## SUMMARY

The aims of the studies described in this thesis were (1) to describe longitudinal patterns of [$^{11}$C]PIB and [$^{18}$F]FDDNP binding and [$^{18}$F]FDG uptake, (2) to investigate the inter-relationships between amyloid burden, glucose metabolism and cognition in cognitively normal elderly, (3) to explore distributions of amyloid pathology and glucose metabolism according to age-at-onset and APOE genotype in order to find plausible mechanisms underlying clinical heterogeneity in AD, and (4) to determine the additional value of [$^{11}$C]PIB and [$^{18}$F]FDG PET in the diagnostic work-up in a memory clinic.

In this chapter, the main findings of these studies are summarized and discussed. In addition, possibilities and directions for future research are given.

### Main findings

First, longitudinal aspects of Alzheimer pathology were assessed. In **chapter 2.1** several models for analyzing [$^{11}$C]PIB data were evaluated in order to identify the method of choice for measuring longitudinal changes in amyloid deposition. Repeat [$^{11}$C]PIB scans, with on average an interval of 2.5 years, were analyzed using receptor parametric mapping (RPM2), reference Logan and standardized uptake value ratios (SUVr). SUVr values overestimated [$^{11}$C]PIB binding with approximately 13%, whereas reference Logan values were on average 6% lower than RPM2. Furthermore, tracer delivery to the cortex relative to reference cerebellar grey matter ($R_1$) decreased over time in AD patients, but not in MCI patients and controls. Simulations showed that SUVr highly fluctuate as a function of uptake period and of heterogeneous changes in blood flow. It was therefore concluded that for reliable assessment of [$^{11}$C]PIB binding over time, for example in drug intervention studies or when studying pathophysiological changes associated with progression of disease, quantitative methods for data analysis are essential.

In **chapter 2.2** temporal changes in [$^{11}$C]PIB and [$^{18}$F]FDDNP binding and [$^{18}$F]FDG uptake were assessed. A significant increase in global cortical [$^{11}$C]PIB binding was found in MCI patients, but not in AD patients or controls. No changes were observed in specific [$^{18}$F]FDDNP binding. [$^{18}$F]FDG uptake was reduced at follow-up in the AD group only, especially in frontal, parietal and temporal cortices. These findings indicate that [$^{11}$C]PIB and [$^{18}$F]FDG track molecular changes in different stages of AD and thus provide complementary information. It was also established that [$^{18}$F]FDDNP is not useful for tracking progression of AD.

**Chapter 3** describes the inter-relationships between amyloid deposition, glucose metabolism and cognition in cognitively normal elderly. A longstanding debate in the field of cognitive aging is centred on how some individuals maintain cognitive function despite molecular evidence of amyloid pathology, whereas others show less brain resilience. Higher [$^{11}$C]PIB retention in the precuneus was associated with higher metabolic activity in AD specific regions and with worse visual episodic memory performance. [$^{18}$F]FDG uptake did not correlate with cognitive function across groups. Within individuals with elevated [$^{11}$C]PIB retention, however, increased metabolic activity related to better performance on verbal episodic memory tasks. These findings suggest that asymptomatic elderly with cerebral amyloidosis are, at least temporarily, able to preserve cognitive function through enhanced neuronal function.

**Chapter 4** aims to characterize variability in disease pathways that may account for clinical heterogeneity often observed in AD patients. For instance, early-onset AD patients often present with a distinct (non-memory) cognitive profile. In **chapter 4.1** 100 AD patients were divided into younger and older groups (by median split at age 62) in order to investigate the role of age-at-onset on extent and distribution of amyloid deposition and glucose metabolism. Younger patients showed increased [$^{11}$C]PIB binding and decreased [$^{18}$F]FDG uptake in the parietal cortex. Furthermore, parietal amyloid pathology and metabolic activity were directly related to visuo-spatial functioning (for both [$^{11}$C]PIB and [$^{18}$F]FDG) and executive functions and attention ([$^{18}$F]FDG only) in younger AD patients. This led to the conclusion that increased amyloid burden, together with metabolic dysfunction, in the parietal cortex of younger AD patients may contribute to the distinct cognitive profile frequently observed in these patients.
The same data set was used to investigate the relationships between APOE genotype and distributions of amyloid load and glucose metabolism (**chapter 4.2**). AD patients without an APOE ε4 allele showed greater amyloid pathology than APOE ε4 carriers, whereas carrying APOE ε4 was associated with more profound metabolic impairment in posterior parts of the brain in a dose-dependent fashion. This differential impact of APOE genotype provides evidence for the notion that AD develops along distinct disease pathways in APOE ε4 carriers and non-carriers. In addition, this may partially explain differences in clinical presentation according to APOE status.

**Chapter 5** focuses on the application of molecular imaging using PET in a clinical setting. **Chapter 5.1** describes the diagnostic performance of [$^{11}$C]PIB and [$^{18}$F]FDG PET in 154 memory clinic patients with a wide variety of cognitive and behavioural deficits. Outcome measures were (change in) clinical diagnosis and confidence in that diagnosis before and after disclosing PET results. PET results led to a diagnostic change in 23% of the patients and diagnostic confidence increased from 71 to 87% after PET. Diagnostic change only occurred in cases of low diagnostic confidence (≤80%) prior to PET. It was concluded that combined [$^{11}$C]PIB and [$^{18}$F]FDG PET is of additional value in the diagnostic work-up in a memory clinic. In **chapter 5.2** the potential of [$^{11}$C]PIB PET to identify AD in a prodromal phase is discussed. Review of the literature shows that MCI patients who progress to AD have cerebral amyloidosis in the vast majority of cases, whereas [$^{11}$C]PIB negative patients rarely convert. [$^{11}$C]PIB PET is thus a strong predictor for clinical progression in prodromal AD patients.