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Authors
Rosenberg, Carl
Nudleman, Kenneth
Starr, Arnold

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Cognitive Evoked Potentials (P300) in Early Huntington's Disease

Carl Rosenberg, MD; Kenneth Nudleman, MD; Arnold Starr, MD, PhD

• **The P3 component of both auditory-event– and visual-event–related potentials of 13 patients with Huntington's disease was studied and compared with the P3 component of normal patients. The latencies of the patients' P3 components were compared with the latency-age regression lines generated by the normal population in both modalities. A P3 latency was considered abnormal if it fell above the 2-SE limit for the latency-age regression line. The incidence of normal or abnormal P3 latencies in the two modalities was compared with the results of computed tomography, electroencephalography, and neuropsychological testing. Nine patients had abnormal P3 latencies and ten patients had abnormal visual P3 latencies, with seven having abnormal latencies on both tests and 12 having abnormal latencies on one of the two tests. An abnormal P3 latency in one modality did not imply an abnormal P3 latency in the other. An abnormality of the P3 latency did not correlate with an abnormality in results from computed tomography, electroencephalography, or neuropsychological testing.**

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There are several components of event-related potentials recorded from the scalp using computer-averaging techniques that reflect cognitive processing.[1] One component, the P3, occurs at a modal latency at 300 ms in young adults and is recorded when a subject notes the presence of an infrequent signal embedded in a train of irrelevant frequent signals. The P3 component seems to be related to stimulus processing, either through context updating,[2] information content,[3] or uncertainty resolution.[4] The latency of this component is considered to be a measure of the speed of cognition and been shown to increase with age and in patients with dementing illness (J. M. Polich, L. Howard, A.S., unpublished data, 1984).[5-8] The P3 component is an electrophysiological marker in patients with disorders of cognition.

Huntington's disease is a genetically inherited disorder characterized by a gradual deterioration of mental function and chorea.[9] Disturbances of mood, memory, and personality may be the first features of the disease and can predate the appearance of motor signs.[10,11] This study evaluates the P3 component in patients with Huntington's disease and compares these event-related potential results with clinical evaluation, computed tomography (CT), electroencephalography (EEG), and neuropsychological tests.

SUBJECTS AND METHODS

Subjects

We studied 13 patients with Huntington's disease, including three men and ten women between the ages of 26 and 66 years. The diagnosis was confirmed by clinical examination and family history. The mean duration of symptoms in these patients was 4.8 years (SD, 2.4 years), with a range of one to nine years. Only one of the patients was living in a skilled-care facility and the others were living at home. Six patients were treated with haloperidol (Haldol) at the time of testing, with the maximum dose for any patient being 6 mg/day. One patient was receiving 75 mg/day of chloropromazine (Thorazine). The procedures were explained to all of the patients and informed consent was obtained.

Event-Related Potentials

Event-related potentials were recorded in an "oddball" paradigm in both the auditory and visual modalities. The subject was required to press a button when a rare target stimulus appeared interspersed in a train of frequent nontarget signals. For both modalities, the target stimulus had a probability of 20%. The event-related potentials for both the target and nontarget stimuli were averaged separately. Those trials that were incorrectly identified as target or nontarget were not included in the averages. Each patient was tested twice in each modality to replicate results. Silver chloride or gold-plated electrodes, secured to the scalp with electrode paste, were placed at F_z, C_z, and P_z (10-20 International Electrode System), and all were referenced to the right ear—A_2. All of the electrode impedences were less than 5 kΩ and the filter bandpass was set at 1 to 30 Hz with a 12-dB per octave rolloff. An oculogram utilizing electrodes above and below the eye was used to monitor eye movement. Three channels of EEG activity from F_z, C_z, and P_z, and one channel for the electro-oculogram, were analyzed for each stimulus modality.

In the auditory modality, a sequence of tonal signals was presented; the target tone had a fundamental frequency of 2,220 Hz and the nontarget tone had a fundamental frequency of 440 Hz. Each tone had an 8-ms rise, 12-ms fall, and 50-ms plateau. The target tone was 15 dB more intense than the nontarget tone. Stimuli were presented binaurally through earphones. The stimulus intensity was adjusted for each patient at a level determined to be "comfortable" yet still sufficient for the patient to distinguish easily between the target and nontarget tones. Thus, the intensities used ranged from a 60- to 90-dB sound-pressure level.

In the visual modality, two white characters on a black background were displayed on a television monitor: an "X" was the target, and an "O" was the nontarget. There was a delay between the computer signal used to time the onset of the visual stimulus and the appearance on the screen of the character, due to the rate of the raster of the television. The time delay was not constant for each trial, as the raster could be at any line when the computer triggered the appearance of the stimulus. Measurement of this time using a photoresistor circuit varied from 1 to 17 ms, with a mean of 9 ms. The values of the individual time delays were equally distributed throughout this range.

The event-related potentials were averaged for 1,000 ms and consisted of a 100-ms period prior to stimulus onset and a 900-ms period after the stimulus appearance. In both modalities the interstimulus interval was 1.5 s.

A test trial consisted of the presentation of 200 stimuli with the sequence of target or nontarget stimuli determined by a pseudorandom number generator of the computer.

The amplitudes and latencies of components, N1, P2, N2, and P3 were measured in the target averages at F_z, C_z, and P_z. N1 was defined as the first large negativity occurring with a latency of 70 to 120 ms. P2 followed N1 as the next large positive peak, with a latency range of 150 to 250 ms. N2 followed P2 as the next large negative deflection, and was succeeded by the P3 component. In many subjects, the P3 component could be divided into two subcomponents: the first, P3a, was largest at F_z; the second, P3b, was of maximal amplitude at P_z. The latency of the second subcomponent, the P3b, was used when two components were present. If only one component was present, the latency of the single component was used.

The electro-oculogram monitored vertical eye movement. The averaged potentials that were collected when there was little time-locked eye movement were accepted for analysis. Those averaged potentials with coincident eye movement were also accepted for analysis if the scalp distribution of the P3 component was larger at P_z than at F_z, indicating that the contribution of eye movement–related potentials to the P3 was probably insignificant. If these two

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From the Department of Neurology, University of California Medical Center at Irvine, Orange.

Reprint requests to Electrodiagnostics Laboratory, Route 13, University of California at Irvine Medical Center, 101 City Dr S, Orange, CA 92668 (Dr Rosenberg).

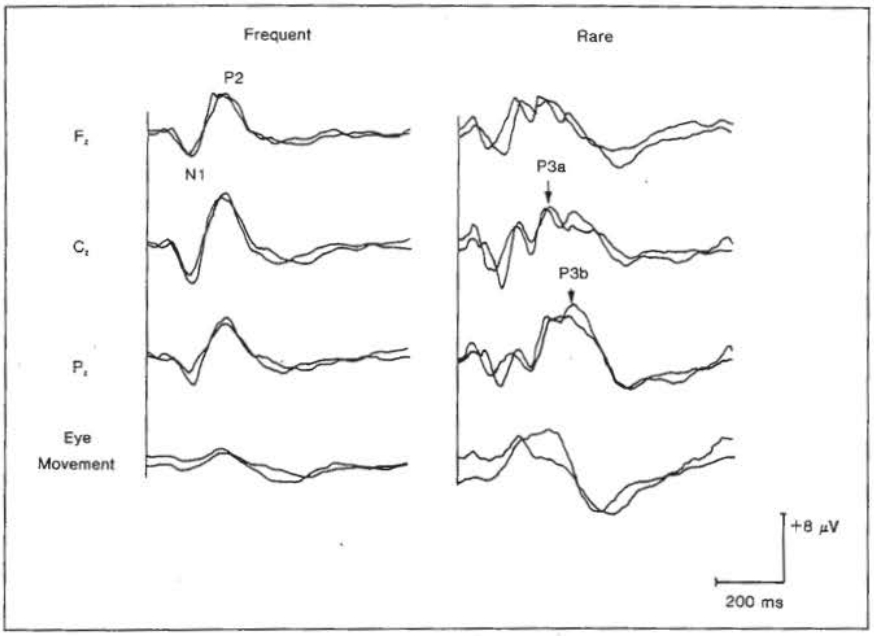

Fig 1.—Replicate event-related potentials and eye movements in response to auditory signals in normal subject (age, 50 years) and differences between target and nontarget averages. Note that scalp distribution of components P3a and P3b differ.

Mean N1 and P2 Component Latencies Measured at P_z

	Mean Latency, ms (SD)			
	Auditory Stimulus		Visual Stimulus	
Component	Normal Subjects	Patients	Normal Subjects	Patients
N1	102 (10)	122 (6)	106 (34)	114 (33)
P2	168 (15)	195 (26)*	183 (32)	188 (44)

*$P < .01$.

criteria were not met, the tracings were not included in the results.

The mean latencies of components N1 and P2 were compared with the normal values for the two modalities developed in our laboratory from individuals between the ages of 20 and 80 years (C.R., A.S., L.W. Meyer, unpublished data, 1983). The P3 latency of the patients with Huntington's disease was defined as abnormal if the absolute latency fell above twice the SE of the P3 latency-age regression line of the normal subjects for the same modality.

The results of the P3 measures in both modalities were compared with the results of 16-channel EEG, CT, neuropsychological testing, and the haloperidol medication history.

For each component, a normalized amplitude at F_z and P_z was calculated by defining the ratio of the amplitude at F_z or P_z to C_z. The P3 amplitude at C_z and the normalized amplitudes at F_z and P_z were compared between the patients and the normal subjects.

Ten of the 13 patients were also tested with a pattern-reversal stimulus to evoke sensory visual potentials. Each eye was tested separately with an alternating checkerboard pattern subtending 15° of visual field, with each check covering 60 minutes of arc. A stimulus rate of 1.1/s was used. Potentials were measured at O_z and 5 cm laterally, referenced to F_z. The filter bandpass was from 5 to 100 Hz. The latency of the P100 was measured at O_z and compared with the normative data used in our clinical laboratory, in which the upper limit of the P100 latency is 112 ms (+2.5 SD).

EEG

Ten of the 13 patients had an EEG, performed within one year of this study, that was made according to the guidelines of the American Electroencephalographic Society. Each EEG was classified as "normal," "low voltage," or "abnormal."

CT

Eleven of the 13 patients underwent CT scanning that was enhanced, unenhanced, or both. All of the scans were performed within one year of this study and classified as "normal," "caudate atrophy," "diffuse cortical atrophy," or a combination of caudate and cortical atrophy.

Neuropsychological Evaluation

Ten patients were tested with the Wechsler Adult Intelligence Scale Trails A and Trails B tests within 18 months of this study. One of us (K.N.) recorded a clinical impression of each patient's degree of dementia as "normal" or "impaired." The latter category was subdivided into "mild," "moderate," or "severe."

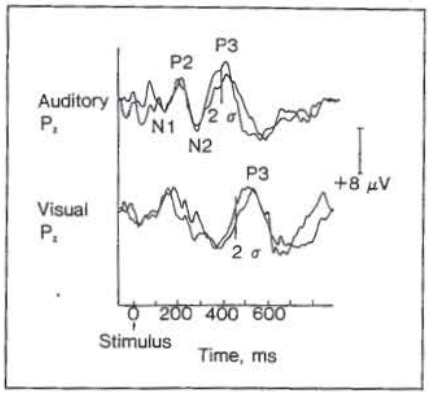

Fig 2.—Event-related potentials in response to auditory and visual stimuli in patients (age, 50 years) with Huntington's disease. Vertical line indicates 2-SE (2 σ) latency limit for age.

RESULTS

Event-Related Potentials

The patients performed well on both the auditory and visual tasks. The mean auditory reaction time was 414 ms (SD, 129 ms), with a range of 207 to 644 ms. The mean visual-reaction time was 451 ms (SD, 112 ms) with a range of 207 to 644 ms. There was a mean of six errors on the visual task, with a range of zero to 18 errors. By comparison, the mean auditory reaction time of the control subjects was 243 ms (SD, 60 ms) and their mean visual reaction time was 300 ms (SD, 85 ms), both being faster than those found in the patients. Statistically the differences were insignificant. The control mean number of errors was one in both the auditory and visual tasks.

Figures 1 and 2 show the potentials elicited to the target and nontarget stimuli (both auditory and visual signals) in both a normal subject and a patient. As neither the N1 nor the P2 latencies has a significant correlation with age in normal subjects, the patients' mean latency of these components was compared with the mean latency in normal subjects in both modalities. In the auditory modality the patients' P2 latency was significantly later than normal subjects' ($P < .01$; 195 vs 165 ms). There was no difference in the N1 latency to both auditory and visual stimuli, nor to the visual P2 latencies (Table).

The latencies of the P3 component to auditory and visual stimuli are plotted in Fig. 3. In the auditory modality, four patients had a normal P3 latency and nine patients had an abnormal P3 latency. In the visual

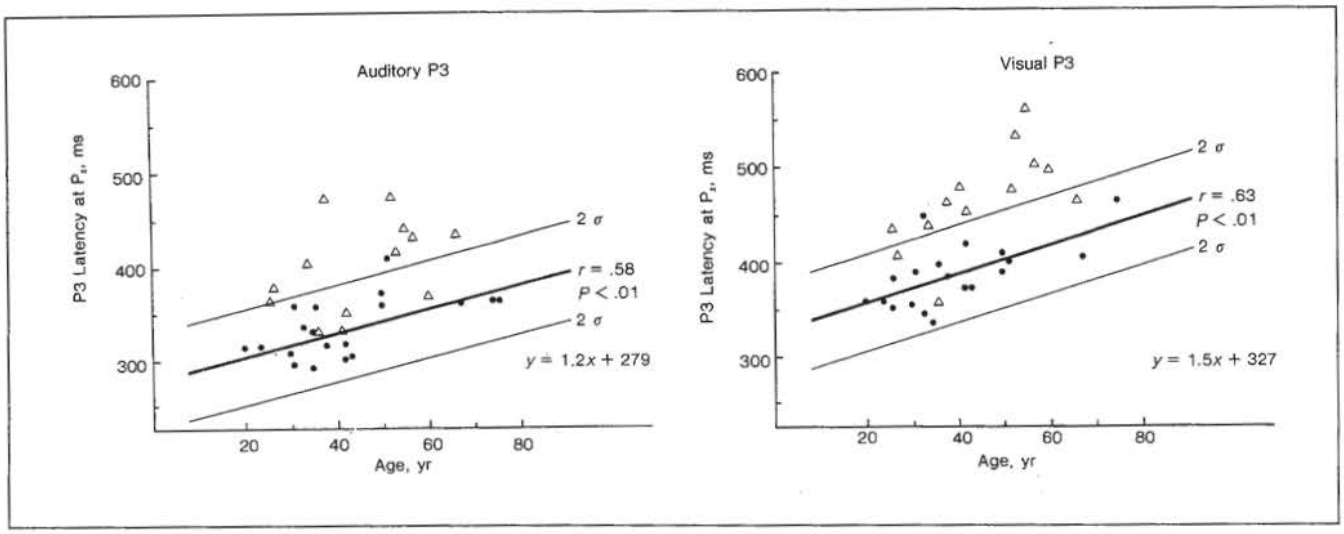

Fig 3.—P3 latencies of patients with Huntington's chorea (open triangles) on latency-age regression lines of normal subjects (closed circles) to both visual and auditory modalities. 2 σ indicates 2 SEs.

modality three patients had a normal P3 latency and nine patients had an abnormal P3 latency. One patient's visual P3 latency could not be measured because of excessive eye movement. An abnormal auditory P3 latency did not necessitate an abnormal result on the visual test or vice versa. Thus, of the nine patients with abnormal auditory P3 latencies, seven also had abnormal visual P3 latencies. Likewise, of the nine patients with abnormal visual P3 latencies, five also had abnormal auditory P3 latencies. Only one of the 13 patients had both a normal auditory and visual P3 latency. There were no significant differences in amplitude or normalized amplitudes at any of the scalp locations in either modality between the patients and the control subjects.

EEG

Six patients had normal EEGs, three had abnormal EEGs (diffuse slow activity), and one had a low-voltage EEG. There was no correlation between the P3 latencies and the status of the EEG in either modality.

CT

One patient had a normal CT scan, one patient had cortical atrophy only, five patients had only caudate atrophy, and four patients had atrophy of both the caudate nucleus and the cortex. There were no significant differences between the CT scans of those patients with normal P3 latencies compared with those patients with abnormal latencies.

Neuropsychological Evaluation

The mean full-scale IQ was 89 (SD, 16), with a range of 76 to 117; the mean verbal IQ was 91 (SD, 17), with a range of 71 to 118, and the mean performance IQ was 85 (SD, 18), with a range of 63 to 117. The mean difference between the verbal and performance IQs was 6 (SD, 12), with a range of −15 to 23. All of the patients who were tested had abnormal scores on the Trails A and the Trails B tests. In the clinical assessment of dementia, four patients were classified as normal, four as mildly affected, and five as moderately affected. There were no significant differences between those patients with normal and abnormal P3 latencies in relation to the results of these measures.

Haloperidol

Of the six patients taking haloperidol at the time of this study, two had normal auditory P3 latencies and one had a normal visual P3 latency. Of the remaining six patients (excluding the patient taking chlorpromazine), two had normal auditory P3 latencies and two had normal visual P3 latencies. There was no significant difference between the distribution of normal and abnormal P3 latencies between those patients taking haloperidol and those not taking haloperidol in either modality.

Pattern-Reversal Visual-Evoked Responses

The potentials from the right eye of one patient and from both eyes in another patient could not be interpreted because of movement artifact. In the remaining patients, the P100 latencies from both eyes were normal except in one patient, whose P100 from the right eye was prolonged (114 ms). The mean P100 latency from testing the right eye was 98.2 ms (SD, 3.9 ms), with a mean amplitude of 0.79 μV (SD, 0.50 μV). The mean P100 latency from testing the left eye was 97.5 ms (SD, 6.6 ms), with a mean amplitude of 0.71 μV (SD, 0.53 μV).

COMMENT

This study demonstrates a high incidence of abnormal P3 latencies of event-related potentials to auditory and visual stimuli in patients with Huntington's chorea. Nine patients had abnormal auditory P3 latencies and ten patients had abnormal visual P3 latencies. Twelve of the 13 patients had an abnormal latency in one of the two test criteria. The P3 latency did not correlate with the presence of cerebral or caudate atrophy, slowing on the EEG, or abnormalities in neuropsychological testing.

In this study, a P3 latency was abnormal if it fell outside twice the SE of the appropriate latency-age regression-line limits comparable with the 95% confidence limit in a two-tailed test, but when only one end of the distribution curve was used the confidence limit was 97.5%. The determination of normal limits attempts to balance the rate of false-positives and false-negatives. Ninety-five percent confidence limits are routinely used in the clinical pathology

laboratory and evoked-potential laboratories use 99.5% to 99.9% confidence limits (2.5 to 3 SD, one-tailed tests). Extending the normal range of the P3 latencies to the 99.9% confidence limits (3 SEs) demonstrates that five patients have an abnormal auditory P3 latency and six patients have abnormal visual P3 latencies. The number of patients with an abnormal latency on one of the two tests becomes eight. Utilizing 3-SE analysis did not yield correlations between P3 latencies and CT, EEG, or neuropsychological testing, as did testing with the SE of 2.5.

We also examined the possibility that performing two separate tests (ie, visual and auditory) effectively lowered the confidence limits of the one-tailed comparison from 97.5% to 95%, thus increasing the number of patients, who were classified as abnormal. Using a 2.3 SE as the criteria of the one-tailed test (98.8% confidence limit) yielded no major difference from the results seen using only twice the SE.

There are several other problems in using event-related cognitive potentials in a clinical setting. The first is in the establishment of the extent of variability of the P3 latency in normal subjects. Our normative data had an SE of 26 ms, which compares favorably with the results reported by others: Goodin et al,[5] 21 ms; Syndulko et al,[12] 22.4 ms; Brown et al,[13] 28.6 ms; Polich et al (unpublished data, 1984), 32 ms; and Picton et al,[8] 35 ms). In contrast, Pfefferbaum et al[7] reported an SE almost twice that of the other normative data—51 ms in their auditory task and 58 ms in their visual task. The possibilities to account for such a range of variability include (1) differences in task, (2) differences in the method of defining the P3 peak latency, (3) sample size, and (4) the selection of individuals to be placed in the sample. We used a select group of normal subjects; all of them had graduated college and many had postgraduate training. All of our subjects were in excellent health. In our task, we required a button press with the result that only correct responses were included in the determination of target P3 latency.

Certainly, some aspects of intellect such as digit span show an inverse correlation with P3 latency (J. M. Polich, L. Howard, A.S., unpublished data, 1984). Attention to the cognitive backgrounds of the control subjects certainly could affect the designation of both the mean and variance of P3 latency.

The adjective "early" is appropriate in our population of patients. The mean duration of symptoms was only 4.8 years, which is small compared with a 12-year life expectancy after the appearance of symptoms. Huntington's disease is characterized by a progressive deterioration of motor and mental functioning resulting in the inability to perform many of the simplest of daily activities. The patients in our study were, with one exception, all living at home. The one patient who required skilled care was relatively preserved intellectually but had severe motor impairment. The degree of intellectual deterioration in our patient population can be estimated from the results of neuropsychological testing, in particular on the full-scale IQ test. The lowest full-scale IQ measured in our population was 76, just below the lower limit of normal (80). Our patients' mean score was 89, which is within the normal range.

The P3 latency was abnormal in at least one of the two modalities in 92% of the patients. This rate of abnormality was similar to the rate of abnormality seen in these patients with CT scanning (9/10), and on the Trails A and Trails B tests (8/8). The rate of abnormality of the P3 latency was greater than that seen with EEG (4/10) and on the full-scale Wechsler Adult Intelligence Scale (2/8, with the lower limit of normal being 80). Consideration of the performance and verbal scores separately did not enhance the definition of abnormality.

The pathologic characteristics of Huntington's disease include diffuse cortical atrophy with wide neuronal loss, especially in the caudate nucleus and the third, fifth and sixth layers of the cerebral cortex.[14] Autopsy studies are generally derived from individuals who died in the later stages of the disease. The variability of symptoms and signs in this disease suggests that the sequence of affected structures can vary from patient to patient and, perhaps, account for the delay in cognitive procession of one modality and not the other. The finding of a normal P100 latency on the visual-evoked potential eliminates a disorder of transmission time along the primary visual pathway as the explanation of the prolonged visual P3 latencies. One can postulate that the processing of various sensory modalities are differentially affected in individuals with Huntington's disease.

None of the findings of EEG studies or neuropsychological testing are specific for Huntington's disease, whereas isolated caudate atrophy combined with the clinical examination is diagnostic of the disease. The P3 latency is also a nonspecific measure of dysfunction. A prolongation of P3 latency in patients with dementias of various causes has been described.[5] Moreover, the mean P3 latency of patients with Parkinson's disease has been shown to be longer than the mean latency of age matched control subjects.[6] There is also evidence that the P3 latency can be "normal" in a significant proportion of patients with dementia.[7] In our study, the probability of detecting an abnormal P3 latency was enhanced by testing two different sensory modalities.

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References

1. Hillyard SA, Kutas M: Electrophysiology of cognitive processing. *Ann Rev Psychol* 1983; 34:33-61.

2. Donchin E: Event related brain potentials, in Begleiter H (ed): *Evoked Brain Potentials and Behavior.* New York, Plenum Publishing Corp, 1979, pp 13-88.

3. Courchesne E: Changes in P3 waves with event repetition: Long-term effects on scalp distribution and amplitude. *Electroencephalogr Clin Neurophysiol* 1978;46:754-766.

4. Sutton S: P300 13 years later, in Begleiter H (ed): *Evoked Brain Potentials and Behavior.* New York, Plenum Publishing Corp, 1979, pp 107-126.

5. Goodin DS, Squires KC, Henderson BH, et al: Age related variations in evoked potentials to auditory stimuli in normal human subjects. *Electroencephalogr Clin Neurophysiol* 1978;44:447-458.

6. Hansch EC, Syndulko K, Cohen ZI, et al: Cognition in Parkinson's disease: An event-related potential perspective. *Ann Neurol* 1982;11:599-607.

7. Pfefferbaum A, Wenegrat BG, Ford JM, et al: Clinical application of the P3 component of event-related potentials: II. Dementia, depression and schizophrenia. *Electroencephalogr Clin Neurophysiol* 1984;59:104-124.

8. Picton TW, Stuss DT, Champagne SC, et al: The effects of age on human event-related potentials. *Psychophysiology* 1984;21:312-325.

9. Paulson GW: Diagnosis of Huntington's disease. *Adv Neurol* 1979;23:177-184.

10. Klawans HL, Goetz CG, Perlik S: Presymptomatic and early detection in Huntington's disease. *Ann Neurol* 1980;8:343-347.

11. Lyle OE, Gottesman II: Subtle cognitive deficits as 15 to 20 year precursors of Huntington's disease. *Adv Neurol* 1979;23:227-238.

12. Syndulko K, Hansch EC, Cohen SN, et al: Long-latency event related potentials in normal aging and dementia, in Courjon J, Maugierer F, Revol M (eds). *Clinical application of Evoked Potentials in Neurology.* New York, Raven Press, 1981, pp 279-286.

13. Brown WS, Marsh JT, LaRue A: Expotential electrophysiological aging: P3 latency. *Electroencephalogr Clin Neurophysiol* 1983;55:227-285.

14. Shoulson I, Chase TN: Huntington's disease. *Ann Rev Med* 1975;26:419-436.