Evoked and event related coherence of Alzheimer patients manifest differentiation of sensory–cognitive networks

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ABSTRACT

In previous studies on Alzheimer's patients it was shown that, in frontal and parietal locations, delta and theta responses of AD patients were greatly reduced. The present study analyzed coherence functions in these highly affected frontal and parietal areas. Visual sensory and event related coherences of patients with Alzheimer type dementia (AD) were analyzed comparatively. A total of 38 mild, probable AD subjects (19 untreated, 19 treated with cholinesterase inhibitors) were compared with a group of 19 healthy controls. The sensory evoked coherence and event related target coherences were analyzed for delta (1–3.5 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (15–30 Hz) and gamma (28–48 Hz) frequency ranges for long-range intra-hemispheric (F3–P3, F4–P4, F3–T5, F4–T6, F3–O1, F4–O2) electrode pairs. The healthy control group showed significantly higher values of event related coherence in "delta", "theta" and "alpha" bands in comparison to the de novo and medicated AD groups (p<0.01 for the delta, theta and alpha) upon application of a target stimuli. In contrast, almost no changes in event related coherences were observed in beta and gamma frequency bands. Furthermore, no differences were recorded between healthy and AD groups upon application of simple light stimuli. Besides this, coherence values upon application of target stimuli were higher than sensory evoked coherence in all groups and in all frequency bands (p<0.01). The cognitive networks of AD patients were highly impaired in comparison to networks activated by sensory stimulation, thus showing separate activation of sensory and cognitive networks.

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Abbreviations: AChEI, Cholinesterase inhibitor; AD, Alzheimer type dementia; DSM IV, Diagnostic and Statistical Manual of Mental Disorders 4; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association; CT, Computed tomography; EEG, Electroencephalogram; EOG, Electrooculograph; EROs, Event Related Oscillations; GDS, Reisberg’s Global Deterioration Scale; HIV, Human Immunodeficiency Virus; MMSE, Folstein’s Mini-Mental State Examination; MRI, Magnetic Resonance Imaging; RF, Reticular Formation; VDRL, Venereal Disease Research Laboratory; MCI, Mild Cognitive Impairment

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1. Introduction

For almost a decade, the concept and methods of the fast emerging field of “oscillatory brain dynamics” have been prominent in both the neurophysiology literature and also in clinical applications. The number of reports is rapidly increasing, as presented in a recent review on brain oscillations in clinical impairment (Başar and Güntekin, 2008). Electroencephalography and event related potentials are proposed by several authors as biomarkers in Alzheimer’s disease (for reviews, see Herrmann and Demiralp, 2005; Uhlhaas and Singer, 2006; Jackson and Snyder, 2008).

EEG coherence globally describes the coupling of, or relationship between, signals in a given frequency band. Long distance coherence has been analyzed in the context of parallel processing by several authors. (Başar, 1980; Miltner et al., 1999; Schürmann et al., 2000; Kocsis et al., 2001). EEG coherence is considered an important large-scale measure of functional relationships or synchronized functioning between pairs of cortical regions, and therefore the brain’s functional connectivity (Nunez, 1997).

Alzheimer’s disease (AD) is a neurodegenerative disease that, in its most common form, is generally found in people aged over 65. Approximately 24 million people worldwide have dementia, of which the majority (approximately 60%) is due to AD (Ferri et al., 2005). Clinical signs of Alzheimer’s disease are characterized by progressive cognitive deterioration, together with declining activities in daily life, and by neuropsychiatric symptoms or behavioral changes. Although the ultimate cause of AD is unknown, genetic factors are clearly indicated, as dominant mutations in three different genes have been identified (Waldemar et al., 2007). Acetylcholinesterase inhibitors appear to moderate symptoms; however, they do not permanently alter the course of the underlying dementing process (Bont et al., 2006; Dougall et al., 2004; Marksteiner et al., 2007).

Several research groups have previously published a number of studies related to analysis of oscillatory dynamics in MCI and AD patients. Babiloni et al. (2006, 2007, 2009) published core results on EEG rhythms in MCI patients. Zheng-yan (2005), Hogan et al. (2003), Güntekin et al. (2008), Yener et al. (2007, 2008) and Dauwels et al. (2010) published results on Alzheimer patients. In these studies, it was demonstrated that the most affected frequency bands upon the application of oddball paradigms are the delta and theta bands. The most marked findings of these studies were lower delta amplitude in central areas (Yener et al., 2008) and lower phase locking values in the theta band in frontal areas (Yener et al., 2007). Evoked coherence studies (Hogan et al., 2003) showed reduced evoked coherence in AD patients between central and right temporal electrodes upon application of a memory paradigm, whereas Güntekin et al. (2008) showed reduced evoked coherence in the fronto-parietal recording sites upon application of an oddball paradigm. Zheng-yan (2005) reported that, during photic stimulation, the interand intra-hemispheric EEG coherences of AD patients were lower in the alpha (9.5–10.5 Hz) band than those of the control group.

At this point, it is vital to emphasize that there are important functional differences between “EEG Coherence”, “Evoked Coherence” and “Cognitive Response Coherence”. In the spontaneous EEG analysis, only sporadically occurring coherences from hidden sources can be measured. Sensory evoked coherences reflect the property of sensory networks activated by a sensory stimulation. Event related (or cognitive) coherences manifest coherent activity of sensory and cognitive networks triggered by a cognitive task. Accordingly, the cognitive response coherences comprehend activation of a greater number of neural networks that are most possibly not activated, or less activated, in the EEG and sensory evoked coherences. Therefore, event related coherence merits special attention. Particularly in AD patients with strong cognitive impairment, it is relevant to analyze whether medical treatment (drug application) selectively acts upon sensory and cognitive networks manifested in topologically different areas and in different frequency windows. Such an observation may provide, in the future, a deeper physiological understanding of distributed functional networks and, in turn, the possibility of determining biomarkers for medical treatment. According to the statements above, there are new steps and newly emerging questions for the present study in comparison with earlier AD results.

Preliminary findings of an event related coherence study with 22 AD subjects were published by Güntekin et al. (2008); that preliminary report, did not include a comparative analysis with sensory coherence. Besides this, beta and gamma frequency windows were not yet evaluated. The present study aims to provide a more complete picture of the topology of functional brain oscillations in AD patients, by employing recent methodological extensions and also a greater number of study participants (n=38).

The initiation of our new measurements had four goals: (1) comparisons of evoked coherences and event related coherences in healthy elderly subjects should provide a measure for interpretation of coherence changes induced by simple light sensory stimulation and by a simple cognitive load by means of a P300 oddball paradigm. This comparison of simple light and simple cognitive load should also demonstrate the efficiency of computed coherence function, despite criticisms, for measuring the coherence function in human subjects (Srinivasan et al., 2007). (2) The comparison between coherence functions upon sensory stimulation and the application of cognitive load to AD subjects, which possibly allow the determination of topology and frequency windows of connected networks. (3) To observe results following the administration of drugs to AD patients. (4) The evaluation of coherence function in frequency windows of delta, theta, alpha, beta and gamma frequency range for frontal-central-temporal-parietal-occipital locations.

2. Results

The results of the study will be grouped in 5 different frequency windows, covering delta, theta, alpha, beta and gamma frequency ranges.

Table 1 presents the mean evoked-event related response coherence values of untreated AD (u-AD), treated AD (t-AD) and healthy control subjects (Cont) in delta (0.5–3.5 Hz), theta
The peak-to-peak delta central and parietal electrodes were as follow: F3: 7.94 (±3.18), P3: 6.81 (±0.79), P4: 6.40 (±0.71). The mean values of untreated AD subjects for frontal, central and parietal electrodes were as follow: F3: 6.32 (±3.54), F4: 5.79 (±2.81), Cz: 5.46 (±6.00), C3: 4.5 (±5.18), C4: 5.6 (±3.50), P3: 4.7 (±2.13), P4: 5.6 (±5.51). The mean values of untreated AD subjects for frontal, central and parietal electrodes were as follow: F3: 7.75 (±7.52), F4: 7.68 (±4.62), Cz: 6.87 (±6.66), C3: 6.06 (±7.29), C4: 6.71 (±3.08), P3: 6.43 (±2.26), P4: 5.95 (±2.61). The given mean values were in good accordance with our previous study (Yener et al., 2008).

For further information on oscillatory time course in delta, theta, alpha, beta and gamma, please see Yener et al. (2008).

2.1. Delta (1–3.5 Hz)

In the analysis of intrahemispheric coherence differences, ANOVA of the delta response coherence revealed a significant effect between stimuli (F(1,154)=9.86; p<0.000) and the post-hoc comparisons revealed that delta response coherence was significantly higher for target responses than for simple light responses. The ANOVA of the delta response coherence revealed a significant effect between the stimuli × group (F(2,54)=5.39; p<0.009). The post-hoc comparisons revealed that delta response coherence upon application of target stimuli was significantly higher for healthy subjects than for untreated AD patients (p<0.000) and also treated AD patients (p<0.000); this difference was not significant for simple light stimuli. The ANOVA of delta response coherence revealed a significant effect for location (F(2,108)=23.07; p<0.000), indicating increased delta response coherence for unprocessed AD subjects. Post-hoc comparisons between groups showed significant results for controls versus untreated AD and treated AD patients. Post-hoc comparisons revealed that delta response coherence was significantly higher for controls than for untreated AD patients (p<0.007) and was higher for controls than for treated AD patients (p<0.000).

Fig. 1 presents a histogram of mean Z values for the delta frequency range upon application of “simple light” stimuli for all electrode pairs. Fig. 2 presents a histogram of mean Z values for the delta frequency range upon application of “target” stimuli for all electrode pairs. Fig. 2 shows that the healthy subjects had higher delta response coherence compared to both untreated and treated AD subjects upon application of target stimuli for all electrode pairs. The mean Z value of healthy subjects was 40%–50% higher than AD patients in most of the electrodes pairs upon application of “target” stimuli. Comparison of Figs. 1 and 2 shows that the evoked delta coherence upon “simple light” stimuli is not high and no differences were recorded between healthy and AD subjects.

| Table 1 – Mean evoked-event related response coherence values in specific frequency bands (delta, 0.5–3.5 Hz; theta, 4–7 Hz; alpha, 8–13 Hz; beta, 15–30 Hz; gamma, 28–48 Hz) in treated AD (t-AD), untreated AD (u-AD) and healthy elderly controls (Cont) for all electrode pairs. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Delta | Theta | Alpha | Beta | Gamma |
| u-AD | t-AD | Cont | u-AD | t-AD | Cont | u-AD | t-AD | Cont | u-AD | t-AD | Cont | u-AD | t-AD | Cont |
| Visual evoked response coherence | F3 | 0.357 | 0.449 | 0.356 | 0.363 | 0.359 | 0.308 | 0.325 | 0.355 | 0.266 | 0.374 | 0.431 | 0.275 | 0.444 | 0.474 | 0.334 |
| | F4 | 0.428 | 0.435 | 0.385 | 0.345 | 0.347 | 0.344 | 0.75 | 0.360 | 0.313 | 0.376 | 0.381 | 0.280 | 0.398 | 0.464 | 0.325 |
| | F3 | 0.411 | 0.438 | 0.370 | 0.401 | 0.419 | 0.369 | 0.411 | 0.422 | 0.372 | 0.399 | 0.465 | 0.344 | 0.505 | 0.586 | 0.396 |
| | F4 | 0.429 | 0.422 | 0.409 | 0.416 | 0.383 | 0.407 | 0.449 | 0.422 | 0.417 | 0.449 | 0.461 | 0.366 | 0.538 | 0.543 | 0.410 |
| | F3 | 0.283 | 0.356 | 0.376 | 0.297 | 0.305 | 0.302 | 0.319 | 0.291 | 0.284 | 0.329 | 0.383 | 0.278 | 0.427 | 0.458 | 0.331 |
| | F4 | 0.381 | 0.346 | 0.387 | 0.305 | 0.273 | 0.316 | 0.354 | 0.302 | 0.301 | 0.336 | 0.357 | 0.320 | 0.456 | 0.414 | 0.343 |
| Visual event related response coherence | F3 | 0.576 | 0.625 | 0.681 | 0.573 | 0.594 | 0.667 | 0.581 | 0.604 | 0.668 | 0.652 | 0.682 | 0.685 | 0.671 | 0.687 | 0.721 |
| | F4 | 0.573 | 0.567 | 0.718 | 0.551 | 0.557 | 0.672 | 0.549 | 0.630 | 0.695 | 0.633 | 0.622 | 0.710 | 0.696 | 0.669 | 0.725 |
| | F3 | 0.626 | 0.578 | 0.709 | 0.637 | 0.658 | 0.712 | 0.546 | 0.659 | 0.724 | 0.658 | 0.722 | 0.705 | 0.746 | 0.765 | 0.744 |
| | F4 | 0.657 | 0.547 | 0.738 | 0.602 | 0.612 | 0.718 | 0.614 | 0.651 | 0.733 | 0.658 | 0.690 | 0.725 | 0.711 | 0.721 | 0.749 |
| | F3 | 0.480 | 0.522 | 0.672 | 0.536 | 0.529 | 0.646 | 0.535 | 0.560 | 0.682 | 0.605 | 0.639 | 0.695 | 0.695 | 0.694 | 0.719 |
| | F4 | 0.495 | 0.544 | 0.682 | 0.547 | 0.528 | 0.668 | 0.551 | 0.608 | 0.698 | 0.628 | 0.622 | 0.690 | 0.693 | 0.666 | 0.728 |
2.2. Theta (4–7.5 Hz)

In the analysis of intrahemispheric coherence differences, ANOVA of the theta response coherence revealed a significant effect between stimuli (F(1,54)=159.43; p<0.000) the post-hoc comparisons revealed that theta response coherence was significantly higher for target responses than for simple light responses. The ANOVA of the theta response coherence revealed a significant effect between the stimuli×group (F(2,54)=4.91; p<0.02). The post-hoc comparisons revealed that theta response coherence upon application of target stimuli was significantly higher for healthy subjects than for untreated AD patients (p<0.000) and also treated AD patients (p<0.000); this difference was not significant for simple light stimuli. The ANOVA of theta coherence revealed a significant effect for location (F(2,108)=49.35; p<0.000), indicating increased theta response coherence over fronto-parietal electrode pairs. The ANOVA of the theta response coherence revealed a significant effect between the groups (F(2,54)=7.04; p<0.003). Post-hoc comparisons revealed that theta response coherence was significantly higher for controls than for treated AD patients (p<0.003).

Fig. 3 shows mean Z values for the theta frequency range upon application of “simple light” stimuli for all electrode pairs. Fig. 4 shows mean Z values for the theta frequency range upon application of “target” stimuli for all electrode pairs. Fig. 4 shows that the healthy subjects had higher theta response coherence compared to both untreated and treated AD subjects upon application of target stimuli for all electrode pairs. The mean Z value of healthy subjects was 30%–40% higher than AD patients in most of the electrode pairs upon application of “target” stimuli. Comparison of Figs. 3 and 4 shows that the evoked theta coherence upon “simple light” stimuli is not high and no differences were recorded between healthy and AD subjects.

Fig. 1 – Mean Z values of healthy control, treated AD and untreated AD subjects for delta frequency range upon simple light stimuli (“★” sign represents p<0.01). Red bars represent the mean Z values for healthy subjects, green bars represent the mean Z value for untreated AD subjects, and blue bars represent the mean Z values for treated AD subjects.

Fig. 2 – Mean Z values of healthy control, treated AD and untreated AD subjects for delta frequency range upon target stimuli (“★” sign represents p<0.01). Red bars represent the mean Z values for healthy subjects, green bars represent the mean Z value for untreated AD subjects, and blue bars represent the mean Z values for treated AD subjects.

Fig. 3 – Mean Z values of healthy control, treated AD and untreated AD subjects for theta frequency range upon simple light stimuli (“★” sign represents p<0.01). Red bars represent the mean Z values for healthy subjects, green bars represent the mean Z value for untreated AD subjects, and blue bars represent the mean Z values for treated AD subjects.
When analyzing variations in intrahemispheric coherence, ANOVA of the alpha response coherence revealed a significant difference between response to stimulus types. (F(1,54)=115.22; p<0.000). Post-hoc comparisons revealed that alpha response coherence was significantly higher for target response stimuli than for simple light responses (p<0.000). The ANOVA of the alpha response coherence revealed a significant effect between the stimuli×group (F(2,54)=4.63; p<0.02). The post-hoc comparisons revealed that alpha response coherence upon application of target stimuli was significantly higher for healthy subjects than for untreated AD patients (p<0.000) and treated AD patients (p<0.000); this difference was not significant for simple light stimuli. The ANOVA of alpha response coherence revealed a significant effect for location (F(2,108)=42.809; p<0.000), indicating increased alpha response coherence over fronto-parietal electrode pairs. The ANOVA of alpha response coherence revealed a significant effect for laterality (F(1,54)=10.685; p<0.003), indicating increased alpha response coherence over the right hemisphere. The ANOVA of alpha response coherence revealed no significant effect between the groups.

Fig. 4 illustrates mean Z values for the alpha frequency range upon application of “target” stimuli for all electrode pairs. Fig. 5 illustrates mean Z values for the alpha frequency range upon application of “simple light” stimuli for all electrode pairs. Fig. 6 shows that the healthy subjects had higher alpha response coherence compared to both untreated and treated AD subjects upon application of target stimuli for almost all electrode pairs. The mean Z value of healthy subjects was 25%–38% higher than AD patients in most of the electrode pairs upon application of “target” stimuli. Comparison of Figs. 5 and 6 shows that the evoked alpha coherence upon “simple light” is not high and no differences were recorded between healthy and AD subjects.
2.4. Beta (15–30 Hz)

In the analysis of intrahemispheric coherence differences, ANOVA of the beta response coherence revealed a significant difference between response to stimulus types \((F(1,54) = 238.812; \ p<0.000)\). Post-hoc comparisons revealed that beta response coherence was significantly higher for target responses than for simple light responses. The ANOVA of beta response coherence revealed a significant effect for location \((F(2,108) = 28.05; \ p<0.000)\), indicating increased beta response coherence over fronto-parietal electrode pairs. The ANOVA of beta response coherence revealed no significant effect between stimuli×group and revealed no significant effect between the groups.

Fig. 7 shows mean Z values for the beta frequency range upon application of “simple light” stimuli for all electrode pairs. Fig. 8 shows mean Z values for the beta frequency range upon application of “target” stimuli for all electrode pairs. Compared to healthy subjects, the AD subjects had higher beta response coherences upon application of “simple light” in a small number of electrode pairs (Fig. 7). The significant differences observed between healthy subjects and AD patients for delta, theta and alpha frequency ranges were not observed for the beta frequency range upon application of a “target stimulus”. Again, in the beta frequency range, it was found that visual stimulation did not evoke higher response coherences upon simple light stimuli, whereas cognitive stimulation evoked higher coherences. However, it is important to note that, in the beta frequency range in AD patients, no significant decrease of coherence was observed.

Fig. 7 – Mean Z values of healthy control, treated AD and untreated AD subjects for beta frequency range upon simple light stimuli (“★” sign represents \(p<0.01\)). Red bars represent the mean Z values for healthy subjects, green bars represent the mean Z value for untreated AD subjects, and blue bars represent the mean Z values for treated AD subjects.

2.5. Gamma (28–48 Hz)

In the analysis of intrahemispheric coherence differences, ANOVA of the gamma response coherence revealed a significant difference between response to stimulus types \((F(1,54) = 150.24; \ p<0.000)\). Post-hoc comparisons revealed that gamma response coherence was significantly higher for target stimuli than for simple light stimuli. The ANOVA of gamma response coherence revealed a significant effect for location \((F(2,108) = 47.14; \ p<0.000)\), indicating increased gamma response coherence over fronto-parietal electrode pairs. The ANOVA of gamma response coherence revealed a significant effect for stimuli×location×laterality \((F(2,108) = 47.14; \ p<0.003)\), indicating increased gamma response coherence over left fronto-parietal \((F3–P3)\) electrode pairs upon application of target stimuli \((p<0.03)\). Fig. 9 shows mean Z values for the gamma frequency range upon application of “simple light” stimuli for all electrode pairs. Fig. 10 shows mean Z values for the gamma frequency range upon application of “target” stimuli for all electrode pairs. The significant differences observed between healthy subjects and AD patients for delta, theta and alpha frequency ranges were not observed for the gamma frequency range upon application of a cognitive paradigm. When compared to healthy subjects, the AD subjects had higher gamma response coherences upon application of “simple light” in a small number of electrode pairs (Fig. 9). Again, similar to other frequency ranges, it was found that, in the gamma range, visual stimulation did not evoke higher coherences upon
simple light stimuli, whereas cognitive stimulation evoked higher coherences.

3. Discussion

The results of the present paper can be analyzed from four perspectives. (1) Firstly, we will review studies of coherence in Alzheimer’s disease, including mild cognitive impairment, by indicating the importance of oscillatory dynamics. (2) After an introductory description, we will introduce a comparative analysis of event related coherences of our study in low and high frequency ranges. (3) A comparative analysis of Alzheimer’s disease and bipolar patients is important, since such comparison will possibly allow future analysis of physiology and neurotransmitters. (4) An analysis of response coherence from the viewpoint of methodology is pertinent, since such an analysis may possibly provide a methodological means to exclude the effects of volume conduction.

3.1. Survey of coherence studies and event related oscillations in mild cognitive impairment and Alzheimer’s disease

The importance of the analysis of event related oscillations, (meaning increase of cognitive load) in the brain by means of external stimulation was described in the Introduction. Accordingly, the results on target responses merit important consideration in comparison to spontaneous activity and sensory evoked oscillations, especially in the case of subjects with cognitive impairment. Relatively few studies of Alzheimer patients using cognitive input were identified within the literature. In the following section, we briefly review the published data in this field, including MCI patients. This discussion outlines the most important electrophysiological deficits in Alzheimer patients.

Resting, eyes-closed EEG data were recorded in 34 Mild Cognitive Impairment (MCI) and 65 AD subjects by Babiloni et al. (2006). The EEG rhythms of interest were delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), and beta 2 (20–30 Hz). The EEG cortical sources were estimated using low-resolution brain electromagnetic tomography (LORETA). Cortical EEG sources were correlated with MR-based measurements of the lobar brain volume (white and gray matter). A negative correlation was observed between the frontal white matter and the amplitude of the frontal delta sources (2–4 Hz) across the MCI and AD subjects. In a subsequent study, Babiloni et al. (2007) showed that the parietal to frontal direction of the
information flux within EEG functional coupling for alpha and beta rhythms was stronger in normal elderly subjects than in MCI and/or AD patients.

Hogan et al. (2003) examined memory-related EEG power and coherence over temporal and central recording sites in patients with early AD and a normal control group. While the behavioral performance of patients with very mild AD did not differ significantly from that of normal controls, the AD patients had comparatively reduced upper alpha coherence between the central and right temporal cortex.

Zheng-yan (2005) stated that, during photic stimulation, the inter- and intra-hemispheric EEG coherences of AD patients were lower within the alpha (9.5–10.5 Hz) band than those of the control group. It was reported that, during a 5 Hz photic stimulation, the AD patients had significantly lower intra-hemispheric coherence in the C3–P4 and C3–O1 electrode pairs for theta band; in the C3–P3, C3–O2, and T3–O2 electrode pairs for alpha band; and in the P3–O1, P3–O2, C3–O1, C3–O2, and T3–O2 electrode pairs for beta band oscillations. Zheng et al. (2007) also investigated the functional relationship between calculated alpha band spectral power and inter-/intra-hemispheric coherence during a three-level working memory task undertaken by patients with mild cognitive impairment (MCI). The inter-hemispheric EEG coherences in frontal (F3–F4), central (C3–C4), parietal (P3–P4), temporal (T3–T4) and occipital (O1–O2) regions in MCI patients were compared to those in normal controls. The coherence in MCI patients was significantly higher than in the controls. The findings of Zheng et al. (2007) indicate that the alpha frequency band may be the characteristic band in distinguishing MCI patients from normal controls during working memory tasks. MCI patients exhibit greater inter-hemispheric connectivity than intra-hemispheric connectivity when memory demand increases.

The results presented by Missonnier et al. (2006) indicate that a decrease in the power of early phasic theta ERO during working memory activation may predict cognitive decline in MCI. This phenomenon is not related to working memory load, but may reflect the presence of early deficits in directed, attention-related neural circuits in patients with MCI.

According to the few published ERO studies, it can be concluded that the left frontal and central areas in AD patients are the regions of the brain that show the most evidence of effects associated with AD (Yener et al., 2007, 2008). In these studies, it was clearly demonstrated that the most-affected frequency-bands upon the application of the oddball paradigms were for central areas in the delta and theta bands (Yener et al., 2008). Lower values of phase locking were observed in the theta band in the frontal areas (Yener et al., 2007). The relevance of these findings is that the most fundamental components of the oddball paradigms are delta and theta responses.

Evoked coherence studies (Hogan et al., 2003) showed reduced evoked coherence in AD patients between central and right temporal electrodes, whereas Güntekin et al. (2008) showed reduced evoked coherence in the fronto-parietal recording sites.

It is also worth noting the drug effects on EROs in AD patients. Drug therapies have been reported to have local effects on theta phase synchrony in the left frontal areas and to have long-range connection effects on the alpha evoked coherence in the left fronto-parietal electrode pairs (Yener et al., 2007; Güntekin et al., 2008).

Güntekin et al. (2008) investigated event related coherence in patients with AD forms of dementia using a visual oddball paradigm. A total of 21 mild, probable AD subjects were compared with a group of 19 healthy controls. The AD group was divided into the untreated (n = 10) and those treated with a cholinesterase inhibitor (n = 11). The authors found that the control group showed higher values of evoked coherence in the “delta”, “theta” and “alpha” bands in the left fronto-parietal electrode pairs compared to the untreated AD group. The healthy subjects showed higher values of evoked coherence in the left fronto-parietal electrode pair in the theta frequency band and higher values of evoked coherence in the right fronto-parietal electrode pair in the delta band when compared to the treated AD group.

The results of the present study add a new perspective to the previous studies on AD mentioned above. According to the results of the present study, the coherence upon cognitive load was reduced, indicating impaired connectivity between fronto-temporal, fronto-parietal and fronto-occipital locations in the lower frequency ranges. Furthermore, in our previous studies, medication was found to improve local circuits in the theta band (Yener et al., 2007). However, this was not the case for the long range circuits; the medication did not have any significant effects on coherence values.

3.2. Remark related to response coherences

More detailed discussion on response coherences (evoked and event related) can be achieved by jointly analyzing the results presented in Figs. 1 to 10.

1) Visual evoked coherences in low frequency range between 1 and 13 Hz

The response coherences upon simple light stimuli do not show any change in healthy subjects, de novo AD subjects and medicated AD subjects in the delta, theta and alpha frequency ranges. Only a slight increase of coherence was observed in healthy subjects, in the delta band between fronto-occipital coherence. In all other cases, the coherence value is almost at the noise\(^1\) level.

2) Visual event related response coherences in the low frequency range

The highest changes in coherence value in this low frequency range were observed in the delta frequency band and in healthy subjects in the fronto-occipital location. Healthy subjects were observed to have almost 40% higher delta coherence response in comparison to AD patients. The increase in the theta and alpha bands are moderate, being in the 10 to 20% range, in theta and alpha bands.

\(^1\) The noise level is the baseline coherence level without sensory or endogenous stimulation. The coherence value without sensory or endogenous stimulation is between 0.25–0.3.
3.3. Differentiation of sensory and cognitive networks by means of response coherences indicates the role of frontal and parietal areas in AD patients

The target response of the applied P300 oddball paradigm in the present study is activated by four basic cognitive functions: “perception”, “focused attention”, “learning” and “working memory” (Rektor et al., 2004; Başar-Ertürk and Başar, 1991; Halgren et al., 2002; Klimesch et al., 2006).

We defined “response coherence” as the coherence of an evoked/event related coherence, which is different from the spontaneous coherence (or the coherence in the unfiltered EEG). It is worthwhile to further discuss the differentiation of evoked coherence and event related (cognitive) coherence. The evoked coherence mostly reflects the augmentation or strengthening of links between various neural networks upon application of pure sensory signals, whereas the event related coherence reflects the strengthening of links (or neural connections) of neural networks upon stimulation by a sensory signal loaded with a cognitive task. Accordingly, upon application of a signal loaded with cognitive task (in this case the oddball paradigm) most possibly extended neural assemblies are activated; in turn, a recorded increase of coherence in a given frequency channel reflects the strengthening of links and amplification of electrical signal flow between the brain areas under examination. This increased coherence is a function of the applied cognitive task. In the present case, the increased coherence observed between left frontal and left parietal areas logically reflects the effect of the tasks of focused attention, learning and working memory. Accordingly, the failure of coherence in AD patients manifests itself in most frequency bands during target detection. Furthermore, while this breakdown of neural connections occurs globally, it might be tentatively pointed out that — depending on task demands — the dysfunction of the frontal-parietal system becomes especially apparent in the major loss of $F_3-P_3$ coherence in Alzheimer patients. Furthermore, no such activation failure is found for sensory processing, implying different networks for processing sensory and cognitive information.

However, it was found that $F_3-O_1$ connection was impaired when a visual sensory stimulation was given, in comparison to failed $F_3-P_3$ connectivity after a visual cognitive stimulation. This differential connectivity implies two distinct networks after two sets of stimuli, i.e. sensory and cognitive.

3.4. Low frequency event related coherences (1–15 Hz) versus higher frequency event related coherences (28–48 Hz) in AD patients

An intriguing result in the present report is the behavior of low frequency and higher frequency coherences in AD patients. Upon cognitive load, long distance coherences in delta, theta and alpha frequency ranges showed marked changes in healthy subjects versus AD patients. From the perspective of electrophysiological analysis, these results give rise to a number of questions that are difficult to answer. Presently, we only mention that analysis of the findings of our research group on euthymic and mania bipolar patients indicated a heavy reduction of gamma target coherences (Özerdem et al., 2009, 2010). We have treated AD patients with cholinesterase inhibitors (AChEI); and bipolar patients with Valproate, which is sensitive to GABA release, as discussed in the previous section.

According to a recent report by our group (Özerdem et al., 2010), there is a clear disruption of long distance gamma band coherence in bipolar manic patients, especially at the right fronto-temporal location, as shown by a 35% lower coherence value among manic patients compared to healthy controls. This may correspond to a functional fronto-temporal connectivity problem in bipolar disorder. As results of the present study showed, no reduction of coherence in the gamma frequency band was observed in AD patients.

The comparison with bipolar patients in the gamma band may provide future research opportunities on the relationship between oscillatory responses and neurotransmitters. It is therefore hoped that the comparison of event related coherences between all frequency windows and between various diseases might provide important information related to the genesis of event related oscillations that are anchored with transmitter release.

3.5. Concluding remarks

1) Cognitive impairment of AD subjects is also manifested by reduced coherences in delta, theta and alpha frequency ranges in response to cognitive target stimulation in a P300 paradigm.

2) In higher frequency bands (beta and gamma), no changes in event related coherences of AD patients were observed upon cognitive load.

3) The results presented in this study provide evidence for the existence of separate sensory and cognitive networks that are activated either on sensory or cognitive stimulation.

4) As a relevant strategy of the present study, we compared coherence values in response to simple light versus a target with a defined cognitive load. Sensory–cognitive stimulation has differentiated activation on a unique network or it activates two different networks. It is important to show that the brain responds differentially to cognitive signals.

Function related oscillations in the spontaneous EEG are mostly activated by hidden sources and, in sensory evoked oscillation, mostly by sensory signals. It is possible that cognitive stimulation activates both sensory and cognitive networks, since the cognitive stimulation employed also includes sensory component.

5) It may be tentatively recommended that the approach employed by Srinivasan et al. (2007) might be reevaluated by the application of different sensory and cognitive paradigms. Possibly, in this way, the approach employed by these authors may provide greater scientific benefit.

6) The application of the paradigm with response coherences as cognitive input may serve in the future as a diagnostic tool in the evaluation of AD patients. It is recommended to use a range of results mentioned in previous studies (see Yener et al., 2007, 2008; Babiloni et al., 2006, 2007, 2009).

7) It is also of note that commonly used forms of medication (cholinesterase inhibitors (AChEI)) were shown to be less effective in AD patients.
4. Experimental procedures

4.1. Subjects

We conducted a prospective open study. Forty-one community-dwelling mild Alzheimer patients were included in the study; three were excluded (n=38) due to motor artifacts. The data previously presented in Güntekin et al. (2008) has been also included in the present extended analysis. All patients were suffering from dementia according to the DSM IV criteria or were diagnosed with probable Alzheimer’s disease according to the NINCDS-ADRDA criteria (McKhann et al., 1984). Twenty-two healthy elderly control subjects volunteered for the study, of which three were excluded (n=19). The AD group was divided into two sub-groups, termed treated and untreated (de novo) in order to determine the drug effects on evoked and event related coherence values. In the treated AD group, nineteen subjects (10 males, 9 females) were given only cholinesterase inhibitors (AChEI) as a psychotropic agent from 3 to 6 months, including the titration period (twelve subjects were given donepezil 10 mg/d, with an initial dose of 5 mg/d that was titrated to 10 mg/d by week 4; seven subjects were given rivastigmine 6–9 mg/d, with an initial dose of 3 mg/d, titrated every 4 weeks either to 6 mg/d or to 9 mg/d, depending on the tolerance of the drug). The untreated AD group comprised nineteen AD patients (9 males, 10 females) not taking any psychotropic medication. Neither of the AD groups differed in terms of Folstein’s Mini-Mental State Examination (MMSE), gender, age, or handedness, as shown in Table 2. The time from the onset of symptoms was between one and two years in both AD groups. The MMSE scores of all AD subjects ranged between 20 and 24, whereas those of healthy “control” subjects were between 28 and 30 points. All of the AD subjects were on stage 4 according to the Reisberg’s Global Deterioration Scale. Control subjects (11 males, 8 females) did not differ significantly from either of the AD groups in terms of age, gender, handedness or education (Table 2). All AD subjects underwent a cognitive and complete neurological, neuro-imaging examination (CT or MRI), and a blood sample was taken for laboratory examination, including blood glucose, electrolytes, liver and kidney function tests, full blood count, erythrocyte sedimentation rate, thyroid hormone, vitamin B12, HIV, and VDRL. The healthy controls were recruited from various community sources; none were consanguineous to the patients. The study was approved by the local ethics committee. All participants in the study and, where necessary, their relatives, gave written informed consent.

4.2. Stimuli and paradigms

Two different stimuli were applied: (1) classical visual oddball paradigm; (2) simple light stimuli. For the oddball paradigm, two types of stimuli were used: standards and deviants. The probability of the deviant stimuli was 0.20 and that of the standard stimuli was 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 and 7 s. Thirty-two deviant stimulations were applied. 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, although this was slightly worse in both AD groups than in the control groups (26% of the AD subjects counted the targets as 32, while 74% of the subjects counted 30–34 targets). In the application of simple light stimuli: as stimulation, a white screen with 35 cd/cm² luminance was used. A series of 60 stimulation signals were applied randomly, with the inter-stimulus intervals varying between 3 and 7 s.

4.3. Electrophysiological recording

The EEG was recorded from F3, F4, C3, C4, T3, T4, T5, T6, P3, P4, and O1 and O2 locations according to the 10–20 system (Jasper, 1958). For the recordings, an elastic cap (Ag/AgCl electrodes) was used. Linked earlobe electrodes (A1+A2) served as a 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

<p>| Table 2 – Group characteristics, SD, standard deviation; NS, non-significant; M, male; F, Female; L, left; R, right; GDS, Reisberg’s Global Deterioration Scale, Folstein’s Mini-Mental State Examination (MMSE). |
|-----------------------------------------------|---------------|---------------|---------------|--------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Controls (n=19)</th>
<th>Untreated (n=19)</th>
<th>Treated (n=19)</th>
<th>Pair-wise group contrast P&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD) (years)</td>
<td>72.1±6.6</td>
<td>74.2±6.5</td>
<td>74.6±6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>9/10</td>
<td>10/9</td>
<td>10/9</td>
<td>NS</td>
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<tr>
<td>Education (5–11/&gt;11 years)</td>
<td>11/8</td>
<td>12/7</td>
<td>11/8</td>
<td>NS</td>
</tr>
<tr>
<td>Handedness (L/R)</td>
<td>1/18</td>
<td>1/18</td>
<td>1/18</td>
<td>NS</td>
</tr>
<tr>
<td>GDS</td>
<td>1–2</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE</td>
<td>28–30</td>
<td>20–24</td>
<td>20–24</td>
<td>NS</td>
</tr>
</tbody>
</table>

SD, standard deviation; NS, non-significant; M, male; F, Female; L, left; R, right; GDS, Reisberg’s Global Deterioration Folstein’s Mini-Mental State Examination (MMSE).
impedances were less than 10 kOhm. A Braindata system was used for the recordings. The EEG was digitized on-line with a sampling rate of 500 Hz with band limits of 0.01–100 Hz and a total recording time of 2000 ms, 1000 ms of which served as the prestimulus baseline. Artifacts were eliminated by manual off-line selective averaging, taking into consideration the EOG recorded from the right eye. The sweep numbers were equalized randomly between the target and simple light stimulation conditions.

4.4. Coherence

For the signal analysis, evaluation of oscillatory dynamics and coherence analysis Brainvision Analyzer Software (Brainamp) was used. First, the Fast Fourier Transform of each epoch (0–800 ms duration) was calculated, and then the coherence analysis was performed.

The selection of the 800 ms time interval following the stimulation is based on a rationale that addresses the complex biological properties of the EEG. In engineering studies, the analyzer usually prefers an analysis period of more than 1000 ms for the delta band. However, in order to optimize the time period of analysis, we first performed a power spectral analysis of EEG response, and found a peak around 1.5 Hz in the power spectrum of the EP and ERP responses. Furthermore, we observed that the filtered ERP in the delta frequency range is a dampened aperiodical signal, which is almost completely flattening around 500 ms to 600 ms. An analysis of coherence over longer periods would therefore include unexpected artifacts and/or alpha after discharges. In the theta band, the second response window is found around 400 ms (Başar-Eroğlu et al., 1992; Demiralp et al., 1999; Stamper and Basar, 1985; Yordanova et al., 2000). These findings, in combination, informed the decision to choose the 0–800 ms interval as the optimal time period for the coherence analysis. We also extended our analysis to 1000 ms; here, similar results with minimal deviation were found. We also recommend that brain research scientists develop appropriate controls, rather than strictly apply formulae presented in some of the engineering textbooks. The method used was the cross-spectrum/autospectrum and the mathematical relations are described in the following:

\[ C_\text{coh}(c_1, c_2)(f) = |C_\text{s}(c_1, c_2)(f)|^2 / (|C_\text{s}(c_1, c_1)(f)||C_\text{s}(c_2, c_2)(f)|) \]

in conjunction with

\[ C_\text{s}(c_1, c_2)(f) = \sum_{i} c_1(f)c_2(f) \].

Fisher’s Z transformation was then used to normalize the distribution of average coherence values.

Coherence was calculated for the target and simple light stimuli for long-distance intrahemispheric pairs for five different frequency bands: delta (1–3.5 Hz); theta (4.7–5.5 Hz); alpha (8–13 Hz), beta (15–30 Hz) and gamma (28–48 Hz). The maximum coherence value in each frequency range was included, for the purpose of statistical analysis, as the coherence value of that range (if there was more than one peak, the peak with the maximum coherence value was accepted as the coherence value). The long distance intrahemispheric pairs were F3–P3, F5–T3, F3–O1, F4–P4, F5–T5, F4–O2.

4.5. Statistics

Fisher’s Z transformation was used to normalize the distribution of coherence values. The Statistical Package for Social Studies (SPSS) program was used for statistical analysis. The differences between the groups for the two different stimuli (target, simple light) for the intrahemispheric locations were assessed separately for each frequency band by means of repeated measures of ANOVA. In the analysis of intrahemispheric 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 stimuli (target, simple light), laterality (right, left) and location (F3–P3, F5–T3, F7–O3 vs. F4–P4, F6–T4, F8–O2). Greenhouse–Geisser corrected p-values are reported; for the post-hoc comparisons between groups, the Bonferroni test was used. Differences between electrode pairs between groups were analyzed with the Mann Whitney U test, and the significance level was set to p<0.01 for post-hoc comparisons. The group differences were analyzed by chi-square and one-way ANOVA tests.

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REFERENCES


