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General introduction
Patients with dementia are progressively robbed of their cognitive and behavioral functions, eventually leading to an inability to function independently. Especially in its later stage dementia poses a major burden on patients, their caregivers and social health services.

The number of patients with dementia in the Netherlands is estimated to be more than 195,000. The prevalence increases dramatically with age, to the effect that no less than 30% of persons older than 85 years suffer from dementia. As the Dutch population ages rapidly, the number of patients with dementia is expected to surpass 590,000 in 2050 [65]. Worldwide there are an estimated 24 million people with dementia, which is expected to increase to 81 million by 2040 [66]. Developing countries such as China and India will be responsible for much of the increase.

The criteria described in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV) are often used by clinicians to recognize dementia [4]. In short, these criteria characterize dementia by progressive memory impairment and at least one or more of the following cognitive disturbances: aphasia (language disturbances), apraxia (impaired motor activities despite intact motor function), agnosia (impaired perception) and disturbances in executive functioning (problems with planning, organizing and abstract thinking). These cognitive deficits cause significant impairments in social or occupational functioning.

Dementia can be caused by various diseases including, among others, Alzheimer’s disease and Huntington’s disease. Although many aspects of these diseases differ considerably, including the nature of neuropathological changes, disease manifestation, prevalence and age at onset (Table 1), the two diseases have a preclinical phase in common during which neuronal degeneration occurs but clinical signs are not yet apparent [14]. This preclinical phase provides a major opportunity to research ‘markers’ of disease onset and progression which will be useful when neuroprotective treatments become available.

**Alzheimer’s disease**

Alzheimer’s disease (AD) is the most common cause of dementia. It is characterized by progressive deterioration of memory and other cognitive functions, increasing problems with daily living and neuropsychiatric problems such as depression or apathy [12]. In a Dutch study, AD accounted for 72% of cases of dementia [38]. AD mostly affects the elderly and usually starts around 70 or 80 years of age. Based on the presence of cognitive deficits such as aphasia, apraxia
and agnosia caused by cortical damage, AD is known as a cortical-type dementia.

Table 1. Main characteristics of Alzheimer’s disease (AD) and Huntington’s Disease (HD)

<table>
<thead>
<tr>
<th>Age at onset</th>
<th>Cause of neuronal degeneration</th>
<th>Diagnosis</th>
<th>First symptom</th>
<th>Brain damage</th>
<th>Pre-clinical stage</th>
<th>Cognitive End-point</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>mostly after 65 years of age</td>
<td>hypothesized amyloid cascade leading to accumulation of neuritic plaques and tangles</td>
<td>no definite test during life</td>
<td>memory deficit?</td>
<td>cortical</td>
<td>memory deficit, but not demented</td>
</tr>
<tr>
<td>HD</td>
<td>mostly around 40 years of age</td>
<td>genetic deficit leading to formation of the mutant Huntingtin protein</td>
<td>genetic test</td>
<td>motor abnormalities?</td>
<td>subcortical and later also cortical</td>
<td>mutation carrier, but no motor abnormalities</td>
</tr>
</tbody>
</table>

To establish the diagnosis of probable Alzheimer’s disease, the most commonly used criteria are those of the National Institute of Neurological and Communication Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) (Table 2) [34]. A definite diagnosis of AD requires the presence of neuritic plaques and neurofibrillary tangles in postmortem brain material to a degree exceeding expectations based on age [60]. AD is characterized by global cortical atrophy, starting in the medial temporal lobes and progressing to other cortical areas with increasing disease severity [35]. There is currently no cure for AD, but pharmacological therapies are available for symptomatic treatment, such as cholinesterase inhibitors and glutamate modulators [30]. Furthermore, cognitive training has proven useful in improving cognitive functions, activities of daily living, depression, and self-rated general functioning in Alzheimer’s patients [54].

Table 2. NINCDS-ADRDA criteria for probable Alzheimer’s disease [34]

- Dementia established by clinical examination and confirmed by neuropsychological tests
- Deficits in two or more areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40 and 90, most often after age 65
- Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition
Mild cognitive impairment

In the early 19th century Prichard was the first to describe the earliest stage of dementia, which he characterized as impairment of recent memory with an intact ability to remember persons or events of the distant past [48]. Later, terms such as ‘benign senescent forgetfulness’, ‘questionable dementia’ and ‘mild cognitive impairment’ were used to identify roughly the same stage [15]. The concept of mild cognitive impairment is now widely used to characterize the transitional zone between normal aging and dementia [5, 42-44, 46]. Several subtypes of mild cognitive impairment, with different presumed etiologies (i.e. degenerative, vascular and psychiatric) have been described [15, 42]. These subtypes are based on neuropsychological profiles, with the main distinction being an impairment in either amnestic or non-amnestic domains (Table 3).

Table 3. Possible causes of mild cognitive impairment per subtype

<table>
<thead>
<tr>
<th>Amnestic mild cognitive impairment</th>
<th>Degenerative</th>
<th>Vascular</th>
<th>Psychiatric</th>
<th>Medical disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single domain</td>
<td>Alzheimer’s disease</td>
<td></td>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Multiple domain</td>
<td>Alzheimer’s disease</td>
<td>Vascular dementia</td>
<td>Depression</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-amnestic mild cognitive impairment</th>
<th>Single domain</th>
<th>Multiple domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontotemporal dementia</td>
<td>Dementia with Lewy bodies</td>
<td>Vascular dementia</td>
</tr>
</tbody>
</table>

Possible causes of mild cognitive impairment shown per subtype. Subtypes are based on neuropsychological profiles, with either amnestic or non-amnestic impairment, and either one or more cognitive functions impaired. The common factor for each subtype of mild cognitive impairment is that the patient is neither normal nor demented, has intact activities of daily life and intact or only minimally impaired complex instrumental functions. Adapted from references 15 and 46.

Patients showing an isolated amnestic disorder (henceforth called MCI) are thought to be at high risk of AD or depression [15]. MCI patients experience abnormal memory loss, but have no problems in other cognitive areas, and function adequately in daily life (Table 4). On memory tests, MCI patients function at a level in between those of normal aging and AD (Fig 1). There are no sharp transitions but rather a
gradient of memory performance. The rate of transition from MCI to un-debatable AD is estimated to be 10%-15% annually [45], while healthy controls convert to AD at a rate of only 1-2% per year [33]. The remaining MCI cases remain stable or even return to their normal level of functioning. The explanation for their temporary memory impairment varies from unknown to other somatic disorders (e.g. epilepsy), psychiatric disorders (e.g. depressive episode) or alternative factors (e.g. fatigue or medication effects) [32, 62].

Faced with the uncertain future of a patient with MCI, physicians are challenged to identify those patients who will develop dementia. In principle this may make early therapeutic intervention possible, thereby reducing health care costs and improving quality of life [31, 33]. Electroencephalography (EEG) is a potentially valuable technique for identifying those MCI patients likely to progress to dementia; it is sensitive to subtle changes in brain function and is widely available, non-invasive and cost-effective.

**Table 4.** Criteria for amnestic mild cognitive impairment [43]

- Memory complaint, preferably corroborated by an informant
- Impaired memory function for age and education
- Preserved general cognitive function
- Intact activities of daily living
- Not demented

**Fig 1.** Visual reproduction test

![Visual reproduction test](image)

Performance of a control subject, a patient with MCI and a patient with AD on a visual reproduction test. The subjects were asked to memorize a figure (top row) for 10 seconds and then reproduce the figure by means of a drawing.
Huntington’s disease

Huntington’s disease (HD) is an autosomal dominantly inherited disease characterized by disorders of movement (chorea and hypokinesia), cognition (dementia) and behavior (e.g. depression and apathy). Cognitive changes in HD include forgetfulness, mental slowing, impaired cognitive flexibility and impaired psychomotor skills. The underlying cause of HD is an extended trinucleotide (CAG) repeat in a gene located on the short arm of chromosome 4 [59]. In healthy individuals the number of repeats is below 27, while 36 repeats or more indicate that the individual will develop HD. This abnormal stretch of DNA produces abnormalities on the protein 'Huntingtin', in turn leading to neurodegeneration starting in the striatum [61]. Furthermore, thalamic, frontal, temporal and parietal atrophy have been observed in the preclinical stages of HD [22, 56]. Genetic testing allows individuals with a family history of HD to be informed about their genetic status with more than 99% accuracy [59]. In the Netherlands, the number of patients and individuals at risk are estimated at 1200 and 6000 respectively [50]. The mean age of onset is around 40 years [51]. However, because of the great variety in symptoms and the gradual development of HD it is difficult to determine the time of onset with any precision. In practice, HD is considered clinically apparent when motor symptoms first appear in someone with a background of a positive family history and confirmation of the genetic deficit. At present there are no ways to prevent or cure HD, but medication is available to suppress choreic symptoms and alleviate neuropsychiatric problems.

As genetic testing allows mutation carriers and non-mutation carriers to be distinguished with almost complete confidence in the ‘preclinical’ phase of HD, much research has focused on identifying the very first manifestations of HD in terms of cognitive, psychological and motor functioning [11, 40, 63]. Unraveling the earliest disease manifestations in HD will be of critical importance in the development and evaluation of neuroprotective trials, which may eventually result in delaying disease onset. Recently, structural and functional neuroimaging have become popular tools for identifying brain changes in preclinical mutation carriers [39, 49, 52]. Few studies focused on the EEG, even though this technique has certain advantages and can potentially reveal early functional brain changes in the preclinical phase of HD.
Electroencephalography (EEG)

The EEG is a non-invasive, cost-effective and easily available tool that records the electrical activity of cortical neurons, thereby providing a direct measure of brain function. The scalp EEG typically consists of about 20 channels, each representing the difference in voltage between at least two scalp sites plotted over time. The main source of EEG activity is synchronous electrical activity in the cerebral cortex [36]. The EEG reflects a multitude of processes, ranging from primary sensory processing and motor planning to emotions and complex cognitive processes. For example, in research with healthy subjects direct links have been found between memory and perception skills on the one hand and frequency and power of brain oscillations on the other hand [6, 24-29]. For clinical purposes the EEG is usually described in a qualitative manner; for example, the EEG of an AD patient can be characterized as exhibiting 'diffuse slowing' (Fig 2). In order to capture and quantify the changes more subtly a quantitative assessment is necessary. As power and coherence analyses are readily available in commercial software packages and thus available for clinical use, these techniques will be used in this thesis.

Despite being non-invasive, cost-effective and easily available, the EEG is not often used in the clinical practice of dementia [1]. This might be related to the finding that the EEG, while highly sensitive to all causes of organic brain damage, is not specific to the cause of an abnormality. The EEG might however be valuable in distinguishing between ‘progressive’ MCI based on a neurodegenerative process and ‘reversible’ MCI with another somatic or a psychiatric basis. In HD, the EEG can provide markers of disease onset by revealing the first functional brain changes. Furthermore, the EEG is potentially useful in monitoring the effects of (future) neuroprotective therapies.

In most clinical EEG studies registration is limited to conventional conditions, such as rest with eyes closed or eyes open. However, the EEG during rest conditions only becomes abnormal in the later stages of neurodegeneration, when patients already suffer from dementia [64]. There is evidence to suggest that, when introducing a verbal, olfactory or memory challenge during registration, the EEG does reveal abnormalities in MCI [20, 21, 37, 41, 47]. The concept of probing the weakest spot is very common. Two examples may suffice: muscle weakness is best brought to light by asking patients to contract at maximal strength, and complaints of reduced attention can be put to the test by asking patients to perform a test that requires prolonged intense attention.
Fig 2. EEG samples of a control subject (above) and an Alzheimer’s patient

Samples of 10 seconds EEG registered during rest eyes closed in a control subject (above) and a patient with Alzheimer’s disease. Diffuse slowing can be seen in the EEG of the Alzheimer’s patient.

The concept of ‘probing for weakness’ can possibly be generalized to reactivity of the EEG as well; it seems intuitive that EEG reactivity may suffer in dementia as more brain resources are needed in a challenging task. Such resources might not be available in patients suffering from cognitive impairment. As memory impairment is the defining criterion of
MCI and is amongst the first cognitive changes in HD, we believed that the EEG during memory activation might be most sensitive in capturing early neurodegenerative changes. Therefore, in this thesis, in addition to using conventional conditions (‘eyes closed’ and ‘eyes open’), the EEG was registered while challenging memory (for an impression see Fig 3).

**Fig 3.** Experimental EEG setup

In a dimly lit room the participant is sitting in front of a computer screen on which stimuli (i.e. words or pictures) are presented. He is asked to memorize them. Meanwhile, EEG registration takes place.

**EEG in Alzheimer’s disease**

The most characteristic phenomenon described in early to mildly severe AD is slowing of the EEG, i.e., increased theta activity (4-8 Hz) combined with decreased alpha (8-12 Hz) and beta activity (13-20 Hz) [2, 3, 8, 19, 57] (Fig 2). In the moderate to severe stages, delta activity (1-4 Hz) was found to increase as well [3]. These EEG changes were widespread over the brain. Furthermore, the degree of EEG abnormality was related to the degree of cognitive impairment. For example, in demented patients increased theta activity in the EEG was found to be correlated with lower scores on the Mini Mental State Examination (MMSE) [9].

In MCI, the EEG during rest with the eyes closed, as conventionally used in daily clinical routine, revealed no differences with cognitively unimpaired controls [17, 18, 55, 64]. However, when using activation paradigms, such as memory activation, olfactory stimulation and verbal tasks, EEG abnormalities became apparent [20, 21, 37, 41, 47]. Interestingly, some studies found evidence for compensatory activity in MCI [20, 21, 47] whilst others found decompensatory activity [37, 41]. In follow-up studies, the baseline EEG during eyes closed was different
in MCI patients that progressed to AD within 14 to 25 months as compared to MCI patients that remained stable [16, 17, 53]. Progressed MCI patients showed higher delta, theta and alpha 1 power, lower beta power, slowing of mean frequency and altered fronto-parietal coherence. Challenging weak cognitive functions, particularly memory functions, might enhance EEG differences between MCI patients reversing back to normal, stable MCI and progressive MCI.

**EEG in Huntington’s disease**

In patients with dementia caused by HD EEG slowing has also been described. The degree of slowing was related to the degree of functional and cognitive impairment [58]. In this respect, the EEG of AD and HD patients is similar. In mild to moderate HD a slightly different pattern emerged, with decreased global alpha and frontal theta power and increased global delta and beta power [7, 10]. In an early study by Bylsma et al. increased frontal delta and beta power were found to best reflect the severity of neurological impairment [10]. As the frontal lobes are intimately connected to the basal ganglia, it was hypothesized that the loss of striatal-cortical inhibitions resulted in the faster beta frequencies observed in the EEGs of HD patients. To the best of our knowledge only one previous study focused on EEG changes in preclinical mutation carriers. In that study, alpha activity during rest was reduced in comparison to controls [13]. However, no associations with cognitive impairment were found. This study used a neural network which successfully discriminated patients and mutation carriers from controls despite a small number of subjects. As neuropsychological studies have described subtle changes in executive functioning and picture memory in preclinical mutation carriers [23, 63], EEG combined with memory or executive tests might reveal additional EEG changes in preclinical HD.
Aims of the thesis

The first objective of this thesis project was to investigate whether the EEG during memory activation, as compared to the EEG during rest conditions, would reveal abnormalities in brain functioning in patients who find themselves in a preclinical, or 'at risk' stage of dementia. As memory loss is amongst the first symptoms of dementia, we hypothesized that EEG abnormalities would become apparent when activating memory functions during EEG registration. To this end we first investigated memory-related EEG changes in MCI patients. After preliminary promising results we took interest in an alternative group of patients in a preclinical stage of dementia, i.e., preclinical HD mutation carriers.

Our second objective was to examine relations between EEG parameters, gathered during both rest and memory activation, and cognitive functions in elderly subjects within a continuum of cognitive decline, i.e., elderly volunteers without cognitive impairment, patients with MCI and patients with AD. We hypothesized that the EEG would be related to cognitive functioning and can provide predictors of cognitive decline.

Chapter 2 reports our first exploratory study describing the EEG during several memory activation paradigms in MCI patients and elderly subjects without objective cognitive deficits. Based on this study we decided to focus on the EEG during picture memory in subsequent studies.

Chapter 3 describes a study on the relation between cognitive functions on the one hand and structural MRI and EEG parameters on the other. This study was performed in elderly subjects from the entire spectrum of cognitive decline, including elderly volunteers without cognitive impairment, patients with MCI and patients with AD. It is discussed whether cognitive functions are best reflected in EEG parameters, structural MRI parameters or a combination of both.

Chapter 4 focuses on the question whether the EEG during memory activation is abnormal in preclinical HD mutation carriers.

Chapter 5 is an elaboration on chapter 3 as it further describes relations between EEG parameters (including EEG power and coherence) and cognitive functioning in several domains, i.e., global cognition, memory, language and executive functioning.

Chapter 6 addresses a notorious methodological problem in EEG research, i.e., artifacts due to eye movements, blinks and electromyographic activity. Instead of viewing these as mere noise, we took a different viewpoint and tested whether electromyographic activity might have a story to tell about MCI and AD.
Chapter 7 describes results from our longitudinal study. At baseline, elderly volunteers without cognitive impairment, patients with MCI and patients with AD underwent a neuropsychological examination and EEG registration. After 20 months the neuropsychological examination was repeated. We report on relations between baseline EEG parameters and future cognitive performance.

Chapter 8 provides a general discussion and conclusions. The main findings and their implications for future clinical and research purposes are discussed. Furthermore, several important methodological issues will be raised.

Chapter 9 summarizes the main findings of this thesis.
References


