CHAPTER 9

Discussion and Future Perspectives

The quantitative nature of PET is an important feature that has fallen into disuse. Therefore, the main aim of this thesis was to explore the use of quantitative parametric images derived from pharmacokinetic modelling in neuroimaging PET studies with a focus on Alzheimer's disease (AD). These results were compared with those obtained using the most common semi-quantitative methods. This thesis was divided into three parts. The first part concerns improvements in parameter estimation for pharmacokinetic modelling studies involving [^{11}C]labelled Pittsburgh Compound B (PIB) PET (**Chapter 2**), which is frequently used for the assessment of amyloid-β (Aβ) brain depositions in AD. In the second part, the use of quantitative parametric images as a surrogate for semi-quantitative [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) PET scans was explored on a region of interest-based approach (**Chapter 3**), and by an automated tool for classifying AD patients (**Chapter 4**). Finally, in the third part, the same quantitative parametric images were used to construct brain disease patterns using Scaled Subprofile Modelling using Principal Component Analysis (SSM/PCA) (**Chapter 5**). Furthermore, a comparison of (semi-)quantitative regional cerebral blood flow (rCBF) and semi-quantitative FDG disease patterns was performed (**Chapter 6**).

The current chapter discusses the relationship between the results described in previous chapters and future directions. Moreover, it will address the possible impact on research practices and clinical routine.

Kinetic Modelling Parameter Estimation for Radiotracers

PIB was one of the first amyloid PET tracers to be introduced in clinical routine and it remains the gold standard imaging method until this day.[1] The first article describing its kinetic modelling was published in 2005 by Price and colleagues.[2] Since then, other studies have tried to make the need for ar-

terial sampling obsolete by using reference tissue models.[3–6] Although the simplified reference tissue model 2 (SRTM2) has been identified as the best parametric model for PIB studies,[5] different research experiments have used different approaches to estimate the efflux from the reference region parameter (k_2'),[7–9] which is an important step when applying this model. Therefore, in **Chapter 2**, a study was performed to evaluate the effects of an incorrect k_2' on the estimation of binding potential (BP_{ND}) using SRTM2. This model uses k_2' parameter resulting from a first estimation using SRTM for a more precise estimation of BP_{ND} and R_1. This k_2' estimation can be done in different ways, but it was found that setting a threshold on BP_{ND} from SRTM for the selection of voxels to be used for the estimation was the least biased method to generate quantitative parametric images.

Because of the high quality of quantitative parametric images, there is an increasing necessity in using them for monitoring disease progression and therapy response.[10] Unfortunately, there is no universal model that may fit all radiotracers, and different tracers behave in different ways. Therefore, it is necessary to identify the pharmacokinetic model that best describes tracer kinetics for every new radiotracer. Furthermore, there is a clear benefit in using simplified semi-quantitative methods, which may decrease study costs and patient discomfort. However, these methods must always be validated using more complex, fully quantitative approaches.[10]

As an example, SRTM2 was originally developed for modelling radiotracers that target neuroreceptors.[11;12] This model is frequently used with radiotracers with a brain region with very high uptake, and this is the region expected to be most suitable for estimating the k_2' parameter. However, the deposition of Aβ is diffuse in brain grey matter of patients, so that there is no well-defined anatomical region with higher uptake. Moreover, subjects without Aβ deposits, such as (the majority of) healthy subjects, only show non-specific binding in white matter. Therefore, it is not a simple task to decide on a method

or a brain region for the estimation of k_2' of all subjects since using regions (or subjects) without high uptake introduce noise to the calculations, defeating the purpose of using STRM2. This point was also addressed in **Chapter 2**, where it was found that using the white matter of the brain is the preferred approach to estimate k_2' when performing volume of interest-based pharmacokinetic modelling. White matter is known to present higher PET signal than grey matter in healthy subjects due to non-specific binding and, therefore, may reduce noise in the estimation of the k_2' parameter.[13]

Possible Applications of Parametric Quantitative Images in Clinical and Research Routines

Radiotracers are developed to visualize (patho)physiological functions in vivo. Their most frequent use in clinical routine is for visual assessment of PET images. However, quantitative parametric images derived from pharmacokinetic modelling, besides being used for quantification of tracer uptake, may also be used for visual assessment. For example, receptor binding images, such as BP_{ND} and distribution volume ratio (DVR), reflect tracer binding in a more precise and specific way than images obtained using semi-quantitative standardized uptake value ratio (SUVR).[10]

The work by Collij and colleagues[14] has shown that BP_{ND} images of [^{18}F]flutemetamol reduce misclassification and improve inter-reader agreement when performing visual assessment of images from patients with low Aβ burden when compared to SUVR. This study also indicated that no additional training is required for experts performing the readings. Similar work with BP_{ND} images derived from PIB PET scans is ongoing at the UMCG and preliminary results point in this direction. This project included images derived from the approaches presented in **Chapter 2** and uses the same cohort of subjects included in all chapters of this thesis. Not only BP_{ND} parametric images

were included, but also R_1 (relative delivery compared with the reference tissue) images. Consequently, this assessment might consolidate the proposal of using quantitative parametric images in clinical routine, also for visual image assessment in case of PET studies in neurodegenerative diseases.

Pharmacokinetic modelling results in more than one quantitative parameter, which can be linked to various functions that are responsible for total uptake in tissue. For instance, rCBF is known to be connected to metabolic activity in the brain.[15] Metabolism can be imaged using FDG PET, which is considered to be a marker for neurodegeneration. Therefore, quantitative parametric images that represent blood flow, such as the relative tracer flow R_1, may show neuronal dysfunction in the same way as FDG PET. This relationship was explored per brain region in **Chapter 3**. The high correlation between both measures suggests that R_1, derived from dynamic PIB scans, might be an alternative for FDG to identify subjects in the AD spectrum. Furthermore, it was observed that changes in metabolism relative to the reference region were greater than changes in R_1, and that patients with Aβ deposition (i.e. in the AD spectrum) present a better correlation between these measures than subjects without it. Nevertheless, some regions such as the brainstem, which are connected to the 'fight or flight response' in the brain, are known to show higher perfusion rates.[16] Results observed in **Chapter 3** were consistent with previous literature.[16] These hyperperfused regions may be further considered for differential diagnosis as well by focusing on the differences between healthy volunteers and AD subjects. Moreover, these images may be used not only for visual assessment, but also to quantify differences in uptake or relative flow, in particular to monitor effects of therapeutic interventions. This could lead to a better selection of subjects for clinical trials or a more precise evaluation of treatment. Furthermore, other kinetic parameters that result from kinetic modelling of dynamic PET scans might also be interesting not only for AD studies, but also for other neurological disorders and/or radiotracers.

Automated Assessment of Images

Although frequently used in the clinic and for subject selection in trials, visual assessment of images relies on reader's expertise and is, therefore, prone to inter-reader disagreement.[17;18] To overcome this potential problem, automated pipelines for image assessment have been designed, such as the ones presented in **Chapters 4** and **5**.

Chapter 4 used PMOD's Alzheimer's Discrimination Tool (PALZ). This tool compares FDG uptake from specific brain regions that are especially affected by AD with values from a database of healthy control subjects, resulting in a specific score for each patient scan. This score reflects whether the subject's image is considered normal or abnormal when compared to the reference dataset. This chapter showed good results for classifying AD patients when (semi-)quantitative rCBF parametric images were compared with the FDG database from PALZ, once more illustrating the similarity between perfusion and metabolism patterns. Although the values of the area under the curve of the receiver operator characteristic curves for rCBF images were high (above 0.9), it can be speculated that better results could be achieved if they were compared to a database of normal R_1 or early PIB frames images. In addition, quantitative R_1 rCBF images outperformed semi-quantitative early PIB frames for the classification of AD patients using PALZ.

In principle, the same idea behind PALZ could also be applied to other neurological disorders and radiotracers. For example, dementia with Lewy Bodies (DLB) is characterized by a reduction in metabolic activity in the occipital, parietotemporal, and frontal regions of the brain.[19] If a similar approach is used for these regions instead of the characteristic AD regions, the tested subjects may be given a score for DLB classification. Moreover, since each radiotracer displays a different (patho)physiological feature, the same pipeline can be adapted to focus more on those regions where the main differ-

ences between a patient group and healthy control subjects may be present. For instance, Aβ deposits in AD patients are known to be present in grey matter, while, in general, healthy subjects display tracer uptake in white matter. A comparison of grey matter uptake between the groups might prove enough to identify subject with these deposits.

Chapter 5 focused on the adaptation of the SSM/PCA method, so that quantitative PET images could be used as input. It was shown that not only FDG and R_1 images could be used for differentiating AD patients from other neurological disorders, but also that AD classification improved by the addition of a second image that provides more information about the subject. Furthermore, the most valuable take-home message from this chapter is that information regarding Aβ deposition and relative rCBF can be obtained by a single dynamic PET scan in combination with pharmacokinetic modelling. In addition, **Chapter 6** showed that (semi-)quantitative rCBF images produce very similar results to those obtained from metabolic images. Apart from investigating the classification performance of AD patients, this chapter also explored the differences and similarities between (semi-)quantitative rCBF and semi-quantitative FDG patterns. Similar results to those obtained in **Chapter 3** were found. Furthermore, it also showed that the quantitative R_1 pattern is more closely related to the semi-quantitative metabolic pattern and outperformed the semi-quantitative rCBF patterns in AD patient classification. Although all these results were focused on identifying AD patients using images derived from dynamic PIB PET scans, the same method could be applied to different neurological disorders and radiotracers.

In addition to the approaches presented in this thesis, other methods for single subject assessment have already been developed.[20;21] Unfortunately, since FDG is the most widely used PET tracer, most of these techniques have been investigated for this tracer. Nonetheless, most of these approaches can be translated to other radiotracers and even to quantitative

images derived from dynamic PET scans with only small adjustments. Therefore, all these techniques have the potential to improve patient diagnosis in a clinical setting. Finally, drug development trials can greatly benefit from these methods by more objectively selecting subjects.

Further Usage of SSM/PCA Technique in Alzheimer's Disease

Although the first studies applying SSM/PCA date back as far as 1987,[22] the work from Spetsieris and colleagues[23] details the approach that most current investigations use. Since then, this technique has mainly been used on datasets of Parkinson's disease patients.[24] Nevertheless, other pathologies have also been explored, such as AD,[19;25] rapid eye movement sleep behaviour disorder,[26;27] and spinocerebellar ataxia type 3.[28] Still, there are plenty of opportunities to explore other datasets using these techniques.

For example, **Chapter 5** established that combining metabolic with Aβ pattern information can improve differential diagnoses, i.e. that it can distinguish AD from other neurological disorders. It would be interesting to assess whether this combined information could also be used for a better prediction of Mild Cognitive Impairment (MCI) subjects who may convert to AD, or even to assess its ability for early detection of subjects that do not show any clinical signs of the disease yet.

Moreover, this technique might provide benefits in supporting drug development studies. As an example, anti-amyloid drug trials have failed to show effectiveness[29] and this could be due to inadequate assessment of disease progression (which is mainly performed using visual assessment or semi-quantitative measures) or inadequate selection of subjects.[30] As previously mentioned, automated tools using multivariate analysis techniques such

as SSM/PCA could offer a more sensitive and objective evaluation of the images from which these trials might benefit. In addition, the use of quantitative images may further improve the accuracy of these estimates. Finally, a characteristic placebo-response network has already been found in drug trials for Parkinson's disease,[24] which may be of importance for more accurate interpretation of drug trial findings.

SSM/PCA is a network analysis technique that shows a characteristic pattern for a neurological disorder depending on the input images being used. Studies conducted in different centres and with different cohorts of Parkinson's disease patients have found similar results.[31] Furthermore, this technique also has proven its value in longitudinal settings and, therefore, the use of SSM/PCA as a network biomarker has been suggested for Parkinson's trials.[24] Hence, these results support the further use of this technique for other disorders that affect the brain. Moreover, a better understanding of the brain networks underlying neurological disorders, which so far has been visualized with FDG PET, can also be achieved with other radiotracers and/or quantitative parametric images, as shown in **Chapter 6** with relative perfusion data. These network biomarkers, together with the assessment of Aβ deposits, might prove a valuable asset in future research.

Further Development of SSM/PCA Technique

The SSM/PCA method generates a characteristic disease pattern based on a number of predefined steps. However, it might be interesting to explore the use of other potential methods. As an example, principal component analysis is in use as a data reduction method and the combination of components is performed using stepwise regression. These procedures could be exchanged with other approaches, such as independent component analysis[32] and a decision tree,[33] respectively. The SSM/PCA technique, as proposed by Spet-

sieris and colleagues[23] was optimized for a cohort of Parkinson's disease patients. It might be interesting to adapt the SSM/PCA method to each specific research setting. Although the technique already provides good separation between patients and healthy subjects, separation may even be improved further by using different settings.

Finally, it is of interest to note that although SSM/PCA was developed for the comparison of two subject groups, it also has the potential to distinguish between more than two groups. This could enable the use of SSM/PCA as a differential diagnostic tool in clinical routine, i.e. a subject's image is loaded and then compared with various characteristic disease pattern. The final result would then be a report on how likely the image of a patient corresponds to the various disease patterns, aiding clinicians in making a final diagnosis.

Concluding Remarks

In conclusion, the findings presented in this thesis indicate that the use of quantitative rather than qualitative PET images could improve the diagnostic performance of PET studies for dementia patients, not only in research settings but also in clinical practice. Furthermore, it is possible to retrieve more information from a single scan when working with quantitative images. Most automated techniques for the assessment or interpretation of PET images use semi-quantitative FDG images. However, quantitative rCBF images can also be used with minimal loss of sensitivity. Use of novel image analysis techniques in combination with quantitative parametric images could even further improve differential diagnosis and/or assessment of disease stage not only for AD patients, but potentially for other neurological disorders as well.

Bibliography

[1] William E Klunk, Henry Engler, Agneta Nordberg, Yanming Wang, Gunnar Blomqvist, Daniel P Holt, Mats Bergström, Irina Savitcheva, Guo-feng Huang, Sergio Estrada, Birgitta Ausén, Manik L Debnath, Julien Barletta, Julie C Price, Johan Sandell, Brian J Lopresti, Anders Wall, Pernilla Koivisto, Gunnar Antoni, Chester A Mathis, and Bengt Långström. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals of neurology*, 55(3):306–19, mar 2004.

[2] Julie C Price, William E Klunk, Brian J Lopresti, Xueling Lu, Jessica A Hoge, Scott K Ziolko, Daniel P Holt, Carolyn C Meltzer, Steven T DeKosky, and Chester A Mathis. Kinetic Modeling of Amyloid Binding in Humans using PET Imaging and Pittsburgh Compound-B. *Journal of Cerebral Blood Flow & Metabolism*, 25(11):1528–1547, 2005.

[3] Yoko Ikoma, Paul Edison, Anil Ramlackhansingh, David J. Brooks, and Federico E. Turkheimer. Reference region automatic extraction in dynamic [11 C]PIB. *Journal of Cerebral Blood Flow and Metabolism*, 33(11):1725–1731, 2013.

[4] Brian J Lopresti, William E Klunk, Chester A Mathis, Jessica A Hoge, Scott K Ziolko, Xueling Lu, Carolyn C Meltzer, Kurt Schimmel, Nicholas D Tsopelas, Steven T Dekosky, and Julie C Price. Simplified Quantification of Pittsburgh Compound B Amyloid Imaging PET Studies: A Comparative Analysis. *Time*, pages 1959–1972, 2005.

[5] Maqsood Yaqub, Nelleke Tolboom, Ronald Boellaard, Bart N M van Berckel, Erica W. van Tilburg, Gert Luurtsema, Philip Scheltens, and Adriaan A. Lammertsma. Simplified parametric methods for [11C]PIB studies. *NeuroImage*, 42(1):76–86, aug 2008.

[6] Yun Zhou, Susan M. Resnick, Weiguo Ye, Hong Fan, Daniel P. Holt, William E. Klunk, Chester A. Mathis, Robert Dannals, and Dean F. Wong. Using a reference tissue model with spatial constraint to quantify [11C]Pittsburgh compound B PET for early diagnosis of Alzheimer's disease. *NeuroImage*, 36(2):298–312, 2007.

[7] Y. J. Chen, B. L. Rosario, W. Mowrey, C. M. Laymon, X. Lu, O. L. Lopez, W. E. Klunk, B. J. Lopresti, C. A. Mathis, and J. C. Price. Relative 11C-PiB Delivery as a Proxy of Relative CBF: Quantitative Evaluation Using Single-Session 15O-Water and 11C-PiB PET. *Journal of Nuclear Medicine*, 56(8):1199–1205, 2015.

[8] Philipp T Meyer, Sabine Hellwig, Florian Amtage, Christof Rottenburger, Ursula Sahm, Peter Reuland, Wolfgang A Weber, and Michael Hüll. Dual-Biomarker Imaging of Regional Cerebral Amyloid Load and Neuronal Activity in Dementia with PET and 11C-Labeled Pittsburgh Compound B. *Journal of Nuclear Medicine*, 52(3):393–400, 2011.

[9] Nelleke Tolboom, Maqsood Yaqub, Ronald Boellaard, Gert Luurtsema, Albert D. Windhorst, Philip Scheltens, Adriaan A. Lammertsma, and Bart N M Van Berckel.

Test-retest variability of quantitative [11C]PIB studies in Alzheimer's disease. *European Journal of Nuclear Medicine and Molecular Imaging*, 36(10):1629–1638, 2009.

[10] Adriaan A. Lammertsma. Forward to the Past: The Case for Quantitative PET Imaging. *Journal of Nuclear Medicine*, 58(7):1019–1024, jul 2017.

[11] Adriaan A. Lammertsma and Susan P. Hume. Simplified Reference Tissue Model for PET Receptor Studies. *NeuroImage*, 4(3):153–158, 1996.

[12] Yanjun Wu and Richard E. Carson. Noise Reduction in the Simplified Reference Tissue Model for Neuroreceptor Functional Imaging. *Journal of Cerebral Blood Flow & Metabolism*, 22(12):1440–1452, 2002.

[13] M. T. Fodero-Tavoletti, C. C. Rowe, C. A. McLean, L. Leone, Q.-X. Li, C. L. Masters, R. Cappai, and V. L. Villemagne. Characterization of PiB Binding to White Matter in Alzheimer Disease and Other Dementias. *Journal of Nuclear Medicine*, 50(2):198–204, 2009.

[14] Lyduine E. Collij, Elles Konijnenberg, Juhan Reimand, Mara ten Kate, Anouk den Braber, Isadora Lopes Alves, Marissa Zwan, Maqsood Yaqub, Daniëlle M.E. van Assema, Alle Meije Wink, Adriaan A. Lammertsma, Philip Scheltens, Pieter Jelle Visser, Frederik Barkhof, and Bart N.M. van Berckel. Assessing amyloid pathology in cognitively normal subjects using ^{18}F-flutemetamol PET: Comparing visual reads and quantitative methods. *Journal of Nuclear Medicine*, 60(4):541–547, 2019.

[15] M Jueptner and C Weiller. Review: does measurement of regional cerebral blood flow reflect synaptic activity? Implications for PET and fMRI. *NeuroImage*, 2(2):148–56, jun 1995.

[16] Ruben C. Gur, J. Daniel Ragland, Martin Reivich, Joel H. Greenberg, Abass Alavi, and Raquel E. Gur. Regional differences in the coupling between resting cerebral blood flow and metabolism may indicate action preparedness as a default state. *Cerebral Cortex*, 19(2):375–382, 2009.

[17] D Borczyskowski, F Wilke, B Martin, W Brenner, M Clausen, J Mester, and R Buchert. Evaluation of a new expert system for fully automated detection of the Alzheimer's dementia pattern in {FDG} {PET}. *Nucl. Med. Commun.*, 27(9):739–743, 2006.

[18] Silvia Morbelli, Andrea Brugnolo, Irene Bossert, Ambra Buschiazzo, Giovanni B. Frisoni, Samantha Galluzzi, Bart N.M. Van Berckel, Rik Ossenkoppele, Robert Perneczky, Alexander Drzezga, Mira Didic, Eric Guedj, Gianmario Sambuceti, Gianluca Bottoni, Dario Arnaldi, Agnese Picco, Fabrizio De Carli, Marco Pagani, and Flavio Nobili. Visual Versus semi-quantitative analysis of ^{18}F-FDG-PET in Amnestic MCI: An European Alzheimer's Disease Consortium (EADC) project. *Journal of Alzheimer's Disease*, 44(3):815–826, 2015.

[19] Laura K. Teune, Anna L. Bartels, Bauke M. De Jong, Antoon T.M. Willemsen, Silvia A. Eshuis, Jeroen J. De Vries, Joost C.H. Van Oostrom, and Klaus L. Leenders. Typical cerebral metabolic patterns in neurodegenerative brain diseases. *Movement Disorders*, 25(14):2395–2404, 2010.

[20] Mite Mijalkov, Ehsan Kakaei, Joana B. Pereira, Eric Westman, and Giovanni Volpe. BRAPH: A graph theory software for the analysis of brain connectivity. *PLOS ONE*, 12(8):e0178798, aug 2017.

[21] Andrea Pilotto, Enrico Premi, Silvia Paola Caminiti, Luca Presotto, Rosanna Turrone, Antonella Alberici, Barbara Paghera, Barbara Borroni, Alessandro Padovani, and Daniela Perani. Single-subject SPM FDG-PET patterns predict risk of dementia progression in Parkinson disease. *Neurology*, 90(12):e1029–e1037, mar 2018.

[22] J. R. Moeller, S C Strother, J. J. Sidtis, and D. A. Rottenberg. Scaled Subprofile Model: A Statistical Approach to the Analysis of Functional Patterns in Positron Emission Tomographic Data. *Journal of Cerebral Blood Flow & Metabolism*, 7(5):649–658, oct 1987.

[23] Phoebe G. Spetsieris, Yilong Ma, Vijay Dhawan, and David Eidelberg. Differential diagnosis of parkinsonian syndromes using PCA-based functional imaging features. *NeuroImage*, 45(4):1241–1252, 2009.

[24] Katharina A. Schindlbeck and David Eidelberg. Network imaging biomarkers: insights and clinical applications in Parkinson's disease. *The Lancet Neurology*, 17(7):629–640, 2018.

[25] Sanne K. Meles, Marco Pagani, Dario Arnaldi, Fabrizio De Carli, Barbara Dessi, Silvia Morbelli, Gianmario Sambuceti, Cathrine Jonsson, Klaus L. Leenders, and Flavio Nobili. The Alzheimer's disease metabolic brain pattern in mild cognitive impairment. *Journal of Cerebral Blood Flow and Metabolism*, 37(12):3643–3648, 2017.

[26] Sanne K. Meles, David Vadasz, Remco J. Renken, Elisabeth Sittig-Wiegand, Geert Mayer, Candan Depboylu, Kathrin Reetz, Sebastiaan Overeem, Angelique Pijpers, Fransje E. Reesink, Teus van Laar, Lisette Heinen, Laura K. Teune, Helmut Höffken, Marcus Luster, Karl Kesper, Sofie M. Adriaanse, Jan Booij, Klaus L. Leenders, and Wolfgang H. Oertel. FDG PET, dopamine transporter SPECT, and olfaction: Combining biomarkers in REM sleep behavior disorder. *Movement Disorders*, 32(10):1482–1486, 2017.

[27] Sanne K. Meles, Remco J. Renken, Annette Janzen, David Vadasz, Marco Pagani, Dario Arnaldi, Silvia Morbelli, Flavio Nobili, Geert Mayer, Klaus L. Leenders, Wolfgang H. Oertel, Elisabeth Sittig-Wiegand, Candan Depboylu, Kathrin Reetz, Sebastiaan Overeem, Angelique Pijpers, Fransje E. Reesink, Teus Van Laar, Laura K. Teune, Helmut Höffken, Marcus Luster, Lars Timmermann, Karl Kesper, Sofie M. Adriaanse, Jan Booij, Gianmario Sambuceti, Nicola Girtler, and Cathrine Jonsson. The Metabolic Pattern of Idiopathic REM Sleep Behavior Disorder Reflects Early-Stage Parkinson Disease. *Journal of Nuclear Medicine*, 59(9):1437–1444, 2018.

[28] Sanne K. Meles, Jelmer G. Kok, Bauke M. De Jong, Remco J. Renken, Jeroen J. de Vries, Jacoba M. Spikman, Aaltje L. Ziengs, Antoon T.M. Willemsen, Harm J. van der Horn, Klaus L. Leenders, and Hubertus P.H. Kremer. The cerebral metabolic topography of spinocerebellar ataxia type 3. *NeuroImage: Clinical*, 19(August 2017):90–97, 2018.

[29] Tengfei Guo, Juergen Dukart, Matthias Brendel, Axel Rominger, Timo Grimmer, and Igor Yakushev. Rate of β-amyloid accumulation varies with baseline amyloid burden: Implications for anti-amyloid drug trials. *Alzheimer's and Dementia*, 14(11):1387–1396, 2018.

[30] Isadora Lopes Alves, Lyduine E. Collij, Daniele Altomare, Giovanni B. Frisoni, Laure Saint-Aubert, Pierre Payoux, Miia Kivipelto, Frank Jessen, Alexander Drzezga, Annebet Leeuwis, Alle Meije Wink, Pieter Jelle Visser, Bart N.M. van Berckel, Philip Scheltens, Katherine R. Gray, Robin Wolz, Andrew Stephens, Rossella Gismondi, Christopher Buckely, Juan Domingo Gispert, Mark Schmidt, Lisa Ford, Craig Ritchie, Gill Farrar, Frederik Barkhof, and José Luis Molinuevo. Quantitative amyloid PET in Alzheimer's disease: the AMYPAD prognostic and natural history study. *Alzheimer's and Dementia*, 16(5):750–758, 2020.

[31] Sanne K. Meles, Remco J. Renken, Marco Pagani, L. K. Teune, Dario Arnaldi, Silvia Morbelli, Flavio Nobili, Teus van Laar, Jose A. Obeso, Maria C. Rodríguez-Oroz, and Klaus L. Leenders. Abnormal pattern of brain glucose metabolism in Parkinson's disease: replication in three European cohorts. *European Journal of Nuclear Medicine and Molecular Imaging*, 47(2):437–450, 2020.

[32] Marco Pagani, Alessandro Giuliani, Johanna Öberg, Fabrizio De Carli, Silvia Morbelli, Nicola Girtler, Dario Arnaldi, Jennifer Accardo, Matteo Bauckneht, Francesca Bongioanni, Andrea Chincarini, Gianmario Sambuceti, Cathrine Jonsson, and Flavio Nobili. Progressive Disintegration of Brain Networking from Normal Aging to Alzheimer Disease: Analysis of Independent Components of ¹⁸ F-FDG PET Data. *Journal of Nuclear Medicine*, 58(7):1132–1139, 2017.

[33] D Mudali, M Biehl, S K Melesc, R J Renken, D Garcıa-Garcıa, P Clavero, J Arbizu, J A Obeso, M C Rodriguez-Oroz, K L Leenders, and J B T M Roerdink. Differentiating Early and Late Stage Parkinson ' s Disease Patients from Healthy Controls. 2016.