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Distinctive Effect of Donepezil Treatment on P300 and N200 Subcomponents of Auditory Event-Related Evoked Potentials in Alzheimer Disease Patients

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Background: Latency of P300 subcomponent of event-related potentials (ERPs) increases in Alzheimer disease (AD) patients, which correlate well with cognitive impairment. Cholinesterase inhibitors (ChEIs) reduce P300 latency in AD patients with parallel improvement in cognition. It is not known whether N200 response to ChEIs is similar to that of P300.

The aim of this study was to evaluate and compare characteristics of P300 and N200 in AD patients, treatment-naïve and on stable donepezil treatment, matched by age, education, sex, and cognitive function.

Material/Methods: We recruited 22 consecutive treatment-naïve AD patients (AD-N group), 22 AD patients treated with a stable donepezil dose of 10 mg/day for at least 3 months (AD-T group), and 50 healthy controls were recruited. Neuropsychological testing (MMSE, ADAS-Cog, and additional tests) and ERP recording was performed and analyzed.

Results: All groups did not differ according to age, duration of education, or sex ($p>0.05$). AD-N and AD-T groups did not differ according to cognitive function. The AD-T group had longer duration of disease than the AD-N group ($p<0.001$). The AD-T and AD-N groups did not differ in P300 latencies ($p=0.49$). N200 latency was longer in the AD-T group ($p<0.001$). The general linear model showed that significant predictors of P300 latency were age ($p=0.019$) and AD treatment status ($p<0.001$). Duration of AD was a significant predictor of N200 latency ($p=0.004$).

Conclusions: The response of N200 latency to donepezil treatment differs from the response of P300. P300 is a better marker of ChEI treatment-dependent cognitive functions. N200 is more dependent on the duration of AD.

MeSH Keywords: Alzheimer Disease • Cholinesterase Inhibitors • Dementia • Event-Related Potentials, P300 • Neurobehavioral Manifestations • Neuropsychological Tests

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Background

Alzheimer disease (AD) is a chronic progressive neurodegeneration that accounts for up to 70% of cases of dementia in the elderly population [1,2]. Due to aging of the population, the worldwide prevalence of AD is increasing rapidly and is estimated to reach 106.8 million by the year 2050 [1–3]. At present there is no treatment to stop or at least slow its progression, although some ChE inhibitors (donepezil, rivastigmine, and galantamine) and modulator of glutamatergic NMDA receptors memantine exhibit temporary symptomatic efficacy improving cognitive dysfunction and activities of daily living (ADL) in some patients. No new symptomatic medication for AD has been approved since 2004 [4]. Disease-modifying treatment (DMT) of AD is not available at all. None of the clinical trials with proposed DMTs were successful so far. The failure of high-profile clinical trials of DMTs in AD has several lessons to teach: 1) reliable diagnosis is needed in very early stages of AD (MCI or even pre-clinical AD); 2) pathophysiology of AD is poorly understood, and proposed DMTs may be missing the relevant target; and 3) changes over time in behavioral measures (cognitive function and activities of daily living) do not necessarily follow the changes in basic neurobiological processes, underlying the symptoms of AD. While behavioral measures (cognitive function and ADL) still remain the primary efficacy measures in clinical trials of DMT for AD, there is an urgent need for biological markers able to reflect the dynamics of basic pathophysiologic processes underlying the decline of cognitive function. Several such biological methods are available, including testing of cerebro-spinal fluid (CSF) for amyloid-beta and tau-protein, positron-emission tomography (PET) imaging techniques for amyloid burden in the brain [4], and measures of brain atrophy using MRI volumetry. These methods are expensive (PET and MRI), often of an invasive nature (e.g., testing of CSF markers), and have only low-to-moderate sensitivity and specificity [5].

Electrophysiological measures, such as cognitive event-related potentials (ERPs), are also used as an objective biological measure of changes in the brain functioning in AD patients. It is an attractive method since it directly reflects electrophysiological changes due to AD and is easily accessible and cost-effective [5].

Early components of auditory ERPs (N100 and P200) are considered to reflect sensory processing and are not usually useful for the diagnosis or follow-up in AD [6], whereas later subcomponents (N200 and P300) reflect cognitive processes and can be useful in monitoring of electrophysiological functioning related to cognitive impairment.

N200 subcomponent is generated in frontal-central cortical areas and it is thought to reflect processes of selective stimulus evaluation and conscious discrimination [5,7]. P300 wave is generated in various regions of the brain, mostly temporal and parietal cortices. It is associated with cognitive processes such as attention, recognition and categorization of the stimuli, working memory, and decision making [6,8,9].

It is well established that P300 latency increases and its amplitude decreases in AD patients [10]. These changes in characteristics of P300 subcomponent correlate well with results of neuropsychological testing, i.e., degree of cognitive impairment [5,7]. P300 characteristics are also known to be affected by AD medications (cholinergic treatment). Centrally-acting cholinesterase inhibitors (ChEIs) reduce P300 latency in AD patients. These effects correlate with improvement of neuropsychological test results. P300 latency decreases in parallel with improvement of cognitive functions due to treatment with ChEIs [6,11–13].

N200 subcomponent is less extensively studied. Only recently has attention has been drawn to N200, in which latency is also prolonged in AD patients. Changes in N200 latency appear early in the course of AD; therefore, they could be useful in differentiating patients with MCI (mild cognitive impairment) and early AD from healthy controls as well as in predicting conversion from MCI to AD [5,7]. Information regarding the dynamics of N200 during the course of AD and especially the effect of treatment with ChEIs on N200 characteristics is very limited. It is usually assumed that changes of N200 are similar to the changes of P300. Some studies were conducted, but no definitive conclusions have been achieved yet [6]. In order for ERP P300 and N200 subcomponents to be a useful measure in monitoring progression of AD in symptomatic and disease-modifying treatment (DMT) clinical trials, more information is needed regarding the changes present in AD patients, their evolution during the course of the disease, and the effect of cholinergic treatment on the characteristics of ERP P300 and N200 subcomponents.

The aim of this study was to evaluate and compare characteristics of P300 and N200 subcomponents of auditory event-related potentials (ERPs) in Alzheimer disease (AD) patients who were treatment-naïve and on stable donepezil treatment, matched by age, education, sex, and cognitive function, to compare results of both AD groups with healthy controls.

Material and Methods

Participants

The study was performed at the Memory Disorders Unit of the Neurology Department, Vilnius University Hospital Santariskiu Clinics. We recruited 44 consecutive AD patients:

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Table 1. Inclusion criteria.

AD-N group (N=22)	AD-T group (N=22)	Control group (N=50)
The patient has late onset sporadic probable AD diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria		Normal cognitive functioning (MMSE score 27–30)
The patient has mild or mild to moderate dementia: Mini-Mental State Examination (MMSE) score of at least 18, and no greater than 23		
The patient is treatment-naïve (newly diagnosed AD)	The patient has been treated daily with the stable donepezil dose of 10 mg/day for at least 3 months prior to assessment	
The patient has had a CT or MRI less than 12 months before the assessment with results consistent with the diagnosis of probable AD		
The patient is aged at least 65 years		
The patient's sight and hearing are sufficient for compliance with the study assessment		
The patient is proficient in the Lithuanian language		

Table 2. Exclusion criteria.

The patient has been treated with any other medication for AD available on the market or any investigational product for AD
The patient has evidence of any neurodegenerative disease, or other serious neurological disorders other than AD including, but not limited to Lewy body dementia, fronto-temporal dementia, Parkinson's disease, Huntington's disease, major stroke, major head trauma, primary or secondary cerebral neoplasia or systemic medical diseases that are likely to affect central nervous system functioning
The patient has a history of seizures
The patient has findings that fulfil the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia
The patient has been tested positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus/antibody (anti-HCV)
The patient has a Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) Axis I disorder other than AD including amnestic disorders, delirium, schizophrenia, schizoaffective disorder, bipolar disorder, current major depressive episode, psychosis
The patient has CT or MRI evidence of stroke, a space-occupying lesion, or any clinically significant brain disease other than AD
The patient has evidence of clinically significant comorbidities including but not limited to pulmonary, gastrointestinal, renal, hepatic, endocrine, cardiovascular system disease, metabolic disturbance or vitamin B12 deficiency that could affect cognition
The patient is currently receiving or has taken any other cognitive enhancing medication within 3 months prior to the assessment including but not limited to Memantine, Rivastigmine, Galantamine, Amantadine, Modafinil, Methylphenidate, Ginkgo biloba

22 treatment-naïve (AD-N group) and 22 AD patients treated with the stable donepezil dose of 10 mg/day for at least 3 months at the time of testing (AD-T group) and 50 healthy controls (Control group, CG) matched according to age, education, and sex. AD-N and AD-T groups were matched by age, education, sex, and cognitive function, based on MMSE and ADAS-Cog Total Scores. Control group participants were recruited from the spouses and relatives of other patients attending the Neurology Department, but with no AD or other dementia. Neuropsychological assessment and event-related potentials (ERP) measurements were performed on the same day. Neuropsychological assessment and ERP measurement were performed in the morning with a time interval no less than 1 hour, but no longer than 3 hours. Inclusion criteria are listed in Table 1 and exclusion criteria are listed in Table 2.

The study protocol was approved by the Lithuanian Bioethics Committee, approval No. 6/2007-03-21. Written Informed consent was obtained from all the participants.

Neuropsychological assessment instruments

The cognitive performance of participants was assessed using the Lithuanian versions of Mini-Mental State Examination

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Table 3. Demographic data.

	AD-N	AD-T	Control group	Test
Number of subjects, N	22	22	50	
Age (years), mean ±SD	74.36±4.75	74.23±5.21	74.06±4.49	ANOVA F=0.034; p=0.967
Education (years), mean ±SD	10.96±4.18	11.27±3.72	11.74±4.11	ANOVA F=0315; p=0.731
Women/men, N	8/14	14/8	26/24	Chi-square 3.31; p=0.19
Duration of AD (years)	1.73±0.83	3.41±1.30	N/A	t-test t=–5.13; p<0.001

(MMSE) and Alzheimer disease assessment scale (ADAS) cognitive subscale (ADAS-Cog). ADAS-Cog total score and scores for 4 separate cognitive domains (memory, orientation, praxis, and language) were evaluated. As ADAS-Cog lacks adequate tests for evaluation of attention, working memory, and executive functions, and additional tests were added to the neuropsychological assessment battery: Digit Span-forwards test, Trail Making A test, and Porteus Maze test.

Event-related potentials measurement

An "oddball" paradigm was used to elicit auditory event-related potentials. Binaural tones were presented over headphones at 60 dB Sound pressure level (SPL). The target stimulus was 2000 Hz and the non-target stimulus was 1000 Hz. Thirty target stimuli were collected for each task, the entire procedure taking about 10 min. The target stimuli occurred randomly with a probability of 1: 4 at an interstimulus interval of 2 s. Subjects were also instructed to press a hand-held button (response switch) with their dominant hand to indicate target stimulus detection. Error rate and response time were recorded. Only correctly detected target trials with responses less than 2000 ms were accepted. The brain activity was recorded at 3 sites of active electrodes: Fz, Cz, and Pz sites of the international 10–20 system using gold-plated electrodes affixed with electrode paste and a tape, with a forehead ground, referred to linked earlobes, and with impedance at 5 KΩ or less. The filter bandpass was 0.01–30 Hz. All subjects were tested while resting comfortably in a bed with their eyes closed. Rest periods were provided between task conditions, as appropriate. Latencies and amplitudes of N200 and P300 subcomponents of ERPs were measured. The P300 response time (P300 response switch time) was also recorded for all subjects.

Statistical analysis

Comparisons between groups were performed using the t test or chi-square test where appropriate. One-way ANOVA with Bonferroni post-hoc test was used for comparisons of multiple groups. Normal distribution of data was checked using the Shapiro-Wilk test. A general linear model was constructed to explore which independent predictors had a significant relationship with ERP characteristics as dependent variables. Both AD-N and AD-T groups were included in the data set for general linear model. Age, education, duration of AD, and ADAS-cog total score were entered as independent continuous predictors, and participant group (AD-N or AD-T) was entered as a categorical predictor (factor). Statistical significance value was set at $p<0.05$.

Results

Demographic data

There were 94 subjects enrolled into the study: 50 of them were healthy controls (Control Group, CG) and 44 were AD patients; 22 AD patients were newly diagnosed with the AD and treatment-naïve (AD-N group); 22 AD patients have been treated with the stable dose of donepezil (10 mg/d) for at least 3 months at the time of assessment (AD-T group). Study groups did not differ significantly according to age (p=0.967), duration of education (p=0.731), or sex (p=0.19). AD-T group had significantly longer duration of the disease compared to treatment-naïve patients (AD-N group) (p<0.001). Demographic characteristics of all groups are shown in Table 3.

Neuropsychological testing

Healthy controls did not differ from AD patients only in the results of Digit span test (one-way ANOVA F=0.908; p=0.407). The results of all other tests were significantly worse in both AD patient groups when compared to cognitively healthy controls. Differences between separate groups were evaluated by means of Bonferroni post-hoc test. AD-N and AD-T groups did not differ based on the results of any cognitive test performed. Results of neuropsychological tests are shown in Table 4.

Event-related potentials

N200 and P300 subcomponents of auditory event-related potentials (ERPs) were recorded in 3 registration electrode sites

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Table 4. Results of neuropsychological testing (mean ±SD).

Test	AD-N	AD-T	Control group	ANOVA	Bonferroni post-hoc
MMSE, (points)	20.73±1.7	20.14±1.36	29.04±0.92	F=561.4 p<0.001	CG>AD-N CG>AD-T AD-N=AD-T (p=0.356)
Digit Span, (points)	4.73±0.55	4.55±0.67	4.78±0.74	F=0.908 p=0.407	CG=AD-N (p=0.548) CG=AD-T (p=0.548) AD-N=AD-T (p=0.99)
Porteus Maze, time (s)	264.61±129.47	292.75±83.63	170.65±97.55	F=12.40 p<0.001	CG<AD-N CG<AD-T AD-N=AD-T (p=0.99)
Porteus Maze, mistakes (N)	2.55±1.36	2.50±1.01	1.54±1.11	F=8.228 p=0.001	CG<AD-N CG<AD-T AD-N=AD-T (p=0.99)
Trail Making A, time (s)	231.68±110.61	247.27±60.1	105.70±54.67	F=40.02 P<0.001	CG<AD-N CG<AD-T AD-N=AD-T (p=0.99)
ADAS-Cog word recall, average number of mistakes (N)	6.59±1.33	7.05±1.05	3.94±1.22	F=67.06 p<0.001	CG<AD-N CG<AD-T AD-N=AD-T (p=0.65)
ADAS-Cog word recognition, average number of mistakes (N)	5.55±2.04	5.59±1.14	2.58±1.72	F=36.72 P<0.001	CG<AD-N CG<AD-T AD-N=AD-T (p=0.99)
ADAS-Cog total, (points)	23.14±4.81	25.0±3.34	7.76±3.51	F=215.3 P<0.001	CG<AD-N CG<AD-T AD-N=AD-T (p=0.326)

(Fz, Cz and Pz). As P300 and N200 subcomponents have different distributions of amplitude and latency across the sites of the international 10–20 system, Cz site is the most suitable for reliable recording and evaluation of both P300 and N200 subcomponents of ERP in AD. Additionally, Cz is believed to reflect the function of both hippocampi and temporal lobes, which are particularly important in pathogenesis of AD. Therefore, the results of the recordings at Cz site were chosen for detailed analysis. One-way ANOVA with Bonferroni post-hoc tests was performed to evaluate the differences between groups regarding ERPs characteristics. P300 latencies at Cz (ms) for all groups are shown in Figure 1. ANOVA showed significant differences of P300 latencies (F=112.96; p<0.001). Bonferroni post-hoc test revealed that both AD-N and AD-T groups differed from control group (p<0.001), but there was no difference found between AD-N and AD-T groups (p=0.49). P300 amplitudes at Cz (μV) are shown in Figure 2. ANOVA did not show significant differences of P300 amplitudes in all 3 groups (F=0.71; p=0.49). N200 latencies at Cz (ms) are shown in Figure 3. ANOVA showed significant differences of N200 latencies (F=88.24; p<0.001). Bonferroni post-hoc test revealed that both AD-N and AD-T groups had N200 latencies compared to control group (p<0.001), but, notably, AD-T group had significantly longer N200 latency than AD-N (p<0.001). P300-N200 interpeak intervals at Cz (ms) are provided in Figure 4. The ANOVA showed significant differences of P300-N200 interpeak intervals (F=12.13; p<0.001). Bonferroni post-hoc test revealed that the AD-N group had longer P300-N200 interpeak intervals than both AD-T (p<0.001) and Control group (p=0.001), but Ad-T and Control groups did not differ significantly by P300-N200 interpeak interval (p=0.166). P300 response times (ms) in all groups are shown in Figure 5. The

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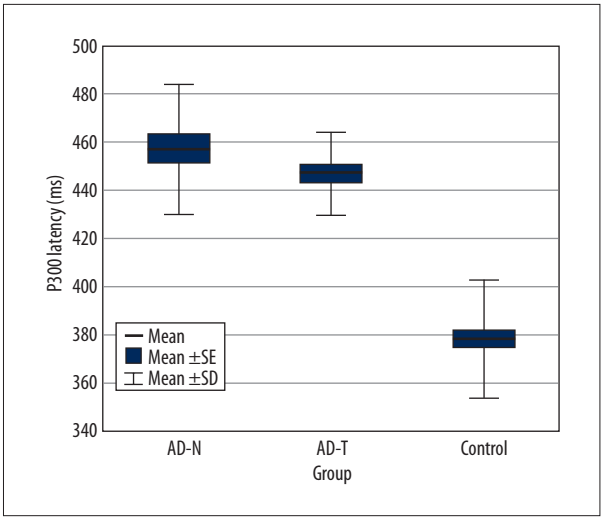

Figure 1. P300 latency in participant groups.

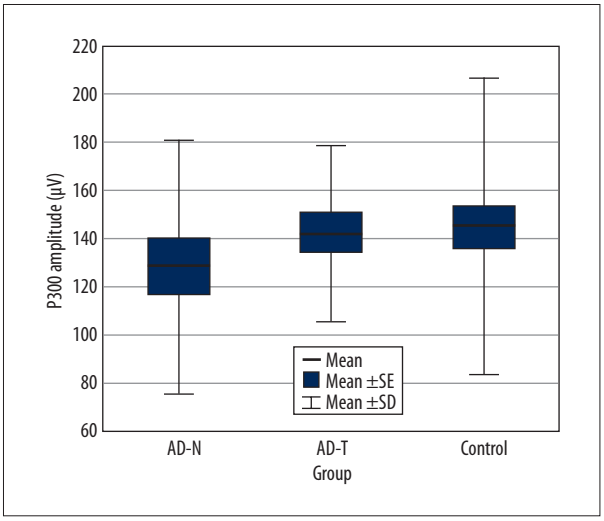

Figure 2. P300 amplitude in participant groups.

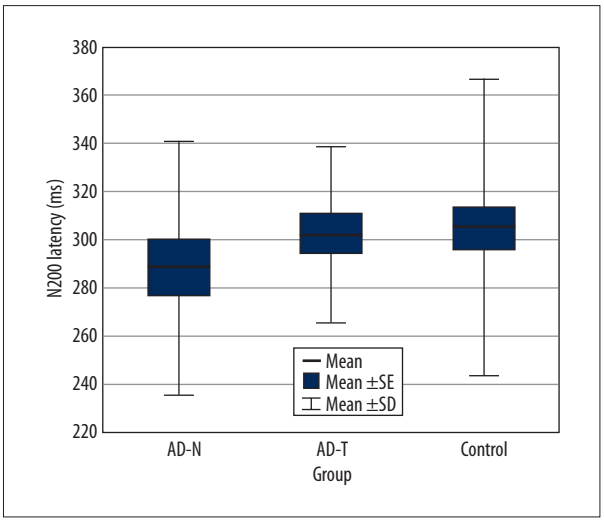

Figure 3. N200 latency in participant groups.

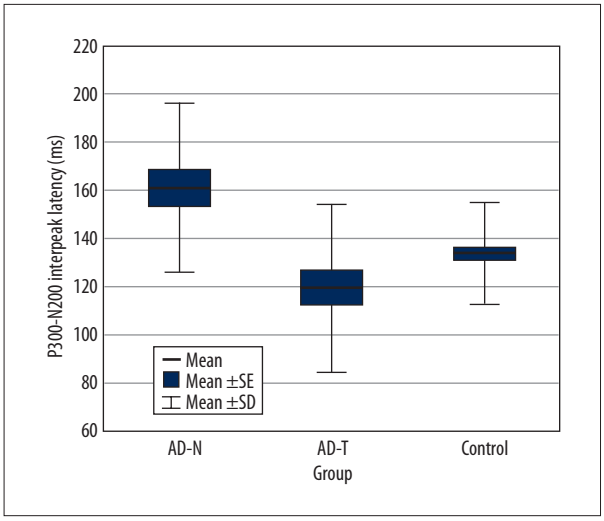

Figure 4. P300-N200 interpeak latency in participant groups.

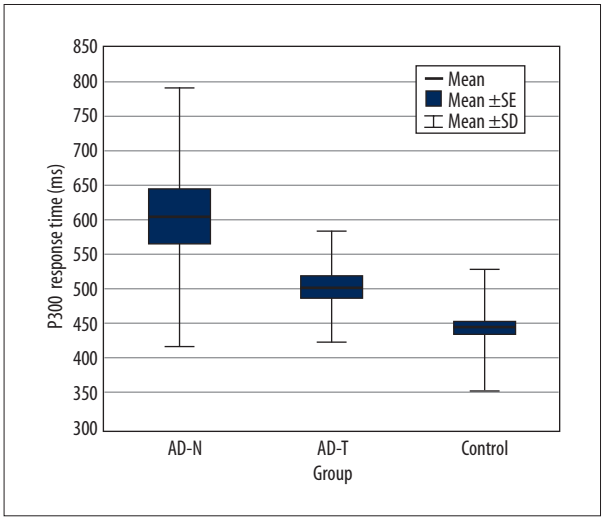

Figure 5. P300 response time in participant groups.

ANOVA showed significant differences of P300 response time ($F=14.55$; $p<0.001$). Bonferroni post-hoc test showed that AD-N group had longer P300 response time than both AD-T ($p=0.02$) and Control group ($p<0.001$), but Ad-T and Control groups did not differ significantly by P300 response time ($p=0.106$).

Since AD-N and AD-T groups did not differ by age, sex, education, and measures of cognitive function, but differed significantly by N200 latency and P300-N200 interpeak latency, a general linear model was constructed to explore which independent (explanatory) variables (predictors) have a significant relationship with ERP characteristics as dependent variables. Both AD-N and AD-T groups were included in the data set for the general linear model. Age, education, duration of AD, and ADAS-cog total score were entered as independent continuous predictors, and participant group (AD-N or AD-T) was entered as a categorical predictor (factor).

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For the dependent variable "P300 latency", the general linear model was significant: Multiple R^2=0.259; F=2.66; p=0.037. The general linear model showed constant (B=290.61; p<0.001), age (B=1.632; p=0.019), and "participant group (AD-N or AD-T)" (B=–26.38; p<0.001) as significant predictors.

For dependent variable "N200 latency" general linear model was significant: Multiple R^2=0.347; F=4.032; p<0.005. The general linear model showed constant (B=271.3; p<0.001) and "duration of AD" (B=14.887; p=0.004) as significant predictors.

For dependent variable "P300-N200 interpeak latency" general linear model was significant: Multiple R^2=0.443; F=6.054; p<0.001. Constant (B=16.47; p=0.047), "duration of AD" (B=15.29; p=0.004), and "participant group (AD-N or AD-T)" (B=–33.25; p<0.001) were found to be significant predictors.

Discussion

In our study, AD patients receiving a stable dose of donepezil and newly diagnosed, treatment-naïve patients did not differ significantly according to the results of neuropsychological testing, although the duration of the disease was significantly longer in treated patients. This could be explained by the positive effect of cholinergic treatment on cognitive functions. It is usually assumed that N200 subcomponent represents such early cognitive processes as target discrimination [14], while P300 subcomponent reflects the target stimulus evaluation and decision making [15,16]. P300 ERP subcomponents are probably associated with the processes of information encoding and memory formation [17,18]. Decrease of P300 latency and improvement of cognitive function during treatment with donepezil was established earlier [6,12,19]. P300 latency, similar to cognitive function, follows the same dynamics during the treatment with donepezil: initial improvement after 3 months of treatment, plateau phase of several months (3 to 6 months), and the gradual decrease after 6–12 months and later [6,11]. There were noticeable differences in the dynamics of P300 and N200 during progression of AD from the stage of mild cognitive impairment (MCI) to dementia, even independently of any external cholinergic influence [20]. Since in our study the duration of Alzheimer disease was significantly longer in the AD-T group (3.41±1.30 years) than in the AD-N group (1.73±0.83 years), it could be hypothesized that those electrophysiological markers, which closely reflect the final stages of memory formation and are related to symptomatic efficacy of ChEI treatment, will be similar in both AD-T and AD-N groups. Those markers, which are independent of cognitive effects of symptomatic treatment, will progress further despite temporary symptomatic improvement of cognition due to the cholinergic treatment. Latencies of P300 were similar in both AD participant groups, as were similar results of cognitive tests.

These findings are in line with the data of other researchers, who reported that P300 latency shortened after treatment of AD patients with donepezil (5 mg/day) for 22 to 23 weeks, while N200 latency did not change [6].

N200 latencies, however, differed significantly between AD patient groups. Treatment-naïve patients (AD-N group), who also had significantly shorter duration of the disease, had significantly shorter N200 latencies than the AD-T group. The general linear model revealed that the duration of the disease is a significant predictor for N200 latency in both the AD-N and AD-T groups. This may be explained by assuming that cholinergic treatment with donepezil did not influence the N200 latency significantly for a longer time period. According to our results, it could be assumed that N200 latency is prolonged in AD patients and it increases even further during the course of the disease relatively independently of cholinergic treatment with donepezil and temporary symptomatic improvement of cognitive function. These suggestions correspond to earlier reported findings that ChEIs do not modulate early cognitive processing, reflected by N200 [6].

Unlike N200, ERP subcomponent P300 characteristics (especially latency) are significantly affected by cholinergic medications (selective AChE inhibitor donepezil in our case), which are a standard treatment option for improving AD symptoms; thus, P300 latency corresponds well to such behavioral measures of cognitive functions, but do not adequately reflect the ongoing process of neurodegeneration.

If this explanation of our findings proves to be correct, N200 could become a valuable biomarker, reflecting biological changes in brain structures and their progression during the course of the disease independently of cognitive (behavioral) measures, which could be affected by symptomatic treatment.

Therefore, P300 latency may be treated as an electrophysiological marker of cognitive status of the patient as reflected by neuropsychological tests. As such, it is a good marker for clinical trials dealing with symptomatic treatment. N200 latency is less dependent on the cholinergic status of the brain, which can be quite quickly altered by ChEI treatment; therefore, N200 might be a very useful electrophysiologic marker of neurobiological AD progression in clinical trials dealing with disease-modifying treatment (DMT). It seems that N200, being at least partially independent of the symptomatic effect of ChEIs, may be able to provide a valuable clue very early during the course of the DMT clinical trial as to whether the biological basis of neurodegeneration is affected by DMT under investigation.

Although our results are encouraging, a prospective long-term follow-up study of *de novo* AD patients is needed to cover all main phases of clinical-cognitive response to donepezil and elucidate

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the dynamics of P300 and N200 in response to cholinergic treatment. Polymorphisms of risk genetics, especially Apolipoprotein E (ApoE), may not only influence differing cognitive response to ChEI treatment, but also different dynamics of ERP. Possibly, participants with ApoE epsilon4 allele should be analyzed separately.

Conclusions

The response of N200 subcomponent latency to cholinergic treatment with donepezil differs from the response of P300. N200 subcomponent is less influenced by symptomatic treatment with ChEIs and depends more on the duration of the disease. P300 is a better marker of cholinergic status-dependent cognitive functions, while N200 reflects the biological progression of AD more or less independently from cognitive-behavioral effects produced by symptomatic treatment.

Conflict of interest

The authors have declared no conflicts of interest.

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