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General introduction

Chapter **1**

1.1 Introduction

Alzheimer's disease

Alois Alzheimer described in 1907 the case of a woman in her fifties who suffered from progressive cognitive decline, ultimately leading to her death four and a half years after disease onset.¹ Upon post mortem examination Alzheimer found a unique pathological pattern of neurofibrillary tangles within the neurons, together with deposition of plaques throughout the brain. The clinical presentation together with these specific neuropathological features did not fit any of the known diseases, leading Alzheimer to propose it as a unique, formerly undefined, disease. A few years later the disease was referred to as 'Alzheimer's disease' by the famous German psychiatrist Emil Kraepelin in the eighth edition of his 'Textbook of Psychiatry'.²

The case described by Alois Alzheimer was a patient in her early fifties, while AD nowadays is seen as a typical disease of old age, with a characteristic presentation with memory disturbances. The prevalence of the disease worldwide is estimated at 35.6 million people in 2010, of whom 2-10% are younger than 65 years. This number is estimated to double every 20 years from now, with an expected prevalence of 115.4 million patients in 2050.³

Heterogeneity in AD

When the onset of disease is at a young age, i.e. before 65 years, patients often present with a different clinical presentation than the typical, or late-onset disease, with for instance aphasia, apraxia, impairment in executive functioning and visuospatial disabilities.⁴⁻⁶ In recent years interest in early onset AD has increased and it has become clear that besides a different clinical profile, young AD patients also have different patterns of cortical atrophy on Magnetic Resonance Imaging (MRI) than late onset AD patients, with more pronounced atrophy in parietal and precuneus regions.⁷⁻⁹ Positron Emission Tomography (PET)-studies have also focused on heterogeneity in AD and have shown quite consistently a pattern of parietal hypometabolism in early onset compared to late onset AD.¹⁰⁻¹² The accompanying findings in amyloid deposition by means of [¹¹C]

Pittsburgh compound-B binding are less consistent. Some studies find a difference in amyloid deposition according to age at onset,¹⁰ while other studies did not find any differences between early and late onset.¹³ The underlying cause for this heterogeneity is not yet entirely known, but several factors, including the Apolipoprotein (APOE) genotype, might play a role. Patients carrying the epsilon 4 allele ($\epsilon 4$) more often have severe memory impairment, while patients without the $\epsilon 4$ allele usually present with more pronounced impairment in other cognitive domains.^{14,15} Cognition is dependent on interaction between separate brain regions^{16,17} and the idea that in AD this interaction gets disturbed has led to the notion of AD as a disconnection syndrome.¹⁸ Various methods, both structural and functional, can be used to measure the breakdown of connections due to disease. An obvious line of study would be to address the heterogeneity in AD from a connectivity point of view. More specifically the question would be whether early and late onset AD would be characterized by different patterns of changes in functional connectivity (the concept of functional connectivity will be discussed in a later paragraph). However, although literature on connectivity in AD is accumulating, very few studies have focussed on the association between connectivity and heterogeneity in AD.

The studies that have been done all focused on the association with APOE genotype.¹⁹⁻²¹ These studies show an association between functional connectivity and APOE genotype, but they are inconsistent in the observed direction of the effect. Two of these studies considered the association with APOE genotype exclusively in the group of AD patients, without a comparison to controls.^{19,21} The first study, by Jelic et al. found that only the homozygotic APOE $\epsilon 4$ carriers differed from the other groups, with a lower alpha band connectivity. The study by Canuet et al. found differences according to APOE genotype in a subgroup of early AD patients, also with a lower alpha band connectivity in APOE $\epsilon 4$ carriers. A study on the association with APOE genotype in both AD patients and controls found an independent effect of diagnosis and APOE genotype.²⁰ In this EEG study APOE $\epsilon 4$ carriers had a higher connectivity than non-carriers, while AD patients had a lower connectivity than controls, irrespective of APOE $\epsilon 4$ status. All effects were shown in very small samples and with different measures of connectivity. Although a diagnosis of AD is consistently associated with a decrease in functional connectivity, the association with APOE genotype is quite variable. To our knowledge, no studies on the difference between early

and late onset AD in association with functional connectivity have been published.

Disentangling the pathways that lead to differences in AD phenotype might be important to find aetiological factors that provide new targets for treatment and in the future be of help in personalized medicine.

Amsterdam Dementia Cohort

The memory-clinic based Amsterdam Dementia Cohort consists of all patients referred to the Alzheimer center of the VU University medical center that gave written informed consent to use their data for research purposes. All patients underwent a standard work up including a history, and when available an informant based history, a standard neurological examination, a cognitive examination including mini mental state examination (MMSE), neuropsychological assessment, EEG, Magnetic Resonance Imaging (MRI) of the brain and screening laboratory tests. Diagnoses were made during a multidisciplinary consensus meeting. From this cohort we selected AD patients and subjects with subjective complaints serving as controls. This large dataset of in total 460 AD patients and 336 controls formed the basis of this thesis. In a stepwise manner all EEG's were analysed, starting with a crude method of visual analysis, up to a complex method of network analysis.

Electroencephalography

The first person to perform EEG on a human (i.e. his son) was Hans Berger, following the work done on animals by Caton (**figure 1**).²² He was also the first to describe abnormalities in the EEG's of patients with dementia and AD.²³ EEG measures the dynamics of electrical activity in populations of neurons that fire together in synchrony.²⁴ EEG time-signals are recorded from scalp-electrodes that are usually placed according to a standardised configuration, the International 10-20 system.²⁵ In healthy awake adults the main components of the EEG are rhythms in the alpha (8-13 Hz) and beta (13-30 Hz) range. Theta (4-8 Hz) and delta (0.5-4 Hz) rhythms usually only occur during drowsiness and sleep.

Characterization of EEG

Visual EEG analysis

There are several techniques available to characterize the EEG. In clinical practice the most frequently used technique is visual inspection, usually performed by a trained clinical neurophysiologist. In our clinic EEG's are scored regarding type of EEG abnormalities, focal or diffuse, and severity of abnormalities. This approach has yielded **K** values for interobserver agreement between 0.60 and 0.87.²⁶ In this former study visual EEG analysis proved to be a helpful tool in distinguishing different patterns of EEG abnormalities in different types of dementia, although within the group of AD patients EEG's could vary from completely normal to severely abnormal. The cause of this heterogeneity has as yet not been clarified.

Quantitative analysis

A more objective quantification of the EEG can be obtained by quantitative EEG analysis (qEEG), where the EEG signal is transformed from the time domain to the frequency domain.²⁷ In the frequency domain the power of each frequency can be represented continuously, or it can be compressed into different frequency bands.²⁷ By dividing the power in a certain frequency band by the total power, the relative power can be obtained, which is often more stable than the absolute power and easier to work with. In healthy adults the peak frequency of the alpha rhythm is around 10 Hz. With aging, a decrease of the alpha peak has been reported, but a slowing beneath 8.0 Hz, a more than 5% increase in delta activity or more than 10-15% of theta activity in the recorded time series are considered to be abnormal.²⁸ In AD the hallmarks of EEG abnormalities are an increase of power in the slower frequency bands, with a parallel decrease of power in the faster frequency bands, a decrease of the alpha peak frequency and diminished reactivity of alpha rhythm to eye opening.^{23,29} Although there has been quite some research on heterogeneity in AD in different modalities, the neurophysiological background of this heterogeneity has hardly been studied, despite the fact that electroencephalography (EEG) is a minimally invasive and inexpensive way to study brain activity directly. The few studies that have been done, in small sample sizes and with only a few electrodes, have shown more slow wave activity and more 'abnormal' EEG's in patients with early onset AD.^{30,31} Studies that have explored the association between APOE genotype and EEG are inconclusive and present conflicting results.^{19,32-34} Some report

more pronounced slowing in $\epsilon 4$ carriers,³²⁻³⁴ while others find no difference according to APOE $\epsilon 4$ status.¹⁹

Functional connectivity

A fairly novel approach to EEG analysis is to study the interactions between different brain regions, also referred to as functional connectivity (see box 1 for a glossary of functional connectivity and network terms).³⁵ This can be done by comparing two separate time signals and calculating the statistical interdependence, as an indication of information exchange between the corresponding brain regions. When the signal recorded at two separate electrodes shows a statistical interdependency it is presumed that there is an interaction between these two time series. Several measures for calculation of synchronization between time series are available, see Stam & van Straaten for a comprehensive overview.³⁶ Two groups of connectivity measures can be distinguished: linear measures, like coherence and non-linear measures, like synchronization likelihood (SL), Phase Lag Index (PLI) and event-synchronization, each with their own advantages and disadvantages.³⁶ Functional connectivity studies using EEG have shown that AD patients have a consistent decrease in alpha band functional connectivity,³⁷⁻⁴³ but results in other frequency bands are less clear-cut.^{38,39,43,44} To be able to make inferences about the effect of age at onset of AD on EEG functional connectivity, it is important to know how functional connectivity changes with normal ageing. So far, the association between aging and functional connectivity measured by EEG has hardly been studied.⁴⁵⁻⁴⁷ Age-related changes in functional connectivity have been studied using functional MRI (fMRI) studies, showing a decrease in connectivity in the Default Mode Network (DMN),^{48,49} a network that becomes active in a resting condition and subsides during tasks that require attention.⁵⁰ The DMN has also been implicated in AD.⁵¹ The EEG and MEG studies on the association between aging and functional connectivity that have been done are scarce and render it difficult to make inferences whether the effect of aging on EEG functional connectivity is comparable to the effect AD has.⁴⁵⁻⁴⁷

Network analysis

By calculating the synchronization value between every pair of electrodes a synchronization or connectivity matrix is obtained and from this matrix a brain network can be derived (**figure 2**). Networks in the brain can be studied by means of modern network theory, which is derived from three different branch-

es of mathematics and physics, namely graph theory, statistical mechanics of networks and dynamical systems theory.³⁶

Graph theory is a way of describing networks, which starts with a few basic concepts. Every network consists of nodes and edges. Nodes can represent numerous concepts, for instance people, railway stations, websites on the Internet, players in a soccer team, etcetera. Edges represent the connections between these nodes, friendships between people, tracks connecting the railway stations, the links between different websites or a pass from one player in the field to another. A measure that is often used to describe the local connectivity within a network is the clustering coefficient, which states to what extent the neighbors of a specific node are also neighbors of each other. The global integration of a network can be described by the path length. This measure gives the minimum number of steps that is needed to get from one node in the network to another node. It has been shown that many biological, social and technological networks all have the same basic configuration with a high local clustering, making it easy to interact with nodes close by, with short characteristic path lengths, making it easy also to communicate with nodes on the other side of the network. This configuration is known as a 'small-world network'.⁵² It possibly represents the most optimal organisation that is necessary for cost-effective information processing.^{53,54}

In our case the nodes are represented by time series produced by EEG electrodes and the edges are the synchronization values between pairs of time signals (**figure 2**). With this information we can calculate how efficient different parts of the brain are connected to each other. Normal cognition depends on a balanced integration and segregation of information flow between separate brain regions.¹⁷ It has been shown that in healthy persons the brain network structure also follows a 'small-world' configuration.^{52,54,55} When cognitive functions are at stake, as in AD, this is presumably reflected in a deterioration of this optimal configuration. Network studies in AD have indeed shown a loss of optimal network configuration.^{56,57} As far as we know, no network studies on (age dependent) heterogeneity in AD have been performed in any modality yet.

Since EEG is a widely available, inexpensive and non-invasive technique that reflects synaptic activity directly, it could prove to be a reliable outcome meas-

ure in clinical trials with interventions tempting to affect synaptic function in AD patients by means of changes in functional connectivity and network measures.

1.2 Aims and outline

The aims of this thesis were to study the neurophysiological background of heterogeneity in AD in order to elucidate differences in disease mechanism that lead to variations in clinical presentation. In addition we aimed to study the usefulness of EEG as an outcome measure in a clinical trial. In our studies we addressed the following research questions:

- Is there a difference in EEG abnormalities according to age at onset and APOE genotype in AD patients?
- What is the independent effect of aging and diagnosis of AD on functional connectivity measured by EEG?
- How is the brain network configuration in AD patients different from controls and how is this associated with age at onset?
- How does the network configuration in AD patients change as result of an intervention aimed at improving synaptic function?

As a first step, we used in **chapter 2** a crude measure of visual EEG analysis to study the difference in EEG abnormalities according to age at onset and APOE genotype. To further specify the findings from the first study we used in **chapter 3** quantitative EEG analysis, to study the association between aforementioned factors and regional oscillatory brain dynamics. In **chapter 3.1** we studied the association between age and oscillatory brain dynamics, while in **chapter 3.2** we studied the association between APOE genotype and oscillatory brain dynamics. Since AD has been conceived of as a disconnection syndrome our next step was to study functional connectivity measured by EEG. However, before inferences about the association between age at onset of AD and functional connectivity could be made, we also set out in **chapter 4** to study the association between aging and functional connectivity measured by EEG. The last

technique to study EEG measures was modern network theory. In **Chapter 5** we explored the differences in brain network configuration between AD patients and controls and the association between age at onset in AD patients and network measures. As it is presumed that EEG is a reflection of synaptic activity in the brain, EEG network studies could form a very helpful tool to study the influence of an intervention on brain network topology. In **chapter 6** we used a graph theoretical approach to show whether the medical food Souvenaid, designed to have an influence on synaptic functions, has an influence on brain network configuration in mild AD patients. Finally in **chapter 7** the main findings of this thesis are summarized, followed by a general discussion and some recommendations for future research.

Box 1: Glossary of functional connectivity and network terms

- **Clustering coefficient:** the interconnectedness of a node's immediate neighbors
- **Connectivity matrix:** a symmetric matrix that represents the strength of connectivity between all pairs of nodes.
- **Default Mode Network:** a network that becomes active in a resting condition and subsides during tasks that require attention
- **Edge:** a connection between two nodes
- **Functional connectivity:** the presence of functional connections between distributed neural elements.
- **Graph:** a set of nodes and edges, which together form a network
- **Graph theory:** a field in mathematics that describes phenomena from different fields in terms of network topology.
- **Network:** a large collection of interconnected nodes. Many real-world situations can be modelled as a network.
- **Node:** a basic network element that can for example represent an EEG electrode.
- **Path length:** the number of intermediate links between one node and another node
- **Small-world network:** a network topology characterized by a high clustering coefficient and a low characteristic path length, presumably representing the most optimal network configuration in many real-world networks.
- **Synchronization:** when two dissipative systems are coupled in time
- **Time-signal:** (in our case) the recorded EEG-trace from one electrode

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Figure 1 (p. 22)

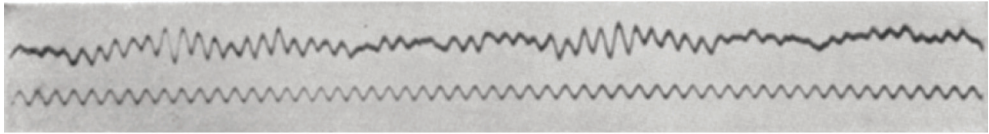
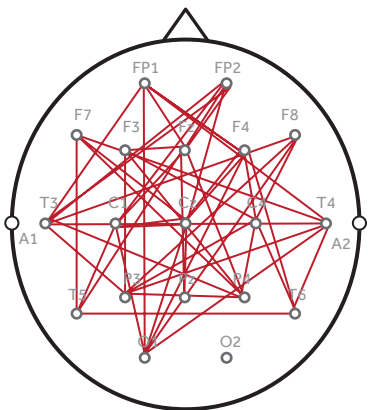
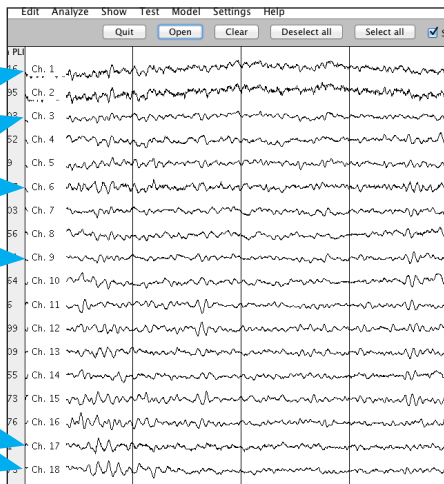
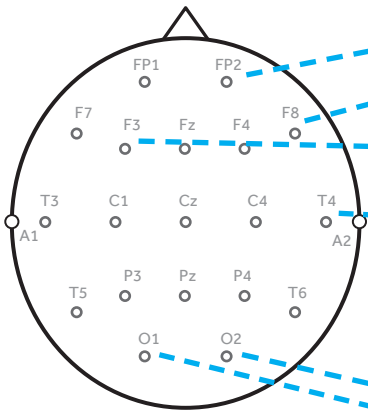


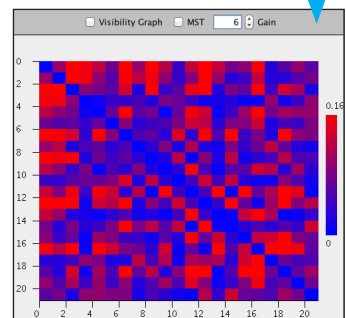
Figure 2 (p.22)

Brain Electrode positions according to 10-20 system

EEG time series



Connectivity matrix



Functional brain network

Figure 1

First human EEG, recorded by Hans Berger. Source: Berger H. Über das Elektrenkephalogramm des Menschen. Archives für Psychiatrie. 1929; 87:527-70

Figure 2

Schematic representation of how a brain network is derived from EEG times series, through the calculation of a connectivity matrix. Each electrode produces a time series. The synchronization between each pair of electrodes is calculated and a connectivity matrix is obtained. From the connectivity matrix, the brain network can be derived.