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Abnormalities of Cognitive Functions in IDDM Revealed by P300 Event-Related Potential Analysis

Comparison With Short-Latency Evoked Potentials and Psychometric Tests

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The possible influence of diabetes on the higher mnestic and cognitive functions has been investigated. The P300 wave latency, an endogenous electrophysiological event, was explored and compared with the multimodal short-latency evoked potential (EP) recordings (visual [VEP], brainstem auditory [BAEP], and median and tibial nerve somatosensory EPs [mSEP and tSEP, respectively]) and psychometric test measures in 16 insulin-dependent diabetic (IDDM) patients, in 16 age- and (IDDM) sex-matched nondiabetic subjects, and in a large normal reference population. The age of subjects, the duration of IDDM, and the metabolic control of patients were taken into account. P300 values were significantly increased in IDDM versus matched control subjects ($P < 0.001$), and 3 patients showed values above the reference value range. Abnormal VEP recordings were present in 1 of 16 patients, BAEP in 3 of 16, mSEP in 7 of 16, and tSEP in 6 of 16. Digit-span backward test results were significantly ($P < 0.02$) modified in the diabetic cohort. There was no tendency for anomalies of P300, short-latency EPs, and psychometric test values to be contemporarily present, except in 1 patient. Electrophysiological or psychometric abnormalities were not clearly correlated with the duration of IDDM or the degree of short-term metabolic control. These findings give evidence that *1*) higher cognitive functions may be affected in diabetes as documented by P300 analysis and short-term memory tests, *2*) endogenous electrophysiological analysis highlights neuropsychological changes not detectable by psychometric tests, *3*) an alteration of evoked potentials was present in half of the IDDM subjects studied, and *4*) anomalies of the CNS are patchily distributed in diabetes. *Diabetes* 40:952–58, 1991

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Morphological and clinical studies (1–5) have amply documented that diabetes can alter the peripheral nervous system and the CNS. Electrophysiological studies have objectified the peripheral nervous system (6–9) and, more recently, the CNS damage caused by diabetes both in diabetic patients (10–13) and experimental models (14,15). In particular, the so-called short-latency evoked potentials (EPs) (visual [VEP], brainstem auditory [BAEP], and median and tibial nerve somatosensory EPs [mSEP and tSEP, respectively]) have proven to be a reliable tool to document anatomofunctional anomalies during diabetes, even at an early stage of the disease (16,17). The combined use of these electrophysiological methods (multimodal EPs) has also shown that the distribution of such abnormalities in diabetic patients is rather patchy, confirming a frequent multifocal CNS involvement, and that they can appear at an early stage of the disease and tend to persist over time (16,17). Whether the diabetic milieu can influence the higher cognitive functions during disease is an open question with important scientific and social implications. Possible cognitive abnormalities might be due to diabetes per se or to recurrent hypoglycemic episodes (18–22).

Several studies, based mostly on psychometric tests, have attempted to determine whether there is a decreased psychometric performance in diabetic subjects. The question is still open (23), even though several studies have responded positively as far as insulin-dependent diabetes mellitus (IDDM) is concerned (18,19,24,25). Indeed, all psychometric tests may be influenced by a number of psychosocial variables (i.e., personality style and education experience), which are unlikely to be related to underlying brain damage (21).

Now, new possibilities of thoroughly investigating and quantitatively assessing higher cognitive human brain functions have been opened up by the clinical application of event-related potentials (also termed *endogenous* EPs).

They express the aptitude of the human brain to discriminate, classify, decide, and memorize the significance of an exogenous stimulus purposely presented to the subject being tested (26–28). Among these, the P300 (or P3) wave has been identified as a late cortical neurophysiological event reflecting the activity of cognitive and mnemonic functions in humans: it combines cognition with electrophysiology (29–31). The P300 latency reflects the speed of neuronal events underlying information processing (32,33), and it appears to be strongly associated with attention and short-term memory but not with general intelligence and reasoning (30,31,34,35). In normal subjects, P300 latency increases in conditions of cerebral dysfunction, as has been shown after insulin-induced hypoglycemia (36), and with age, so that it has been used by several investigators as a biological marker of senile cerebral decline (34,37–40). Nevertheless, the correlation between P300 latency and age is more complex than a linear one because latencies decrease in childhood and increase again during senescence (41,42).

In an attempt to give an insight into the influence of diabetes on CNS function, the specific aims of this study were to investigate mnestic and higher cognitive capabilities in adult IDDM subjects and in matched control subjects, with both a sophisticated objective and quantitative approach, P300 wave latency analysis, and traditional indirect semiquantitative digit-span memory tests. We also compared and integrated these results with those obtained in the same subjects from short-latency EP recordings while taking into account clinical and metabolic parameters.

RESEARCH DESIGN AND METHODS

Sixteen IDDM patients (group 1) were included in the study together with 16 age- and sex-matched nondiabetic control subjects (group 2). Group 1 was comprised of 11 men and 5 women, with a mean ± SD age of 33.2 ± 12.6 yr (range 20–64 yr) and a duration of diabetes of between 1 and 27 yr (mean ± SD 9.0 ± 7.7 yr). Mean ± SD values of morning blood glucose and HbA_{Ic} at the time of recruitment were 10.05 ± 4.70 mM and 7.01 ± 1.60%, respectively. The educational level was taken into account. Group 2 included 16 nondiabetic control subjects (11 men, 5 women, 33.4 ± 12.5 yr) individually matched for age, sex, and educational level to patients in group 1.

The subjects were included in the study on the basis of a normal neurological examination. Diabetic patients were excluded if there was evidence or history of ketoacidosis or recurrent ketonuria, recurrent hypoglycemic reactions, peripheral nerve dysfunction (above stage 0, evaluated with the staging system devised by Dyck [43]), dementia and/or cerebrovascular disease, or psychiatric disorders. No subject was being treated with psychoactive drugs or was addicted to toxic substances (alcohol, hallucinogens, etc.). All patients showed normal cholesterol and triglyceride levels, whereas two patients were on antihypertensive treatment. Tests were performed in the morning after the patient's usual breakfast in two sessions within 3 days. In the first session, the P300 latency was recorded, whereas the psychometric test was done in the second session, immediately followed by the short-latency EP recordings. Blood glucose levels were not <6 mM in any patient, and no hypoglycemic episodes or presence of ketoacidosis were recorded at the time of the electrophysiological tests.

As an additional approach to analyze neurophysiological test results in patients from group 1, findings were also compared to short-latency EPs obtained in 40 normal individuals of comparable age and sex (group 3) and with endogenous EPs obtained in 80 normal individuals of different age and sex (group 4) acting as normal reference control populations.

Endogenous EPs. P300 recordings were obtained with an aural stimulus (100-ms duration with a rise-decay time of 0.5 ms and a frequency of 250 or 4000 Hz) presented binaurally every 6 s at an intensity of 70 dB sound pressure level. The bioelectrical signal was recorded by electrodes placed along the midline at F_z, C_z, and P_z, according to the 10–20 International System of EEG electrode placement (44), referred to linked mastoids. A ground electrode was sited on the forehead. Eye movement and blink artifacts were recorded horizontally and vertically by electrodes affixed to the outer canthi of both eyes and supra- and suborbitally to the left eye. In the first recording, a single sound (either high or low) was presented to the subject, who was asked to listen without performing any task (initial nontarget test). In the second recording, both stimuli were presented in a randomized and separate sequence. Twenty percent of the stimuli were emitted at 4000 Hz (rare) and the remainder were at 250 Hz (frequent). The subject was asked to silently count all the rare sounds and to report the total at the end of the session (target test). In the last recording, the same two aural stimuli were repeated, and the subject was asked to listen only (final nontarget test). Further details are given elsewhere (45).

In the analysis of recordings, the P300 wave was taken into account, i.e., the latency of the positive peak (derived from the C_z wave form), which clearly appeared during the execution of the target test. This component is representative of higher cognitive level analysis of sensorial stimuli compared with the target stimuli in the memory (27). When the P300 wave was present in broad bands or in multiple peaks, straight lines were extrapolated from the slopes of the wave, and latency was measured to the point of intersection (46).

Short-latency EPs. VEP recordings were performed with a checkerboard pattern reversal on a television monitor, subtending an angle of 17°. The spatial checkerboard frequency was 0.78 cycles/degree, and the temporal frequency of pattern reversal was 2 Hz. The mean luminance was 60 cd/m^2, and the contrast between dark and bright checks was 50%. The active electrode was placed 5 cm above the inion along the midline, the reference electrode was at F_z, and a ground electrode was placed on the mastoid. The latency of the positive wave with the highest voltage (P100), which represents the response of the visual cortex to retinal stimulation, was taken into account (47,48).

BAEP recordings were performed with an acoustic stimulus in the form of clicks (unfiltered square waves of 0.120 ms duration with alternating polarity and a frequency of 10 Hz). The active electrode was placed at the vertex, the reference electrode on the mastoid ipsilateral to the stimulated ear, and the ground contralateral. The interpeak latency (IPL) values of waves I–III (conduction time [CT] from the acoustic nerve to the pons), III–V IPL (central CT from the

pons to the midbrain), and I–V IPL (expression of activity of the auditory pathways from the periphery to the midbrain) were considered (49,50).

SEP recordings were obtained with an electrical stimulus (a square wave of 0.1–0.3 ms duration and 7 Hz frequency) with surface electrodes on the median nerve (mSEP) at the wrist and on the posterior tibial nerve (tSEP) at the ankle. When stimulating the upper limb, the bioelectrical signal was recorded by electrodes placed *1*) in the medio-claveal area (Erb), *2*) in the cervical area (C_7), and *3*) on the scalp in relation to the specific somatosensory receiving area (C_3^1 or C_4^1: 2 cm posterior to C_3 or C_4) contralateral and ipsilateral to the stimulated limb. A noncephalic reference was used (NC; contralateral shoulder to the stimulated side). A ground electrode was placed on the ipsilateral arm to the stimulated limb. During stimulation of the lower limb, electrodes were placed in relation to the cauda equina (L_3–L_2), the thoracic region (T_{12}–T_{11}), and the scalp (2 cm behind C_z: C_z^1 and F_{pz}). A ground electrode was placed on the sacral region. Further details regarding these techniques have been previously reported (16,51). Parameters taken into account in the evaluation of the results for mSEP were *1*) the wrist-Erb conduction velocity (CV) (representative of CV along the peripheral nerve fibers from the wrist to the brachial plexus), *2*) the interval between Erb and N_{13} (CT across the brachial plexus and the cervical cord), *3*) the N_{13}–N_{20} interval (CT from the cervical cord–lower brainstem lemniscal pathways to the cortex), and *4*) the Erb-N_{20} transit time (CT from the brachial plexus to the cortex) (52,53). Parameters for tSEP were *1*) the ankle-L_3 CV (along the peripheral nervous fibers from the ankle to the cauda equina), and *2*) the propagation velocity L_3-C_z^1 and central CV T_{12}-C_z^1 (CV with which the nerve impulse is carried along the afferent somatosensory pathways from the cauda equina-L_3 and from the spinal cord-T_{12} to the cortex-C_z^1, respectively; 54,55).

Psychometric tests. Each subject performed the digit-span test as a measure of attention and immediate memory capacity. This subtest of the Wechsler Adult Intelligence Scale (56) was performed via the oral presentation of three to nine digits, which the subject was asked to listen to carefully and then repeat correctly, first in the same sequence (digit-span forward [DSF]) and then backward (digit-span backward [DSB]). If the first set of digits was repeated correctly, a second series of digits was immediately presented. If the subject failed, a sequence with the same number of digits was proposed. The test was stopped when the subject failed to recall the sequence after two series of the same length had been presented. The final score, in each of the two tests, was the largest number of digits the subject was able to recall without error, with maximum being nine (DSF) or eight (DSB).

Other methods. A blood sample to measure levels of glycemia and HbA_{Ic} was collected from each fasting patient in the morning. HbA_{Ic} was assayed by ion-exchange chromatography, with 6% as the upper limit of the normal range. Wilcoxon's paired and related *t* tests were used to evaluate results in the matched groups. Fisher's exact test and Pearson's correlation coefficient were used where indicated. The method of partial correlation analysis (30) was used to take into account the effects of age on both the P300 latency and the psychometric scores as

$$r_{12.3} = \frac{r_{12} - r_{13}r_{23}}{(1 - r_{13}^2)^{1/2}(1 - r_{23}^2)^{1/2}}$$

where *r* is the correlation coefficient, 1 is the P300 latency, 2 is the digit-span score, and 3 is age.

RESULTS

Endogenous EPs. Diabetic patients in group 1 showed a significant lengthening of the P300 wave latency compared with their age- and sex-matched control subjects in group 2 ($P < 0.001$; Fig. 1). Mean P300 latency values were 358.8 ms in group 1 and 320.9 ms in group 2 ($P < 0.002$). The slope of the function relating age and P300 latency was 0.57 ms/yr in the reference control group (group 4). Three patients in group 1, in contrast with none of the matched control subjects in group 2, presented a P300 latency that fell outside the 2SD band of the age-derived regression of P300 latency in normal reference subjects (group 4) ($y = 0.672$ age + 316.4; Fig. 2).

Short-latency EPs. VEP recordings were 106.7 ± 5.4 ms in group 1 and 104.8 ± 2.8 ms in group 2 ($P < 0.05$); one patient showed a pathological monolateral increase in the P100 wave latency that was above the mean ± 3SD of normal reference values (group 3) (107.1 ± 3.2 ms; Table 1). Mean ± SD BAEP recordings were as follows: I–III, III–V, and I-V, 2.2 ± 0.2, 1.8 ± 0.1, and 4.1 ± 0.2 ms in group 1 (NS,

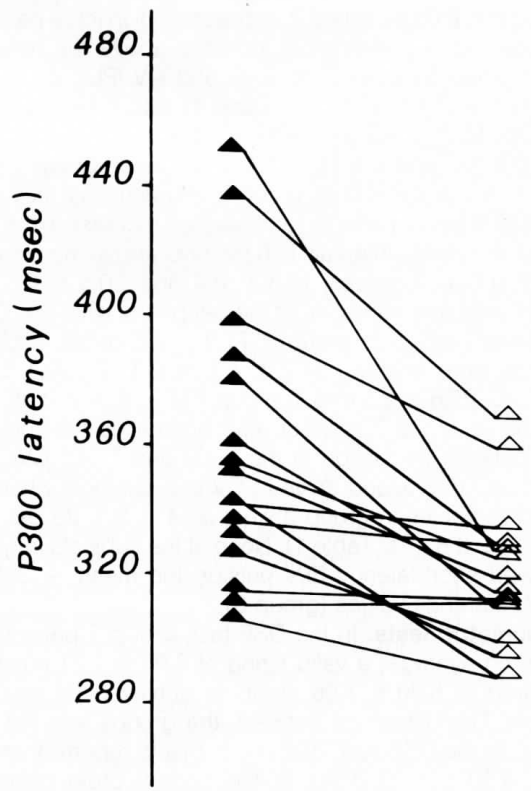

FIG. 1. Comparison of P300 latency in group 1 diabetic patients (▲) and matched group 2 control subjects (△). For description of groups, see METHODS.

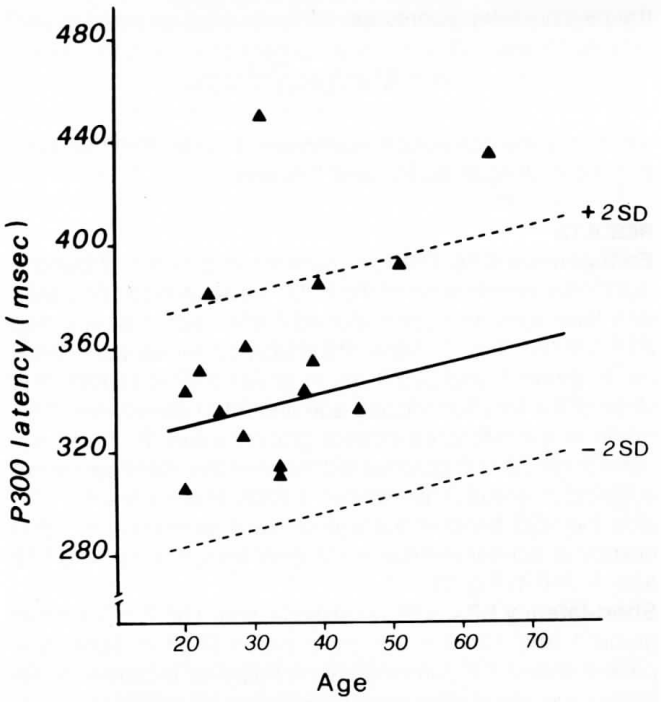

FIG. 2. P300 latencies of diabetic patients (▲, group 1) compared with regression line (*solid line*) and 2SD of estimate (*dashed lines*) relating age and P300 latency in nondiabetic subjects (group 4). For description of groups, see METHODS.

NS, and $P < 0.05$ vs. group 2, respectively); in three patients, we observed a pathological increase above the mean + 3SD of group 3 values (I–III, III–V, and I–V IPLs, 2.1 ± 0.1, 1.9 ± 0.1, and 4.0 ± 0.1 ms; Table 1). mSEP findings were wrist-Erb, 65.3 ± 4.3 m/s; Erb-N_{13}, 5.1 ± 0.5 ms; N_{13}–N_{20}, 6.0 ± 0.6 ms; and Erb-N_{20}, 11.1 ± 0.6 ms in group 1 ($P <$ 0, $P < 0$, NS, and $P < 0$ vs. group 2, respectively); they were abnormal in seven patients (pathological increase in the Erb-N_{13} and/or Erb-N_{20} intervals in 6 patients above the mean + 3SD of group 3 values, [4.3 ± 0.4 and 10.5 ± 0.5 ms, respectively] and reduction of the peripheral wrist-Erb CV in 4 subjects [values in group 3 71.9 ± 2.8 m/s]). tSEP recordings were ankle-L_3 54.2 ± 4.1 m/s, L_3-C_z' 29.1 ± 2.6 m/s, T_{12}-C_z' 27.6 ± 2.5 m/s in group 1 ($P < 0$, $P < 0.05$, and $P < 0.05$ vs. group 2, respectively); anomalies were present in six patients (reduction in the L_3-C_z' and T_{12}-C_z' CVs in 1 patient and decreased ankle-L_3 CV in 5 subjects when the respective values in group 3 were 30.4 ± 2.1, 29.2 ± 2.0, and 62.0 ± 3.6 m/s; Table 1). None of the subjects in group 2 showed short-latency EPs outside the mean + 3SD of normal reference values (group 3).

Psychometric tests. In the DSF test, group 1 patients reported, on average, a valid string of 6.00 ± 1.21 numbers compared to 6.20 ± 1.06 numbers achieved by group 2 subjects. The difference between the groups was not significant. In the DSB test, diabetic subjects reported, on average, 4.50 ± 1.03 digits in the correct order, whereas control subjects recalled a significantly longer string of 5.60 ± 1.26 ($P < 0.02$). Two diabetic patients showed a score lower than the normal range (Table 1). There was no

TABLE 1
Tabulation of diabetic patients with electrophysiological abnormalities

Subject	Age (yr)	Sex	P300	DSF	DSB	Side	Visual evoked potential (P100)	Brain stem auditory evoked potential			Median somatosensory evoked potential				Tibial somatosensory evoked potential		
								I–III	III–V	I–V	Wrist-Erb	Erb-N_{13}	N_{13}–N_{20}	Erb-N_{20}	Ankle-L_3	L_3-C_z'	T_{12}-C_z'
2	20	M	308	6	4	Right	110	2.12	2.22*	4.32	67.0	5.4	6.6	12.0*	50.5*	27.4	26.3
						Left	108	2.24	2.00	4.24	65.5	5.2	6.0	11.2	50.9*	29.7	28.2
3	45	F	338	7	4	Right	104	2.00	2.00	4.00	63.3*	5.4	5.8	11.2	51.0*	35.0	33.1
						Left	104	2.16	1.80	3.96	63.3*	5.8*	6.0	11.8	50.5*	32.4	30.0
4	64	M	438†	4	3‡	Right	112	2.52*	1.92	4.44*	68.1	6.2*	5.8	12.0*	49.0*	28.8	27.1
						Left	112	2.00	2.24*	4.24	67.7	5.0	7.0	12.0*	49.5*	27.8	26.0
5	51	F	396	8	5	Right	106	2.32	1.72	4.04	64.8	5.6*	5.6	11.2	54.4	27.9	27.8
						Left	110	2.40	1.72	4.12	65.1	4.8	5.8	10.6	55.7	28.8	27.8
6	38	M	354	5	4	Right	108	2.28	2.12	4.40	55.4*	4.8	5.2	10.0	55.4	28.4	26.4
						Left	104	2.44	2.12	4.56*	54.5*	5.2	5.6	10.8	56.5	27.4	25.4
8	23	F	380†	8	7	Right	106	2.28	1.64	3.92	57.0*	6.0*	5.6	11.6	47.6*	25.8	24.6
						Left	108	2.24	1.88	4.12	57.0*	5.6*	5.8	11.4	43.5*	26.7	25.1
11	28	M	360	6	5	Right	112	2.24	1.84	4.08	62.7*	5.0	5.8	10.8	53.4	31.6	30.4
						Left	120*	2.12	1.88	4.00	62.5*	5.6*	5.0	10.6	49.5*	30.0	28.5
14	39	F	388	5	3‡	Right	94	2.04	1.92	3.96	63.6	5.2	6.0	11.2	54.7	23.3*	22.8*
						Left	100	1.96	1.84	3.80	64.2	5.2	6.4	11.6	52.8	28.3	27.4
15	31	F	452†	5	5	Right	108	2.00	1.80	3.80	65.9	4.4	7.0	11.4	53.3	32.8	31.6
						Left	108	1.84	1.84	3.68	67.0	4.2	6.6	10.8	55.9	31.0	31.0

Electrophysiological values are in milliseconds (P300; I–III, III–V, I–V interpeak latencies; Erb-N_{13}, N_{13}–N_{20}, Erb-N_{20}) and in meters per second (wrist-Erb; ankle-L_3, L_3-C_z', T_{12}-C_z'); DSF, digit-span forward score; DSB, digit-span backward score. *Abnormal value vs. control group 3. †Abnormal value vs. control group 4. ‡Abnormal value vs. control group 2.

significant correlation between psychometric test scores and the duration of diabetes or HbA_{1c} levels in group 1 patients.

Overall analysis. Of the patients in group 1, 56.2% revealed one or more abnormalities in the electrophysiological recordings and psychometric test measures. One patient showed abnormal endogenous and short-latency EPs and psychometric test values (subject 4, Table 1); another only presented anomalies of the endogenous potentials (subject 15, Table 1). There was no significant correlation between event-related potential recordings and the different short-latency EP parameters in diabetic patients. The correlation between P300 latency and DSB score did not reach statistical significance in diabetic or nondiabetic subjects (r_{12} = 0.001 and −0.40, respectively; see METHODS). Both P300 latency and DSB score were weakly correlated with age in diabetic patients (r_{13} = 0.49, $P < 0.05$ and r_{23} = −0.50, $P < 0.05$, respectively), whereas the correlation in nondiabetic control subjects was r_{13} = 0.90, $P < 0.001$ and r_{23} = −0.40, NS, respectively. Even with the partial correlation analysis of P300 latency and DSB score, the correlation coefficients did not reach statistical significance in both diabetic (0.32) and nondiabetic (−0.10) subjects.

No clear correlation was found between the P300 latency, short-latency EPs, and psychometric measures with the duration of the disease or metabolic control.

DISCUSSION

The P300 wave is the result of electrochemical changes in neuron structure. Despite its maximal amplitude over the parietal areas of the scalp, the neural origins of P300 are unknown. Evidence suggests that its generator site is represented by the medial temporal lobe, including the hippocampus and amygdala, a brain area associated with learning and memory (57,58). The P300 wave represents a noninvasive investigative technique for the study of these areas of the CNS and is widely utilized in elderly subjects. Because it has been seen that its latency increases with age, the P300 wave provides an objective neurobiological marker of senile cerebral deterioration (35,46,59). Additionally, it has been used for the study of different neurological diseases (60–62) and various toxic-metabolic conditions (e.g., alcoholism, hypoglycemia; 36,63–65). Regarding diabetes, an attempt to clarify possible P300 modifications during this form of metabolic derangement has been reported for non-insulin-dependent diabetes, although subjects with abnormal P300 recordings were not found (66).

This study demonstrates P300 wave latency changes in IDDM patients. There was an overall increase of P300 latency in diabetic patients compared with matched control subjects, and in a few patients, the values were overtly pathological. Psychometric tests have shown alterations in short-term memory storage, and short-latency EP recordings have highlighted pathological changes in many of the patients studied. These results are of particular value because the presumed influence of age on both P300 latency and psychometric tests (42) has been minimized. Findings in diabetic patients have been compared with those of age-matched control subjects, and subjects in the extremes of the age spectrum have not been included.

These results document a significant impairment of higher brain functions during diabetes. This points to the potential role of an increased P300 latency as a biological marker of cerebral deterioration in diabetic patients. However, neither disease duration nor metabolic control appear to correlate clearly with the presence of such neuropsychological damage. Alterations of the CNS may be expected after cerebrovascular insults (67,68) or hypoglycemic episodes (69), which can occur more frequently in diabetic patients. Nevertheless, the patients recruited in this study had no sign of vascular damage, and both at the time of the tests and in the months before, they showed no signs or symptoms of hypoglycemia. Other pathogenetic mechanisms may then play a major role in the genesis of these anomalies. The question of whether the neurophysiological changes found in diabetic patients represent an accelerated aging phenomenon opens a stimulating but unexplored area of research. It is worth remembering that nonenzymatic glycosylation, which irreversibly modifies tissue proteins and organ functions, is an aging process and is exaggerated in diabetes (70,71).

As far as the psychometric tests are concerned, our findings showed a significant reduction in DSB test scores in diabetic patients that could reflect a reduced cognitive flexibility necessary for the performance of this test; the greater difficulty in comparison with the DSF test task may explain the different results and suggests that attention and immediate memory are substantially unaffected by the presence of diabetes. Our results are in accordance with those reported by other neurobehavioral studies in IDDM patients in which abnormalities of cognitive functions have been reported (18,19,24,25).

In diabetic patients, the event-related EPs were not in correlation with psychometric test values; similarly, in nondiabetic subjects, the correlation between P300 latencies and psychometric test scores failed to reach statistical significance, probably as a consequence of the limited number of individuals. Because both the digit-span memory test and P300 latency appear to be related to memory capacity in normal individuals (30,31) (although their methodological approaches are substantially different, the P300 wave recording is objective and accurately quantitative), their combined evaluations are of value in evaluating cognitive dysfunctions in diabetes. This way of exploring the neurobehavioral aspects may highlight subtle cognitive deficits and help us understand the mechanisms and monitor their evolution. Theoretically, other techniques such as the so-called "reaction time," which has proved sensitive to metabolic changes (18,36,69), could be added to more broadly depict the cerebral dysfunction in diabetes.

As for the short-latency EPs, the results are consistent with those reported by others, which showed that central and peripheral conduction may be involved along the afferent sensory pathways (10–13,72); the two abnormalities are not always associated in the same subject. Moreover, EP abnormalities have been documented by our group, even at an early stage of the disease, and tend to be persistent over time (16,17). Note that a greater number of changes are observed as the EPs are applied with a multimodal approach (13,16,17). Therefore, it is possible to show the patchy distribution of nervous system anatomofunctional anomalies in diabetes. This finding is also documented by P300 wave recordings, in so far as endogenous EP abnormalities were

not always associated with short-latency EP disturbances in the same patient. This could reflect a different individual vulnerability of different anatomofunctional neurological structures to pathological noxa.

In conclusion, the study of P300 wave—if complemented by short-latency EP recordings—allows us to identify, even in the absence of any clinical sign, possible changes of nervous impulse conduction through various structures, together with anomalies concerning the higher associative brain activity, such as message comprehension and mnemonic capacities. This is important because detectable changes in the higher cognitive functions appear to occur more frequently than is commonly believed.

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