MR-Less Surface-Based Amyloid Estimation by Subject-Specific Atlas Selection and Bayesian Fusion

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Abstract. For clinical evaluation, assessing amyloid deposition with PiB-PET is desirable without requiring MR acquisition and associated fusion/segmentation techniques. A useful clinical tool is to estimate PiB-PET against the brain surface, which is however challenging using PET alone because of the lack of structural information. We propose a method to generate such estimate, where multiple atlases are selected and combined with local weights in a Bayesian framework. Qualitative and quantitative comparison with and without MRI are presented. Using PET only, the average error on the brain surface was around 13% compared to MRI-dependant method.

1 Introduction

Beta-amyloid ($A\beta$) plaques found in gray matter are among the most prevalent pathological characteristics of Alzheimer's disease (AD), and can be imaged in vivo by Positron Emission Tomography (PET) using ^{11}C -PiB marker. Estimating and visualizing cortical gray matter (GM) $A\beta$ deposition is important for the diagnosis of the disease and the monitoring of plaque reducing therapy.

Because $A\beta$ plaques are present mostly in the gray matter, visualisation on the cortical surface would be a very valuable clinical tool. Such tools are widely used for FDG-PET to assess hypo-metabolism, and a good example is Neurostat [1]. These tools benefit from the fact that the uptake of FDG in the white matter (WM) is very low compared to that of the GM, and therefore a straightforward sum or maximum projection in the GM on the cortical surface is possible. This assumption is not valid for amyloid imaging as most markers, including PiB, have significant retention in the WM, and therefore the 3D surface separating WM and GM is not well-defined and has to be estimated. This is very challenging as PET imaging lacks the anatomical details and the resolution to resolve this surface. As a result, Magnetic Resonance Imaging (MRI) is required to segment the brain into GM and WM, and extract the separating surface. This surface is then registered to the PET scan where GM PiB retention can be measured and displayed.

In standard clinical setup, when PET amyloid imaging is visually assessed, MRI scans are not always available (e.g. different system, posterior scanning time) and in a substantial number of cases not possible (e.g. presence of metallic implant). This paper proposes a method to estimate PiB-PET on the cortical surface without the need of an MRI scan. Our proposed “PET-only” approach is compared to the best case scenario when an MRI is available, which we refer to as the MRI-dependent method.

A PET-only method was reported in [2]. It employed a single MRI atlas with segmented tissues and co-registered to a PET image from the same subject. When a new subject PET was registered to the atlas PET, the atlas MRI could be used to estimate the subject GM. The maximal PiB uptake within the subject GM was measured along the normal direction of the brain surface. Although no quantitative precision analysis of this method is reported, our experiments found that its estimation accuracy highly depends on the atlas selection due to i) different anatomy between the single atlas and the subject, and ii) using hard PET tissue partitions simply copied from the single warped MRI atlas.

In this paper we address these problems by introducing a robust PET-only method that significantly improved upon [2]. In particular we achieved this by using 1) multiple possible GM-WM surfaces, 2) multiple likely GM tissue maps, 3) local and adaptive atlas selection customized for each subject and 4) a probabilistic framework to combine the estimates from individual atlases. Our method was evaluated both visually and quantitatively. Our experiments showed that the estimate without MRI is about 13% different from that with MRI at each vertex, and the intra-class correlation between these two methods is reached 0.94.

2 Method

2.1 Overview

Our proposed method directly estimates GM PiB-PET retention without an explicit GM segmentation by using multiple atlases.

Twenty subjects (with both PET and MRI) were used as atlases, whose MRI images were co-registered and segmented into GM, WM and CSF tissue maps. These atlases were randomly selected to match the full range of disease progression and are reasonably representative. The 3D GM-WM surfaces of the atlases were extracted and registered to a canonical space (arbitrary subject) to obtain vertex correspondence (Section 2.2). For each new subject without MRI, the subject PET image was registered with the twenty atlas PET images (Section 2.3), allowing the subject PiB to be estimated within the atlas GM tissue maps independently. Finally, the most similar atlases for each subject were selected by local and adaptive weighting (Section 2.4), and combined using a Bayesian framework (Section 2.5) to generate the subject’s unique GM PiB estimate.

2.2 Surface Registration

To attain vertex correspondence, all atlas surfaces were registered using a multi-scale EM-ICP [3]. Briefly, surface curvatures were obtained by geometric surface

simplifications at different scales to reveal local structures. By controlling the degree of surface simplification, only major sulci and gyri common to all the subjects were kept for EM-ICP registration, while the subject-specific structures were ignored. After registration, the atlas surfaces were resampled with the same number of vertices (80,000).

2.3 Affine Registration for PET Images

The subject and atlas PET images were co-registered to transform i) the 20 atlas surfaces and ii) the 20 sets of the tissue probability maps to the subject space. Affine registration based on block matching of feature points in PET images was employed [4] instead of non-rigid registration because of the limited resolution and noise in the PET.

2.4 Local Subject-Specific Atlas Selection

For a given subject, not all 20 atlases were suitable for its GM PiB estimation. Some atlases could be very different due to the variation of individual brain shapes and the $A\beta$ deposition that could be affected by atrophy. Therefore, an optimal subset of atlases was selected for each subject. The selection number is set as 10, which was experimentally found a suitable choice.

Our atlas selection was local and adaptive. “Local” means the selection of atlases was determined by a local metric computed between small PET image blocks. “Adaptive” means the selected subset of atlases was different from vertex to vertex. Our atlas selection process was elaborated as follows. For a given surface vertex, the PET image similarity between the subject and an atlas was assessed in a $30 \times 30 \times 30$ (voxels) neighborhood by normalized mutual information (NMI) [5]. The neighborhood size should not be set too small to avoid overfitting noise due to the low resolution of PET. The ten most similar atlas PET images were selected to generate the final estimation at each vertex. We found that local weighting provided superior results over global weighting. Moreover, keeping only a subset of the most similar atlases can further improve the scenario where all atlases are used [6]. Our local adaptive atlas selection reduces errors due to mismatches in the distribution of the plaques and GM shapes, allowing it to successfully handle more unusual cases.

2.5 Surface-Based Measurement by Atlas Fusion

We propose a Bayesian fusion framework for PiB quantification by multi-atlases.

Given a PET image $\mathbf{I}(x)$, where x denotes an image voxel, our target is to measure the mean PIB uptake in GM along the normal directions of the transformed atlas surface $\mathbf{S}^T$. That equals to estimate the expectation $\mathbb{E}_{x \in \Delta} [\delta(\mathbf{I}, x, l)]$, where $\delta(\mathbf{I}, x, l)$ is an indicator function:

$$\delta(\mathbf{I}, x, l) = \begin{cases} \mathbf{I}(x), & \text{for } l = 1 \\ 0, & \text{elsewhere,} \end{cases}$$

and Δ denotes the line where the surface normal direction meets the image. The symbol l is the tissue label at the voxel x , representing GM, WM and CSF with the values of 1, 2 and 3, respectively. Taking discrete x , we have

$$\begin{aligned}\mathbb{E}[\delta(x, l)] &= \sum_{x \in \Delta} \delta(\mathbf{I}, x, l) P(\mathbf{I}, x, l) dx \\ &= \sum_{x \in \Delta} \mathbf{I}(x) P(l = 1 | \mathbf{I}, x) P(\mathbf{I}, x) dx.\end{aligned}\quad (1)$$

Assuming that x is evenly sampled from Δ , the probability $P(\mathbf{I}, x) = 1/|\Delta|$, where $|\Delta|$ is the length of Δ . The posterior label probability $P(l | \mathbf{I}, x)$ is estimated from the transformed atlases $\mathbf{A}_i^T$ ($i = 1 \cdots n$, n is the number of atlases) by maginalizing the joint probability $P(l, \mathbf{A}_i^T | \mathbf{I}, x)$:

$$P(l | \mathbf{I}, x) = \sum_{i=1}^n P(l, \mathbf{A}_i^T | \mathbf{I}, x) = \sum_{i=1}^n P(l | \mathbf{A}_i^T, \mathbf{I}, x) P(\mathbf{A}_i^T | \mathbf{I}, x). \quad (2)$$

Here $P(l | \mathbf{A}_i^T, \mathbf{I}, x)$ represents the GM probability at the voxel x in the atlas $\mathbf{A}_i^T$, which was obtained in our case from the transformed atlas tissue maps. The term $P(\mathbf{A}_i^T | \mathbf{I}, x)$ is the probability to be well aligned at the voxel x between the target image $\mathbf{I}$ and the transformed atlas $\mathbf{A}_i^T$. In our approach, $P(\mathbf{A}_i^T | \mathbf{I}, x)$ was set proportional to the reciprocal of the NMI metric estimated locally within the neighborhood $N(x)$ of x , i.e., $P(\mathbf{A}_i^T | \mathbf{I}, x) = P(\mathbf{A}_i^T | \mathbf{I}, N(x))$. As aforementioned, the size of $N(x)$ should be reasonably set to avoid overfitting noise. In our approach, $N(x)$ covers all likely GM voxels along the line Δ . Thus, $P(\mathbf{A}_i^T | \mathbf{I}, N(x))$ is constant to the variable x ($x \in \Delta$). Combining (1) and (2), we have

$$\begin{aligned}\mathbb{E}[\delta(x, l)] &= \frac{1}{|\Delta|} \sum_{x \in \Delta} \mathbf{I}(x) P(l = 1 | \mathbf{I}, x) \\ &= \frac{1}{|\Delta|} \sum_{x \in \Delta} \mathbf{I}(x) \sum_{i=1}^n P(l = 1 | \mathbf{A}_i^T, \mathbf{I}, x) P(\mathbf{A}_i^T | \mathbf{I}, N(x)) \\ &= \sum_{i=1}^n P(\mathbf{A}_i^T | \mathbf{I}, N(x)) \left[\frac{1}{|\Delta|} \sum_{x \in \Delta} \mathbf{I}(x) P(l = 1 | \mathbf{A}_i^T, \mathbf{I}, x) \right]\end{aligned}\quad (3)$$

Eqn. (3) shows an additive property: the estimation from multiple atlases can be attained from each single atlas independently and then linearly combined by local weights. Such a combination is nonlinear for the whole surface. This additive property is important because it allows to refine the estimate with new atlases without recomputing the whole set, thus being computationally efficient.

When estimating the PiB value $\mathbf{I}(x)$ from a single atlas $P(\mathbf{A}_i^T | \mathbf{I}, N(x))$, the weights were the GM probability at x . This implicitly defined a gray matter region with a soft boundary, which reflected the variation observed in the training population. Unlike [2] where hard GM segmentation in a single atlas was used, we found our approach more robust to registration error between PET and MRI.

2.6 SUVR Normalization

In some applications, to ensure inter-subject comparisons, the PiB-PET uptake values need to be normalized by standard uptake value ratio (SUVR) [7]. SUVR is defined as the value of a region containing specific binding to one without specific binding (such as cerebellar gray matter). In such cases, the intensity values $\mathbf{I}(x)$ in the original PET image are homogeneously scaled by a parameter k . As NMI matches structures instead of intensity values, $P(\mathbf{A}_i^T | \mathbf{I}, N(x))$ is invariant to k , and so is the GM probability $P(l = 1 | \mathbf{A}_i^T, \mathbf{I}, x)$. Thus,

$$\mathbb{E}[\delta(x, l)] = k \sum_{i=1}^n P(\mathbf{A}_i^T | \mathbf{I}, N(x)) \left[\frac{1}{|\Delta|} \sum_{x \in \Delta} \mathbf{I}(x) P(l = 1 | \mathbf{A}_i^T, \mathbf{I}, x) \right], \quad (4)$$

where k is determined by SUVR. Eqn. (4) shows that when SUVR changes, our estimation (3) can be simply scaled by k .

PiB-only SUVR normalization is beyond the scope of this paper and several methods have been proposed [8]. In the following, we set $k = 1$ to focus on evaluating the pure performance of our method by comparing surface PiB estimation with and without MRI.

2.7 Validation

The proposed method was validated on 143 subjects from the Australia Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL). Please note that, the validation on our method does not require SUVR normalization that can be computed without MRI. We nonetheless preprocessed SUVR using MRI cerebellum just for the purpose of clinically relevant analysis (grouping subjects) and display (Fig. 1). With a cutoff value of 1.5, these subjects were categorized into 73 PiB⁺ and 70 PiB⁻ subjects.

To compare our method with the best case of senario, MRI-dependent method was applied as ground truth. The estimation difference VAR (%) between the two methods was measured in ratios and averaged over all subjects. It was computed at both ROI and vertex levels. In addition to VAR, we also computed the Pearson correlation and the intra-class correlation (ICC) between the two methods by correlating the estimations at each vertex.

3 Experimental Results and Discussion

We compared the performance of the proposed method with i) the MRI-dependent method (ground truth) and ii) the single-atlas based PiB-only method.

3.1 Comparison with MRI-dependent Method

In Fig. 1, four typical examples are shown. MRI-dependent (top row) and our PET-only (bottom row) methods present similar patterns and are visually very

Fig. 1. Surface-based PIB measurements from the MRI-dependent method (the top row) and the proposed method (the bottom row) for four examples: (a) PiB^+ AD, (b) PiB^+ NC, (c) PiB^+ NC, and (d) PiB^- NC.

close, for example, the asymmetric patterns in the left and right hemispheres for subjects (a) and (d).

Table 1 summarizes the quantitative results between the MRI-dependent and the PET-only methods. As shown, the PiB^+ group had lower VAR ($2.2 \pm 1.5\%$ for ROI, $13.1 \pm 1.5\%$ for vertex) than the PiB^- group ($3.6 \pm 2.3\%$ for ROI, $16.4 \pm 2.1\%$ for vertex), as well as attaining higher Pearson correlation / ICC ($0.75 / 0.94$) than the PiB^- group ($0.42 / 0.73$). This difference is expected, because the PiB^- group has minimal PiB retention, whose image signal is proportionally overwhelmed by noise than that of the PiB^+ group. The high estimation accuracy of the PiB^+ group in our method is promising as the PiB^+ group is clinically more interested due to its association with possible AD. Meanwhile, the estimate accuracy for the PiB^- group was sufficient for identifying visually similar patterns to the MRI-dependent method (Fig. 1 (d)). We also found that our estimation errors for both groups were close to the reported reproducible errors of PiB quantification using only 30 min imaging [9] (cited in Table 1), which reinforced the precision of our method. Finally, although PET-based SUVR estimation was not included in our method, we also tested the overall performance with the SUVR method in [8]. It showed that the SUVR method would increase the error per vertex by approximately 4% for both groups.

3.2 Comparison with Single Atlas Approach

To demonstrate the advantage of using multiple atlases, the VAR and the correlations with the MRI-dependent method were compared between 10 randomly selected single-atlas and the proposed multiple-atlas approach. The VAR and correlations were compared subject by subject (averaged over all vertices within each subject, Fig. 2 (a) and (b)), and ROI by ROI (averaged over PiB^+ subjects¹, Fig. 2 (c) and (d)). In Fig. 2, the red line was the result from the multiple-atlas approach, and the ten other lines corresponded to the ten single-atlas in comparison. As shown, the proposed approach exhibited significantly lower average VAR

¹ Improvement on PiB^- is similar to that of PiB^+ .

Table 1. Comparison of estimations from the MRI-dependent and PET-only methods

PiB ⁺		All	Frontal	Occipital	Temporal	Parietal	Post-cingulate	Putamen
ROI	VAR (%)	2.2 ± 1.5	2.3 ± 1.6	2.1 ± 1.5	2.1 ± 1.4	2.1 ± 1.5	2.4 ± 1.7	2.0 ± 1.4
	cited VAR (%)	-	3.9	3.7	3.3	3.7	4.9	5.1
Ver- tex	VAR (%)	13.1 ± 1.5	13.2 ± 1.6	13.1 ± 1.5	12.9 ± 1.5	13.2 ± 1.5	13.2 ± 1.6	13.3 ± 1.7
	P-Corr (R)	0.75	0.74	0.75	0.76	0.75	0.75	0.75
	ICC	0.94	0.94	0.94	0.94	0.94	0.94	0.94
	cited ICC	-	0.95	0.94	0.97	0.94	0.88	0.89
PiB ⁻		All	Frontal	Occipital	Temporal	Parietal	Post-cingulate	Putamen
ROI	VAR (%)	3.6 ± 2.3	3.6 ± 2.4	3.4 ± 2.1	3.5 ± 2.2	3.5 ± 2.4	3.2 ± 2.3	3.8 ± 2.4
	cited VAR (%)	-	2.7	3.2	2.5	2.0	0.9	4.1
Ver- tex	VAR (%)	16.4 ± 2.1	16.4 ± 2.1	16.3 ± 2.0	16.2 ± 2.0	16.6 ± 2.2	16.4 ± 2.2	16.6 ± 2.1
	P-Corr (R)	0.42	0.42	0.43	0.42	0.41	0.43	0.41
	ICC	0.72	0.73	0.73	0.72	0.72	0.76	0.68
	cited ICC	-	0.73	0.75	0.69	0.59	0.75	0.66

Fig. 2. Comparison of the proposed multi-atlas approach with ten single-atlas approaches by error ratios for (a) each subject and (c) each ROI, and by correlations for (b) each subject and (d) each ROI

and higher correlations over almost all subjects than any single atlas produced. Consistently, when breaking the estimates into surface ROIs and averaged over subjects, the proposed approach revealed an even more salient advantage than any single-atlas in all the ROIs.

4 Conclusion

In this paper, we propose to estimate amyloid deposition against brain surfaces utilizing only PiB-PET images without MRI. The demonstrated accuracy of our method suggests it could provide a CAD tool for evaluation of amyloid imaging. In future, we will extend our approach to include the PiB-PET based SUVR estimation.

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