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EEG during memory activation: a study of early functional brain changes in Alzheimer's disease and Huntington's disease

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General discussion & conclusions

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, amnesic 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, 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.

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.

In this chapter the main findings are discussed and a number of important methodological issues are raised. The chapter closes with implications for clinical practice and suggestions for future research.

Main findings

1. Memory activation reveals EEG abnormalities in MCI while the EEG during conventional rest conditions (i.e. rest eyes closed and eyes open) does not.

In previous research it was found that the EEG during rest eyes closed - as conventionally used in daily clinical routine- revealed no differences between MCI patients and cognitively unimpaired controls [12, 13, 33, 41]. As memory impairment is among the first neuropsychological manifestations of AD [2, 15], we hypothesized that memory activation could reveal abnormalities in brain functioning in MCI patients. In the exploratory study described in chapter 2 we found that MCI patients, as compared with controls, showed significantly less reactivity in the lower alpha band during picture memory activation. Interestingly, there were no differences between groups in the rest conditions. Our findings confirm that EEG during memory activation is more sensitive to altered brain activity in MCI than conventional EEG. Although memory activation is our first choice in activation paradigm, in future studies it may also be useful to activate other cognitive functions known to be impaired early in the neurodegenerative process in AD, such as perceptual speed [2] .

2. Memory activation reveals EEG abnormalities in preclinical HD while the EEG during rest eyes closed does not.

Little research is available on EEG changes in preclinical HD. Our literature search revealed one neural network study in preclinical mutation carriers that found reductions in alpha activity in the EEG during rest eyes closed [8]. As with AD, memory impairment is among the first neuropsychological manifestations of HD [7, 40]. We therefore examined whether memory activation would reveal EEG abnormalities in preclinical HD mutation carriers (chapter 4). We found that the EEG during picture memory activation showed less relative alpha power in mutation carriers as compared to non-mutation carriers. No differences were found during rest eyes closed. These findings confirm that the EEG during memory activation is sensitive to brain changes in preclinical HD. It may be of interest to also study the EEG during other functions that are impaired early in HD, such as motor or psychomotor functioning [17, 22, 40].

3. EEG power measures gathered during eyes closed, eyes open and memory activation are related to both baseline and future cognitive performance.

Most studies relating EEG measures to cognitive functions in the elderly focused on compound cognitive tests such as the Mini Mental State Examination (MMSE), Global Deterioration Scale (GDS) or Cambridge Cognitive Examination (CAMCOG) [5, 14, 21, 31]. Relations were found between higher theta activity during rest and lower alpha activity during memory activation on the one hand and decreased MMSE or GDS scores on the other hand. In the current thesis we elaborated on these findings using a wider variety of EEG conditions (i.e. eyes closed, eyes open and memory activation). Furthermore, we examined more specific cognitive functions impaired in dementia, i.e., memory, language and executive functioning.

In a study of 33 elderly subjects, we discovered that the main EEG variable associated with cognitive functioning was alpha reactivity upon eyes opening. This variable was found to be positively related to performance on tests of global cognition, memory, language and executive functioning (chapter 3). EEG parameters gathered during eyes closed and memory activation were also related to cognition. We found that increased theta relative power and lower mean frequency during eyes closed were associated with worse performance on tests of global cognition, memory, language and executive functioning. During memory activation, less alpha reactivity was associated with worse memory performance. In a second study with a larger group of 56 elderly subjects we investigated EEG power and coherence parameters gathered during eyes closed and memory activation. We found that increased theta relative power during eyes closed was related to decreased global cognition, memory, language and executive functioning (chapter 5). During memory activation, less alpha reactivity was related to worse performance on tests of global cognition, memory and executive functioning, but not language. Interestingly, alpha coherence was unrelated to cognition. In summary, these two cross-sectional studies showed that power measures reflecting slowing and decreased reactivity of the EEG are associated with decreased performance in a wide range of cognitive functions. These EEG power measures might prove useful in prospective studies aimed at predicting longitudinal cognitive decline.

In a small prospective study we investigated the value of EEG parameters gathered during rest eyes closed, eyes open and memory activation in predicting cognitive performance after 20 months (chapter 7). We were able to include 40 elderly subjects with different levels of cognitive functioning and controlled for age, follow-up time and baseline

cognition. Unfortunately, the number of AD patients was limited and not all AD patients completed all tests. Nevertheless, we found that increased baseline theta relative power during eyes closed indicated lower global cognition and executive performance at follow-up. Alpha reactivity upon eyes opening was positively related to future language and executive performance at trend significance. Furthermore, decreased alpha reactivity during memory activation was related to decreased follow-up global cognition, again at trend significance.

In conclusion, we found that EEG power parameters are related to both baseline and future cognitive performance. Although the EEG showed moderate predictive value, the results from our small prospective study encourage further study into EEG changes leading up to dementia.

4. When searching for markers of cognitive decline a combination of the EEG with neuropsychological and structural MRI data is advocated.

Recent studies have highlighted the use of neuroimaging tools (MTI, (f)MRI, SPECT, PET), neuropsychological tests and the EEG as early markers of AD [2, 13, 19, 20, 29, 41]. However, no single marker has come forward as the best marker for AD. The solution might consist of a combination of the above mentioned techniques. In line with this reasoning, we created models of cognition using a combination of EEG and MRI variables (chapter 3). We found that EEG alpha reactivity during eyes open and global brain atrophy were each associated with different cognitive functions and complemented each other in their relations to psychomotor speed. Furthermore, in a follow-up study we discovered that a combination of baseline global cognition, executive functioning and theta relative power during eyes closed best predicted future global cognitive performance (chapter 7). Unfortunately, the number of subjects with MRI results was too small to also include this factor in the predictive model. Based on these studies, it seems plausible that a combination of findings from EEG, structural MRI and neuropsychology better reflects early AD than each technique used separately.

Methodological issues

Study sample

The main part of this thesis focused on elderly subjects with different levels of cognitive impairment recruited through the outpatient memory clinic. After three years of data collection the number of patients remained relatively low. There were several reasons for this, the most important being: (1) the exclusion of patients using psychotropic medications (2) the exclusion of patients with vascular pathology on

MRI, and (3) patients with no wish to participate in research. Our selection criteria were obviously based on excluding potential confounding effects. In practice this means that we only examined the EEG as a potential diagnostic tool in a selective patient group, thereby limiting its clinical utility. More specifically, our selection criteria possibly created a bias towards an MCI sample more likely to be in a preclinical stage of AD as opposed to preclinical vascular dementia (no vascular pathology on MRI) or depression (most common users of psychotropic medications). As our main intention was to eventually be able to use the EEG as a prognostic tool for all MCI patients, future studies might use more lenient criteria. Of course, record should be kept of any potential confounding factors. These factors can be statistically controlled for later on (e.g. by using white matter lesion load as an indicator of vascular pathology) or can be used to create subgroups of MCI patients (e.g. high or low level of vascular pathology on MRI).

We rigorously excluded the use of any psychotropic medication, while not all medications have observable effects on the EEG. We did so to reduce the number of possibly confounding factors. However, exclusion of all psychotropic medication will restrict the use of the EEG in clinical practice, as many patients use such drugs. In future studies, more detailed research might reveal whether such medication indeed affects the EEG, and whether this harms the assessment of dementia-related variables.

Finally, cooperation with several other memory clinics could help increase the number of participants.

Follow-up study

Even though this thesis included a fairly small follow-up, some issues concerning longitudinal studies should be addressed.

We experienced a fairly high drop-out rate (24%) due to death, illness and motivational factors. An often encountered problem is that those subjects that drop out are usually among the more impaired subjects at baseline neuropsychological assessment. This means that a selection of cognitively less impaired subjects inevitably takes place, which was also the case in our study sample. We therefore did not capture the entire spectrum of cognitive aging. However, for clinical practice this might not be a problem as we are particularly interested in cognitively less impaired subjects that find themselves in a preclinical stage of Alzheimer's disease.

Another issue with follow-up studies is that there is a chance of practice effects with repeated neuropsychological testing. This happens not only because subjects become familiar with the general design of the neuropsychological tests, but also because they usually feel more at

ease. These practice effects positively biased cognitive performance at follow-up, particularly in cognitively unimpaired elderly subjects.

EEG parameters

A difficulty with EEG research in dementia is the large diversity of parameters and techniques used. This makes it hard to compare research findings. A few examples are the use of fixed versus individually adjusted frequency bands [11, 16] or the use of linear (e.g. coherence) [14, 38] versus non-linear measures (e.g. synchronization likelihood) [30, 33]. These differences are in part based on the purpose of the study, i.e., research with a direct clinical application requires other methods than more fundamental research into the pathophysiology of dementia.

Our focus on possible clinical utility explains our preference for a small set of easily available, evidence-based EEG parameters that cannot be affected overly by recording problems. The trade-off is that we were unable to look into location effects or examine a wider frequency range. Research into the pathophysiology of dementia might focus on new ways to measure neuronal activity. For example, previous research using a more refined and detailed approach have unraveled interesting EEG and MEG abnormalities in MCI and AD [3, 4, 10, 33-35]. Hopefully, this type of research will eventually also lead to new clinical tools.

MCI

The diagnostic criteria for MCI have been the subject of much debate and subsequent refinement over the years [9, 18, 23-28]. Several MCI subtypes with different presumed etiologies (i.e. degenerative, vascular and psychiatric) have been described. As a result of these ongoing refinements various different MCI criteria have been proposed and used, hindering the comparison of results.

In the current study we used a set of MCI criteria that were defined at the start of the research project, while alternative criteria were defined afterwards. Consensus on MCI criteria should soon be reached and uniformly used in research [6].

Another approach is to abandon the use of diagnostic states such as MCI and AD and instead use a score of underlying cognitive impairment as an outcome measure. An advantage of this approach is that the artificial boundaries between 'normal aging', MCI and AD are let go and the presence of a gradual continuum of cognitive decline is appreciated. In a follow-up study we took such an approach and aimed to predict future cognition. However, we experienced several practical limitations. That is, which cognitive test score should be used? and why focus solely on cognition instead of including, for example, scores on tests for functional impairment or neuropsychiatric tests? A diagnostic label such as AD is commonly based on several sources of information and not just on a

cognitive test. It seems that predicting progression to another diagnostic state (from 'normal aging' to MCI or from MCI to AD) is simply more comprehensible and best usable in clinical practice [28].

Conclusions

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. Furthermore, we discovered relations between EEG parameters and (future) cognition. Finally, our results suggest that EEG data can best be combined with neuropsychological and structural MRI data when searching for early markers of dementia. Our results have the following implications:

1. The EEG is a potential marker of cognitive decline and dementia, particularly when combining rest and memory activation conditions

The EEG is not often used in the standard diagnostic work-up of dementia. A possible reason is that it is unable to sufficiently distinguish between types of dementia or to detect true dementia in a preclinical stage. However, these findings are based on the EEG during 'conventional' conditions such as rest eyes closed and eyes open. In this thesis it was found that when using memory activation during EEG registration early brain changes can be observed in MCI and preclinical HD (chapter 2 and 3). Apparently, the EEG during memory activation is sensitive to brain changes in the preclinical or 'at risk' stage of dementia. Furthermore, in follow-up research we discovered that EEG power measures during both rest and (at trend significance) during memory activation were associated with cognitive performance after an average time interval of 20 months (chapter 7). Due to the small number of participants we were unable to compare baseline EEG activity between MCI patients who converted to dementia and MCI patients who remained stable or returned to a normal level of cognitive functioning. Based on the above studies, the EEG seems to be a promising tool which might eventually provide biomarkers of dementia in its preclinical stages. Alternative cognitive paradigms, such as executive or psychomotor tests, may also be useful in this respect. Large studies with longitudinal follow-up are needed to further examine EEG changes leading up to dementia. Furthermore, as previous research has shown the EEG's utility in the evaluation of cholinesterase inhibitor therapy in AD [1, 32], the EEG during cognitive activation may be used to evaluate the effects of cognitive enhancement treatments.

2. EEG changes in the preclinical stages of dementia do not necessarily follow a linear pattern of decline but may be influenced by cognitive reserve mechanisms that modulate EEG activity

A recent review article postulated that cognitive reserve -in the form of neural reserve or neural compensation- may modulate the clinical expression of AD [36, 37]. Individuals with more cognitive reserve are better able to cope with AD pathology because they can tap into more efficient, greater capacity or compensatory networks. Evidence suggests that cognitive reserve depends on life exposure, i.e., individuals with higher IQ, education, occupational attainment or participation in leisure activities have more cognitive reserve. According to this theory cognitive reserve may take two forms: neural reserve and neural compensation. Neural reserve refers to the use of brain networks that are more efficient or have greater capacity. Neural compensation reflects an attempt of the damaged brain to keep performance intact by using brain structures or networks otherwise not engaged [36, 37].

In this thesis we discussed a possible compensation mechanism in preclinical mutation carriers and the absence of compensation in MCI.

In chapter 2 we described that alpha reactivity in response to memory activation was decreased in MCI patients. This EEG response was combined with worse performance on the memory activation task and was interpreted as a failure of the neuronal system to adequately react to memory stimulation. Other EEG researchers hypothesized possible compensation mechanisms in MCI as they found increased brain activity during working memory [14, 30]. Differences may be explained by the level of task difficulty, disease severity, or differences in life exposure as described above.

In chapter 4, preclinical HD mutation carriers showed less alpha activity during memory activation as compared with non-mutation carriers, while performance was similar. Alpha activity is expected to decrease when an effort takes place to memorize stimuli and, as this took place in excess, we discussed a possible compensation mechanism to keep memory performance intact.

In retrospect we neglected to distinguish between neural reserve and neural compensation, but simply labeled increased activity as neural compensation. However, as we did not study different brain locations, we were unable to investigate whether normal brain networks were more efficiently employed, as in neural reserve, or whether alternative brain networks were used, as in neural compensation.

The question rises when in the disease process cognitive reserve fails and in which patients cognitive reserve is available? The EEG may be used to further study cognitive reserve in AD by following individuals at risk over time. As cognitive reserve modulates the clinical expression of

diseases such as AD, information concerning a patient's cognitive reserve would provide a more complete account of disease status [37] and might help predict cognitive decline.

Overall, it seems that EEG changes do not necessarily follow a linear pattern of decline, but are influenced by cognitive reserve mechanisms that modulate EEG activity.

3. When researching early manifestations of dementia, it may pay to keep an open mind regarding the nature of the parameter to be measured

When comparing elderly volunteers without cognitive impairment, MCI patients and AD patients we observed a gradual continuum of decline on several neuropsychological and EEG parameters. For example, when looking at neuropsychological data we found declining memory performance. In the EEG we observed decreasing alpha reactivity during memory activation, although it should be mentioned that EEG changes do not necessarily follow a linear pattern of decline. In our research there was never a clear cut-off point between normal elderly and patients. It seems obvious that, instead of directly reflecting the presence of a pathogenic agent, i.e., the accumulation of neuritic plaques and tangles, the EEG reflects its functional consequence, namely altered cerebral activity. In that light, we took interest in a group of parameters usually regarded as 'artifacts' in the EEG, i.e., muscle activity (EMG activity). We hypothesized that the amount of muscle activity would reflect behavioral consequences of dementia such as agitation, irritability and depression (chapter 6). Interestingly, we found that EMG activity differed systematically between groups and was correlated with depressive complaints and cognition. 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 regarding the nature of the parameter to be measured.

4. In future clinical practice, the EEG might be used, in combination with neuropsychological testing and MRI, to determine a 'risk profile' of patients more likely to develop dementia

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' of MCI patients who are more likely to show

rapid cognitive decline and progress to dementia (chapter 3 and 7). A similar profile can be created for MCI patients likely to return to a normal level of functioning.

As a possible future scenario, it can be imagined that the EEG is used as an additional diagnostic instrument for patients with MCI. In this scenario, the EEG examination would result in an EEG profile with several evidence-based EEG parameters rated on, for example, a five-point scale. While certain profiles would be suggestive of progression to AD, others would suggest reversion to a normal state. Subsequently, this prognostic information could be used by clinicians, in combination with neuropsychological and MRI profiles, in the choice of treatment and counseling strategies. When at low risk, patients with MCI should be informed that the experienced memory problems are not of a progressive nature, while patients at higher risk are informed of the possible risk of dementia. In a similar manner, the EEG might provide information concerning disease progression in preclinical HD mutation carriers. Providing prognostic information to preclinical mutation carriers is debatable however; it might mean relief for those with a larger zone of onset, but in case of persons nearer to onset such information might signify the end of subjective health [39]. In both MCI and HD mutation carriers, information on the disease process is essential for timing neuroprotective treatments, when they become available.

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