9

Summary
Dementia can be caused by various diseases including, among others, Alzheimer’s disease (AD) and Huntington’s disease (HD). Although many aspects of these two diseases differ considerably, both are preceded by a ‘preclinical phase’ during which neuronal degeneration occurs but clinical signs are not yet apparent. In many cases, amnestic mild cognitive impairment (MCI) can be considered a preclinical phase of AD, although some MCI patients remain stable or even return to their normal level of functioning. In HD genetic testing allows mutation carriers to be identified regardless of the onset of motor, cognitive or psychiatric symptoms. This preclinical phase creates a major research opportunity to discover ‘markers’ of disease onset and progression, which is extremely important for the development and evaluation of neuroprotective therapies. The EEG is a promising tool in this respect as it is sensitive to subtle changes in brain functioning and has the advantages of being non-invasive, cost-effective and easily available. However, the EEG during conventional rest conditions (i.e. ‘eyes’ closed and ‘eyes open’) only becomes abnormal in the later stages of neurodegeneration, when patients already suffer from dementia. There is evidence to suggest that the yield of EEG studies can be extended using activation paradigms. As memory loss is among the first symptoms of dementia, we hypothesized that early changes in brain function would be revealed when using a memory challenge during EEG registration.

The first objective of this thesis was to investigate whether the EEG during memory activation, as compared to the EEG during rest conditions (eyes closed and eyes open), could reveal abnormalities in brain functioning in patients who find themselves in a preclinical stage of dementia. We hypothesized that EEG abnormalities would become apparent when activating memory during EEG registration.

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., cognitively unimpaired elderly, patients with MCI and patients with AD. We hypothesized that the EEG would be related to cognitive functioning and can provide markers of cognitive decline.

Chapter 2 reported on our first exploratory study into EEG power changes during memory activation in patients with MCI. Twelve MCI patients and 16 age-matched volunteers without cognitive impairment underwent EEG registration during two conventional EEG conditions (eyes closed and eyes open) and three memory conditions (word memory, picture memory and animal fluency). For all memory conditions, EEG power in theta (4-8 Hz), lower alpha (8-10.5 Hz) and upper alpha (10.5-13 Hz) bands was expressed as the percentile change...
as compared to eyes closed. We found that MCI patients showed significantly less reactivity in the lower alpha band than controls during picture memory activation. The word memory task showed a trend towards a similar effect. No differences between groups were found during the eyes closed and eyes open conditions. We concluded that memory activation reveals EEG differences between MCI patients and controls while the EEG during eyes closed and eyes open does not.

In chapter 3 we investigated whether cognitive function in the spectrum of ‘normal’ aging to AD was best reflected in parameters derived from the MRI, the EEG, or a combination of both. Cognitive functions were tested in 33 elderly subjects: 10 with AD, 11 with MCI and 12 volunteers without cognitive impairment. Structural brain parameters were derived from conventional MRI (providing a measure of brain atrophy) and a MR-technique called Magnetization Transfer Imaging (providing measures of gray and white matter integrity). The EEG provided measures of brain function. We performed multiple linear regression analyses to relate EEG and MRI parameters to global cognition, memory, language and psychomotor speed. The regression model showed EEG alpha reactivity upon eyes opening to be the primary factor associated with global cognition, memory and language skills. Brain atrophy as revealed by MRI was the primary factor associated with psychomotor speed. Furthermore, EEG alpha reactivity upon eyes opening explained significant additional variability in psychomotor speed. We concluded that EEG and MRI are each associated with different aspects of cognitive functioning and complement each other in their relations to psychomotor speed.

In chapter 4 we studied whether the EEG during memory activation revealed abnormalities in preclinical HD as it did in MCI. To this end, 16 mutation carriers for HD and 13 non-mutation carriers underwent neurological, neuropsychological, MRI and EEG investigations. The EEG was registered during rest eyes closed and memory activation. In each condition we determined absolute power in the theta and alpha bands and subsequently calculated relative alpha power. We found that the EEG during eyes closed did not differ between groups. The EEG during memory activation showed less relative and less absolute alpha power in mutation carriers compared to non-mutation carriers, even though their memory performance was similar. No correlations were found between absolute and relative alpha power on the one hand and neuropsychological scores, motor scores or number of CAG repeats on the other. We concluded that memory activation reveals functional brain changes in HD before clinical signs become overt.
In chapter 5 we examined relations between EEG power and coherence measures on the one hand and performance on tests of global cognition, memory, language and executive functioning on the other hand. Sixteen patients diagnosed with AD, 18 patients with MCI and 22 volunteers without cognitive impairment underwent neuropsychological and EEG investigations. We used the following EEG measures: theta relative power during eyes closed, alpha reactivity during memory activation, and alpha coherence during eyes closed and memory activation. We found that increased theta relative power was related to decreased performance in global cognition, memory, language and executive functioning. Decreased alpha reactivity was related to decreased performance on tests of global cognition, memory and executive functioning. Alpha coherence was unrelated to cognition. We concluded that EEG power measures are associated with performance on tests of global cognition, memory, language and executive functioning, while coherence measures are not.

Chapter 6 addressed a methodological problem in EEG research, i.e., artifacts due to eye movements, blinks and electromyographic (EMG) activity. Many efforts have been directed to decrease their influence on the EEG, a problem that is particularly bothersome in severely demented patients. However, these ‘artifacts’ might have a story to tell and might reflect some aspects of dementia just as the EEG does. Eleven patients diagnosed with AD, 13 with MCI and 13 age-matched volunteers without cognitive impairment underwent EEG registration. We measured theta relative power during eyes closed and alpha reactivity upon eyes opening and memory activation. Frontal and temporal 50-70 Hz activity was registered as a measure of EMG activity. The area under the curve in the Receiver Operating Curves (ROC) was used as an indicator of how well a parameter distinguishes between groups. We found that the EEGs of AD patients displayed higher theta activity, less alpha reactivity and more frontal EMG than the EEGs of age-matched controls. Interestingly, increased EMG activity indicated higher cognitive impairment and more depressive complaints. EEG variables on the whole distinguished better between the groups than EMG variables. However, for the distinction between MCI and controls, an EMG variable had the highest area under the ROC curve. We concluded that EMG activity in the EEG is more than noise; it differs systematically between groups and is apparently related to cerebral functions.

Chapter 7 described an exploratory follow-up study in which we researched whether baseline EEG parameters gathered during eyes closed, eyes open and memory activation could provide markers of cognitive performance assessed 20 months afterwards. Forty elderly subjects, i.e., 21 volunteers without cognitive impairment, 11 patients
diagnosed with MCI and 8 patients with AD underwent baseline EEG registration and neuropsychological examination. The latter examination was repeated at follow-up. We assessed relations between EEG measures and future cognitive performance (i.e. global cognition, memory, language and executive functioning), controlling for age, follow-up time and baseline cognitive performance. Regression models were constructed to predict performance on the Cambridge Cognitive Examination (CAMCOG), a widely used tool within dementia screenings. Baseline EEG measures, i.e., increased theta activity (4-8 Hz) during eyes closed and less alpha reactivity (8-13 Hz) during eyes open and memory activation, indicated lower global cognition, language (trend significant) and executive performance at follow-up. A regression model combining baseline cognitive and EEG measures provided the best prediction of future CAMCOG performance (93%). EEG and cognitive measures alone predicted respectively 43% and 92% of variance. We concluded that EEG and cognitive measures combined provided the best prediction of future cognitive performance. Although the ‘cognition only’ model showed similar predictive value, the EEG provided significant additional value.

**Main findings**

The results presented in this thesis portray the EEG as a potentially valuable tool for studying brain changes leading up to dementia. The EEG proved sensitive to early brain changes even when using a set of simple, easily obtainable, global EEG parameters. We have successfully demonstrated the additional value of ‘probing the weak spot’ during EEG registration, i.e., memory activation. In both MCI patients and preclinical HD mutation carriers memory activation revealed EEG abnormalities while the EEG during conventional rest conditions did not (chapters 2 and 4). Furthermore, we discovered relations between EEG parameters and cognition. EEG power measures gathered during eyes closed, eyes open and memory activation were related to both baseline and future cognitive performance (chapters 3, 5 and 7). Finally, our results suggest that EEG data can best be combined with neuropsychological and structural MRI data when searching for early markers of dementia (chapters 3 and 7). Interestingly, we also discovered that EMG activity, which is usually regarded as noise, was correlated with depressive complaints and cognition (chapter 6). Apparently, EMG activity in the EEG is more than noise and may reflect other functions than the EEG. Although we do not suggest that EMG parameters should henceforth be used to diagnose dementia or depression, we do suggest that when searching for early markers of dementia it may pay to keep an open mind.
Conclusions

Our results imply that the EEG is a potential marker of cognitive decline and dementia, particularly when combining rest and memory activation conditions. However, further study is needed to clarify the pattern of EEG changes leading up to dementia. It seems that EEG changes do not necessarily follow a linear pattern of decline but may be influenced by cognitive reserve mechanisms that modulate EEG activity. At present, we do not believe that the EEG should be used as a single diagnostic marker of AD in the sense that a cut-off value on some EEG measure determines who will progress to AD. However, it can be envisioned that the EEG is used in combination with other diagnostic tools, such as neuropsychological testing and structural MRI, to determine a ‘risk profile’ for MCI patients. While certain profiles would be suggestive of progression to dementia, others would suggest reversion to a normal state. This prognostic information could be used by clinicians in the choice of treatment and counseling strategies. In a similar manner, the EEG might provide information concerning disease manifestation and progression in preclinical HD mutation carriers. In both MCI and HD mutation carriers, information on the disease process will be essential for timing neuroprotective treatments, when they become available.