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Associations of event-related brain potentials and Alzheimer's disease severity: A longitudinal study

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ABSTRACT

Background: So far, no cost-efficient, widely-used biomarkers have been established to facilitate the objectivization of Alzheimer's disease (AD) diagnosis and monitoring. Research suggests that event-related potentials (ERPs) reflect neurodegenerative processes in AD and might qualify as neurophysiological AD markers.
Objectives: First, to examine which ERP component correlates the most with AD severity, as measured by the Mini-Mental State Examination (MMSE). Then, to analyze the temporal change of this component as AD progresses.
Methods: Sixty-three subjects (31 with possible, 32 with probable AD diagnosis) were recruited as part of the cohort study Prospective Dementia Registry Austria (PRODEM). For a maximum of 18 months patients revisited every 6 months for follow-up assessments. ERPs were elicited using an auditory oddball paradigm. P300 and N200 latency was determined with regard to target as well as difference wave ERPs, whereas P50 amplitude was measured from standard stimuli waveforms.
Results: P300 latency exhibited the strongest association with AD severity (e.g., $r = -0.512$, $p < 0.01$ at Pz for target stimuli in probable AD subjects). Further, there were significant Pearson correlations for N200 latency (e.g., $r = -0.407$, $p = 0.026$ at Cz for difference waves in probable AD subjects). P50 amplitude, as measured by different detection methods and at various scalp sites, did not significantly correlate with disease severity-neither in probable AD, possible AD, nor in both subgroups of patients combined. ERP markers for the group of possible AD patients did not show any significant correlations with MMSE scores. Post-hoc pairwise comparisons between baseline and 18-months follow-up assessment revealed significant P300 latency differences (e.g., $p < 0.001$ at Cz for difference waves in probable AD subjects). However, there were no significant correlations between the change rates of P300 latency and MMSE score.
Conclusions: P300 and N200 latency significantly correlated with disease severity in probable AD, whereas P50 amplitude did not. P300 latency, which showed the highest correlation coefficients with MMSE, significantly increased over the course of the 18 months study period in probable AD patients. The magnitude of the observed prolongation is in line with other longitudinal AD studies and substantially higher than in normal ageing, as reported in previous trials (no healthy controls were included in our study).

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and is most prevalent in elderly populations (Alzheimer's Association, 2014). Already, our ageing society is confronted with an alarming increase in AD cases (Prince et al., 2013; Ferri et al., 2005). Besides its devastating impact on memory and cognition, AD impairs basic bodily functions such as walking and swallowing and eventually leads to death. The combination of its looming global epidemic status and severity makes AD a major public health concern (Alzheimer's Association, 2014).

Due to its degenerative nature, early accurate diagnosis and effective clinical monitoring are crucial. However, when it comes to routine clinical practice, AD assessment is most commonly done by subjective clinical interpretations at a progressed stage of the disease, i.e. when symptoms are already apparent. So far, no cost-efficient, widely-used biomarkers have been established to facilitate the objectivization of diagnosis and disease progression assessment. To promote the screening and monitoring of as many individuals as possible, such markers should not be dependent on costly equipment, such as magnetic resonance imaging (MRI), or positron emission tomography (PET) scanners. Therefore, we focus on inexpensive apparatuses that are part of daily clinical practice in secondary and tertiary neurological care, namely electroencephalography (EEG) devices. Their non-invasiveness and low noise level (as opposed to most neuroimaging techniques) add to their suitability for large-scale use in irritable patients such as those found within the spectrum of AD.

Research suggests that event-related potential (ERP) recordings reflect neurodegenerative processes in AD (for reviews, see Olichney et al., 2011; Drago et al., 2011; Dauwels et al., 2010). For instance, meta-analyses have shown that long latency ERPs are significantly prolonged for patients with mild cognitive impairment (MCI) and AD as compared to healthy controls (for N200, see Howe, 2014; for P300, see Howe et al., 2014). Furthermore, shortened P300 latencies were observed when comparing patients with MCI to patients with AD (Howe et al., 2014).

Besides the more prominent N200 and P300, the P50 has received increasing attention as a putative neurophysiological biomarker and surrogate marker in recent years. Both patients with MCI and AD show increased P50 amplitude relative to age-matched controls (Golob et al., 2002; Golob and Starr, 2000). Moreover, in a five-year MCI longitudinal study (Golob et al., 2007) the extent of amplitude increase of P50 over time has been shown to relate to both the type of amnestic MCI (larger in multiple domain MCI than in single domain MCI) and clinical outcomes (larger in MCI who converted to dementia than in MCI who remained stable). Green et al. (2015) successfully used P50 amplitude to dichotomously classify MCI patients according to their relationship with AD pathology as measured by amyloid-beta (Aβ42) levels in cerebrospinal fluid (CSF).

Whereas various studies have examined the usefulness of ERP markers to classify between AD patients and MCI and/ or healthy control subjects, only a few studies have investigated associations between ERP markers and AD severity (e.g., Lee et al., 2013; Onofrj et al., 2002; Ball et al., 1989). Furthermore, only a couple of studies exist in the domain at hand today that have used a longitudinal design. Most of these experiments examined subjects with MCI or subjective memory complaints (Papaliagkas et al., 2011; Bennys et al., 2011; Chapman et al., 2011; Papaliagkas et al., 2008; Golob et al., 2007; Gironell et al., 2005) while only a few studies longitudinally tracked actual AD progression (Lai et al., 2010; Onofrj et al., 2002; Ball et al., 1989; St Clair et al., 1988).

We therefore, first, investigate which ERP component demonstrates the strongest correlation with AD severity, as measured by the Mini-Mental State Examination (MMSE; Folstein et al., 1975), one of the best known and most widely used psychometric assessments of global cognition in clinical practice (Sheehan, 2012; O'Bryant et al., 2008). Then, we longitudinally follow this component at distinct scalp locations over time (6-, 12-, and 18-months follow-up assessments) and empirically examine its presumed change as AD progresses.

To the best of our knowledge, this is the ERP study with the highest number of AD patients longitudinally followed when considering study periods longer than 6 months. Furthermore, our study is the first to report on correlation coefficients between AD severity and P50 amplitude. Finally, we could not find any other prospective study that included more AD subjects (in our examination N = 63) for the computation of correlations between ERP markers and a measure of disease severity.

2. Methods

2.1. Subjects

Sixty-three subjects (31 with possible, 32 with probable AD diagnosis according to NINCDS-ADRDA criteria; 39 Apolipoprotein E (ApoE) ε4 allele carriers; 39 with anti-dementia drug treatment (acetylcholinesterase inhibitors, N-methyl D-aspartate (NMDA) receptor antagonists); 38 females; mean age 75.92 ± 8.82 standard deviation (SD); mean MMSE score 23.25 ± 3.6 SD; mean years of education 10.46 ± 2.26 SD; mean duration of illness (months) 22.89 ± 14.65 SD) were recruited prospectively at the tertiary-referral memory clinic of the Medical University of Innsbruck as part of the cohort study Prospective Dementia Registry Austria (PRODEM). When comparing the group characteristics of probable and possible AD patients, only age showed a significant difference ($p = 0.003$). Importantly, there was no significant difference in anti-dementia medication status between probable and possible AD patients ($p = 0.921$). For further details, see Table 1.

PRODEM is a longitudinal multicenter study of AD and other dementias in a routine clinical setting by the Austrian Alzheimer Society (for quantitative EEG (QEEG) results of the PRODEM study, see Waser et al., 2016; Garn et al., 2015; Garn et al., 2014; Fruehwirt et al., 2017). Ethics committee approval was obtained and patients as well as their caregivers gave written informed consent. Inclusion criteria encompassed: (I) diagnosis of Alzheimer-type dementia according to NINCDS-ADRDA criteria, (II) minimum age 40 years, (III) non-institutionalization and no need for 24-hour care, (IV) availability of a caregiver who agrees to provide information on the patient's condition. Patients with comorbidities likely to preclude termination of the study were excluded. For a maximum of 18 months assessments were repeated every 6 months, i.e., 6 months (FU1), 12 months (FU2) and 18 months (FU3) after baseline (BL). Twenty-nine out of the 63 patients at BL returned for each of the three follow-up assessments (characteristics at BL: 14 with possible, 15 with probable AD diagnosis; 17 ApoE ε4 carriers; 18 with anti-dementia drug treatment; 19 females; mean age 73.52 ± 8.42; mean MMSE score 23.55 ± 3.34 SD; mean years of education 10.62 ± 2.24 SD; mean duration of illness (months) 25.69 ± 17.83 SD).

2.2. EEG recording

Participants were seated in an upright position on a comfortable chair with neck rest. The room where recording took place was sound attenuated and controlled at pleasant ambient temperature. Horizontal and vertical electrooculogram (EOG) electrodes were placed to detect eye movements. The system employed was a 32-channel AlphaEEG amplifier with NeuroSpeed software (alpha trace medical systems, Dr. Grossegger & Drbal GmbH, Vienna, Austria). EEG electrode placement (Au-plated cups; Grass F-E5GH, Grass Technologies, West Warwick, RI, USA) was in accordance with the international 10–20 system. The electrodes were referenced to connected mastoids, the ground being positioned at FCz. The EEG amplifier had a bandpass of 0.3 to 70 Hz (3 dB points) with a 50 Hz notch filter and a sampling rate set at 256 Hz.

Table 1
Clinical characteristics of AD subjects at baseline assessment.

	All AD patients	Probable AD patients	Possible AD patients	χ2	p
N	63	32	31		
APOE ε4 carriers	39	20	19	0.01	0.921
Anti-dementia medication	39	20	19	0.01	0.921
Females	38	20	18	0.13	0.719

	All AD patients	Probable AD patients	Possible AD patients	t	p
Age (years)	75.92 ± 8.82	72.72 ± 10.23	79.23 ± 5.51	−3.12	0.003
MMSE score	23.25 ± 3.6	22.44 ± 4.32	24,10 ± 2.47	−1.87	0.067
Education (years)	10.46 ± 2.26	10.59 ± 2.17	10.32 ± 2.37	0.47	0.637
Duration of illness (months)	22.89 ± 14.65	20.03 ± 13.49	25.84 ± 15.43	−1.59	0.116

AD: Alzheimer's disease, ApoE: Apolipoprotein, MMSE: Mini-Mental State Examination, mean values ± standard deviations. Comparisons between the groups of probable and possible AD subjects were done using Chi-squared (χ2) tests (categorical variables) and Student's t-tests (interval variables).

Impedance levels were held below 10 kΩ.

2.3. Behavioral paradigm

The widely used two-tone oddball paradigm, a simple auditory discrimination task, was applied to elicit ERPs. Subjects were instructed to detect infrequent (57), high-pitched (2000 Hz) target tones embedded in a stream of frequent (141), low-pitched (1000 Hz) standard tones. The tone duration was 100 ms, with rise and fall times of 10 ms, interstimulus intervals varied between 1000 and 1500 ms. Subjects were instructed to press a reaction time button, with the dominant hand, to target stimuli only. All stimuli were presented binaurally via headphones. Volume levels were individually adjusted to a comfortable, audible level for each participant. Hearing aid devices were allowed during the experiment when necessary.

2.4. ERP preprocessing and analysis

After automatic horizontal and vertical regression-based EOG correction in the time domain (Anderer et al., 1992), the data were bandpass filtered at 0.3–30 Hz. Individual sweeps to targets were visually screened for artefacts before being accepted into the average. As a rule, sweeps to standard tones were automatically rejected if the voltage on any recording site exceeded 75 µV or fell below −75 µV. For two subjects with high-voltage EEG the thresholds were set to ± 100µV.

The P300 is most commonly measured at Pz. However, Howe et al. (2014b) could not find statistically significant differences between midline electrode sites in their meta-analysis. Therefore, besides confirmatory analysis of Pz, we exploratively investigated correlations at Fz and Cz. The N200 has a centro-frontal scalp distribution. According to Howe et al. (2014a) N200 is more commonly measured at Cz than at Fz in the AD context. Nonetheless, since there was no statistically significant electrode effect between all sites in their conducted meta-analysis, we exploratively examined the other midline positions as well. Golob et al. (2007) only used Cz for P50 detection. Green et al. (2015) compared various electrode sites in their study and concluded that C3 showed the best results. Therefore, we used C3 as confirmatory and Cz and C4 as exploratory sites.

To isolate target components of interest target-minus-standard difference waves (difference waves) were computed by deducting the standard from the target waveforms.

Latencies and amplitudes were determined by the following procedure: P50 amplitude was measured from standard waveforms, whereas N200 and P300 latency was determined with regard to target and difference wave ERPs.

First, peaks were automatically marked within the following time windows: the N200 component was defined as the the maximum negativity between 175 and 350 ms after stimulus onset, and the P300 component was the maximum positivity between 280 and 600 ms after stimulus onset. To ascertain the validity of the computed peaks, peak detection was visually verified and corrected wherever necessary. For the determination of inconclusive peaks, waveforms of targets, nontargets and difference waves were compared. P50 amplitude was computed by averaging the amplitude measurements across the 40–80 ms time window after stimulus onset adjusted for a 100 ms prestimulus baseline.

2.5. Assessment of disease severity

MMSE scores were used as measures for AD disease severity. The MMSE items include tests of orientation, registration, recall, calculation and attention, naming, repetition, comprehension, reading, writing, and drawing. The summed score of the individual items indicates the severity of cognitive impairment, where decreasing scores mark deterioration in memory and cognition (Cockrell and Folstein, 2002).

2.6. Statistical analysis

Statistical analyses were performed in SPSS 23.0.0.0 (IBM Corporation, Armonk, NY, USA) and MATLAB 2016a (Mathworks Inc., Natick, MA, USA).

Partial Pearson correlation coefficients were computed to examine the relationship between AD severity and MMSE scores at BL. Significant differences between correlation coefficients of AD subgroups were determined by two-sample z-tests.

To investigate potential changes of ERP marker values over time, analyses of variance (ANOVAs) for repeated measures were conducted with the within-subject factor time (BL, FU1, FU2, FU3). Anti-dementia drug treatment (constant versus variable medication during the study period) was introduced as between-subject factor, to test if time x medication interactions were significant. In case Mauchly's sphericity test (Mauchly, 1940) was significant, ANOVA results were adjusted for sphericity using Greenhouse-Geisser correction (Greenhouse and Geisser, 1959). Paired Student's t-tests were used for comparisons of BL measurements to follow-up values.

Statistics for partial correlations were performed on data of all 63 subjects at BL, whereas longitudinal analyses were done using patients which completed all of the four time points, i.e., the BL measurement as well as all three follow-up assessments. Comparisons between those two groups (all sessions versus not all sessions) were done using Chi-squared (χ2) tests for categorical variables and Student's t-tests for quantitative variables. All p-values are reported in a two-tailed form. To account for multiple comparisons (familywise error), we used Bonferroni adjustments of alpha levels (α).

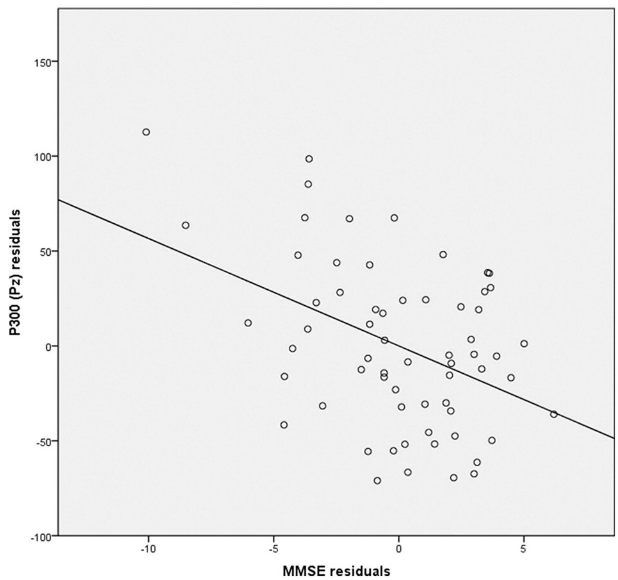

Fig. 1. Partial Pearson correlation plot (correcting for age and years of education) for MMSE values and P300 latency measurements at Pz in all Alzheimer's disease subjects.

3. Results

3.1. Correlations between ERP components and MMSE scores at baseline

Pearson correlations at BL were corrected for the covariates age and years of education, the partial correlation plot (Fig. 1) depicts respective residuals. Sex, duration of illness, treatment with anti-dementia drugs, and ApoE status (carriers versus non-carriers of the ε4 allele) were also tested as potential covariates, but were not significant.

Correlation coefficients are reported at Pz for P300 latency, at Cz for N200 latency, and at C3 for P50 amplitude (see 'ERP preprocessing and analysis' for the underlying rationale). Detailed results can be obtained from Table 2. The results of the exploratory examination of correlation coefficients at additional electrode positions (Fz and Cz for P300 latency; Fz and Pz for N200 latency; Cz and C4 for P50 amplitude) can be seen in Table 3.

For the group as a whole, P300 latency for targets showed the strongest correlation with MMSE ($r = -0.425$, $p < 0.001$, see Fig. 1). P300 latency for difference waves resulted in $r = -0.334$ ($p = 0.009$). Difference waves showed the strongest correlation coefficient for N200 latency ($r = -0.377$, $p = 0.003$), while corresponding target analysis resulted in $r = -0.335$ ($p = 0.008$). All of the aforementioned results remained significant after Bonferroni adjustment of the alpha level ($\alpha = 0.05/5 = 0.01$). P50 amplitude did not correlate significantly with MMSE scores, even before Bonferroni correction ($r = -0.011$, $p = 0.931$).

For the subgroup of probable AD patients, P300 latency for targets showed the maximal coefficient of correlation ($r = -0.512$, $p = 0.005$), constituting the highest value over all, whereas P300 latency for difference waves resulted in $r = -0.379$ at $p = 0.043$. N200 latency correlated at $r = -0.304$ ($p = 0.102$) for targets and at $r = -0.407$ ($p = 0.026$) for difference waves. The result for P50 amplitude was not significant ($r = 0.221$, $p = 0.240$). Only P300 latency correlation for targets remained significant after correction for multiple testing.

For the subgroup of possible AD patients, none of the correlations were significant, even before correction for multiple comparisons.

Table 2
Confirmatory correlation results between ERP components and MMSE scores at baseline.

ERP measure	Waveform	Site	Pearson's r	p
All subjects				
P300 latency	Targets	Pz	−0.42500	0.00071**
P300 latency	Difference waves	Pz	−0.33374	0.00916**
N200 latency	Targets	Cz	−0.33493	0.00833**
N200 latency	Difference waves	Cz	−0.37654	0.00278**
P50 amplitude	Non-targets	C3	−0.01135	0.93081
Probable AD				
P300 latency	Targets	Pz	−0.51191	0.00453**
P300 latency	Difference waves	Pz	−0.37891	0.04266*
N200 latency	Targets	Cz	−0.30403	0.10239
N200 latency	Difference waves	Cz	−0.40682	0.02568*
P50 amplitude	Non-targets	C3	0.22110	0.24033
Possible AD				
P300 latency	Targets	Pz	−0.28425	0.13507
P300 latency	Difference waves	Pz	−0.24574	0.19880
N200 latency	Targets	Cz	−0.36339	0.05267
N200 latency	Difference waves	Cz	−0.34075	0.07048
P50 amplitude	Non-targets	C3	−0.16824	0.38299

Partial Pearson correlation coefficients (correcting for age and years of education) and corresponding p-values, * significant at $\alpha = 0.05$, ** significant at $\alpha = 0.01$ (5-fold Bonferroni correction).

Table 3
Exploratory correlation results between ERP components and MMSE scores at baseline.

ERP measure	Waveform	Site	Pearson's r	p
All subjects				
P300 latency	Targets	Fz	−0.38968	0.00209
P300 latency	Targets	Cz	−0.32919	0.01022
P300 latency	Difference waves	Fz	−0.34807	0.00643
P300 latency	Difference waves	Cz	−0.33302	0.00932
N200 latency	Targets	Fz	−0.36404	0.00393
N200 latency	Targets	Pz	−0.39440	0.00166
N200 latency	Difference waves	Fz	−0.37211	0.00315
N200 latency	Difference waves	Pz	−0.41471	0.00089
P50 amplitude	Non-targets	Cz	−0.02728	0.83468
P50 amplitude	Non-targets	C4	0.07255	0.57846
Probable AD				
P300 latency	Targets	Fz	−0.38104	0.04141
P300 latency	Targets	Cz	−0.43744	0.01764
P300 latency	Difference waves	Fz	−0.35702	0.05727
P300 latency	Difference waves	Cz	−0.38296	0.04031
N200 latency	Targets	Fz	−0.32647	0.07828
N200 latency	Targets	Pz	−0.42375	0.01962
N200 latency	Difference waves	Fz	−0.37492	0.04121
N200 latency	Difference waves	Pz	−0.45461	0.01161
P50 amplitude	Non-targets	Cz	0.22660	0.22853
P50 amplitude	Non-targets	C4	0.23796	0.20542
Possible AD				
P300 latency	Targets	Fz	−0.35588	0.05813
P300 latency	Targets	Cz	−0.19826	0.30255
P300 latency	Difference waves	Fz	−0.34291	0.06860
P300 latency	Difference waves	Cz	−0.27421	0.15002
N200 latency	Targets	Fz	−0.41431	0.02545
N200 latency	Targets	Pz	−0.33995	0.07118
N200 latency	Difference waves	Fz	−0.35290	0.06042
N200 latency	Difference waves	Pz	−0.34939	0.06320
P50 amplitude	Non-targets	Cz	−0.21407	0.26481
P50 amplitude	Non-targets	C4	−0.02862	0.88282

Partial Pearson correlation coefficients (correcting for age and years of education) and corresponding p-values. Due to the exploratory nature of the analysis, there is no adjustment of the alpha level.

3.2. Longitudinal change of P300 latency

When comparing the group characteristics of patients who revisited all three follow-up assessments with the ones of patients who did not, only age showed a significant difference ($p = 0.045$). There was no

Table 4
Clinical characteristics of subjects who accomplished all three follow-up assessments versus subjects who did not.

	All sessions (N = 29)	Not all sessions (N = 34)	χ2	p
Probable AD patients	15	17	0.02	0.891
APOE ε4 carriers	17	22	0.25	0.620
Females	19	19	0.61	0.436
Anti-dementia medication	18	21	0.00	0.980

	All sessions (N = 29)	Not all sessions (N = 34)	t	p
Age (years)	73.52 ± 8.42	77.97 ± 8.76	2.04	0.045
MMSE score	23.55 ± 3.34	23.00 ± 3.84	−0.60	0.549
Education (years)	10.62 ± 2.24	10.32 ± 2.29	−0.52	0.606
Duration of illness (months)	25.69 ± 17.83	20.50 ± 10.98	−1.41	0.163

All values given for baseline assessment, AD: Alzheimer's disease, ApoE: Apolipoprotein, MMSE: Mini-Mental State Examination, mean values ± standard deviations. Comparisons between groups were done using Chi-squared (χ2) tests (categorical variables) and Student's t-tests (interval variables).

significant difference between the groups of probable and possible AD subjects regarding the proportion of subjects who completed all three follow-up assessments. For further information, see Table 4.

Out of the 29 patients longitudinally followed, 18 subjects had already received anti-dementia medication (acetylcholinesterase inhibitors (AChEI) only, and no N-methyl-D-aspartate (NMDA) antagonists) before BL, whereas for the rest (11 subjects), medicotherapy was initiated at BL. In 23 out of 29 subjects, AChEI treatment was kept constant after BL (prescription was changed in two patients and dosage adjustment was carried out in four patients).

We longitudinally tracked the P300 as the component exhibiting the strongest correlation with disease severity at BL and closely investigated change rates of latency at putatively meaningful scalp locations and for the modalities target wave and difference wave.

Repeated-measures ANOVAs were used to determine whether mean values differed significantly ($\alpha = 0.05$) between time points. Significant effects were followed by post-hoc paired t-tests with strict correction of the alpha level by the Bonferroni method (maximum of three pairwise comparisons, six P300 variants; $\alpha = 0.05/18 = 0.00278$). For detailed ANOVA results, see Table 5.

For the group of all AD patients, mean values differed significantly between time points for all P300 measures tested. This was true for all tested variants. Pairwise comparisons revealed significant increases between BL and FU3 for all markers. After Bonferroni correction, the results for target waves at CZ and Pz, as well as for difference waves at Fz, Cz, and Pz remained significant.

For the subgroup of probable AD patients, latencies differed significantly between time points for all variants analyzed. Before Bonferroni correction, all pairwise comparisons between BL and FU3 were significant. After the Bonferroni method was applied to account for multiple comparisons, results for target waves at Cz and Pz, as well as for difference waves at Fz, Cz, and Pz remained significant.

Results of possible AD patients showed significant effects for difference waves at Cz and Pz. However, none of these results remained significant after Bonferroni adjustments of alpha levels.

Difference wave measurements showed lower p-values at all electrode sites and for all groups (all subjects, probable AD, possible AD) than target measurements. For a comparison between BL and FU3, corresponding difference waves are depicted in Fig. 2.

The lowest p-values per group were always obtained at Cz for difference waves (all subjects, $p < 0.001$; subgroup of probable AD subjects, $p < 0.001$; subgroup of possible AD subjects, $p = 0.0379$). On average, corresponding latencies for subjects as a whole, were 335.16 ± 41.29 ms (BL), 357.25 ± 46.71 ms (FU1), 350.78 ± 52.88 ms (FU2), and 387.29 ± 57.59 ms (FU3).

When anti-dementia drug treatment (constant versus variable anti-dementia medication during the study period) was additionally introduced as ANOVA between-subject factor, time x medication interactions were not significant in any instance.

To examine whether changes in P300 markers were associated with changes in disease severity as measured by MMSE, we computed Pearson correlation coefficients for differences between BL and FU3. There was no significant relationship between any of the P300 markers and MMSE, even before Bonferroni correction, although MMSE scores changed in the expected direction (for all AD subjects: BL, 23.55 ± 3.34; FU1, 22.41 ± 3.20; FU2, 22.48 ± 3.79; FU3, 20.72 ± 4.21).

4. Discussion

We investigated correlations between AD severity and three ERP components, namely, the P300, N200, and P50. The strongest association with disease severity was found for the P300, which constitutes the most often analyzed ERP component in the study of cognitive processes (Drago et al., 2011). Although recently challenged by a meta-analysis (Howe et al., 2014) as the most useful P300 scalp location, Pz displayed the strongest relationship with disease severity in our study.

Probable AD subjects showed stronger correlation coefficients than possible AD patients. However, these differences were not significant.

When comparing correlation coefficients with other AD studies demonstrating significant relationships between P300 latency and MMSE score, our results lie in between (e.g., Lee et al., 2013, Spearman's rho (ρ) = –0.365 (N = 31 probable AD patients); Onofrj et al., 2002, $\rho = -0.55$ for mild AD (N = 30) and $\rho = -0.66$ for moderate-severe AD (N = 30)). It should be noted that no previous study has adjusted correlation for covariates (partial correlation) when investigating associations between ERPs and AD or MCI severity. This might have led to biased estimates of effect sizes.

For the N200 component, markers for difference waves showed higher correlation coefficients than those for targets. Exploratory examination at Pz (probable AD, r = –0.455) resulted in even stronger correlations than at Cz (probable AD, r = –0.407). Posterior N200 (also referred to as N2c) shows similarities with P300, as it appears for task-relevant targets and elicits larger amplitudes for infrequent than frequent target stimuli (Luck, 2014). Renault et al. (1982) hypothesised that posterior N2c reflects the stimulus categorization process, as its duration (measured from difference waves) depends on categorization difficulty. However, Luck (2014) concludes that the functional significance of the component remains unclear, as increasing categorization difficulty also leads to an increase in onset latency of the P300, which in turn might change the apparent duration of the N2c. Hence, the effect observed in our experiment might actually be attributed to P300 dynamics.

We could not find any study reporting on posterior N200 correlations with MMSE in AD, but Papaliagkas et al. (2011) found ρ = –0.488 in MCI patients (N = 22).

Surprisingly, P50 amplitude did not significantly correlate with MMSE - neither in probable AD, possible AD, nor in both subgroups of patients combined. In an exploratory attempt, we changed the P50 amplitude computation method from averaging amplitude values across a time window (Green et al., 2015), to detecting the maximum positivity within it (Golob et al., 2007). Further, we investigated alternative electrode positions (Cz, C4). However, there was not a single significant correlation, even before Bonferroni adjustments of the alpha level.

Both, Green et al. (2015) and Golob et al. (2007) used the auditory oddball paradigm for eliciting P50 deflections and examined responses

Table 5
P300 latencies at baseline and follow-up assessments

			Latency (ms)				ANOVA		T-Test (p)		
Wafeform	Site	N	Mean (BL)	Mean (FU1)	Mean (FU2)	Mean (FU3)	F	p	BL vs FU1	BL vs FU2	BL vs FU3
All subjects											
Target	Fz	29	338.80 ± 43.85	351.59 ± 51.56	346.2 ± 49.64	365.47 ± 69.52	3.59	0.01695*	0.12284	0.22996	0.01384
Target	Cz	29	335.83 ± 49.96	354.02 ± 49.28	355.5 ± 56.19	378.13 ± 73.33	6.10	0.00255**^{GG}	0.04718	0.01775	0.00215**
Target	Pz	29	330.04 ± 40.94	356.98 ± 43.14	359.00 ± 52.29	370.05 ± 57.27	9.00	0.00025**^{GG}	0.00071**	0.00048**	0.00101**
Difference wave	Fz	29	344.72 ± 39.07	360.08 ± 52.12	352.80 ± 45.79	383.25 ± 57.67	4.80	0.00255**^{GG}	0.13490	0.22043	0.00134**
Difference wave	Cz	29	335.16 ± 41.29	357.25 ± 46.71	350.78 ± 52.88	387.29 ± 57.59	10.60	0.00006**^{GG}	0.01305*	0.03336	0.00005**
Difference wave	Pz	29	335.70 ± 41.75	357.25 ± 39.51	358.19 ± 53.82	377.59 ± 54.05	7.41	0.00018**	0.00828*	0.01175*	0.00024**
Probable AD											
Target	Fz	15	331.66 ± 42.07	354.31 ± 58.76	346.5 ± 59.81	364.47 ± 65.94	4.64	0.00687**	0.03400*	0.14300	0.00500*
Target	Cz	15	323.32 ± 42.71	355.88 ± 56.28	342.85 ± 62.67	366.03 ± 65.93	8.41	0.00017**	0.00286*	0.05201	0.00108**
Target	Pz	15	319.94 ± 42.56	356.92 ± 51.31	346.76 ± 62.46	362.91 ± 55.38	9.26	0.00008**	0.00018**	0.01678	0.00064**
Difference wave	Fz	15	341.55 ± 39.06	361.08 ± 51.18	351.19 ± 55.30	382.18 ± 56.37	5.88	0.0019**	0.09504	0.32007	0.00056**
Difference wave	Cz	15	324.63 ± 40.84	359.78 ± 52.41	345.72 ± 61.07	378.27 ± 58.47	8.71	0.00013**	0.00285*	0.04825	0.00006**
Difference wave	Pz	15	328.27 ± 43.99	361.61 ± 44.21	349.89 ± 64.91	369.94 ± 54.13	6.89	0.0007**	0.00099**	0.04633	0.00024**
Possible AD											
Target	Fz	14	346.45 ± 45.97	348.68 ± 44.61	345.89 ± 38.14	366.53 ± 75.66	0.91	0.41326^{GG}	n/a	n/a	n/a
Target	Cz	14	349.24 ± 55.11	352.03 ± 42.55	369.05 ± 46.79	391.09 ± 80.93	2.26	0.12856^{GG}	n/a	n/a	n/a
Target	Pz	14	340.87 ± 37.61	357.05 ± 34.25	372.12 ± 36.47	377.69 ± 60.32	2.93	0.08452^{GG}	n/a	n/a	n/a
Difference wave	Fz	14	348.12 ± 40.25	359.00 ± 55.03	354.54 ± 34.87	384.39 ± 61.15	1.89	0.17683^{GG}	n/a	n/a	n/a
Difference wave	Cz	14	346.44 ± 40.13	354.54 ± 41.53	356.21 ± 44.10	396.95 ± 57.15	4.05	0.03789*^{GG}	0.54690	0.35286	0.03007
Difference wave	Pz	14	343.66 ± 39.23	352.58 ± 34.83	367.09 ± 39.20	385.79 ± 54.75	2.94	0.04514*	0.49059	0.11942	0.04415

Mean P300 latencies (ms) ± standard deviations measured at baseline and follow-up assessments, ANOVA and post-hoc t-test results (pairwise comparisons), ^{GG} Greenhouse-Geisser correction. For ANOVA p-values: * significant at α = 0.05, ** significant at α = 0.00833 (6-fold Bonferroni correction). For post-hoc t-test p-values: * significant at α = 0.01667 (3-fold Bonferroni correction), ** significant at α = 0.00278 (18-fold Bonferroni correction)

to standard tones. As this is identical to our approach, methodological differences should not explain our unexpected results.

Green et al. (2015) argue that previous investigations that could not demonstrate P50 amplitude differences between AD patients and age-matched controls included a more severe cohort (in terms of MMSE scores) than studies that did report significant differences. However, mean MMSE score in our study (23.55 at BL) compares well to values reported by Green et al. (2015) for AD studies successful in differentiation (e.g., 23.00, Golob and Starr, 2000).

Green et al. (2015) argue that, consistent with the progression of the underlying AD neuropathology (Arnold et al., 1991; Golubic et al., 2014) AD first attacks inhibitory mechanisms restraining P50 amplitude and only at later stages impairs the sensory cortical areas primarily responsible for generating P50. Therefore, P50 amplitude is thought to increase during the early stages of AD, while it reverts to relatively normal levels during the progression of the disease. This problematic association might have attenuated the correlational effects in our study. It is also the reason why Green et al. (2015) regard the P50 marker only as useful for pre-screening purposes during prodromal and asymptomatic stages, when the inhibitory mechanisms, but not the neural generators of P50, are compromised.

We could not find any P50 amplitude correlation coefficient report for AD or MCI subjects in the literature.

For a discussion on why there may appear differences between target and standard waveforms and therefore deflections in difference waves for components where this would not be expected (e.g., N1 or P2), as can be observed in our experiment, see Luck (2004). Briefly, physical differences between experimental stimuli can have substantial effects on early components, motor responses to targets might contaminate target ERP waves, stronger sensory gating and corresponding attenuation of early component amplitudes may arise for frequent standard stimuli as compared to infrequent target stimuli, and higher signal-to-noise ratios for more frequent standard tones might lead to smoother and therefore smaller amplitude ERPs than for target tones.

We utilized a two-tone auditory oddball task to elicit ERPs, as is common in ERP studies of AD patients (e.g., Lee et al., 2013; Ashford et al., 2011; Lai et al., 2010; Bonanni et al., 2010; van Deursen et al., 2009; Caravaglios et al., 2008; Juckel et al., 2008; Gungor et al., 2005;

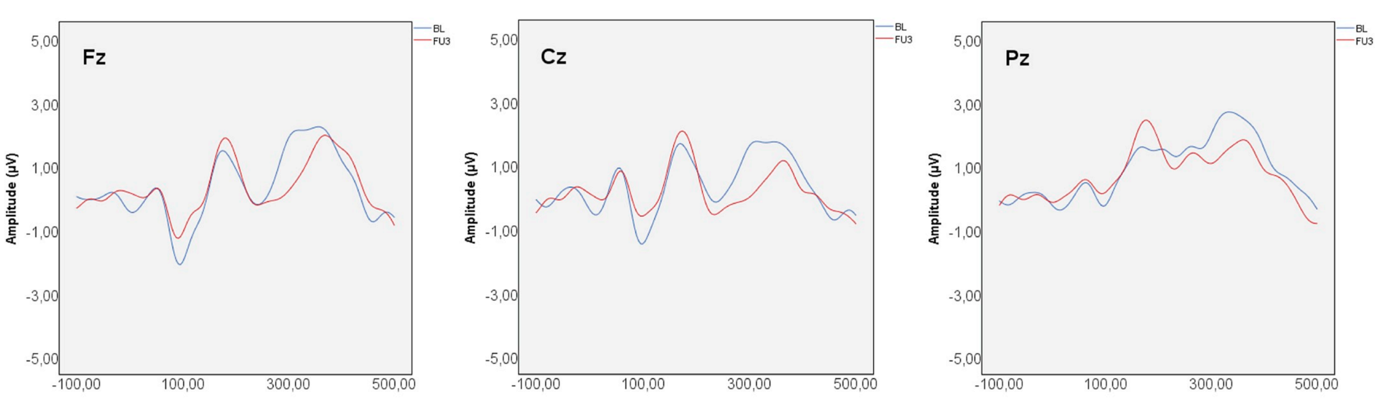

Fig. 2. Grand-average auditory ERP difference waves for the electrode sites Fz, Cz, and Pz during the baseline session (BL, blue line) and the third follow-up session (FU3, red line) in Alzheimer's disease patients. Positivity is shown as upward deflection. Time is given as difference to stimulus onset.

Ball et al., 1989). When comparing oddball paradigm settings across previous auditory AD ERP trials, we found a high level of heterogeneity. In fact, we could not identify two distinct research groups that used the same settings. Furthermore, numerous articles do not provide all the information necessary to replicate the study. However, there was some overlap between studies, and the characteristics chosen for the present study (57 high-pitched (2000 Hz) target tones; 141 low-pitched (1000 Hz) standard tones; tone duration, 100 ms; rise and fall times, 10 ms; interstimulus intervals, 1000–1500 ms) were consistent with or in the range of settings reported by other studies.

As in the present study, a number of studies selected a frequency of 2000 Hz for target tones and 1000 Hz for standard tones (Lai et al., 2010; van Deursen et al., 2009; Caravaglios et al., 2008; Gungor et al., 2005). The number of frequent and infrequent stimuli varied greatly in the literature (target tones, standard tones; Lee et al., 2013, 60, 340; Ashford et al., 2011, 50, 200; Lai et al., 2010, 50, 275; van Deursen et al., 2009, 32, 181; Caravaglios et al., 2008, 40,160; Juckel et al., 2008, 100, 400; Ball et al., 1989, 32, 128). Several manuscripts reported tone duration and interstimulus intervals (tone duration, interstimulus intervals; Lee et al., 2013, 100 ms, 1500 ms; Lai et al., 2010, 20 ms, 1000–2000 ms, 1500 ms; Bonanni et al., 2010, 150 ms, n.a.; van Deursen et al., 2009, 100 ms, 2000 ms; Caravaglios et al., 2008, n.a., 3500–5500 ms; Juckel et al., 2008, 40 ms, 1500 ms; Gungor et al., 2005, n.a., 2000; Ball et al., 1989, 100 ms, 1500 ms). Rise and fall times were only reported by a few studies, and were mostly consistent with the durations used by us (Lee et al., 2013, 10 ms; Bonanni et al., 2010, 5 ms; Caravaglios et al., 2008, 10 ms; Juckel et al., 2008, 10 ms; Gungor et al., 2005, 10 ms).

Given the differences between studies, and the corresponding difficulties of comparison, we would like to stress the importance of harmonization and standardization of behavioral paradigm settings in future research attempts.

Compared with other studies we found relatively low P300 latencies at BL. This might be attributed to the fact that most patients in our experiment ranged in the mild AD domain. However, latencies at FU3, at a more progressed stage of the disease, are well in line with previous AD findings.

Longitudinally tracking the P300- as component with the highest correlation with disease severity- we determined which scalp location and modality (target wave, difference wave) is most sensitive to change over time. The Cz difference wave marker showed the most significant change after 18 months as compared to BL measurement. As suggested by Luck (2004), the isolation of target components via differences waves therefore proved valuable.

In some cases, FU2 showed higher mean value than FU3, however, differences between FU2 and FU3 were never significant.

Although P300 latency increased over time as expected, latency changes did not significantly correlate with changes in MMSE scores. Since we had no control group in our study, an alternative explanation to the observed increments in P300 latency might therefore be, that they were caused by normal ageing. Age-related P300 latency increase during adulthood has been reported on numerous occasions (for a meta-analysis, see van Dinteren et al., 2014).

Nonetheless, our results (e.g., 40 ms change at Pz after 18 months) show a way more rapid increase when compared to physiological progression rates in elderly subjects (e.g., control groups of Lai et al., 2010, 13.86 ms change after 12 months; Ball et al., 1989, 3.2 ms change after 12 months).

Moreover, our results are well in line with P300 progression rates of previous longitudinal AD experiments (Ball et al.,1989, 18 possible and probable AD patients, 23.0 ms change after 12 months; Lai et al., 2010, 18 probable AD patients, 56.87 ms change after 12 months; Onofrj et al., 2002, 15 mild AD patients, 11.8 ms change after 6 months, 15 moderate–severe AD patients, 12.8 ms change after 6 months).

Finally, Ball et al. (1989) longitudinally examined P300 latency and MMSE scores in AD patients but did not report a significant relationship of change rates. An explanation for the lack of significant correlation might be that P300 latency is more sensitive to individual differences in AD severity than the MMSE score (Ball et al., 1989).

In conclusion, P300 and N200 latency significantly correlated with disease severity in the group of all AD patients, as well as the subgroup of probable AD patients at BL, whereas P50 amplitude did not show significant correlations in any group. P300 latency, which showed the strongest association with MMSE at BL, significantly increased over the course of the experiment. Although we did not find significant correlation coefficients between the change rates of P300 latency and MMSE score, the observed latency prolongation is in line with previous reports, while being substantially stronger than in healthy controls of other AD studies.

The results of this study add to a growing body of evidence that ERPs reflect neurodegenerative processes in AD and might therefore serve as supplementary, cost-effective markers to facilitate the objectivization of AD assessment in daily clinical practice.

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