



Chapter 1

Introduction and outline





Introduction

Over the past two decades, positron emission tomography (PET) tracers have been developed for *in vivo* visualisation and quantification of Alzheimer's disease (AD) pathology. Previously, detection of AD pathology was only possible at post mortem examination of the brain or at brain biopsy. The possibility to image the amount and distribution of AD pathology during life has initiated a new research area. It shows promise to facilitate early and accurate diagnosis of AD, provide more insight in the time course and regional deposition of pathology during life and assist in the development and individual assessment of potential treatments. This thesis is dedicated to evaluate and compare the performance of two promising ligands for *in vivo* imaging of AD pathology, [¹¹C]PIB (1) and [¹⁸F]FDDNP (2).

Alzheimer's disease

AD is a progressive neurodegenerative disorder. The diagnosis of AD can be preceded by a prodromal phase, which is characterised primarily by episodic memory impairment, often referred to as mild cognitive impairment (MCI) (3-4). At present, a clinical diagnosis of AD is made when, in addition to progressive memory impairment, impairment in at least one other cognitive domain, e.g. aphasia, apraxia, agnosia or executive dysfunctioning is present (5).

Neuropathologically AD is characterised by the accumulation of amyloid-beta (A β) in senile plaques and hyperphosphorylated tau in neurofibrillary tangles (NFT) (6). This hallmark pathology starts to accumulate many years before cognitive symptoms arise and especially NFT spread in a predictable manner throughout the brain. NFT are mainly present in the medial temporal (MTL) and lateral temporal lobes and, to a lesser extent, in frontal, parietal, and occipital lobes (7). Amyloid plaques are more evenly distributed throughout the cortex with relatively mild involvement of the hippocampal formation. Although accumulation of amyloid is thought to play a key role in AD (8), it is the deposition of NFT that is thought to be more directly associated with degree of cognitive impairment and thus severity of disease (9).

In the past decades, the biological basis of AD has increasingly been unravelled and the "amyloid cascade hypothesis" has been put forward (8). The essence of this hypothesis is that increased production or decreased clearance of A β peptides cause AD. At present, potential disease modifying therapies are being developed, targeting the pathological accumulation of A β peptides. Together with development of therapies, earlier and more accurate diagnosis of AD is essential, as treatment potentially will have most effect early during the course of the disease. For this purpose new research criteria have been proposed recently (10), incorporating novel techniques for early diagnosis of AD. For an individual to meet the new criteria for probable AD, a combination of episodic memory impairment together with at least one supportive biomarker is necessary. These supportive criteria consist of: presence of medial temporal lobe atrophy on MRI (11), abnormal cerebrospinal fluid biomarkers (CSF) (i.e. low

amyloid β concentrations, increased total tau or phosphor-tau concentrations or a combination of the three (12), reduced glucose metabolism in bilateral temporal parietal regions on [^{18}F]FDG PET (13) or a proven autosomal dominant mutation within the immediate family. *In vivo* visualisation and quantification of AD pathology using PET is likely to be the next supportive biomarker.

Positron emission tomography

PET enables *in vivo* visualisation and quantification of physiological and pathophysiological processes using positron emitting radionuclides (14/15). Using PET, the time course of radioligand uptake in the target tissue can be measured accurately and subsequently these measurements can be translated into quantitative values of specific (patho)physiological parameters (e.g. blood flow, glucose metabolism, specific binding at a receptor site, etc) using appropriate tracer kinetic models (16). This analysis does require an input function describing delivery to the tissue. The gold standard input function is a metabolite corrected arterial plasma curve. However, if a reference tissue (devoid of specific binding) can be defined, arterial sampling can be avoided, greatly enhancing clinical applicability of PET (17).

A well validated PET tracer for differential diagnosis of dementia is [^{18}F]FDG. This tracer assesses glucose metabolism and, in AD, typically reveals hypometabolism in bilateral temporal parietal regions and posterior cingulate (13/18). [^{18}F]FDG PET has a high negative predictive value for the presence of neurodegenerative disease, but suffers from low specificity as many other causes of cognitive impairment can induce disturbances in glucose metabolism (19/20).

Imaging Alzheimer pathology using PET: [^{11}C]PIB and [^{18}F]FDDNP

Recently, it has become possible to image the pathology associated with AD. Just seven years ago, the first clinical PET study using a tracer for *in vivo* imaging of AD pathology was published with 2-(1-{6-[(2-[^{18}F]fluoroethyl) (methyl)amino]-2-naphthyl}ethylidene)malononitrile ([^{18}F]FDDNP) (2) as pioneering ligand. This was shortly followed by the first clinical N-methyl-[^{11}C]2-(4-methylaminophenyl)-6-hydroxybenzothiazole ([^{11}C]PIB) study (1). [^{11}C]PIB was designed to measure the amount of fibrillar A β deposits (21/22), whilst [^{18}F]FDDNP was supposed to label not only amyloid plaques but also neurofibrillary tangles. Both tracers displayed increased retention in AD patients compared with controls (1/2/23/25), but magnitude and regional distribution of the signal obtained with [^{18}F]FDDNP differed from that obtained with [^{11}C]PIB. Highest specific to non-specific binding ratio was found for [^{11}C]PIB with AD patients displaying 1.5–2.0-fold specific signal in cortical areas, with respect to the reference tissue.

Initial PET studies with both ligands used simplified tracer kinetic methods for data analysis, with cerebellum (1/2) or pons (23) as a reference region. Typically, these simplified methods, facilitating data analysis and improving clinical use, are derived from and validated with full kinetic analysis using compartmental modelling and a metabolite corrected arterial plasma

input function. For [^{11}C]PIB, such validation studies have been reported (24-25) but this is not the case for [^{18}F]FDDNP. Validated quantitative tracer kinetic models with high accuracy of measurements and known test-retest variability are especially important when evaluating the natural time course of A β depositions and for monitoring therapeutic effects of novel drugs designed to reduce A β accumulation in the brain.

Following the early studies (1-2), several groups have replicated the initial results found with [^{11}C]PIB (26-30), but relatively limited new information has become available for [^{18}F]FDDNP (31-36). Results so far indicate that [^{11}C]PIB seems to be the most promising candidate as a clinical tool for (early) diagnosis of AD, having the highest specific binding and most supporting *in vivo* data. However, the ability of [^{18}F]FDDNP to bind to NFT shows promise not only for early detection of disease, but also for measurement of disease severity (2). Paired [^{11}C]PIB and [^{18}F]FDDNP studies in the same subjects with validated tracer kinetic models are necessary to enable a meaningful comparison.

Outline of the thesis

In vivo imaging of AD pathology shows promise to facilitate early and accurate diagnosis, to provide more insight in the deposition of pathology during life and to assist in the development of potential treatments. At present, it is not clear which tracer is best suitable for which purpose and whether both could contribute to the diagnosis of AD. The aim of this thesis is therefore to validate initial results with both ligands and to obtain more insight in their (dis)similarities. To this end, optimal reference tissue methods were identified and validated for both ligands, paired scans were performed in subjects across the spectrum of cognitive decline, and PET results were compared with other aspects of AD.

Methodological investigations

In **Chapter 2** various parametric reference tissue models for quantification of [^{11}C]PIB (**Chapter 2.1**) and [^{18}F]FDDNP studies (**Chapter 2.2**) were evaluated using both simulations and clinical data. The aim of these studies was to find optimal parametric methods for both ligands. The aims of **Chapter 3** were, first, to assess test-retest variability of [^{11}C]PIB studies and, second, to investigate whether cerebellum could serve as a reference tissue for [^{11}C]PIB studies in AD.

Evaluation across the spectrum of cognitive decline

Chapter 4 presents paired [^{11}C]PIB and [^{18}F]FDDNP studies in the healthy control subjects, AD patients and MCI patients. It focuses on a direct comparison of global and regional uptake of both ligands using the quantitative methods validated in previous chapter 2. In **Chapter 5** potential relationships between other biomarkers of AD pathology, CSF measurements of A β 42 and tau, and [^{11}C]PIB and [^{18}F]FDDNP binding are investigated. In **Chapter 6** associations



of [^{11}C]PIB and [^{18}F]FDDNP with impairment in specific cognitive domains over the broader spectrum comprising cognitively normal elderly subjects, MCI and AD are investigated.

Use in the diagnosis of Alzheimer's disease

In **Chapter 7** the use of visual interpretation [^{11}C]PIB and [^{18}F]FDDNP PET as potential supportive diagnostic markers for AD is evaluated. Finally, **Chapter 8** presents an illustration of the clinical use of the new PET biomarkers in the differential diagnosis of AD.

In **Chapter 9** the main findings of this thesis are summarised and discussed and recommendations for future research are given.



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Methodological investigations



