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# Sequential changes in the P3 component of the auditory evoked potential in confusional states and dementing illnesses

**Article abstract**—The P3 component of the auditory evoked potential has been shown to reflect “endogenous” processes related to cognition. This component was measured serially in seven patients who had confusional states or dementing illnesses that fluctuated in severity over time. The latency of P3 component reflected the clinical impression of changes in mental function for each of the patients. These results suggest that the P3 component of the auditory evoked potential provides an objective serial measure of cognitive state that may be useful in following patients with dementing illnesses and in evaluating the effectiveness of any specific therapy.

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**The serial evaluation of cognitive function** presents a special problem for the neurologist. Traditionally, clinical examination and specialized neuropsychological testing have been the methods used to evaluate mental function. Unfortunately, these methods frequently depend upon subjective interpretation, and the testing procedures themselves can be so time-consuming that they are impractical as serial measures of cognitive ability. Also, these testing procedures may show apparent fluctuations in cognitive skills that relate to the interaction of the patient with the examiner rather than to actual changes in the patient's clinical condition. These factors combine to make the assessment of mental function extremely difficult, and there is a great need in neurology for an objective and more easily administered serial measure of cognitive state in patients with dementing illnesses.

One approach might be the use of sensory evoked potentials, which have recently been used as objective serial measures of sensory function, especially in difficult-to-test populations and where changes may not be clinically evident.<sup>12</sup> Unfortunately, these “stimulus-related” components do not reflect electrical activity in those areas of the brain thought to be involved with cognition and, thus, are unlikely to be of much use in the assessment of mental status. It seems reasonable, however, that analogous procedures might well be developed using the “event-related” potentials that have been closely associated with cognitive function.<sup>1,2,6-10</sup> Indeed, we recently reported that the latency of the event-related P3 component of the auditory evoked potential was markedly delayed in patients with dementia of various etiologies.<sup>4</sup> Consequently, in the present study, we investigated whether or not the latency of the P3 component accurately reflects the variations in cognitive function that result from disease progression or improvement. This paper reports the findings in seven patients with prominent changes in mental status who were studied with this evoked potential technique during a 2½-year period.

**Method.** Seven patients with marked changes in

mental status during their illness were studied with serial evoked potential studies of their P3 component latency during the course of their illnesses.

The evoked potential procedure has been described previously.<sup>4,5</sup> Briefly, an audio tape was prepared containing 400 tone bursts (50-msec duration; 10-msec rise/fall times; 60 dB HL). The tones were presented binaurally through earphones at a rate of one tone every 1.5 seconds. Eighty-five percent of the tones had a frequency of 1,000 Hz, and 15% had a frequency of 2,000 Hz. The stimulus sequence was random with the constraint that no two rare (2,000-Hz) tones occurred consecutively.

All patients were able to hear the tones clearly and distinguish the two pitches. Each patient was instructed to count silently the occurrences of rare, high-pitched tones and report the total number at the end of the block of trials. Each patient was able to perform this task, although the accuracy of the count was widely variable.

Silver disk electrodes were affixed to the scalp at F<sub>z</sub>, C<sub>z</sub>, and P<sub>z</sub>, referred to linked mastoid electrodes. Additional electrodes were positioned superior and lateral to the right eye in order to monitor any systematic potentials due to eye blinks or movements. The electroencephalogram was amplified 10,000 times with a bandpass of 0.3 to 70 Hz. Evoked potential waveforms were averaged separately for the rare and frequent tones for 768 msec, beginning at tone onset.

The P3 component latencies were obtained from the evoked potential waveform elicited by the rare (2,000-Hz) tone by extrapolating lines from the leading and trailing slopes of the peak and measuring the latency of the intersection of the lines. The latency measures reported here were obtained from the waveform recorded from the C<sub>z</sub> electrode. The waveforms recorded at the other two electrode sites were used to help define the P3 component. The P3 latencies (L) obtained were then compared to the normal latency for the patient's age established previously,<sup>4,5</sup> and the variation from normal converted to units of standard error ( $\sigma$ ). The equation used for calculating the normal latency (L<sub>N</sub>) of the P3 component (in

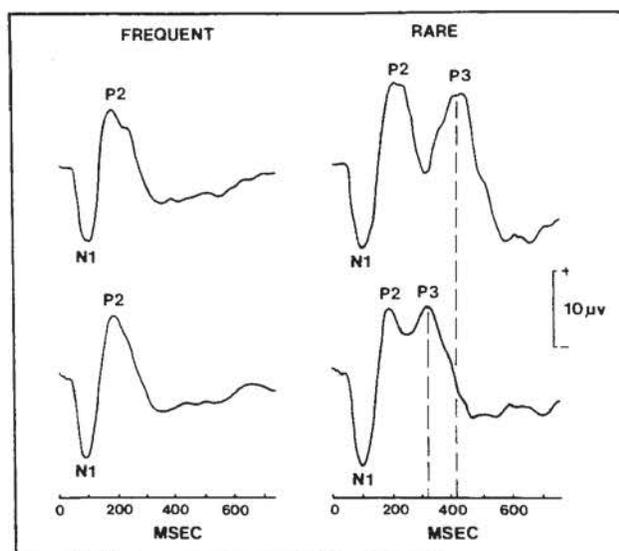


Figure 1. Evoked potential waveforms from patient 1 obtained for the frequent and rare tones recorded from a  $C_2$  electrode referenced to linked mastoids. The evoked potential waveforms in the top row were obtained when the patient was confused, and those in the bottom row were obtained after the patient had recovered. Note that the P3 component is present in both rare-tone waveforms and that its latency has decreased by almost 100 msec between the two clinical conditions, while the N1 and P2 latencies have remained stable.

msec) as a function of age is:

$$L_N = 310 + (\text{Age} - 15) \times 1.64$$

The formula used for calculating the deviation of the P3 latency ( $L_D$ ) from normal in units of standard error is:

$$L_D = (L - L_N) / 21$$

In addition to the traditional bedside evaluation of mental function, the "Mini-mental State" (MMS) examination of Folstein et al<sup>3</sup> was administered at the time of evoked potential test sessions to provide a uniform numerical measure of mental status. A score of 25 or less of a possible 30 points was considered consistent with dementia.

**Results.** An example of the typical evoked potential waveforms obtained for the two tones is shown in figure 1. To the frequent tone the characteristic negative (N1) and positive (P2) components of the auditory "vertex" potential was obtained. To the rare tone, in addition to the N1 and P2 components, a large positive component (P3) could also be identified. The upper panel of figure 1 shows the frequent and rare tone waveforms obtained when the subject had an altered mental status marked by confusion, and the lower panel shows the equivalent waveforms obtained after recovery. It can be seen that, with recovery, the P3 latency decreased dramatically ( $-90$  msec;  $-3.22 \sigma$ ), while the N1 and P2 latencies were unchanged (see table, patient 1 for details). For

comparison, a normal subject tested with this procedure ten times in a 2-month period had a spread of only 15 msec ( $0.75\sigma$ ) in the latency of the P3 component.

Brief case histories of all seven patients and a tabulation of the clinical impressions, mini-mental state scores, and P3 latency measurements are presented in the table and illustrated in figure 2. In each case, except subject 3's third P3 study, a clinical impression of improved mental state was associated with a decreased P3 latency, while a clinical impression of deterioration in mental state was associated with an increased P3 latency. Additionally, the magnitude of the change in P3 latency seemed to reflect the magnitude of the clinical change.

**Discussion.** The "stimulus-related" evoked potentials have been used extensively in clinical situations to test the function of specific sensory pathways, but cannot be used to test the higher cognitive aspects of sensory utilization. The "event-related" or "endogenous" potentials, however, have been shown to be intimately related to cognition<sup>1,2,6-10</sup> and might well serve as a tool to monitor cognitive state in clinical situations. In our previous studies, we have shown that the latency of the "event-related" P3 component is sensitive to variations in mental status and can discriminate between patients with neurologic and psychiatric disorders.<sup>4,11</sup> Thus, in our limited experience, patients who may appear demented but are actually depressed have normal P3 latencies, while patients with dementia have abnormal P3 latencies.

The present results, obtained by sequential testing of seven patients, further extend the possible clinical uses of the P3 latency. In addition to distinguishing pseudodementia from dementia, it seems to provide a sensitive indicator of fluctuations in mental state experienced by individual patients as a result of changes in their underlying illness. In each of our patients, a decrease in the P3 latency was associated with clinical improvement in mental function, while a prolongation in P3 latency was associated with clinical deterioration. Unlike the routine sensory evoked potential latencies that may remain abnormal even when function has been restored,<sup>12</sup> the P3 latency seems to reflect dynamic aspects of cognitive function in neurologic illnesses that affect cognition. This is not to suggest, however, that a measurement of P3 latency can replace the clinical exam in the evaluation of cognitive function of an individual. Rather, it complements the exam by providing an objective measure of cognitive function that corresponds well with the clinical impression. In this respect it seems clearly superior to other measures, such as the MMS score, which may show only small changes when both the clinical impression and P3 latency show wide fluctuations (eg, patients 1, 2, 3, 4, and 5).

All variations in mental status, however, do not

Table. Summary of electrical and clinical findings

Pt	Age/Sex	Diagnosis	Date*	Clinical impression of mental state	MMS <sup>†</sup> score	P3 latency <sup>‡</sup> (msec)	Comments on mental status
1	60/M	Hyponatremia	0	Markedly confused	—	—	Disoriented; short attention span; vs poor recent and remote memory; 0/3 objects at 3 min
			9 d	Improved	28	420 (+1.06σ)	Mentation very slowed, otherwise normal
			2 w	Recovered	29	330 (-3.22σ)	Mentation quick; marked improvement from before
2	45/F	Multiple sclerosis (definite)	0	Normal	30	360 (+0.2σ)	—
			1 y	Isolated memory loss	29	380 (+1.05σ)	Alert, oriented, able to calculate; poor recent memory; 2/3 objects at 3 min
			1 y	Confused	7 <sup>§</sup>	440 (+2.86σ)	Disoriented, uncooperative, poor calculations; decreased recent and remote memory; short attention span; 0/3 objects at 3 min
			1 d	Slightly less confused	23	440 (+2.86σ)	Partially oriented and more cooperative; otherwise no change
			9 m	Isolated memory loss	26	340 (-0.95σ)	Fully recovered except for memory; 1/3 objects at 3 min
3	40/F	Subdural hematoma	0	Confused	19	420 (+3.24σ)	Disoriented; poor attention span; poor calculations; impaired recent and remote memory; 0/3 objects at 3 min
			1 y	Increased confusion	13	567 (+5.43σ)	Disoriented, poor attention span; unable to calculate; poor recent and remote memory; 1/3 objects at 3 min
			1 m	Slightly improved	17	576 (+5.85σ)	Partially oriented; able to do only simple calculations; memory still impaired; 1/3 objects at 3 min
			1 y	Markedly improved	19	378 (+1.45σ)	Completely oriented; calculations much improved; memory still impaired; 1/3 objects at 3 min
4	49/F	Coma after thoracotomy	0	Coma	—	—	—
			3 w	Confusion	0 <sup>§</sup>	642 (+13.86σ)	Disoriented; continuously palpating objects; occasionally repeating what examiner said but would not respond to commands
			3 m	Markedly improved	24	427 (+3.62σ)	Alert, oriented, able to do some calculations; 2/3 objects at 3 min
5	54/F	Hydrocephalus	2 m	Recovered	27	366 (+0.75σ)	—
			0	Demented	—	422 (+2.24σ)	Alert, oriented, unable to calculate; poor recent and remote memory; 0/3 objects at 3 min
6	52/F	Phenobarbital overdose	2 y	Improved	27	366 (+0.75σ)	Alert, oriented, able to do simple calculations, improved long-term memory; 0/3 objects at 3 min
			0	Confused	24	414 (+2.14σ)	Oriented; short attention span; unable to calculate or reverse numbers; 3/3 objects at 3 min
7	47/M	Hepatic encephalopathy	3 m	Recovered	30	402 (+1.43σ)	—
			0	Confused	0 <sup>§</sup>	456 (+4.42σ)	Pt awake but would not respond to questions
			1 d	Slightly improved	10	438 (+3.57σ)	Disoriented; unable to calculate; unable to follow commands; 0/3 objects at 3 min
			1 m	Recovered	30	390 (+1.29σ)	—

\* Date of subject's examination: 0 is arbitrary starting point, and each subsequent date is time from previous exam: d = day, w = week, m = month, y = year.

<sup>†</sup> Mini-mental State score of Folstein et al<sup>3</sup> (see text).

<sup>‡</sup> Numbers in parentheses are latencies converted to units of standard error (see text).

<sup>§</sup> Scores considered unreliable because patients were not fully cooperative during testing.

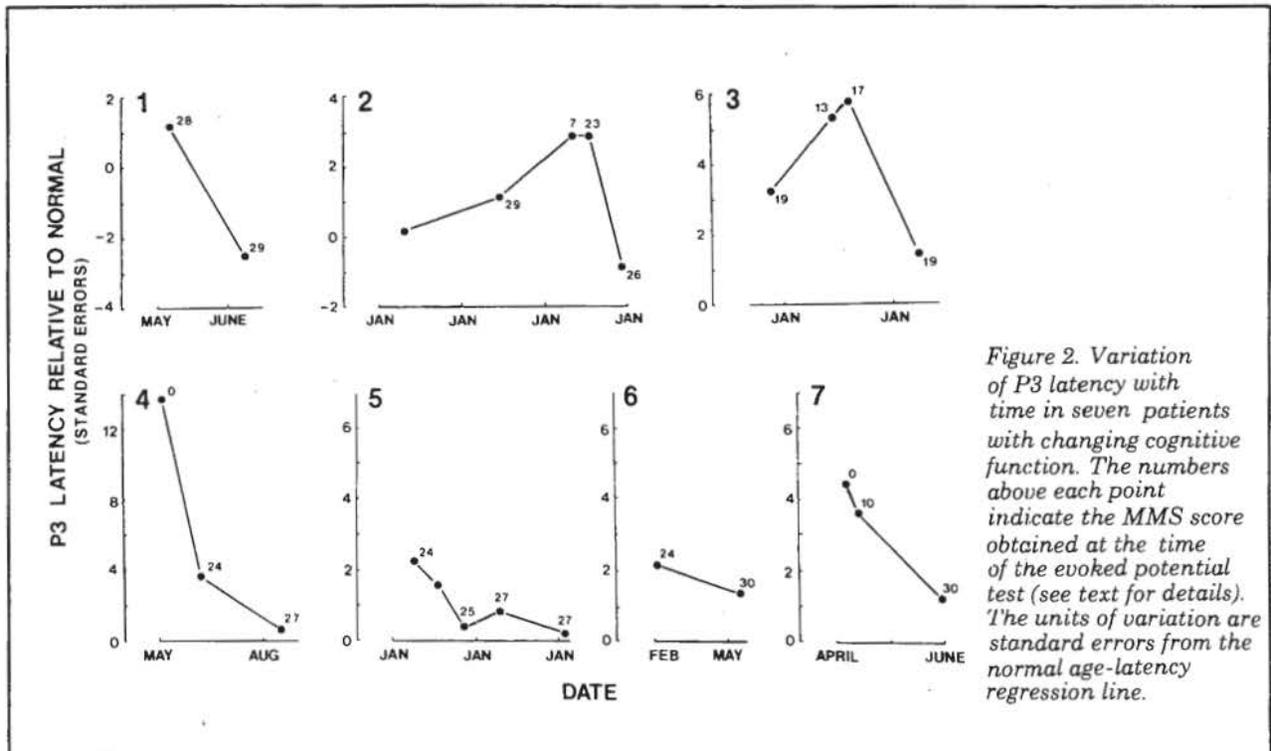


Figure 2. Variation of P3 latency with time in seven patients with changing cognitive function. The numbers above each point indicate the MMS score obtained at the time of the evoked potential test (see text for details). The units of variation are standard errors from the normal age-latency regression line.

result in P3 latency shifts, so caution must be exercised when using P3 latency to follow patients with restricted cognitive deficits. Indeed, we have observed one patient in whom discrete lesions producing a profound and isolated amnesic syndrome were associated with an unequivocally normal P3 latency.<sup>4</sup> Similar examples are presented by our patients 2, 3, and 5, in whom the residual cognitive deficits were largely restricted to memory impairment, and in whom P3 latencies were normal. It seems likely that the simple task used in these studies to generate the "event-related" potentials does not depend to a great extent upon short-term memory. Perhaps, with the proper selection of tasks and testing conditions, these "event-related" potentials can be useful in patients with restricted cognitive deficits, but this is, at present, only speculative and the subject of current study. The principal conclusion of the present study is that the P3 latency may provide an objective measure with which to serially follow cognitive function in patients with dementing illnesses and with which to evaluate the effectiveness of any specific therapy.

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