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Early modifications of auditory event-related potentials in carriers of the Huntington's disease gene

Marina DE TOMMASO, Vittorio SCIRUICCHIO, Nicola SPECCHIO, Olimpia DIFRUSCOLO, Carmela VITALE, Luigi Maria SPECCHIO and Francomichele PUCA
First Neurologic Clinic, University of Bari, Bari, Italy

Abstract

The P3 wave is one cognitive component of event-related potentials (ERP) used to investigate various types of dementia. The aim of this study was to use the odd-ball paradigm to evaluate the P3 in Huntington's Disease (HD) gene carriers who showed no symptoms of chorea, compared to a group of mildly affected HD patients. We selected 14 HD patients and six individuals who, despite testing positive for the HD gene, did not show any clinical evidence of the disease. Thirty-six normal subjects were also selected as controls. Statistical evaluation of N1, P2, N2 and P3 latencies and amplitudes was performed in each group. Both the N2 latency and the P3 latency corrected for age (cP3) were significantly correlated with the duration of illness in pooled symptomatic and presymptomatic gene carriers. However, these latencies did not correlate with any clinical scale or psychometric test, including WAIS subtests. As the individual P3 latency of the majority of HD patients and all presymptomatic gene carriers was distributed within normal confidence intervals, and no correlation existed between ERP parameters and the signs of illness progression, the data appear to provide preliminary evidence against the valence of P3 in detecting the early cognitive impairment of HD.

Key words : Huntington's Disease ; presymptomatic gene carriers ; auditory event-related potentials.

Introduction

The P3 wave is one cognitive component of event-related potentials (ERP) used to investigate cognitive processes that is also useful in the study of patients affected by various types of dementia. Goodin and Aminoff (1986) suggested that the pattern of auditory ERP produced by the odd-ball paradigm was different in cortical dementia of Alzheimer type compared to subcortical dementia in Parkinson's and Huntington's disease. Specifically, while the N2 and P3 latency should be delayed in all types of dementia, only the subcortical type of dementia was characterized by prolongation of N1 and P2 latency. This assertion was not confirmed by other studies (Filipovic *et al.*, 1990), which found no differences in N1 and P2 waves in response to an odd-ball paradigm between patients with Alzheimer's disease, Huntington's disease and demented patients with Parkinson's disease. Although the value of P3 as a diagnostic index is not entirely established, it can provide a useful recording of patients' information processing, and can thereby indicate the severity of the clinical state and its possible prognosis (Hansenne, 2000).

Following identification of the genetic defect in HD as an abnormal expansion of a CAG trinucleotide repeat in the first exon of the HD gene (The Huntington's Disease Collaborative Research Group, 1993), it was possible to identify gene carriers before clinical manifestation of the disease. This discovery raised many questions, including the use of genetic counselling to help manage the mild cognitive and psychiatric impairments that may appear before choreatic movements (Paulsen *et al.*, 2001). Recent studies have outlined the need for accurate assessment of phenoconversion of HD, implementing several methods able to point out impairment before more manifest motor disease. Such methods include quantified neurological rating scales, computerized physiological measures, neuropsychological evaluation and high resolution MR images ; early identification of clinical changes in HD may be an aid for clinical trials to slow the progression of the disease (Kirkwood *et al.*, 2000 ; Paulsen *et al.*, 2001 ; Rosas *et al.*, 2002). Electrophysiological studies in HD patients and subjects at risk may be useful to improve knowledge about the development of functional impairment and its relationship to pathological changes. Several neurophysiological abnormalities have been described in HD, and some of these were in asymptomatic gene-carriers, confirming that the underlying functional changes are a feature of the disease rather than a consequence of chorea (de Tommaso *et al.*, 2001, 2003). In addition to the early identification of clinical changes in HD, slowing the progression of the disease is of critical

Table 1

Clinical and neuropsychological features in carriers of the HD gene

HD patients	Age	Duration of illness (years)	Sex	CAG repeat size	Total IQ	Verbal IQ	Perf. IQ	MMSE	Shoulson functional capacity scale	Marsden and Quinn chorea scale	AIMS
1	69	5	F	41	66	72	70	23.2	9	12	14
2	51	6	M	44	58	71	10	22.1	4	31	30
3	48	12	M	44	108	109	105	25.6	7	6	6
4	51	9	F	43	64	63	70	19.7	7	33	28
5	60	12	M	45	88	86	91	25.9	6	25	23
6	43	4	F	46	71	73	72	19.3	10	21	21
7	47	11	M	45	79	76	86	21.2	12	21	15
8	55	4	M	42	120	120	117	30.00	12	17	16
9	60	11	M	44	55	60	54	17.99	4	16	20
10	57	7	F	44	85	86	84	25.1	8	22	18
11	37	4	F	47	66	72	61	18.74	10	8	12
12	48	7	F	43	60	66	57	27.42	11	12	19
13	39	3	M	46	84	77	96	16.10	13	10	8
14	41	1	F	45	90	94	87	25.62	11	10	8
Presymptomatic gene carriers		Expected duration of illness (years)									
1	27	-21.5	M	43	113	118	106	30	13	0	0
2	22	-21	M	45	93	91	97	30	13	0	0
3	46	-7	F	41	102	105	99	30	13	0	0
4	57	-1	F	40	85	87	85	25.8	13	1	1
5	34	-11.5	F	44	125	122	127	30	13	0	0
6	40	-1	M	46	104	104	104	28.4	13	1	1

importance for the design and implementation of clinical trials (Paulsen *et al.*, 2001). In a study by Homberg *et al.* (1986) that was performed before genetic testing, an abnormal P3 wave was observed in 25% of clinically normal, at-risk relatives : correlation of the P3 with detailed psychometric analysis revealed a particularly high association between the P3 latencies and information processing performance.

Therefore, the aim of this study was to verify whether the P3 produced by the odd-ball paradigm is able to detect early clinical markers of disease in at-risk people who have not yet been diagnosed with HD, compared to a group of mildly affected HD patients.

Methods and materials

Subjects

Among a population of 25 subjects who were at risk for HD, 11 showed an abnormal CAG expansion. The mutation analysis was performed for the CAG expansion within HD gene trinucleotide repeat (CAG) sequence on the short arm of chromosome 4, using HD 333-HD 447 as oligonucleotide primers. Of these, 6 gave informed consent for participation in the study, which was approved by the local Ethics Committee of our Department. In addition, 14 HD patients agreed to participate in the study : all patients had been attending the clinic for at least 10 years, so 10 of them had been observed clinically before the appearance of chorea. All at-risk subjects and HD patients were evaluated by two different neurologists who were blind to their condition, with scores from all scales calculated as the mean of the two evaluations. They applied the functional capacity scale developed by Shoulson (1981), the Marsden and Quinn chorea scale and the Abnomal Involuntary Movement Scale (AIMS) (Marsden and Schacter, 1981). In two cases, the Marsden and Quinn chorea scale and the AIMS produced a score of 1, owing to the presence of frequent blinking and a slight motor inaccuracy ; however, no evidence of involuntary movements was present in these subjects (Table 1). The estimated duration of illness was computed for presymptomatic gene carriers, according to the following equation : Log (age) = $a + \beta$ (CAG number repeats), where a = 6.15 (SE = 0.095), and β = -0.053 (Rubinsztein *et al.*, 1997). In addition, all patients and gene carriers completed the Mini Mental State Examination (MMSE) (Folstein *et al.*, 1975) and the basic Italian version of WAIS-R (Wechsler, 1987). Results of the MMSE were corrected for education and age using the Italian standardization and rating suggested by Measso *et al.* (1993) ; an Italian standardization was also used

for the WAIS-R (Orsini *et al.*, 1997). All the patients were drug-free for three to seven days before the recording session. Thirty-six normal subjects were also selected as control, comprising 18 females and 17 males aged 24-68 years. Subjects with general internal, neurological, or psychiatric diseases according to DSM-IV (American Psychiatric Association, 1994), were not included in the control group.

Stimulation

Stimulation consisted of delivery of a binaural auditory tone stimulus, with two easily distinguishable tones of different pitches presented in random order (Goodin *et al.*, 1994). Presentation of the two tones was unequal, differentiated into 'frequent' and 'rare' tones (presented in 85% and 15% of the trials, respectively). The frequent tone was of 50 ms duration at 65 dB HL, with a pitch of 1000 Hz ; the rare tone, in contrast, was of 50 ms duration at 65 dB HL, with a pitch of 2000 Hz. A 10 ms rise and fall time was used. The interstimulus interval was about 1.5 sec. Sixty rare tones were presented during each repetition of the test. All patients and subjects were requested to keep a mental record of the number of rare tones presented. Between the two recordings, the examiner verbally interacted with the subjects to avoid drowsiness.

Recording

The EEG was recorded at the vertex, frontal and parietal sites (Cz, Fz and Pz electrode sites of the International 10-20 system) using silver-silver chloride electrodes, referred to the linked earlobes with a forehead ground, and with impedance ≤ 2 kΩ. Eye movements were monitored with an electrode placed intraorbitally. Responses to the frequent and rare tone were recorded separately. The low and high frequency filters were set at 0.1 and 100 Hz, respectively. A 50 Hz notch filter was also used. Recordings were made for 1000 ms after stimulus onset, with a dwell time of 2 ms. Three repetitions were made and the grand average was computed for each case. Stimulation and recording sets were provided by Micromed apparatus and System 98 software.

The peak latency for N1, P2, N2 and P3 were determined by extrapolating lines from the ascending and descending portion of the waveform for the component of interest and measuring the latency at the point of intersection (Goodin *et al.*, 1994) : the latency of N1 and P2 were measured from the response to the frequent tone, whereas N2 and P3 were measured from the response to the rare tone. In some cases, the P3 was composed of two distinct peaks, with the second one used to score latency. The amplitude of all waves was measured from the baseline.

Statistical analysis

The N1, P2, N2 and P3 latencies and amplitudes were correlated with age in control and patient groups using Pearson's correlation. For each age-related component, an age regression line was constructed based on the data of control subjects. The individual values of HD patients and presymptomatic gene carriers were compared to the regression lines to determine whether they fell within this limit. Age-related components were corrected using an age regression factor, based on control subjects before performing any statistic evaluation. ANOVA was completed using groups as the factor and ERP parameters as dependent variables, with Bonferroni post hoc analysis. All event-related components of gene carriers who showed significant differences from control subjects were correlated with clinical and psychometric scales using Pearson's correlation. All statistical analyses were performed using the SPSS package, version 10.1 for Windows.

Results

In all participants, the response to the frequent tone consisted of a clear negative (N1)-positive (P2) complex. Further, the rare tone resulted in another negative (N2)-positive (P3) complex in all cases except for one control subject, a 29-year-old female, who was excluded from the following analysis. Age showed no statistically significant correlation with N1, P2 and N2 latencies and amplitude in any group ; further, P3 amplitude did not correlate with age. The N1 and P2 latencies and the N1, P2, N2 and P3 amplitudes were similar among groups (Table 2). In contrast, the N2 latency was prolonged in HD patients compared to both controls and not-at-risk gene carriers (Table 2). In eight of the 14 HD patients, the N2 latency differed from control values by more than two standard deviations.

P3 latency was significantly correlated with age in the control group ($r = 0.562$; $p < 0.001$). P3 latency was corrected for each HD patient and presymptomatic gene carrier using the age regression factor, which was based on values from control subjects. The mean values of the corrected latency of P3 (cP3) were significantly different among groups ($F = 2.75$; $p < 0.05$) ; a mild increase of the cP3 mean latency was observed in HD patients compared to the other groups, although *post hoc* Bonferroni analysis did not show any significant differences (Table 2). Considering the age regression line of P3 latency in control subjects, no presymptomatic gene carrier and three HD patients showed values outside the two SD range (Fig. 1 ; Fig. 2). The N2 latency and the corrected P3 latency were significantly correlated with the duration of illness in the pooled group of symptomatic and

Table 2

Latencies (ms) and amplitudes (μV) of event-related components. The P3 latency was corrected for age (cP3). Results of Bonferroni test are shown : *p < 0.05

		N1 (ms)	P2 (ms)	N2 (ms)	cP3 (ms)	N1 (μV)	P2 (μV)	N2 (μV)	P3 (μV)
HD patients	mean	97.4	182.9	274.7*	376.5	5.6	5.7	5.3	9.5
	n	14	14	14	14	14	14	14	14
	SD	12.4	35.7	52.1	64.61	4.8	6.7	2.3	6.2
Controls	mean	91.5	168.5	222.3	343.5	9.7	8.1	8.2	15.8
	n	35	35	35	35	35	35	35	35
	SD	14.6	24.6	35.9	44.8	13.1	5.14	8.5	10.4
presymptomatic gene carriers	mean	98.7	174.3	231.2	328.4	3.9	8.4	8.8	16.7
	n	6	6	6	6	6	6	6	6
	SD	20.7	22.6	31.4	38.59	2.07	7.1	7.9	5.4

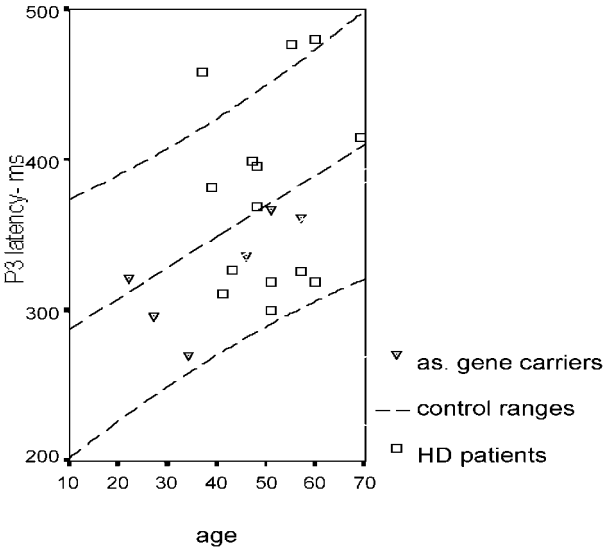

FIG. 1. —Relationship between age and wave latency for component P3 in the normal population, as indicated by a linear regression links were elicited by a rare target stimulus, and the other by a frequent tone (F). The time analysis was 1 s and sensitivity was 10 μV.

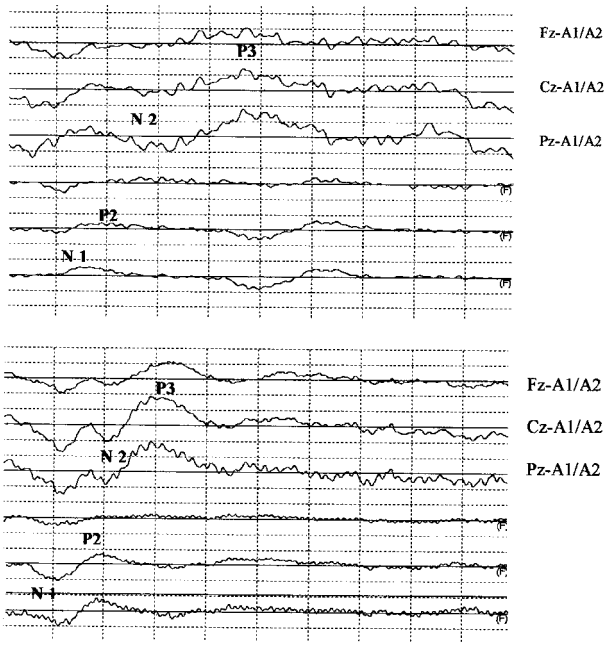

FIG. 2. — Evoked response waveform from a 37-year-old female HD patient who has had the disease for four years (top), as well as a 34-year-old female presymptomatic gene carrier, expected to develop the disease in 11 years. The grand averages of two repetitions are shown in each case : the upper tracks were elicited by a rare target stimulus, and the other by a frequent tone (F). The time analysis was 1 s and sensitivity was 10 μV.

presymptomatic gene carriers, while the same values did not correlate with any clinical scale and psychometric tests (Table 3), including WAIS subtests (Table 4).

Discussion

The current study demonstrated a small prolongation of cP3 latency in HD patients. This finding displays only partial agreement with previous studies (Goodin and Aminoff, 1986 ; Filipovic *et al.*, 1990 ; Homberg *et al.*, 1986), because the magnitude of latency abnormality was clearly weaker in the present sample of HD patients. Although only three HD patients exceeded the normal range of P3 latency (Fig. 1), a small prolongation of the mean cP3 value in HD patients was supported by a slightly statistically significant ANOVA among groups (Table 2). In accordance with the small prolongation of cP3 latency prolongation, an increase in the latency of the N2 component was observed in HD patients compared to both presymptomatic gene carriers and controls (Table 2). The latency of this component was not significantly correlated with age in control subjects, as reported in some studies (Filipovic *et al.*, 1990). Examination of individual values revealed that this component was within normal limits in almost half of the patients. The six presymptomatic gene carriers showed ERP parameters within the normal ranges, despite two of them approaching the onset of HD.

Table 3

Pearson's correlations between clinical psychometric and ERP features in 20 carriers of the HD gene : $p < 0.05$; ** $p < 0.01$

	AIMS	MQ	TFC	Length of illness	Age	MMSE	WAIS full scale IQ	WAIS verbal IQ	WAIS performance IQ	N2 lat.	cP3 lat.
AIMS	1										
MQ	0.673*	1									
TFC	-0.77**	-0.71**	1								
Length of illness	0.71**	-0.69**	-0.644**	1							
Age	0.54*	0.52*	-0.54*	0.73**	1						
MMSE	-0.53*	0.48	-0.48*	-0.57*	-0.23	1					
WAIS full scale IQ	-0.69**	-0.59*	0.57*	-0.52*	-0.31	0.790*	1				
WAIS verbal IQ	-0.66**	-0.67**	0.51*	-0.55	-0.3	0.741*	0.97**	1			
WAIS performance	-0.69**	-0.58**	0.64**	-0.42	-0.29	0.790*	0.9**	0.79**	1		
N2 latency	0.16	0.14	-0.17	0.52*	0.32	0.03	-0.06	-0.03	n.s.	1	
cP3 latency	0.16	0.12	-0.13	0.51*	0.38	-0.1	-0.02	-0.06.	n.s.	0.9**	1

Abbreviations : MMSE : Mini Mental State Examination ; TFC : Total Functional Capacity Scale by Shoulson ; MQ : Marsden and Quinn Chorea Scale ; AIMS : Abnormal Involuntary Movement Scale.

Table 4

Pearson's correlations between ERP, clinical features and WAIS subtests in 20 carriers of the HD gene : *$p < 0.05$; **$p < 0.01$

	Length of illness.	Inf	Compr	Arithm	Simil	Digit span	Vocab	Digit symb	Pict comp	Block des	Pict arrang	Obj assem	TFC	MQ	N2 lat.	cP3 lat.
Length of illness	1															
Inf	-0.26	1														
Compr	-0.37	0.62**	1													
Arithm	-0.61**	0.75**	0.66**	1												
Simil	-0.39	0.68**	0.64**	0.73**	1											
Digit span	-0.81**	0.46*	0.62**	0.75**	0.60**	1										
Vocab	-0.13	0.66**	0.68**	0.77**	0.67**	0.48*	1									
Digit symb	-0.55*	0.68**	0.74**	0.78**	0.70**	0.68**	0.63**	1								
Pict comp	-0.44	0.62	0.70	0.77	0.79	0.65	0.61	0.80	1							
Block des	-0.53*	0.72**	0.72**	0.79**	0.71**	0.68**	0.62**	0.73**	0.86**	1						
Pict arrang	-0.41	0.4	0.4	0.59*	0.6**	0.39	0.5*	0.56*	0.67**	0.7**	1					
Obj assem	-0.66**	0.52*	0.7**	0.75**	0.71**	0.72**	0.57*	0.74**	0.81**	0.90**	0.81**	1				
M	-0.64**	0.17	0.51*	0.37	0.5*	0.61**	0.13	0.57*	0.63*	0.53*	0.43	0.69**	1			
MQ	0.69**	-0.19	-0.57*	-0.48*	-0.49*	-0.65**	-0.23	-0.59*	-0.52*	-0.54*	-0.24	-0.68**	0.71**	1		
N2 lat	0.52*	0.14	-0.00	-0.07	0.16	-0.24	0.09	-0.05	0.12	0.03	-0.06	-0.11	-0.01	0.14	1	
cP3lat	0.51*	0.08	-0.09	-0.21	0.08	-0.22	-0.11	-0.08	0.06	-0.00	-0.15	-0.16	-0.03	0.12	0.9	1

Abbreviations : Inf : information ; Simil : similarities ; Vocab : vocabulary ; Pict comp : pictures completion ; Block des : block design ; Pict arrang : picture arramengement ; Obj assem : objects assembly ; TFC : Total Functional Capacity ; MQ : Marsden and Quinn chorea scale.

This study is the first to examine ERP in presymptomatic gene carriers. A previous investigation by Homberg *et al.* (1986) did not distinguish positive gene carriers from the total population of relatives at risk for HD. The authors found a prolonged P3 latency in 25% of the total population of those who were clinically normal but at risk, however omission of genetic assessment did not allow identification of those subjects who were approaching the onset of HD. In the present evaluation, when symptomatic and presymptomatic HD gene carriers were pooled, a positive correlation was found between the increase in N2 and cP3 latency and the actual or expected duration of the disease (Table 3). It is therefore presumable that these ERP patterns are sensitive to subtle changes in the course of the phenotypic expression of the disease. Our patients were either slightly or not at all demented, despite the relatively long duration of illness, generally estimated from appearance of the first signs of disease. This contrasts with previous studies of ERP in HD in which patients were clearly demented (Goodin and Aminoff, 1986 ; Filipovic *et al.*, 1990).

According to previous studies (Filipovic *et al.*, 1990 ; Rosemberg *et al.*, 1985), a delayed P3 latency may be an electrophysiological marker of disorders of cognition, including HD. Studies that have examined neuropsychological features in large series of presymptomatic HD gene carriers showed subtle cognitive impairment in digit symbol, picture arrangement and arithmetic subscales of the WAIS-R (Kirkwood *et al.*, 2000), tests of attentional set shifting and semantic verbal fluency (Lawrence *et al.*, 1998), and in the neuropsychological assessment of the Unified Huntington's Disease Rating Scale (UHDRS) (Paulsen *et al.*, 2001). In the current carriers of the HD gene, longer duration of illness was associated with a clear decrease in WAIS-R subtests. In addition, it was also related to deterioration of cognitive performance as expressed by the total IQ, particularly in some subscales related to motor and functional impairment (Table 2 and Table 3). These findings confirm that features of slight cognitive impairment in HD could reflect illness severity at the onset and early stages of the disease (Paulsen *et al.*, 2001). Differential N2 and cP3 latency prolongation over the duration of the illness seemed to be independent of disease severity, so the cognitive deficit expressed by this ERP pattern is a late symptom that is not evident at the onset and early phase of HD.

The N2 wave is elicited by both expected and unexpected rare stimuli, and it is followed by the P3 wave when subjects perform the recognizing task : it may be the expression of a mismatch process and an orienting reflex, both of which are independent of voluntary control (Naatanen, 1986). The P3 wave reflects the modifications in neuronal activity that take place during the cognitive process : it is hypothesized that P3 could either represent the adaptation of working memory to further environmental input (context updating) (Donchin and Coles, 1998) or a closing process (context closure) (Desmedt, 1980). Regarding the physiological aspects of P3 and its association with cortical networks, several cortical generators may co-exist, including the medial temporal lobe, the temporal-parietal junction and the medial and lateral frontal lobe, which are independently activated during information analysis processes (Johnson, 1993) and the dorsolateral prefrontal cortex as reported by McCarthy (McCarthy *et al.*, 1997). High-resolution magnetic resonance (MR) images from HD patients showed that the more posterior cortical regions and the sensorimotor cortex degenerate earlier in the disease (Rosas *et al.*, 2002), and it is possible that the cortical regions that generate the N2-P3 complex may not be involved in the initial degenerative process. Concurring with the results of Filipovic *et al.* (1990), our HD patients did not show increased N1 and P2 wave latency : Goodin and Aminoff (1986) found that the increased N1 and P2 latency could distinguish subcortical dementia in HD from cortical dementia in Alzheimer's disease. Our results suggest that this particular abnormality does not emerge in mildly demented HD patients and it probably appears with the exacerbation of dementia. Moreover, N2 and P3 latency prolongation was also unable to detect early cognitive decline in HD gene carriers, as observed also in other kinds of dementia (Kriuhin *et al.*, 1990).

Although the major limitation of our study was the small number of participants, the results deserve confirmation by studies using larger groups. Nevertheless, the distribution of the individual P3 latency values within the normal confidence intervals for the majority of HD patients and all presymptomatic gene carriers, combined with absence of a correlation between ERP parameters and the signs of illness progression, seem to provide preliminary evidence against the valence of P3 in detecting early cognitive impairment in HD.

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M. DE TOMMASO,
Clinica Neurologica I,
Dipartimento di Scienze
Neurologiche e Psichiatriche,
Policlinico,
P.zza G.Cesare, 11,
70124 Bari (Italy).
E-mail : m.detommaso@neurol.uniba.it.