A comparative analysis of sensory visual evoked oscillations with visual cognitive event related oscillations in Alzheimer's disease

Görsev G. Yener a, *, Bahar Güntekin b, Elif Tülay b, Erol Başar b

a Brain Dynamics Multidisciplinary Research Center, Departments of Neurology and Neurosciences, Dokuz Eylül University, İzmir 35340, Turkey
b Brain Dynamics, Cognition and Complex Systems Research Center, İstanbul Kultur University, İstanbul 34156, Turkey

ARTICLE INFO

Article history:
Received 29 March 2009
Received in revised form 12 June 2009
Accepted 12 July 2009

Keywords:
Visual evoked potential
Sensory
Event related potential
Alzheimer
Cholinergic
Oscillation

ABSTRACT

We compared visual evoked oscillatory responses of subjects with Alzheimer's disease (AD) (n=22) to healthy elderly controls (n=19) elicited by simple light stimuli. The visual evoked oscillatory responses in AD subjects without cholinergic treatment (n=11) show significant differences (df=2.38, F=4.957, P=0.012) from the controls and the AD subjects treated with a cholinesterase inhibitor (n=11). Higher theta oscillatory responses in untreated AD subjects are seen on the electrode locations over bi-parietal and right occipital regions after simple light stimuli with less, if any, cognitive load. These changes were restricted to the theta frequency range only and are related to location, frequency bands and drug effects. In our previous work we observed that visual event related oscillations elicited after the visual stimuli with a higher cognitive load, i.e. an oddball target, display lower amplitudes: between controls and AD subjects in delta frequency band without a drug effect, over the left and mid-central region. These differences between the visual evoked oscillations and the visual event related oscillations imply that there are at least two different cognitive circuits that are activated upon visual stimuli in AD patients.

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 is due to AD [9]. Clinical signs of AD are characterized by progressive cognitive deterioration, together with declining activities in daily life and by neuropsychiatric symptoms or behavioral changes.

Although there exist numerous publications on the electrophysiology of the visual system in AD [10,11,12], no previous study has compared brain visual oscillatory responses after visual sensory and visual oddball target responses in AD subjects. Also, there is no visual evoked oscillatory response study taking into consideration the cholinergic drug effects in AD. In the present study, we investigated visual evoked oscillations in response to simple light stimulus in healthy elderly subjects and two groups of AD subjects, (1) untreated de novo, (2) treated with cholinesterase inhibitors. We then compared the results of the present study with our earlier findings on visual event related oscillations in relation to oddball targets [17,18]. We tentatively propose that there exist different visual theta oscillatory networks, depending on type of stimuli (sensory or cognitive), and that cholinergic medication may have modulating effects on these circuits.

There is much evidence for the presence of visual deficits in AD in relation to parietal and occipital regions of the brain. An earlier study investigating the link between visual impairment and regional cerebral metabolic rate of glucose in AD, demonstrated a hypometabolism both in the primary and secondary visual fields located in these areas [14]. Previous functional imaging studies in AD demonstrate a relatively greater attenuation of activations in parietal and occipital [6,15] regions than temporal areas. Also, a behavioral study of Alzheimer’s disease indicated that navigational impairment seems to be linked to a disorder of extrastriate visual cortical processing related to parietal lobes [12].

Cholinesterase inhibitors are widely used in the treatment of AD. In a study investigating visual attention task-dependent responses, functional MRI showed that activity of the right parietal and prefrontal cortices were diminished in AD, but improved following medication with physostigmine, a cholinesterase inhibitor [5]. In our earlier studies of event related oscillation, cholinergic medication was also found to improve oscillatory responses of AD [10,18].

In healthy subjects, oscillatory brain responses change upon the cognitive load of the stimuli [13]. With the use of EEG source images, it was shown that different evoked frequency band responses may emerge from different sources during early-stage visual processing in a mental state-specific manner in AD [11]. The oddball task requires the focusing of attention to target stimuli, and the hemispheric association areas related with selective attention are
expected to be affected in the early phase of AD. In our previous studies on visual event related oscillatory responses to oddball targets, in an untreated AD group, we found lower delta and theta coherences between left fronto-parietal areas [10], and less theta phase locking at the left frontal region [18], and; lower delta responses over left and mid-central regions [17]. In the present study, we investigate visual sensory evoked oscillations of AD subjects and healthy controls. We compared oscillations functionally related to cognitive networks with oscillations related to sensory networks which may be differentially affected by AD, and; cholinesterase inhibitor treatment of AD.

**Subjects:** The same subjects as in our earlier studies participated also in this study [10,17,18]. One patient had to be excluded because of artifacts in her recordings (Table 1).

A visual sensory paradigm was used in the experiments. A white screen with 35 cd/cm² luminance was used as the stimulus. 60 stimulation signals were applied randomly, with the inter-stimulus intervals varying between 3 and 7 s.

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. For the recordings, an EEG-CAP (Ag/AgCl electrodes) was used. Linked earlobe electrodes (A1 + A2) served as a reference. The EEG from the medial upper and lateral orbital rim of the right eye was also registered. For the reference electrodes and EEG 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.

Before the averaging procedure, the epochs with artifacts were rejected by an off-line technique. In the off-line procedure, single sweep EOG recordings were examined visually and trials with eye-movement or blink artifacts were rejected. Subject averages and grand averages were calculated for each electrode site and experimental condition. The data was digitally filtered according to the frequency bands of interest.

In the present study, two approaches were applied in determining the frequency: the transient response frequency characteristics (TRFC) method and the digital filtering (DF) method.

Filtering produces visual displays of the time courses of oscillatory components within the frequency limits of the utilized filters. Digital filters are advantageous because they do not produce the phase shifts that are a characteristic of electronic filters. Digital filtering was employed in the present study for the digital pass-band filtering of the event related potentials (ERPs) and thus to demonstrate peak amplitude values of the event-related oscillations (EROs) in selected frequency-bands, as follows: delta (0.5–3.5 Hz) 0–600 ms, theta (4–7 Hz) 0–500 ms, alpha (8–13 Hz) 0–300 ms, and beta (15–30 Hz) 0–250 ms.

Numerical evaluation of the frequency characteristics was accomplished using a Fast Fourier transform (FFT) of the following form: Let \( X_n \) be a discrete time series \( X_n = X(nDt), T = [(N-1)/D] \). Then the Fourier transform of \( Y_k \) of \( X_n \) is:

\[
Y_k = \sum_{n=0}^{N-1} X_n \exp(-i2\pi n^{-1}k); \quad \omega_k = 2\pi kT^{-1},
\]

where \( Y_k = ak + ibk \) are the complex Fourier coefficients whose geometric mean is the amplitude spectrum. The results of the amplitude frequency characteristics (AFC) determined the frequencies of interest and defined the frequency ranges for the digital filtering. For the frequency ranges, grand averages were computed based on a single subject’s averages of the AFCs for each condition and location.

SPSS was used for statistical analysis. Peak-to-peak maximum amplitude responses were analyzed separately for each frequency band by means of a repeated measure ANOVA including the between-subjects factor as groups (healthy aged controls, untreated AD, treated AD) and the within-subject factors location (frontal [F3, F4], central [C3, C4], temporal-1 [T1, T2], temporal-2 [T3, T4], parietal [P3, P4], occipital [O1, O2]), and laterality (left [F3, C3, T3, P3, O1], right [F4, C4, T4, P4, O2]).

Greenhouse–Geisser corrected P-values are reported. For the post hoc comparisons, between groups Bonferroni test were used. Differences between electrode pairs of groups were analyzed using a t-test.

The only change observed was in theta oscillatory responses, but not in alpha, beta, or delta responses using the repeated measures of ANOVA for group or electrode location or hemispheric laterality in visual evoked oscillations. In the theta frequency range, there was a significant difference between subject groups in visual evoked oscillations (df = 2.38, \( F = 4.957, P = 0.012 \)). Post hoc Bonferroni tests showed significant differences between the untreated AD group and controls (\( P = 0.031 \)) and between treated and untreated AD groups (\( P = 0.021 \)) (Table 2).

Significant differences were recorded between locations (df = 5.19, \( F = 12.746, P < 0.000 \)), being higher in frontal and central regions in theta visual evoked oscillations. Bilateral parietal and right occipital differences were observed in theta responses. At the P3, P4 and O2 electrode locations, the untreated AD group had higher theta responses than either treated AD (respectively \( P < 0.01 \); \( P < 0.008 \); \( P < 0.05 \)) or control groups (respectively \( P < 0.007 \); \( P < 0.009 \); \( P < 0.03 \)). There was no significant difference between treated the AD group and controls. No difference was found in laterality.

No differences were found in repeated measures of ANOVA in group × electrode locations, group × laterality, or group × electrode locations × laterality.

The discussion of results is based on the present results together with the findings of our previous studies on AD [10,17,18]. As the most common form of dementia, the visual system in Alzheimer’s disease has been studied using various techniques. However, a comparison of visual sensory networks and cognitive networks has not been investigated previously. As a new step, in this study, we have compared the results of the present study on visual evoked oscillations to simple light stimulus to those of visual event

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**Table 1**

<table>
<thead>
<tr>
<th>Group characteristics.</th>
<th>Controls (n = 19)</th>
<th>Alzheimer (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment (...) (n = 11)</td>
<td>Treatment (+) (n = 11)</td>
</tr>
<tr>
<td>Mean age (SD) (yrs)</td>
<td>72.1 (6.6)</td>
<td>74.2 (6.7)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>11/8</td>
<td>4/7</td>
</tr>
<tr>
<td>Education (5–11/11 yrs)</td>
<td>11/8</td>
<td>7/4</td>
</tr>
<tr>
<td>Handedness (L/R)</td>
<td>1/18</td>
<td>1/10</td>
</tr>
<tr>
<td>GDS</td>
<td>1–2</td>
<td>4</td>
</tr>
</tbody>
</table>

related oscillations to oddball targets reported in our previous work [10,17,18]. There is an increased theta response in visual sensory evoked oscillatory responses of the untreated AD group at the electrodes over the right primary visual (occipital, O2) and both visual dorsal stream areas (both parietals, P3, P4) following simple light stimulation without cognitive task. In our previous work on visual event related oscillations in relation to oddball targets, the results indicated that untreated the AD group showed less theta phase locking over the left frontal region [18]; less delta and theta coherence between left fronto-parietal areas [10], and; lower delta response over left and mid-central regions [17]. There are four aspects of the dissociation between the visual evoked oscillatory responses elicited after simple visual sensory stimulus and the visual event related oscillations after cognitive task related stimulus, i.e. oddball target: (1) the location; (2) the frequency band; (3) cholinergic medication effects; and (4) the amplitudes (Fig. 1).

In the visual evoked oscillations in response to simple light stimulus, the increased theta responses in untreated AD patients is observed over posterior regions with a predilection to the right; i.e. right occipital and both parietals. Our previous work on visual event related oscillations after oddball targets, indicated that decreased responses in untreated AD are located in frontal areas with a predilection to the left; left frontal theta [18] and mid- and left central delta activities [17].

In the visual evoked oscillatory responses to simple light stimulus, the difference in the untreated AD group is seen only at the theta frequency range and not in the delta range. Our previous work on visual event related oscillations to oddball targets showed that delta responses were lower in AD patients (treated and untreated) in comparison to healthy subjects [17].

Cholinergic medication causes changes in oscillatory brain dynamics [2]. There was a discrepancy in the responses of the untreated AD group differentially from controls and the treated AD group. The untreated AD group had higher theta responses in the visual evoked oscillatory responses to simple light stimulus over both parietal and right occipital (P3, P4, O2) electrodes. It is important to note that our previous work indicated that peak delta amplitudes of visual event related oscillations to oddball targets are diminished in the same group over the mid- and left central regions (C3–C4) [17].

Fig. 1 describes the sensory evoked responses to visual stimuli in AD, together with responses to the target in a visual oddball paradigm in the theta and delta frequency bands of healthy controls, de novo untreated AD patients and treated AD patients [17]. It is of note that significant results are recorded only in visual evoked theta oscillatory responses and visual event related delta responses to oddball target stimuli.

The untreated AD group shows higher theta oscillatory activity in parietal and occipital areas, in response to simple visual stimulus, whereas event related oscillatory responses to oddball targets in untreated AD and treated AD groups have lower delta oscillatory response in left and mid-central regions [17]. The effect of cholinergic medication cannot be seen between the AD subgroups in delta oscillatory response of event related oscillations to oddball target. On the contrary, the effect is prominent in the theta oscillatory response to simple sensory stimulus, showing an increase upon cholinergic medication (Fig. 1).

One of the core implications of the delta responses is the possibility of differentiating the existence of two different networks, sensory and cognitive. The reasoning for this proposal is founded on two empirical findings:

1. The delta responses (0.5–3.5 Hz) of healthy subjects are significantly enhanced in central areas of the cortex upon application of visual target stimuli. Simple light stimulation does not elicit such largescale enhancements.
2. In contrast, the application of the same visual target stimuli does not enhance delta responses in Alzheimer patients. This finding indicates that, most possibly, the cognitive networks that are tuned for short-term memory, attention and decision making are disabled in order to respond to relevant cognitive load.

In other clinical conditions such as Parkinson’s disease or schizophrenia, after an oddball paradigm, decreased modulation of the prefrontal cortex is found [4,16]. As to the enhancement of posterior theta response in AD after a simple light signal, a possible tentative interpretation is the over-attendance of the posterior cortex to sensory stimulus in untreated AD. However, in order to analyze this possibility, a single trial analysis including prestimulus activity should be performed, since it was shown that the

<table>
<thead>
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<th>Table 2</th>
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<tr>
<td>The mean values and standard deviations of peak amplitudes of visual evoked oscillations in controls and untreated AD [T(−) AD], treated AD [T(+) AD] groups. The values elicited from the electrode locations (P3, P4, O2) with significant differences between the groups were written in bold.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visual evoked oscillatory responses</th>
<th>Controls (n = 19)</th>
<th>T(−) AD (n = 11)</th>
<th>T(+) AD (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>F3</td>
<td>3.91</td>
<td>2.35</td>
<td>5.15</td>
</tr>
<tr>
<td>F4</td>
<td>4.07</td>
<td>2.10</td>
<td>5.74</td>
</tr>
<tr>
<td>C2</td>
<td>4.83</td>
<td>2.76</td>
<td>7.16</td>
</tr>
<tr>
<td>C3</td>
<td>4.00</td>
<td>2.28</td>
<td>5.92</td>
</tr>
<tr>
<td>C4</td>
<td>4.41</td>
<td>2.52</td>
<td>5.89</td>
</tr>
<tr>
<td>T3</td>
<td>2.49</td>
<td>1.31</td>
<td>3.59</td>
</tr>
<tr>
<td>T4</td>
<td>2.56</td>
<td>1.68</td>
<td>2.75</td>
</tr>
<tr>
<td>T5</td>
<td>3.09</td>
<td>1.84</td>
<td>4.54</td>
</tr>
<tr>
<td>T6</td>
<td>3.45</td>
<td>2.54</td>
<td>3.92</td>
</tr>
<tr>
<td>P3</td>
<td>3.75</td>
<td>1.79</td>
<td>6.32</td>
</tr>
<tr>
<td>P4</td>
<td>3.48</td>
<td>2.10</td>
<td>6.14</td>
</tr>
<tr>
<td>O1</td>
<td>3.79</td>
<td>2.80</td>
<td>5.17</td>
</tr>
<tr>
<td>O2</td>
<td>3.34</td>
<td>2.43</td>
<td>6.30</td>
</tr>
</tbody>
</table>
theta pre-stimulus activity controls the theta response in healthy subjects [1,3].

Moreover, the theta and the alpha spontaneous activity are altered in dementia [19]. In addition to this information, Buckner and Vincent suggest inhibitory control of the prefrontal cortex on the dorsal attention system [7]. We suppose that the control of the prefrontal cortex on primary and secondary visual sensory areas in AD would fail to a certain extent, and then the responses of the visual areas to simple flash light stimuli could increase compared with healthy controls. All of these findings would be in agreement with previous findings showing a higher spontaneous EEG activity in slow oscillatory frequency ranges (theta and delta) over the posterior regions of the brain in AD [8,19]. The role of theta response and coherence in processing of the oddball paradigm were discussed in details in a previous study published by our research group [10].

In conclusion, comparing evoked oscillatory responses to simple light stimulus with event related oscillatory responses to oddball targets in AD, when the task involves little or no cognitive load, we observe that: (1) The amplitude of theta oscillatory responses changes, as contra-intuitively incremental responses are seen in untreated AD over primary and secondary sensory areas of the brain. (2) A different scalp distribution is seen, as posterior regions show higher theta activity in untreated AD. This may be an indication of a different circuit for the sensory network, since oddball target stimuli elicit lower frontal theta and delta responses in untreated AD. (3) The effects of cholinergic medication appear in the theta visual evoked oscillation responses to simple light stimuli. However, they are prominent in the event related coherences of the alpha frequency band to oddball targets [10]. (4) It is clear that the prefrontal area plays an important role in a visual cognitive task, but it appears to have a different role after a visual stimulus with less cognitive load.

The present study emphasizes once more the utility of electrophysiological measures in understanding brain dynamics in cognitive impairment, possible as a biomarker. Further studies should include longitudinal evaluation of EEG or event related oscillations with the combination of other biomarkers as such as positron emission tomography.

References

