English Summary

Driven by the largely unexplained clinical heterogeneity of Alzheimer’s disease (AD), the general aim of this thesis was to investigate which neurobiological factors influence cognitive manifestations of AD. In the studies described in this thesis we found that:

- Profiles of cognitive impairment in AD were related to age at onset, abnormalities on electroencephalogram (EEG) and region of brain atrophy on magnetic resonance imaging (MRI).
- A test to measure apraxia could be validated in our memory clinic population and apraxia was a common feature of AD, even in mildly demented patients and in a small proportion of patients with Mild Cognitive Impairment (MCI).
- Trajectories of cognitive decline on memory, language, executive functioning, attention and visuo-spatial functioning differed between patients with AD, vascular dementia (VaD), dementia with Lewy Bodies (DLB), behavioural variant frontotemporal dementia (bvFTD) and language variant frontotemporal dementia (lvFTD).
- Patients who developed AD despite the absence of the two most important risk factors (higher age and apolipoprotein (APOE) €4 carriership), showed steeper cognitive decline on non-memory cognitive domains than patients who had these risk factors.

This chapter summarizes and discusses the main findings of the studies described in this thesis.

Summary

Cross-sectional studies

In chapter 2 we investigated the associations between cognitive profile and age at onset, functional abnormalities as measured by EEG and structural abnormalities as measured by MRI in a cross-sectional manner. In chapter 2.1 we investigated the main cognitive domains (memory, language, executive functioning, attention and visuo-spatial functioning) in AD patients according to age-at-onset. We found that, despite the same level of dementia severity, early onset patients performed worse than late onset patients on visuo-spatial functioning, executive functioning and attention. Late onset patients tended to perform worse on memory, although this did not reach significance. When we stratified for dementia severity we found that in mildly demented early onset patients, memory function was remarkably preserved compared to late onset patients. In moderate AD, differences in memory function disappeared, but early onset patients performed worse on visuo-spatial functioning, executive functioning and attention than late onset patients. This study showed that patients with an early onset have a different cognitive profile than patients with late onset AD, providing further evidence for the heterogeneity in clinical manifestation of AD.

In chapter 2.2 we studied associations between different cognitive profiles in AD and their underlying functional brain changes as measured by EEG. In our cohort, 72 patients (28%) had a normal EEG, 82 (32%) had focal abnormalities, 34 (14%) diffuse abnormalities and 66 (26%) had both focal and diffuse abnormalities. Patients with a normal EEG presented with a cognitive profile in which memory was mostly impaired. Patients with focal and diffuse EEG abnormalities presented with a non-memory profile. We concluded that specific types of EEG abnormalities are associated with different cognitive profiles in AD and provide biological support in terms of brain functioning for variability in pathophysiological mechanisms in AD.
In chapter 2.3 the relation between regional atrophy on MRI and cognition in AD was studied. We evaluated whether occurrence of posterior atrophy (PA) and medial temporal lobe atrophy (MTA) could account for differences in cognitive domains affected. We found that 84 patients (26%) had both MTA and PA, 98 (30%) had MTA, 57 (17%) had PA, and 90 (27%) had neither. MTA was associated with worse performance on memory, language, and attention, and PA was associated with worse performance on visuo-spatial and executive functioning. Stratification for age showed associations between MTA and impairment on memory, language, visuo-spatial functioning, and attention in patients with late onset AD. In early onset AD, patients with PA tended to perform worse on visuo-spatial functioning. We concluded that regional atrophy is related to impairment in specific cognitive domains in AD. In addition, the prevalence of PA in a large set of patients with AD and its association with cognitive functioning provided support for the usefulness of this visual rating scale in the diagnostic evaluation of AD.

In chapter 2.4 we evaluated the reliability and validity of the Van Heugten test for apraxia (VHA) in a memory clinic population. In addition, we investigated the presence and severity of apraxia in MCI and AD and investigated the risk factors for apraxia in AD. The intrarater reliability was 0.88 and interrater reliability was 0.73. AD patients performed worse on the VHA than controls and MCI patients (both p<0.001). Apraxia was prevalent in 35% of AD patients, in 10% of MCI and was never observed in controls. In AD, dementia severity was the main factor associated with apraxia; moderately demented patients had an almost 7 times higher risk to have apraxia. The second risk factor was APOE Ɛ4 genotype. APOE Ɛ4 non-carriers had a twofold-increased risk to have apraxia compared to APOE Ɛ4 carriers. Patients with an early age at onset tended to have more often apraxia, although this did not reach significance. We concluded that apraxia can be reliably measured with the VHA and that it was present in a proportion of patients with MCI and AD. The presence of apraxia in AD was related to dementia severity and APOE Ɛ4 genotype.

Longitudinal studies

In chapter 3 we used neuropsychological follow up data to investigate trajectories of cognitive decline on the main cognitive domains: memory, language, attention, executive functioning and visuo-spatial functioning. In chapter 3.1 the trajectories of cognitive decline in several types of dementia (AD, VaD, DLB, bvFTD and IvFTD) compared to controls were studied. At baseline, patients with dementia performed worse than controls in all cognitive domains, except visuo-spatial functioning, which was only impaired in patients with AD and DLB. During follow-up, patients with AD declined in all cognitive domains, while VaD patients showed decline in attention and executive functioning. DLB patients showed decline in every cognitive domain except language and Mini-Mental State Examination (MMSE). In patients with bvFTD rapid decline in memory, language, attention and executive functioning occurred, while visuo-spatial functioning remained quite stable. IvFTD declined mostly in attention and executive functioning. These estimations of natural disease course could have important value for the design of clinical trials as neuropsychological measures are increasingly being used as outcome measures and trials for non-AD dementia are emerging.

In chapter 3.2 we studied how age at onset and APOE Ɛ4 influence rate of decline on the main cognitive domains in AD. We found that over time, early onset patients declined faster on executive functioning than late onset patients, but age was not related to decline in the other cognitive domains. APOE Ɛ4-negative patients declined faster on language than APOE Ɛ4-positive patients. When we took age and APOE genotype simultaneously into account, we found that compared to late onset-Ɛ4 positive patients, early onset-Ɛ4 negative patients declined faster on language, attention, executive functioning and visuo-spatial functioning. Late onset-Ɛ4 negative and
early onset-ɛ4 positive showed intermediate rates of decline. We found no differences between groups in decline on memory.

**Methodological considerations**

The studies described in this thesis have some methodological considerations. We have an extensive standard diagnostic work-up and apply appropriate diagnostic criteria [1-9]. In addition, CSF biomarkers and amyloid imaging were available for a majority of patients, to provide additional information on the underlying pathology. However, a diagnosis of AD can only be confirmed by post-mortem verification. For a subset of patients we had post-mortem verification available.

The VUmc Alzheimer Center is a tertiary referral Center with special interest in young patients with dementia. As a consequence the cohorts in the studies are relatively young and our findings might not be directly generalizable to every patient with dementia. However, we consider a young age as an advantage as younger patients have less co-morbidity than older patients, and therefore we believe that we look at a more pure form of the diseases. Besides that, non-AD types of dementia often develop at a younger age and for this reason we were able to study other types of dementia as well.

We used a standardized extensive neuropsychological assessment covering several cognitive domains, at baseline and follow-up. Unfortunately, tests assessing visuo-spatial functioning and in particular praxis were not available for all studies, since they were added more recently to the standardized neuropsychological test battery. Not all patients were able to complete all tests, especially the Trail Making Test part B was aborted frequently because of lack of time. We wanted to avoid a selection bias (including solely patients that were able to complete the extensive neuropsychological assessment) so we decided to impute the missing neuropsychological data for the studies described in chapters: 2.3, 3.1 and 3.2. By imputing missing data we were able to investigate patients with more severe cognitive impairment as well, creating a more representative study sample. Overall, the size of the samples in our studies was large, except for some of the non-AD samples described in chapter 3.1. Collecting extensive neuropsychological follow up data in itself is a challenge and especially in these less common types of dementia.

In two studies persons with subjective memory complaints served as controls (chapters 2.4 and 3.1). There is evidence that these subjects have a higher risk to progress to dementia over time [10]. In our sample, however none of the controls progressed to MCI or dementia within the time of follow up described in the studies.

**Clinical implications**

In this thesis we provided further evidence that AD is a heterogeneous disease in terms of cognitive presentation. From previous work it is already known that an early age at onset is often associated with a non-memory presentation [11]. We extended on this by showing that patients with an early onset were more impaired on visuo-spatial functioning, executive functioning and attention than patients with a late disease-onset (chapter 2.1). Therefore, tests assessing visuo-spatial functioning are of value in the diagnostic work-up of dementia, as early onset dementia patients often show most impairments on this domain. Not taking this domain into account may even lead clinicians to miss the diagnosis.

In an earlier study by our group, based on clinical presentation, we also found that a visuo-spatial/apraxia presentation was the most common for patients with early onset AD [12]. A validated, widely used test for apraxia
in dementia is however lacking. In this thesis we investigated an apraxia-test that was developed for a stroke population [13]. It appeared that this test was useful within a dementia cohort as well. We found that patients with an early dementia onset are likely to have more often apraxia (chapter 2.4). Tests assessing praxis might also be of help to recognize atypical presentations. We therefore recommend, besides examination of visuo-spatial functioning, examining praxis in the standard work-up, especially in younger patients.

In literature, the absence of the APOE $\varepsilon 4$ allele has been associated with a non-memory presentation and the presence of APOE $\varepsilon 4$ allele with a typical memory presentation [14]. In line with this, we found that patients who were APOE $\varepsilon 4$-negative had a higher risk of having apraxia. Besides that we found that APOE $\varepsilon 4$-negative patients, especially when they were young, also showed faster decline on non-memory domains than late onset APOE $\varepsilon 4$-positive patients (chapter 3.2).

In two studies we explored relationships between cognitive profiles and biological factors. In the first study, we measured brain function by EEG. In patients with AD we found that patients with focal and diffuse EEG abnormalities were the youngest and had a non-memory profile, whereas patients with normal EEGs had a memory profile. The effect was independent of disease severity or global cognitive decline (chapter 2.2). One explanation for our finding could be the deep location of the hippocampi, which possibly does not admit the electrodes to capture (changed) signals in subjects with a memory profile. In this study we show that EEG abnormalities do not seem to be associated with disease severity, but rather with the clinical presentation of AD. Earlier studies showed that patients with an early disease onset show more abnormalities on EEG [15,16]. Besides that, APOE $\varepsilon 4$ also seems to influence EEG, as APOE $\varepsilon 4$ non-carriers have more prominent focal and diffuse abnormalities [15] and they show slower activity, most prominent in parieto-occipital regions [17]. In this study, we did not take the influence of age or APOE $\varepsilon 4$ into account, but it seems probable that the patients in our cohort who have a non-memory profile did have focal and diffuse abnormalities and are more often APOE $\varepsilon 4$ non-carriers.

In a second study we investigated associations between cognitive profile and regional atrophy as visually rated on MRI. Besides MTA we also studied the newly developed visual rating scale for PA (chapter 2.3). The AD patients in this cohort were in the same stage of the disease given their comparable MMSE-scores. We found evidence that patterns of cognition and patterns of atrophy were related to each other, as MTA was associated with impaired memory, language and attention and PA seems to predispose for non-memory symptoms. In addition, we observed that a proportion of AD patients did not have MTA. We recommended to also investigate PA on MRI in clinical practice, especially when taking into account the new clinical criteria for AD that include non-amnestic presentations as well.

Two studies in this thesis had a longitudinal setup. One investigated cognitive trajectories amongst AD in various types of dementia (chapter 3.1) and the other took a closer look at cognitive decline in AD for age at onset and APOE $\varepsilon 4$ status (chapter 3.2). Studies that investigate cognitive change over time in various types of dementia in one single cohort are rare [18-21]. Studies that use an extensive neuropsychological assessment in this setup are even harder to find [18,19]. With our study (chapter 3.1) we aimed to provide estimates of trajectories of cognitive decline for several types of dementia by using the same neuropsychological test battery at baseline and follow up in all subjects. This is an important advantage, as the study was not limited to the MMSE or to one test per domain as is often seen in literature [20, 21]. The findings of our study are highly timely as recently the Food and Drug Administration proposed to revise
the criteria for drug approval. They suggested that in trials (in very early stages of disease) cognitive tests able to capture subtle changes should be used as end-point and preferred above crude measures, like interference of daily living scales or the MMSE. To be able to effectively implement such a strategy, reliable estimates of natural disease progression are dearly needed. Besides that, clinical trials for other types of dementia than AD are currently designed and the first trial to FTD has started. Therefore, estimates of cognitive trajectories of different types of dementia are essential for trial design.

Few studies investigated the rate of cognitive decline according to age at onset in AD with conflicting results; some found that a younger age at onset was associated with more rapid decline [22-24], while another found that that late onset patients declined faster [25]. The influence of APOE Ɛ4 status on rate of cognitive decline has more widely been studied, but also with conflicting results [26-28]. In an earlier study by our group, APOE Ɛ4-negative patients decline faster on MMSE and this effect was most prominent in APOE Ɛ4-negative patients with an early onset [24]. We extended on this finding (chapter 3.2) by showing that APOE Ɛ4-negative patients with an early onset particularly decline fastest on attention, language, executive functioning and visuo-spatial functioning, fits with cross-sectional observations that early onset, APOE Ɛ4-negative patients often have a non-memory presentation. Our results might be explained by earlier findings that APOE Ɛ4-negative patients show also more rapid whole brain atrophy over time, which could lead to faster cognitive decline in several cognitive domains [29]. These findings could provide neuronal support for a different cognitive expression of AD.

Towards a hypothetical framework

In the following paragraph we try to put together all evidence gathered in this thesis into a hypothetical framework. The different studies all point towards cognitive heterogeneity in AD. Although specific profiles differ it seems plausible that we can broadly distinguish two profiles: (1) prominent impairment of memory and (2) impairment of visuo-spatial functioning, executive function and, or praxis with relative sparing of memory (non-memory). Figure 1 visualizes these two profiles. A memory profile is mostly characterized by 1) late age at onset of the disease, 2) an EEG with no or mild abnormalities, 3) prominent MTA on MRI 4) high prevalence of APOE Ɛ4-positivity. Non-memory profiles are characterized by 1) an earlier age at onset, 2) focal and diffuse abnormalities on EEG, 3) prominent PA on MRI and 4) high prevalence of APOE Ɛ4-negatvity. Besides that, the rate of cognitive decline seems faster in the latter group (of APOE Ɛ4-negative, early onset patients) on non-memory domains.

In literature there is consensus about three extreme phenotypes with non-memory presentations: Posterior Cortical Atrophy (PCA), logopenic progressive aphasia and frontal variant AD [14,30]. In clinical practice these extreme presentations are rare; in the different studies described in this thesis five patients had a diagnosis of PCA. Our data illustrate that even in the ‘normal’ spectrum of AD, there is considerable heterogeneity in cognitive profile, with variable involvement of early memory problems. It is important to make an early diagnosis as soon as possible in patients with a non-memory presentation, so that appropriate accompaniment like tools and strategies to cope with visual dysfunction can be started.
The studies described in this thesis have a hypothesis driven approach. Currently, our group is also taking another approach by using a data driven method in order to investigated cognitive subtypes of AD. We are using latent class analysis to analyse the results of an extensive neuropsychological test battery. Preliminary results are promising as this method is able to identify cognitive subtypes in AD and these subtypes correspond with earlier findings regarding the association between neurobiological characteristics and cognition. Another developing topic is to consider AD a disconnectivity disease and to investigate relationships between pathological processes and clinical phenotypes in AD in terms of brain networks. It is of importance to identify why certain regions are more vulnerable than others and how this might explain differences in cognitive profile in AD. If we understand the aspects of cognitive heterogeneity in AD better, we might be one step closer to unravel the pieces of the jigsaw we call Alzheimer’s disease.
References


