Diagnostic Value of Event-Related Evoked Potentials N200 and P300 Subcomponents in Early Diagnosis of Alzheimer's Disease and Mild Cognitive Impairment

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Summary: Event-related potentials (ERPs) have a large application in the evaluation of cognitive processes, particularly in Alzheimer's disease (AD). The aim of the present study was to evaluate the clinical relevance of event-related evoked potentials (N2 and P3 subcomponents) in early diagnosis of AD and mild cognitive impairment (MCI). We prospectively studied 60 subjects. They all underwent the following investigations: neurologic and neuropsychological examination; functional evaluation, i.e., ERPs; cerebral imagery (morphologic and functional). Subjects were classified into 3 groups: group 1: 30 dementia of Alzheimer type (NINCDS-ADRDA, DSM-IV criteria); group 2: 20 MCI; and group 3: 10 control subjects. ERPs were significantly different between the groups (AD, MCI, control subjects), with a marked increase of P3 latencies, particularly when compared with N2 latencies ($P < 0.0001$). Furthermore, sensitivity was 87% to 95% for the differentiation of AD patients from MCI and control subjects, using prolonged P3 latencies (specificity, 90% to 95%), whereas using N2 prolonged latencies, sensitivity was 70% to 75% (specificity, 70% to 90%). Moreover, in the MCI group, N2 latencies strongly discriminated MCI from control subjects, with 90% sensitivity and 70% specificity and correctly categorized 80% of MCI subjects against 73% for P3. The abnormalities of N2 and P3 components may be linked, in AD and MCI, to an alteration of automatic and controlled attention processing.

Key Words: Event-related evoked potentials, Alzheimer's disease, Mild cognitive impairment, Aging.

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A better knowledge of pathophysiological mechanisms involved in Alzheimer's disease (AD) should lead in the future to preventive and even curative strategies. An early diagnosis for AD is therefore essential. AD is clinically defined as an acquired impairment of the cognitive functions, progressively altering the social, family and professional activities of the patient. Mild cognitive impairment (MCI) is a recent nosological creation (Petersen et al., 1997, 1999, 2004) aiming to fill the gap between normal brain aging and pathologic dementia-type brain aging. The concept is not strictly limited to predementia AD anymore (Gauthier and Touchon, 2005; Portet et al., 2006; Winblad et al., 2005). It allows detecting patients prone to develop AD and mostly to better understand the predementia stages. Moreover, there is, until now, no specific biologic or biochemical marker of AD and diagnosis can only be rendered in terms of probability. There is a crucial need for such markers to perform an early diagnosis for AD which is now essentially based on asset of clinical, neuropsychological, neuroimaging (functional and morphologic), biologic, and eventually genetics data. Alterations of the brain functions driven by cognitive or motor tasks can be detected by electrophysiological techniques such as event-related potentials (ERPs) (Hansenne, 2000). ERPs are obtained from an answer to experimental conditions: expecting an event, detection of an unpredictable event, decision-making according to a previously given order. They are essentially the mirror image of activated cognitive phenomena (perception, attention, decision-making process, answering, memory process, language) in the framework of experimental conditions (Brandeis and Lehmann, 1986). These ERPs depend on various factors including stimulus relevance, task performed, patient psychological and affective state, underlying lesions of the nervous system, and the use of drug (Hansenne, 2000). Many ERPs are generated and can be analyzed. P3 and N2 are the most frequently recorded potentials in current practice (Sutton et al., 1965). P3 is the positive wave emerging from the parietal area of the scalp, with a latency of 300 ms after a discordant stimulus. Two subcomponents are individualized: P3a and P3b. P3 is preceded by a negative wave, N2. The cognitive processes evaluated by these components are still under discussion. N2 might be linked to the detection of the target stimulus and be the reflection of the selective attention processes coming into action. P3a is generally considered to be related to the degree of focal attention whereas P3b is supposed to index the

working memory update (Polich and Criado, 2006). ERPs were demonstrated to be altered in AD, vascular dementia or dementia associated with a Parkinsonian syndrome (Bokura H et al., 2005; Goodin et al., 1978, 1987). P3b latency increase and amplitude decrease are the most consensual objective parameter.

The aim of this study was to assess ERPs, mainly N2 and P3 subcomponents relevance, in the evaluation of MCI and mild to moderate forms of AD.

METHODS

Subjects

Sixty subjects were prospectively evaluated within the Memory Center of the University Hospital of Montpellier. They benefited from an initial evaluation usually proposed when consulting for cognitive disorders. This evaluation included a neurologic examination, a neuropsychological evaluation, lab tests, a morphologic (TDM) and functional (SPECT) brain imaging as well as ERP recording. At the time of the evaluation, exclusion criteria were drugs that affect CNS functions or symptomatic AD treatments (cholinesterase inhibitors) as well as deafness or major hypoacusis. Patients presenting other form of dementia were excluded from the study. This evaluation led to select 3 groups of patients: 1) 30 patients with potential Alzheimer's disease, mild to moderate according to the NINCDS-ADRDA criteria (McKhann et al., 1984) and DSM-IV (1994), 2) 20 patients with MCI (Petersen et al., 1999), 3) 10 healthy subjects.

Neuropsychological Evaluation

All patients were submitted to a neuropsychological battery including MMSE (Folstein et al., 1975; Kalaft et al., 2003) and Mattis Dementia Rating Scale (Mattis et al., 1988). For episodic memory: Grober-Buschke scale was used (Van Der Linden et al., 2004). Executive functions and attention were investigated using spans, Trail Making Test and Stroop test (Golden et al., 1976; Reitan et al., 1985) and Frontal Assessment Battery (FAB) (Slachevsky A et al., 2004). The psychological and behavioral evaluation included a depression scale, MADRS (Pellet et al., 1987).

Recording the Cognitive ERPs

Recording and Analysis of the EEG Signal

Electrical brain activities were recorded from four scalp derivations (frontal: Fz, central: Cz, parietal: Pz, occipital: Oz) according to the international 10/20 standards, with, as a reference, two linked electrodes attached to the right and left earlobes (A1-A2). Impedances were less than 5 KΩ. EEG activities (sampling rate of 512 Hz) were amplified with a 40,000 gain, processed with band pass filters of 0.5 to 150 Hz and visualized on the screen of an ERP machine. The recording started 100 ms before the stimulation to serve as a baseline and kept going 900 ms after that. The EEG sequences distorted by ocular movements were automatically rejected.

Experimental Paradigm

Recording of cognitive ERPs was done according to the auditory oddball paradigm. Patients lay down on an "examination bed," with eyes opened, in a soundproof, darkened room. Tones (60 dB SPL, 100-ms duration) were presented binaurally through a headset up to a total of 150 stimuli. Patients were instructed to identify the odd 2000 Hz high-pitched stimuli (target sounds), which had a 20% occurrence probability among the standard 1000 Hz low-pitched stimuli (common sounds). The cognitive task required paying attention to the odd stimuli and counting them. The stimulus order of appearance was random and there was at least a 1140-ms gap between each stimulus. Three tests were recorded with a 2-minute pause followed by repeated instructions. The test was stopped once the 90 (3×30) target stimuli have been played out and the patient was asked to give out his/her count of the oddest sounds. Separate averaging of single records corresponding to frequent and rare stimuli were processed on line. Grand average of the evoked potentials was calculated from the three trials for Fz and Pz electrodes.

Evoked potentials amplitudes were measured relative to the prestimulus baseline from the records collected at Fz and Pz:

N2 wave was the most negative peak in the range (75 to 150 ms), whereas P2 was the most positive peak between 150 and 250 ms.

o N2 Wave Was the Most Negative Peak Between 196 and 300 Ms

o P3 was the most positive wave after N2 between 279 and 440 ms. Latencies and amplitudes of the P3b subcomponent of P3 were taken from the signals recorded from Fz and Pz electrodes and used for statistical analysis.

Statistical Analysis

Statistical tests were done using Statview (Statwiew 5.0 for Windows). First error margin was set at 0.05 for all tests.

Correlation *z*-test was used to find a link between electrophysiological parameters (latency and amplitude of cognitive components) and neuropsychological tests. Group comparisons of AD, MCI, and control subjects, two by two were made using the Student *t*-test.

ROC method (MedCalc software 8.2.00) was used to assess the capacity of ERPs parameters (latencies and amplitudes of N2 and P3) to discriminate AD patients from MCI subjects and control subjects. A line diagram was built with the sensitivity (true positive rate); plotted vertically and the false positive rate (1 minus specificity), on horizontal axis and the ROC curve was constructed by finding the sensitivity and specificity for a range of values of the continuous variable (latency and amplitude of N2, P3). The tests were considered to be the best when the ROC curves were drawn into the top left corner of the diagram. The area under the curve (AUC) was also estimated and used as a quantitative measure of test performance.

A multivariate analysis was done using a model of binary logistic regression due to the nature of the dependent variable (AD versus control group and MCI group versus control group).

TABLE 1. Clinical Characteristics of the Subjects

	N	Gender	Age	MMSE	Education
AD	30	15 f 15 m	70.9 ± 6.8	22.2 ± 2.6†	8.8 ± 2.2
MCI	20	15 f 5 m	64.4 ± 7.6	27.0 ± 1.6*	10 ± 3.7
Control subjects	10	5 f 5 m	61.6 ± 6.4	29.6 ± 0.5	10.8 ± 2.3

*$P < 0.001$ (MCI vs. control).
†$P < 0.0001$ (AD vs. MCI and control).

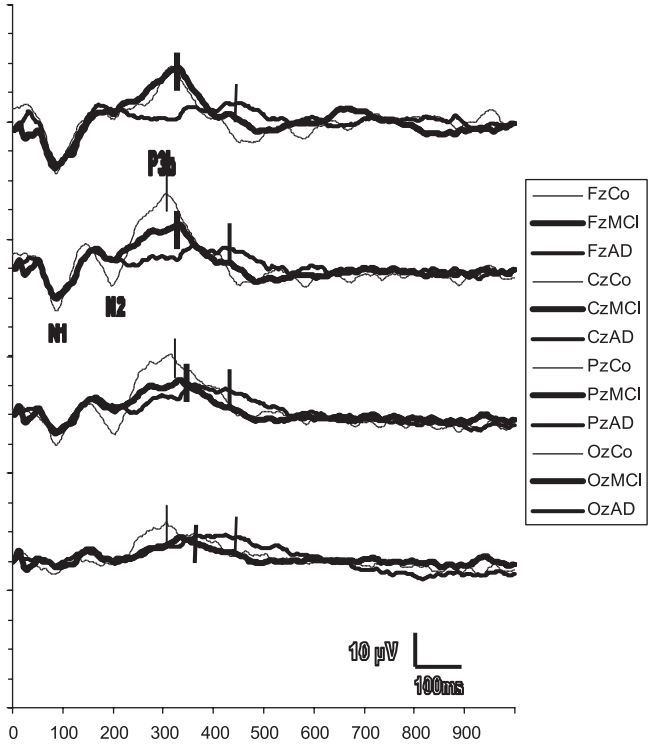

FIGURE 1. Grand average ERPs to standard and target stimuli in control subjects, MCI and AD patients. Bars represent the latencies of P3b in the three groups.

RESULTS

Subjects' Clinical Characteristics

The social and cognitive data are presented in Table 1. MCI patients did not differ from control group in age and education level. MMSE allowed for a highly significant differentiation ($P < 0.0001$) of AD and MCI patients from the control group. Attention, executive and free recall tests strongly differentiate AD from control subjects ($P < 0.0001$). Attention and free recall tests differentiate MCI from control subjects ($P < 0.0001$). MCI and AD differed in all tests ($P < 0.05$), attention excluded.

ERP Recordings

Grand averages of ERPs were calculated from individual data recorded in the three groups. The results are displayed in Fig. 1.

Correlation Between N2 and P3 and Neuropsychological Tests

Table 2 shows a significant negative correlation between MMSE and the latencies of N2 and P3 for frontal (Fz) and parietal (Pz) derivations. A significant positive correlation between those same electrophysiological parameters and the attention and executive tests was observed. A positive correlation between MMSE and P3 parietal amplitude was noticed. There was no significant link between the free-recall test (immediate and delayed) in episodic memory and the various potentials. A negative correlation between attention tests and P3 amplitude was observed in frontal and parietal area. Regarding the overall score enabling to assess the executive functions, results were only significant in parietal region.

ERP Characteristics in the Various Groups

Figure 2 a and b, shows that N2 and P3 latencies enable to differentiate AD from MCI, AD from the control group and MCI from control subjects.

P3 latency, both at the parietal and frontal site, discriminated the three groups ($P < 0.0001$ for AD versus. MCI and AD versus control group and $P = 0.02$ for MCI versus control group). There was no overlap between the various groups.

N2 latency, measured from potentials recorded from frontal and parietal electrodes, differentiated the three groups (AD versus. control subjects $P < 0.0001$). There was however an overlap between the groups, mostly between AD and MCI. This overlap was not observed between MCI and control subjects. It was at the frontal recording site that N2 was the most discriminative between MCI and control subjects. Furthermore, N2 latency significantly differentiate MCI from control subjects ($P = 0.002$), if we compare it to the results obtained for P3 latency ($P = 0.02$).

Figure 3 shows that the amplitude of P3 at parietal site differentiated AD from MCI ($P = 0.036$) and control subjects ($P = 0.014$) while P3 amplitude at frontal site segregated AD from MCI ($P = 0.04$). Furthermore, we clearly noticed a topographic inversion of P3 in MCI, with maximum P3 amplitude under the frontal derivation.

Comparison Between AD Patients and Control Subjects

Table 3 shows the results for the diagnosis sensitivity and specificity regarding latencies and amplitudes of N2 and P3 subcomponents in frontal and parietal regions. The same data are graphically illustrated in Fig. 4, which draws the ROC curve for AD/control subjects comparison. P3 latencies were sensitive and

TABLE 2. Correlation Between Latencies and Amplitude of N2 – P3 Components and Neuropsychological Tests

	N2Fz (L)	N2Fz (A)	N2Pz (L)	N2Pz (A)	P3Fz (L)	P3Fz (A)	P3Pz (L)	P3Pz (A)
MMSE	r :-0.431†	r :0.038	r-:0.428†	r :0.237	r :-0.662‡	r :0.240	r :-0.652‡	r :0.375*
Free recall	r :0.338*	r :0.061	r :0.344†	r :-0.148	r :0.452†	r :-0.181	r :0.443†	r :-0.240
Attention	r :0.474†	r :0.065	r :0.492†	r :-0.188	r :0.594‡	r :-0.346*	r :0.584‡	r :-0.405*
Executive functions	r :0.498‡	r :-0.035	r :0.475†	r :-0.379*	r :0.475†	r :-0.146	r :0.439†	r :0.364*

Statistically significant difference when *$P < 0.05$; †$P < 0.001$; ‡$P < 0.0001$; A, amplitude; L, latencies; P, significance; r, correlation.

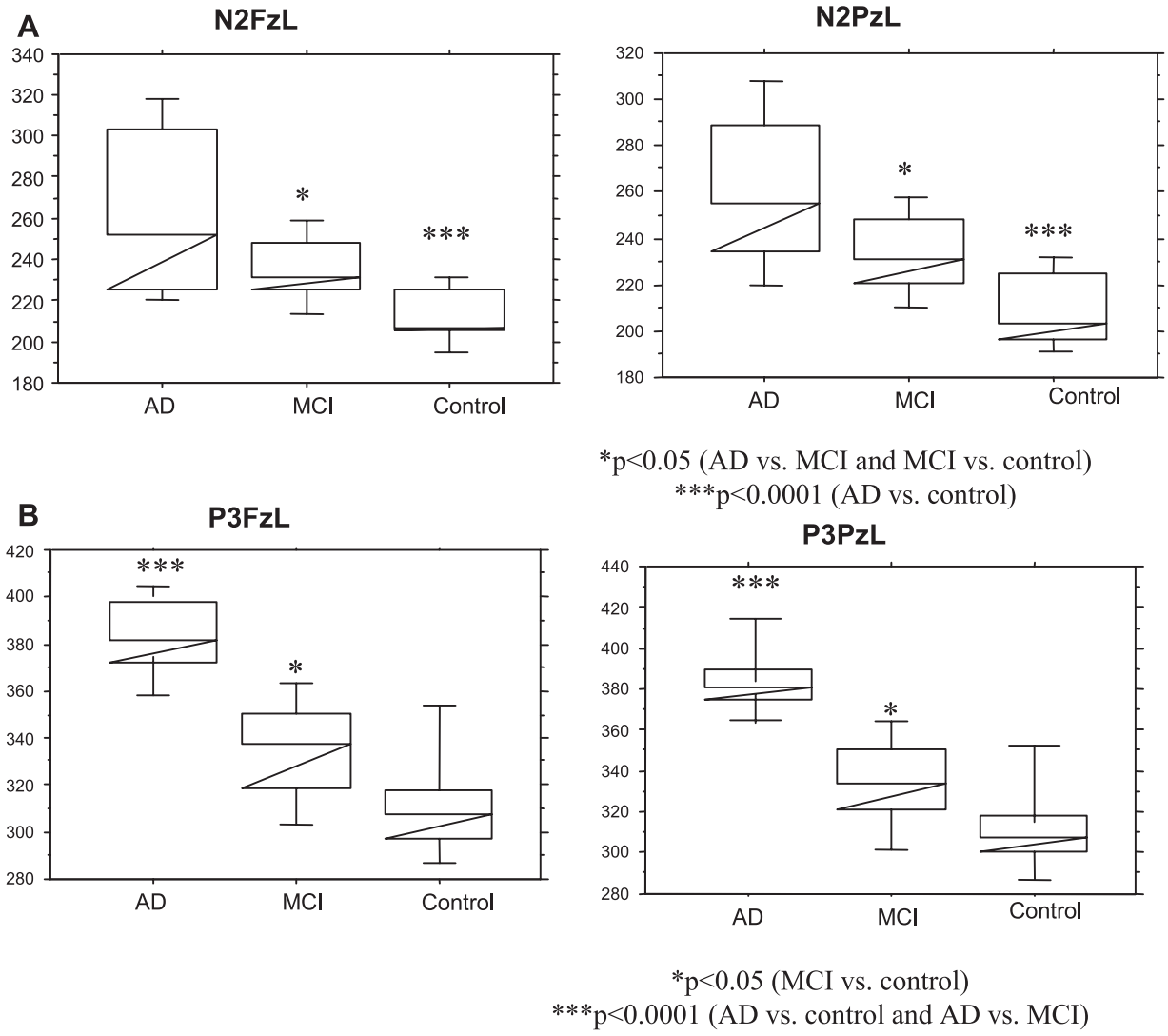

FIGURE 2. **A:** Comparison of latencies of N2 in Fz and Pz between AD, MCI and control subjects. **B:** Comparison of latencies of P3 in Fz and Pz between AD, MCI and control subjects.

specific in the discrimination between AD and control subjects with a 100% sensitivity and 90% specificity in frontal regions and a 91% sensitivity and 100% specificity in parietal region [area under the curve: 0.989 (Fz) and 0.991 (Pz)]. N2 latencies were more specific than sensitive, with a sensitivity around 70% and a specificity of 100% in both parietal and frontal regions. Regarding N2 and P3 amplitudes, only P3 amplitudes allowed for a relatively good discrimination between AD and control subjects with 64% sensitivity and 90% specificity in parietal regions. The analysis by multiple logistic regression showed that P3 latencies and amplitudes correctly categorized, respectively 96.8% and 83% of AD patients.

Comparison Between AD and MCI Patients

Table 4 summarizes sensitivity and specificity parameters for N2 and P3 latencies and amplitudes in frontal and

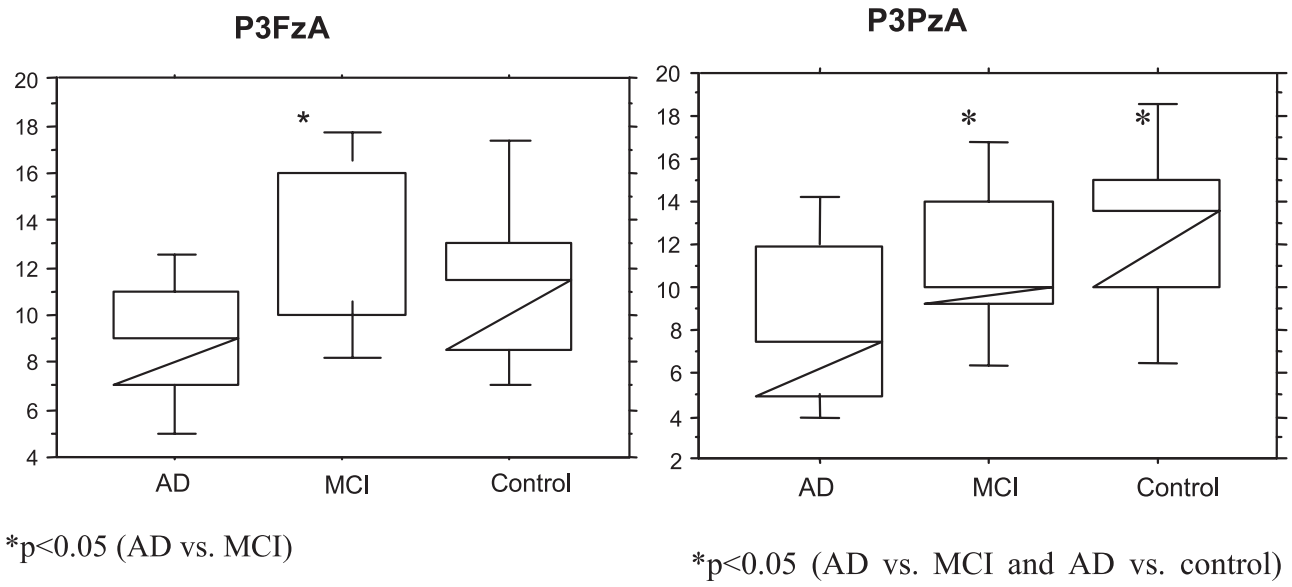

FIGURE 3. Comparison of amplitudes of P3 in Fz and Pz between AD, MCI and control subjects.

TABLE 3. Sensitivity and Specificity for Latencies and Amplitudes of N2 and P3 Under Fz and Pz: Comparison Between AD and Controls

	N2-Fz (L)	N2-Fz (A)	N2-Pz (L)	N2-Pz (A)	P3-Fz (L)	P3-Fz (A)	P3-Pz (L)	P3-Pz (A)
Se (%)	72	48	75	58	100	60.9	90.9	63.6
Sp (%)	100	80	100	80	90	78.9	100	90
AUC	0.932	0.572	0.939	0.710	0.989	0.672	0.991	0.764
Cut-off	**239**	**7**	**239**	**6**	**348**	**9.4**	**363**	**8**
LR̃	0.28	0.65	0.25	0.52	0.00	0.50	0.09	0.40

Latencies (L) in ms; amplitudes (A) in μV.

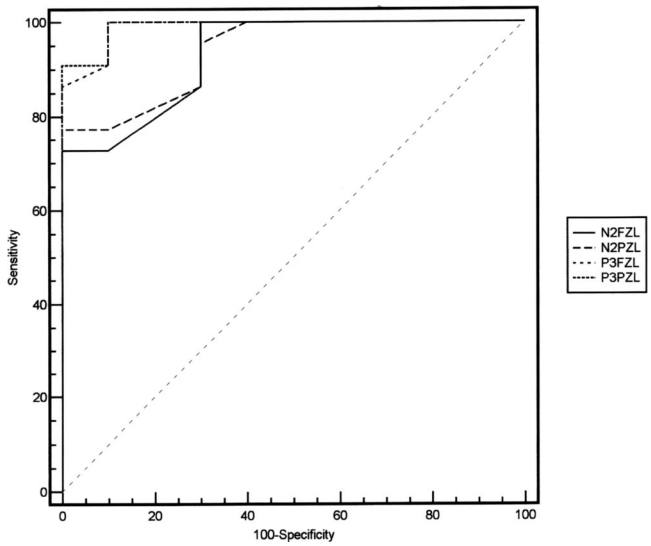

FIGURE 4. Receiver-operating characteristics curves (ROC) for the AD/control subject comparison.

parietal regions. The same data are graphically represented in Fig. 5, which displays ROC curve for the comparison between AD and MCI patients. P3 latencies discriminated AD from MCI with 86 to 87% sensitivity and 100% specificity [area under the curve was 0.969 in frontal and 0.976 in parietal]. N2 latencies had weaker discriminative capacities with only 75% sensitivity and 70% specificity for parietal derivation. Regarding P3 and N2 amplitudes, P3 had the best discriminative value, with diagnosis sensitivity, respectively, of 64% and 61% in parietal and frontal regions as well as 79% specificity in both regions. N2 allowed for keeping sensitivities and specificities, whatever were the parameters (latency, amplitude, localization), under 75%. Analysis by multiple logistic regression showed that P3 latencies and amplitudes correctly categorized, respectively 88% and 67% of the patients.

Comparison Between MCI Patients and Control Subjects

Table 5 summarizes sensitivity and specificity parameters for latencies and amplitudes of N2 and P3 subcomponents in frontal and parietal regions. These same data are graphically illustrated in Fig. 6 with the ROC curve for the MCI/control subject comparison.

N2 latencies in frontal regions strongly discriminated MCI from control subjects with 90% sensitivity and 70% specificity [area under the curve at 0.870]. If N2 amplitude

TABLE 4. Sensitivity and Specificity for Latencies and Amplitudes of N2 and P3 Under Fz and Pz: Comparison Between AD and MCI

	N2-Fz (L)	N2-Fz (A)	N2-Pz (L)	N2-Pz (A)	P3-Fz (L)	P3-Fz (A)	P3-Pz (L)	P3-Pz (A)
Se (%)	68	68	75	70.8	87	60.9	86	63.6
Sp (%)	75	47.4	70	57.9	100	78.9	100	78.9
AUC	0.717	0.556	0.745	0.632	0.969	0.672	0.976	0.687
Cut-off	**246**	**8**	**240**	**7**	**369**	**9.4**	**369**	**8**
LR̃	0.43	0.68	0.36	0.50	0.13	0.50	0.14	0.46

Latencies (L) in ms; amplitudes (A) in μV.

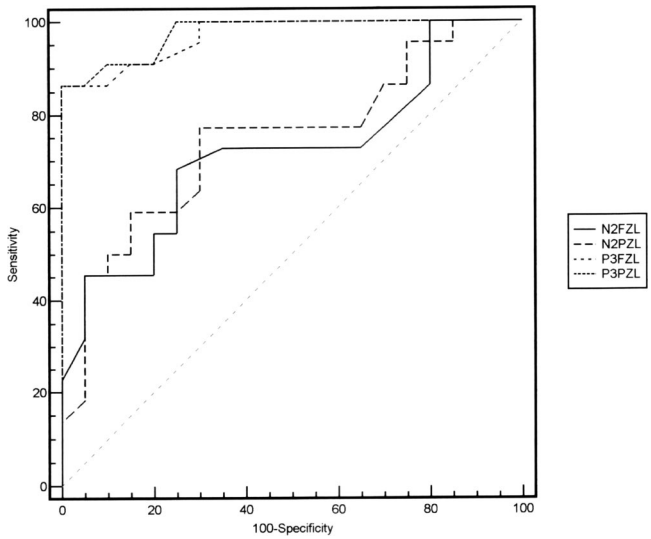

FIGURE 5. Receiver-operating characteristics curves (ROC) for the AD/MCI comparison.

had a weak diagnosis sensitivity, specificity was high in frontal (90%) and parietal regions (100%). P3 latencies had weaker discriminative capacities, with 75% diagnosis sensitivity and 80% specificity. N2 latency correctly categorized 80% of MCI against 73% for P3.

DISCUSSION

This study investigated the diagnostic interest of N2 and P3 subcomponents in AD at dementia level and MCI. Contrary to many studies (Gironell et al., 2005; Pfefferbaum et al., 1984), the electrophysiological parameters were correlated to neuropsychological data. A negative correlation was found between MMSE and N2 and P3 latencies in frontal and parietal regions. A positive correlation was also found between N2 and P3 latencies and executive and attention functions: the lowest the performances, the highest the latencies. A similar correlation was observed with P3 amplitude at the parietal level, but only for the global cognitive process and the attention tests. It is interesting to stress the lack of correlation with episodic memory evaluation. Thus, early changes of event related potentials might reflect the deficit of attentional processes linked to working memory and dysfunctional frontal processing in early stage of Alzheimer's disease (Baddeley et al., 2001; Sebastian et al., 2006). Furthermore, N2 and P3 subcomponent might be useful as objective measures of Alzheimer progression.

Analyzing the general characteristics of N2 and P3 subcomponents, we observed that P3 latencies, both at parietal and frontal site can help to differentiate the three groups, without any overlap between the groups. P3 latency is thus, in this study, highly specific (100%) of AD diagnosis versus MCI. This specificity is even more remarkable now that the heterogeneity of MCI subject is recognized (Artero et al., 2003; Petersen et al., 2004). Moreover, it is interesting to note the inversion of the normal amplitude gradient of P3 in MCI group, with a peak in the frontal regions. P3 amplitude mostly refers to numerous factors, such as selective attention, stimulus occurrence probability, motivation, and vigilance (Hansenne et al., 2000) even if stimulus characteristics may play a role. The increase of P3 amplitude in frontal region of MCI subjects could be linked to the capacity of staying focused on a given task, and the necessity of engaging all attention resources to complete the cognitive task. According to the decrease of P3 amplitude, patients with AD would have loosened their capacity to access their attention resources. N2 latencies modifications also index the clear impairment of the

TABLE 5. Sensitivity and Specificity for Latencies and Amplitudes of N2 and P3 Under Fz and Pz: Comparison Between MCI and Controls

	N2-Fz (L)	N2-Fz (A)	N2-Pz (L)	N2-Pz (A)	P3-Fz (L)	P3-Fz (A)	P3-Pz (L)	P3-Pz (A)
Se (%)	**90**	47.4	65	26.3	75	68.4	75	68.4
Sp (%)	**70**	90	90	100	80	60	80	60
AUC	0.870	0.671	0.855	0.524	0.760	0.516	0.752	0.632
Cut-off	**216**	**8**	**225**	**5**	**318**	**10**	**318**	**12**
LR̃	0.14	0.58	0.39	0.74	0.31	0.53	0.31	0.53

Latencies (L) in ms; amplitudes (A) in μV.

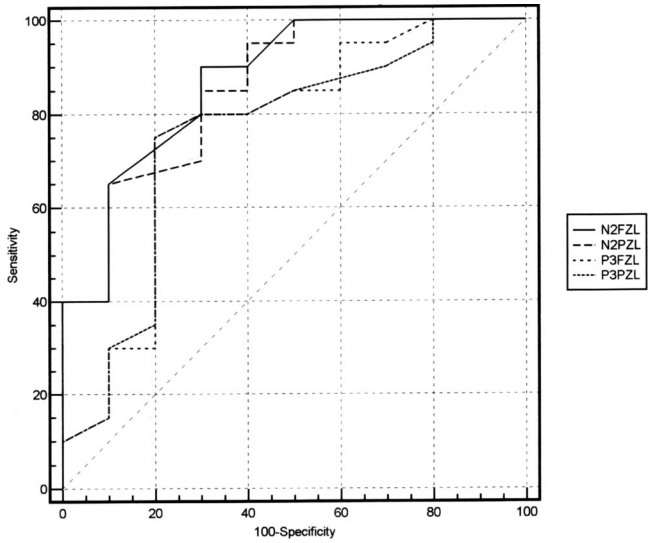

FIGURE 6. Receiver-operating characteristics curves (ROC) for the MCI/control subject comparison.

selective attention processes in this nosological framework. Topographic changes we observed in P3a and P3b are similar to those reported by Polich and Criado (2006) in chronic drug users suggesting that MCI and AD patients have a deficit in cholinergic and dopaminergic neurotransmission. Indeed this assumption is coherent with courant hypothesis on the physiopathology of AD. A cholinergic deficit and a decrease in dopamine transmission should sustain in our patients the modification of early ERPs components (Hansenne et al., 2000). Topographical change of P3b and shift in N2 latency could be used as indices of high risk conversion to AD in MCI patients. This will open new perspective in the therapeutic approach of this population.

In this study, ERPs appear to be a sensitive method to discriminate between AD, MCI and control subjects. Comparing AD with control subjects, P3 latencies had 90% diagnosis sensitivity and 100% specificity. Considering the MCI group, latency of N2 in frontal region is the parameter which gave the better discrimination between MCI and control subjects with a good categorizing in 80% of cases against 75% with P3 latency. These results can be explained by the MCI group heterogeneity, as already detailed (Artero et al., 2003; Petersen et al., 2004; Portet et al., 2006). In our MCI group, the impairment of cognitive processes is not only limited to the memory area but also to selective attention which might be linked to the best discriminative value of N2. Our results meet the few studies evaluating ERPs relevance to classify patients at a predementia stage of Alzheimer's disease. Most of these studies are transversal (Blackwood et al., 1988; Boutros et al., 1995; Fernandez–Lastra et al., 2001; Frodl et al., 2002; Golob et al., 2001; Kindermann et al., 2000; Portin et al., 2000, Swanwick et al., 1999). As an example, Fernandez et al. listed 77% diagnosis sensitivity and 83% specificity in P3 latencies analysis. One longitudinal study underlining the ERP interest in evaluating patients at-risk for developing AD was reported (Gironell et al., 2005): a cohort of 116 patients with memory complaints was followed for a 2-year period; clinical, neuropsychological and ERPs evaluations were performed initially and repeated at Month 12 and Month 24. The value of the initial ERP (P3 latency on entering the study) for an AD-type dementia had 52.9% sensitivity and 76.9% specificity; odd-ratios were 3.75 (95% confidence interval).The electrophysiological data used in the present study demonstrate robust performances when compared with other diagnostic methods Clinical NINCDS-ADRDA items showed low sensitivity and specificity of 81% and 73%, respectively (Blacker et al., 1994). Volumetric measurement of hippocampal area from RMN images led to higher sensitivity and specificity (90%) (Golebiowski et al., 1992; Laakso et al., 1998), whereas SPECT data, according to Borroni et al., 2006, allowing to detect high-risk subject with a sensitivity and sensibility of 78%. Biochemical markers (Hampel et al., 2004) used as predictive indices have a rather low sensitivity (59% for Abeta and 83% for Tau protein) but a high specificity (100% and 90%, respectively).

Our study confirms the relevance of ERPs in evaluating cognitive disorders. These noninvasive examinations are able to point at an early stage an alteration of the cognitive functions and can contribute to the diagnosis for Alzheimer's disease with both good sensitivity and specificity. Moreover, these neurophysiological tools could be as predictive conversion markers for MCI patients. Only longitudinal follow-up studies, taking into account the new MCI diagnosis criteria, will help to confirm their predictive value.

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