Research Report

Decrease of evoked delta, theta and alpha coherences in Alzheimer patients during a visual oddball paradigm

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ABSTRACT

In this study event related coherence of patients with Alzheimer type of dementia (AD) was analyzed by using a visual oddball paradigm as stimuli. A total of 21 mild probable AD subjects (10 untreated, 11 treated) were compared with a group of 19 healthy controls. The members of the groups had their EEG recorded from 12 electrodes by means of a visual oddball paradigm. The evoked coherence was analyzed for delta (1–3.5 Hz), theta (4–7 Hz) and alpha (8–13 Hz) frequency ranges for inter-hemispheric (F3–F4, C3–C4, T3–T4, T5–T6, P3–P4, O1–O2) and long range intra-hemispheric (F3–P3, F4–P4, F3–T5, F4–T6, F3–O1, F4–O2) electrode pairs. The control group showed higher values of evoked coherence in “delta”, “theta” and “alpha” bands in the left fronto-parietal electrode pairs in comparison with the untreated AD group (p<0.01 for all frequency bands). Furthermore, the control group showed higher values of evoked coherence in the left fronto-parietal electrode pair in theta frequency band (p<0.01) and higher values of evoked coherence in the right fronto-parietal electrode pair in delta band (p<0.01) when compared to treated AD group. The only significant difference between the treated and untreated AD groups was in the alpha band. The treated AD group showed higher values of evoked coherence at the left fronto-parietal pair in alpha band in comparison to the untreated AD group (p<0.01). During a working memory process the coherence in the left fronto-parietal electrode pair (F3–P3) of AD patients is significantly decreased, thus indicating reduced connectivity between frontal and parietal sites.

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1. Introduction

One of the leading neurological conditions most responsible for neuropsychiatric morbidity in elderly individuals is the Alzheimer type of dementia (AD). The present study analyzes the differences between the evoked coherence between AD patients (treated, untreated) and healthy controls upon the application of oddball paradigm. The coherence function was used as early as four decades ago by Adey et al. (1960), who began pioneering work on theta...
rhythms of the limbic system of the cat brain during conditioning. These authors used spectral and coherent functions to investigate how the rhythmic field potential of the cat brain is related to behavior. The use of the coherence function in comparing EEG activity in various nuclei of the cat brain was one of the essential steps in refuting the view that the EEG is an epiphenomenon (Adley, 1989). Accordingly, the induced theta rhythm and the task relevant increase of coherence in the limbic system are a milestone in EEG research. When carrying out a behavioral task, the cat hippocampal activity exhibits a transition from irregular activity to coherent induced rhythms. The results of Adley et al. (1960) were the deciding factor in the choice of the hippocampus as a model for a resonance processes in the brain for the Başar research group (1980, 2004). Based on several experiments concerning the behavior of the cat Başar (1980) assumed that if the brain receives a sensory stimulation, and if a structure has its own intrinsic activity, then the structure would respond with its natural frequency.

There is some evidence that the midline pre-frontal region of the cortex can generate theta activity in certain cognitive states. This result was reported by Mizuki et al. (1980): EEG rhythms of 5 Hz frequency appeared during the performance of simple mental arithmetic tasks. Miller (1991) argued that all this data is compatible with the thesis that theta activity in frontal regions is associated with theta activity in the hippocampus (Başar, 1999).

Evoked coherence is defined as the application of coherence function to Event Related Potentials. An analysis of the evoked coherence was first carried out by Başar et al. (1979a, 1979b), demonstrating increased coherence function, upon auditory and light stimulation, between primary cortex, thalamic structures, reticular formation, brain stem and cerebellum. In these studies the existence of long distance coherences was firstly demonstrated in the cat brain. In order to survey varying degrees of spatial coherence that occur over long distances as parallel processing the reader is referred to the following authors; Başar (1980, 1999), Kocsis et al. (2001), Miltner et al. (1999) and Schürmann et al. (2000).

The changes in coherence in brain during the evolution of species have been the major points of research in T.H. Bullock’s research group. According to Bullock and Başar (1988) and Bullock et al. (1995) no significant coherences were found in the neural networks of the invertebrates, in contrast, in mammalians and the human brain higher coherences between distant structures were recorded. The highest coherences were found in the subdural structures of the human brain (Bullock, 2006).

Many studies reported the successful use of EEG coherence to measure functional connectivity (Lopes Da Silva et al., 1980; Petsche and Ellinger, 1998; Rappelsberger et al., 1982). According to all of these studies, EEG coherence may be considered to be an important large scale measure of functional relationships between pairs of cortical regions (Nunez, 1997). Since coherence is, in essence, a correlation coefficient per frequency band it is used to describe the coupling or relationship between signals for a certain frequency band. According to Bullock et al. (2003) increased coherence between two structures, namely A and B, can be caused by the following processes. 1) Structures A and B are driven by the same generator. 2) Structures A and B can mutually drive each other. 3) One of the structures, A or B drives the other one.

In clinical studies the measure of coherence has been used by several authors in order to investigate the connectivity between the various cortical areas of Alzheimer patients in resting conditions. The most common result in these studies is the decrease of the alpha and beta band coherences between distant structures (Adler et al., 2003; Besthorn et al., 1994; Dunkin et al., 1994; Leuchter et al., 1987; Locatelli et al., 1998). There are few studies analyzing the evoked coherence differences between AD patients and healthy controls during the application of different memory paradigms (Hogan et al., 2003; Zheng-yan, 2005).

The analysis of working memory has been one of the major studies on working memory and sustained attention, several paradigms including the P300-oddball paradigm were used in order to analyze working memory and attention by means of EROs (Event Related Oscillations) (Başar-Eroğlu et al., 1992, 2001; Schürmann et al., 2001). Working memory (Reid et al., 1996) and visuo-spatial skills (Amieva et al., 2005) are among the impaired cognitive domains at the earliest stage of Alzheimer disease. Sauseng et al. (2005) calculated coherence during a visuo-spatial working memory task in group of healthy subjects. The results of these authors’ work indicate that the involvement of pre-frontal areas in executive functions are reflected in a decrease of anterior upper alpha short-range connectivity and a parallel increase of fronto-parietal long range coherence mirroring the activation of a fronto-parietal network. From these results, it was hypothesized that there could be an increase in the anterior upper alpha short-range connectivity and a parallel decrease of fronto-parietal long range coherence in AD patients during the application of oddball paradigm.

According to a group of authors, event related potentials or P300 responses are generated in the neocortex, especially in frontal locations (McCarthy and Wood, 1985) or the centroparietal/temporoparietal association cortices (Verleger et al., 1994). Involvement of limbic system or hippocampal formation in the generation of P300 has been also proposed (Halgren and Smith, 1987; Wood et al., 1980). The amplitude of delta response increasing during oddball paradigms may be related to signal detection and decision making (Başar-Eroğlu et al., 1992). As the major determining oscillatory activity of P300, delta responses are related to the basic information processing mechanisms of attention allocation and immediate memory (Polich and Kok, 1995).

Our group published recently results on the differences between AD subjects and a control group upon the application of oddball paradigm. Yener et al. (in press) found significant differences between the healthy controls and two groups of AD subjects in delta oscillatory responses regardless of cholinergic medication. This difference was steady over C3 and C4 in both AD groups in comparison to the control group. Yener et al. (2007) also reported that phase locking of the visual event-related theta oscillations of an untreated AD group has lower phase locking than controls on the left frontal region. However, the treated AD group showed that phase locking in theta frequency range was no different from controls (Yener et al., 2007). Previous histopathological studies at the earliest stages of AD indicate that the frontal lobe is not
more densely affected than the parietal lobe (Bierer et al., 1995). Yet our group’s earlier work has shown that the frontal lobe is especially prone to be more affected in event related oscillatory activity at the early stages of AD.

Therefore, the aim of the present study is to explore whether a strong impairment in the fronto-parietal functional connection prevails in AD. In this study the investigation of the differences of evoked coherence between treated AD, untreated AD and healthy control group was carried with the analysis of inter-hemispheric and long range intra-hemispheric evoked coherence analyses.

2. Results

Fig. 1 shows the grand averages of evoked coherence for delta, theta and alpha frequency bands for the F3-P3 electrode pair for the control, treated AD and untreated AD groups. In the delta frequency band (1–3.5 Hz) the coherence reached a value of 0.68 for the control group. In both AD groups this value was lower, 0.58 in the treated and 0.56 in the untreated. In the theta frequency band (4–7 Hz) coherence reached a value of 0.65 for the control group, however, in both AD groups this was found to be lower at 0.59. In the alpha frequency band (8–13 Hz) the coherence reached a value of 0.66 for the control and the treated AD groups, but in the untreated AD group at 0.60, this value was lower. The grand averages of delta and theta coherences of the healthy controls were higher than those of both the AD groups, whereas only the alpha coherence in the untreated AD group was lower than both of the healthy controls and treated AD subjects.

The statistical results of delta, theta and alpha coherences that will be described in the following section support the results of grand average coherences.

2.1. Delta (1–3.5 Hz)

In the analysis of intra-hemispheric coherence differences the ANOVA on the delta coherence revealed a significant effect between the groups (F(2,37)=6.027; p<0.01). The results on the delta coherence revealed significant effects for laterality only indicating larger right hemisphere coherences (F(1,37)=8.75; p<0.01). The ANOVA on delta coherence revealed a significant effect for location only (F(2,74)=9.196; p<0.0001) indicating an increased delta coherence over frontal–parietal pairs. Post-hoc comparisons between groups showed significant results for controls versus either treated AD or untreated AD, but not between treated and untreated AD. Post-hoc comparisons revealed that delta coherence at the left fronto-parietal (F3–P3) electrode pair was significantly higher for controls than for untreated AD (p<0.01) (Fig. 2); and it was significantly higher for controls than for treated AD at the right fronto-parietal (F4–P4) electrode pair (p<0.01).

In the analysis of inter-hemispheric coherence differences, the ANOVA on delta coherence revealed no significant effect between the groups (F(2,37)=1.63; p>0.05). The ANOVA on delta coherence revealed a significant effect for location only (F(5,18)=9.196; p<0.0001) indicating a higher delta coherence over frontal, central electrode pairs.

2.2. Theta (4–7 Hz)

In the analysis of intra-hemispheric coherence differences the ANOVA on theta coherence revealed significant effect between groups (F(2,37)=5.51; p<0.01). The ANOVA on theta coherence revealed significant effects for laterality only indicating larger right hemisphere coherence values (F(1,37)=8.75; p<0.02). The ANOVA for theta coherence revealed a significant effect for location only (F(2,74)=18.647; p<0.0001) indicating an increased theta coherence over frontal–parietal pairs. Post-hoc comparisons between groups did not show significant results for treated AD versus untreated AD, but showed significant results for control versus treated AD and control versus untreated AD. Post-hoc comparisons revealed that theta coherence was significantly higher for controls than for both the untreated AD and treated AD groups at the F3-P3 electrode pair (p<0.01) (Fig. 2).

In the analysis of inter-hemispheric coherence differences the ANOVA on theta coherence revealed no significant effect between groups (F(2,37)=1.63; p>0.05). The ANOVA on theta
coherence revealed a significant effect only for location \((F(5,18)=11.532; p<0.0001)\) indicating a higher theta coherence over the frontal, central electrode pairs.

2.3. **Alpha (8–13 Hz)**

In the analysis of intra-hemispheric coherence differences the ANOVA on alpha coherence revealed significant effect between groups \((F(2,37)=3.54; p<0.05)\). The ANOVA on alpha coherence revealed a significant effect only for location \((F(2,74)=15.873; p<0.0001)\) indicating a higher alpha coherence over the fronto-parietal pairs. Post-hoc comparisons between groups showed significant results for the treated AD versus untreated AD groups and for control versus untreated AD groups. Post-hoc comparisons revealed that alpha coherence was significantly higher for the treated group over the untreated AD group at the \(F_3P_3\) electrode pair \((p<0.01)\). Further alpha coherence result was significantly higher for the control group than for the untreated AD at the \(F_3P_3\) electrode pair \((p<0.01)\) (Fig. 2).

In the analysis of inter-hemispheric coherence differences the ANOVA on alpha coherence revealed no significant effect between the groups \((F(2,37)=0.41; p>0.05)\). The ANOVA on alpha coherence revealed a significant effect only for location \((F(5,18)=12.178; p<0.0001)\) indicating an increased alpha coherence over the frontal, central and occipital electrode pairs.

As mentioned above, in order to avoid a type I error, the level of significance was set to \(p<0.01\) for post-hoc comparisons. However, it is important to note that post-hoc comparisons also showed some results with a \(p\) value of lower than 0.03. Post-hoc comparisons revealed that delta coherence had a tendency to be higher for the controls than for the treated AD group at the \(F_3-P_3\) electrode pair \((p<0.03)\), at the \(F_3-O_1\), and \(F_4-T_6\) electrode pairs \((p<0.03)\). Post-hoc comparisons revealed that the theta coherence had a tendency to be higher for the control group than for the untreated AD at the \(F_3-T_5\) electrode pair \((p<0.03)\).

### 3. Discussion

#### 3.1. General remarks

The study of coherence can be performed successfully only after analysis of selectively distributed oscillatory responses in various topological areas. Additional to the important findings related to amplitudes of oscillatory responses an analysis indicating the increased or decreased connectivity between various areas of the cortex can be reached by analysis of coherence. When we compare the results of previous studies related to alpha band it is clearly seen that the alpha response was affected in the untreated AD patients in comparison to treated AD patients and healthy subjects. The results of Sauseng et al. (2005) indicate that in the healthy subjects, the involvement of pre-frontal areas in executive functions is reflected in an increase of fronto-parietal long range coherence mirroring the activation of a fronto-parietal network. The relevance of the coherence findings is based on this issue. The coupling in the alpha frequency range at \(F_3P_3\) pair (this means coherence between left fronto-parietal areas) is significantly decreased in untreated AD patients, thus showing an important dysfunction of very strong connections between heteromodal areas.

In our previous work (Yener et al., in press) the analysis of the peak amplitudes of EROs showed differences in the delta frequency range in \(C_3\) and \(C_4\) location. However, no difference between the \(F_3\) or \(F_4\) locations in delta, theta, beta or alpha frequency ranges was shown. In the present study no inter-hemispheric significant coherence differences between the groups were found in \(F_3-F_4\) electrode pairs. However, coherence analyses imply that only between \(F_3-P_3\) locations, lower delta, alpha and theta coherences are seen in the untreated AD group. The treated AD group differs from controls in that there are lower values of coherence in the delta range between the right fronto-parietal electrodes and in the theta range between the left fronto-parietal electrodes. Furthermore, there is also a tendency for less coherence at the left fronto-parietal electrodes for the delta band \((p<0.03)\). Our results show that in AD subjects the failure of connectivity between long distance structures is possibly the most marked pathological manifestation. It is known that histological changes are very important and closely related to dementia severity, being earlier (Arriga-gada et al., 1992) or greater in hippocampal area or temporal lobe than frontal lobe (Bierer et al., 1995; Blennow et al., 1996). According to references there are many functional connectivity between hippocampus, frontal and parietal lobes (Demiralp et al., 1994). These connections are the earliest to get affected in AD (Allen et al., 2007; Catani, 2007; Grady et al., 2001). Possibly a more probable explanation for a wider abnormality is seen in coherence values.

Our earlier reports emphasized the left laterality of abnormal phase locking of theta (Yener et al., 2007) or amplitude reduction in delta oscillatory activity over the left fronto-central and mid central regions in AD (Yener et al., in press). Regarding the higher values of coherences in the right hemisphere over those of the left when compared inter-hemispherically, it can be tentatively stated that left hemisphere may be more prone to be affected at the earliest stages of AD. Previous functional neuro-imaging studies report left sided abnormalities in mild AD and further the clinical responders to medication show improvements on left frontal areas (Nobili et al., 2002; Mega et al., 2005; Vennerica et al., 2002).

#### 3.2. **Coherence function in Alzheimer patients**

As described in the introduction above, the measure of spontaneous EEG coherence in psychophysiological studies has been used to evaluate the coupling between various cortical areas of Alzheimer patients. Below, the previous results related to clinical studies will be described.

Zheng-yan (2005) investigated inter- and intra-hemispheric electroencephalography (EEG) coherence at rest and during photic stimulation of patients with Alzheimer’s disease (AD). The authors showed that the general decrease of AD patients in inter- and intra-hemispheric EEG coherence was more significant than that of the normal controls at resting EEG, with the most striking decrease observed in the alpha-1 (8.0–9.0 Hz) and alpha-2 (9.5–12.5 Hz) bands.

Adler et al. (2003) analyzed the coherence during resting EEG in 31 AD patients. These authors reported that left
temporal alpha coherence and inter-hemispheric theta coherence were decreased in AD group.

Locatelli et al. (1998) studied EEG coherence in patients affected by probable AD and they reported that alpha band coherence was decreased in the AD group compared with the control group, more evidently between electrodes over the temporoparietal regions. The decrease was more accentuated for the inter-hemispheric coherences of the posterior regions. The decrease of alpha coherence was more relevant in more cognitively impaired patients. Furthermore, inter-hemispheric delta and theta coherences tended to increase in almost all the analyzed pairs of electrodes with the exception of F7–F8 and T5–T6. Locatelli et al. (1998) additionally reported that at F7–F8 and T5–T6 electrode pairs, a coherence decrease was present in the delta, theta and beta bands in the AD group compared with the controls.

Van der Hiele et al. (2007) investigated the relationship between EEG measures and performance on tests of global cognition, memory, language and executive functioning and found that alpha coherence did not differ between AD and control groups and was unrelated to cognition. The most common result in all these studies is the decrease of the alpha and beta band coherences between distant structures (Adler et al., 2003; Besthorn et al., 1994; Dunkin et al., 1994; Leuchter et al., 1987; Locatelli et al., 1998; Zheng-yan, 2005).

There are only few studies which analyze the evoked coherences between AD patients and healthy controls upon the application of different memory paradigms. Zheng-yan (2005) stated that during photic stimulation, inter- and intra-hemispheric EEG coherences of the AD patients showed lower values in the alpha (9.5–10.5 Hz) band than those of the control group. The author reported that during 5 Hz photic stimulation, the AD patients had significantly lower values of intra-hemispheric coherence in the C4–P4 and C4–O2 pairs for theta band, in the C7–P3, C7–O1, and T5–O2 pairs for alpha band, and the F3–O1, F8–O2, C3–O1, C4–O2, and T6–O2 pairs for beta band.

Hogan et al. (2003) examined memory-related EEG power and coherence over temporal and central recording sites in patients with early Alzheimer’s disease (AD) and normal controls. While the behavioral performance of very mild AD patients did not differ significantly from that of normal controls, when compared with normal controls, the AD patients had reduced upper alpha coherence between the central and right temporal cortex. Our results have some parallels with Hogan’s work, however, in the present study, the lower values of alpha coherence were found only in the untreated group and not in the treated group since the patients were not divided into treated and untreated de novo in Hogan’s work, it is important to mention that the drug has effects on long distance evoked alpha coherence.

3.3. Inter-hemispheric and long distance intra-hemispheric coherence

The inter-hemispheric coherence difference between AD and healthy subjects, in the theta frequency range between two frontal structures (F3–F4), is not high whereas the F3–P3 intra-hemispheric coherence difference reaches a much higher value. It is important to note that the distance between F7–F8 is much greater in comparison to the distance between F3–F4. In spite of this, significant decrease of coherence in the theta band of AD patients (treated and untreated) was found in F3–P3 electrode pair. What does this mean from the physiology perspective? It can be argued that another brain structure, possibly the hippocampus is augmenting the connectivity between these structures. There is also a good possibility that hippocampal structures drive parietal and frontal structures (also see Introduction). As regards parallel processing, in our earlier results related to the phase synchronization and break of synchrony in frontal locations of untreated AD patients, and healthy subjects, that in healthy subjects very good synchronization is seen both in F3–P3 locations. However, this is not the case when the coherence function is analyzed. The administration of pharmacological agents does not contribute to the increase of coherence function between parietal and frontal locations in theta band. The only frequency band, in which the coherence of AD subjects is higher than the untreated AD subjects, is the alpha band at the F3–P3 electrode pair. The Ach mimicking agents augment the synchrony in single locations, but do not necessarily contribute to an increase in the "coupling" between locations for all frequencies. In other words, the "association" between various structures is not necessarily facilitated by the use of pharmacological agents.

3.4. Conclusion

1. During a working memory process the coherence in the left fronto-parietal electrode pair (F7–P3) of AD patients is significantly decreased, thus indicating reduced connectivity between frontal and parietal sites.

2. Although the decrease of the spontaneous alpha coherence of AD patients is a common finding in the literature, the present study introduced two important new steps: a) untreated and treated AD subjects were analyzed as separate groups. b) Moreover, evoked coherence was analyzed upon application of a memory paradigm. This allowed the description of detailed changes in the delta, theta and alpha evoked coherences during sensory-cognitive loading. Evoked alpha coherence was increased upon application of Ach mimicking agents.

4. Experimental procedures

4.1. Subjects

A prospective open study was conducted with twenty-one consecutive, community-dwelling patients suffering from dementia according to the DSM IV criteria and also with the diagnosis of probable Alzheimer’s disease according to the NINCDS-ADRDA criteria (McKhan et al., 1984). The AD group was subdivided into two, the treated and the untreated. In the treated AD group, eleven subjects (4 males, 7 females) were medicated by only cholinesterase inhibitors (AChEI) as a psychotropic agent for 3 to 6 months including the titration period (eight subjects were taking donepezil 10 mg/d with the initial dose of 5 mg/d that was titrated to 10 mg/d by 4 weeks, and three subjects were taking rivastigmine 6–9 mg/d with the initial dose of 3 mg/d, titrated by every 4 weeks either to 6 mg/d or to 9 mg/d depending on the patient’s tolerance of the drug) and ten de novo AD
patients (3 males, 7 females) receiving no psychotropic medication comprised the untreated AD group. The time lapse from the onset of symptoms to the time of recording ranged from 12 to 24 months in both AD groups. Neither group differed from each other regarding Folstein’s Mini-Mental State Examination (MMSE) scores, Reisberg’s Global Deterioration Scale (GDS), gender, education, age, or handedness as shown in Table 1. The MMSE scores of all AD subjects were in the range between 20 and 24, whereas, those of healthy subjects were between 28 and 30 points. All the AD subjects were at stage 4 according to the GDS. In the treated AD group, the majority (8 out of 11 females) were not significantly different from both AD groups with regards to age, gender balance, handedness and education (Table 1). All AD subjects underwent a cognitive and complete neurological, neuro-imaging (CT or MRI) and a blood sample was taken for laboratory examination including blood glucose, electrolytes, liver and kidney function tests, full blood count, eye was also registered. For the reference electrodes and EOG recordings, Ag/AgCl electrodes were used. Linked earlobe electrodes (A1+A2) served as reference. The EOG from the medial upper and lateral orbital rim of the right eye was also registered. For the reference electrodes and EOG recordings, Ag/AgCl electrodes were used. All electrode impedances were less than 5 kΩ and a decrease in their scores. Twenty-one healthy elderly control subjects volunteered for the study, two subjects were excluded for motor artifacts, the remaining 19 control subjects (11 males, 8 females) were recruited from various community sources; none was consanguineous to the patients.

### 4.2. Stimuli and paradigms

A classical visual oddball paradigm was used in the experiments. Two types of stimuli were used: standards and deviants. The probability of the deviant stimuli was 0.20 and that of the standard stimuli 0.80. As stimulation a white screen with 35 cd/cm² luminance was used for standard signals. The luminance of the deviant stimuli was 20% lower (i.e. 28 cd/cm²), the duration of the stimulation was 1000 ms. In all the paradigms, the deviant stimuli were embedded randomly within a series of standard stimuli. These stimulation signals were applied randomly with the inter-stimulus intervals varying between 3 to 7 s. The task required was mental counting of the target stimuli. During the elicitation period of event related oscillations, all the subjects had displayed sufficient accuracy in the mental count of the target stimuli, this was slightly worse in both AD groups than in the control groups. The evoked coherence responses to the target stimuli were analyzed only, during a visual working paradigm; since our aim was to analyze focused attention and working memory.

### 4.3. Electrophysiological recording

The EEG was recorded from F3, F4, C3, C4, T3, T4, T5, T6, P3, P4, O1 and O2 locations according to the 10–20 system (Jasper, 1958). For the recordings, an EEG-CAP (Ag/AgCl electrodes) was used. Linked earlobe electrodes (A1+A2) served as reference. The EOG from the medial upper and lateral orbital rim of the right eye was also registered. For the reference electrodes and EOG recordings, Ag/AgCl electrodes were used. All electrode impedances were less than 5 kΩ. The EEG was amplified by means of a Nihon Kohden EEG-4421 G machine with band limits of 0.1–100 Hz 24 dB/octave. A Brain-Data-System device was used for signal analysis and evaluation of oscillatory dynamics. The EEG was digitized on-line with a sampling rate of 512 Hz and a total recording time of 2000 ms, 1000 ms of which served as the pre-stimulus baseline.

### Table 2 – Results of event related coherences at left and right fronto-parietal electrode pairs and oscillatory activity at F3 and F4 electrode locations in Alzheimer groups compared with controls

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4.4. Coherence

In this research, traditional EEG spectral analysis was performed using magnitude squared coherence. The magnitude squared coherence $C_{xy}(f)$, as a function of the frequency $f$, was defined for every pair of channels as the square of the modulus of the mean cross power spectral density (PSD) normalized to the product of the mean auto PSDs. The magnitude squared coherence between two channel waveforms $x$ and $y$ was calculated as:

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)}$$

where $P_{xy}(f)$ is the cross PSD estimate of $x$ and $y$, $P_{xx}(f)$ and $P_{yy}(f)$ are the PSD estimates of $x$ and $y$, respectively, using Welch’s averaged, modified periodogram method. In the calculation, each signal is divided into sections of 650 ms length with a 50% overlap, each section is windowed with a Hanning window and each signal is divided into sections of 650 ms length with a 50% overlap, each section is windowed with a Hanning window and averaged. In order to form $P_{xy}(f)$, the cross PSD of $x$ and $y$, the products of the length 650 ms FFTs of the sections of $x$ and $y$ are averaged. Similarly, the magnitude squared of the length 650 ms FFTs of the sections of $x$ and the sections of $y$ are averaged to form $P_{xx}(f)$ and $P_{yy}(f)$, the PSDs of $x$ and $y$, respectively. $C_{xy}(f)$ is a real function of frequency ranging from 0 to 1, indicating how well the waveform $x$ corresponds to the waveform $y$ at each frequency. The Matlab program was used for coherence analysis.

The EEG signals were recorded with a sampling rate of 512 Hz. One sweep consisted of 2000 ms, for coherence a post stimulus time window of 650 ms was analyzed, 14 artifact-free sweeps per subject were processed with a spectral resolution of 0.5 Hz. The average coherence was calculated as the average of the coherence values between channel pairs. Then, Fisher’s Z transformation was used to normalize the distribution of average coherence values.

Coherence was calculated for the target stimuli for long range intra-hemispheric and inter-hemispheric pairs for three different frequency bands (delta (1–3.5 Hz); theta (4–7 Hz); alpha (8–13 Hz). The long range intra-hemispheric pairs were $F_3-F_4$, $F_3-T_5$, $F_3-O_1$, $F_4-P_3$, $F_4-T_6$, $F_4-O_2$; the inter-hemispheric pairs were $F_3-F_2$, $C_2-C_4$, $T_3-T_4$, $T_3-T_6$, $P_3-P_4$, $O_1-O_2$.

4.5. Statistics

Fisher’s Z transformation was used to normalize the distribution of coherence values. The Statistical Package for Social Studies (SPSS) was used for statistical analysis. The differences between the groups were assessed by means of a repeated measure ANOVA for each frequency band, and for the intra-hemispheric and inter-hemispheric locations. In the analysis of intra-hemispheric coherence differences, repeated measure ANOVA included the between-subjects factor as groups (healthy elderly controls, untreated AD, treated AD), and included the within-subject factors as hemisphere (right, left) and location ($F_3-F_3$, $F_3-T_5$, $F_3-O_1$ vs $F_4-P_3$, $F_4-T_6$, $F_4-O_2$). In the analysis of inter-hemispheric coherence differences, repeated measures of ANOVA included the between-subjects factor as groups (healthy elderly controls, untreated AD, treated AD) and included the within-subject factors as location ($F_3-F_4$, $C_2-C_4$, $T_3-T_4$, $T_3-T_6$, $P_3-P_4$, $O_1-O_2$). Greenhouse-Geisser corrected $p$-values are reported, for the post-hoc comparisons $t$-tests were used and a level of significance was set to $p < 0.01$ for post-hoc comparisons. The group differences were analyzed by Chi-square and one way ANOVA tests (Table 1).

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