Electrophysiological assessment of working memory maintenance in mild cognitive impairment
Doctoral theses

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1. INTRODUCTION

Dementia affects 55 million people worldwide which is a growing social, economic and health challenge. Recent research has focused on the identification of potential risk factors and on the early detection of cognitive decline, including mild cognitive impairment (MCI), identified as a 'precursor' to dementia, with early symptoms of working memory impairment.

Although several EEG abnormalities have been identified (increasing δ-θ power, decreasing α-β power) that may facilitate early detection of cognitive decline, previous research has focused mainly on resting-state activity. Less is known about the EEG differences associated with (memory) tasks, although presumably the differences on task-related EEG are more pronounced compared to resting-state EEG.

Most of the previous studies detected reduced reactivity of the α- and β-frequency bands in MCI

during working memory tasks, however, others have measured increased reactivity, which was explained by the higher needs of cognitive resource mobilization of patients. α- and β-activity sensitively reflects cognitive load and increases in parallel with its magnitude, however, it is not known whether this modulation is preserved in MCI. The source of the oscillatory differences is not precisely known; however, the sensory recruitment model of working memory suggests that they may be due to differences in the activity of regions involved in sensory information processing.

The neuropathological processes of Alzheimer's disease (AD) lead to impaired functional and anatomical connectivity of brain networks, therefore, it has been identified as a disconnection syndrome. In AD and MCI, a decrease in α- and β-resting functional connectivity was described. Less is known, however, about changes in task-related functional connectivity and previous studies had

mixed results. An increase in functional connectivity has been observed with increasing cognitive load, but it is not known whether this modulation also occurs in MCI patients. During the development of AD, network integration increases initially, followed by a decrease in centralization and a breakdown of the modular structure of the network. Late decentralization has been supported by the results of several previous EEG studies, however, an increase in network integration has not been previously confirmed in MCI.

We also examined whether the observed EEG differences (in event related oscillations and functional connectivity) correlate with other early markers of cognitive decline and structural impairment, such as performance on neuropsychological tests and structural and functional impairment of the medial temporal lobe.

2. OBJECTIVES

In this thesis, we have analyzed different aspects of electrophysiological data of mild cognitive impairment (MCI) and healthy elderly with subjective memory complaints during working memory maintenance.

We aimed to answer the following questions:

1st study:

1. Is there a difference in α- and β-synchronization during working memory maintenance between MCI patients and controls?
2. Is cognitive load-dependent modulation of α- and β-synchrony preserved in MCI patients?
3. Which brain structures' different level of activity underlies the supposed differences in synchronization?
4. Is there a connection between the supposed differences in synchronization and the early

structural markers of cognitive decline and performance on neuropsychological tests?

2nd study:

1. Is there a difference in mean α and β functional connectivity during working memory maintenance between MCI patients and controls?
2. Is cognitive load-dependent modulation of α and β functional connectivity preserved in MCI patients?
3. Is there a connection between the supposed differences in functional connectivity and the early structural markers of cognitive decline?
4. Are there differences in brain network topology between MCI patients and controls?

3. METHODS

In both studies, we analyzed high-resolution 128-channel EEG recordings, which were recorded using a BioSemi ActiveTwo amplifier with 100 Hz low-pass band-pass filtering and a sampling rate of 1024 Hz. The diagnosis of MCI was based on the Petersen criteria. Built-in and self-developed functions as well as the freeware EEGLAB toolbox in the MATLAB development environment was used for subsequent off-line data analyses. We used paradigms that allow the separate analysis of the maintenance phase of working memory. In the first study, during the Sternberg test, at the beginning of each round 3-5 one-digit numbers were presented consecutively on the screen, and after the maintenance period, participants had to determine whether the numbers presented during the retrieval phase were part of the previous memory sequence. A bandpass filter between 0.5 and 45 Hz was applied to the EEG recordings, and the ADJUST software based on Independent Component Analysis (ICA) was used to remove artifacts. After interpolation, we applied the event-related spectral perturbation (ERSP) method, a two-dimensional representation of the average change in

spectral power relative to baseline power, to investigate changes in α and β activity during the early and late maintenance period. The eLORETA software was used for source localisation. T1-weighted images of participants acquired with a 3T MR scanner were used for the analysis. In the second study, during the Paired Association Learning (PAL) test, 2-4 abstract shapes were presented, and after the maintenance period, participants were asked to determine whether the shapes appeared in the same positions during the retrieval phase as previously presented. A band-pass filter between 0.5 and 45 Hz was applied to the EEG recordings, and then, as the use of interpolation can have a distorting effect on functional connectivity and network parameters, four noisy channels (P2, FT7h, P7, P9) were removed from each participant's recordings. To remove the artifacts, we used an ICA-based machine learning algorithm (MARA). EEG functional connectivity (measured by corrected amplitude envelope correlation (AEC-c)) and network parameters were calculated using BrainWave software. The minimum spanning tree (MST) method was used for network analysis.

In the first study, a two-way repeated measures analysis of covariance (ANCOVA) was used to examine the effect of group × region on ERSP, while a three-way ANCOVA model was used to examine the effect of memory load × group × region on ERSP. In the second study, the effect of group × memory load on functional connectivity and network parameters was examined using a two-way ANCOVA model. All the main effects including age, two-way and three-way interactions for the second model were included into the models. For the assessment of the interactions, a pairwise post-hoc analysis was performed using the Hochberg correction for multiple comparisons. The magnitude of the differences was characterised by the values of effect size (Cohen's d). The correlations of EEG parameters and structural and diffusion-weighted MR parameters were tested using Pearson's correlation and Spearman's correlation for variables deviating significantly from the normal distribution.

4. RESULTS

In our first study, 17 MCI patients (*mean age = 69.2 ± 7 years; 8 women*) and 21 healthy controls (*mean age = 64.9 ± 5.2 years; 14 women*) were included, while in our second study, 17 MCI patients (*mean age = 69.9 ± 6.5 years; 7 women*) and 20 healthy controls (*mean age = 65.2 ± 6.9 years; 14 women*) were included. There were no significant differences between groups in gender, education, depressive and anxiety symptoms (GDS, STAI score). The MCI patients were older than the control group members, therefore age was included as a covariate in the statistical tests. In addition, MCI patients scored significantly lower on neuropsychological tests (AKV, MMSE, RAVLT, MMSE, TMT) than controls.

4.1 RESULTS OF THE 1ST STUDY

In the Sternberg test, the response accuracy of the MCI group was significantly lower compared to the control group (*MCI: mean = 82.3%, SD = 19.7, control: mean 91.7%, SD = 8.5, U = 111, p = 0.049*).

During the early retention phase, significantly lower α ERS (*F(1,34) = 4.44, p = 0.04*) and β ERS (*F(1,34) =*

6.69, p = 0.01) was measured in the MCI group compared to the control group. Age had no significant main effect in any frequency range (*p > 0.05*). In the α band the largest between group differences were found in the right central (*Cohen's d = 1.1*) and left temporal regions (*0.9*), while in the β band in the midline (*frontal: 0.9 central: 1.0 parieto-occipital: 0.9*), pariteo-occipital (*left: 1.0 right: 0.9)* and left frontal (*0.9*) regions. Source localization analysis revealed significantly lower (*corrected non-parametric p<0.05*) β activity in the temporal, occipital and frontal lobes in the MCI group compared to control participants, which was mainly related to reduced β activity in the inferior temporal gyrus, medial temporal gyrus, and fusiform gyrus.

In the late retention phase, we investigated the effect of cognitive load: higher memory load induced significantly higher α-activity in both study groups (*F(1,34) = 42.9, p < 0.0001*), however, there was no significant difference between the two groups. The MCI group showed a significantly decreased ERS in the β-frequency range (*F(1,34) = 6.26, p = 0.02*). As memory load increased, β ERS showed a similar increase in the two groups (*F(1,34)*

= 45.97, p < 0.0001), as the three-way interaction of group, memory load and region was not significant ($p > 0.05$). The cognitive load-related modulation of β ERS was high in all regions (*Cohen's d > 0.8*), most pronounced in the right central region (*Cohen's d = 1.2*). The β ERS measured during early retention showed a significant correlation with the cortical thickness of the entorhinal cortex and parahippocampal gyrus and with the volume of the hippocampus, whereas the β ERS detected during late retention correlated significantly with the cortical thickness of the entorhinal cortex and parahippocampal gyrus and with the volume of the hippocampus. No significant correlation was found between α ERS and the size of medial temporal lobe structures.

4.2 RESULTS OF THE 2ND STUDY

In the PAL task response accuracy of the MCI patients showed a trend level decrease compared to the control group (*MCI: mean = 77.2% SD = 21.2, HC: mean 88.4 = % SD = 7.2, U = 106.5, Z = 1.9, p = 0.05, Cohen's d = 0.8*).

During the retention period, memory load had a significant modulatory effect on average functional connectivity (AEC-c) in the α frequency band (*F(2,34) = 5.92, p = 0.006*). Group and memory load showed a trend-level interaction (*F(2,34) = 3.03, p = 0.06*).

The post-hoc analysis showed that the memory load-related modulation of AEC-c followed different dynamics in the two groups: while in the control group, significantly increased mean AEC-c was measured for both medium (*t = 2.59, df = 34, p = 0.01, Cohen's d = 0.4*) and high memory load (*t = 2.88, df = 34, p = 0.007, Cohen's d = 0.4*) compared to low memory load, in the MCI group, although significantly increased AEC-c values were observed at medium memory load compared to low memory load (*t = 2.28, df = 34, p = 0.03, Cohen's d = 0.3*), significantly decreased connectivity was observed at high memory load compared to medium load (*t = 2.5, df = 34, p = 0.02, Cohen's d = 0.3*).

In the β frequency band, task difficulty and age had no significant effect on mean functional connectivity (*p > 0.05*). The interaction between the control group and memory load was not significant, however, post-hoc

analysis revealed that the control group had significantly increased mean β functional connectivity at high memory load compared to low memory load (*t = 2.82, df = 34, p = 0.008, Cohen's d = 0.4*), whereas the MCI group had no significant modulatory effect of memory load. There was no significant effect of study group and age on α and β mean functional connectivity ($p > 0.05$).

The mean α and β AEC-c showed a significant positive correlation with the relative hippocampal volume (*α AEC-c: Spearman rho = 0.47, p = 0.02, β AEC-c: Spearman rho = 0.54, p = 0.004*) and with the cortical thickness of the parahippocampal gyrus (*α AEC-c: Spearman rho = 0.40, p = 0.04, β AEC-c: Spearman rho = 0.48, p = 0.01*) and a significant negative correlation with the mean diffusivity of the right hippocampal cingulum (*α AEC-c: Spearman rho = -0.41, p = 0.03, β AEC-c: Spearman rho = -0.50, p = 0.008*). Furthermore, mean β AEC-c correlated significantly with the cortical thickness of the entorhinal cortex (*β AEC-c: Spearman rho = 0.44, p = 0.02*).

Spectral analysis showed no significant correlation of relative α- and β-power with study group and age. Memory

load had a significant modulatory effect on α-performance (*F(2,34) = 4.04, p = 0.03*), and group and memory load showed a trend-level interaction (*F(2,34) = 3.13, p = 0.06*). The control group showed a significant increase in relative α-power at high memory load compared to low memory load (*t = 3.69, df = 34, p = 0.0006, Cohen's d = 0.3*). In the β-frequency band, memory load showed no significant correlation with relative β-power.

For the network analysis, the minimum spanning tree (MST) approach was used. In the two frequency bands we found similar differences between the two groups, suggesting that the network topology of MCI patients was more centralized and integrated compared to control subjects. In both the α and β bands, the MST networks of the MCI group had significantly smaller diameter (*α: F(1,34) = 5.36, p = 0.03, β: F(1,34) = 4.58, p = 0.04*) and eccentricity (*α: F(1,34) = 4.64, p = 0.04, β: F(1,34) = 5.62, p = 0.02*), as well as significantly higher maximum degree (*α: F(1,34) = 5.69, p = 0.02, β: F(1,34) = 7.55, p = 0.01*), degree divergence (*α: F(1,34) = 6.12, p = 0.02, β: F(1,34) = 7.15, p = 0.01*) and maximum betweenness centrality (*α: F(1,34) = 7.37, p = 0.01, β: F(1,34) = 6. 95,*

p = 0.01). Age also had a significant effect on some network parameters (*α diameter: F(1,34) = 4.64, p = 0.04, α eccentricity: F(1,34) = 4.14, p = 0.05, β degree: F(1,34) = 5.2, p = 0.03, β degree divergence: F(1,34) = 5.44, p = 0.03*). In addition, memory load had a significant modulatory effect on betweenness centrality in the α band (*F(2,34) = 3.53, p = 0.04*): a significantly increased value was measured in medium memory load compared to low memory load (*t = 2.6, df = 34, p = 0.01*).

5. CONCLUSIONS

The two studies presented in this thesis focused on different aspects of the neurophysiological phenomena accompanying working memory retention, in order to shed light on the background of working memory impairment in MCI. Overall, our results are in line with the literature and confirm the early decline of working memory by neurophysiological markers.

The results of our first study suggest that working memory maintenance is characterized by reduced α- and β-event-related synchronization in MCI, suggesting the reduction of α- and β-power modulation in MCI. However, while there was a significant difference between the groups, memory load-related modulation was preserved in the MCI group, which may indicate partially preserved cognitive reserve capacity. We could confirm that reduced activity of the working memory network, mainly of the temporal lobe, underlies the decrease in β-synchronization, and that the extent of this decrease correlated with medial temporal lobe atrophy.

Results from our second study suggest that the functional connectivity of the α- and β-frequency bands sensitively

reflects cognitive load-related modulation and impairment of memory maintenance in MCI. Global α and β functional connectivity showed a significant correlation with medial temporal lobe atrophy and reduced hippocampal fiber integrity, thus as a functional marker it may reflect the onset of structural impairment at the earliest stages of cognitive decline. The MCI group showed a more centralized and integrated MST network topology compared to the control group, supporting the idea that in MCI, presumably as part of a compensatory mechanism, neuronal network transformations occur that may lead to uneven load distribution, and overloading and failure of central nodes (hubs).

Our results suggest that the functional markers of electrophysiological changes detected during working memory tasks are strongly correlated with the early markers of structural impairment. Therefore, EEG analysis may provide a useful complementary diagnostic tool for the early detection of cognitive impairment and might be a step toward establishing functional biomarkers. However, further research using similar paradigms and with follow-up data is needed to verify our results.

6. PUBLICATIONS RELATED TO THE DISSERTATION

1. Fodor Z, Horváth A, Hidasi Z, Gouw AA, Stam CJ, Csukly G. (2021) EEG Alpha and Beta Band Functional Connectivity and Network Structure Mark Hub Overload in Mild Cognitive Impairment During Memory Maintenance. Frontiers in Aging Neuroscience, 13. (IF: 5,702)

2. Fodor Z, Siraly E, Horvath A, Salacz P, Hidasi Z, Csibri E, Szabo A, Csukly G. (2018) Decreased Event-Related Beta Synchronization During Memory Maintenance Marks Early Cognitive Decline in Mild Cognitive Impairment. J Alzheimers Dis, 63: 489-502. (IF: 3,517)

OTHER PUBLICATIONS

1. Becske M, Marosi C, Molnár H, Fodor Z, Tombor L, Csukly G. (2022) Distractor filtering and its electrophysiological correlates in schizophrenia. Clin Neurophysiol, 133: 71-82. (IF: 4,861)

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