Towards Clinical Implementation of Dynamic Positron Emission Tomography in Neurodegenerative Diseases

MY JONASSON
Abstract


Alzheimer’s disease (AD) and Parkinson’s disease (PD) are the two most common neurodegenerative disorders worldwide. Positron emission tomography (PET), together with suitable biomarkers, can aid in the clinical evaluation as well as in research investigations of these diseases. Straightforward and quantitative assessments of the parameters of interest estimated on a voxel-level, as parametric images, are possible when PET data is acquired over time. Prerequisites to facilitate clinical use of dynamic PET are simplified analysis methods and scan protocols suitable for clinical routine.

The aim of this thesis was to validate simplified analysis methods, suitable for clinical use, for quantification of dopamine transporter (DAT) availability in patients with parkinsonism using $[^{11}C]$PE2I PET andtau accumulation in AD patients with $[^{18}F]$THK5317 PET.

The included subjects comprised of both healthy controls and patients with parkinsonism, AD or mild cognitive impairment and each subject underwent a dynamic PET scan with either $[^{11}C]$PE2I or $[^{18}F]$THK5317. Models for quantitative voxel-based analysis, resulting in parametric images of tracer binding and overall brain function, were validated in both patients and controls. These parametric methods were compared to region-based values acquired using both plasma- and reference-input models. Clinically feasible scan durations were evaluated for both $[^{11}C]$PE2I and $[^{18}F]$THK5317, and a clustering method to obtain a reference time activity curve directly from the dynamic PET data was validated. Furthermore, images of DAT availability and overall brain functional activity, generated from one single dynamic $[^{11}C]$PE2I PET scan, were compared to a dual-scan approach using $[^{123}I]$FP-CIT single photon emission computed tomography (SPECT) and $[^{18}F]$FDG PET, for differential diagnosis of patient with parkinsonism.

Study I-III supply valuable information on the feasibility of dynamic $[^{11}C]$PE2I in a clinical setting for differential diagnosis of parkinsonian disorders, by having easily accessible images of DAT availability and overall brain functional activity. The work in study IV-V showed that reference methods can be used for quantification of tau accumulation, and suggests that simplified analysis methods and shorter scan durations can be applied to further facilitate applications of dynamic $[^{18}F]$THK5317 PET.

Keywords: Positron emission tomography, PET, Molecular imaging, Quantification, Kinetic modelling, Parametric images, Alzheimer’s disease, Parkinson’s disease

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ISSN 1651-6206
ISBN 978-91-513-0238-6
urn:nbn:se:uu:diva-341786 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-341786)
To Patric and Milo
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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List of Non-Thesis Publications


Cover image
Artwork by Helena Mutanen, Lock Pick, 2009
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<td>One tissue compartment model</td>
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<td>Two tissue compartment model</td>
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<td>AD</td>
<td>Alzheimer’s disease</td>
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<td>BP&lt;sub&gt;ND&lt;/sub&gt;</td>
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<td>COV</td>
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<td>DVR</td>
<td>Distribution volume ratio</td>
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<td>HC</td>
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<td>SUVR</td>
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<td>Time activity curve</td>
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<td>VOI</td>
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Introduction

Alzheimer’s disease (AD) and Parkinson’s disease (PD) are the two most common neurodegenerative disorders worldwide. Functional molecular imaging methods such as positron emission tomography (PET), using different radiotracers, can aid in the clinical evaluation as well as in research investigations of these diseases. Parkinsonism is a group of neurodegenerative disorders, where PD is the most common one, but with several other disorders that are often misdiagnosed. The use of PET with \[^{11}\text{C}\text{PE2I}, a tracer that binds to dopamine transporters (DAT), can support the differentiation between parkinsonian disorders since the central dopaminergic and overall brain functional activity are altered differently. AD is characterized by a cascade of complex pathophysiologic processes, for example accumulation of tau proteins, which is closely associated with neurodegeneration and cognitive impairment. \[^{18}\text{F}\text{THK5317 is a tau-specific PET tracer, showing high retention in patients with AD and can possibly aid in the diagnosis.}

To facilitate clinical use of dynamic PET there are some prerequisites: straightforward visual assessments, as parametric images, where the parameters of interest are estimated for each voxel, simplified analysis methods and scan protocols suitable for clinical routine. This thesis aims to evaluate simplified methods for acquisition and quantification of dynamic PET data for clinical use in neurodegenerative diseases, with focus on AD and PD.
Background

Positron emission tomography

Basic principles

PET is a molecular imaging technique used for investigations of a variety of physiological and molecular functions \textit{in-vivo} by measuring the distribution of radiolabelled compound, so called radioligands or tracers, after intravenous injection. The PET tracers are labelled with short-lived radioisotopes that decay by positron emission and the most commonly used positron emitting nuclides are fluorine-18 ($^{18}\text{F}$), carbon-11 ($^{11}\text{C}$) and oxygen-15 ($^{15}\text{O}$). When the radioisotope decays, the emitted positron travels a very short distance from the initial decay site before it interacts with an electron and a positron-electron annihilation occurs. This produces two photons with an energy of 511 keV, that are emitted simultaneously in opposite direction and detected by an opposing pair of detectors in the PET scanner. A simplified drawing of this process is showed in Figure 1.

![Figure 1](image.png)

\textit{Figure 1.} Schematic drawing of the positron emission and annihilation, resulting in two 511 keV photons. The ring represents the PET scanner where the photons are detected by two opposing detectors.

The PET system consists of rings of detector blocks where each detector element is operating in coincidence with multiple elements on the opposite side to record the annihilation photons. The detector blocks commonly consist of
bismuth germinate (BGO) or lutetium oxyorthosilicate (LSO) scintillation crystals, segmented into arrays of smaller elements, and photomultiplier tubes. The axial field of view is determined by the extent of the detectors and is typically in the range of 15-25 cm. The near simultaneous detection of the annihilation photons by the PET system makes it possible to determine a line between the detection sites, which gives an indication of where in the body the positron emission occurred and defines the volume from where they were emitted. The coincidence events collected by the PET detectors are reconstructed into a tomographic image. The reconstructed PET images are corrected for attenuation, random coincidences, scattered radiation, dead time and physical decay of the radioisotope, and show the distribution of the tracer as the radioactivity concentration (Bq/mL). The resolution of the PET image is in the order of mm, and is affected by several different parameters such as the size of the detector elements, the range that the positron travels before the annihilation occurs, which is dependent on the positron energy, and the non-collinearity of the emitted photons, meaning that due to residual momentum of the positron and the electron, the photons are not exactly emitted at 180-degree opposing direction [1].

Quantification

In order to quantify the physiological parameters of interest, such as the binding of the tracer to a specific target or the blood flow, from the PET image, there is a need for information regarding the rate of change of the radioactivity concentration over time. Collecting the data in separate time frames, as a dynamic scan, will show how the concentration of the tracer in tissue changes throughout the course of the PET study, as illustrated in Figure 2A. From the dynamic scan, time activity curves (TACs) can be obtained, showing the radioactivity concentration over time in a specific volume of interest (VOI) or a voxel. The shape of the TAC is dependent on the properties of the tracer and the tissue as seen in Figure 2B.

The measured radioactivity concentration in the PET image is a combination of the different states of the tracer in the tissue, such as radioactivity in the blood within the tissue, tracer bound to its intended target or tracer bound to other entities. These states are commonly depicted as different compartments and there are different approaches to differentiate between the compartments and estimate the parameters of interest.
Figure 2. A) Examples of a range of frames from a dynamic $[^{11}\text{C}]$PE2I brain PET scan with a duration of 80 min. Each frame is showing the distribution of tracer in the brain, while the collection of frames shows the temporal changes of tracer concentration. B) Time activity curves, showing radioactivity concentration over time in a region with high and with no specific binding.

Compartmental modelling

To calculate the parameters of interest, there is a need for a mathematical model that describes the measured radioactivity concentration over time. The most commonly used compartment models are the two tissue compartment models (2TCM) and the one tissue compartment model (1TCM), shown in Figure 3A and B respectively.

Figure 3. Schematic drawing of A) the two tissue compartment model and B) the one tissue compartment model. $C_p$, $C_f$, $C_b$ and $C_t$ represents the radioactive concentration in the different compartments and $K_1$, $k_2$, $k_3$ and $k_4$ represents the rate constants.
$C_p$, is the radioactivity concentration in arterial plasma, which is measured by taking arterial blood samples during the PET scan. $C_f$ is the free and non-specifically bound tracer in the tissue, while $C_b$ represents the tracer bound to the target. The different rate constants $K_1$, $k_2$, $k_3$ and $k_4$ represent the exchange of tracer between plasma and tissue, and between the different compartments. The signal measured by PET in a certain VOI or voxel is a combination of $C_f$ and $C_b$ plus a fractional blood volume in tissue. In case of regions with no specific binding, or when the free and bound tracer are assumed to be indistinguishable due to fast exchange between the compartments, the model can be simplified to a 1TCM. The compartment models can be described by differential equations and the parameters of interest can be derived using non-linear regression analysis. The parameters of interest are often the non-displaceable binding potential ($BP_{ND}$), where $BP_{ND}=k_3/k_4$ [2]. $BP_{ND}$ is not always possible to be determined accurately, instead, the distribution volume ($V_T$) can be estimated which under equilibrium equals $V_T=K_1/k_2$ for the 1TCM and $V_T=(K_1/k_2)(1+k_3/k_4)$ for the 2TCM. An alternative approach for parameter estimation is the Logan plot [3], a graphical analysis represented by linear equations that can be solved graphically where the resulting slope = $V_T$.

Reference region

A reference region is a region that is devoid of target, that is, with no specific binding of the tracer, and with a non-specific distribution volume similar to the target region. If it is not possible to determine $BP_{ND}$ directly by $k_3/k_4$, it can be estimated as the ratio of the distribution volumes in the target tissue and the reference tissue minus one. However, this still requires arterial blood sampling. Arterial blood sampling during the PET investigation is invasive, labour intensive and sometimes not feasible. It is possible to eliminate the dependency of the model on the plasma input function if there is a proper reference region in the brain. A TAC from the reference VOI can then be used as an indirect input function to a reference tissue model. The simplified reference tissue model (SRTM) [4], as illustrated in Figure 4, is the most commonly used reference tissue model. In addition to the two requirements mentioned before, SRTM requires that both reference and target TACs can be approximated by the 1TCM. SRTM estimates three parameters, $BP_{ND}$, $k_2$ and $R_1$, where $R_1$ is the relative tracer delivery, which is closely related to blood flow, assuming that tracer extraction is uniform throughout the brain. A further simplification of SRTM can be made by fixing $k_{2a}$ to a pre-defined value, and by so, reducing the number of estimated parameters to two (SRTM2) [5], and both models can be linearized using a set of basis functions, receptor parametric mapping (RPM and RPM2) [6]. The Logan graphical approach can also be calculated using a reference region instead of a plasma input function and the slope of the graphical analysis then corresponds to the ratio of volumes of distribution in the target and the reference region (DVR) [7]. Another reference tissue approach is the multilinear reference tissue models (MRTM),

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solved using multilinear regression after a certain equilibrium time. There are three versions of MRTM, and as for RPM, either three or two parameters can be estimated (MRTM, MRTMo, MRTM2 [8, 9].

![Diagram of reference tissue model](image)

*Figure 4.* The simplified reference tissue model (SRTM) where $C_p$, $C_r$ and $C_t$ represent the radioactivity concentration in the different compartments and $K_1$, $K_1'$, $K_2$ and $K_2'$ represent the different rate constants.

**VOI-based reference**

Most commonly, the reference region VOI, as well as other regions of interest, is obtained by manual definition of the volume. Due to the poor anatomical information in the PET images, this is usually performed on co-registered images from other imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI), after which the VOIs are transferred to the PET images. This process is both time consuming and prone to inter-user variability. Automated software based on pre-defined VOI template, matched to the individual subjects MRI scan by non-rigid co-registration, can overcome these limitations and the advantage is that a whole set of VOIs can be defined simultaneously.

**SVCA-based reference**

An automatic way to define the reference region VOI directly from the dynamic PET data, without the need for a structural MRI for manual or template-based region definition, is the supervised cluster analysis (SVCA) method. The SVCA algorithm segments voxels in the dynamic PET volume based on the shape of their TACs with no spatial constraint, i.e. the whole brain is considered. Voxels with kinetic behaviour most resembling the TACs of the proposed reference region are included in the reference VOI. The SVCA method has demonstrated to be a robust and reliable alternative as an automatic way of extracting a reference region in previous studies for $(R)$-[11C]PK1119 [10, 11], [11C]PIB [12], [11C](R)-rolipram [13] and [11C]TMSX [14].

**Parametric images**

In addition to estimating the parameters of interest on a VOI-basis, the estimation can also be performed on a voxel-level. This results in a spatial map,
also known as a parametric image, of the parameters of interest and gives a straightforward visualisation of the parameter estimates. Using a standard non-linear regression analysis for the parameter estimations is very time consuming and sensitive to noise, and thus not practical for voxel-based analysis. Instead, linearization of the models such as the RPM- and MRTM-methods for calculation of $B_{PND}$ and $R_1$ parametric images, as well as voxel-level estimation of DVR using reference Logan, are implemented. Quantification of dynamic PET data, where both the specific binding and flow characteristics of the tracer are assessed, resulting in $B_{PND}$ and $R_1$ [15, 16], can make dynamic PET investigations even more attractive for clinical use.

**Semiquantitative measures**

A semi-quantitative estimate of the binding is the standard uptake value ratio (SUVR), relating the radioactivity concentration in the target region to that in the reference region. The optimal time for assessment of SUVR, in terms of agreement with $B_{PND}$, is at transient equilibrium (TE) which is the time when the specific binding curve, calculated as the difference between target and reference tissue, peaks [17] and theoretically $B_{PND}$ equals SUVR-1. Since SUVR can be obtained using a static scan, and can be estimated on a VOI-basis as well as on a voxel-level, it is an attractive alternative to the more advanced methods requiring dynamic scanning.

**PET in Parkinson’s disease and Alzheimer’s disease**

The application of PET in brain research is growing and PET is used in a wide variety of applications within neurology [18]. This includes investigation of pathophysiological processes, disease diagnosis and progression, monitoring treatment response, drug development as well as increasing the understanding of normal brain functions. In this thesis, the focus lies on PET in neurodegenerative diseases, specifically parkinsonian disorders and Alzheimer’s disease, and the clinical applicability of dynamic PET, utilizing its full potential in these disorders.

**Parkinsonian disorders**

Parkinsonism is a clinical syndrome characterized by the typical motor symptoms such as bradykinesia, rigidity, tremor and postural instability. There are also several non-motor symptoms associated with parkinsonism, for example depression, cognitive impairment and sleep disorders [19]. The different parkinsonian disorders include Parkinson’s disease, which is the most common one, and other neurological conditions, such as multiple system atrophy (MSA), progressive supranuclear palsy, dementia with Lewy bodies and corticobasal degeneration, with overlapping clinical symptoms. There are also
some non-neurodegenerative causes for PD-like symptoms, such as vascular parkinsonism and drug-induced parkinsonism. Although progression and pathology differs between different parkinsonian syndromes, an unambiguous diagnosis can be difficult to achieve based on the clinical symptoms, especially at early stages of the disease [20, 21].

Several brain regions and neurotransmitter systems are affected in parkinsonism where the degeneration of dopaminergic neurons in the nigrostriatal pathway, which is responsible for the classic motor symptoms in PD, are the most prominent. PET can aid in the differentiation between parkinsonian disorders because the central dopaminergic and overall brain functional activity are altered differently [22-27]. There are several PET tracers targeting the dopaminergic system such as $[^{11}C]$raclopride [28], $[^{18}F]$FDOPA [29], $[^{18}F]$FP-CIT [30] and $[^{18}F]$FE-PE2I [31], as well as the single photon emission computed tomography (SPECT) tracer $[^{123}I]$FP-CIT [32] and $[^{123}I]$PE2I [33]. To aid in the differentiation between various parkinsonian disorders, $[^{18}F]$FDG PET is commonly used to examine the metabolic activity in the brain which is closely related to the overall brain function. However, the focus of this thesis, when targeting patients with parkinsonism will be the dopamine transporter (DAT) PET tracer $[^{11}C]$PE2I. DAT is a transmembrane protein responsible for the reuptake of dopamine in the synaptic cleft. Decreased DAT availability is associated with different neurodegenerative disorders such as Parkinson's disease [34, 35].

$[^{11}C]$PE2I

The cocaine analog N-(3-iodoprop-2E-enyl)-2β-carbomethoxy-3β-(4-methyl-phenyl)nortropane (PE2I) has shown an excellent binding to DAT, in both in-vitro autoradiography studies, using $[^{125}I]$PE2I [36] and in-vivo PET studies with $[^{11}C]$PE2I [37-39]. It has shown a high accumulation in striatum, where the concentration of DAT is high, an intermediate binding in midbrain, and no or very little specific binding in the cerebellum. The high selectivity of $[^{11}C]$PE2I for DAT offers a high potential for in-vivo exploration of DAT function [40] and has been used in both research studies [41, 42] and in clinical trials [43, 44]. $[^{11}C]$PE2I PET studies can thus be a valuable tool for early detection and differentiation of neurological disorders where changes in DAT concentration are involved, such as parkinsonism. In Figure 5, examples of $[^{11}C]$PE2I PET images 60-80 min post-injection (p.i.) are shown from one patient with PD and one healthy control (HC).

It has been shown that reference tissue methods on a VOI-basis using SRTM, although underestimating $BP_{ND}$, show a high correlation to plasma-input compartment models [37, 45] and also a good reproducibility and reliability in test-retest studies [38]. $[^{11}C]$PE2I $BP_{ND}$ has previous been estimated on a voxel-level [46-48], but no extensive validation of parametric methods
had been performed for \([^{11}C]PE2I\). Previous studies have proposed an acquisition time of 70 up to 120 min for \([^{11}C]PE2I\) to be able to robustly determine DAT binding in the striatum [37-39, 45].

![Figure 5. \([^{11}C]PE2I\) PET images of the uptake 60-80 min post-injection in a PD patient, top row, and a healthy control, bottom row. The reduced DAT availability is clearly visible in the PD patient compared to the control. PET images are fused with the subjects’ MRI images.]

Alzheimer’s disease

AD is an irreversible neurodegenerative disease that is characterized by progressive decline in cognition, personality changes and other symptoms common for dementia. As for PD, differential diagnosis between different causes of dementia can be difficult based on the clinical symptoms alone. The development of molecular imaging has provided valuable biomarkers for accurate and early detection of AD and has also led to proposal of new diagnostic criteria [49, 50]. There are several complex pathophysiological processes that characterize AD, such as deposition of amyloid-beta plaques, tau filaments in the form of neurofibrillary tangles and neurodegeneration. Several tracers that bind to amyloid-beta plaques have been investigated and are widely used in both clinical settings and research studies, such as \([^{11}C]PIB\) [51], [\(^{18}F\)]flutemetamol and [\(^{18}F\)]florbetapir. However, the amyloid pathology plateaus quite early in the progression of the disease [52] and PET-imaged amyloid pathology appeared not to correlate with clinical symptoms [53]. Because of the close association between tau pathology, neurodegeneration and cognitive impairment [54] there is an increasing interest in developing PET tracers
that binds specifically to tau [55, 56]. A number of them has undergone tracer kinetic studies in humans, such as $^{[18}\text{F}]$THK5351 [57], $[^{11}\text{C}]$PBB3 [58] and $^{[18}\text{F}]$AV1451 [59]. The part of this thesis targeting patients with AD will focus on quantification of the PET tracer $^{[18}\text{F}]$THK5317.

$^{[18}\text{F}]$THK5317

One of the promising tau tracers developed in recent years is 6-[(3-$^{[18}\text{F}]$fluoro-2-hydroxy)propoxy]-2-(4-methylaminophenyl)quinoline ($^{[18}\text{F}]$THK5117), which has shown good affinity for the tau protein aggregates and fast uptake and clearance [60]. $^{[18}\text{F}]$THK5117 is a racemic compound and for further analysis of the assessment of tau accumulation the $S$-enantiomeric form was used ((S)-$^{[18}\text{F}]$TKH5117) which from here on will be referred to as $^{[18}\text{F}]$THK5317. Examples of $^{[18}\text{F}]$THK5317 PET images 60-90 min p.i. in one AD patient and one HC are given in Figure 6.

![Figure 6. $^{[18}\text{F}]$THK5317 PET images of the uptake 60-90 min post injection in an AD patient, top row, and a healthy control, bottom row. PET images are fused with the subjects MRI images.](image-url)
Aims of the thesis

The overall aims of this thesis were: 1) to facilitate clinical use of dynamic \([^{11}C]PE2I\) PET by easy accessible images of DAT availability and overall functional activity for use in differential diagnosis of parkinsonian disorders, and 2) to evaluate models for quantification and simplified methods for assessment of tau accumulation in AD patients using dynamic \([^{18}F]THK5317\) PET.

More specifically, the aims of each study were the following:

I To validate different methods for producing parametric BP\(_{\text{ND}}\) and R\(_1\) images of dynamic \([^{11}C]PE2I\) data.

II To compare \([^{11}C]PE2I\) R\(_1\) and BP\(_{\text{ND}}\) images to imaging-based evaluation of parkinsonian disorders with \([^{18}F]FDG\) PET and \([^{123}I]FP-CIT\) SPECT.

III To investigate a shorter scan protocol for \([^{11}C]PE2I\) and to validate a supervised cluster analysis method for automatic extraction of a reference time activity curve directly from the dynamic \([^{11}C]PE2I\) data.

IV To evaluate different tracer kinetic models for quantitative analysis of \([^{18}F]THK5317\) binding to tau, based on plasma and reference tissue input data.

V To determine optimal timing for SUVR-1 and R\(_1\) measures for \([^{18}F]THK5317\) and to validate a supervised cluster analysis method for automatic reference region extraction.
Materials and methods

Participants
This thesis is based on data from a total of 61 subjects, including healthy controls, subjects with social anxiety disorder (SAD) and patients with parkinsonism, AD or mild cognitive impairment (MCI). Briefly, the participants were included as follow: Paper I-III comprise of a set or subset of 16 patients with parkinsonism (10 women and 6 men, mean age 69 ± 6 years). In Paper I, 6 of these patients were included (5 women and 1 man, mean age 68 ± 6 years) together with 6 SAD subjects (3 women and 3 men, mean age 35 ± 11 years). Paper II included all 16 parkinsonism patients and paper III comprised of 12 of the patients with parkinsonism (7 women and 5 men, mean age 70 ± 6 years), 12 HC (4 women and 8 men, mean age 47 ± 8 years) and 5 additional healthy subjects (men, mean age 25 ± 4 years) included as a separate set of data for definition of kinetic classes in the SVCA algorithm. In paper IV, 5 AD patients (57-74 years) and 4 MCI patients (65-79 years) were included. Paper V comprise of a total of 9 AD patients (57-75 years) and 9 HC (21-71 years). Ten of the subjects (5 AD and 5 HC) were included for the analysis and remaining subjects were included for definition of SVCA kinetic classes. Patients were included based on their clinical diagnosis and each subject signed a written informed consent and the studies were approved by regional ethical review boards.

Data acquisition
All subjects underwent a dynamic PET scan, with either an 80 min \([^{11}\text{C}]\text{PE2I}\) PET duration (Paper I-III) or a 60 or 90 min \([^{18}\text{F}]\text{THK5317}\) PET duration (Paper IV-V). All \([^{11}\text{C}]\text{PE2I}\) and \([^{18}\text{F}]\text{THK5317}\) PET investigations were performed on an ECAT Exact HR+ scanner (Siemens/CTI, Knoxville) in 3D mode after a 10 min transmission scan with rotating \(68\text{Ge}\) rod sources for attenuation correction. The scans were reconstructed using ordered subset expectation maximization (OSEM) with 6 iterations and 8 subsets, and a 4 mm Hanning post-filter, with all appropriate corrections applied as included in the scanner software. Each subject received a T1-weighted structural MRI scan for VOI definition. In addition to the \([^{11}\text{C}]\text{PE2I}\) scan, all patients in Paper II
also underwent a dual examination with a 10 or 20 min $[^{18}\text{F}]$FDG PET scan and a 30 min $[^{123}\text{I}]$FP-CIT SPECT scan.

$[^{11}\text{C}]$PE2I

Simultaneously with the start of the PET scan, 350-400 MBq of $[^{11}\text{C}]$PE2I was administered to the subjects in papers I-III. Data were acquired dynamically for 80 min and reconstructed into 22 frames of increasing duration (4 × 60, 2 × 120, 4 × 180 and 12 × 300 s). $[^{11}\text{C}]$PE2I was synthesized using previously described methods [38, 61].

$[^{18}\text{F}]$THK5317

In papers IV-V, circa 3 MBq/kg $[^{18}\text{F}]$THK5317 was administered to the subjects at the start of the scan. Nine AD patients, four MCI patients and nine HC received a 90 min dynamic PET scan (25 frames; 6 × 10, 3 × 20, 2 × 30, 2 × 60, 2 × 150, 4 × 300 and 6 × 600 s) while remaining subjects received a 60 min scan (22 frames; 6 × 10, 3 × 20, 2 × 30, 2 × 60, 2 × 150, 4 × 300 and 3 × 600 s). The radiosynthesis of $[^{18}\text{F}]$THK5317 are described in the supplementary material of paper IV.

Blood sampling

All subjects in paper IV underwent arterial blood sampling during the $[^{18}\text{F}]$THK5317 PET scan. Discrete arterial blood samples were used for metabolite analysis and for measurement of whole-blood and plasma radioactivity to be applied as an input function in the analysis. Blood was drawn continuously during the first 10 min of the scan (3 mL/min) and discrete blood samples (5 mL) were taken at 5, 10, 15, 20, 30, 45, 60, 75 and 90 min p.i.

Image analysis

Image processing and VOI definition

All PET data were realigned to correct for subject movement using a rigid frame-to-frame realignment procedure in VOIager (GE Healthcare, Uppsala, Sweden). The MRI scans were co-registered to the first part of their respective $[^{11}\text{C}]$PE2I or $[^{18}\text{F}]$THK5317 PET images, 0-3 min and 0-5 min respectively, and segmented into grey matter, white matter and cerebrospinal fluid (CSF), using Statistic parametric imaging (SPM5 or SPM8; Wellcome Trust Center for Neuroimaging, University College London, UK). Volumes of interest were defined on the co-registered MRI images using a probabilistic VOI template implemented in the PVELab software [62]. Figure 7 shows the PVELab-obtained VOIs from one HC. In paper II, the $[^{18}\text{F}]$FDG scans were summed
over all frames, and the $^{[123]}$FP-CIT SPECT data were analysed by an automated VOI template [63] using the BRASS software (Hermes Medical Solution).

Figure 7. Example of PVElab VOIs from one healthy control fused with the subjects’ MRI image. Different VOIs are shown in different colors.

Tracer kinetic analysis

**Plasma input models**

In order to obtain a plasma input function for the subjects in Paper IV, where blood sampling had been performed, the measured whole-blood data was multiplied by a single exponential fit to plasma–to–whole-blood ratios and a sigmoid fit to the measured fraction of intact $^{[18]}$FTHK5317 in plasma. 1TCM and 2TCM were applied to the $^{[18]}$FTHK5317 data in Paper IV, using the plasma input function. $BP_{ND}$ values were calculated both directly and indirectly as DVR-1 and DVR-1 was also computed using plasma-input Logan.

**Reference tissue models**

SRTM was used for VOI-based analysis of $^{[11]}$CPE2I in Paper I, calculating both $BP_{ND}$ and $R_1$, which in previous studies has shown a good correlation with compartmental modelling using plasma input [37, 45]. VOI-based analysis with SRTM was also performed for $^{[18]}$FTHK5317, including the calculated $BP_{ND}$ values in Paper IV and the $R_1$ values in Paper V. In both Paper IV and V, DVR-1 values were estimated for $^{[18]}$FTHK5317 on a VOI-basis using reference Logan. For the reference region methods, grey matter cerebellum was considered the standard reference region for both $^{[11]}$CPE2I and $^{[18]}$FTHK5317, since it is a region with no concentration of both DAT [61] and tau.

**Parametric images**

Voxel-wise analysis was performed for all $^{[11]}$CPE2I and $^{[18]}$FTHK5317 data included in this thesis. First, in order to validate the models for generation of
parametric $[^{11}\text{C}]\text{PE2I BP}_{ND}$ and $R_1$ images in Paper I, two basis function methods (RPM and RPM2) and three multilinear reference tissue models (MRTM, MRTMo and MRTM2) were applied. Additionally, DVR-1 images were generated using reference Logan using a time interval of 30-80 min, and SUVR-1 was estimated for each voxel for the last 20 min of the scan, 60-80 min. Voxel-level analysis of $[^{18}\text{F}]\text{THK5317}$, in Paper IV was performed using RPM and RPM2 for generation of parametric BP$_{ND}$ images. Reference Logan DVR-1 images were generated on a time interval of 30-90 min and SUVR-1 images were estimated at 70-90 min.

Furthermore, RPM was used to generate BP$_{ND}$ and $R_1$ images for $[^{11}\text{C}]\text{PE2I}$ in Paper II and III, for both quantitative and visual comparison to $[^{123}\text{I}]\text{FP-CIT}$ and $[^{18}\text{F}]\text{FDG}$ images, respectively, and for comparison to the simplified analysis methods implemented in Paper III. In Paper V, parametric DVR-1 images of $[^{18}\text{F}]\text{THK5317}$ were generated using reference Logan and $R_1$ images was calculated with RPM.

In Paper II, the $[^{18}\text{F}]\text{FDG}$ volumes were co-registered to the $[^{11}\text{C}]\text{PE2I R}_1$ image of the respective subject, in order to be able to apply the same set of VOIs to both images. The summed $[^{18}\text{F}]\text{FDG}$ images were then normalized to cerebellum to obtain uptake ratio images.

Simulations
Simulations were performed in Paper I and IV to assess accuracy and precision of the models. Time-activity curves were simulated using 2TCM with a plasma input curve. The kinetic parameters were based on typical values from the literature for $[^{11}\text{C}]\text{PE2I}$ [39, 45] in Paper I and with typical values from the clinical data for $[^{18}\text{F}]\text{THK5317}$, in Paper IV, and a plasma input function from one typical subject. For each set of parameters, 100 TACs were created and Gaussian noise was added randomly. The noise level was set to 2% to resemble the noise of a typical striatum- or cortical-VOI for $[^{11}\text{C}]\text{PE2I}$ and $[^{18}\text{F}]\text{THK5317}$ respectively and to 10% to resemble the noise of a typical $[^{11}\text{C}]\text{PE2I striatal-voxel}$. Two set of rate constants were used for both $[^{11}\text{C}]\text{PE2I}$ and $[^{18}\text{F}]\text{THK5317}$, to reflect both high and low binding.

Shorter acquisition time
Different durations of the acquired PET data were considered in order to evaluate the possibility of a shortened scan protocol. For $[^{11}\text{C}]\text{PE2I}$, the first 20 min (10 frames), 30 min (12 frames) and 40 min (14 frames) of the original 80 min data were considered in Paper III, as shown in Figure 8. DAT availability was approximated as SUVR-1 for the last two frames of each data set (14-20 min, 20-30 min and 30-40 min). In addition, parametric $R_1$ images were generated for each shortened data set using RPM.
Figure 8. Schematic overview of the different durations of the acquired \([11C]\)PE2I and \([18F]\)THK5317 PET data considered for analysis.

For \([18F]\)THK5317, the initial 40 min (20 frames) and 60 min (22 frames) were evaluated in addition to the full 90 min data in Paper IV. For the shortened data sets, plasma-input Logan and reference Logan analysis were performed at a time interval of 20–40 min and 30–60 min, and SUVR-1 were calculated for 20–40 min and 40–60 min. The optimal timing of the SUVR measurements of \([18F]\)THK5317 was investigated in Paper V. The time at which TE occurred was determined as the peak of the specific binding curve for each considered VOI, calculated by subtraction of the grey matter cerebellum TAC from the VOI TAC. SUVR-1 was calculated for a 20 min interval centred around TE as well as for seven consecutive 20 intervals between 10 and 90 min p.i., see Figure 8.

Supervised cluster analysis

Although the principles of an implementation of the SVCA algorithm are similar for each tracer, this method needs to be validated for both \([11C]\)PE2I and \([18F]\)THK5317. An SVCA algorithm specific for \([11C]\)PE2I and \([18F]\)THK5317 was developed in Papers III and V. A set of kinetic classes was predefined on the dynamic PET data from the set of subjects that were included specifically for this purpose. Different regions were used for the definition of kinetic classes for \([11C]\)PE2I and \([18F]\)THK5317, but common for both tracers were the use of a grey matter cerebellum VOI as a class corresponding to non-specific binding. The definition of the classes other than grey matter cerebellum was aimed at avoiding inclusion of their associated voxels in the cerebellum class. The TACs from each kinetic class were normalized to their respective area under the curve. In order to generate reference TACs from the subjects included in the analysis, the TAC of each voxel in the dynamic data sets was also normalized to its area under the curve and a non-
negative least-squares algorithm was used to find a linear combination of the probability for each voxel to correspond to each kinetic class. Voxels with a probability higher than a specific limit, investigated for each tracer separately as described in Paper III and V, were assigned to that specific class. The voxels selected for the cerebellum class were regarded as reference region and a mean of the TACs of the selected voxels was calculated. The SVCA-extracted reference TAC was then used as input function to generate new parametric images for $[^{11}\text{C}]\text{PE2I}$ and $[^{18}\text{F}]\text{THK5317}$.

$[^{11}\text{C}]\text{PE2I}$

In Paper III, five HC subjects were included for the predefinition of five kinetic classes. Except for the grey matter cerebellum class, striatum (corresponding to high specific binding), white matter, blood and a class to collect remaining voxels were defined. The SVCA-extracted reference TAC was then used as input function to generate new parametric BP$_{ND}$ and R$_1$ images for the full 80 min $[^{11}\text{C}]\text{PE2I}$ data, as well as SUVR-1 and R$_1$ images for the shortened data sets in the 12 HC and 12 patients with parkinsonism that were included for the analysis.

$[^{18}\text{F}]\text{THK5317}$

In Paper V, a set of four kinetic classes was predefined on dynamic $[^{18}\text{F}]\text{THK5317}$ data from 4 AD patients and 4 HC. Except for the grey matter cerebellum class, grey matter, white matter and a blood pool class were defined. The cerebellum class was defined on the HC subjects, to ensure that only healthy tissue was included, while the grey matter, white matter and blood pool classes were defined on the AD patients. New parametric SUVR-1 images for the optimal time window as well as RPM R$_1$ images were generated with the SVCA extracted reference TAC as input function.

All modelling, simulations and SVCA analysis were implemented in Matlab (Mathworks Inc., Natick, MA, USA).

Data evaluation

For quantitative evaluation of the parametric methods, regionally averaged voxel values were retrieved by projecting the MRI based PVElab VOIs onto the parametric images. The VOIs considered were specific for each study. Correlation and agreement between the different methods were assessed using the square of the correlation coefficient ($R^2$) and slope of a linear or orthogonal regression analysis.
Paper I
Evaluation of the parametric methods for $[^{11}C]PE2I$ in Paper I was performed by comparing regionally averaged BPND, DVR-1 and SUVR-1 values, as well as $R_1$ values, from the parametric images to VOI-based SRTM values. Seven different VOIs were considered: putamen, caudate, thalamus, midbrain, hypothalamus, amygdala and hippocampus, averaged over left and right. Mean values of the within subject correlation and agreement in these seven VOIs were assessed for both BPND and $R_1$. BPND and $R_1$ values of the parametric methods and VOI-based SRTM were also compared across subjects in a striatal VOI (mean of caudate and putamen) and in thalamus. In the simulation study, performance of the parametric methods was assessed by calculating the bias and coefficient of variation (COV) for the BPND and $R_1$ estimates of the parametric models considered.

Paper II
For comparison of the DAT availability of $[^{11}C]PE2I$ and $[^{123}I]FP-CIT$ SPECT images, VOIs over caudate and putamen were considered. Regionally averaged voxel values from the $[^{11}C]PE2I$ BPND images were retrieved using the PVElab VOIs while for $[^{123}I]FP-CIT$, regional uptake values were normalized to occipital cortex, and retrieved using an automated VOI template as implemented in the BRASS software (Hermes Medical Solution). For comparisons of $[^{11}C]PE2I$ $R_1$ and normalized $[^{18}F]FDG$ images, four different sets of VOIs were considered including anterior cortical regions (cingulate and frontal cortex), posterior cortical regions (occipital-, parietal and somatosensory-motor cortex), striatal region (putamen and caudate) and a limbic region (amygdala, hippocampus, hypothalamus and thalamus). The imaging data was evaluated visually by two blinded nuclear medicine specialists. The image-based diagnosis was based on DAT availability in the $[^{11}C]PE2I$ BPND or $[^{123}I]FP-CIT$ images, rated as normal or abnormal, and the overall brain functional activity using the $[^{11}C]PE2I$ $R_1$ or $[^{18}F]FDG$ images, based on specific pathological patterns for glucose metabolism a reported for various parkinsonian disorders [24, 25, 64]. The most probable type of parkinsonism was determined for the set of BPND and $R_1$ images and for the $[^{18}F]FDG$ and $[^{123}I]FP-CIT$ images separately.

Paper III
In Paper III, the regions considered for evaluation of $[^{11}C]PE2I$ BPND were, as in Paper I and II, putamen and caudate. For $R_1$, three set of VOIs were considered; striatum (caudate, putamen), a cortical group (frontal-, parietal, occipital, somatosensory and motor cortex) and a limbic group (thalamus, hypothalamus and amygdala). SUVR-1 and $R_1$ values of the shortened data sets; 20,
30 and 40 min, were compared to the $\text{BP}_{\text{ND}}$ and $R_1$ values of the complete 80 min data. $\text{BP}_{\text{ND}}$ and $R_1$ values obtained using of the full 80 min $[^{11}\text{C}]$PE2I data with either an MRI-based or SVCA-based reference were compared. In the same way, SUVR-1 and $R_1$ values of the shortened data sets with SVCA-based reference were compared to the $\text{BP}_{\text{ND}}$ and $R_1$ values with MRI-based reference. The standardized difference between the mean $\text{BP}_{\text{ND}}$ and SUVR-1 values (Cohens d), between the HC and the subjects with parkinsonian disorders, was calculated for each scan duration and with both MRI- and SVCA-based reference.

**Paper IV**

Eleven VOIs were included in the evaluations of the tracer kinetic analysis of $[^{18}\text{F}]$THK5317; thalamus, putamen, hippocampus, amygdala, midbrain, parietal-, frontal-, temporal entorhinal- occipital- and sensory motor cortex, all averaged over left and right hemispheres. The optimal plasma-input compartment model was determine using Akaike [65] and Schwarz [66] criteria. Furthermore, VOI-based $\text{BP}_{\text{ND}}$ and DVR-1 from the reference tissue models, SRTM and reference Logan, were compared to the optimal plasma input compartment model and plasma input Logan. The parametric methods were quantitatively evaluated by comparison to the VOI-based values from the optimal reference method. Bias and COV were calculated for the $\text{BP}_{\text{ND}}$, DVR-1 and SUVR-1 estimates of the simulated $[^{18}\text{F}]$THK5317 data.

SRTM $\text{BP}_{\text{ND}}$, reference Logan DVR-1 and SUVR-1 of the shortened data sets, 40 and 60 min, were compared their respective binding estimates when using the full 90 min data.

**Paper V**

The relationship between SUVR-1 of the different time interval for the $[^{18}\text{F}]$THK5317 scan and reference Logan DVR-1 were assessed by correlation and bias analysis. SUVR-1 values at the optimal time interval calculated with SVCA-based reference were compared to those using an MRI-based reference region. Parametric RPM $R_1$ values of the shortened scan duration, matching that of the optimal time found for SUVR-1 estimations, were compared to SRTM $R_1$. 
Results

\[^{11}\text{C}]\text{PE2I}\]

Parametric images

For \[^{11}\text{C}]\text{PE2I}\), the results of Paper I showed that the receptor parametric methods, RPM and RPM2, provided qualitatively the best images for both the parkinsonism patients and SAD subjects, especially with regards to the R\(_1\) images. None of the multi linear reference tissue models could provide qualitatively good images. The within-patient comparison of the parametric methods to VOI-based SRTM showed a high correlation for the BP\(_{ND}\) estimates for all methods, while only RPM- and RPM2-based R\(_1\) values showed a high correlation to SRTM R\(_1\) values. In the across-subject comparison in thalamus and striatum separately, RPM and RPM2 showed the highest correlation to SRTM, regarding both BP\(_{ND}\) and R\(_1\). Both DVR-1 values obtained using reference Logan and SUVR-1 showed a high correlation to SRTM BP\(_{ND}\), whereas SUVR-1 values were greatly overestimated as compared to BP\(_{ND}\). Parametric RPM BP\(_{ND}\) and R\(_1\) images are shown in Figure 9.

Simulations

The highest accuracy and precision of \[^{11}\text{C}]\text{PE2I}\) BP\(_{ND}\) and R\(_1\) estimates of the different parametric method was found for the receptor parametric mapping methods, with a better accuracy for RPM than RPM2, for both high and low BP\(_{ND}\) values.

Relationship between \[^{11}\text{C}]\text{PE2I}\) and the dual scan approach

Comparison between \[^{11}\text{C}]\text{PE2I}\) BP\(_{ND}\) and \[^{123}\text{I}]\text{FP-CIT}\) uptake ratio values showed a high correlation in putamen, R\(^2\)=0.92 and a lower correlation in caudate, R\(^2\)=0.57. Relationship between the \[^{11}\text{C}]\text{PE2I}\) R\(_1\) and normalized \[^{18}\text{F}]\text{FDG}\) values showed a variety of correlation values over different brain regions, ranging from R\(^2\)=0.37 – 0.88, with the lowest correlations in the midbrain and limbic regions and the highest correlations in the cortical regions.
Figure 9. Parametric $[^{11}\text{C}]$PE2I images from one patient with parkinsonism and one HC. Top row comparing $\text{BP}_{\text{ND}}$ and SUVR-1 and bottom row $R_1$ for different scan durations with either an MRI- or SVCA-based reference region.

Figure 10. Parametric $[^{11}\text{C}]$PE2I $\text{BP}_{\text{ND}}$ and $R_1$ images compared with $[^{123}\text{I}]$FP-CIT and $[^{18}\text{F}]$FDG images from one patient with parkinsonism.
Visual image assessment

Regarding the diagnosis of the patients, based on the visual image assessment of both DAT availability and overall brain function, there were 4 discrepancies between the two data sets of $^{[11]}C$PE2I $R_1$ and $BP_{ND}$ or normalized $^{[18]}F$FDG and $^{[123]}I$FP-CIT uptake images. Discrepancies from the clinical diagnoses was found in 9 cases compared to parametric $^{[11]}C$PE2I images and in 8 cases compared to the dual scan approach. An example of a comparison between the $^{[11]}C$PE2I $BP_{ND}$ and $R_1$ images and normalized $^{[18]}F$FDG and $^{[123]}I$FP-CIT uptake images is given in Figure 10.

Acquisition time

Striatal SUVR-1 calculated on time intervals of 20-30 and 30-40 min showed a high correlation to $BP_{ND}$ values of the full 80 min scan ($R^2=0.82$ and 0.87, respectively), while correlation was lower for SUVR-1 at 14-20 min.

SUVR-1 values were underestimated compared to $BP_{ND}$ values, with the underestimation increasing for decreasing scan time. $R_1$ values of the shortened data sets showed a high correlation to $R_1$ of the full 80 min data in all regions and for all scan durations. One subject was found to deviate in terms of high $R_1$ values. This outlier corresponds to a parkinsonism subject with probable MSA with cerebellar atrophy. The decreased blood flow in cerebellum of this subject (see Figure 3 in Paper II) resulted in excessively high $R_1$ values when using cerebellum as a reference region.

Supervised cluster analysis

The relationship between $BP_{ND}$ using an MRI- and SVCA-based reference region at the full scan duration showed a high correlation, $R^2=0.99$. $R_1$ values computed with SVCA-based reference region also showed high correlations compared to an MRI-based reference. When comparing the parametric estimates of the shortened scan durations with SVCA-based reference to $BP_{ND}$ and $R_1$ values of the full scan duration calculated using MRI-based reference, the correlation was high regarding striatal SUVR-1 estimates with SVCA-reference region for all scan durations, $R^2>0.85$. $R_1$ values calculated with SVCA-based reference showed a high correlation to MRI-based $R_1$ values for all scan duration, in both striatal and limbic regions ($R^2=0.84-0.94$), but with an overestimation compared to 80 min $R_1$ with MRI-based reference. A lower correlation was found between the $R_1$ values of the shortened scan durations and SVCA-based reference compared to 80 min $R_1$ with MRI-based reference in cortical regions. A comparison between 80 min $BP_{ND}$ and $R_1$ images with MRI-based reference and 30-40 min SUVR-1 and 40 min $R_1$ images with SVCA-based reference are shown in Figure 9. $BP_{ND}$ and SUVR-1 values in putamen for the two groups separately, is shown in Figure 11A, for all scan
durations using an SVCA-based reference, as well as for the full 80 min data using MRI-based reference. The effect size (Cohen’s d) is shown in Figure 11B, with values ≥4 for all acquisition times with SVCA-based reference, indicating a high degree of discrimination between patients with parkinsonism and HCs.

**Figure 11.** A) BP\textsubscript{ND} values for the full 80 min acquisition time with both MRI- and SVCA-based reference region, and SUVR-1 values for the shorter scan durations with SVCA-based reference, in putamen, for the HCs and the patients with parkinsonism. Horizontal bars show mean and standard deviation of each group. B) Standardized difference of the mean (Cohen’s d) of BP\textsubscript{ND} and SUVR-1 values in putamen between the patients with parkinsonism and the HCs for varying scan durations

[^18F]THK5317

Tracer kinetic analysis

The 2TCM showed a better fit to the data than 1TCM and was also the preferred method according to both Akaike and Schwarz criteria in all cases except two. However, BP\textsubscript{ND} was not possible to determine directly with any robustness using 2TCM. A high agreement between 2TCM DVR-1 and plasma-input Logan DVR-1 was found, and plasma-input Logan was used for evaluation of the reference methods. Both reference Logan DVR-1 and SRTM BP\textsubscript{ND} showed high accuracy when compared to plasma input models, with R\textsuperscript{2} and slope values close to, or equal to, one. SUVR-1 values for a late time window of 70-90 min showed a poor correlation and were overestimated compared to both plasma input Logan DVR-1 and SRTM BP\textsubscript{ND}.
Parametric images

Three of the four methods used for generating parametric methods; RPM RPM2 and reference Logan, showed a very high correlation to VOI-based SRTM values, with $R^2\geq0.98$. However, the agreement, as indicated by the slope was best for reference Logan. SUVR-1 at 70-90 min was overestimated compared to the other methods and showed only moderate correlation to SRTM. Parametric reference Logan DVR-1 and RPM R₁ images are shown in Figure 12 for one AD and on HC.

![Figure 12. Parametric [¹⁸F]THK5317 images from on AD patient and one HC. Top row comparing DVR-1 and SUVR-1 and bottom row R₁ for different scan durations with either an MRI- or SVCA-based reference region.](image)

Simulations

Accuracy and precision of the simulated $BP_{ND}$, DVR-1 and SUVR-1 values for the different methods were in general better for low binding than for high binding. Reference Logan performed best among the reference methods and showed a lower COV than plasma input Logan. SUVR-1 was the least accurate for both high and low binding.

Acquisition time

There was no appreciable effect on SRTM $BP_{ND}$ and reference Logan DVR-1 when decreasing the scan duration to 60 min, while the correlation was poorer with the 40 min data set. SUVR-1 at 20-40 min values were underestimated
compared to the 70-90 min interval. Time to TE varied across regions, which is shown in Figure 13A, but over all subjects and regions, SUVR-1 for a 20-40 min time window correlated best with reference Logan DVR-1, and showed the lowest mean bias. Cohen’s d between AD patients and HCs of DVR-1 and SUVR-1 at TE and the different time intervals, for amygdala, parietal-, temporal- and entorhinal cortex are shown in Figure 13B.

Supervised cluster analysis

High correlation was found both between SUVR-1 for an 20-40 min time window, with MRI- and SVCA-based reference ($R^2=0.93$) and between 40 min $R_1$ values with SVCA-based reference and 90 min $R_1$ values with MRI-based reference ($R^2=0.94$). A comparison between reference Logan DVR-1 and $R_1$ images with MRI-based reference and 20-40 min SUVR-1 and 40 min $R_1$ images with SVCA-based reference is shown in Figure 12. Highest Cohen’s d values were found for parietal cortex for time windows centred around 30 min and higher.

Figure 13. A) Mean time to TE for the investigated regions. B) Cohen’s d as a function of DVR-1 and SUVR-1 at TE and the different time intervals, between AD patients and HCs.
Discussion

[11C]PE2I

The first step in this thesis was to validate parametric methods for voxel-wise quantification of [11C]PE2I. The results in Paper I showed that the receptor parametric mapping methods, RPM and RPM2, showed robust and quantitatively correct results, both for clinical data and simulated data. Previous studies have shown an underestimation of 30-50% for BPND in DAT rich regions when using a reference region method compared to plasma-input models [38, 39]. It has been discussed previously that the kinetics of the cerebellum may be affected by possible uptake of metabolites retaining the 11C label. In this case, the reference tissue methods will show an underestimation compared to BPND estimated using plasma-input method. However, if metabolites are not binding specifically, and their uptake is uniform across brain regions, this should not affect correlation between plasma- and reference-tissue-based BPND estimates. The importance of an underestimation of BPND is small as long as there is a good correlation between the estimates obtained from the reference tissue and plasma input model [67].

The results from Paper II shows that [11C]PE2I BPND and R1 images comprised information equivalent to the dual scan approach with [123I]FP-CIT SPECT and [18F]FDG PET scans, in terms of specific pathologic patterns and correlations of quantitative values. In about half of the patients, the clinical diagnosis deviated from the imaging results. A previous study has reported similar results, with more than 50% of the initial clinical diagnosis changed after imaging with [123I]FP-CIT SPECT [68]. To date, no long-term follow-up is available to assess the correctness of the image-based diagnosis for the included patients.

The major challenge for clinical use of [11C]PE2I is the long scan acquisition time required which is not suitable in a clinical setting and especially not for patients suffering from movement disorders, as well as the need for an additional structural MRI scan for reference region definition. These issues were addressed in Paper III, where a clinically feasible scan protocol and analysis methods were evaluated. For the shorter scan duration, the DAT availability was estimated as SUVR-1, with the time window of 30-40 min showing the highest correlation the 80 min BPND values. For [11C]PE2I, TE occurs at around 30 min which further supports use of the 30-40 min time interval for SUVR estimations.
Irrespective of the use of an MRI- or SVCA-based reference region, SUVR-1 values for scan durations shorter than 40 min showed a low correlation and agreement to the 80 min BP\textsubscript{ND} values, and a lower difference between SUVR-1 of the group of parkinsonism patients and the control group.

The shorter scan durations did not to any major extent affect the accuracy of R\textsubscript{1} values as long as an MRI-based reference region was used. A lower correlation to R\textsubscript{1} values for the original 80 min data with an SVCA-based reference was however observed in cortex R\textsubscript{1}. One reason for this may be the relatively narrow range of cortical R\textsubscript{1} values. However, the within-subject correlation between the R\textsubscript{1} values of the based on an SVCA reference region and the 80 min R\textsubscript{1} values with MRI-based reference was high for all scan durations.

A limitation in the study in Paper III is the significantly higher age of the patients than of the controls. Previous PET studies have reported an age-related decline of DAT in both caudate and putamen of 6-8% per decade [69, 70]. This suggests that the difference between the two groups in Paper III would have been lower if they had been of the same age. Recently, we investigated the age related-effect of DAT availability measured with \textsuperscript{[11]}C\textsubscript{PE2I}, using both BP\textsubscript{ND} and SUVR-1 measures and using the methods presented in this thesis. In line with a previous study with \textsuperscript{[18]}F\textsubscript{FE-PE2I}, there was a mean decline of 7.6% and 6.2% per decade of BP\textsubscript{ND} and SUVR-1, respectively, in caudate. However, no significant decline of either BP\textsubscript{ND} or SUVR-1 was observed in putamen, see Appendix A. These results, deviating from previous studies, need to be further investigated. Thus, while using the same analysis methods as implemented for \textsuperscript{[11]}C\textsubscript{PE2I} analysis in Paper III, these findings indicates that there would be no further decrease of the difference between the two groups in putamen, regardless of using age-matched controls. However, for clinical assessment of DAT availability, the age-related decline needs to be considered for both BP\textsubscript{ND} and SUVR-1 values in caudate.

Another challenge for the clinical application of \textsuperscript{[11]}C\textsubscript{PE2I}, is the short half-life of \textsuperscript{11}C, 20.4 min. This requires access to a cyclotron and on-site tracer production, in contrast to for example \textsuperscript{[123]}I\textsubscript{FP-CIT} or \textsuperscript{18}F-labelled DAT ligands such as \textsuperscript{[18]}F\textsubscript{FE-PE2I}. However, in generally, the differential diagnosis of parkinsonism takes place at specialized hospitals that often have access to a tracer production facility.

Advantages of using \textsuperscript{[11]}C\textsubscript{PE2I} PET over \textsuperscript{[123]}I\textsubscript{FP-CIT} are the higher resolution of PET compared to SPECT as well as the inherently quantitative nature of PET, which is further utilized by generating parametric images. \textsuperscript{[11]}C\textsubscript{PE2I} also has a higher selectivity to DAT than \textsuperscript{[123]}I\textsubscript{FP-CIT}, which also binds to serotonin and norepinephrine transporters [71]. In addition, there is a reduction of the radiation dose of about 70% when using a single \textsuperscript{[11]}C\textsubscript{PE2I} PET scan compared to the dual scan approach with both \textsuperscript{[123]}I\textsubscript{FP-CIT} and \textsuperscript{[18]}F\textsubscript{FDG}, and the need for a single hospital visit only, to assess both DAT availability and overall brain functional activity.
The results from Paper IV showed that the $^{[18F]}$THK5317 kinetics were best described applying the 2TCM, with tau binding estimated as DVR-1. Both SRTM BP$_{ND}$ and reference Logan DVR-1 agreed well with plasma-input models. Reference Logan DVR-1 performed best when applied on a voxel-level and agreed best to VOI-based SRTM values. The evaluation of shorter scan durations in Paper IV showed that 60 min was sufficient for accurate quantification using reference Logan DVR-1 measures. The results from Paper V demonstrated that the scan duration could be further decreased when estimating $^{[18F]}$THK5317 binding using SUVR-1. There was a high variation of time to TE across the different brain regions, and between AD and HC, which complicates the definition of a general time interval for SUVR-1 calculations. However, SUVR-1 for the 20-40 min time interval showed highest correlation and agreement to the DVR-1 values overall, for both AD and HC subjects.

As shown in Paper IV, there is a high white matter uptake primarily because of the lower clearance rate in white matter than in grey matter regions. The parametric BP$_{ND}$ or DVR-1 images considerably reduced the high with matter signal as compared with SUVR-1 at 70-90 min. Partial volume corrections were not assessed in this work but could possibly improve the quantitative accuracy by accounting for white-matter spill-over.

SUVR-1 at the time interval of 20-40 min using an SVCA-based reference showed a high agreement to SUVR-1 with MRI-based reference indicating that the SVCA method can be used to provide a reference TAC directly from the dynamic $^{[18F]}$THK5317 scan.

As previously shown, R$_1$ estimate from the dynamic $^{[18F]}$THK5317 scan demonstrates a high correlation to $^{[18F]}$FDG uptake [72] and as shown here, a 40 min scan duration is sufficient for measuring R$_1$ with an SVCA-based reference. This makes it possible to use dynamic $^{[18F]}$THK5317 for dual-biomarker investigations and could potentially serve as a substitute for $^{[18F]}$FDG.

There has been some concern about binding of tau tracers such as the structurally related tracer $^{[18F]}$THK5351 to monoamine oxidase-B (MAO-B) present in astrocytes [73]. A recent in vitro study of the racemic compound $^{[3H]}$THK5117 showed relatively low affinity to monoamine oxidase-B indicating that competitive binding of the corresponding $^{[18F]}$THK5317 would not present a problem at the concentrations encountered during clinical PET studies [74, 75], although in vivo, an off target binding is evident in the basal ganglia [76]. However, newly developed tau tracers that are being evaluated, such as $^{[18F]}$MK6240, are showing much lower off-target binding [77, 78].
General discussion

The use of short, static scans is attractive for clinical applications. A dynamic PET scan can however result in parametric images showing both the binding of the tracer and also the relative tracer delivery, which can be used for assessment of overall brain function. Using simplified analysis methods and decreased scan duration, while maintaining quantitative accuracy, can facilitate the use of dynamic PET in clinical practice as well as in research investigations.

Even though an MRI in many cases is performed in patients with neurodegenerative disease, an automated way of extracting the reference region can still be of value to simplify the analysis of dynamic PET data. In some cases, as seen for example in the MCI subject with degeneration of cerebellum, in Paper III, the use of an SVCA-based reference provided more correct quantification than when cerebellum was used as reference. This may also apply to other types of brain injuries with associated tau pathology, as for example brain trauma patients where the cerebellum can be impaired.

The results in this work are not directly applicable to other PET tracers. Issues such as differing kinetics may influence the choice of cluster classes for implementation of SVCA and an optimal time window for calculations of semi-quantitative values, such as SUVR-1, should be evaluated carefully for each tracer. However, the underlying methods evaluated in this thesis can be useful for many different applications.
Concluding remarks

The overall focus of this thesis has been to evaluate models for quantification of dynamic $^{11}$CPE2I and $^{18}$FTHK5317 PET data, and to validate simplifications of these methods, suitable for use in a clinical setting.

$^{11}$CPE2I

Papers I-III supply valuable information on the feasibility of the clinical use of dynamic $^{11}$CPE2I for differential diagnosis of parkinsonian disorder. The main findings in Papers I-III were the following:

I Parametric $^{11}$CPE2I images showing DAT availability, $\text{BP}_{\text{ND}}$, and the relative tracer delivery, $R_1$, can be robustly obtained using RPM.

II The parametric $\text{BP}_{\text{ND}}$ and $R_1$ images from a single dynamic $^{11}$CPE2I scan can be used to evaluate parkinsonian disorders and their use is a powerful alternative to a dual scan approaches with $^{123}$IFP-CIT and $^{18}$FFDG.

III Simplification of the acquisition and analysis methods for $^{11}$CPE2I is possible by shortening the scan acquisition time to 40 min and using a clustering method to obtain a reference region directly from the dynamic scan, while still adequately being able to discriminate between control subjects and patients with reduced DAT availability.

In 2015, $^{11}$CPE2I was introduced clinically at Uppsala University Hospital and in 2017 over 120 patients with parkinsonian disorders have been investigated with $^{11}$CPE2I and the methods developed in this thesis.
The work in Papers IV-V showed that simplified analysis methods can be applied for quantification of \(^{18}\text{F}\)THK5317 and the main findings were the following:

I. A reference tissue method can be used for quantification of tau pathology with \(^{18}\text{F}\)THK5317 on both VOI- and voxel-level, overcoming the need for arterial blood sampling.

II. An SVCA-based reference region combined with a scan duration of 40 min, for assessment of both SUVR-1 and R\(_1\) measures, can be applied to further exploit applications of \(^{18}\text{F}\)THK5317 PET.

Future perspectives

The methods developed and validated in this thesis have shown great potential for clinical applications. Although these results are not directly applicable to other PET tracers, evaluation of these methods for quantification of dynamic PET data using other tracers could possibly further facilitate use of dynamic, multi-parameter PET in clinical settings.

For example, as mentioned in the discussion, the use of \(^{11}\text{C}\)PE2I is limited to hospitals with access to a cyclotron and tracer production facilities. Therefore, implementation of these methods for a \(^{18}\text{F}\)-labelled tracer such as \(^{18}\text{F}\)FE-PE2I would make the methods described for \(^{11}\text{C}\)PE2I available outside of the university hospitals. This could also enable multi-centre research collaborations to increase the knowledge of Parkinson’s disease and similar syndromes.

The use of a supervised clustering method could also be of great potential when investigating diseases where the cerebellum may be affected and implementation of SVCA could be a strategy for accurate quantification of dynamic PET data these patients.
Positronemissionstomografi (PET) är en funktionell avbildningsmetod som bygger på att en spårsubstans märkt med en radioaktiv isotop, till exempel kol-11 (¹¹C) eller fluor-18 (¹⁸F), administreras i kroppen. Den strålning som spårsubstansen ger upphov till kan registreras av PET-kameran och distributionen av spårsubstansen i kroppen kan mätas. Genom att göra PET-mätningen över tid, en så kallad dynamisk undersökning, fås information om hur koncentrationen av spårämnet i kroppen förändras över tid. Med den informationen, och med hjälp av olika matematiska modeller, kan kvantitativa parametrar som till exempel relativa blodflödet och bindning av spårsubstansen till specifika mål i kroppen, beräknas. Dessa beräkningar kan göras för varje pixel i PET-bilden, vilket ger en tydlig visuell uppskattning av de parametrar som är av intresse. På detta sätt kan alltså mycket mer information fås från en PET-undersökning än om man bara en statisk bild hade tagits, men det kräver vanligtvis en längre undersökningsstid (60-90 min istället för 10-20 min) och i vissa fall samtidig blodprovstagnation, vilket gör undersökningen svår för patienterna.


PET kan spåra relativt små biologiska förändringar i hjärnans funktion och kan var till stor nytta både vid forskningsstudier och vid klinisk utvärdering av dessa sjukdomar. För att beräkna parameterbilderna från dynamiska PET-undersökningar utan att behöva ta blodprover krävs att det går att definiera en region i hjärnan som inte har någon bindning av spårsubstansen, en så kallad referensregion. Detta görs vanligtvis manuellt eller med automatiska metoder som kräver att man har tillgång till en strukturl bild av patientens hjärna, tex
från en magnetresonanstomografi (MRT) undersökning. För att förenkla användningen av dynamisk PET är det önskvärt att de relativt långa undersökningsstiderna kan förkortas och att det går att använda förenklade analysmetoderna för kvantifiering av de parametrar som är av intresse samt att kunna definiera en referens-region direkt från det dynamiska PET-datat.


Resultaten från de ingående arbetena i avhandlingen har visat att de parameterbilder som tagits fram från en dynamisk $[^{11}C]$PE2I PET undersökning i hög grad överensstämmar med de upptagsmönster som man ser vid de tidigare undersökningsmetoderna. Det har också visats att det är möjligt att korta ner den dynamiska PET-undersökningen från 80 till 40 min och fortfarande behålla den kvantitativa informationen avseende DAT-tillgänglighet och relativt blodflöde. Dessutom kan en klustermetod användas för att ta fram en referensregionen direkt från den dynamiska PET undersökningen, vilket ytterligare förenklar analysen av bilderna. Liknande resultat sågs för $[^{18}F]$THK5317, där både reducerad undersökningsstid, från 90 till 40 min, och förenklade analysmetoder för kvantifiering av tau-bindning och relativt blodflöde kan användas för att dra nytta av dynamisk $[^{18}F]$THK5317 PET.

Metoderna som har utvecklats i denna avhandling gör det möjligt att till fullo använda de möjligheter PET ger när det gäller att mäta flera olika processer i hjärnan under en och samma undersökning, med en undersökningsstid som är tillräckligt kort för att kunna användas i kliniken och med nästan helt automatiskt bildanalys. Sedan 2015 har $[^{11}C]$PE2I, och de metoder som utvecklats och validerats i den här avhandlingen, använts kliniskt på Akademiska sjukhuset i Uppsala för differentialdiagnostik av patienter med parkinsonism.
Acknowledgments

The work to finalize this thesis would not have been possible without collaborations and the support by many. I would like to specially thank a few people:

First of all, my main supervisor, Mark Lubberink. I am so grateful that you took me on as a PhD student, for having the opportunity to learn from you and to work with you. Thank you for your patience, your enthusiasm and for believing in me. My co-supervisors; Lieuwe Appel, for interesting discussions and all the time you spent to thoroughly improving my manuscripts and Jens Sörensen, for your great expertise and valuable scientific input.

Everyone, past and present, at ‘våning 5’ for making the work environment more enjoyable. Especially Ezgi, Kerstin, Camilla, Elin, Naresh and Joao, for being a part of this journey, for being great room-mates and friends and for cheering me up through times of stolen computers and broken hard drives. I want to thank all my past and present colleagues at the PET centre and medical physics at Uppsala University Hospital, especially Anders Wall, Torsten Danfors, Charles Widström and Jonas Eriksson for valuable scientific (as well as non-scientific) discussions and Lars Lindsjö and Tomas Nyholm for assistance with data handling.

The group of psychologists that I have had the opportunity to collaborate with from the start; Andreas Frick, Jonas Engman, Tomas Furmark and Mats Fredrikson. Thank you for always being super optimistic and for providing me with a lot of data.

I want to thank Dag Nyholm and Håkan Askmark for collaboration in the $^{[11]}$C]PE2I project and for inclusion of the patients with parkinsonism.

Thanks to Agneta Nordberg for the possibility to work with the $^{[18]}$F]THK5317 data and for the interesting collaboration with your group, including Konstantinos Chiotis, Laure Saint-Aubert and Antoine Leuzy, at the Center for Alzheimer Research at Karolinska Institutet. Thanks for sharing your knowledge in the field of PET in Alzheimer’s disease.

All co-authors not already mentioned; Gunnar Antoni, Helena Wilking, Margareta Sprycha, Beatrice Borg and Alf Thibblin. I want to thank everyone that has contributed to the papers in this thesis with invaluable feedback and great input. I also want to take the opportunity to thank all research participants, without whom these studies would not have been possible.
My friends and family that have supported me on this journey. Especially Josse and Chris for always believing in me, even though you had no clue what I was doing ;-). Emma and Daniel for all the ‘fredagsmys’, I would not have stayed sane without it. My mother Eva and father Arnold, thank you for always telling me that it is fun to learn new thing. My siblings with families and Janne and Ingrid.

And finally, Patric, for your endless love and support, and Milo, for giving everything a new meaning. I dedicate this thesis to you!
References


Appendix A

Age-related dopamine transporter availability measured using \([^{11}C]PE2I\) PET

Introduction

\([^{11}C]PE2I\) is a positron emission tomography (PET) ligand with high affinity and selectivity for the dopamine transporter (DAT). Decreased DAT availability is associated with various neurological disorders such as Parkinson’s disease. We have recently shown that an 80 min dynamic \([^{11}C]PE2I\) PET scan can be used for differential diagnosis of patients with parkinsonian disorder, (Paper II). For routine clinical application, we have validated the use of shorter acquisition times, with DAT availability estimated using standard uptake value ratio (SUVR)-1 at 30-40 min p.i. (Paper III). Age-related decline of DAT availability has previously been investigated with PET using \([^{18}F]FE-PE2I\), showing a reduction of striatal DAT of about 7% per decade as measured with BP\(_{ND}\). The purpose of this study was to investigate the age-related changes of DAT availability measured with \([^{11}C]PE2I\) PET using both BP\(_{ND}\) and SUVR-1 estimates.

Materials and Methods

Thirty healthy controls (HC) were included, age 20-67 years, as given in Supplemental Table 1. Each subject underwent an 80 min dynamic PET scan after injection of 350-400 MBq \([^{11}C]PE2I\). Each subject also received a T1-weighted MRI scan, for structural information, to be co-registered to the PET scan. Volumes of interest (VOIs) were defined on the MRI image applying an automated probabilistic VOI template (PVElab).

*Supplemental Table 1.* Mean age ± standard deviation (SD) and numbers of males and females included in each age-group.

<table>
<thead>
<tr>
<th>Age-group</th>
<th>Number of HC (males / females)</th>
<th>Mean age ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-30</td>
<td>6 (3 / 3)</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>30-40</td>
<td>6 (3 / 3)</td>
<td>33 ± 2</td>
</tr>
<tr>
<td>40-50</td>
<td>7 (3 / 4)</td>
<td>44 ± 3</td>
</tr>
<tr>
<td>50-60</td>
<td>5 (4 / 1)</td>
<td>54 ± 3</td>
</tr>
<tr>
<td>60-70</td>
<td>6 (3 / 3)</td>
<td>65 ± 2</td>
</tr>
</tbody>
</table>
Parametric BPND images were calculated using receptor parametric mapping (RPM) for the full 80 min data set and SUVR-1 images were calculated for a 30-40 min time window. Cerebellar grey matter was used as reference region. BPND and SUVR-1 values in caudate and putamen were retrieved from the parametric images by projecting the MRI-based VOIs, mean of left and right side. Relation between the BPND and SUVR-1 values and age was assessed using linear regression and mean changes per decade were calculated.

Results

The relationships between age and DAT availability measured with BPND and SUVR-1 are given in Supplemental Figure 1. A decrease of BPND was found in both caudate and putamen with 7.6 and 2.5 % mean decrease per decade respectively, although the decrease was only significant in caudate (p<0.05). A significant decrease was also found for SUVR-1 values in caudate, 6.2 % per decade, while no age-related effect on SUVR-1 values was observed in putamen.

Supplemental Figure 1. Relationship between age and a) 80 min BPND and b) 30-40 min SUVR-1, in putamen and caudate.

Discussion

The decline of 7.6 % of DAT availability per decade in caudate, measured with BPND, is in line with previous studies. When estimating DAT availability with SUVR-1 on a 30-40 min interval the age-related decrease is lower, which may be explained by the previously demonstrated underestimation of SUVR-1 compared to BPND which decreases with decreasing BPND values (Paper III). Our result regarding the non-significant decline of DAT in putamen deviates from previous studies and needs further investigation. While using these methods for clinical assessment of DAT availability, age effects need to be considered for both BPND and SUVR-1 values in caudate.
A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)