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# LONG LATENCY EVENT-RELATED COMPONENTS OF THE AUDITORY EVOKED POTENTIAL IN DEMENTIA

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## INTRODUCTION

EVOKED potentials are now used as an objective test of afferent function in patients with neurological and sensory disorders (Starr, 1978). The testing of the optic nerves in multiple sclerosis (Feinsod, Abramsky and Auerbach, 1973; Halliday, McDonald and Mushin, 1972; Namerow and Enns, 1972; Richey, Kooi and Tourtellotte, 1971), the evaluation of hearing in infants and retarded individuals (Galambos and Hecox, 1977; Rapin and Schimmel, 1977; Starr, Amlie, Martin and Sanders, 1977), and the definition and location of brain-stem lesions (Starr and Hamilton, 1976; Stockard and Rossiter, 1977) are particular examples of successful application of evoked potential measures to neurological disease.

There is also a need in neurology for an objective measure of the physiological state of those areas of the brain which are involved in perception and cognition. The presence of normal, or near normal, sensory evoked potentials does not guarantee that sensory information is actually utilized. For example, perfectly normal auditory brain-stem potentials may be recorded from comatosed patients who are not responsive to acoustic stimuli (Starr and Achor, 1975) and visually evoked cortical potentials have been recorded from individuals who were behaviourally blind (Bodis-Wollner, Atkin, Raab and Wolkstein, 1977). Thus, even though evoked potentials may indicate that an afferent system is intact, a deficit in other neural structures can render the input functionally useless.

There are certain components of the evoked potential, however, that seem to be associated with cognitive processes. Evoked potentials may be separated into two sets of components; 'stimulus-related' components that are sensitive to the physical characteristics of the stimulus, and 'event-related' components that are dependent on the information content of the stimulus (Sutton, Braren, Zubin and John, 1965). Event-related potentials appear only when a subject 'attends' to stimuli, and then only when a stimulus has meaning for the subject. They may also

appear in the absence of stimulus-related potentials when the eliciting event is the omission of an expected stimulus (Weinberg, Walter and Crow, 1970; Picton and Hillyard, 1974).

The event-related potentials have relatively long latencies (greater than 150 ms) and are of largest amplitude at the midline overlying the parietal lobes and posterior frontal lobes (Picton and Hillyard, 1974; Simson, Vaughan and Ritter, 1977), structures which have traditionally been considered as being involved in cognition. The stimulus-related potentials, on the other hand, occur at shorter latencies (less than 180 ms) and include the far-field reflection of events rising from sensory pathways within the brain-stem and spinal cord (Cracco and Cracco, 1976; Jewett and Williston, 1971; Wiederholt and Iraqui-Madoz, 1977) and cortical potentials distributed for the most part over the primary sensory regions (for example, over the occipital lobes for visual stimuli, over the central regions for somatosensory and acoustic stimuli, Goff, Allison and Vaughan, 1978).

The most prominent of the event-related potentials is the P3 component, a positive wave occurring at a latency of 300 to 500 ms. Many studies with normal subjects have linked the P3 component to processes involved in perception and cognition (*see* Tueting, 1978, or Donchin, Ritter and McCallum, 1978, for a review). In particular, the latency of the P3 component is closely correlated with the latency of decision processes, when such latencies are measured by behavioural reaction time (Kutas, McCarthy and Donchin, 1977; Ritter, Simson and Vaughan, 1972; Roth, Ford and Kopell, 1978; Squires, Donchin, Squires and Grossberg, 1977). Thus, any factor which modifies the timing of neural mechanisms underlying perception and cognition may conceivably be reflected in changes in the latency of the P3 component. It was our hypothesis that neurological disorders characterized by altered mental functions might be associated with an alteration in the P3 component.

Dementia is a cardinal example of disordered cognitive function. The affected individual has deficits in attention, memory and the processing of sensory input. This study was conducted to determine whether patients with dementia would show alterations in the P3 component. Fifty-three patients were tested. Twenty-seven of the patients were demented, and the other 26 had normal mental functions. The evoked potentials from these patients were compared with data collected previously from 40 normal adult subjects ranging in age from 15 to 76 years (Goodin, Squires, Henderson and Starr, 1978).

## METHODS

### *Subjects*

The first group of patients consisted of 16 females and 11 males, ranging in age from 25 to 80 years, who were diagnosed as demented by clinical neurological assessment. The aetiologies of their disorders were established by appropriate laboratory procedures. Their mental function was quantified in our laboratory by the Mini-mental Status examination (Folstein, Folstein and McHugh, 1975) and a mark of 25 or less out of a possible 30 points was used to define dementia. Normal subjects with no known

disease usually scored either 29 or 30 points on this test. The range of scores for the demented group was 12 to 25, with a mean of 20.7 ( $\pm 3.8$ ). The diagnoses and mean mental status examination scores for this group are shown in Table 1.

TABLE 1. DIAGNOSES AND MENTAL-STATUS EXAMINATION SCORES OF THE DEMENTED PATIENTS

	No.	MMS*
Presenile dementia	9	18.0*
Metabolic encephalopathy***	5	18.0
Hydrocephalus	5	20.6
Cerebrovascular disease	2	21.5
Brain tumour	1	17.0
Uncertain aetiology	5	21.8
Mean	27	20.7

\* Mini-mental Status score (MMS) based on test of Folstein *et al.* (1975). \*\* One patient could not be tested and is not included in the calculations. \*\*\* Hypothyroidism, alcoholic with severe electrolyte disturbances, anoxia (2), steroid encephalopathy.

The second group of patients consisted of 12 females and 14 males ranging in age from 19 to 78 years. None was considered by the neurologists to have any deficit in mental function. The scores on the mental status examination for this group ranged from 27 to 30, with a mean of 28.8 ( $\pm 0.84$ ). The diagnoses and mean mental status examination scores for this group are shown in Table 2.

TABLE 2. DIAGNOSES AND MENTAL-STATUS EXAMINATION SCORES OF THE NON-DEMENTED PATIENTS

	No.	MMS*
Multiple sclerosis	4	29.0
Depression	4	28.5
Cerebrovascular disease	3	28.7
Parkinson's disease	3	29.3
Schizophrenia	2	27.5
Hydrocephalus	1	29.0
Porencephalic cyst	1	30.0
Miscellaneous**	8	29.8
Mean	26	28.8

\* Mini-mental Status score (MMS) based on test of Folstein *et al.* (1975). \*\* Diabetic neuropathy, causalgia, bilateral subdural haematoma, diffuse cortical atrophy, anosmia with left arm weakness, gait apraxia (2), vertigo.

#### Procedure

It was important to develop a procedure which could be used in a clinical electrodiagnostics laboratory. Consequently, the procedure had to be designed such that it could be completed in a single short-duration testing session; the equipment required for stimulus generation and evoked potential recording had to be kept at a minimum, the behavioural task had to be simple and not require any preliminary training, and finally, the evoked potential results had to be easily quantified.

An audio tape was prepared containing four hundred tone bursts (50 ms in duration with 10 ms rise/fall times and an intensity of 55 dB SL). The tones were presented binaurally through earphones at a rate of one every 1.5 s. Eighty-five per cent of the tones had a frequency of 1000 Hz and 15 per cent a frequency of 2000 Hz. The stimulus sequence was random with the constraint that no two rare (2000 Hz) tones appeared in succession.

Each patient was first presented with a portion of the tape containing the tone sequence. The patient was then questioned about what was heard. Testing was continued if the patient was able to clearly hear the tones and distinguish between the two pitches.

The patients were then instructed to count and keep a mental record of the number of rare tones in the sequence and to report the total at the end of the run. They were also cautioned to refrain from moving their eyes and to avoid movements associated with counting. Normally the sequence was presented twice to each patient. The total testing procedure was usually completed in thirty minutes.

Silver disc electrodes were affixed to the scalp at  $F_z$ ,  $C_z$  and  $P_z$  with collodion and referred to linked mastoids. Additional electrodes were positioned superior and lateral to the right eye in order to monitor eye-related potentials. The electroencephalogram was amplified 10,000 times with a bandpass of 0.3 to 70 Hz. The evoked potential waveforms were averaged separately for the rare and frequent tones for 768 ms (6 ms per point) following the onset of tone.

The amplitudes and latencies of the various peaks of the averaged evoked potentials were measured from x-y plots of the waveforms. Peak latencies and amplitudes of the stimulus-related N1 and P2 components of the evoked potentials were obtained from the evoked potentials for the frequent (1000 Hz) tone. The amplitude of the stimulus-related potential was taken as the voltage difference between the N1 and P2 peaks. The peak latency for the P3 component was obtained from the potentials evoked by the rare (2000 Hz) tone by extrapolating lines from the leading and trailing slopes of the peak and measuring the latency at the intersection of the lines. The amplitude of the P3 component was taken at the most positive point of the peak, regardless of whether it matched the latency derived from extrapolation, and was measured with respect to a baseline voltage over the first 50 ms of the waveform. The bandpass of the recording system effectively attenuated the brain-stem and middle-latency potentials that occur in this time period (Picton, Hillyard, Krausz and Galambos, 1974), making this portion of the waveform flat. All latency and amplitude measures were derived from the  $C_z$  waveform; the waveforms for the other two electrode sites were however used to help define the components.

## RESULTS

### *Task Performance*

Normal subjects had no trouble performing the task. In virtually every case their count was within two or three of the actual number of rare-tone presentations. The neurological patients who were not demented were also able to perform the task satisfactorily. They were, however, susceptible to losing count and their tallies were more variable than for the normal subjects. Many of the demented patients were also able to perform the task, though their counts were widely variable. When patients were apparently unable to carry out the task or to maintain their attention to the tonal stimuli, frequent reminders to listen for the 'different' tones were given by one of the examiners. These reminders were adequate since the patients were co-operative and highly motivated to please the examiners, even though they sometimes had difficulty remembering the task.



### Evoked Potentials

(1) *Normal subjects.* Evoked potential waveforms recorded from the vertex ( $C_2$ ) for a normal subject are shown in fig. 1. The waveform for the frequent tone shows the characteristic negative (N1) and positive (P2) components of the auditory 'vertex potential' (Davis and Zerlin, 1966) with latencies of about 100 and 200 ms, respectively. These components are considered to be stimulus-related since they are elicited by both rare and frequent tones. The evoked potential for the rare tone, however, was quite different, being characterized not only by the stimulus-related components but also by a large event-related positive component labelled P3.

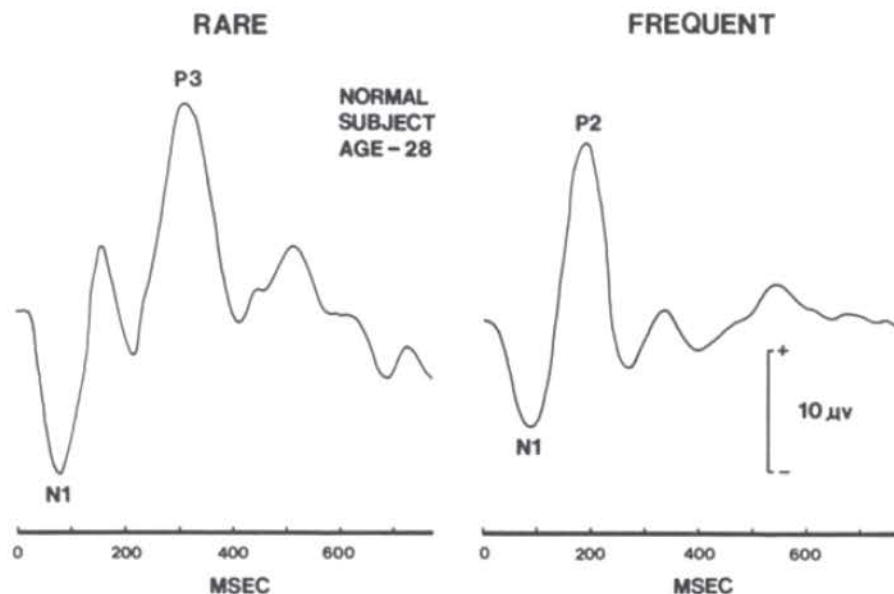


FIG. 1. Evoked potential waveforms recorded between the vertex ( $C_2$ ) and linked mastoids for a normal subject. The potential evoked by the rare tone is on the left and the potential evoked by the frequent tone is on the right. In these and all subsequent figures positive voltage at the vertex is plotted upwards.

In a previous report we described changes in the amplitudes and latencies of the evoked potential components in normal subjects as function of age using this experimental procedure (Goodin *et al.*, 1978). The results of a standard regression analysis, in which the best-fit straight line was derived to describe the changes in each component as a function of age, are summarized in Table 3. The resulting regression equations for each component (defined by the slope as a function of age and the intercept value at age 15 years) indicated that, in general, the evoked potential components both shifted to longer latencies and decreased in amplitude with increasing age. This was most striking for the P3 component. A calculation of the expected change in P3 latency between ages 15 and 75 from the regression equation revealed an increase of nearly 100 ms (from 310 ms at age 15 to 408 ms at age 75). A similar calculation for the P3 amplitude yielded a decrease of about 11  $\mu\text{V}$  (from 14.9  $\mu\text{V}$  to 4.1  $\mu\text{V}$ ) over that age range. Smaller amplitude and/or latency changes were seen for the stimulus-related components.

TABLE 3. AGE-RELATED VARIATIONS IN THE AMPLITUDES AND LATENCIES OF AUDITORY EVOKED POTENTIAL COMPONENTS FOR NORMAL SUBJECTS AGED 15 TO 76 YEARS

	Slope	Correlation coefficient	Standard error about regression line	Value at age 15 yrs	Significance
N1 latency	0.13 ms/yr	0.228	8 ms	94 ms	—*
P2 latency	0.74 ms/yr	0.560	19 ms	168 ms	$P < 0.001$
P3 latency	1.64 ms/yr	0.810	21 ms	310 ms	$P < 0.001$
N1-P2 amplitude	-0.15 $\mu\text{V}/\text{yr}$	-0.420	5.56 $\mu\text{V}$	15.6 $\mu\text{V}$	$P < 0.01$
P3 amplitude	-0.18 $\mu\text{V}/\text{yr}$	-0.476	5.84 $\mu\text{V}$	14.9 $\mu\text{V}$	$P < 0.005$

\* Non-significant

(2) *Patients.* Evoked potential waveforms ( $C_z$ ) for one normal subject, one neurological patient without dementia and one demented patient are shown in fig. 2. Because of the effect of age on the evoked potential components, three individuals of approximately the same age were selected for the figure. The peak latencies for the normal subject are indicated by the dashed lines. A comparison of the waveform peaks for the two patients with the dashed lines illustrates the principle findings of this study. The latency of the P3 component for the demented patient (Mini-mental Status score 22) was 50 ms greater than for the normal subject, while the latency for the non-demented neurological patient (Mini-mental Status score 29) was nearly the same as for the normal subject (10 ms earlier).

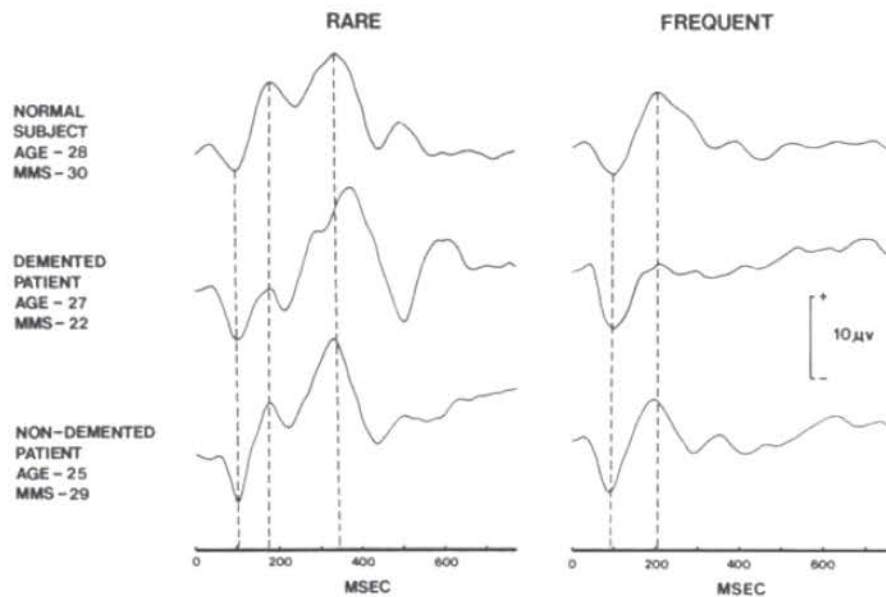


FIG. 2. Evoked potential waveforms for the rare and frequent tones recorded between the vertex ( $C_z$ ) and linked mastoids for a normal subject (*top*), a demented patient (*middle*) and a non-demented patient (*bottom*). MMS = Mini-mental Status score (see Table 1).

The P3 latencies for the normal subjects and the patients are plotted as a function of age in fig. 3. The upper panel shows the results for the normal subjects with the calculated regression line and the lines indicating one and two standard deviations ( $\sigma$ ) superimposed. In the middle and bottom panels the results for the demented and non-demented patients, respectively, are plotted with the regression and standard deviation lines for the normal subjects superimposed.

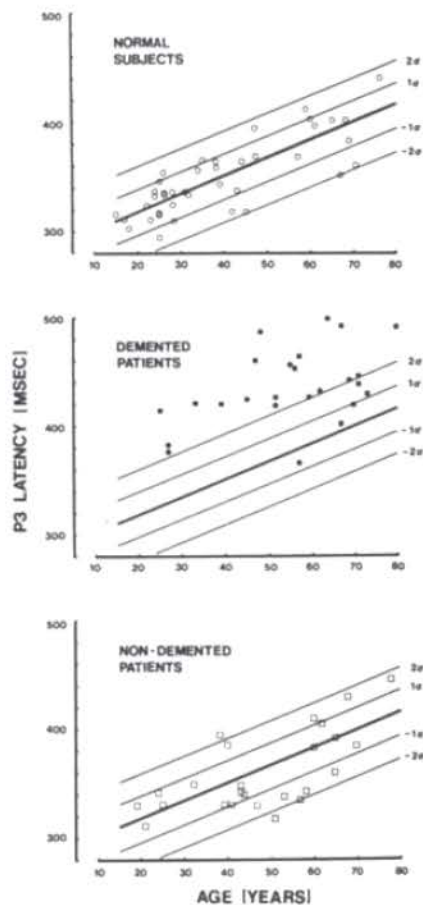


FIG. 3. The latencies of the P3 component are plotted as a function of age for normal subjects (*top*), demented patients (*middle*) and a non-demented patients (*bottom*).

Of the 53 patients tested, a reliable measure of the P3 latency could not be made in just 3 cases; 2 demented patients and one non-demented patient. One of the patients (demented) would not be still during the test and the waveforms were contaminated by muscle artifact. For the other 2 patients, the evoked potentials consisted of the N1 and P2 components followed by a broad positivity between 300 and 500 ms without any clear peak.

It is clear from fig. 3 that the P3 latencies for patients with dementia generally exceed the normative values for each patient's age. Only one demented patient had a P3 latency which was shorter than the norm and 80 per cent had a P3 latency



which exceeded the norm by two or more standard deviations. The distribution of the P3 latencies for the patients without dementia was essentially identical to that for the normal subjects.

TABLE 4. DEVIATIONS FROM NORMAL OF THE AMPLITUDES AND LATENCIES OF AUDITORY EVOKED POTENTIAL COMPONENTS FOR DEMENTED AND NON-DEMENTED PATIENTS

		Mean deviation from normal ( $\sigma$ )	$t(df=62)$	Significance
N1 latency	Dementia	$0.50 \pm 1.46$	1.58	—*
	Non-dementia	$0.39 \pm 1.00$	1.49	—
P2 latency	Dementia	$-1.10 \pm 1.3$	0.36	—
	Non-dementia	$0.46 \pm 1.2$	1.69	—
P3 latency	Dementia	$2.83 \pm 1.5$	8.88	$P < 0.001$
	Non-dementia	$0.11 \pm 1.3$	0.20	—
N1-P2 amplitude	Dementia	$-0.24 \pm 1.50$	0.99	—
	Non-dementia	$0.36 \pm 1.30$	1.26	—
P3 amplitude	Dementia	$-0.60 \pm 0.97$	2.31	$P < 0.05$
	Non-dementia	$0.23 \pm 1.19$	0.82	—

\* Non-significant.

Table 4 presents an analysis of the amplitudes and latencies of the various evoked potential components for the two groups of patients compared to normal values for each patient's age. The values are expressed in terms of their deviation from the appropriate regression line for normal subjects. For example, the P3 latency deviation for each patient was obtained by subtracting the expected P3 latency for the patient's age from the actual latency, and the difference was divided by the standard deviation about the normal regression line (for the P3 latency this was 21 ms, *see* Table 3). This procedure converts the data to a form where direct comparisons with normal can be made regardless of age. The magnitude of any deviation can also be interpreted on a statistical basis in terms of the probability that it is within a defined normal range.

The non-demented patients did not differ significantly from normal for any of the amplitude or latency measures. The demented patients also did not differ significantly from normal in terms of their N1 and P2 components. However, the latency of the P3 component for the demented patients was significantly greater than normal, and the amplitude of the P3 component was significantly smaller than normal.

A breakdown of the mean P3 latency deviations from normal for the various subgroups of patients is presented in Table 5. These results demonstrate the consistency of the latency effect within the various diagnostic categories.

TABLE 5. MEAN DEVIATION FROM NORMAL IN P3 LATENCY FOR PATIENTS

Demented patients	$\Delta P3$ latency ( $\sigma$ )
Presenile dementia	+2.30*
Metabolic encephalopathy	+3.87*
Hydrocephalus	+2.32
Cerebrovascular disease	+3.06
Brain tumour	+4.00
Uncertain aetiology	+3.51
Mean	+2.93
Non-demented patients	
Multiple sclerosis	+0.32
Depression	-0.54
Cerebrovascular disease	-0.26
Parkinson's disease	+0.94
Schizophrenia	+0.90
Hydrocephalus	-0.93
Porencephalic cyst	+0.83
Miscellaneous	-0.15*
Mean	-0.02

\* One patient could not be assigned a P3 latency and is not included in the computation.

## DISCUSSION

This study demonstrates that impaired mental functioning in dementia is highly correlated with changes in the latency and amplitude of the P3 component of the auditory evoked cortical potential. As a group, the patients with dementia had P3 components which were both delayed in latency and smaller in amplitude than normal. These changes in the P3 component cannot be attributed to the presence of a nervous system disease *per se* or to being in hospital. This is demonstrated by the results from the control group of non-demented patients, which were within the normal range. The P3 changes apparently stem from the underlying dementia regardless of the aetiology (*see* Table 5).

The magnitude of the P3 latency increase with dementia was, on the average, 2.93 standard deviation units from normal, and reliably separated the patients with dementia from both normal subjects and from neurological patients with normal mental function. Twenty of the 25 demented patients who had identifiable P3 components had a P3 latency which exceeded the normal value for the patient's age by more than two standard deviations. For 12 of the demented patients the latency difference exceeded three standard deviations. In contrast, only one non-demented patient had a P3 latency that exceeded the predicted value by more than two standard deviations, which would be expected merely on statistical grounds. Thus, if a P3 latency which exceeds normal by two standard deviations is adopted as the criterion for electrophysiologically defining dementia, a rate of 5 per cent false positives would be expected while 80 per cent of the patients with dementia

would be correctly classified. This suggests that the P3 latency can provide a sensitive and perhaps specific test for dementia. Such a test would be extremely useful in distinguishing dementia from psychiatric disorders such as depression or schizophrenia which may be accompanied by an apparent, but not actual, deterioration in mental function. Four patients with depression and 2 with schizophrenia were tested here and all had normal latency P3 components. Clearly, however, a more extensive investigation of the effects of psychiatric illness on the P3 component is required before the reliability of this distinction between psychosis and dementia can be fully documented.

The amplitude of the P3 component also changed (decreased) in dementia, but the magnitude of the change was small relative to the normal variation in the measure ( $0.60 \sigma$ , Table 4). Thus, it is unlikely that the P3 amplitude alone can provide a measure of mental function which is adequate for assessing individual patients.

This procedure seems eminently suitable for the testing of patients. Of the 53 patients examined, only 3 did not have a reliable P3 component. We did not, however, test patients who were unco-operative or who had gross involuntary movements which might have interfered with the recordings.

It is unclear to what extent the task of counting the rare tones is itself involved in eliciting the P3 component. Several of the demented patients probably did not understand the task. Clear P3 components, however, were present for the rare tones but not the frequent ones, even for those patients. From an operational standpoint it would appear then that the sequence of tones itself is in some instances sufficient to induce the differential cognitive processing of the rare and frequent tones. Similar results have been reported for normal subjects (Ritter *et al.*, 1968; Roth, 1973).

While patients with dementia showed changes in the P3 component of the cortical potential, there were no significant effects on the earlier stimulus-related components, N1 and P2. In a previous study of visual evoked potentials, Visser, Stam, Van Tilburg, Op Den Velde, Blom and De Rijke (1976) reported significant latency changes for peaks corresponding to the stimulus-related components. The differences between their results and those reported here may be either due to a modality difference or to the fact that they failed to compensate for age differences between their normal subjects and their demented patients, which can affect visual evoked potential latencies (Celesia and Daly, 1977).

The cognitive changes associated with senescence and dementia may be distinguished on the basis of differential effects on the various components of the evoked potential. The normal aging process is associated with a significant effect on the latency of both the P2 and P3 components, though the former change is smaller than that for the P3. However, if in dementia P2 and P3 changes occurred in the same ratio as they did for normal aging, the P2 latency change would have amounted to approximately 25 ms. The lack of any significant change in the P2 component other than that associated with aging clearly distinguishes the

physiological processes affecting evoked potentials in aging and dementia. This is particularly relevant in the case of presenile dementia which has been suggested to be due to an accelerated aging process (Terry, 1976). For the senile patients tested here, there was a clearly significant change in the mean P3 latency ( $2.30 \sigma$ , 48 ms) without a concomitant change in P2 latency ( $-0.16 \sigma$ ,  $-3$  ms).

One possible explanation for the increase in P3 latency found in dementia is that the demented patients were slow in identifying and processing the stimuli relative to the normal subjects or non-demented patients. In normal subjects, increases in both task difficulty (Ritter *et al.*, 1972; Squires *et al.*, 1977) and task complexity (Kutas *et al.*, 1977) prolong the P3 latency, presumably because the decision processes involved take longer to complete. The increased decision latencies can also be inferred from behavioural reaction times (c.f. Squires *et al.*, 1977). In such situations proportional changes in the latencies of the stimulus related components are not found (Ritter *et al.*, 1972). Thus, there seems to be a parallel between the effects of dementia and the effects of increasing task difficulty in normal subjects on the latencies of the stimulus-related and event-related potentials. The possibility exists that in both instances the sequence of processes following the occurrence of the stimulus-related components, N1 and P2, require an increased amount of time and this is reflected in a change in the P3 latency.

In conclusion, the P3 latency appears to provide a measure for objectively defining dementia. As a clinical tool it is sensitive enough to differentiate a large proportion of demented patients from normal (nearly 80 per cent) with a low rate of false positives (5 per cent). In an electrodiagnostics laboratory the procedure can be readily implemented, it is applicable to most patients, and the resulting data can be easily analysed once normative data has been collected on a wide age range of normal subjects. These findings also raise the possibilities for experimental analysis of the cognitive factors contributing to the P3 component and their alterations following neurological lesions.

#### SUMMARY

Long-latency auditory evoked potentials were recorded from two groups of patients, with and without dementia, and were compared with those from a population of normal subjects ranging in age from 15 to 76 years. A sequence of tones of two different frequencies (1000 Hz and 2000 Hz) was presented and each patient was asked to count the occurrences of the rare ( $P = 0.15$ ) tones in the sequence. Evoked potential waveforms were averaged separately for the rare and frequent tone.

Of the various evoked potential components elicited by the tones, the P3 component (latency 300–500 ms) was found to be the most sensitive to aging in normal subjects. It was also the only component which could be used to differentiate between the demented patients and the normal subjects or non-demented patients.



The non-demented patients did not differ from normal in any waveform measure. The magnitude of the latency change of the P3 component in dementia relative to normal was sufficiently large that it may provide a practical and objective measure of dementia in a clinical setting.

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