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REVIEW

Event-related potentials in Parkinson's disease: a review

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This article reviews the findings of event-related potentials (ERP) in Parkinson's disease (PD) published during the last 10 years. Basic principles and methods of ERP are briefly presented with particular regard to the auditory "odd-ball" paradigm almost uniquely employed for the ERP assessment in PD to date. The results of respective studies are overviewed and discussed with respect to three main axes:
(1) The slowing down of cognitive processing in PD is reflected by the delays of N2 and P3 components of ERP which are more important in demented than in non-demented patients. The N1 component is delayed in demented patients with PD as well as in other dementias of presumed subcortical origin.
(2) Various neuropsychological deficits observed in PD correlate with the delays of ERP evoking the implication of common subcortico-cortical cerebral mechanisms.
(3) The variations of ERP under dopaminergic manipulation suggest conflicting effects of levodopa treatment on cognition, at least in certain categories of PD patients. These findings are discussed in the light of current knowledge on neurotransmitter brain systems and some hypothetic explanations are proposed.
Finally, an attempt is made to outline further perspectives of clinical and research utilization of ERP in Parkinson's disease.

Keywords: Cognition – Dementia – Dopamine – Event-related potentials – Parkinson's disease – P3

INTRODUCTION

Changes of mental status are recognized as common features in Parkinson's disease (PD). However, the diagnosis of cognitive impairment in PD is not always easy, especially when characteristic motor deficits interfere with neuropsychological examination. Therefore, event-related potentials (ERP), which are considered to be independent from disabled motor output, have been proposed as an objective electrophysiological index of cognitive function in PD. The aim of this review is to evaluate the role of ERP in clinical investigation of PD and to summarize its contribution to research into physiopathological mechanisms implicated in cognitive impairment in PD.

BASIC PRINCIPLES OF EVENT-RELATED POTENTIALS

ERP are a class of long-latency evoked potentials which were shown to reflect human information processing (Sutton *et al.*, 1965; Donchin *et al.*, 1978). By combining information on latency, amplitude and topography of ERP components, the timing, functional and anatomical divisions of the underlying cognitive processes can be characterized. According to the kind of processing involved, the components of ERP can be divided into two categories: early *exogenous* components which mainly depend on the physical characteristics of the stimulation (e.g. N1, P2 in auditory modality) and late *endogenous* components depending almost entirely on the conditions of the cognitive task associated with the stimulation (e.g N2 and P3). The generators of the earlier components, reflecting the sensorial processes, have been considered to occur in cortico-thalamo-cortical connections and in primary sensory and association cortex areas (Picton *et al.*, 1974). Later components are thought to originate from multiple cortical and subcortical generator sites. For instance, generators of P3 ERP were detected in frontal and temporal lobes (Wood and McCarthy, 1985; Stapleton and Halgren, 1987) as well as in hippocampus, amygdala and thalamic nuclei (Halgren *et al.*, 1980; Okada *et al.*, 1983; Yingling and Hosobuchi, 1984). The P3 component (also called

P300), which is the most prominent and probably the most studied positive ERP, is considered to be an index of stimulus evaluation, reflecting the timing of neural events underlying perception and discrimination of the target stimuli, their matching against memory representations of stimulus categories, and decisional processes. Hence, the *latency* of the P3 component reflects the time necessary for stimulus evaluation (Kutas *et al.*, 1977), relatively independently from the processes of motor selection and response execution (McCarthy and Donchin, 1981). As suggested by Johnson (1986), the *amplitude* of the P3 component is influencd by numerous factors such as information transmission, subjective probability, and stimulus meaning. The *scalp distribution* of the P3 wave depends on respective contributions of its particular subcomponents, reflecting different mental processes and generated by distinct neural sources (Squires *et al.*, 1975). For instance, in an "odd-ball" paradigm (see below), the main contribution to the P3 wave is a centroparietal component P3b corresponding to the active discrimination of attended target stimuli.

The variations of ERP parameters have been proposed as diagnostic markers of mental impairment in various neurobehavioral disorders, for instance in dementia (Goodin *et al.*, 1978), depression and schizophrenia (Pfefferbaum *et al.*, 1984). During the last 10 years, since the original report of Hansch *et al.* (1982), several studies have attempted to specify ERP indices of cognitive disturbances occurring in Parkinson's disease.

METHODS OF ERP INVESTIGATION IN PD

Up to now, the predominant clinical approach of the majority of ERP studies in Parkinson's disease has involved the almost exclusive use of the auditory ERP elicited by a tone-discrimination "odd-ball" paradigm, a method which is widely used because of its relative simplicity. The examination is based on a task requiring a mental count of rare target tones randomly occurring in a sequence of more frequent standard tones usually differing in pitch. Button press response to the target tones may provide a measure of reaction time. In the studies reviewed here, ERP are recorded from vertex lead (Cz) and, eventually, from midfrontal (Fz) and midparietal (Pz) leads referenced to linked mastoid or earlobe electrodes. The stimulus-locked sequences of electroencephalographic activity of about 1000 ms duration are amplified and averaged in separate channels for target and standard tones. The resulting ERP waveforms consist of N1 and P2 components present after both standard and target stimuli and of N2 and P3 potentials, normally distinguishable only after target stimuli.

Other types of long-latency evoked potentials have also been studied in PD (contingent negative variation, Bereitschaftspotential). These methods, however, do not share the clinical extent of proper ERP, and will not be considered further in the present article (see review in Dick *et al.*, 1987; Amabile *et al.*, 1990).

ERP FINDINGS IN PD

The methods of ERP assessment were similar in all the studies reviewed; their findings, therefore, can be compared and somewhat generalized. It must be kept in mind, however, that direct matching of separate samples of PD patients is difficult because of dissimilar ranges of age, disease duration and severity and different treatment schedules in the different studies. Diagnostic inclusion criteria also vary. ERP findings obtained in parkinsonian patients were mostly compared with control data of age-matched normal subjects, or, comparisons were done between groups of PD patients with different degrees of mental impairment. In addition, several authors studied ERP in distinct conditions related to dopaminergic treatment.

In the following, the findings concerning ERP latencies will be shown in descending order of their incidence and importance in particular studies. The amplitude parameters as well as topography of ERP have only rarely been discussed and the results are rather inconsistent as yet.

P3

Prolongation of P3 wave latency was the most prominent finding in almost all studies in ERP in PD (see Table I).* In patient groups unselected for mental status, the mean P3 wave latencies were generally prolonged in comparison with normal data. Moreover, the P3 was significantly delayed in demented (or cognitively deteriorated) compared with non-demented (or non-deteriorated) patients (Goodin and Aminoff, 1987; Hautecoeur *et al.*, 1991). There were no statistical differences of P3 latency values between non-demented parkinsonians and normal subjects (Hautecoeur *et al.*, 1991; Ebmeier *et al.*, 1992; see also the pre-treatment P3 latency in Prasher and Findley, 1991, Table IV).

N2

Latency values of the N2 wave were generally prolonged in parallel with P3 latencies (except for a slight delay of N2 latency without P3 prolongation observed by Ebmeier *et al.* (1992)).

* Some creditable reports should be mentioned in addition here even if the number of observations was too small to demonstrate statistical significance. In their original study of ERP in dementia, Goodin *et al.* (1978) reported slight delays of the P3 wave of ERP in three patients suffering from PD, but no details or individual ERP results concerning these patients were shown. P3 wave latency prolongation in PD was further reported by Bodis-Wollner *et al.* (1984).

TABLE I. Studies of ERP in PD—comparison of results

Ref.	Number of patients	Mean age (years)	Mean duration of PD (years)	Hoehn & Yahr mean score	Mental status	MMS mean	N1 latency	P2 latency	N2 latency	P3 latency	N1 amplitude	P3 amplitude
Hansch *et al.* (1982)	20	64	10	—	Unselected	28.2	111 (105)	203* (190)	—	387** (359)	8.0 (6.7)	11.0 (9.4)
Goodin and Aminoff (1986)	13	72	—	—	Demented	21.9	104*** (90)	184 (173)	289*** (232)	395*** (321)	—	—
Goodin and Aminoff (1987)	14	71	4.8	2.5	Demented	23.2	103***	186	293***	399*	—	—
	14	67	5.0	2.7	Non-demented	27.9	90 (—)	182 (—)	245 (—)	361 (—)		
O'Donnell *et al.* (1987)	16	66	6.3	2.6	Unselected	23.9	95 (89)	—	249** (196)	366* (315)	—	—
Gil *et al.* (1989)	50	64	4.5	—	Unselected	—	92 (89)	173* (159)	268** (237)	370*** (321)	9.0 (7.8)	4.2 (6.1)
Pang *et al.* (1990)	43	63	9.6	Range 2–4	Non-demented	—	102 (—)	—	263 (—)	371 (—)	—	—
Hautecoeur *et al.* (1991)	28	72	3.2	2.3	Deteriorated	—	107***	185**	285***	411***	8.5	4.8*
	55	69	3.1	2.0	Non-deteriorated		98 (98)	175 (178)	244 (232)	363 (354)	7.8 (8.3)	7.6 (9.0)
Ebmeier *et al.* (1992)	16	69	—	2.4	Non-demented	25.7	—	202* (178)	261* (238)	357 (354)	—	—

The results of ERP are expressed as mean values of latencies in ms and mean values of amplitudes in μV.
Control mean values, if available, given in parentheses.
Statistical significance (comparisons between patients and controls or between different subgroups of patients): $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$.
—, Data not available.

P2

No consistent changes of P2 wave latency can be extracted from the present findings. Delays of P2 wave latency were found in non-demented (Ebmeier *et al.*, 1992) as well as in unselected patients with PD. On the contrary, in the demented patients of Goodin and Aminoff (1986, 1987), P2 latencies were not statistically different from the control values.

N1

Modifications of N1 wave latency were found in three ERP studies in PD. N1 wave delays were observed in the demented patients of Goodin and Aminoff (1986, 1987) and in the "deteriorated" patients of Hautecoeur *et al.* (1991) in comparison with non-demented or non-deteriorated patients as well as with normal values. In other studies done with patients unselected for mental status, N1 latency values were within normal limits.

Dementia and ERP findings in PD

Dementia is estimated to occur in 10–30% of patients with PD (Lieberman *et al.*, 1979; Brown and Marsden, 1984; Mayeux *et al.*, 1988). Coincidental Alzheimer's disease (AD) does not seem to be responsible for the majority of cases of dementia in PD although the neuropathological indices of AD have been found in a certain number of parkinsonian brains (Hakim and Mathieson, 1979; Gaspar and Gray, 1984). The parkinsonian dementia, however, was shown to be clearly neuropsychologically and neuropathologically different from AD (Huber *et al.*, 1986a,b).

According to the above results, delayed ERP latencies seem to be associated with the presence of dementia in PD.

Nevertheless, in the study of Goodin and Aminoff (1986), of the patients with dementia diagnosed according to DSM-III, only 60% showed the prolongation of P3 latency with 2 S.D. or more above the normal value. On the other hand Hansch *et al.* (1982) in a group of PD patients with mean mental scores reflecting very mild impairment, found as many as 30% of subjects with abnormally prolonged P3 latencies. Consequently, even if ERP may represent the global level of cognitive impairment in selected PD patient groups, the diagnosis of dementia in an individual patient can be scarcely based on ERP examination only. It is, after all, in accordance with the general notion (concerning ERP studies in dementia) that "the differences observed between individual demented patients and controls have been neither large nor reliable enough to be clinically useful" (Johnson, 1992). ERP thus seem to be sensitive to the presence of dementia in PD, but do not reliably reveal its respective importance in individual patients.

Moreover, latency increases of the N2 and P3 components of the auditory ERP have been frequently reported in patients with dementias of varying causes (see below). The P3 delays have also been found in various pathological conditions associated with mental confusion (Goodin *et al.*, 1983). The prolongations of ERP latencies in PD patients should, therefore, be cautiously considered as a rather non-specific sign of disturbed cognitive processing, with a certain relation to dementia.

ERP signs of subcortical vs cortical dementia

The cognitive disorder in PD has frequently been identified with the symptoms reported by Albert *et al.* (1974) under the name of subcortical dementia. Indeed, the syndrome characterized by frontal lobe deficits with impaired manipulation of acquired knowledge, concept formation and set shifting, and usually accompanied by slowness of thought and depression, corresponds well to the deficiency frequently observed in PD (Dubois *et al.*, 1991). As a distinctive criterion, the absence of cortical signs such as aphasia and apraxia can be established in most cases. The underlying mechanisms of the cognitive impairment include lesions of subcortical structures resulting in decreased activation of cerebral cortex.

The ERP findings in demented PD patients consist of delays of both early (N1) and late (N2, P3) ERP components. The parallel variations of N2 and P3 latencies correspond to the notion of physiological interrelationship between the two potentials (Michalewski *et al.*, 1986). On the contrary, the prolongation of N1 wave latency seems to represent some particular mechanism involved in parkinsonian cognitive impairment, or in subcortical dementias in general. Indeed, similar changes of the ERP were reported in Huntington's disease (Rosenberg *et al.*, 1985; Homberg *et al.*, 1986; Goodin and Aminoff, 1986)* and in progressive supranuclear palsy (Johnson, 1992). These findings seem to be in accordance with the clinical, neuropsychological and neuropathological data, suggesting that in PD (as well as in Huntington's disease or in progressive supranuclear palsy), subcortical pathogenic mechanisms of dementia prevail (Cummings and Benson, 1984). On the contrary, in Alzheimer's disease which is characterized by cortical dementia, ERP studies reported, as a rule, N2 and P3 wave delays only (Goodin *et al.*, 1978; Polich *et al.*, 1986; Neshige *et al.*, 1988; Patterson *et al.*, 1988).

Consequently, the delays of the early ERP N1 and P2 components were proposed as distinctive markers of subcortical dementias (Goodin and Aminoff, 1986). From the psychophysiological point of view, these changes may correspond to perturbations of early sensorial processing, possibly involving neural transmission on the level of thalamic sensory relay nuclei modulated by an attentional mechanism (Hillyard, 1985). In favor of the notion of N1 wave delay as an index of subcortical impairment, several recent findings have shown N1 wave changes in various encephalopathies, possibly involving subcortical physiopathological mechanisms, even without an overt dementia. Thus, N1 (and P3) wave delays were found in multiple sclerosis patients (Hautecoeur *et al.*, 1991), in ARC/AIDS complex (Goodin *et al.*, 1990) and in liver cirrhosis patients with mild metabolic encephalopathy (Ruzicka *et al.*, 1993).

ERP AND NEUROPSYCHOLOGICAL PERFORMANCE IN PD

ERP have been considered as sensitive indicators of neuronal activity during specific phases of cognitive processing (Hillyard and Kutas, 1983). Hence, ERP variations should confirm and reinforce the information obtained by neuropsychological testing in PD. Interactions between electrophysiological and neuropsychological measures have been studied by means of correlational analysis applied to the latencies of ERP components and test scores in individual patients. In view of unequal choice of tests and different composition of patient samples, comparisons between the results of particular studies can be made only approximately (see Tables II and III).

P3

The correlations of P3 wave latency with the results of neuropsychological tests are surveyed in Table II. On

* Goodin and Aminoff (1986) reported delays of N1, P2, N2, and P3 components of the ERP in a group of demented patients with Huntington's disease who were assessed in parallel with the PD group (see the results in Table I). Moreover, they presented a group of patients with Alzheimer's dementia where only N2 and P3 wave latencies were delayed.

TABLE II. ERP in PD—correlations between psychometric tests and P3 wave latency

Test	Hansch *et al.* (1982)	O'Donnell *et al.* (1987)	Gil *et al.* (1989)	Pang *et al.* (1990)	Hautecoeur *et al.* (1991)	Ebmeier *et al.* (1992)
General intellectual abilities						
MMS (Folstein)	−0.28	−0.50*				−0.26
ERFC (Gil)			−0.61**		−0.60***	
Information (Wechsler)				−0.19		
Verbal IQ (Wechsler)						−0.15
Abstract reasoning						
Conceptualization (Mattis)				−0.24		
Progressive matrices (Raven)	−0.56*			−0.45		
Attention						
Attention (Mattis)				−0.29		
Selective attention		−0.60*				
Digit span forward	−0.34	−0.21				
Digit span backward	−0.27	−0.58*				
Trail making A			0.47***			
Symbol digit modalities	−0.81**	−0.64*				
Visuospatial abilities						
Multiple choice visual retention (Benton)						−0.36
Visual form discrimination (Benton)				−0.44*		
Line orientation (Benton)				−0.44*		−0.38
Face recognition (Benton)				−0.22		−0.55*
Language						
Verbal fluency (Benton)				−0.20		
Initiation (Mattis)				−0.09		
Sentence repetition		−0.59*				
Vocabulary (Peabody)		−0.59*				
Memory						
Memory (Mattis)				−0.37*		
Logical memory (Wechsler)				−0.62**		
Verbal learning (Rey)		−0.46				
Depression						
Hamilton scale		0.39				

The results are expressed as the correlation coefficient (r) between P3 latency values and appropriate test scores. If blank, data not available.
Statistical significance: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

average, P3 latency increases with decreasing scores of the tests measuring general intellectual abilities. These negative correlations, however, were significant only for ERFC test (Gil *et al.*, 1986), while for Mini-Mental Status examination (MMS; Folstein *et al.*, 1975) a borderline significance was shown only in one of three studies.

As to more specific neuropsychological tests, significant correlations were observed between P3 wave latency and Symbol Digit Modalities Test (SDMT; Smith, 1973). Further, some isolated findings concerned correlations of P3 latency with Raven's Progressive Matrices (Raven *et al.*, 1977), Goldman-Fristoe-Woodcock Selective Attention test, Trail Making Test A (Spreen and Benton, 1965) and Backward Digit Span test (Wechsler, 1955). Fewer observations concerned the measures of visuospatial abilities and their results were rather inconsistent. With regard to language and memory, significant negative correlations with P3 latency were reported for Sentence Repetition and Peabody Vocabulary tests as well as for the Logical Memory subtest of the Wechsler Memory scale and the Memory subtest of the Mattis Dementia Rating Scale (Mattis, 1976). Regarding depression, an insignificant correlation of P3 latency with Hamilton Depression Rating Scale (Hamilton, 1960) was demonstrated in one study.

N2

The interactions of the N2 component latency with neuropsychological measures were communicated in three

TABLE III. ERP in PD—correlations between psychometric tests and N2 wave latency

Test	Gil *et al.* (1989)	Pang *et al.* (1990)	Ebmeier *et al.* (1992)
General intellectual abilities			
MMS (Folstein)			−0.39
ERFC (Gil)	−0.69**		
Information (Wechsler)		−0.33	
Verbal IQ (Wechsler)			−0.36
Abstract reasoning			
Conceptualization (Mattis)		−0.30	
Progressive matrices (Raven)		−0.35	
Attention			
Attention (Mattis)		−0.35	
Trail making A	0.59***		
Visuospatial abilities			
Multiple choice visual retention (Benton)			−0.49*
Visual form discrimination (Benton)		−0.54**	
Line orientation (Benton)		−0.32	−0.58**
Face recognition (Benton)		−0.34	−0.30
Language			
Verbal fluency (Benton)		−0.26	
Initiation (Mattis)		−0.18	
Memory			
Memory (Mattis)		−0.42*	
Logical memory (Wechsler)		−0.70***	

The results are expressed as the correlation coefficient (r) between N2 latency values and appropriate test scores. If blank, data not available.
Statistical significance: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

papers only (see Table III). Correlations concerning the tests of general intellectual abilities, attention and visuospatial abilities, as well as language and memory were not substantially different from those found for P3.

P2

Hansch *et al.* (1982) observed a significant correlation of P2 wave latency with SDMT scores ($r = -0.499$, $p < 0.05$).

N1

A non-significant negative correlation of N1 wave latency with MMS scores ($r = -0.236$) was found by Hansch *et al.* (1982). In the study of Goodin and Aminoff (1987), the N1 latency significantly correlated with the scores of MMS in the group of demented PD patients ($r = -0.678$; $p = 0.022$).

ERP and global cognitive impairment

The distinction of global cognitive impairment from isolated ("specific") cognitive deficits seems to be rather artificial. In reality, the cognitive disorders in PD occur along a continuum of deterioration (Pirozzolo, 1982). The notion of global cognitive disorder is, however, of some heuristic value with regard to the tests mostly used for rapid evaluation of mental functions in these patients.

In the studies reviewed here, predominantly non-significant negative correlations between the results of MMS examination and the parameters of the ERP were found. Only in supposedly demented patients of O'Donnell *et al.* (1987) did the correlation achieve a significant level. The exceptional finding of MMS score relationship with N1 wave latency (Goodin and Aminoff, 1987) might be explained in the terms of specific changes of the early ERP components in subcortical dementia, as discussed above. Tighter correlations were shown by Gil *et al.* (1989) and by Hautecoeur *et al.* (1991) between the results of the ERFC test and P3 wave latency values. Although both MMS and ERFC evaluate the general level of intellectual impairment, the ERFC (including measures of attention and verbal fluency) may be more specific towards cognitive deficits presumably occurring in PD. In fact, the most customary MMS examination is heavily weighted with

items sensitive to language deficits and, therefore, it may be not fully appropriate for the evaluation of cognitive impairment observed in PD (see below). Obviously, ERP weigh the particular elements of global cognitive decline in a somewhat different manner to common psychometric tests. The ERP results may thus be more influenced by the specific pattern of cognitive deterioration than by its overall degree.

ERP and isolated cognitive deficits

Besides global cognitive impairment or overt dementia, various isolated ("specific") cognitive deficits were reported even in non-demented PD patients (for a review, see Dubois *et al.*, 1991). These deficits, occurring in the absence of generalized intellectual deterioration, may concern memory (Bowen *et al.*, 1976; Pirozzolo *et al.*, 1982; Taylor *et al.*, 1987), language (Matison *et al.*, 1982; Lees and Smith, 1983), visuospatial abilities (Boller *et al.*, 1984; Brown and Marsden, 1986; Hovestadt *et al.*, 1988), concept formation and behavioral regulation (Bowen *et al.*, 1975; Lees and Smith, 1983; Taylor *et al.* 1986).

Several studies of ERP in PD attempted to find electrophysiological correlates of specific cognitive deficits in PD and, at the same time, to shed some new light on putative mechanisms of parkinsonian mental impairment. The latency parameters of ERP components correlated, in general, with the measures of attention and, to a lesser extent, of visuospatial abilities and of abstract reasoning. Particularly important correlations were shown between SDMT scores and P3 latency values. Besides the overall level of attention, this test investigates visuospatial perception, perceptual organization, visual scanning and response translation speed. It may, therefore, be specifically sensitive to the principal isolated cognitive deficits presumed to occur in PD patients. From this point of view, the close correlation found between SDMT and ERP parameters in PD patients may reveal the impairment of some psychological mechanisms involved in the performance of both tests.

Frontal lobe dysfunctions supposedly underlie the most common isolated cognitive deficits in PD (Taylor *et al.*, 1986; Gotham *et al.*, 1988). The correlations found between ERP and neuropsychological data may support the assumption of a frontal lobe generator of the P3 component (Wood and McCarthy, 1988). Accordingly, the correlations shown between P3 latency and some neuropsychological measures corresponding to "cortical" processing may reflect the impairment of presumed subcortical and cortical generators of P3 (see above).

ERP AND DOPAMINERGIC TREATMENT IN PD

Recently, three ERP studies contributed to the debate concerning possible dopaminergic mechanisms of cognitive impairment in PD (see Table IV).

Starkstein *et al.* (1989) examined seven parkinsonian

TABLE IV. Studies of ERP in PD—dopaminergic stimulation

Ref.	Number of patients	Mean age (years)	Mean duration PD (years)	Hoehn & Yahr score	Mental status	L-Dopa mean dose	Situation	NI latency	P2 latency	N2 latency	P3 latency	NI amplitude	P3 amplitude	Mean reaction time (ms)
Starkstein *et al.* (1989)	7	65	11.6	—	Non-demented	718 mg	Off				336*		6.8	341
							On	—	—	—	324 (—)	—	6.4 (—)	329 (—)
Stanzione *et al.* (1991)	18	65	3.0	I-IV (mean 2.3)	Non-demented	375 mg	Withdrawal after L-dopa	—	—	—	387*** 356 (351)	—	—	—
Prasher and Findley (1991)	27	56	2.0	I-II	Non-demented		Easy task							
							Before L-dopa	106		247	347			400
							After	106		244	373**			379
						395 mg	L-dopa	(107)	—	(230)	(339)	—	—	(367)
							Hard task							
							Before L-dopa	106		310	420			515
							After	110		294	460***			460***
							L-dopa	(107)		(277)	(420)			(453)

The results of ERP are expressed as mean values of latencies in ms and mean values of amplitudes in μV.
Control mean values, if available, given in parentheses.
Statistical significance (comparisons between paired values obtained in patients): $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$.
—, Data not available.

patients suffering from severe motor fluctuations, all of them being treated by L-dopa. The ERP recording was done twice in the same day—when the patients were "off" after an overnight withdrawal of the drug, and when optimal motor status ("on") was reached after reintroduction of the treatment. A significant shortening of P3 wave latency was found in the "treated" condition compared with the withdrawal one. The performance in several neuropsychological tasks executed in respective "on" and "off" phases in the same subjects was not significantly changed.

Stanzione *et al.* (1991) studied ERP in 18 PD patients when L-dopa treatment was withdrawn and several days after reintroduction of the therapy. A significant shortening of P3 latency was observed in the treated state. On the other hand, in a group of 12 healthy volunteers, a significant *increase* of P3 latency was shown after the experimental administration of L-dopa.

In a more elaborate study using two tasks of various difficulty performed in a group of 27 patients with newly diagnosed PD, Prasher and Findley (1991) assessed the ERP before the introduction of L-dopa treatment and several weeks afterwards. On the first examination, in the "easier" task (tone pitch discrimination), latencies of ERP as well as reaction times (RT) were normal. However, the "hard" task (discrimination based on different durations of tones) disclosed a marked lengthening of RT in comparison with normal values, and a slight prolongation of N2 wave latency. When comparing the above results obtained before the introduction of L-dopa with those under treatment, significantly longer latencies of P3 wave were found under L-dopa therapy in both test conditions, whereas RT were relatively shortened after L-dopa. Moreover, a positive correlation of P3 wave latency with the duration of L-dopa treatment was found in "hard" task conditions.

ERP correlates of physiopathological mechanisms in PD

Destruction of the nigrostriatal dopaminergic system, considered to be the major site of damage in PD (Hornykiewicz, 1966), is responsible for the classic triad of rigidity, akinesia and tremor. The role of nigrostriatal and/or mesocortico-limbic dopaminergic depletion was hypothesized in parkinsonian cognitive deficits (for review, see Dubois and Pillon, 1992). However, the involvement of non-dopaminergic neuronal systems, thought to have modulatory effects on cognitive functions, was also shown in PD (Agid *et al.*, 1990), indicating that cognitive impairment in PD may stem from widespread cortical dysfunction due to deafferentation from ascending cholinergic and monoaminergic projections (Growdon *et al.*, 1990).

Numerous clinical studies have attempted to analyze the mechanisms of cognitive and motor impairment in PD by evaluating the effects of dopaminergic treatment. The patients were studied during both L-dopa stimulated and unstimulated phases. The benefit from L-dopa administration on cognition is usually less impressive than that on motor symptoms. Some specific aspects of cognition, such as verbal fluency, memory and perceptual organization, may improve with dopaminergic treatment (Loranger *et al.*, 1972; Bowen *et al.*, 1975; Delis *et al.*, 1982; Mohr *et al.*, 1987), whereas other functions remain unchanged (Gotham *et al.*, 1988; Hovestadt *et al.*, 1988; Pillon *et al.*, 1989a). Several authors reported even a worsening of some cognitive functions under L-dopa. For instance, Rafal *et al.* (1984) observed in several patients with newly diagnosed PD, a faster rate of memory scanning before introduction of the drug than afterwards. Similarly, in a group of PD patients with motor fluctuations, Poewe *et al.* (1991) showed a deterioration of memory scanning after L-dopa administration compared with previous performance in the "off" condition.

In the three ERP studies mentioned above, the apparently discordant data concerning P3 wave latency changes related to exogenous L-dopa stimulation are not necessarily contradictory, and may in fact mirror different mechanisms of dopamine (DA) effects in various stages of PD (or in normal conditions in healthy volunteers). To summarize the findings, after an administration of L-dopa, P3 latency was shortened parallel to RT only in patients with longstanding PD who, eventually, were suffering from motor fluctuations (Starkstein *et al.*, 1989; Stanzione *et al.*, 1991). On the contrary, in younger patients with early PD, the P3 wave was delayed after L-dopa administration (Prasher and Findley, 1991). Similarly, in healthy subjects, a single dose of L-dopa provoked a prolongation of P3 wave latency in comparison with basal values (Stanzione *et al.*, 1991). Various underlying mechanisms can be hypothesized.

(1) Lesions of the nigrostriatal DA pathway underlying parkinsonian motor symptoms precede the impairment of other systems (for instance mesocortico-limbic dopaminergic) which are considered to be involved in cognitive dysfunction (Javoy-Agid and Agid, 1980). Therefore, in the early stages of the disease, the increase, after administration of L-dopa, of DA levels compensating for depleted nigrostriatal transmission may, in turn, stimulate supersensitive DA autoreceptors (Graham *et al.*, 1990) on unaffected dopaminergic cells subserving non-motor functional systems (Agid *et al.*, 1984). As a result, the activity of these cells and the amount of DA released on their axonal endings are reduced. This is in agreement with the claim that exogenous L-dopa may even shut off the natural spontaneous production of DA from exogenous tyrosine (Melamed, 1990). These mechanisms, which in a similar way might intervene in normal healthy subjects, would in early PD disturb DA-mediated processes underlying the P3 potential. In patients with long-term disease,

where already both nigrostriatal and mesocortico-limbic systems are depleted in DA, L-dopa treatment simply compensates for this combined depletion. Therefore, in these patients, cognitive processes reflected by P3 wave latency may be restored in parallel with motor improvement.

(2) The balance of dopaminergic effects on DA autoreceptors and postsynaptic receptors is dose dependent (Roth, 1979). In fact, the DA autoreceptors are more sensitive to DA stimulation than postsynaptic receptors. Moreover, the pharmacological responsiveness of DA autoreceptors is higher in the mesocortico-limbic than in the nigrostriatal system. Therefore, in newly diagnosed PD patients where relatively low doses of L-dopa are administered, the inhibitory effects in the mesocortico-limbic system may prevail involving adverse cognitive manifestations (Corsini *et al.*, 1977), whereas nigrostriatal transmission (and motor functions) are improved under the same treatment.

(3) Finally, studies indicate the importance of non-dopaminergic lesions which might play the principal role in parkinsonian cognitive disorders (Pillon *et al.*, 1989b). Dopaminergic manipulations would thus affect only indirectly (if at all) the cognitive functioning and its manifestations, including the electrophysiological ones. Any correspondence between ERP results and L-dopa treatment would then be incidental.

CONCLUSIONS

Several consistent findings can be extracted from the studies reviewed here.

(1) The N2 and P3 ERP components are delayed in PD and the latency increases are more important in demented PD patients. These changes suggest the slowing down of cognitive processes, probably due to the impairment of mechanisms that underlie stimulus discrimination, categorization and decision making. On the other hand, the P3 latency delay could be related to focal cognitive deficits observed in PD, which have been attributed to frontal lobe impairment and to subcortico-cortical dysfunction.

(2) The N1 ERP component is delayed in demented patients with PD as well as in other forms of dementia of presumed subcortical origin. This may reflect deficits in the early information processing stages, possibly due to defective attentional mechanisms.

(3) The ERP findings may reveal different effects of dopaminergic treatment on cognitive functions in various stages of the disease. Based on ERP data, a deterioration of cognitive functions has been suggested after L-dopa introduction in *de novo* PD patients.

Considering the predominant "diagnostic" goals of the majority of ERP studies, the results obtained have not been specific enough to allow an individual diagnosis. In addition, some important parameters (amplitude and scalp distribution), have often been disregarded in the studies reviewed here. When using these indices, one must keep in mind that a given electrophysiological profile (a reproducible electrophysiological "abnormality" through several subjects for example) may reflect a particular dysfunction in psychological processing, however no direct correspondence with any particular clinical symptomatology could seriously be inferred. An approach consisting of sorting the patients into different categories only based on the changes of ERP parameters could thus be misleading.

A more fruitful research direction for ERP studies would be to improve our understanding of psychological processes such as attention or memory. ERP are particularly useful in what is called "mental chronometry" (Meyer *et al.*, 1988). This approach is concerned with segmenting the sensory-motor information processing chain. The objective is to qualify and quantify different mental processes involved in information processing analysis from the sensory input to the behavioral response. The use of ERP in this framework constitutes a powerful tool to assess complex cognitive processes and appears to be a useful method for providing further information on the psychological nature and neurophysiological basis of cognitive impairment in PD. In this context, it is clear that focusing on only one ERP component would lead to a consistent reduction in the information that one can draw from examining the different ERP components in relationship to each other.

Parkinson's disease may be regarded as a model disorder with a well-known underlying neurotransmitter pathology. In spite of a detailed morphological, neuropharmacological and neuropsychological analysis, cognitive deficits in PD are not fully understood. ERP may help to identify the physiopathological mechanisms that underlie parkinsonian cognitive impairment and may contribute to a better understanding of the role of the dopaminergic system in cognitive processing.

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