EEG changes in Alzheimer’s disease: EEG spectrum, coherence, complexity, event-related potentials

Doctoral theses

Balázs Czigler, MD

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Tutor: Dr. Márk Molnár, MD, DSc

Doctoral School in Psychology
Head of School: Prof. Dr. György Hunyady, DSc

Doctoral Programme in Cognitive Psychology
Head of Programme: Prof. Dr. Éva Bányai, PhD
1. Aims and General introduction

The aim of our studies were the investigation of electrophysiological changes in Alzheimer’s disease (AD). We compared the spectral, coherence, complexity characteristics of resting EEG as well as the N1, P2, N2b, P3a, P3b and CNV event related potential components in a group of AD patients and in healthy elderly subjects. Participants also performed a set of neuropsychological tests so as to characterize our patients and also to validate our electrophysiological results.

Our purpose was the assessment of cognitive changes in AD on the one hand, and to find measures that can be useful in the early diagnosis, monitoring progression, appraisal of therapeutical success on the other hand.

The practical significance of our research is underlined by the fact that dementias are amongst the most common diseases in the elderly population. According to the latest epidemiological data the estimated number of dementia sufferers is more than 35 million worldwide. This number increases by 4 million every year, meaning a newly diagnosed patient every 7 seconds (Alzheimer Europe, 2009).

Considering the European Union, the expectations are still gloomier: the number of dementia patients is foretold to double every 20 years, so their number will reach 15 millions by the year of 2030 (Alzheimer Europe, 2009). These facts lead the European Union to declare dementias – and AD in particular – a priority in the fields of public health, social insurance, research, ethics and law. At the present time there are 280 clinical AD trials on the way, and the number of concluded studies is well over 500. AD has a world day now (the 21th of September). The reason of the special importance of AD is that this disease is responsible for 60-65% of dementias. This also makes AD the most prevalent neurodegenerative disease.

2. Methods

2.1. Subjects, inclusion and exclusion criteria

We examined 12 patients with mild AD (according to NINCDS-ADRDA and ICD, MMSE 20-24). All patients had neurological and psychiatric assessment. A CT or MR scan was performed in every case. The control group consisted of 21 healthy elderly patients, of whom 12 participated in the visual memory task and the neuropsychological testing.

2.2. EEG-recording

EEG was recorded with a NuAmps amplifier and Neuroscan 4.3 software (sampling rate: 1000 Hz, badpass filter: 0.5-45 Hz). 21 Ag/AgCl electrodes were used according to the international 10-20 system, with nose reference, FCz as ground. Vertical and horizontal eye movements were also recorded.
Epoching and linear detrending was followed by an automatic and visual artefact screening (epochs exceeding 70 µV were rejected).

2.3. Resting EEG, spectral analysis, coherence, complexity measures

2 minute recordings were made for the analysis of the resting EEG. These recordings were bandpass filtered offline (0.1-30 Hz, slope: 48 dB/oct) then epochs of 2048 ms were made.

The following frequency bands were analysed during both the spectral and coherence and also for the complexity measures: delta (0.5-4 Hz), theta (4-8 Hz), alpha1 (8-11 Hz), alpha2 (11-14 Hz), beta1 (14-25 Hz), beta2 (25-35 Hz). Relative frequency spectra were calculated using Fast Fourier Transformations.

Coherence measures were also computed by using Neuroscan 4.3 for the aforementioned frequency bands. Two types of values were calculated. Short-term coherence was measured between intrahemisphaerically neighbouring channels, while long-term coherence meant distal but still intrahemisphaeric electrode-pairs.

Two complexity measures, Omega-complexity and Synchronization Likelihood were calculated. The latter (SL) numerates the dynamic interaction between two or more time-series (EEG channels in this case). The X and Y state of dynamical systems X and Y – like two neural networks corresponding to two EEG electrodes – can be described by vectors Xi and Yi in their state space. SL can be defined as the probability that the state of system X can be defined as a function of system Y. It is operationalized as the likelihood that if system X is in the same state in times i and j then system Y is also in its same state at the same points in time i and j. Calculation is performed for a number of electrode-pairs, than the average of these values constitutes the SL. This method is sensitive to both the linear and nonlinear synchronization between time series and also for the time-dependent changes thereof (Molnár, 2000).

Omega complexity describes the covariance relations of multi-channel EEG data, thus it quantifies the spatial and temporal dynamics of cerebral electric activity. After having computed the covariance-values between the channels, a principal component analysis is performed so as to assess whether the variance of the variables can be described by a small number of mutual factors. The eigenvalues of these components expresses the amount of variance each component carries. The Shannon entropy of the (normalized) eigenvalues equals to the logarithm of Omega. In case all series can be described by one component (i.e. the dynamics of the EEG-data is generated by one source) then \( \log \Omega = 0 \), so Omega=1. If the channels are completely independent the value of Omega equals to the number of channels.

\[ \log \Omega = - \sum (\lambda_i \log \lambda_i) \]

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Accordingly, lower value of Omega corresponds to „simpler“, while higher Omega corresponds to „more complex” signs.

2.4. Auditory oddball task

The participants performed an auditory oddball task following the recording of resting EEG. Their task was to signal the appearance of a target stimuli (deviant, 1500Hz, 80 dB (SPL), 100ms, p=10%) amongst standard sounds (1000 Hz, 80 dB (SPL), 100ms, p=85%). Novelty stimuli were also presented (short, non-repeating complex sounds, p=5%), with which the subjects had no task to do.

2.5. CNV task

To elicit contingent negative variation subjects were presented trains of stimuli consisted of 5 (standard, 63%) or 4 (deviant, 37%) tones (1000Hz, 200ms, 80 dB (SPL), ISI: 650 ms). The delay between the series was 5 or 6 sec (with 50-50% probability). Participants had to response by button press if she/he heard 4 tones, i.e. the omission of the 5th stimulus.

2.6. Visual memory task

During this task the subjects were presented the figures they had to recognise later for 30 seconds. After the presentation they had 30 seconds to „memorize“ the stimuli with eyes closed. In the recognition phase these target pictures were exposed amongst other, nontarget stimuli. Participants had to press a button when seeing a target picture. Each stimulus was displayed for 1 second, the time to respond was 2 seconds.

The situation consisted of 3 consecutive tasks with increasing difficulty with 3, 5 and 7 pictures to remember.

2.7. Neuropsychological tests

After the electrophysiological tasks participants performed four neuropsychological tests. Digit span is considered to measure attention, concentration and – principally – working memory. Trail-Making assesses visual attention, psychomotor speed, executive functions, flexibility of reckoning and also working memory. Of the latter, inhibitory processes are supposed to play a major role. Benton’s Visual Retention Test is sensitive to a variety of neuropsychological deficits, e.g. frontal lobe lesions lead to perseveration errors, parietal lobe lesions cause impairments of spatial relations’ reproduction, etc. (Golden et al., 2000). Rey-Osterreith Complex Figure Test (ROCFT) measures perceptual, motor and visual memory functions and also capabilities of planning, perceptual organization and problem solving (Golden et al., 2000).
3. Results, conclusions

According to the results of spectral analyses the expected „slowing” of the EEG could be demonstrated in AD. Theta power increased along with the decrease of alpha power. This result was observed with eyes open and closed, either above the left and right hemisphere for both the anterior and posterior electrodes. Also, the peak frequency of alpha band was significantly - 1 Hz - lower in the patients’ group.

The changes of theta power could discriminate the patients’ group from controls with a sensitivity of 91% and specificity of 90%.

Our results differ from the previous findings in that they were obtained at the early stage of dementia, and also because of the higher sensitivity in the present study. The reason lies probably in the stringent and state-of-the-art registration and artefact screening methods used in this study.

The dysfunction of cholinergic neurotransmission is supposed to be involved in the „slowing” of EEG in AD. Several studies demonstrated that the integrity of the basal forebrain and of the cholinergic projection stems from it is necessary to maintain desynchronized EEG activity. These systems are affected early in AD (Dringenberg, 2000). There is also evidence that the monoaminergic systems also contribute to the generation of normal EEG rhythms. The impairment thereof is also presumably in AD.

Our knowledge about the functional significance of the alpha and theta bands is also in accordance with their changes in AD. According to Klimesch (1999) the wide-range increase of resting theta activity mirrors states when the capacity to process new information is reduced or even blocked. Some studies also showed that alpha band can be an indicator of cognitive performance, especially in case of memory tasks. Greater alpha power as well as higher alpha peak frequency corresponds to better performance and faster reaction times in healthy subjects.

Thus, higher theta and lower alpha power foretells poor memory performance, which is also the leading symptom of dementia. This is underlined by the correlations between our spectral data and the neuropsychological test as well. Theta power showed a negative correlation with performance of Trail-making, ROCTF (memory trial) and Benton tests, while it correlated positively with the difference of the memory and copy tasks of ROCTF, that is a very sensitive marker for memory deficits. The power of the alpha2 band correlated with digit span.

**EEG coherence** decreased in AD in case of several electrode-pairs. In the eyes closed condition such changes could be observed for both the fast and the slow frequency bands, while with eyes open reduced coherence could be seen mainly in the slow (delta, theta) bands. The most conspicuous differences affected long-term coherence measures. Long-tem coherence is supposed to depend on long cortico-cortical axonal connections (e.g. fasciculus longitudinalis superior), so they provide information about the functional interaction of remote cerebral areas (Thatcher et al., 1986). These observations led to the view of AD as a „disconnection syndrome”. Our results are in accordance with this conception. Earlier studies found decreased coherence characteristics for the faster activity (alpha and beta) only,
while reduction of coherence in the slower bands indicating deterioration of subcortico-cortical connections was described in the later stages. In our study both changes were found in the early stage of AD. In sum, these alterations of coherence did not prove to be robust enough with respect to clinical applications. In this regard the coherence changes due to cognitive tasks seem to be more promising (Hidasi et al., 2007).

The results obtained by complexity analyses were very consequent for both Omega complexity and Synchronization likelihood. In AD brain electrical activity is substantially more complex compared to the healthy elderly population. Omega was higher, accordingly SL was lower in patients in the delta, theta, alpha1, alpha2 and beta1 bands. Increase of complexity – especially in case of SL – corresponded with worse performance in several neuropsychological tests.

Though former results concerning complexity changes in AD were far from consistent, in our study, using the above methods we achieved 100% sensitivity and specificity. This means remarkable predictive power even if the aforementioned predictive values are posterior probabilities. Accordingly, a large independent sample will be necessary to validate the findings.

It may seem surprising that brain electrical activity is more complex in AD patients. In our view the reason behind this finding is the deterioration of the organization of neural activity. Due to the decline of subcortical and cortico-cortical afferentation and the synaptic loss, the integration of neural assemblies may also be reduced.

Neural networks of greater spatial expansion like those connecting subcortical and cortical areas are synchronized by lower frequency oscillations, while the integration of small cortical networks is attained by faster oscillations (von Stein és Sarnthein, 2000). The fact that increased complexity was observed in both the slow and fast frequencies implies that the decline affects both short and long-range synchronization.

According to our results complexity measures proved to be more sensitive to the alterations of AD compared to the conventional electrophysiological methods. We see the reason of this in the fact that global measures are more suitable in detecting diffuse pathological alteration on the one hand and on the other hand in the better compatibility of nonlinear methods for the nonlinear nature of the nervous system.

Marked differences were found between control subjects and AD patients for every event related potential component in our study. The earliest component was the – visual – N1-P2 complex. Both N1 and P2 appeared with significantly longer latencies in the patients, while no amplitude difference was found between the groups. N1 mirrors the early phase of visual stimulus representation. Amplifying operations processes that tune the sensitivity of perceptual activity play a part in this, so attention affects this component (Hillyard et al., 1995). The longer latencies imply the slowing of these neural processes, and also the decline of their efficacy. The latter is supported by the fact that the patients showed much lower performance in the recognition task, and this decline of performance was
propotional with the increase of N1 latencies. Latencies correlated negatively with neuropsychological scores.

Former studies failed to demonstrate differences of N1 latencies in AD, although in the healthy elderly similar changes were observed compared to the young population (Zanto et al., 2010).

P2 emerges as a part of the stimulus-classification procedures and similarly to the N1 it denotes attention-modulated processes. In some earlier studies the increase of its latency was found in AD (Tanaka et al., 1998). However, such results were observed in later stages of the disease, while in our study the increase of P2 latencies was found in the early stage of dementia, that was also proportionate with the decline of performance in the visual recognition task and the ROCTF and Benton tests.

The N2b, P3a and P3b event related potentials elicited in the auditory oddball task were lower in amplitude in AD. Including the three potentials in a discimination function resulted in a – posterior -specificity and sensitivity of 100%.

In case of target stimuli the N2b could be observed with a very low amplitude, while it was practically missing for novel stimuli. If it was elicited at all, its distribution was more posterior in comparison to the healthy elderly – in whom the maximum was already more posterior than in the young population. N2b amplitudes correlated negatively with ROCTF scores.

Decrease of N2b can be attributed to the decline of attentional resources available for the automatic processes of orientation and selection. It seems that the processing of novel stimuli is affected most. These facts and the alteration of the components’ scalp distribution in the patients imply the dysfunction of anterior cingular cortex.

The amplitude of P3b was also smaller in AD. Former studies did not yield univocal results. The increase of latency was found, but also the lack of it along with decreased, increased, or unchanged amplitudes (e.g. Polich and Pitzer, 1999;).

The decrease of P3b can be interpreted by the neuropsychological alterations in AD. In the generation of the component the contribution of mediotemporal areas (especially that of hippocampus) is very likely (Knight et al., 1989), and these are the very areas most affected in the early phase of the disease. Also, the role of the cholinergic neurotransmission is proved, that of the serotonergic is probable in the genesis of P3b, and these are the transmitter systems most severly affected in AD (Ropper és Brown, 2005).

Reduced P3b amplitudes indicate the deterioration of working memory. The increase of N1 latencies described formerly also demonstrates this, although the latter on the level of early cognitive processes.

P3a amplitudes also proved to be significantly lower in the patients’ group. AD research has hardly dealt with this component previously, the studies that did not demonstrate any differences either in latency or or amplitude (e.g. Reinvang et al., 2005). The amplitude decreases markedly with age though (Gaál, 2009), and this effect is more pronounced in AD.
The decrease of novelty P3 signifies the decline of orientation, detection of change, in which the deterioration of frontal cortical inhibitory processes play an important role. The neuropathological alterations leading to these electrophysiological changes most likely affect the frontal cortex, the hippocampus and their connections.

The changes of the CNV were in the opposite directions than that of the other components. The CNV was elicited with higher amplitude (and area under curve) and shorter latency in AD. Discriminace analysis showed significant sensitivity and specificity (81.8% and 90%, respectively).

The patients’ performance in the task was much lower however, as their response times were significantly longer. The increase of CNV amplitude was proportionate to the decline of performance in the neuropsychological tests as well.

Formerly only a few and inconsistent results were available concerning CNV features is AD. Some studies reported lower amplitudes, some failed to find any difference in the patients. In the healthy elderly an increase of CNV amplitudes was observed though (Gaál, 2009).

We assume that the increase of CNV in AD can be attributed to compensatory mechanisms. This difficult task must have recruited additional attention resources. Increase of arousal may have resulted in greater CNVs because of increased cortical excitability. This can be interpreted as the patients compensating for the deficits of lower level processes by greater involvement of higher level operations. The price they pay is the lengthening of reaction times. These compensatory mechanisms may not be available in the latter stages of AD, explaining the failure of previous studies to demonstrate differences in CNV amplitudes.

**Performance** of patients in the experimental tasks did not differ from that of controls in the simple discrimination problem (auditory oddball), their reaction times lagged though. In the more complex visual memory task involving working memory load and the CNV situation, the performance of AD patients was notably lower though, altogether with an increment of response times.

Although the analysis of neuropsychological changes was not one of our primary purposes, it is worth mentioning that of the test we used, the memory trial of ROCTF (and the difference of the two trials), and the Trail-Making test proved to be the most sensitive to cognitive decline in AD. These were also the ones that correlated most strongly with the eclectropsychological data. Both tasks put a heavy load on working memory, but ROCTF is also a rather complicated problem that involves planning and perceptual organisation as well. Trail-Making (especially its trial „B”) demands strong involvement of executive functions and frontal inhibitory mechanisms.

To sum it up, the study of event-related potentials demonstrates the deterioration of early, elementary cognitive processes already early in the course of the disease. The basic mechanisms of stimulus classification, perceptual sensitivity – denoted by the N1-P2 complex – is affected more severely than later, higher level processes concerning e.g. working memory (P3b). Thus the decline of cognitive capabilities appears to be caused by the deterioration of elementary sensory-perceptual functions.
The processing of novel stimuli, and even the orientation towards them seems especially effected in AD, that is proved by the changes of the P3a and –partially – N2b components. This is in accordance with the view that the neural assemblies participating in the processing of novelty are less redundant than those involved in target stimuli (as indexed by the smaller effects on P3b), so their compensatory functional plasticity is lower as well.

The dysfunction of frontal functions is very pronounced in AD. The deterioration of orientation and inhibitory processes in shown by the N2b, P3a and P3b components and also by the neuropsychological tests that involve executive functions.

Our results also show that there are resources available in the early stage of the AD that may compensate - at least partially - for the deficits of „low-level” cognitive processes.

The most conspicuous differences of resting cerebral electric activity in AD were found in the alpha and theta band of the frequency spectrum and in the complexity analyses. The changes of power spectra is a well known phenomenon - even if only in the later stages of the disease. However, the widespread increase of EEG complexity in AD is a novel finding. It implies a severe deterioration of the possible level of achievable synchronization of neural networks that involves both local and distant connections. It is noteworthy that such profound global functional disturbances can be demonstrated already in the early phase of the disease.

Complexity analyses deserves application in clinical work as well. As these calculations are easy to perform on routine clinical EEG recordings, they may become a valuable addition to spectral analysis. The N1-P2 and N2-P3 ERP components can be elicited easily as well, and as it was shown they are sensitive markers of cognitive performance change, especially together with the involvement of ”novel” types of stimuli. The application of these methods can prove to be useful in monitoring the progression of the disease, and in the evaluation of the therapeutic effects.

We will need to extend our studies in several ways. Although our methods promise identification of patients and controls with high sensitivity and specificity, the discrimination functions will have to be validated on greater samples. It would be also important to assess whether such changes can be demonstrated in mild cognitive impairment and – most importantly – if they could be used for the prognosis of the conversion from MCI to AD.

In light of the severe impact AD has on the patient, family and society it is obvious how important every tool is that allows the evaluation and quantification of various aspects of the function of the nervous system. Accordingly, we trust that our methods will find their applications not only in the field of basic research but also in clinical practice.
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