Journal of Neurology, Neurosurgery, and Psychiatry 1988;**51**:1120–1125

Auditory long latency event-related potentials in Alzheimer's disease and multi-infarct dementia

RYUJI NESHIGE, GEOFF BARRETT,* HIROSHI SHIBASAKI

From Division of Neurology, Department of Internal Medicine, Saga Medical School, Nabeshima, Saga City, Japan

SUMMARY An auditory discrimination paradigm was employed to elicit event-related brain potentials in 13 patients with Alzheimer's disease and 14 patients with multi-infarct dementia. The P300 latency was significantly prolonged in 12 patients with dementia compared with age-matched controls and showed a significant negative correlation with the score of Wechsler Adult Intelligence Scale (WAIS), especially with that of Digit Span subtest. There was no disease specificity. After physostigmine treatment, P300 latency decreased and WAIS score increased in 6 among 10 cases.

A long-latency component of the event-related potential (ERP), especially P300, occurs when a subject attends and discriminates stimulus events which differ from one another along some dimension (for example intensity, duration or modality).[1] P300 has been reported to be associated with cognitive processing,[2] and the temporal lobes including hippocampus and amygdala have been proposed as its possible generator sites.[3 4] Thus, any factor which modifies the timing of neural mechanisms underlying perception and cognition may lead to changes in the morphology or latency of P300. There is a general consensus that P300 latency evoked by an auditory target stimulus increases with age by 1·0 to 1·8 m s per year for ages ranging from 20 to 80 years.[5–9]

Goodin *et al*[10] demonstrated that P300 latency in demented patients was significantly prolonged as compared with normal controls regardless of the aetiology of dementia. This finding has been supported by other subsequent studies.[7 11] Furthermore, Goodin and Aminoff[12] distinguished between cortical and subcortical dementia by comparing each component of event-related potentials.

The purpose of this study was to examine the utility of P300 as a diagnostic test of dementia both in Alzheimer's disease (AD) and in multi-infarct dementia (MID); to clarify whether there is a correlation between P300 measures and intelligence quotients (IQ) in demented patients; and to evaluate the effect of physostigmine on IQ as well as P300.

*Visiting scientist from Medical Research Council External Scientific Staff, The National Hospital for Nervous Diseases, London, UK.

Address for reprint requests: Ryuji Neshige MD, Department of Internal Medicine, Saga Medical School, Nabeshima, Saga City, Saga, 840-01 Japan.

Received 29 January 1988 and in revised form 13 April 1988.
Accepted 15 April 1988

Materials and methods

Subjects

Thirteen patients with clinically definite Alzheimer's disease (AD) (9 females and 4 males, mean age 74 years; range 60 to 82 years, mean Wechsler Adult Intelligence Scale (WAIS) score = 69) were diagnosed on the basis of the criteria proposed by the NINCDS-ADRDA work group.[13] All patients showed dementia of insidious onset and slow progression, and had no other systemic or brain diseases that could account for the progressive memory disturbance and other cognitive deficits. Other causes of dementia were eliminated by appropriate laboratory tests. A group of 14 patients with multi-infarct dementia (MID) consisted of 4 females and 10 males (mean age 74; range 66 to 82 years, mean WAIS score = 67) who were diagnosed by clinical, EEG and CT findings. Hachinski's ischaemic score[14] was 5 or above in all cases of MID.

Every patient selected showed only a mild to moderate disability since severely demented patients were not capable of performing the test. As normal controls, data of 27 healthy subjects previously reported by us[5] were used to compare the age-related parameters, and data of nine oldest subjects among those 27 were used to compare the non-age-related parameters (see *Statistical analysis*).

WAIS was tested, without knowledge of P300 results, on the day of P300 recording or no more than 2 days apart. The battery consisted of Verbal Scale determined by six subtests and Performance Scale determined by five subtests.

Five patients each with AD and with MID were given physostigmine with the initial daily dose of 2 mg by mouth divided into four doses during the daytime. The dose was

gradually increased up to 10 mg per day and was maintained on that level for a week. Approximately 2 weeks after starting the medication, tests of P300 and WAIS were repeated. Each test was actually initiated 30 minutes after the first or the second dose of the test day.

Task and recording procedures

Each subject participated in an oddball paradigm using auditory stimulation. The stimulus was a pure tone delivered binaurally through light headphones at an intensity of 75 dB SPL and with the interstimulus interval of 1·4 s. Tones of two different frequencies, 1 kHz and 2 kHz, were presented at a rate of 85 and 15%, respectively, in a random order. The subject responded to the target stimulus by pressing a push-button with his right index finger. The push-button was connected to a lamp which was observed by the experimenters to assess the response capability and accuracy. When patients were unable to maintain their attention to the tones, frequent reminders to perform the task were given by one of the examiners. Two hundred artifact-free trials were averaged in each of two runs of an experiment. Responses from two runs were combined so that averages were based on approximately 340 sweeps for frequent stimuli and 60 sweeps for targets.

EEG activity was recorded from scalp electrodes at Fz, C3, Cz, C4, P3, Pz and P4 (International 10–20 system) which were referred to linked ear lobe electrodes. An electro-oculogram (EOG) was recorded by referring an electrode at the glabella to a lateral suborbital electrode below the right eye. Inter-electrode impedance was reduced to below 3K ohm. Time constant of amplifiers was 3 s and the high frequency cut-off was set to 1 kHz. Trials including artifact were excluded from the averages. Activity was sampled for a total of 768 ms (including a 75 ms pre-stimulus period) at an ordinate period of 1·5 ms. The peak amplitude was measured with respect to the prestimulus baseline.

STATISTICAL ANALYSIS

I. Criteria for abnormalities

1. Amplitude of all components and latencies of N1 and P2

We have studied P300 in 27 healthy subjects of various ages,[5] and found that the above parameters were not related to age. In the present study, therefore, nine oldest subjects among those 27 were used as age-matched normal control for intergroup comparison. Student's *t* test with a one-way analysis of variance was used for statistical analysis.

2. Latencies of N2 and P300

N2 and P300 latencies in individual patients were defined as abnormal if the values were outside the 95% confidence limits based on the regression equation of latencies on age obtained from our previously studied 27 normal subjects.[5] As these parameters were found to be related to age,[5] the intergroup differences were tested with an analysis of covariance by using data standardised with respect to age. In other words, the actual latency values for each individual subject were standardised to the values for the age 61 years according to the regression equation of normal group. This standard age was determined as the mean age of all subjects, patients and healthy controls inclusive.

II. Correlation between P300 parameters and WAIS

Linear regressions were performed between the latencies as well as amplitudes of P300 and the scores obtained from WAIS tests for each patient group.

III. Comparison before and after physostigmine treatment

P300 latencies and WAIS scores before and after physostigmine treatment were compared by paired *t* test for all of the 10 patients treated.

Results

I. Comparison of ERP wave forms among three groups

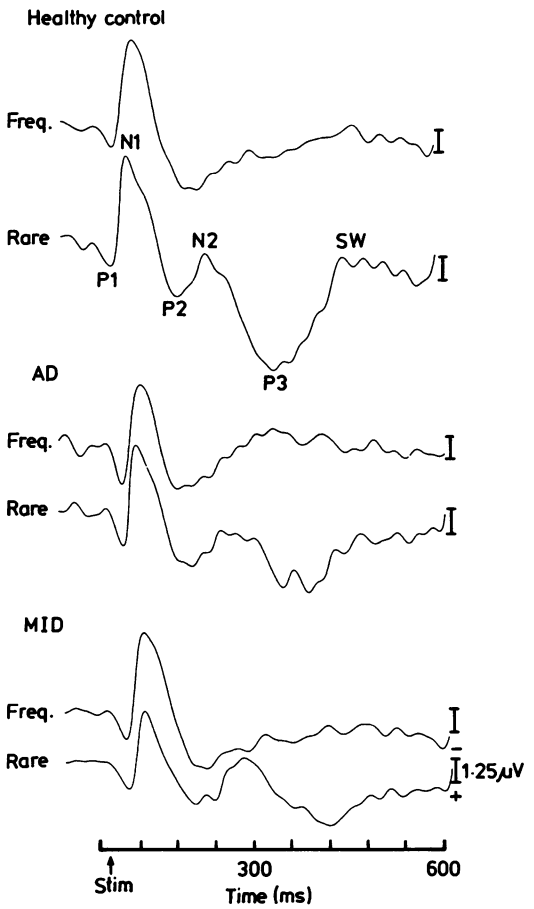

Fig 1 *Grand mean waveforms of event-related potentials in response to frequent and rare (target) tones in the auditory oddball stimulus paradigm for healthy aged controls and patients with Alzheimer's disease (AD) and multi-infarct dementia (MID). Healthy aged controls were selected from our normative data pool.[5] P1, N1 and P2 showed no difference between the three groups. N2 and P300 latencies in the two dementia groups were significantly prolonged compared to the normal group.*

Table 1 *Component latency (ms) and amplitude (μV) in Alzheimer's disease, multi-infarct dementia and normal controls. Mean (standard deviation)*

Component	*AD (n = 13)*	*MID (n = 14)*	*Normal (n = 9)*
N1			
Latency	94·2 (16·0)	89·5 (10·2)	101·0 (16·9)
Amplitude	−2·8 (2·1)	−2·2 (1·9)	−2·7 (2·3)
P2			
Latency	191·5 (27·5)	197·8 (25·1)	180·4 (25·5)
Amplitude	4·2 (2·9)	3·2 (2·9)	4·3 (2·2)
N2			
Latency*	252·0 (25·9)†	268·7 (25·5)†	223·4 (28·1)
Amplitude	1·1 (1·8)	−0·14 (2·0)	−0·89 (3·8)
P300			
Latency*	415·1 (42·0)†	414·4 (34·5)†	356·0 (26·4)
Amplitude	8·2 (4·2)	6·6 (4·3)	9·5 (5·9)

Task: Button, Recording: Pz

†$p < 0.001$ (compared with control).
*As these parameters were found to be related with age, the inter-group comparison was made with an analysis of covariance by using the standardised data with respect to age (standard age = 61). Student's *t* test was used for other parameters.

All three groups showed waveforms which were essentially the same in amplitude and morphology (fig 1). In every group, ERPs to target rare tone stimuli showed a prominent P300 component which was not evident in the ERPs to the frequent tone. P1, N1 and P2 appeared to be different in latency among the three groups (fig 1), but the difference did not reach the statistical significance (table 1).

N2 and P300 latencies in the two dementia groups were significantly prolonged compared with the normal group (fig 1, table 1). N2 latency in all patients but one of each patient group was greater than the predicted mean value for their age. N2 latency was above the 95% confidence limits in 17% of AD patients and in 38% of MID patients. P300 latencies of all demented patients were greater than the predicted mean value for their age (fig 2). P300 latency was above the 95% confidence limits in 46% of AD patients and 43% of MID patients. With regard to amplitude of N1, P2, N2 and P300, there were no statistically significant differences between patients and aged controls or between AD and MID (table 1).

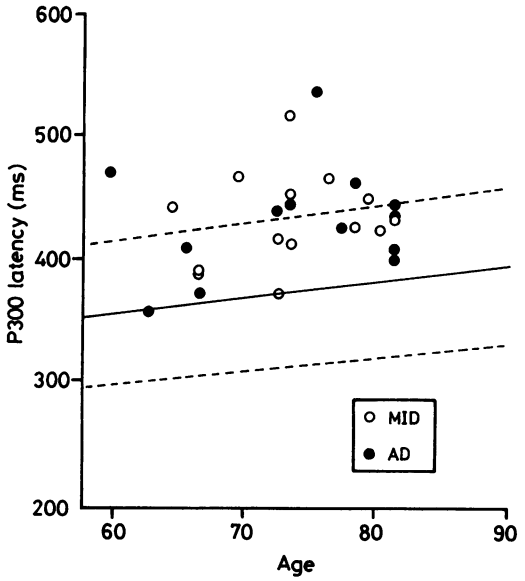

Fig 2 *P300 latency of each individual patient plotted against age along with a part of the linear regression (solid line) and 95% confidence limits for 27 neurologically normal adults taken from our previous study.[5] P300 latency in demented patients was above the 95% confidence limits in 46% of AD patients and 43% of MID patients.*

II. Correlation between P300 and WAIS

In the demented patients P300 latency showed a

Table 2 *Degree of association of WAIS with P300 latency*

	Both disease n = 27 r	*AD n = 13 r*	*MID n = 14 r*
Full Scale	−0·71†	−0·75*	−0·69
Verbal	−0·63*	−0·74	−0·52
1 Range of information	−0·51	−0·50	−0·54
2 Comprehension	−0·37	−0·76*	0·01
3 Arithmetic reasoning	−0·51	−0·55	−0·49
4 Similarity	−0·61*	−0·60	−0·64
5 Digit span	−0·63*	−0·64	−0·64
6 Vocabulary	−0·36	−0·49	−0·21
Performance	−0·66*	−0·72	−0·60
7 Digit symbol	−0·60*	−0·75*	−0·47
8 Picture completion	−0·61*	−0·72	−0·51
9 Block design	−0·43	−0·61	−0·26
10 Picture arrangement	−0·49	−0·34	−0·64
11 Object assembly	−0·51	−0·19	−0·74*

* = $p < 0.01$.
† = $p < 0.001$.
Task: Button, Recording: Pz.

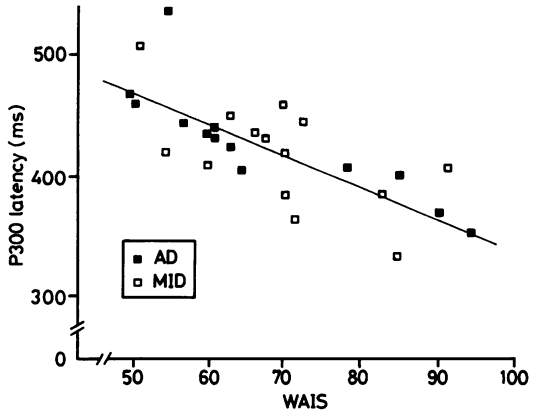

Fig 3 *P300 latency and WAIS in patients with AD and MID. P300 latency in demented patients showed a significant negative correlation with WAIS score. The negative correlation with WAIS score was more significant in patients with AD than in those with MID.*

AD: $r = -0{\cdot}747$ $p < 0{\cdot}01$, MID: $r = -0{\cdot}687$ $p < 0{\cdot}05$
Total: $r = -0{\cdot}710$ $p < 0{\cdot}001$

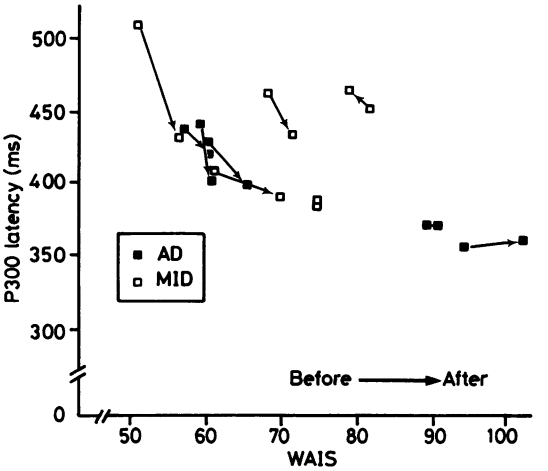

Fig 4 *P300 latencies and WAIS scores in patients with dementia before and after the administration of physostigmine. In general, the direction of change was comparable in the two measures.*

significant negative correlation with WAIS scores, that is, shorter P300 latencies were associated with higher WAIS scores (fig 3, table 2). Patients in the AD group tended to have higher correlations between P300 latency and WAIS scores than those in the MID group, but only the Comprehension subtest yielded a correlation which was significantly different between the two groups ($p < 0{\cdot}025$). P300 amplitude in demented patients did not correlate with WAIS scores.

III. Change after physostigmine treatment

In six among 10 patients who were given physostigmine, P300 latency reduced and WAIS scores increased after the medication (fig 4). In two cases, medication made no difference to either P300 latency or WAIS scores. In one MID case, the WAIS score decreased and P300 latency became longer. The mean reduction of P300 latency was 18·7 ms (paired $t = 2{\cdot}23$ NS) and the mean increase in WAIS score was 3·4 points (paired $t = 3{\cdot}8$, $p < 0{\cdot}01$). Thus, in general, the direction of change in P300 latency and WAIS scores was as expected from the regression line shown in fig 3. In fact, seven of 10 patients showed a change in P300 latency in the direction predicted from the change in WAIS score ($p = 0{\cdot}055$, Sign test). With regard to the effect of physostigmine on the WAIS subtests, Picture Arrangement showed the greatest improvement followed by Comprehension. All but two patients were unaware of change in their own performances. Those two cases showed improvement in both P300 latency and WAIS score. Side-effects consisting of nausea and diarrhoea developed in one AD patient at the daily dose of 6 mg. There were no changes in pulse rate, blood pressure, serum electrolytes or liver function tests.

Discussion

The principal findings in this study are (1) a significantly increased latency in approximately 45% of both AD and MID patients for the P300 component of the auditory ERP, (2) a high correlation between P300 latency and WAIS score in demented patients, and (3) a close correspondence between changes in P300 latency and WAIS scores following the administration of physostigmine.

All patients in the present series had P300 latencies greater than the mean values expected from the normal regression equation on age in spite of the fact that all cases had only a mild to moderate disability. This pattern has been found across the previously reported studies[7 10 11] and supports the hypothesis that P300 latency is strongly affected by dementing illness. However, the proportion of cases with significantly delayed P300 latency was well below the rate described in those with dementia (80%) (Goodin *et al*[10]) and in those with AD (83%) (Syndulko *et al*[7]). Brown *et al*[11] also reported that P300 latency was significantly prolonged in more than half of 15 demented patients. However, Pfefferbaum *et al*[15] reported that P300 latency was significantly prolonged in fewer than 50% of demented patients. The main difference between those reports seem to lie in the response task required of the subject. Goodin *et al*,[10] Syndulko *et al*[7] and Brown *et al*[11] had their

subjects keep mental count, whereas Pfefferbaum *et al*[15] and ourselves used a button-pressing task which might be easier to perform than the count task.

N2 latency in our patient groups was also significantly prolonged compared with the normal control. Ritter *et al*[16] and Goodin *et al*[17] reported that N2 and P300 latencies changed almost identically with increasing task difficulty. Since, in the present study. P300 latency was beyond 95% confidence limits in a larger number of demented patients than N2 latency, P300 might be more sensitive to dementing illness than N2.

In the present study, P300 latency was shown to be strongly correlated with WAIS score. The highest negative correlation with P300 latency among the subtests of WAIS was seen for Digit Span, followed by Digit Symbol. The Digit Span subtest involves the oral repeating of two series of numbers one forward and one backward. The observed association between P300 latency and Digit Span, therefore, suggests that these measures may index common dimensions of disrupted cognitive processing. In the clinical interpretation of the WAIS,[18] the Digit Span subtest allows a rapid check on verbal short term memory and attention. According to Hansch *et al*,[19] a high correlation between Symbol Digit Modality test scores and P300 latency was observed in Parkinson's disease. By testing 20 neurologically normal subjects, Polich *et al*[20] found a negative correlation between P300 latency and Digit Span. Most recently, Homberg *et al*[21] also demonstrated in Huntington's disease that P300 latency was highly correlated with neuropsychologic tests especially requiring concept formation and selective attention.

The P300 component has been associated with a variety of cognitive processes. P300 latency is considered to reflect the speed of neural events underlying perception and discrimination of the target or rare stimulus; matching that particular information against stimulus categories in memory; and making an appropriate decision whether to respond or not.[22 23] Thus, slowed neural processing involved in stimulus evaluation or decision-making functions is postulated to underlie the associated impairment of P300 latency and Digit Span. In other words, P300 latency appears to be strongly associated with attention and short term memory but not with general intelligence and reasoning.

One of the purposes of this study was to test whether P300 latency might serve as a useful tool to evaluate the effectiveness of specific drugs. Canter *et al*[24] reported that lecithin did not affect EEG spectra or P300 in Alzheimer's disease, which is consistent with reports that lecithin administration alone did not improve memory in patients with Alzheimer's disease.[25] We used physostigmine because its administration has been reported to show memory improvement transiently in demented patients.[18 26 27] In our study, there was a high correlation between the change of P300 latency and that of WAIS score after medication. Furthermore, the WAIS score showed a significant improvement after physostigmine while P300 latency just failed to show a significant reduction (observed $t = 2{\cdot}23$, t value for $p < 0{\cdot}05 = 2{\cdot}25$). In fact, had we predicted that P300 latency would decrease after treatment then we could have accepted our P300 result as significant at $p < 0{\cdot}05$ on the basis of one-tailed test. It is still difficult to make any conclusion from these findings, however, because the comparison was not performed blind and the effects of practice on both the ERP test and the WAIS need to be taken into consideration although most patients forgot about the ERP or WAIS tested before. Thus, the question as to whether physostigmine improves cognitive function or not awaits further study. However, the results indicate that ERP tests can provide useful objective information in the evaluation of drug effects in demented patients.

We thank Mr Makomoto Sakai for WAIS testing, Dr R Kramer for his comment, Christine Skibiniski and Gerald R Beck, Cleveland Clinic Foundation, for statistical analysis.

References

1 Sutton S, Braren M, Zubin J, John ER. Evoked potential correlates of stimulus uncertainty. *Science* 1965;**150**:1187–8.
2 Donchin E, Ritter W, McCallum WC. In: Callaway E, Tueting P, Koslow S. eds. *Cognitive Psychophysiology. The endogenous components of ERP*. Event-related brain potentials in man. New York, Academic Press, 1978:349–411.
3 Halgren E, Squires NK, Wilson CL, Rohrbaugh JW, Babb TL, Crandall PH. Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. *Science* 1980;**210**:803–5.
4 Okada YC, Kaufman L, Williamson SJ. The hippocampal formation as a source of the slow endogenous potentials. *Electroencephalogr Clin Neurophysiol* 1983;**55**:417–26.
5 Barrett G, Neshige R, Shibasaki H. Human auditory and somatosensory event-related potentials, Effects of response condition and age. *Electroencephalogr Clin Neurophysiol* 1987;**66**:409–19.
6 Goodin DS, Squires KC, Henderson BH, Starr A. Age-related variations in evoked potentials to auditory stimuli in normal subjects. *Electroencephalogr Clin Neurophysiol* 1978;**44**:447–58.
7 Syndulko K, Hansch EC, Cohen SN, *et al*. Long latency event-related potentials in normal aging and dementia. In: Courjon J, Mauguiere F, Revol M. eds. *Clinical Applications of Evoked Potentials in Neurology*. New York, Raven Press, 1982:279–86.
8 Pfefferbaum A, Ford JM, Wenegrat BG, Roth MT, Kopell BS. Clinical application of the P3 component of event-related potentials. 1. normal agings. *Electroencephalogr Clin Neurophysiol* 1984;**59**:85–103.
9 Picton TW, Stuss DT, Champagne SC, Nelson RF. The effects of age on human event-related potentials. *Psychophysiology* 1984;**21**:312–25.

10 Goodin DS, Squires KC, Starr A. Long latency event-related components of the auditory evoked potential in dementia. *Brain* 1978;**101**:635–48.
11 Brown WS, Marsh JT, LaRue A. Event-related potentials in psychiatry: Differentiating depression and dementia in the elderly. *Bull Los Angeles Neurol Soc* 1982;**47**:91–107.
12 Goodin DS, Aminoff MJ. Electrophysiological differences between subtypes of dementia. *Brain* 1986;**109**:1103–13.
13 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology* 1984;**34**:939–44.
14 Hachinski VC, Phil LDHM, Zilhka E, *et al.* Cerebral blood flow in dementia. *Arch Neurol* 1975;**32**:632–7.
15 Pfefferbaum A, Wenegrat BG, Ford JM, Roth WT, Kopell BS. Clinical application of the P3 component of event-related potentials. 11. dementia, depression and schizophrenia. *Electroencephalogr Clin Neurophysiol* 1984;**59**:104–24.
16 Ritter W, Simson R, Vaughan HG Jr, Friedman D. A brain event related to the making of a sensory discrimination. *Science* 1979;**203**:1358–61.
17 Goodin DS, Squires KC, Starr A. Variations in early and late event-related components of the auditory evoked potential with task difficulty. *Electroencephalogr Clin Neurophysiol* 1983;**55**:680–6.
18 Zimmerman IL, Woo-Sam JM. *Clinical Interpretation of the Wechsler Adult Intelligence Scale,* New York: Grune and Stratton, 1973.
19 Hansch EC, Syndulko K, Cohen SN, Goldberg ZI, Potvin AR, Tourtellotte WW. Cognition in Parkinson disease: an event-related potential perspective. *Ann Neurol* 1982;**11**:599–607.
20 Polich J, Howard L, Starr A. P300 latency correlates with digit span. *Psychophysiology* 1983;**20**:665–9.
21 Homberg V, Hefter H, Granseyer G, Stauss W, Lange H, Hennerici M. Event-related potentials in patients with Huntington's disease and relatives at risk in relation to detailed psychometry. *Electroencephalogr Clin Neurophysiol* 1986; **63**:552–69.
22 Kutas M, McCarthy G, Donchine E. Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. *Science* 1977;**197**:792–5.
23 Squires KC, Squires NK, Hillyard SA. Decision-related cortical potentials during an auditory signal detection task with cued observation intervals. *J Exp Psychol* 1975;**1**:268–79.
24 Canter NL, Hallett M, Growdon JH. Lecithin does not affect EEG spectral analysis or P300 in Alzheimer disease. *Neurology* 1982;**32**:1260–6.
25 Corkin S, Davis K, Growdon J, Usdin E, Wurtman RJ. *Alzheimer's Disease: a Report of Progress in Research.* New York: Raven Press, 1982.
26 Signoret JL, Whiteley A, Lhermitte F. Influence of choline on amnesia in early Alzheimer's disease. *Lancet* 1978;**ii**:837.
27 Etienne P, Gauthier S, Johnsen G, *et al.* Clinical effects of choline in Alzheimer's disease. *Lancet* 1978;**i**:508–9.
28 Thal LJ, Fuld PA, Masur DM, Sharpless NS. Oral physostigmine and lecithin improve memory in Alzheimer disease. *Ann Neurol* 1983;**13**:491–6.

Auditory long latency event-related potentials in Alzheimer's disease and multi-infarct dementia.

R Neshige, G Barrett and H Shibasaki

J Neurol Neurosurg Psychiatry 1988 51: 1120-1125
doi: 10.1136/jnnp.51.9.1120