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Quantitative Brain PET Analysis Methods in Dementia Studies

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# CHAPTER 7

# Summary

Positron Emission Tomography (PET) is a molecular imaging technique that allows for the visualization and quantification of (patho)physiological processes in vivo. The latter is an important feature that is often overlooked in the clinical routine and research, where visual inspection or semi-quantitative approaches are mostly applied. Nonetheless, pharmacokinetic analysis of dynamic PET studies can provide quantitative parametric images, methods that offer more precise information on specific tracer binding than what can be obtained by visual assessment or semi-quantitative approaches. In addition, these methods can more specifically characterize underlying (patho)physiological processes as well as provide additional quantitative parameters that might be affected in specific conditions and/or diseases.

Particularly in the field of Alzheimer's disease (AD), the quantitative aspects of amyloid PET imaging remain largely unexplored. As the most common form of dementia, AD is characterized by the deposition of amyloid-$\beta$ (A$\beta$) plaques in grey matter, as well as by reduced brain metabolism in temporo-parietal and frontal lobes. Both aspects of this disease can be visualized through PET imaging using, for example, respectively, [$^{11}$C]labelled Pittsburgh Compound B (PIB) and [$^{18}$F]-2-fluoro-2-deoxy-D-glucose (FDG) radiotracers. Generally, images provided by these tracers are used for visual reading, as the clinical use of PET is to determine the underlying pathology within the context of differential diagnosis of neurodegenerative disorders. However, as it starts being used more frequently in research, disease-modifying trials, and in earlier stages of the disease in the clinic, quantitative information becomes more relevant and there are a number of opportunities for the use of available quantitative methods.

While quantitative models such as the simplified reference tissue model 2 (SRTM2) have been previously validated for the analysis of PIB scans, accurate parameter estimation remains a challenge. **Chapter 2** specifically focused on the estimation of the clearance rate of the reference tissue ($k_2^{'}$)

parameter when using SRTM2 in dynamic PIB PET scans. A suboptimal determination of this parameter may result in the inaccurate estimation of binding potential ($BP_{ND}$), which is frequently the main parameter of interest in these studies. However, even though many studies have already applied this model to the data, there is no consensus on how to best estimate $k_2^{'}$. For that purpose, a cohort of thirty subjects was divided into PIB+ and PIB- groups based on whether they presented high PIB signal in cortical areas or white matter, respectively. Thirteen volumes of interest (VOIs) were defined for the selection of voxels to estimate $k_2^{'}$: the whole brain, five combinations of grey and white matter, three anatomical regions based on areas of known AD-related hypometabolism, one based on the main differences between groups, and three using different minimum BPND value thresholds. A first SRTM estimation of $k_2^{'}$ is done for all brain voxels and, then, the median value from each of these VOIs is taken for a final $BP_{ND}$ estimation using SRTM2. These final $BP_{ND}$ estimates were compared to $BP_{ND}$ estimations from the original SRTM model fits, since the latter has been previously validated against the standard reference model for PIB, i.e. the 2-compartmental model with plasma input. Due to the lack of statistical differences in $k_2^{'}$ estimation between subject groups and higher $BP_{ND}$ correlations between SRTM and SRTM2 estimations, a 0.1 threshold value was found to be the best method to estimate $k_2^{'}$. However, this method is not viable when performing pharmacokinetic modelling based on a VOI approach, as information at the voxel level is not obtained to apply such a threshold. Thus, in this case, the use of white matter region for the estimation of the $k_2^{'}$ parameter was found to be the best alternative for this modelling method. The findings of this chapter were subsequently used for the rest of the thesis, where the $BP_{ND}$ threshold approach was used during the voxel-based pharmacokinetic modelling (SRTM2) of dynamic PIB PET scans.

In addition to $BP_{ND}$, SRTM2 is an advantageous model in that it also provides a parametric image for the relative tracer influx ($R_1$), which can serve

as a proxy to regional cerebral blood flow (rCBF). In addition, when dynamic PET scans are performed, the early frames of the scan have also been suggested to reflect rCBF. Interestingly, rCBF has been demonstrated to closely relate with brain metabolism, a process that has also been implicated in AD and is usually assessed by FDG scans. While PIB and FDG scans offer complementary information for subject diagnosis, dual-tracer studies are more expensive and increase patient discomfort, scanning time, and exposure to radiation. Therefore, if rCBF and FDG measures are comparable, the first may be used as an alternative for FDG clinical and research studies.

Considering this opportunity, **Chapter 3** aimed at exploring more thoroughly the relationship between rCBF and metabolism by comparing (semi-)quantitative rCBF and semi-quantitative FDG PET measures. Two approaches were used to generate rCBF images: the $R_1$ parameter obtained from SRTM2 and the SUVR of the time-weighted average from the initial (early) frames of the dynamic PIB PET scan (ePIB). Five different time intervals were considered for this study: 20 s to 40 s, 20 s to 60 s, 20 s to 100 s, 20 s to 130 s, and 1 min to 8 min. While the first two time intervals were found to be too noisy and presented close to no relationship with metabolism measures, ePIB(20-130s) and ePIB(1-8min) had the highest resemblance to FDG SUVR images. Nonetheless, quantitative $R_1$ parametric images presented, in general, a better correlation with FDG SUVR and should, therefore, be preferred over semi-quantitative ePIB for (differential) diagnosis of neurodegenerative disorders as an alternative to an FDG PET scan.

The subsequent chapters were focused on more automated approaches for classification of scans in clinical practice. Generally, PET scans are only visually assessed in a clinical setting, supporting (differential) diagnosis by visually detecting patterns of radiotracer uptake. However, this type of analysis relies on the reader's expertise and sometimes results in a low agreement between readers. Therefore, automated discrimination tools may

support the identification of specific diseases. In this context and considering the correlations between rCBF and FDG found in Chapter 3, **Chapter 4** assessed the ability of PMOD's Alzheimer's discrimination tool (PALZ) to classify (semi-)quantitative rCBF images. The PALZ tool was developed to provide physicians with an automated score for FDG scans of patients, comparing them to a dataset of healthy control (HC) subjects. It analyses specific brain regions that are known to have their metabolism affected in AD, and it provides the tested subject with a unique score which, when above the threshold of 1, indicates that the scan is considered to have an 'abnormal' FDG pattern, meaning that its pattern more closely resembles that of a typical AD patient than that of a HC subject. While this tool was originally developed for FDG images, it was hypothesized that rCBF images would perform equally well in this analysis. Therefore, a cohort of fifty-two subjects was included in this study, including subjects with a diagnosis of AD or mild cognitive impairment (MCI), and HC subjects. All included subjects had FDG SUVR, $R_1$, ePIB(20-130s), and ePIB(1-8min) images generated. A good correlation between rCBF and FDG scores was found. However, a new threshold for AD classification had to be estimated for each rCBF method using receiver operating characteristic curves. With this new threshold, AD discrimination performance of rCBF images using the PALZ tool was comparable to FDG's. As was seen in Chapter 3, $R_1$ images outperformed ePIB approaches by showing better score correlations with FDG and higher sensitivity in AD patient identification based on PALZ score.

While PALZ's workflow focuses specifically on the AD metabolic pattern, alternative methods such as the scaled subprofile model using principal component analysis (SSM/PCA) can generate disease-specific patterns (DPs) for any disorder and radiotracer. From its development until current uses, this technique mainly focuses on semi-quantitative FDG PET scans. However, more disease-specific DPs may be generated through quantitative images.

Therefore, **Chapter 5** explored the feasibility of SSM/PCA to generate DPs from quantitative parametric images, using amyloid PET scans as an example. To this end, quantitative ($R_1$ and $BP_{ND}$) and semi-quantitative (FDG and PIB(40-60min) SUVR) images from fifteen AD patients and fifteen HC subjects were used to generate DPs. The obtained patterns were in line with the distinctive characteristics of AD, where both $R_1$ and FDG DPs showed a reduction in cerebral blood flow/metabolism, respectively, in frontal, temporal, and parietal lobes, and both $BP_{ND}$ and PIB DPs presented a general increase of A$\beta$ plaques in grey matter. Then, forty-nine subjects with a variety of diagnoses (AD, MCI, frontotemporal dementia, dementia with Lewy bodies, and HC) were used to test the capability of these patterns to identify AD pathophysiological changes. The inner product between subject's image and DP results in a score that reflects how much their images resemble the AD pattern. Based on these scores, it was found that the combination of quantitative parametric images derived from a single dynamic PIB PET scan were sufficient to properly characterize the AD pattern and identify possible patients. Therefore, this approach provides further support to the use of a dynamic amyloid PET image as an alternative to performing two independent static PET scans, one using FDG and another using PIB as a radiotracer.

Lastly, with the adapted version of the SSM/PCA workflow introduced in Chapter 5, **Chapter 6** thoroughly compared the results from (semi-)quantitative rCBF approaches with FDG SUVR for the identification of AD, as was performed in Chapters 3 and 4. One of the advantages of SSM/PCA is that the rCBF images can be compared to rCBF-specific DPs, while PALZ compared them with a database of HC FDG images. Fifteen AD patients and sixteen HC subjects were used to generate FDG SUVR, $R_1$, ePIB(20-130s), and ePIB(1-8min) DPs. The first three DPs resulted in a similar pattern, equivalent to what was found in Chapter 5 for metabolism and rCBF, while ePIB(1-8min) showed a pattern that resembled the A$\beta$ pat-

tern also found in Chapter 5. Although this time interval has been previously recommended by literature as the best time interval, it was found that this interval is too long and might be already be affected by specific binding to A$\beta$ deposition. As in the previous chapters, quantitative $R_1$ images resulted in a better correlation with FDG SUVR scores and a larger difference between AD and HC scores, outperforming semi-quantitative rCBF approaches in the discrimination of AD patients.

The use of quantitative PET images could improve diagnostic performance of PET studies for dementia patients not only in research settings, but also in clinical practice. However, as shown in Chapter 2, the selection of model settings for the pharmacokinetic modelling of dynamic PET scans influences the final quantitative parametric images and, thus, should be made with caution. Furthermore, Chapters 3, 4, and 6 showed that rCBF images are a good alternative to FDG SUVR images both when looking at regional values and through automated assessment of scans. Chapter 5 demonstrated that data analysis techniques can be adapted for the use of quantitative parametric images rather than semi-quantitative approaches. In summary, quantitative parametric images derived from pharmacokinetic modelling of dynamic PET scans offer complementary information that usually requires more than a static PET scan to be obtained. In the context of AD, for example, the use of two static scans, one for the evaluation of brain metabolism (FDG) and another for A$\beta$ deposit assessment (such as PIB), can be replaced in research or clinical routine by a single dynamic PET scan using an A$\beta$ radiotracer, thereby reducing radiation exposure and improving patient comfort (i.e. only one visit to the PET imaging centre is required).