

# Event-related delta oscillatory responses of Alzheimer patients

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**Background and purpose:** Alzheimer type of dementia (AD) is the most common neuropsychiatric morbidity in elderly individuals. Event-related oscillations (ERO) provide an useful tool for detecting subtle abnormalities of cognitive processes with high temporal resolution. **Methods:** In the present report, event-related oscillations of patients with AD were analyzed by using a visual oddball paradigm. A total of 22 mild probable AD subjects according to NINCDS-ADRDA criteria and 20 age-, gender-, and education-matched healthy control subjects were compared. AD group consisted from 11 untreated patients and 11 patients treated with cholinesterase inhibitor. Oscillatory responses were recorded from 13 scalp electrodes. **Results:** Significant differences in delta frequency range were seen between the groups by using repeated measures of ANOVA analysis [ $F(9,120) = 2.228$ ;  $P = 0.022$ ]. Post-hoc analyses using Wilcoxon test showed that at mid- and left central regions, (Cz, C3) peak amplitudes of delta responses of healthy subjects were significantly higher than either group. Also cholinesterase inhibitors did not have effect on delta oscillatory responses. **Conclusions:** Our findings imply that the delta oscillatory responses at central locations are highly instable in mild probable AD patients regardless of treatment when compared to the healthy aged controls. This study supports the importance of oscillatory event-related potentials for investigating AD brain dynamics.

## Introduction

One of the leading neurological conditions most responsible for neuropsychiatric morbidity in elderly individuals is Alzheimer type of dementia (AD). Event-related oscillations (ERO) provide a powerful technique, with high temporal resolution, which can be used as a tool for detecting subtle abnormalities of cognitive processes [1,2]. It has been well known for several decades that P300 is attenuated in AD. However, the full potential of electrophysiological methods in helping to predict [3–5], to diagnose [6–10], and to monitor either treatment or progress [11] in AD patients has not been reflected into routine clinical practice.

Event-related oscillatory activity in various frequency bands may reflect different aspects of information processing [1,2]. Alpha oscillatory responses increase with simple memory tasks and decrease with demanding memory tasks [12,13]. Beta oscillatory responses are important in attention related tasks in cats and [14], recognition of facial expression in humans [15,16].

Event-related theta oscillatory responses have been proposed to be related to the memory processes [12,17]. In subjects with Parkinson's disease or schizophrenia, theta oscillations seem to be less than controls, indicating that these oscillations appear to be involved in mnemonic networks [18,19]. Also theta responsiveness in frontal lobes is interpreted as an indication of the function of the hippocampo-fronto-parietal system during cognitive processes [20,21]. Our recent report evaluating phase locking of the visual event-related theta oscillations indicated that *untreated* AD group has lower phase locking than controls at left frontal region and the cholinesterase inhibitor treatment increases phase locking in theta frequency ranges similar to controls [22]. The question whether cholinergic mechanisms affect or modulate event-related oscillations in other frequency ranges still remains to be clarified. Investigating these oscillations may help to understand differences in brain dynamics of AD subjects.

We hypothesized that the AD group would show lower oscillatory responses than controls. In this report, we aimed to compare the peak amplitudes of event-related oscillatory responses in specific frequency ranges in AD subjects, either the untreated or those on cholinesterase treatment, to those of healthy elderly.

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## Methods

### Subjects

We conducted a prospective open study. Twenty-two consecutive, community-dwelling patients suffering from dementia according to the DSM IV criteria and also with the diagnosis of probable Alzheimer disease according to the NINCDS-ADRDA criteria [23] were included in the study. AD group was divided into two groups as the *treated* and the *untreated*. In the *treated AD* group, eleven subjects (four males, seven females) were taking only cholinesterase inhibitors (AChEI) as a psychotropic agent for 3–6 months including the titration period (eight subjects were on donepezil 10 mg/day with the initial dose of 5 mg/day that was titrated to 10 mg/day by 4 weeks, and three subjects were on rivastigmine 6–9 mg/day with the initial dose of 3 mg/day, titrated by every 4 weeks either to 6 mg/day or to 9 mg/day depending on the tolerance of the drug) and eleven AD patients (four males, seven females) not taking any psychotropic medication comprised the *untreated AD* group. Both AD groups did not differ 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. 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 subjects were between 28 and 30 points. All of the AD subjects were on stage 4 according to the GDS. In treated AD group, the majority (8 out of 11 subjects) was 'responder' defined as 'at least 1 MMSE point increase' 3 months after onset of treatment, while three showed decrease in their scores. Twenty-two healthy elderly control subjects volunteered for the study, two subjects were excluded for motor artifacts, remaining 20 *control subjects* (12 males, 8 females) were not significantly different from both AD groups regarding age, gender, handedness and education (Table 1). All AD subjects under-

went a cognitive and a complete neurological, neuro-imaging (CT or MRI) and laboratory examination including blood glucose, electrolytes, liver and kidney function tests, full blood count, erythrocyte sedimentation rate, thyroid hormone, vitamin B12, HIV, VDRL. *Healthy controls* were recruited from various community sources; none of them were consanguineous to the patients. The study was approved by the local ethics committee. All subjects and relatives gave written informed consent.

### Stimuli and paradigms

A classical visual oddball paradigm was used in the experiments. Two types of stimuli were used: the standards and the deviants. The probability of the deviant stimuli was 0.20 and that of standard stimuli 0.80. As stimulation we used a white screen with a luminance of 35 cd/cm<sup>2</sup> for standard signals. The luminance of the deviant stimuli were 20% lower (i.e. 28 cd/cm<sup>2</sup>). The rise-time of the stimulation signal was 10 ms, the duration of the stimulation was 1 second. In all the paradigms, the deviant stimuli were embedded randomly within a series of standard stimuli. The application of the signal including the rise-fall time and the duration occurs electronically and is supported by a MATLAB program. Further, the rise time and the duration of the signal were also checked by means of a photo-sensor recorded in a storage oscilloscope. The task required was mental counting of the target stimuli. These stimulation signals were applied randomly with the inter-stimulus intervals varied between 3 and 7 s. During the elicitation period of event-related oscillations, all subjects had displayed enough accuracy of mental count of target stimuli, with being slightly worse in both groups of AD than that of controls.

### Electrophysiological recording

The EEG was recorded from F<sub>3</sub>, F<sub>4</sub>, C<sub>z</sub>, C<sub>3</sub>, C<sub>4</sub>, T<sub>3</sub>, T<sub>4</sub>, T<sub>5</sub>, T<sub>6</sub>, P<sub>3</sub>, P<sub>4</sub>, O<sub>1</sub> and O<sub>2</sub> locations according to the

	Controls ( <i>n</i> = 20)	Alzheimer ( <i>n</i> = 22)		Pair-wise group contrast, <i>P</i> < 0.05
		Untreated ( <i>n</i> = 11)	Treated ( <i>n</i> = 11)	
Mean age (SD) (years)	71.7 (6.6)	74.2 (6.7)	72.1 (5.4)	NS <sup>b</sup>
Gender (M/F)	12/8	4/7	4/7	NS <sup>a</sup>
Education (5–11 / > 11 years)	12/8	7/4	8/3	NS <sup>a</sup>
Handedness (L/R)	1/19	1/10	1/10	NS <sup>a</sup>
GDS	1–2	4	4	

SD, standard deviation; NS, non-significant; M, male; F, female; L, left; R, right; GDS, Reisberg's Global Deterioration Scale. <sup>a</sup>Chi-square test; <sup>b</sup>Kruskal–Wallis and *post-hoc* LSD tests.

**Table 1** Group characteristics

International 10–20 system. For the recordings an EEG-CAP was used. For the reference, EMG and EOG recordings Ag/AgCl electrodes were used. Linked ear-lobe electrodes (A1 + A2) served as reference. EOG from medial upper and lateral orbital rim of the right eye was also registered. The EEG was amplified by means of a Nihon Kohden EEG-4421 G apparatus with band limits 0.1–100 Hz 24 dB/octave. 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.

### Computation of selectively averaged ERPs and digital filtering

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 visually studied 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 determined frequency bands of interest.

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

Filtering produces visual displays of the time courses of oscillatory components within the frequency limits of the utilized filters. The digital filters are advantageous because they do not produce the phase shifts that are a characteristic of electronic filters. The digital filtering was employed in the present study for the digital pass-band filtering of the event-related potentials (ERPs) and thus to demonstrate the event-related oscillations (EROs) in selected frequency-bands (delta: 0.5–3.5 Hz, theta: 4–7 Hz, alpha: 8–13 Hz, and beta: 15–30 Hz) [2].

The 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 ( $X_n = X(nDt)$ ,  $T = ((N - 1)Dt)$ ). Then the Fourier transform of  $Y_k$  of  $X_n$  is:

$$Y_k = Y(\omega_k) = \sum_{n=0}^{N-1} X_n \exp(-i2\pi N^{-1}nk); \omega_k = 2\pi kT^{-1},$$

where  $Y_k = ak + ibk$  are the complex Fourier coefficients whose geometric mean is the amplitude spectrum. According to the results of the amplitude frequency characteristics (AFC) the frequencies of interest were determined and the frequency ranges for the digital filtering defined. For the frequency ranges grand averages were computed based on single subjects' averages of the AFCs for each condition and location.

As oscillatory responses, we measured the peak-to-peak amplitudes of each subject's averaged responses filtered in the frequency ranges of delta, theta, alpha, and beta. The post-stimulus time intervals for peak amplitudes of oscillatory responses were chosen as follows: frequency ranges of delta and theta, 0–600 ms; of alpha and beta 0–250 ms. According to the literature of brain oscillations and basic principles of systems theory, the range of oscillatory signals are chosen in correlation to the frequency signal studied [24].

### Statistical analysis

Statistical Package for the Social Sciences (SPSS) was used for statistical analysis. Peak-to-peak maximum amplitude responses were separately analyzed 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 factor location ( $F_3$ ,  $F_4$ ,  $C_z$ ,  $C_3$ ,  $C_4$ ,  $T_3$ ,  $T_4$ ,  $T_5$ ,  $T_6$ ,  $P_3$ ,  $P_4$ ,  $O_1$  and  $O_2$ ). Greenhouse-Geisser corrected  $P$ -values have been taken into consideration. *Post-hoc* analysis was conducted using Wilcoxon paired sample test.

### Results

The peak amplitudes of oscillatory responses in delta, theta, alpha and beta frequency ranges were measured. The only difference in peak amplitudes between groups was seen in delta oscillations (Table 2).

For the delta frequency range digital filtering was determined between 0.5 and 3.5 Hz according to the AFC. Oscillatory delta responses showed significant differences between event-related responses of healthy aged controls, untreated and treated AD subjects. The main differences are observed at the central electrode locations: From the values of Table 3, one can recognize that in central locations the peak-to-peak amplitudes can be 50–100% larger for controls than for AD subjects.

The ANOVA on delta oscillatory responses revealed a significant effect for group  $X$  location [ $F(9,120) = 2.228$ ;  $P = 0.022$ ] indicating higher delta response in controls. *Post-hoc* comparisons using the Wilcoxon paired sample test revealed that the peak-to-peak delta response was significantly larger for controls than for either treated or untreated AD subjects over left and mid-central electrodes ( $P < 0.05$  for all comparisons) (Figs 1 and 2 and Table 2).

The single sweeps of a typical healthy aged control subject show good congruence and accordingly phase locking of delta responses at  $C_z$ , whereas responses of

**Table 2** The mean (SD) peak amplitudes ( $\mu\text{V}$ ) of oscillatory activities in specific frequency bands in treated AD (t-AD), untreated AD (u-AD) and healthy elderly controls (Cont). The statistically significant ( $P < 0.05$ ) results were indicated in bold style

Site	Beta			Alpha			Theta			Delta		
	u-AD	t-AD	Cont	u-AD	t-AD	Cont	u-AD	t-AD	Cont	u-AD	t-AD	Cont
F <sub>3</sub>	5.10 (1.91)	4.32 (2.32)	4.45 (2.37)	5.27 (2.76)	4.57 (1.90)	5.34 (3.15)	5.05 (2.79)	4.16 (1.53)	3.93 (1.74)	6.19 (2.86)	5.90 (2.09)	8.08 (3.21)
F <sub>4</sub>	5.02 (2.48)	4.40 (1.60)	4.83 (2.26)	5.76 (2.66)	5.21 (2.55)	5.45 (3.02)	5.74 (3.18)	4.05 (1.83)	3.74 (1.75)	6.56 (2.86)	5.43 (2.09)	7.51 (3.11)
C <sub>z</sub>	4.01 (1.14)	3.56 (1.27)	3.78 (1.70)	5.53 (3.46)	4.60 (2.06)	5.79 (2.85)	5.74 (3.13)	4.43 (1.05)	4.45 (2.22)	<b>5.52 (1.64)</b>	<b>4.77 (1.93)</b>	<b>8.38 (3.38)</b>
C <sub>3</sub>	4.28 (2.02)	3.97 (1.27)	3.79 (2.05)	5.64 (3.22)	4.48 (2.04)	5.52 (2.63)	4.97 (2.93)	3.84 (1.09)	3.98 (2.03)	<b>4.48 (2.03)</b>	<b>3.45 (1.76)</b>	<b>7.25 (3.15)</b>
C <sub>4</sub>	4.40 (1.60)	5.02 (2.48)	4.83 (2.26)	6.12 (2.58)	6.11 (3.09)	5.94 (3.53)	4.74 (2.61)	4.10 (1.73)	4.17 (2.37)	5.97 (2.42)	4.91 (1.06)	7.28 (3.92)
T <sub>3</sub>	3.85 (1.25)	4.37 (2.55)	3.85 (2.30)	3.42 (2.27)	3.49 (2.06)	3.75 (2.38)	3.00 (1.82)	2.18 (0.69)	2.66 (1.75)	2.94 (1.03)	2.73 (1.15)	4.52 (2.21)
T <sub>4</sub>	4.90 (2.12)	4.96 (4.01)	3.67 (1.76)	3.97 (1.23)	4.35 (3.38)	4.38 (2.27)	3.15 (1.70)	2.26 (1.40)	2.59 (1.17)	3.96 (2.13)	2.70 (0.85)	4.35 (2.34)
T <sub>5</sub>	4.05 (1.90)	4.35 (2.05)	4.35 (2.93)	4.14 (1.74)	4.21 (2.09)	3.68 (2.04)	4.39 (2.46)	2.93 (1.10)	3.01 (1.83)	4.40 (1.92)	3.49 (2.11)	5.39 (2.08)
T <sub>6</sub>	4.34 (2.06)	4.63 (5.77)	4.95 (3.10)	6.87 (6.05)	4.21 (4.17)	5.16 (3.67)	4.40 (2.58)	2.97 (0.55)	3.80 (2.46)	4.19 (1.50)	3.91 (1.57)	5.56 (3.26)
P <sub>3</sub>	3.67 (0.87)	4.52 (2.29)	4.54 (2.44)	6.39 (3.22)	4.61 (2.60)	5.00 (2.75)	5.94 (1.76)	2.71 (1.76)	4.05 (2.61)	5.9 (2.03)	3.61 (1.14)	6.88 (3.87)
P <sub>4</sub>	3.63 (1.42)	3.61 (1.36)	4.98 (2.75)	7.02 (4.70)	4.51 (2.62)	5.05 (2.53)	5.04 (1.72)	2.85 (1.20)	4.34 (3.14)	5.00 (1.63)	4.90 (2.33)	6.29 (4.37)
O <sub>1</sub>	4.71 (3.38)	5.45 (2.59)	4.79 (2.82)	5.63 (2.53)	4.65 (2.22)	5.17 (2.84)	6.70 (2.93)	4.39 (2.34)	5.12 (3.28)	8.40 (5.91)	5.74 (2.67)	5.69 (3.25)
O <sub>2</sub>	4.54 (2.04)	4.15 (1.83)	4.87 (2.77)	5.43 (2.03)	4.29 (1.85)	4.98 (2.45)	5.91 (3.60)	4.06 (1.52)	5.20 (3.12)	8.91 (6.34)	5.58 (2.40)	5.92 (3.81)

**Table 3** Mean values and standard deviations of delta oscillatory responses and comparisons of the treated AD (t-AD), untreated AD (u-AD) and healthy elderly controls (Cont) groups with *post-hoc* Wilcoxon paired test

				Cont vs.			
				u-AD		Cont vs. t-AD	
		AD ( <i>n</i> = 22)					
Controls		Untreated	Treated				
Site	( <i>n</i> = 20)	( <i>n</i> = 11)	( <i>n</i> = 11)	<i>Z</i> value	<i>P</i>	<i>Z</i> value	<i>P</i>
C <sub>3</sub>	7.25 (3.15)	4.48 (2.03)	3.45 (1.76)	-2.134	0.033	-2.490	0.013
C <sub>z</sub>	8.38 (3.38)	5.51 (1.64)	4.77 (1.93)	-2.045	0.041	-2.667	0.008

an AD subject do not (Fig. 1). Phase locking indicates a stronger response to a given stimulus [25].

In the grand-averages of delta oscillatory responses at C<sub>z</sub>, it is shown that the control group has larger amplitude in comparison to either treated or untreated AD groups (Fig. 2). Peak-to-peak amplitudes of the control group are 7.25 (3.15) and 8.38 (3.38)  $\mu\text{V}$  in C<sub>3</sub> and C<sub>z</sub> locations, showing a regular oscillatory pattern. On the contrary, treated and untreated AD subjects have smaller amplitudes with an irregular shape (Table 3).

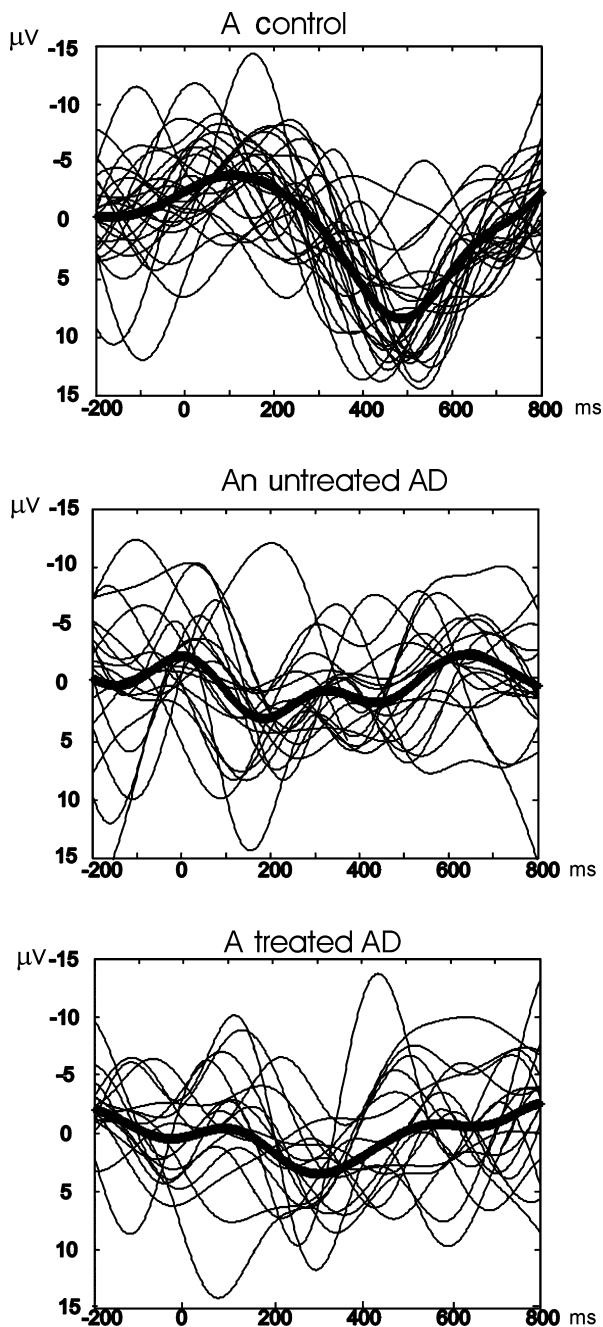
## Discussion

### Generation of P300

According to a group of authors, ERPs or P300 responses are generated in the neocortex, especially in frontal locations [26] or centroparietal/temporoparietal association cortices [27]. Involvement of limbic system or hippocampal formation in the generation of P300 has been also proposed [28,29]. Intracranial recordings also suggested that basal ganglia, especially putamen,

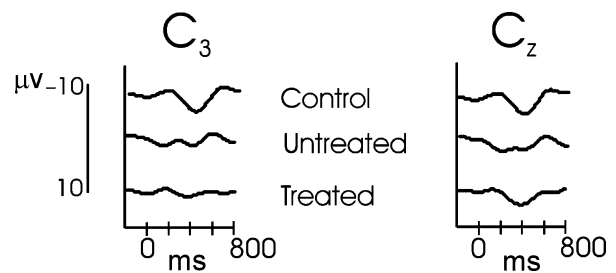
may play an integrative role in cognitive information and in generation of P300 [30]. The possibility of volume conduction from C<sub>3</sub> layer of the hippocampus to the cortex in the generation of P300 is excluded as animal experiments showed [31]. In human intracranial recordings, visual working memory task activates briefly visual association cortex and then activation soon spreads at once to multiple occipital, parietal and frontal sites, which all remains active for the entire epoch. Phase-locked oscillations in theta and alpha frequency ranges are prominent in multiple structures including the prefrontal cortex [32].

Further, according to several authors event-related potentials arise by superposition of event-related oscillations in various frequency ranges [1]. These approaches hypothesize that the EEG consists of the activity of an ensemble of generators producing oscillatory activity in several frequency ranges. These oscillators are active usually in a random way. However, by application of sensory stimulation these generators couple and act together in a coherent way. Evoked potentials representing ensembles of neural population responses were considered as a result of transition from a disordered to an ordered state [25]. Among event-related oscillations, theta (4–8 Hz) oscillations are correlated with memory load, task difficulty or recognition of previous stimuli [12,13,19,33]. Oscillations at delta frequency range are related to ‘focused attention’, ‘signal detection’, ‘recognition’ and ‘decision making’ [29,34,35]. In these reports late theta responses behave similarly to delta oscillatory responses. Brain oscillations in lower frequencies are proposed to play a role in mediating long range interactions [36]. In agreement with this, simulation studies have indicated that lower frequencies such as delta or theta oscillations



**Figure 1** Examples from each group showing single sweeps in delta oscillatory frequency range, to the target stimuli elicited by a classical visual oddball paradigm recorded from the scalp electrode of  $C_z$ . The black and thick line indicates the average of single sweeps, and the grey and thin lines show each single sweep for the subject. (a) An elderly healthy control. (b) An untreated Alzheimer subject. (c) A treated (cholinesterase inhibitor) Alzheimer subject.

are better suited to sustain long range synchronization [37]. Not only thalamic neurons but also cortical neurons may discharge in the slow frequency range as delta [38]. The amplitude of delta response increases during



**Figure 2** Grandaverages of delta oscillatory response of each group to the target stimuli elicited by a classical visual oddball paradigm recorded from electrodes of  $C_3$  and  $C_z$ . (a) The healthy elderly control group ( $n = 20$ ). (b) The untreated Alzheimer group ( $n = 11$ ). (c) The treated (cholinesterase inhibitor) Alzheimer group ( $n = 11$ ).

oddball paradigms and may be related to signal detection and decision making [20]. As the major shape determining oscillatory activity of P300, delta responses are related to basic information processing mechanisms of attention allocation and immediate memory [39]. Since memory and complex attention functions are highly reduced in AD [40], our results are in accordance with cognitive deficits from the psychophysiologic viewpoint.

#### Topologic distribution and frequency ranges of brain oscillations in AD subjects

Earlier reports have shown that the P300 amplitudes are decreased in Alzheimer's disease [8,10,39]. Reports on AD using other functional methods such as PET, SPECT or f-MRI also have a tendency to show deficits at left centro-frontal, left temporo-parietal locations. A recent report on the event-related oscillatory activity in AD has reported that the significant differences have been noted in peak amplitudes of alpha oscillatory activity (7–17 Hz) over frontal, central and left temporal electrodes [9].

In the present paper, we also found significant differences between healthy controls and two groups of AD subjects in delta oscillatory responses regardless of cholinergic medication. This difference was insistent prominently over  $C_3$  and  $C_z$  in both AD groups in comparison to the control group.

In our study, classical oddball paradigm was used. In this task, mental counting of visual target stimuli is considered to be related to memory and complex attention functions. Major reduction in working memory and complex attention observed in Alzheimer patients may be possibly correlated with reduction of electrical response in central regions. However we cannot exclude the possibility of higher error rates in detecting target stimuli of AD group may have lead to reduced responses in delta activity.

Delta difference in left and mid-central positions are also in accordance with earlier reports of AD subjects studied with fMRI or PET reflecting mainly frontal or cingulate regions of left hemisphere. Our recent and other earlier reports imply that in AD, either effects of disease or response to treatment can be more readily seen over the left frontal hemisphere.

#### **Differentiation of delta and theta oscillations in AD subjects on cholinergic treatment**

Earlier functional imaging studies in AD showed that after administration of AChEI, clinical responders to treatment selectively display improvements mainly over left prefrontal areas or left anterior cingulate [41]. Cortical acetylcholine (ACh) is hypothesized to mediate the subjects' abilities to select stimuli and associations for further processing. The ability of prefrontal cortex to regulate transmission in more posterior cortical regions may represent a 'top-down' mechanism to control attention [42]. Basal forebrain is the main source of ACh in the neocortex and Alzheimer patients show depletion in cortical ACh due to degeneration of basal forebrain early in the course of illness [43].

We believe that delta oscillatory responses are not affected by cholinergic agents, because in our AD group, the degree of clinical impairment did not differ between the treated and untreated; and subjects in the treated group was not more advanced than the untreated. Finally, majority of the treated group was considered as responder to treatment. However, a randomized controlled study can give a more probabilistic result on this matter.

Our recent report evaluating phase locking of the visual event-related theta oscillations indicated that *untreated* AD group has lower phase locking than controls at left frontal region. However, *the treated AD group* showed phase locking in theta frequency range similar to controls [22]. In the present report, peak amplitudes of delta oscillatory responses are highly reduced in AD regardless of cholinergic treatment. Therefore cholinergic agents seem to have differentiated effect on delta and theta responses in AD subjects. In other words, phase locking in theta oscillatory response may be sensitive to cholinergic interventions in AD, whereas amplitudes of delta oscillatory responses are not affected by these agents.

One might question whether the separation of delta and theta responses is a natural way of decomposition. If delta and theta responses would behave in a similar way such a separation could not be strongly assumed. These selective responses to pharmacological agents demonstrate the independent functional correlates of delta and theta responses. However, the underlying

mechanism is yet obscure. Although a great number of studies establish that both components are physiologically separable, we have another argument: This is the selectivity based on the application of a pharmacological agent enhancing cholinergic transmission. We also mention here the selectivity of another pharmacological agent such as valproate with GABAergic or glutamatergic activity which reduces delta responses in bipolar affective disorder [44].

Certainly, it can be stated that in cognitive functions of Alzheimer patients there is a high decline in working memory and complex attention [37,45,46]. Since cholinergic medication improves theta phase locking, but not delta oscillatory response; other transmitters such as serotonin which increases delta activity in animal studies [47] may help to enhance delta oscillatory activity in human.

The present paper opens new conjecture to search a new type of physiological intervention to restore reduction of delta response in central regions. This question cannot be answered by this study, but remained to be searched.

There are a few conclusions and remarks related to our findings on AD patients at the initial phase of disease:

1. Amplitudes of delta oscillatory responses are lower in Alzheimer disease regardless of medication over left and mid-central regions. Activation upon cholinergic medication is observed in theta oscillatory response but not in delta frequency range.
2. In a way, these two slow oscillatory activities behave separately upon application of cholinergic agents. Possibly, the separation of delta and theta oscillatory response in AD patients on cholinergic medication will gain high importance in future similar studies.
3. The studies on event-related oscillations may help for the diagnostic purposes and also for monitoring the effects of pharmacological agents, therefore in evaluating the transmitter effects.

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