MP2RAGE UNI, [19]) images acquired at a resolution of
 161 $1 \times 1 \times 1 \text{ mm}^3$ with a 3T Siemens Verio scanner and a 32-channel head-coil.
 162 Fixed CBF values were considered for gray matter (GM) and white matter
 163 (WM), equal to 70 and 25 ml/100g/min respectively [20]. These values were
 164 affected to the probability maps obtained by means of the SPM12 segmen-
 165 tation algorithm [21], leading to the application of the following equation:

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

166 with cbf_i the simulated CBF value at voxel i , and $p_{GM,i}$ and $p_{WM,i}$ the re-
 167 spective partial volume probability values for GM and WM provided by the
 168 segmentation at the same voxel location.

169 These HR simulated CBF maps were then downsampled to a resolution of
 170 $2 \times 2 \times 2 \text{ mm}^3$ by applying a gaussian blurring before downscaling by a factor
 171 of 2 in the 3 directions. The downsampled images were then reconstructed
 172 at the original resolution using the proposed SR reconstruction method. In

173 order to assess the influence of the ASL and structural related terms on the
174 proposed reconstruction, implementations with different β_{asl} and β_{struct} val-
175 ues were evaluated. Images reconstructed by only taking the ASL or the
176 structural related term into account were generated. β_{asl} and β_{struct} pairs
177 equal to [0.25; 0.75], [0.5; 0.5] and [0.75; 0.25] were also evaluated.

178 Images reconstructed by means of nearest neighbor interpolation, trilinear
179 interpolation and 3rd order B-splines interpolation were then generated and
180 compared to the CBF maps reconstructed by means of the proposed method
181 performed with the selected β_{asl} and β_{struct} .

182 The root mean square errors (RMSE) between the original HR simulated
183 CBF maps and the reconstructed images were calculated in order to evalu-
184 ate the ability of each method to provide reconstructed images close to this
185 reference.

186 As ASL images acquired in clinical conditions are usually affected by noise,
187 commonly considered as gaussian in CBF maps due to the averaging of multi-
188 ple label-control pairs, we also studied the behavior of each of these methods
189 as a function of the amount of noise. Downsampled images affected by gaus-
190 sian noise with standard errors corresponding to 3 to 14% of the GM CBF
191 value were reconstructed at the original resolution in order to evaluate this
192 behavior. Figure 1 illustrates these images generation and the processing
193 steps.

194 2.3.2. *Healthy controls*

195 The SR reconstruction method was also evaluated on images acquired
196 on 4 healthy subjects (3 females, 1 male, age = 34 ± 6 years). For each of
197 these volunteers, images were acquired on a 3T Siemens Verio scanner with
198 a 32-channel head-coil. The structural image was a MP2RAGE UNI (reso-
199 lution: $1 \times 1 \times 1$ mm³). pCASL (resolution: $3.5 \times 3.5 \times 5$ mm³, interslice
200 gap: 1 mm, 30 control-label pairs repetitions, PLD: 1800 ms, labeling dura-
201 tion (LD): 1800 ms, 20 slices [22]) and M0 (resolution: $3.5 \times 3.5 \times 5$ mm³, inter-
202 slice gap: 1 mm, 5 repetitions, 20 slices) images were acquired as the low reso-
203 lution data used to generate the CBF maps to be reconstructed by increasing
204 their dimensions by a factor of 2 in each direction. HR pCASL images were
205 also acquired for the evaluation purpose (resolution: $1.75 \times 1.75 \times 2.5$ mm³,
206 interslice gap: 0.5 mm, 100 control-label pairs repetitions, PLD: 1800 ms,
207 LD: 1800 ms, 20 slices), as well as HR M0 (resolution: $1.75 \times 1.75 \times 2.5$ mm³,
208 interslice gap: 0.5 mm, 10 repetitions, 20 slices). While not allowing to cover
209 the entire brain, a number of 20 slices was selected for these HR acquisitions

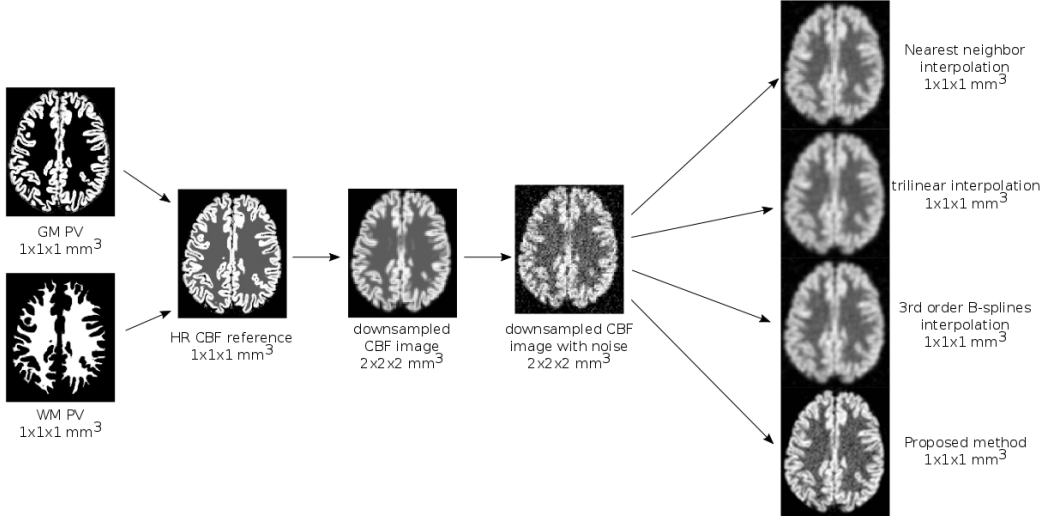


Figure 1: Pipeline describing the generation of the simulated dataset and the different reconstruction methods to be compared, applied to the downscaled and noise corrupted images.

210 as a matter of acquisition time. Image SNR being proportional to voxel
 211 volume, 100 repetitions were acquired in order to generate the HR pCASL
 212 images. While not entirely compensating for the SNR decrease in compari-
 213 son with the 30 repetitions low resolution acquisitions, this repetition number
 214 was chosen as a compromise between scan time (10 minutes), risk of subjects
 215 motion and SNR.

216

217 CBF maps were obtained by applying the general kinetic model for pCASL
 218 acquisitions [2]:

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

219 with λ the blood/brain partition coefficient ($\lambda : 0.9$), α the labeling efficiency
 220 ($\alpha : 0.85$), ΔM the control-label difference, and $T_{1,blood}$ the blood T_1 relax-
 221 ation time ($T_{1,blood} : 1650$ ms).

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

225 *2.3.3. Correlation with DSC*

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

235 The dataset contains images of 10 patients imaged for brain tumors (3 fe-
 236 males, 7 males, age = 63 ± 13 years, 5 grade IV tumors, 1 grade III, and
 237 3 patients not showing hyper-perfusion signals after evaluation by an ex-
 238 periented neuroradiologist). Images were acquired on a 3T Siemens Verio
 239 scanner with a 32-channel head-coil. A 3D T1w sequence (resolution: $1 \times 1 \times$
 240 1 mm^3) was acquired, as well as a PICORE Q2TIPS PASL sequence with
 241 flow crusher gradients (EPI readout, TR: 3000 ms, TE: 18 ms, FOV: $192 \times$
 242 192 mm^2 , flip angle: 90° , in plane resolution: $3 \times 3 \text{ mm}^2$, slice thick-
 243 ness: 7 mm, interslice gap: 0.7 mm, inversion time (TI): 1700 ms, bolus width
 244 (TI_1): 700 ms, 30 control-label repetitions) and a DSC sequence (GRE EPI
 245 readout, TR: 1500 ms, TE: 300 ms, FOV: $230 \times 230 \text{ mm}^2$, flip angle: 90° ,
 246 in plane resolution: $1.8 \times 1.8 \text{ mm}^2$, slice thickness: 4 mm, interslice gap: 1.2 mm,
 247 100 measures).

248
 249 The CBF maps were generated from the DSC images by use of the MR
 250 manufacturer software. An arterial input function was manually chosen to
 251 calculate the DSC relative CBF on a voxel basis. The method in use is based
 252 on a singular value decomposition deconvolution, as described in Østergaard
 253 et al. [23]. The general kinetic model for PASL acquisitions was applied to
 254 the ASL scans [2]:

$$CBF = \frac{6000 \cdot \lambda \cdot \Delta M \cdot \exp\left(\frac{TI}{T_{1,blood}}\right)}{2 \cdot \alpha \cdot TI_1 \cdot M0}, \quad (8)$$

255 The other parameters are the same as in (7), except $\alpha : 0.98$.

256 Although linear correlation between ASL and DSC relative CBF has not
 257 been strictly demonstrated, in a first approximation as shown in [24, 25,
 258 26], we assume that positive correlations should be obtained between both

259 estimations. Therefore, the Pearson correlation coefficients were calculated
260 between the low resolution ASL CBF and the registered HR DSC CBF maps,
261 and the SR reconstructed ASL CBF and DSC CBF maps.

262 *2.4. Implementation details*

263 An in-house image processing pipeline based on Python, Cython, Nipype [27]
264 and SPM12 functions was used to conduct the experiments. Considering re-
265 sults presented in [16] and our own experiments, the patch size was chosen
266 equal to $3 \times 3 \times 3$ voxels in the non-local patched-based regularization, and
267 the search volume to $7 \times 7 \times 7$ voxels.

268 **3. Results**

269 *3.1. Simulated dataset*

270 Figure 2 presents the mean RMSE values obtained between the high res-
271 olution simulated references and the images reconstructed by means of the
272 proposed SR reconstruction method for noise levels equal to 3%, 6% and 9%
273 of the GM CBF value. One can first notice that referring to only one of the
274 ASL or structural images provides less satisfactory reconstructions. Indeed,
275 taking only the ASL image into account does not allow to recover details
276 absent from the downsampled CBF maps. In the contrary, a reconstruction
277 only based on the structural image will not allow to consider and preserve
278 CBF patterns only visible in the ASL image. One can then notice that the
279 balance between β_{asl} and β_{struct} does not lead to significant differences when
280 a low level of noise is added to the simulated CBF maps. However, differences
281 in this balance have a higher influence on the quality of the reconstruction
282 when dealing with images corrupted by a higher noise level. In the case
283 of $[\beta_{asl}; \beta_{struct}] = [0.25; 0.75]$, the weights generated to perform the recon-
284 struction are more governed by the ASL related term, which can explain the
285 higher RMSE values obtained when the level of noise increases. $[\beta_{asl}; \beta_{struct}]$
286 $= [0.5; 0.5]$ and $[0.75; 0.25]$ provide lower RMSE values when a realistic
287 noise level is added to the images, and no significant difference between their
288 RMSE distributions can be noted. Therefore, in the context of this work,
289 we propose to keep an equal contribution of the ASL and structural related
290 terms, meaning $[\beta_{asl}; \beta_{struct}] = [0.5; 0.5]$.
291 Images corresponding to reconstructions of a low resolution CBF map cor-
292 rupted by gaussian noise with a standard deviation equal to 9% of the GM
293 CBF value, which we qualitatively suppose being a close example to effective

294 low resolution acquired images, are displayed in Figure 3. The images gener-
 295 ated by use of interpolation techniques (nearest neighbor, trilinear and 3rd
 296 order B-spline interpolations) appear flattened, compared to the SR recon-
 297 structed map, which enables to recover sharp structures and edges. Table 1
 298 confirms these observations, with lower mean RMSE values (in bold) calcu-
 299 lated between the simulated reference images and the SR reconstructed ones
 300 than between the references and the interpolated images. In addition, the
 301 evolution of these RMSE values indicates that the more the standard devi-
 302 ation of noise increases, the closer to the reference the reconstructed image
 303 is in comparison with the interpolated images. This result is associated with
 304 the capability of the proposed method to denoise the images. Significant
 305 RMSE distribution differences between the proposed reconstruction method
 306 and all interpolation techniques are found for levels of noise superior to 9%
 307 of the GM CBF value ($p < 0.00111$ after Bonferroni correction for an α level
 308 equal to 0.01), and are marked by asterisks in table 1.

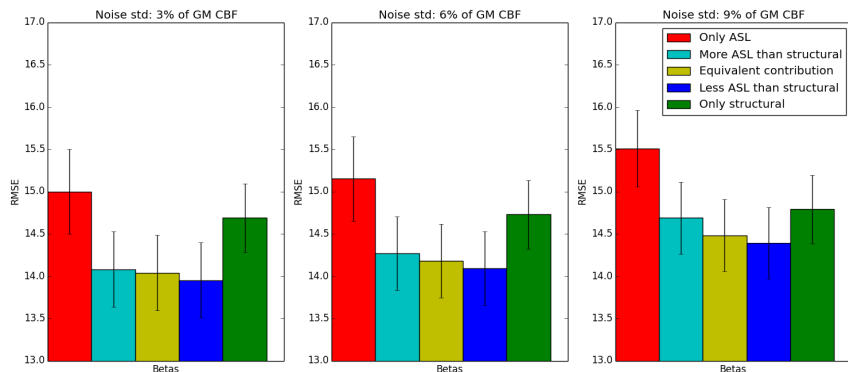


Figure 2: Graphs showing the RMSE values calculated between the reference HR image and images reconstructed with the proposed high resolution reconstruction method, by taking only the ASL, $[\beta_{asl}; \beta_{struct}]$ equal to $[0.25; 0.75]$ (more ASL than structural), $[0.5; 0.5]$ (equivalent contribution), $[0.75; 0.25]$ (less ASL than structural), or only the structural image into account. The displayed noise levels correspond to 3%, 6% and 9% of the GM CBF value.

309 3.2. Healthy controls

310 Figures 4, and 5 present the images obtained from one of the 4 volunteers.
 311 Sagittal slices are shown, notably to insist on the influence of the methods on

Noise std	3	6	9	11	14
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	13.92 ± 1.05	14.05 ± 1.04	14.34 ± 1.01	14.79 ± 0.99	15.56 ± 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. Asterisks are joined to RMSE values corresponding to significant differences compared to the values obtained by application of the proposed method.

312 the staircase effect related to the particularly low initial resolution in the slice
313 acquisition direction (5mm + 1mm gap). This effect is strongly corrected by
314 the proposed SR reconstruction method. The RMSE values are reported in
315 table 2, the proposed method providing images closer to the HR references
316 than common interpolation techniques for three of the four subjects.

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	26.34	25.04	29.68	22.49
Proposed method	26.44	24.49	29.12	22.20

Table 2: 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).

317 3.3. Comparison with DSC

318 Figure 6 reports, for each of the subjects, the values of the Pearson cor-
319 relation coefficients obtained between the reference DSC CBF images and
320 the low resolution acquired ASL CBF maps, their interpolations by trilinear
321 and 3rd order B-splines and the images generated with the proposed SR re-
322 construction method. For each subject, the reconstructed image was more
323 correlated to the DSC reference than the others. The significance of the dif-
324 ferences was assessed by applying a Fisher transformation to the correlation

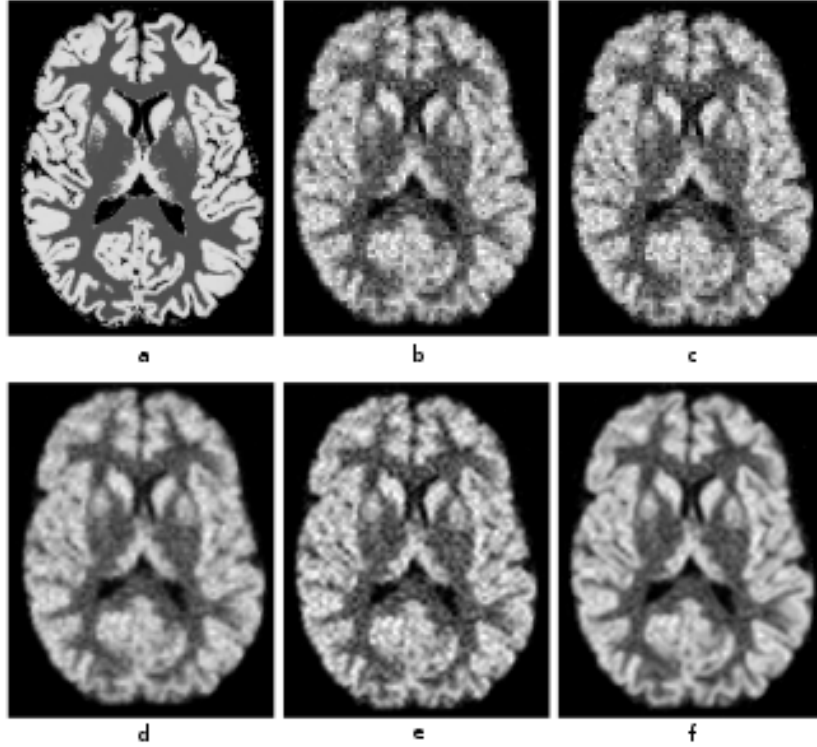


Figure 3: Simulated dataset: comparison of a) a HR reference image and b) the corresponding low resolution downsampled image corrupted by noise with $\text{std}=9\%$ of the GM CBF value, c) nearest neighbor interpolation, d) trilinear interpolation, e) 3rd order B-splines interpolation, and f) proposed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

325 coefficients. The p-values obtained after this transformation indicate a sig-
 326 nificant difference between the correlation coefficients distributions. Indeed,
 327 a paired t-test between the correlation values obtained for the proposed re-
 328 constructions and the low resolution acquisitions provided a p-value equal to
 329 1.4×10^{-4} , $p = 8 \times 10^{-5}$ by comparison with the trilinear interpolation, and
 330 $p = 3.33 \times 10^{-4}$ by comparison with the 3rd order B-splines. Figure 7 dis-
 331 plays the DSC CBF images, low resolution ASL CBF maps and CBF maps
 332 reconstructed with our method for two of the patients.

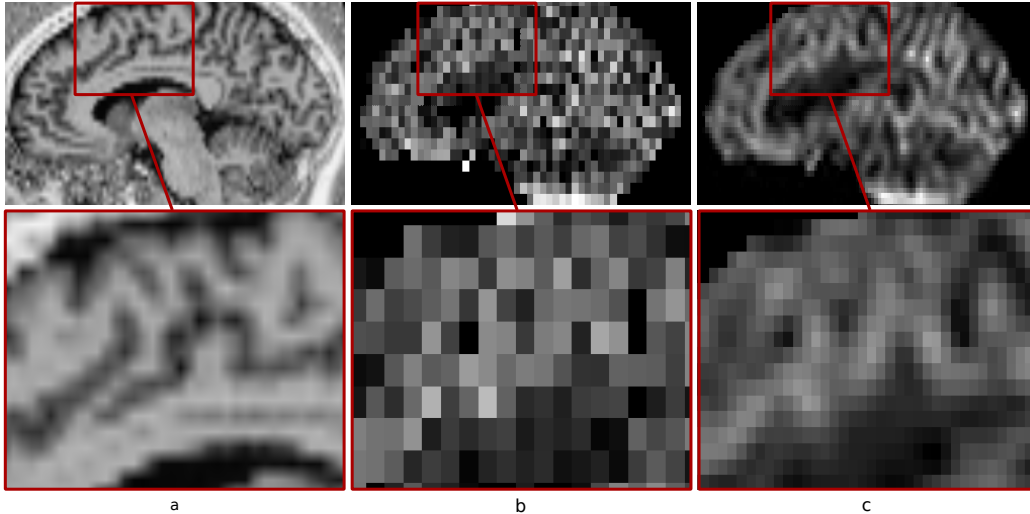


Figure 4: Healthy subject: sagittal slices of a) a structural image, b) the corresponding CBF map from the low resolution pCASL acquisition, and c) the proposed SR reconstruction. Upper line: sagittal slice, bottom line: zoom on the same slices.

333 4. Comparison with Partial Volume Correction methods

334 4.1. Method

335 Typical low resolution ASL acquisitions lead to well known PVE in ASL
 336 images, sometimes unfortunately preventing clinicians to interpret MRI ob-
 337 servations such as reduced CBF values in regions of interest. Indeed, they
 338 could be the consequences of an effective reduced perfusion, a thinner GM or
 339 small subject motion. Because of the fact that the method described in this
 340 paper enables the recovery of high frequency details that are not visible in
 341 low resolution acquisitions, we propose to evaluate the influence of this recov-
 342 ery on a potential reduction of PVE. This is of particular interest, since the
 343 PVE correction methods that are currently the most commonly applied to
 344 ASL images correct CBF values at the voxel level, thus not providing better
 345 detailed images. Moreover, the method that we present in this work is only
 346 dependent on the registration of a HR structural image on an interpolated
 347 ASL one, while classical PVE correction methods require the use of tissue
 348 partial volume estimates. These partial volume estimate maps are provided
 349 by segmentation algorithms, and are therefore subject to potential additional
 350 errors.

351 In order to compare the impact of these algorithms on PVE, a simulation was

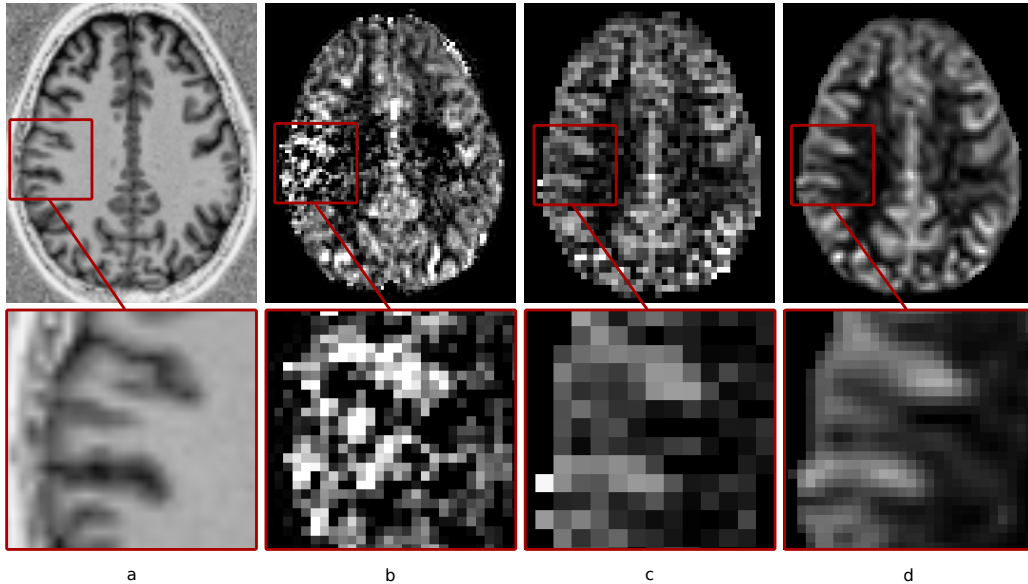


Figure 5: Healthy subject: axial slices of a) a structural image, b) the corresponding CBF maps from the acquired HR pCASL and c) low resolution pCASL acquisitions, and d) the proposed SR reconstructed CBF image. Upper line: sagittal slice, bottom line: zoom on the same slices.

352 conducted from the same 9 structural images as presented in 2.3.1, in which
 353 we aimed at having the most possible information about intensity values. In
 354 order to construct these 9 HR ASL images in which we knew the exact voxel
 355 constitution and associated values, images containing 100% GM or WM vox-
 356 els were created, by thresholding the partial volume estimates generated by
 357 the SPM12 segmentation algorithm. Perfusion maps were generated by af-
 358 fecting ΔM values of 10 for GM and 1.5 for WM, with additional sinusoidal
 359 variations of 20% amplitude to make them more realistic, and evaluate the
 360 capability of the tested algorithms to preserve spatial variations and details
 361 [28]. The same process was used to create M0 images, with values of 1350
 362 and 1000 in GM and WM respectively. These HR perfusion and M0 maps
 363 were downsampled by averaging $2 \times 2 \times 2$ voxel cubes, therefore reducing the
 364 size of the images and adding PVE, while knowing the exact brain tissue mix-
 365 ture of these new low resolution voxels. Different amount of gaussian noise
 366 (SNR=5,10) were added to these images in order to evaluate the influence of
 367 noise on PVE correction. The general kinetic model for pCASL acquisitions
 368 was then applied to obtain the corresponding CBF maps ($\lambda : 0.9, \alpha : 0.85,$

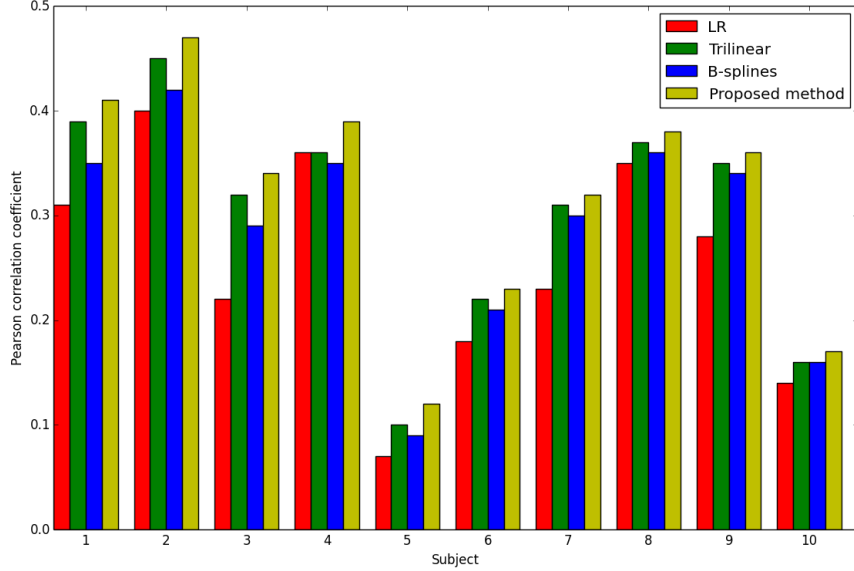


Figure 6: Pearson correlation coefficient between the reference DSC CBF maps and low resolution CBF images, the same images after trilinear interpolation, 3rd order B-splines interpolation and the proposed SR reconstruction method. These coefficients are presented for each of the 10 subjects.

369 $T_{1,blood}$: 1650 ms, LD: 1800 ms, PLD: 1800 ms).

370 The effect of the proposed algorithm on PVE was evaluated by analyzing its

371 ability to recover the effective GM contribution in the CBF values observed

372 in each voxel, in comparison with the linear regression method, which is one

373 of the standard PVE correction technique applied to ASL images [6].

374 Our proposed SR method provides high resolution CBF maps unlike the lin-

375 ear regression method, which produces two partial volume maps at the initial

376 resolution. This is the reason why our SR CBF maps have been downsam-

377 pled, in order to be able to compare the two results. The GM contributions

378 in the CBF maps obtained by applying the general kinetic model to the HR

379 perfusion and M0 images, without noise, were considered as the references

380 to which the generated images had to be compared. Figure 8 illustrates the

381 pipeline that corresponds to the above-mentioned operations.

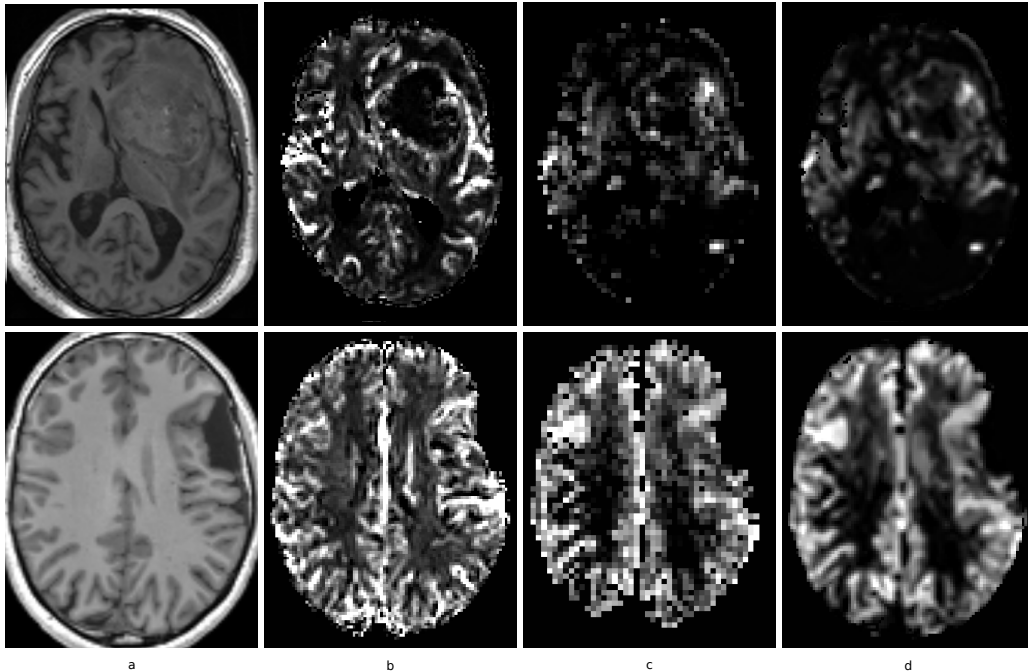


Figure 7: a) structural image, b) DSC CBF image, c) low resolution ASL CBF image and d) SR reconstructed ASL CBF map. The two lines correspond to images of two different subjects.

382 *4.2. Results*

383 Contrary to differences in the produced GM contribution maps reported
 384 in Zhao et al. [28], between an application of the linear regression to the
 385 calculated CBF map and to perfusion and M0 images before the CBF cal-
 386 culation, our method did not show such significant differences while testing
 387 for the influence of this effect. Figure 9 presents the GM contributions to
 388 the CBF values in a reference image, their recovery by application of the
 389 linear regression method to the low resolution CBF map, by applying the
 390 same method to perfusion and M0 images before CBF calculation, and after
 391 increasing the CBF image dimensions with our method. Figure 10 shows
 392 the difference images obtained after the subtraction of each of the produced
 393 images listed above and the corresponding reference. An important aspect il-
 394 lustrated in these difference images is the fact, already stated in [6, 7, 12, 28],
 395 that the linear regression method implies a smoothing of the GM contribu-
 396 tions. On the contrary, the sinusoidal variations are retained in the image

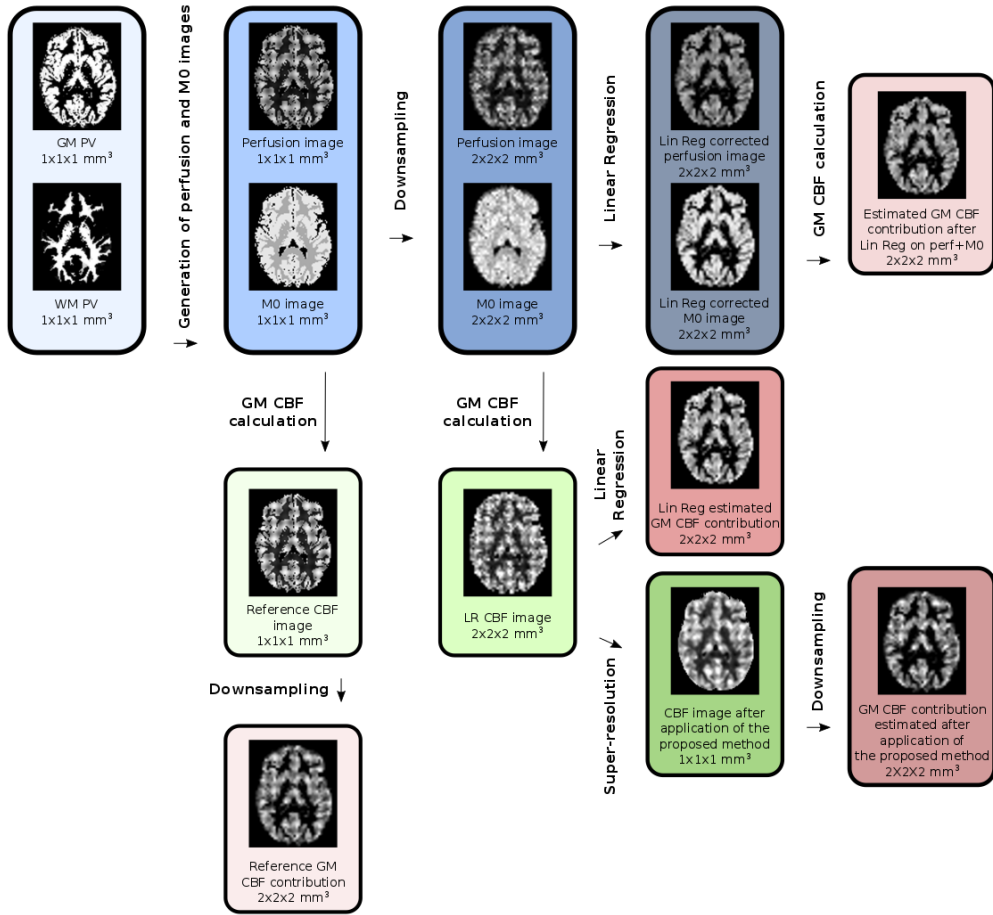


Figure 8: Pipeline describing the operations applied to each of the 9 images of the simulated dataset and the GM contribution assessment maps to be compared.

397 originating from the proposed algorithm.
 398 Table 3 presents the evolution of the mean RMSE values calculated between
 399 the generated GM contribution images and their references as a function of
 400 noise (SNR=inf, 10, 5). In practice, both applications of the linear regression
 401 method to the CBF maps or to the perfusion and M0 images are commonly
 402 accepted [28]. Since the mean RMSE values obtained by applying our method
 403 to CBF maps are bounded by the mean RMSE provided by these two linear
 404 regressions, we can presume that our method reduces the influence of PVE.
 405 Moreover, the linear regression method is based on the use of information
 406 provided by partial volume estimates, which makes it dependent upon the

407 chosen segmentation algorithm and sensitive to potential segmentation er-
 408 rors. On the contrary, our SR reconstruction method is independent of any
 409 segmentation algorithm. In order to investigate the influence of these seg-
 410 segmentation corruptions on the GM contribution maps resulting from the ap-
 411 plication of the linear regression, we simulated variations in the segmented
 412 partial volume estimates by introducing gaussian noise or by applying an
 413 opening and closing morphological operation to these partial volume maps.
 414 Tables 4 and 5 show a significant increase in the mean RMSE values when
 415 the partial volume estimates are modified. These results indicate that the
 416 property of the SR reconstruction to be independent of the use of partial
 417 volume estimates could be of great interest to avoid potential errors due to
 418 segmentation corruption.

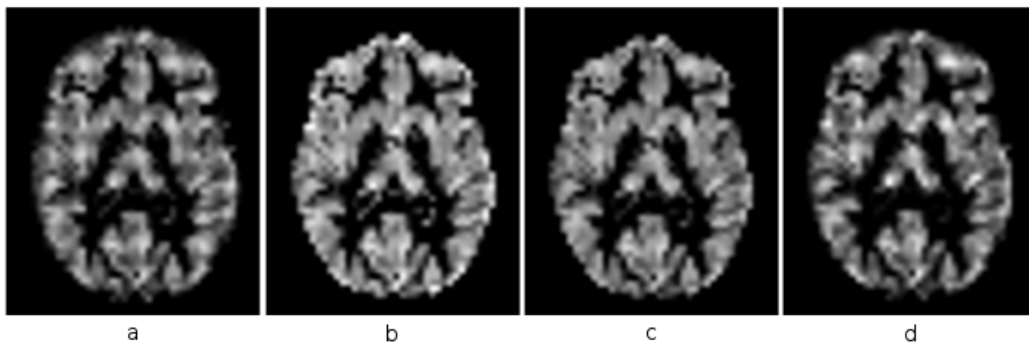


Figure 9: Comparison of gray matter cerebral blood flow contribution maps: a) GM contribution maps from the reference image, b) linear regression applied to the low resolution CBF image, c) linear regression applied to the low resolution perfusion and M0 images, and d) proposed SR method applied to the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

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

Table 3: 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.

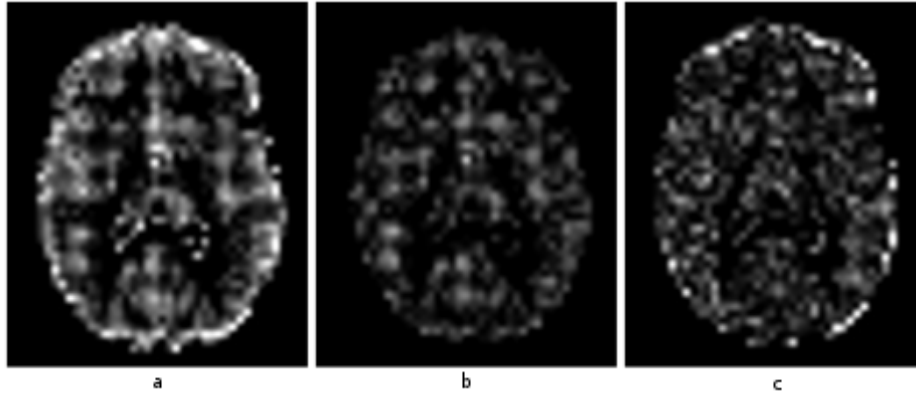


Figure 10: Comparison of gray matter cerebral blood flow contribution maps: a) difference images obtained by subtraction of the reference GM contribution map from the images obtained by applying the linear regression (Lin Reg) to the low resolution (LR) CBF image, b) the linear regression to the LR perfusion 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	7.46 ± 0.60	7.65 ± 0.59	8.09 ± 0.62
Lin Reg on Perf & M0	5.84 ± 0.23	5.97 ± 0.24	6.24 ± 0.22
SR on CBF	5.66 ± 0.11	5.94 ± 0.13	6.77 ± 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 and on the perfusion and M0 images, with noise added to the partial volume estimates needed by the Lin Reg method, and the proposed SR method applied to the LR CBF images.

Method	SNR=inf	SNR=10	SNR=5
Lin Reg on CBF	11.68 ± 0.70	11.78 ± 0.70	12.10 ± 0.75
Lin Reg on Perf & M0	11.19 ± 0.50	11.23 ± 0.49	11.42 ± 0.51
SR on CBF	5.66 ± 0.11	5.94 ± 0.13	6.77 ± 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 an opening+closing operation added to the partial volume estimates needed by the Lin Reg method, and the proposed SR method applied to the LR CBF images.

419 5. Discussion

420 In this work, we have presented and investigated different properties of a
 421 SR reconstruction method dedicated to ASL images. This method enables to

422 increase the level of details, while providing a denoising of the reconstructed
423 images. It is based on the assumptions of an appearing accordance between
424 neighborhoods in the image to be reconstructed and a classically acquired
425 HR anatomical image, and that distant neighborhoods could serve as a learn-
426 ing database in the reconstruction process.

427 On a simulated dataset, we have shown that the contributions of the ASL and
428 structural related terms can be considered as equivalent in the reconstruction
429 process, by selecting $[\beta_{asl}; \beta_{struct}] = [0.5; 0.5]$. Our method is also shown to
430 provide images closer to references than common interpolation techniques.
431 The fact that this result could be obtained with different levels of noise added
432 to the images to be reconstructed is an indication of the ability of the pro-
433 posed method to denoise the reconstructed images.

434 Experiments on low resolution data acquired on healthy subjects confirmed
435 these findings in 3 over 4 subjects. The main limitation of this study is
436 nonetheless the relevance of the definition of the HR ASL images as ref-
437 erences, because of their low SNR. In order to maintain the scan time rea-
438 sonable and avoid subject motions that would almost certainly happen after
439 10 minutes of continuous scanning, 100 control-label repetitions have been
440 acquired to generate the high resolution ASL images. This number is cer-
441 tainly still not sufficient to obtain an appropriate image quality, which could
442 explain the fact that a better RMSE value was obtained by applying a 3rd
443 order B-spline interpolation for the first subject. This limitation is precisely
444 the reason why we chose to conduct the two other studies, meaning with a
445 simulated dataset and the comparison with DSC images.

446 The study based on images of patients with brain tumors revealed a signifi-
447 cantly increased correlation between DSC and images reconstructed with our
448 method, supporting the capability of the proposed method to recover details
449 by driving the reconstruction of ASL images with a high resolution struc-
450 tural one. The TI value chosen to acquire these PASL data was possibly
451 a little short for subjects 5, 6 and 10, associated to intense ASL signals in
452 their macrovasculature, which could explain the reduced correlation values
453 obtained for these three subjects.

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

459 Despite the three validation approaches that were addressed in the context

460 of this work, we did not evaluate the method on pathologies implying subtle
461 and localized perfusion changes. Investigating the capability of the method
462 to preserve CBF modifications appearing before structural changes, as it is
463 the case for early stages of neurodegenerative disease for exemple, would be
464 of interest as a future work.

465 The method proposed in this paper only depends on the accurate registration
466 of a HR structural image on the initially interpolated ASL image to be recon-
467 structed. Indeed, experiments revealed that the initial interpolation method
468 selected in order to increase the dimension of the image to reconstruct does
469 not have a significant influence on the generated image, and denoising is per-
470 formed jointly with the increase in the level of details. This aspect makes
471 our method an appropriate tool to increase the quality and the fidelity of
472 ASL images, and particularly CBF maps, with respect to effective physio-
473 logical processes. Another promising aspect is its capability to recover well
474 detailed ASL images from standard clinical acquisition protocols, therefore
475 not increasing the acquisition time and patient discomfort. We believe that
476 such a post-processing procedure could help clinicians to establish even more
477 accurate diagnosis, by reducing interrogations concerning the reasons of re-
478 duced perfusion values and being able to distinguish GM thickness reduction
479 or an effective perfusion reduction for example.

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