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MRI-Guided Partial Volume Correction in Brain PET Imaging: Comparison of Five Algorithms

Gaël Boivin[1], Vassilis Genoud[1], Habib Zaidi[1,*]

1. Division of Nuclear Medicine and Molecular Imaging, Geneva University Hospital, Switzerland.

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ABSTRACT

Purpose: Positron Emission Tomography (PET) imaging offers the possibility of measuring brain metabolic activity in vivo. However, brain PET images remain difficult to interpret in clinical setting because of the limited spatial resolution of current generation clinical PET scanners. Therefore, the resulting partial volume effect (PVE) is a challenging issue for brain PET image interpretation and quantitative analysis. To overcome this limitation, several algorithms allowing the correction for PVE (PVC) have been developed and assessed mainly in research setting. In this work, we perform a comparative study of 5 different PVC methods using clinical studies.

Methods: 17 clinical studies of patients suffering from neurodegenerative disease were included in our study protocol. 3D T1-weighted MRI and FDG-PET were acquired on dedicated MR and PET-CT systems, respectively. MR images were rigidly co-registered to corresponding PET images using the Hermes multimodality platform and segmented using statistical parametric mapping package (SPM8). The resulting images were corrected for PVE using four voxel-based techniques proposed by different groups including Alfano, Muller-Gartner, Meltzer, and Shidahara, and one volume of interest (VOI)-based technique proposed by Rousset.

Results: Our results demonstrate a significant increase of the activity concentration in the gray matter. Consequently, the activity in the white matter decreases considerably when using all PVC methods, except for Meltzer and Shidahara. The comparative analysis demonstrates that, among all considered techniques, Alfano's method appears to substantially increase the GM signal. When applying the different PVC methods to specific regions of interest linked to a specific pathology, the results highlight the bias when using uncorrected PET images, but still respecting specific modification patterns of the disease.

Conclusion: Our results confirm the necessity of applying PVC to brain PET images in order to obtain more reliable and accurate quantification. This applies particularly to elderly patients with neurodegenerative disease where atrophy induces underestimation of the true PET signal.

Keywords:
PET,
MRI,
Brain Imaging,
Partial Volume Effect,
Partial Volume Correction.

1. Introduction

Positron Emission Tomography (PET) is a nuclear medical imaging technique enabling to measure functional and molecular processes in vivo. PET is routinely used in various clinical and research applications, including but not limited to oncology, neuroscience, psychiatry, cardiology and pharmacology. The principle of PET is to record the simultaneous emission of two annihilation photons resulting from positron-electron annihilation, after injection of a radiolabelled tracer.

Despite many noteworthy advances, PET images still suffer from poor spatial resolution compared to other clinically used anatomical imaging modalities. Spatial resolution determinants are either physical (positron

** Corresponding Author:*
Habib Zaidi, PhD
Division of Nuclear Medicine and Molecular Imaging, Geneva University Hospital, Switzerland.
Tel: +41 22 372 7258
E-mail: habib.zaidi@hcuge.ch
Gaël Boivin, Vassilis Genoud contributed equally to this work

range, non-colinearity, etc.), related to instrumentation or the detector system (inter-crystal scattering, parallax error, pulse pile-up effect) and the reconstruction procedure used (span, arc correction, convergence rate in iterative reconstruction, voxel sampling and partial volume effect) [1]. Even though significant efforts were undertaken to offset most of these factors, correction for partial volume effect (PVE) is not often performed yet in the clinic. However, previous studies correcting for PVE have revealed relevant information concerning a priori well established disease characteristics, that is, the reduced brain metabolism in Alzheimer disease is not only due to the CSF increase linked to atrophy [1, 2]. In epileptic foci characterization, atrophy alone does not explain the resulting hypometabolism [3]. PVC is also relevant when measuring DOPA decarboxylase activity in Parkinson patients [4].

PVE is the loss of recorded activity due to resolution limits of the imaging system. In PET imaging, it can be subdivided in two types. The most important is attributed to the point spread function (PSF) of the PET scanner, resulting in spill-over of counts (known as cross contamination) between different regions within the image. The second, also referred to as tissue-fraction effect, is linked to the sampling or voxel size of the image. It occurs when different tissue types are contained within a single voxel in a so thin scale that their relative activity concentration cannot be interpreted separately.

We consider three main compartments in the brain, namely the grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The GM/WM activity ratio for [18F]-Fluorodeoxyglucose (FDG) is around 4 in a normal subject. The CSF activity can reasonably be considered to be zero. The thickness of the human cortex is about 2-4 mm, but some disorders can cause sporadic atrophy. This is why current measurements of brain metabolism may be erroneous because the cortex characteristics make the activity of tracer mapping particularly sensitive to PVE. In Alzheimer disease (AD), the loss of activity concentration has been demonstrated to be overestimated if PVE correction is not performed [5].

Several PVC strategies have been proposed in the literature. They can be classified under different categories: techniques which primarily enhance images, techniques using anatomical information provided by co-registered anatomical (CT/MR) images that might be coupled with a region of interest repertory, and finally wavelet resolution recovery integrating synergically functional and structural information.

In this work, we perform a comparative evaluation of methods belonging to the second and third category of techniques to evaluate the impact of partial volume correction on quantitative analysis and try to emphasize a method that could be relevant for routine application in the clinic in terms of methodology robustness and ease of use. The method proposed by Rousset (RM) [6] is a region of interest (ROI)-based technique that consists in defining a set of ROIs to correct the crosstalk between them. The methods proposed by Meltzer (Mm) [7], Muller-Gartner (MGm) [8], MG Rousset (MGRm), MG Alfano (MGAm) [9], Alfano Centrum Semi-ovalum (ACSm), Alfano-Rousset (ARm) and Alfano-Alfano (AAm) use different implementations of MRI-guided voxel-based approaches to correct for PVE. Finally, a novel method using wavelet integration proposed by Shidahara was also considered.

2. Methods

2.1. Partial Volume Effect Correction Techniques

Five different PVC algorithms were compared in this work. First, Rousset's method is a ROI-based PVC technique. This method processes the brain as a set of different ROIs and corrects for the interaction (spill-in and spill-out) between all these different ROIs. Consequently, the mean activity within the defined ROI was calculated taking into account all the ROIs adjacent to it.

The second class of methods uses a voxel approach for correcting PVE. One of the first techniques falling under this category was described by Meltzer [7]. This method originally takes into account two compartments, namely the GM and WM. The recovery of GM achieved by this technique was reported to be close to 81.4% [10]. Muller-Gartner (MGm) [8], then extended this method to get more accurate estimates of the GM metabolism, separating the GM and the WM, thus resulting in a three-compartment method. Focusing on the GM estimation, the WM and CSF are considered as background regions. If the CSF is arbitrarily, but reasonably set to 0 activity, the WM activity has to be estimated in order to get most reliable results for the GM. This is why this method includes 3 variations. The first WM estimation is based on the use of the centrum semi-ovale (CS) region, an exclusive WM ROI large and far enough from the GM to be estimated as uncontaminated by PVE, this method will be reported as MG-CS. The GM recovery using MGm was reported to be 96.2% [10]. The remaining techniques include MG-Rousset (MGRm) and MG-Alfano (MGAm), where the second

part of the acronym corresponds to the method of estimating the WM activity.

The ROI-based method doesn't produce a corrected image since it only estimates the corrected activity concentration within predefined ROIs. However, this technique was reported to be more accurate when quantifying deep structures [11] and does not homogenize all the WM compartment. This technique is different from voxel-based approaches considered to be more accurate for the cortex [11], but produces average values for the defined ROIs without taking into account possible variation of the activity within them.

Alfano et al. [9] developed a method combining both approaches with the aim to take advantage of both of them. Since the method still requires an estimate of the WM activity, 3 different subtypes, Alfano-CS (ACSm), Alfano-Rousset (ARm) and Alfano-Alfano (AAm) were considered.

The last method explored belongs to a new category of PVC techniques based on a wavelet integration approach. In order to recover the high frequency information lost during Fourier transformation of the initial signal, Shidahara proposed a method that incorporates this high frequency information from an MR image. The method was initially described by Calvini et al [12] and improved by Boussion [13]. Shidahara et al [14] demonstrated that the incorporation of segmented images could improve performance. The originality of the approach and promising results obtained by its developers motivated us to include it in the comparative analysis reported in this work.

2.2. Clinical Data Acquisition

The clinical data used in this work consist of a set of images used in a previous study [15]. The database is composed of 18 patients suffering from neurodegenerative disease. Patients underwent FDG PET/CT scans at Geneva University Hospital. Examinations were performed on a Biograph HiRez Sensation 16 PET/CT scanner (Siemens Healthcare, Erlangen, Germany) using the usual clinical protocol for brain PET imaging. Data acquisition started 30 minutes after injection of 370 MBq of [18F]-FDG. The CT study (120 kVp, 320 mAs, 16x0,75 collimation, pitch of 0.8 and 1.5s per rotation) was performed just before the PET emission study (20 min, 1 bed position).

MR images were acquired on a Philips 1.5-T Eclipse scanner (Philips Medical Systems, Best, The Netherlands) using a 3D T1-weighted gradient-echo sequence with the following parameters: TR = 15 ms, TE = 4.4 ms and a flip angle of 25°. The image matrix consisted of 256 × 256 × 160 voxels, with a resolution in the transaxial direction of 0.97 mm × 0.97 mm, and an axial resolution of 1.1 mm.

Out of the 18 patients, one had to be excluded from the study because of recurrent segmentation error (fig. 6). Four patients were suspected to suffer from Alzheimer disease, 3 from semantic dementia, 3 from fronto-temporal dementia, 2 from dementia with Lewy bodies, 1 from Parkinson like dementia, 1 from cortico-basal dementia, and the remaining 3 with non-specific dementia. Their age was within the range 50 to 91 years (mean ± SD = 72 ± 9.15).

2.3 Algorithmic Implementation of PVC Techniques

PET and MR images were co-registred using a rigid-body registration technique (6 degrees of freedom: 3 translations, 3 rotations) on a Hermes platform (Hermes MultiModalityTM, Nuclear Diagnostics AB, Sweden). Images were then converted to ANALYZE format and used as input to the PVElab software [10] to run the different processing steps as follows:

- PET and MR images can be co-registered using statistical parametric mapping (SPM) [16]. This step was skipped, since it was already carried out as described above.
- Segmentation is, then, performed using SPM 8, resulting in 3 compartments corresponding to GM, WM and CSF.
- A re-slicing step follows as for PVC: segmented MR images must be re-sliced.
- Each image is processed for labelling VOIs using the MNI Atlas.
- PET images are corrected for PVE. Here, we correct for PVE using 4 different techniques, Meltzer, Muller-Gartner with 3 variations, Alfano also with 3 variations and with Rousset.

Shidahara's approach was also used to correct for PVE. Based on the images obtained by PVElab, we implemented the wavelet approach in Matlab (Mathworks Inc) to obtain comparable results. Thereafter, all images produced by the PVC techniques were reprocessed, integrating Hammers Atlas [17, 18] for standardized VOIs definition.

Segmentation is an important error factor for PVC [19, 20]. Thus, each segmented MR image is evaluated visually. For an unknown reason, SPM8 segmentation process failed systematically for one patient that was subsequently removed from the study protocol.

2.4. Comparative Assessment Strategy

Since almost all these methods were previously described in detail and partially validated, we focus on the correction brought by these different techniques to GM and WM signal in the whole volume and in specific ROIs depending on patient's pathology. By normalizing all the results with respect to uncorrected images, we compare the difference between the impacts of the correction technique on the signal produced for each patient. Based on the previous validation models, we could observe the prospective accuracy of the methods, and estimate which correction tool best suits the clinical needs.

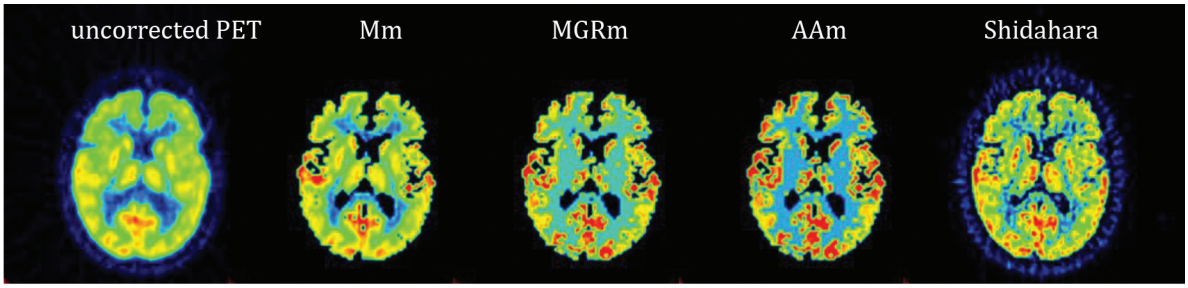

Figure 1. Illustration of the different PVC techniques applied to a clinical brain PET study. From left to right: uncorrected PET, and PVC images corrected using Mm, MGRm, AAm and Shidahara, respectively.

3. Results

Figure 1 shows representative slices of a clinical FDG-PET study and the corresponding images after PVE correction using the different techniques, except RM which provides only PVC quantitative estimates. Qualitative differences between the different PVC methods are visually explicit.

Tables 1 and 2 summarize the differences between the 5 PVC techniques with respect to WM and GM activity in clinical brain PET images. Mean values and standard deviations are also shown. Large differences can be observed between the different techniques. For the GM, Shidahara and Meltzer present the lowest increase, with an average of 17% and 31%, respectively, while the signal enhancement for the other techniques is larger ranging from 52% to 70%. For the WM, Shidahara and

Table 1. GM average values for the 17 patients comparing the signal enhancement (in %) for the different PVC algorithms. The values represent the average change in signal for the GM, depending on the PVC method. All of them have been normalized to the initial uncorrected PET images.

Mean	SD	GM Average	P 1	P 2	P 3	P 4	P 5	P 6	P 7	P 8	P 9	P 10	P11	P12	P13	P14	P15	P16	P17
31%	**4%**	**Meltzer**	33%	31%	32%	34%	34%	29%	36%	33%	30%	27%	29%	37%	23%	27%	32%	27%	30%
54%	**5%**	**MGCS**	53%	57%	57%	54%	55%	48%	66%	55%	51%	46%	47%	60%	45%	51%	55%	53%	55%
52%	**5%**	**MGRousset**	54%	54%	57%	53%	55%	48%	62%	54%	50%	45%	44%	57%	42%	48%	54%	51%	53%
53%	**4%**	**MGAlfano**	53%	55%	57%	53%	54%	48%	61%	55%	52%	45%	47%	59%	45%	51%	54%	54%	54%
68%	**7%**	**AlfanoAlfano**	70%	68%	71%	69%	71%	65%	85%	72%	66%	58%	57%	80%	57%	63%	68%	67%	69%
70%	**9%**	**AlfanoCS**	71%	72%	71%	72%	72%	66%	95%	71%	65%	60%	58%	84%	58%	64%	70%	66%	70%
66%	**9%**	**AlfanoRousset**	72%	67%	70%	68%	72%	66%	86%	70%	62%	57%	53%	74%	52%	57%	69%	61%	67%
63%	**8%**	**Rousset**	66%	65%	66%	67%	68%	62%	84%	66%	59%	54%	52%	69%	50%	57%	65%	59%	64%
17%	**6%**	**Shidahara**	17%	20%	23%	21%	12%	10%	10%	19%	20%	11%	11%	16%	17%	17%	20%	17%	34%
0%	**0%**	**raw PET**	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
		SD	14%	14%	14%	13%	14%	14%	20%	14%	12%	11%	10%	16%	12%	12%	14%	13%	14%

Table 2. WM average values for the 17 patients comparing the signal enhancement (in %) for the different PVC algorithms. The values represent the average change in signal for the WM, depending on the PVC method. All of them have been normalized to the initial uncorrected PET image.

Mean	SD	GM Average	P 1	P 2	P 3	P 4	P 5	P 6	P 7	P 8	P 9	P 10	P11	P12	P13	P14	P15	P16	P17
9%	2%	Meltzer	11%	9%	8%	11%	11%	8%	10%	10%	8%	6%	9%	13%	7%	7%	9%	8%	8%
-29%	4%	MGCS	-28%	-31%	-33%	-27%	-25%	-20%	-28%	-24%	-34%	-30%	-26%	-29%	-31%	-30%	-33%	-36%	-29%
-24%	5%	MGRousset	-30%	-24%	-32%	-21%	-25%	-20%	-19%	-22%	-29%	-26%	-18%	-17%	-22%	-29%	-29%	-28%	-27%
-27%	5%	MGAlfano	-26%	-25%	-34%	-22%	-23%	-19%	-17%	-26%	-35%	-27%	-26%	-24%	-30%	-29%	-29%	-38%	-27%
-27%	5%	AlfanoAlfano	-26%	-25%	-34%	-22%	-23%	-19%	-17%	-26%	-35%	-27%	-26%	-24%	-30%	-29%	-29%	-38%	-27%
-29%	4%	AlfanoCS	-28%	-31%	-33%	-27%	-25%	-20%	-28%	-24%	-34%	-30%	-18%	-29%	-31%	-30%	-33%	-36%	-29%
-24%	5%	AlfanoRousset	-30%	-24%	-32%	-21%	-25%	-20%	-19%	-22%	-29%	-26%	-23%	-17%	-22%	-21%	-31%	-28%	-25%
-27%	5%	Rousset	-34%	-27%	-35%	-25%	-29%	-22%	-21%	-26%	-33%	-29%	2%	-21%	-25%	-22%	-34%	-31%	-26%
3%	3%	Shidahara	4%	2%	0%	6%	6%	4%	6%	6%	1%	3%	11%	8%	1%	2%	-1%	1%	0%
0%	0%	raw PET	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
		SD	17%	15%	18%	14%	15%	12%	14%	15%	18%	15%	14%	15%	12%	15%	17%	13%	14%

Meltzer present with the lowest increase of signal. One can see an important and almost similar decrease in activity for all the other techniques.

Figure 2 presents the average GM activity when using 5 different PVC techniques. The data are normalized to uncorrected PET images, where the relative percentage increase of the GM signal compared to the initial activity is shown. A global trend between patients is respected, but no distinction between associated pathologies can be made. Figure 3 gives the same information for the WM.

Figure 4 shows the results for a patient suffering from a fronto-temporal dementia (FTD). According to Teune et al. [21], typical cerebral metabolic pattern in FTD includes a decreased metabolism in cortical regions, especially in the frontal, mid temporal and anterior cingulate

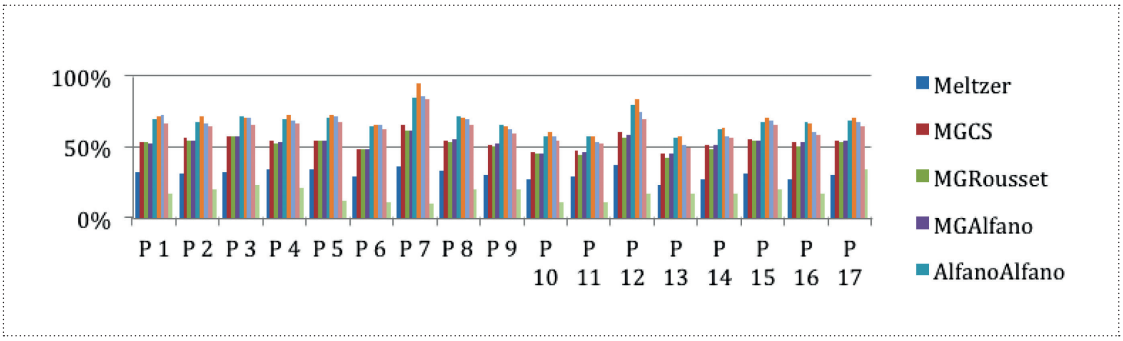

Figure 2. Impact of the 5 different PVC techniques. The results are normalized to uncorrected PET images, where the % displayed represents the relative increase of the GM activity concentration compared to the initial estimate prior to PVC.

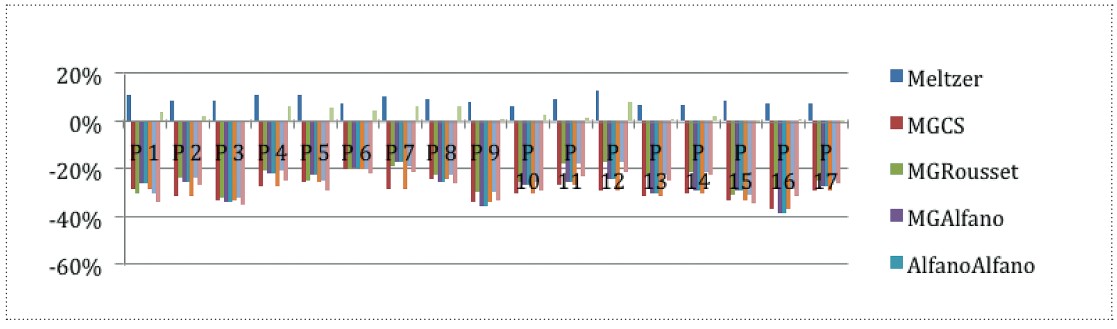

Figure 3. Impact of the 5 different PVC techniques. The results are normalized to uncorrected PET images, where the % displayed represents the relative increase of the WM activity concentration compared to the initial estimate prior to PVC.

gyrus. On the contrary, a small increase of activity can be seen in the occipital area, however, no changes in the parietal cortex, which can be considered as usually left unaffected are to be reported.

In this figure, 3 series are shown. The first bar on the top is from a ROI typically left unaffected by the disorder, the second representing the average GM signal for the patient, and the third a ROI specifically affected

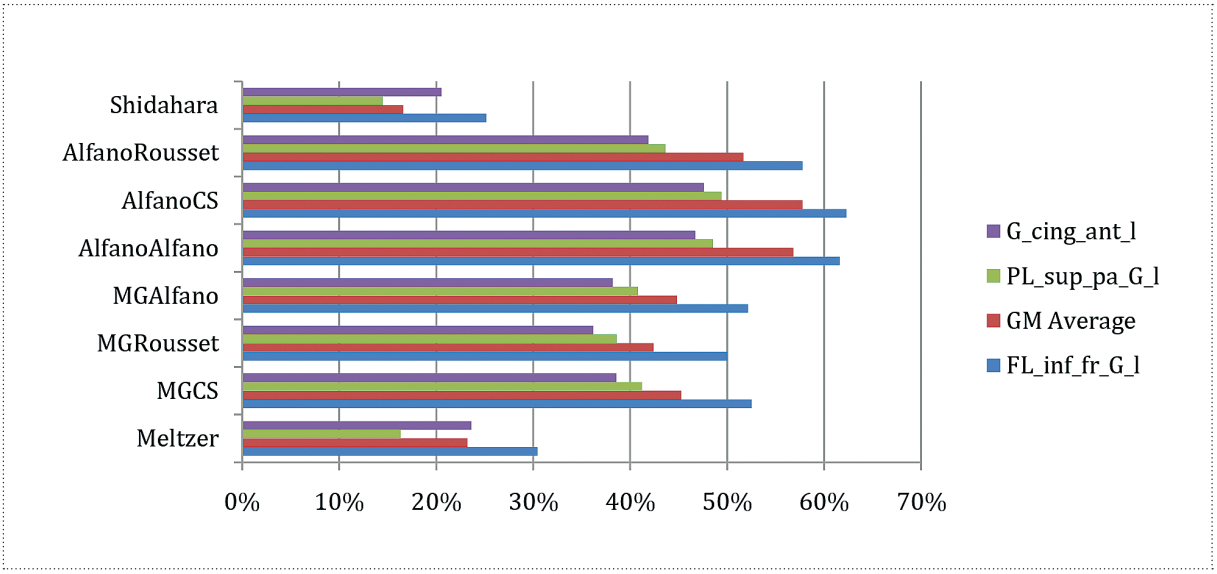

Figure 4. Variation of the PET signal in 3 different ROIs for a patient suffering from cortico basal dementia, where PL_sup_pa_G_I stands for the left superior parietal gyrus, FL_inf_G_I for left inferior gyrus, and G_cing_ant_l for the left anterior cingulate gyrus.

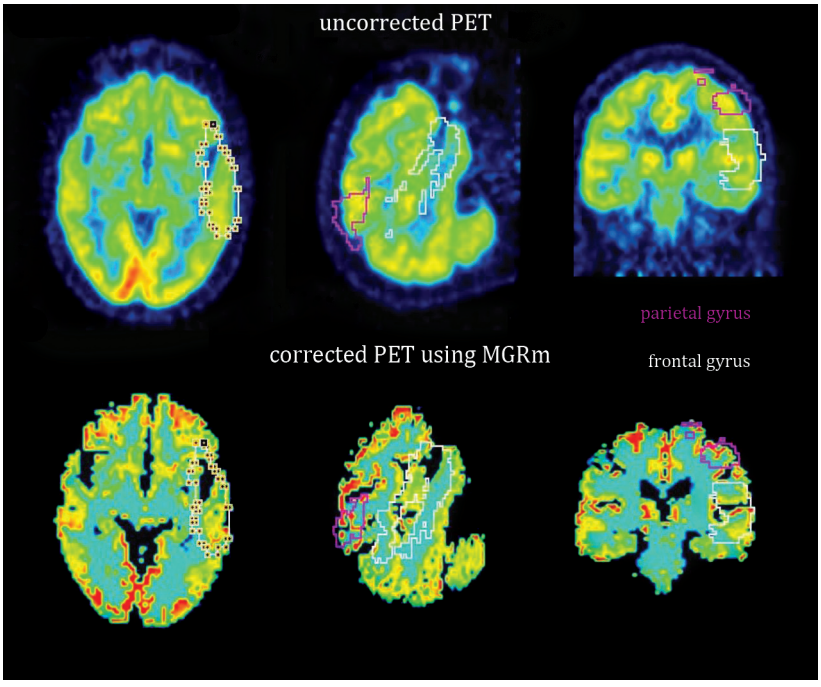

Figure 5. Effect of PVC using the MGRm technique for two different regions specifically modified in Cortico Basal Dementia. The white VOI delineates the frontal gyrus, whereas the pink VOI delineates the parietal gyrus.

by the disorder. One can see that the PVC methods are more effective in the ROI altered by the disease, whereas less correction is apparent in the unaffected region.

Fig. 5 illustrates the previous results by showing clinical images of brain regions specifically involved in the diagnosis of neurodegenerative disease. PVC images are visually different from the uncorrected PET image,

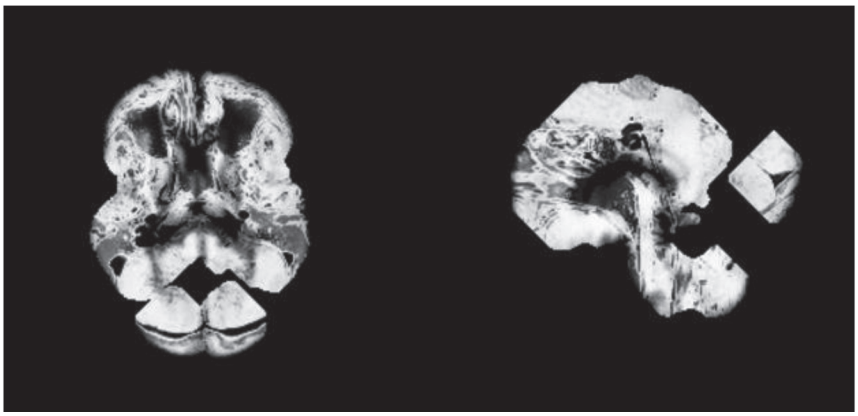

Figure 6. Clinical MR image showing segmentation results of the GM when applying the SPM8 segmentation tool.

pinpointing noticeable spatial resolution recovery. Fig. 6 illustrates a typical segmentation error (using SPM8) for a clinical study that had to be excluded from the study protocol.

4. Discussion

PET imaging is widely used in clinical setting owing to its ability to provide relevant answers to clinical questions using specific molecular probes and to quantify biological processes in vivo. Unfortunately, many technical and physical factors affect image quality and quantitative accuracy of PET images. One of the challenges affecting the quantitative capabilities of PET is PVE. Among the described determinants of image resolution, PVE remains undertreated owing to the lack of recommendations regarding systematic PVC methodologies in clinical routine.

Nowadays, it is commonly accepted that PVE has a significant impact on image quality and quantitative accuracy [22]. The need of PVC tools encouraged the development of different techniques. It is now possible to correct for PVE at different steps of the image processing chain, before, after or during the image reconstruction process. This work focused on 5 of the most widely used techniques for PVC. More sophisticated techniques have been described recently in the literature [23, 24].

The pros and cons of voxel- vs. ROI-based PVC approaches are well addressed in the scientific literature using mostly simulated data; however, only a limited number of studies used clinical studies looking at the relevance of PVC in clinical setting.

There is a global trend regarding the impact of different correction techniques on GM metabolism (table 1, figure 2). However, in the absence of ground truth when using clinical data, it is difficult to draw any conclusions regarding the performance of the different correction techniques. Nonetheless, these techniques have been previously validated using experimental and simulated phantom studies, where reference recovery coefficients are known. The trend observed in figure 2 is consistent with previous validations and comparison studies. AlfanoCS has the largest impact on image correction (+70%) whereas Meltzer has the lowest impact of voxel-based approaches (+31%). The only ROI-based method (Rousset) investigated in this work ranks in the second place (+60%) after the 3 variations of the Alfano approach. It is worth noting that the Shidahara approach, based on the wavelet integration method, is far behind all others techniques, increasing the PET signal by only 17%. This approach is quite new in comparison to others and more validation work is still required to assess the accuracy of this method. One of the most distinguishing features of this technique is that it outperforms the other approaches through the use of a thorough methodology. This approach, however, integrates a brain atlas which is a significant drawback since these atlases are constructed based on the compilation of brains of healthy subjects from a specific population.

Such atlases are dependent on the characteristics and the specific patient population (age, gender) as well as disease (or lack of proof of absence of disease) conditions. As such, using pathological data may be disrupting since some structural details would not be taken into account, certainly affecting the accuracy of the results.

Analyzing the WM results (table 2 and figure 3), one can notice that Meltzer's approach increases the signal. This is probably due to its two-compartment approach, since this method does not separate WM from the GM. Shidahara also appears to increase the WM signal, but this is somehow unexpected since PVE tends to overestimate counts from WM in the uncorrected PET image. This seems to indicate that Shidahara's method is less reliable for WM estimates.

But even if the WM metabolism is less important for clinical interpretation of neurodegenerative diseases, it should be taken into account at least as a metric of image quality control. As an example, we excluded a patient from the study protocol owing to incorrect MR image segmentation (figure 6).

Given the limited number of the cohort (17 patients for 7 categories of neurodegenerative diseases), we did not observe any correlation between the specific pathology and the importance of the correction. It seems that the global GM average correction is independent from the disorder. To generalize and gain more confidence in the obtained results, more work should be performed including a larger clinical database. Nevertheless, some interesting conclusions were drawn when considering the pattern of a specific neurodegenerative disorder.

The ROI-based analysis demonstrated that it performs differently depending on the impact of the disease (figure 5). Compared to the GM average correction, the ROIs affected by the pathology were corrected to a larger extent than those unaffected by the pathology. Even if these findings would require more sustained work, they are consistent with the fact that the correction techniques do not correct the GM as a single structure, but still take into account differences between ROIs allowing in order to find patterns between regions. It has been previously reported that one of the most important drawbacks of voxel-based methods is that they tend to homogenize the signal within a ROI. However, we were able to find out the current pattern of the disease described on uncorrected PET images, even after correction. This observation seems to indicate that the use of a relevant atlas of ROIs is commended. It should offer a correct balance between the size and the numbers of ROIs. We can hypothesize that if the atlas is adapted for clinical interpretation, i.e. with well-sized ROIs focusing on regions of interest, the resulting images after PVC would be clinically interpretable, reasonably diminishing the impact of PVE.

The systematic consideration of PVC involves partial reconsideration and thinking of PET image interpretation and reading. Since PET images should be less dependent on confounding factors, such as atrophy, it will become possible to measure changes in tracer uptake that fit closer to the reality. So far, this does not necessarily imply that clinical interpretation should be more efficient since the differences between normal and atrophic cortex is diminished by PVC. It would be interesting to compare the clinical diagnostic performance of corrected versus uncorrected images. Ultimately, new patterns could emerge. New radiological findings could be discovered, opening the way for an updated classification of neurodegenerative disorders. In addition, a quantitative approach for clinical diagnosis should be considered since some PVC relevant techniques do not provide images as output.

Finally, some methods have been shown to be more reliable depending on the expectations. As observed in table 1, ARm and ACSm produce more dispersed values for different patients. As such, these methods could be of particular interest for group comparison studies, since they exacerbate the differences between subjects. This observation is shared with [25] who also reported that Mm is pertinent for intra-subject analysis, but our work did not confirm this observation given that only one scan per patient was available in this study protocol.

5. Conclusion

PVC is a challenging issue impacting both qualitative interpretation and quantitative brain PET imaging. A number of ROI- and voxel-based approaches have been developed and validated using simulated and experimental studies. However, the relevance of PVC in clinical setting has received little attention. The different techniques proposed so far present different performance in terms of established evaluation metrics. However, the added value of PVC in the assessment of neurological disorders, especially atrophy, still requires to be studied and documented using large clinical databases and objective criteria. It was observed that newly proposed and more complex techniques are not necessarily more adapted to give satisfactory results. Keeping in mind that it would be necessary and highly desirable to establish universal standards of image processing to

fit clinical applications enabling more standardized clinical interpretation, this preliminary work can be considered as one step forward for the routine application of PVC in clinical setting that will likely impact the way clinicians are diagnosing brain disorders.

Acknowledgments

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