Chapter 9

Summary and discussion





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The aim of the studies described in this thesis was to evaluate two novel and promising tracers for imaging AD pathology *in vivo*: [^{11}C]PIB (*1*) and [^{18}F]FDDNP (*2*). This was performed in several steps. First, optimal tracer kinetic models for both tracers were validated. Next, global and regional binding of paired scans performed in subjects across the spectrum of cognitive decline was assessed. Subsequently, in order to further validate both tracers, results of [^{11}C]PIB and [^{18}F]FDDNP scans were compared with CSF measurements of Aβ and tau, and with neuropsychological tests. Finally, the potential of [^{11}C]PIB and [^{18}F]FDDNP for identifying AD was evaluated and the thesis is concluded with an example of the clinical use of these new tracers.

The main findings are briefly summarised and then discussed below. In addition, methodological considerations, suggestions for future research and clinical implications are discussed.

Main findings

First, methodological aspects of analysing [^{11}C]PIB and [^{18}F]FDDNP data were investigated showing that RPM2, an implementation of the simplified reference tissue model using basis functions, with cerebellum grey matter as reference region was the optimal reference tissue approach for [^{11}C]PIB and [^{18}F]FDDNP studies

In **Chapters 2.1 and 2.2** the performance of different parametric methods for measuring binding potential (BP_{ND}) of [^{11}C]PIB and [^{18}F]FDDNP was assessed. For both tracers, best accuracy was achieved with RPM2, a basis function implementation of the simplified reference tissue model with fixed reference tissue efflux rate constant. In **Chapter 3** test-retest variability of [^{11}C]PIB studies was evaluated using several modelling approaches. Test-retest variability was markedly higher in methods using plasma input data as compared to reference tissue methods. Best variability was found for RPM2, indicating that RPM2 is a stable and reliable method for quantifying [^{11}C]PIB binding. In addition, specific binding of [^{11}C]PIB in the cerebellum was investigated using a plasma input model. Average cerebellum volume of distribution values showed no significant differences between controls and AD patients. As such it was concluded that cerebellum grey matter may indeed be used as a reference tissue for [^{11}C]PIB studies in AD patients.

Next, global and regional [^{11}C]PIB and [^{18}F]FDDNP binding was evaluated and compared with other aspects of AD: CSF levels of Aβ and tau and neuropsychological measures of cognitive decline. All findings broadly supported the initial assumption that [^{11}C]PIB reflects amyloid load and that [^{18}F]FDDNP reflects both tangles and amyloid load.

In **Chapter 4** the binding of [^{11}C]PIB and [^{18}F]FDDNP in AD, MCI and controls was assessed revealing marked differences between the two tracers. First, although both tracers were able to distinguish AD patients from controls at a group level, binding of [^{11}C]PIB in AD patients

was 9-fold higher than that of [^{18}F]FDDNP. Second, binding in MCI patients varied between tracers. [^{11}C]PIB binding in MCI was similar to that of either controls or AD patients. With [^{18}F]FDDNP, the distribution of binding was more widespread. A larger number of MCI patients displayed relatively increased [^{18}F]FDDNP uptake, in some patients even exceeding that of AD patients. Third, regional binding patterns of both tracers differed substantially. For [^{11}C]PIB, AD patients showed increased binding in all cortical brain regions compared to healthy controls, with relatively the smallest increase in the MTL. For [^{18}F]FDDNP, although AD patients displayed an overall increase in binding compared to MCI patients and controls, in all three groups, the highest values were found in the MTL. Finally, there was only a moderate correlation between [^{11}C]PIB and [^{18}F]FDDNP BP_{ND}. These findings revealed that both tracers measure related, but different, characteristics of AD. In **Chapter 5** this was further investigated by measuring the relationships between two CSF biomarkers (Aβ42 and tau) and uptake of [^{11}C]PIB and [^{18}F]FDDNP. Increased global [^{11}C]PIB binding was related specifically to low CSF levels of Aβ42. In contrast, increased global [^{18}F]FDDNP binding was associated mainly with high CSF levels of tau. In a subset of subjects with short timeframe between imaging and lumbar puncture, a trend for an inverse association with CSF Aβ42 was found. In **Chapter 6** associations between both tracers and neuropsychological measures of cognitive impairment were assessed. Increased [^{18}F]FDDNP binding was associated specifically with impairment of episodic memory, whilst increased [^{11}C]PIB binding was associated with impairment in a broader range of cognitive functions, especially memory impairment and executive dysfunctioning.

Finally, the use of both tracers for diagnosing AD was investigated. Visual assessment of [^{11}C]PIB showed promise as a supportive diagnostic marker for AD but visual assessment of [^{18}F]FDDNP was less straightforward. Additionally, the use of both tracers in the differential diagnosis of AD was illustrated in two siblings with progressive cognitive decline.

In **Chapter 7**, performance of visual interpretation of [^{11}C]PIB and [^{18}F]FDDNP PET images as supportive diagnostic markers for AD was evaluated and compared with [^{18}F]FDG PET and MTA on MRI. Visual interpretation of [^{11}C]PIB images showed a high diagnostic accuracy combined with high inter-observer agreement. Furthermore, agreement between visual and quantitative assessment of [^{11}C]PIB was high. Moreover, in the present cohort, visual rating of [^{11}C]PIB for identification of AD performed equally well as the combination of [^{18}F]FDG (high sensitivity) and MTA (high specificity). Visual rating of [^{18}F]FDDNP images for identification of AD had the lowest sensitivity, specificity and accuracy. Additionally, agreement with quantitative assessment was only fair. When effects of age on visual interpretation were assessed, for both younger (<65 years) and older subjects (≥65), the same modalities performed best with respect to sensitivity and specificity.

Chapter 8 describes two siblings with progressive cognitive deterioration, clinically resembling AD, in whom CSF and [^{11}C]PIB suggested the absence of underlying amyloid pathology. Subsequently, this suspicion was confirmed by the identification of the R406W *tau* mutation, leading to a diagnosis of frontotemporal dementia (FTD). This study illustrated the power of

CSF measurements of Aβ and [11C]PIB PET in refuting the presence of amyloid pathology in patients fulfilling the clinical criteria of AD.

General Discussion

Although both tracers were designed to image the amount and distribution of AD pathology during life, [11C]PIB and [18F]FDDNP have different characteristics. [11C]PIB was developed to measure the amount of Aβ deposition (*3,4*), which was confirmed in a post-mortem study in AD (*5*). This also was reflected in the regional binding pattern observed *in vivo (chapter 4),* as binding was lowest in the MTL, an area with relatively low accumulation of amyloid plaques (*6*). In addition, an inverse association between [11C]PIB and CSF Aβ42 (*chapter 5*) was observed, confirming previous reports (*7,8*). This inverse association possibly reflects plaques acting as an Aβ42 "sink", hindering transport of soluble Aβ42 from brain to CSF, as a decrease in CSF Aβ42 is typically seen in AD (*9*). It has been reported that [8F]FDDNP not only labels amyloid plaques, but also neurofibrillary tangles. Indeed, post mortem studies in AD indicate that [18F] FDDNP binding co-localises with deposition of both Aβ and tangles (*2,10*). Recently, however, this assumption has been challenged by an *ex vivo* study reporting that [18F]FDDNP at tracer concentrations has little affinity for both structures (*11*), explaining the low specific signal of [18F]FDDNP *in vivo.* Despite this weak binding, the *in vivo* data presented in this thesis suggest that at least part of the specific signal of [18F]FDDNP in AD patients is due to binding to tangles and, to a lesser extent, to amyloid. [18F]FDDNP had highest binding in the MTL (*chapter 4*), an area known to be rich in NFT from post mortem studies (*12*). Recently, this finding has also been described by another comparative study (*13*).
Moreover, there was a strong positive association between increased global [18F]FDDNP binding and increased CSF tau levels and, in a subset of subjects with short timeframe between imaging and lumbar puncture, a trend for an inverse association with CSF Aβ42 (*chapter 5*). Finally, increased [18F]FDDNP binding was associated specifically with impairment of episodic memory (*chapter 6*), which is broadly in agreement with the relationship between dementia severity and NFT established at post mortem studies (*14,15*).

Clinical Implications

Above head-to-head comparison of [11C]PIB and [18F]FDDNP indicate that both tracers measure related, but different, characteristics of AD. Results provide support for the notion that [11C] PIB reflects amyloid load, whilst at least part of the [18F]FDDNP signal reflects tangles and, to a lesser extent, amyloid load. Differences in size and distribution of specific binding of both tracers have consequences for their clinical implications.

[11C]PIB

Increased [11C]PIB binding was seen in all AD patients, indicating high sensitivity for detection of AD (*chapter 7*). Initially, [11C]PIB binding in MCI was reported to be similar to that of either

controls or AD patients (*chapter 4)*. However, after inclusion of more MCI subjects binding turned out to be more variable. More or less increased global binding was seen in approximately 40% of all MCI patients included in this thesis, which is in line with the percentage reported previously (*16·17*). The [^{11}C]PIB 'positive' MCI patients are thought to be the subset of patients that progress to AD (*16*), although this hypothesis still remains to be confirmed in a large prospective study. This notion is, however, supported by the association between [^{11}C]PIB binding and memory impairment, the main characteristic of (prodromal) AD (*chapter 6*). Although negligible global [^{11}C]PIB binding was seen in most healthy controls, a few subjects showed slightly higher binding, and binding in one healthy elderly control was as high as that seen in AD patients. In previous [^{11}C]PIB studies, approximately 10-20% of healthy controls (*18·19*) have been reported to display increased [^{11}C]PIB binding. [^{11}C]PIB load tended to vary, but in general it was lower than that seen in most AD patients (*19·20*). This is largely in line with post mortem studies reporting presence of AD pathology in around 30% of cognitively healthy elderly subjects (*21*). These subjects may be preclinical AD patients, as deposition of pathology is thought to start a decade before cognitive impairment arises (*22*). Alternatively, the deposition of amyloid could be benign. To verify if these subjects are indeed 'preclinical' cases longitudinal follow up is necessary. At present, however, there is no evidence to support this claim.

Nevertheless, the MCI data strongly suggest that [^{11}C]PIB is indeed able to detect early accumulation of AD related pathology. This could enable measurements of time course and deposition of AD pathology, which would facilitate not only early and accurate diagnosis, but also development of new disease modifying therapies. Stratification of participants based on presence of underlying AD pathology, thereby identifying subjects who will potentially benefit from therapies targeting that pathology, will greatly improve the power of therapeutic trials. Furthermore, imaging of AD pathology using [^{11}C]PIB potentially could also be used as a tool to measure treatment efficacy. It remains to be verified, however, whether an actual decrease in pathological load as induced by medication can be measured accurately using [^{11}C]PIB. At present, little is known about how conformational changes of amyloid (and tangles) will affect PET measurements.

[^{18}F]FDDNP

[^{18}F]FDDNP binding in AD patients and healthy controls largely overlapped, displaying a relative small range in binding values from one side of the spectrum of cognitive decline to the other. These results indicate that the accuracy of [^{18}F]FDDNP as a differential diagnostic tool for detection of AD pathology in individual subjects is substantially lower than that of [^{11}C]PIB (*chapter 7*).

In MCI patients, the variability in binding was much larger than with [^{11}C]PIB. A number of MCI patients displayed increased global cortical [^{18}F]FDDNP binding, which in some cases even exceeded that seen in AD patients, a finding that has not been reported before (*2*). Moreover, in MCI patients, there was a discrepancy in binding between [^{18}F]FDDNP and [^{11}C]PIB binding, with some individuals displaying [^{18}F]FDDNP uptake similar to that of controls while [^{11}C]PIB

uptake was increased and vice versa. Increased [^{18}F]FDDNP binding in the latter group could still reflect early pathological processes in the brain. These could possibly be due to effects of age or ApoE genotype (*23*) or a pathological process other than prodromal AD, for instance FTD. This is in line with a preliminary report of [^{18}F]FDDNP in FTD patients revealing elevated cortical binding (*24*).

Although [^{18}F]FDDNP has limited accuracy for early diagnosis of AD, it does show promise in another way, especially since [^{18}F]FDDNP is the only PET ligand available to date with, besides binding to amyloid, also affinity for tangles (*10*). The specific association between increased [^{18}F] FDDNP binding and episodic memory impairment indicates that it somehow reflects clinical status. This suggests a potential ability to monitor progression of disease, which is in keeping with previously reported findings of an increase in binding in (MCI and control) subjects who declined clinically (*2*). Clearly, this potential application remains to be investigated more thoroughly using repeat scans at follow up. Moreover, these characteristics are more likely to be useful in research settings for differentiation at group level, e.g. as surrogate marker of disease progression or as endpoint in therapeutic trials, than in clinical practice.

Accuracy of PET measurements

The accuracy of previously mentioned possibilities relies, among others, on data acquisition and analysis. For both tracers using parametric models best accuracy was found using RPM2, a parametric implementation of the simplified reference tissue model. This model requires the data to be acquired as a dynamic scan, following tracer uptake, retention and clearance over time. Dynamic scanning enables full quantification, as it takes into account differences in plasma clearance and changes in other parameters that affect tracer uptake, such as blood flow. The latter is especially important, as regional blood flow may change with the progression of AD. This is essential for accurately monitoring deposition of pathology (progression of disease) and for assessing therapeutic efficacy. If scans are performed solely for diagnostic purposes, however, simple tissue ratios provide sufficient information, despite the fact that they overestimate specific binding (*25*). This allows for short imaging protocols that are most comfortable for patients and enhance cost-effectiveness of PET scanning.

Towards an early and accurate diagnosis

Amyloid imaging has had a major impact on the field of dementia research and it is likely to do so also with respect to clinical diagnosis of AD in the near future. The work in this thesis focused on the two most widely used amyloid imaging tracers, but currently new tracers are being developed. These new tracers are specifically designed to have a longer half life (*26-30*) or higher specific binding (*31*), aiming to increase their clinical applicabilty. The first clinical study with a [^{18}F] labeled derivative of [^{11}C]PIB, renamed as [^{18}F]Flutemetamol, has recently been published (*29*). Although this ligand seems to be promising, time to equilibrium is long (>80 min). Moreover, non-specific binding in white matter of [^{18}F]Flutemetamol is considerably higher than with [^{11}C]PIB, with can complicate quantification of especially subtle

amyloid deposition. This also seems be the case with other new amyloid imaging agents, like Floripamine ([^{18}F]AV-45) (*30*) or [^{18}F]BAY94-9172 (*26*), of which clinical trials are currently ongoing. An [^{18}F] amyloid imaging agent that does not appear to have this problem is [^{18}F] AZD4694 (*28*). However, human studies with this ligand have not yet been performed.
To date, the best documented tracer for differential diagnostics of AD still is [^{11}C]PIB. Not only is visual assessment of [^{11}C]PIB easy and in good agreement with quantiative values, imaging with [^{11}C]PIB has additional value in diagnosing AD next to MTL atrophy on MRI (*32*) and decreased cerebral glucose metabolism measured using [^{18}F]FDG (*33,34*) (*chapter 7*). In addition, it could validate and expand the diagnostic potential of CSF measures of AD pathology, as PET provides complementary regional information. *In vivo* visualisation and quantification of AD pathology using [^{11}C]PIB is likely to become an additional supportive biomarker for the new research criteria proposed recently (*35*), hopefully leading to earlier diagnosis of AD.

Methodological considerations

Patient selection

The majority of observations came from one relatively limited sample, therefore values from 'outliers' could potentially have affected associations. All PET data, however, underwent multiple quality checks. Aberrant values due to technical issues were excluded. Consequently, conclusions drawn from these data are likely to be valid.

Data acquisition and analysis

PET data were analysed without applying motion correction. This potentially could have affected accuracy of the measurements. During the 90 minutes scanning period, however, patients were continuously checked for motion using laser beams. Subjects with severe motion were excluded from analysis.
PET data were also not corrected for partial volume effects. This choice was made, as potential overcorrection may lead to an artificially high signal. This approach ascertains that any observed increase in binding is real, although underestimation of binding may conceal potential associations. This was most noticeable in the MTL, which showed unexpected low associations between [^{18}F]FDDNP binding and CSF tau levels (*chapter 5)*. The current status and accuracy of PVC in amyloid imaging, however, is not clear and needs to be further evaluated before standard application (*36*).

Suggestions for future research

Enlarging the present sample size would improve power in statistical analyses. Moreover, it would allow for stratification of subjects, for instance according to ApoE genotype as Aβ burden is associated with ApoE ε4 gene dose (*37,38*). Clinical follow up would help to clarify the diverse [^{11}C]PIB and [^{18}F]FDDNP results obtained in MCI patients and would disclose whether there is

predictive value in increased tracer binding. In addition, repeat scans would reveal whether clinical progression is associated with increased binding of both tracers. Finally, comparison of PET data with post mortem studies is warranted.

In particular [^{18}F]FDDNP data need more in depth exploration, preferably after increasing sample size and follow up and possibly even using a related ligand with a higher specific to non-specific binding ratio. Data on [^{18}F]FDDNP binding *in vivo* are still limited, in contrast to the wealth of data on [^{11}C]PIB, accumulated by research groups across the globe. However, results of this thesis indicate that although [^{11}C]PIB is the preferable tracer for early and accurate diagnosis of AD (*39*), [^{18}F]FDDNP has potential in providing complementary information. The relevance of elevated [^{18}F]FDDNP binding, especially in subjects with low [^{11}C]PIB binding, should be further investigated. Moreover, patterns in regional [^{18}F]FDDNP binding should be explored, as these supposedly can differentiate between AD and FTD (*40*) and as they are affected by age and ApoE genotype (*23*). In addition, investigation of potential associations between [^{18}F]FDDNP binding patterns and patterns of grey matter loss on MRI would be interesting, given the association between the latter and tangle density at autopsy (*41*).

New ligands should be developed incorporating qualities of the current ligands but minimising their drawbacks. The knowledge already gained in studies (preclinical and clinical) using [^{11}C] PIB and [^{18}F]FDDNP should be applied to evaluate performance of new tracers. Besides the development of an [^{18}F]-labeled analog to [^{11}C]PIB, new ligands related to [^{18}F]FDDNP should be investigated. The associations found between increased [^{18}F]FDDNP binding and increased CSF levels of tau and impairment of episodic memory are promising. Therefore, improving the specific signal of this ligand and decreasing the non-specific signal, suggested to be due to labeled metabolites in the brain (*42*), is necessary.

In general, amyloid imaging and longitudinal follow up in large cohorts of healthy controls will provide more insight in the deposition of pathology and the role of amyloid imaging before clinical onset of disease. In particular healthy controls with certain risk factors (for example diagnosis of AD in first degree relatives, with an ApoE ε4 allele or abnormal CSF levels of Aβ, tau or ptau) and subjects with subjective memory complaints would be of interest.

Finally, comparing the imaging of AD pathology *in vivo* with other imaging methods might unravel some of the more fundamental questions regarding pathophysiology of AD. For example, an association has been suggested between regionally specific default activity and AD-related changes, including amyloid deposition, metabolic disruption, and atrophy (*43*). This should be further investigated using several imaging modalities in the same subjects.

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