

# Abnormalities of early “memory-scanning” event-related potentials in patients with temporal lobe epilepsy

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We have recorded auditory event-related potentials (ERPs) evoked by the “memory-scanning” (digit-probe identification/matching) paradigm that was originally described by Sternberg (1966), in 17 patients with complex partial seizures (temporal lobe epilepsy) and in 17 matched healthy control subjects. The patients, who had all complained spontaneously of memory difficulties, had significantly reduced scores on psychological tests of memory with relatively intact digit span and cognition. Their performance of the memory-scanning task was characterized by a higher error rate, longer reaction times and an increased slope of the reaction time/set size relationship. The associated ERPs in both patients and controls showed there were significant effects of memory load on several major components, but only a reduced amplitude of the N170 and a prolonged latency of the N290 waves distinguished the patients. In addition, the N170 wave in the patients decreased further as memory load increased. The prolonged N290 latency in the patients appeared to reflect the slowed processing time. This study has shown that ERPs generated by a short-term memory task are abnormal in patients with temporal lobe epilepsy who have neuropsychologically documented cognitive and memory deficits. Some of the significant waveform alterations occur earlier than those reported in previous ERP studies and provide electrophysiological support for the hypothesis that abnormalities of the early stages of short-term memory processing may contribute to the memory difficulties experienced by patients with temporal lobe epilepsy.

**Keywords:** Cognitive deficits – Complex partial seizures – Event-related potentials – Short-term memory – Temporal lobe epilepsy

## INTRODUCTION

Behavioural data from studies of short-term memory (STM) have shown that the time required to “scan” the contents of the “working memory buffer” increases as a linear function of the number of items to be memorized, and that an obligatory and automatic search of the complete memory store is made before a response is initiated (Sternberg, 1966). Subsequently, a number of investigators have reported event-related potentials (ERPs) to similar memory scanning tasks in healthy subjects (Marsh, 1975; Gomer *et al.*, 1976; Roth *et al.*, 1977; Adams and Collins, 1978; Ford *et al.*, 1979; Pratt *et al.*, 1989a,b,c; Pelosi *et al.*, 1992a,b). These ERPs have the advantage that the subject’s performance can be studied and compared under different levels of memory load. In 1987, Starr and Barrett reported that the ERPs generated by a modified Sternberg paradigm showed

abnormalities in four patients with conduction aphasia, whereas the P300 to an auditory “oddball” task was within normal limits. Apart from our own preliminary studies of demyelinating disease (Holly *et al.*, 1990) or depression (Slade *et al.*, 1990), there have been no other reports of “memory scanning” ERPs in patients.

Epilepsy, particularly temporal lobe epilepsy, should provide a useful pathological model for ERP studies of memory processes. It is well known that patients with epilepsy perform significantly worse than control subjects on a variety of memory tests (Brittain, 1980; Loiseau *et al.*, 1983) and that cognitive and memory deficits are particularly evident in temporal lobe epilepsy (Master *et al.*, 1986; Prevey *et al.*, 1988; Bornstein *et al.*, 1988a). Although memory dysfunction in temporal lobe epilepsy is generally

considered an abnormality of long-term memory, there is increasing evidence that STM is also involved. Impaired verbal or non-verbal STM for sequences, particularly the registration of memory traces, occurs during subclinical epileptic discharges (Aarts *et al.*, 1984). In addition, the recall of verbal material from STM is impaired in temporal lobe epilepsy (Delaney *et al.*, 1982), abnormalities of "immediate memory" have been demonstrated (Hermann *et al.*, 1987) and there is impairment of recency on the serial position curve (Powell *et al.*, 1984). In some studies, the only specific area of memory function which distinguished patients with temporal lobe epilepsy from those with generalized seizures, and from healthy controls, was abnormalities of immediate recall (Glowinski, 1973).

There have been several previous attempts to explore the relationship between ERPs and cognition in epilepsy. However, studies of the auditory "oddball" P300 have produced conflicting results, ranging from no abnormalities (Puce and Bladin, 1991), increased latencies (Fukai *et al.*, 1990; Triantafyllou *et al.*, 1992), and increased (Drake *et al.*, 1986), reduced (McCarthy and Wood, 1987), or even absent, P300 waves (Squires *et al.*, 1983). The functional role of the P300 remains unclear, but several hypotheses have implied that it signals the completion of a cognitive process, i.e. "context-updating" (Donchin, 1981), a "non-specific relaxation" (Karlín, 1970), a "post-decision closure" (Desmedt, 1980), or "cortical inhibition or dysfacilitation" (Rockstroh *et al.*, 1992). The oddball P300 appears to be insensitive to even severe degrees of temporal lobe hypofunction (Rugg *et al.*, 1991a). An association between P300 and memory has been contested in studies of patients with memory dysfunction (Onofrij *et al.*, 1992; O'Donnell *et al.*, 1993). While memory-scanning potentials have been shown to be sensitive to the specific deficit of auditory memory associated with conduction aphasia (Starr and Barrett, 1987), they have seldom been investigated in other groups of patients with cognitive deficits (Holly *et al.*, 1990; Slade *et al.*, 1990).

Although the origin of the ERPs generated by the scanning of STM remains unknown, magnetic recordings carried out during the memorization and retrieval of auditory digits in three subjects have suggested dipole sources for early probe-related activity (110 ms) in superior temporal cortex (Heschl's gyrus) and for late activity (300-800 ms) in the medio-basal temporal lobes (Starr *et al.*, 1991). Given the evidence for involvement of STM in temporal lobe epilepsy, and the possible localization in the temporal lobe of the ERP generators associated with memorization and retrieval, we aimed to investigate patients with

temporal lobe epilepsy using "memory-scanning" ERPs for objective pathophysiological evidence of abnormal memory processing.

## METHODS

### Patients and control subjects

We recruited patients with complex partial seizures (ILAE classification; Commission on Classification and Terminology of the International League Against Epilepsy, 1989) who complained spontaneously of memory difficulties during routine follow-up in a general neurology clinic. They were compared with a healthy control group matched for age, gender and years of education. The mean age for the 17 patients was 42 years (range 22-69 years) and for the 17 healthy controls, 43 years (range 21-63 years). The male:female ratio was 8:9 in both groups. The mean duration of education was 11.5 years in the controls and 10.6 years in the patients. Fifteen of the patients and 16 of the controls were right handed. The mean duration of epilepsy was 146 months (range 24-384 months). The mean seizure frequency in the 12 months prior to the recordings was 4.4 (range 1-10) seizures/month. The aetiology of the seizure disorder was idiopathic in 12, post-traumatic in four and post-encephalitic in one. Fourteen patients had computerized tomography (CT) scans; these showed no abnormalities in eight, low density lesions in the temporal regions in four, and mild generalized atrophy in two. EEG abnormalities (temporal spikes or/and sharp waves) were bilateral in five subjects and focal in 12 (eight left, four right). Eight subjects were on one antiepileptic drug (AED; two on phenytoin, four on valproate, two on carbamazepine), eight were on two AEDs (usually phenytoin and carbamazepine or valproate), and one was on three AEDs.

All patients gave informed consent to the study which was approved by a hospital ethical committee.

### ERP procedure

Subjects were presented with "memory sets" of items to be memorized. The sets consisted of one, three or five digits. Each trial commenced with a warning signal (the word "start"), followed 0.85 s later by a single digit, or by a series of digits ("memory set") to be memorized with inter-digit intervals (onset to onset) of 1.2 s. The word "start" and the digits 1 to 9 were presented aurally using a microcomputer fitted with a speech synthesizer chip. A 3 s interval followed the end of each set after which a single probe digit was presented. The probability that the probe was a member of the preceding memory set was 0.5. The

subject was required to indicate whether the probe was present in the preceding memory set (by pressing a button held in the dominant hand), or absent from the set (button in the non-dominant hand). Probe digits which were present in, or absent from, the preceding set are referred to as positive or negative probes, respectively. The digits contained in each trial were selected in a pseudo-random manner with the restriction that no digit could occur as a probe in two consecutive trials and no more than three consecutive positive or negative probes could occur in sequence. The proportion of positive probes relative to the position of the matching digit in the preceding string (i.e. first, second or third position for three digit responses and first, second, third, fourth or fifth position for five digit responses) was adjusted to be approximately equal.

During the recordings the subjects sat in a comfortable armchair in a semidarkened room. After a practice trial of 20 single digit sets, a minimum of 40 trials was presented to each subject in two runs of 20 for each set size. The interval between the onset of the probe digit and the button press was measured as the reaction time (RT) for each response. The accuracy of probe identification was also recorded, including incorrect responses ("button press errors") and failure to respond within 3 s ("time out"). Premature responses (RT less than 200 ms) were excluded from the analysis.

### ERP recording

All recordings were carried out at the same time in the morning. In an effort to avoid the postictal effects of possible asymptomatic seizures, an eight-channel mobile cassette tape recording of the EEG was made during the 24 h period immediately preceding the psychological testing and the ERP recording. No symptomatic seizures, or EEG seizures of which the patient was unaware, were recorded. Recordings were obtained from 10 mm Ag/AgCl electrodes (interelectrode impedance below 5000 ohms), at Fz, Cz and Pz (10-20 International System) using linked earlobes as a common reference. The electrooculogram (EOG) was monitored via a bipolar trace from electrodes positioned above and below the left eye. The analysis time of 960 ms included a 120 ms "pre-stimulus" epoch prior to the presentation of the probe digit. There were 256 ordinates per sweep. The time constant was 3 s. The response to each trial was stored on floppy disc for later analysis. Waveforms were digitally filtered with a high frequency cut-off at 44 Hz for measurement and presentation.

### Analysis of ERPs

All responses from individual trials were visually inspected and selected for averaging only if uncon-

taminated by marked muscle or eye movement artefact (EOG deviations from baseline of less than 100  $\mu$ V). The ERPs were averaged separately according to the memory set size and the type of probe (i.e. positive or negative). After inspection of all responses to single trials, a minimum of 14 satisfactory responses was required for an average to be included in the study group. The group average waveforms in healthy subjects were used to identify the major components according to the polarity and mean peak latencies, and to set latency limits (from mean latencies of the preceding and following waves of opposite polarity) for each electrode position and stimulus condition. The average latency limits across electrodes and all stimuli were: N170, 112-251; P250, 176-303; N290, 251-420; P400, 303-581, and P560, 420-787. The criteria for the P560 also required the wave to be larger than the P400 at the Pz electrode, and to be separated from it by a negative-going wave ("N3"). Components with values within these defined latency limits were accepted as "unequivocal". Components with a single peak of appropriate polarity falling outside these limits were included in the analyses, but classified as "equivocal". "Missing values" included: (1) an absence of potentials of appropriate polarity either within or outside a latency window; and (2) the presence of multiple peaks or subpeaks which prevented accurate identification of a component.

The component amplitudes were measured (for separate analyses) both from the preceding wave of opposite polarity (peak to peak) and from a prestimulus baseline (baseline to peak).

### Neuropsychological test battery

The tests, carried out on the same day as the ERP recordings, included the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955), subtests of the Wechsler Memory Scale (WMS), Recognition Memory Tests and the Benton Visual Retention test (Table I).

### Statistical analysis

A MANOVA with repeated measures analysis of variance (SPSS mainframe version X3) using the between-subject factor of Group (i.e. healthy subject or patient) and the within-subject factors Probe (two levels: positive and negative), Electrode (electrode position; three levels: Fz, Cz, Pz) and Digit (memory set size; three levels: one digit, three digits, five digits) was used to examine differences in ERP between patients and controls. The univariate solution was taken with the Greenhouse-Geisser correction factor being employed whenever appropriate to protect against Type I errors associated with non-sphericity

TABLE I. Means and S.D.s of psychological test scores for patients and controls

	Controls (n = 17)			Patients (n = 17)	
	Mean	S.D.	p	Mean	S.D.
<b>WAIS</b>					
Verbal IQ	111.23	13.00	***	95.17	11.22
Performance IQ	115.53	8.47	***	100.05	9.97
Full scale IQ	113.47	9.63	***	97.11	9.91
Arithmetic	11.41	2.39	**	8.88	2.73
Similarities	12.23	2.01	***	9.64	1.53
Digit span	12.05	3.34	*	9.29	3.09
Digit span forwards	7.11	1.61	*	5.88	1.53
Digit span backwards	5.05	1.24	*	4.00	1.11
Vocabulary	11.70	1.96	***	9.35	1.80
Digit symbol	14.17	2.18	***	9.94	2.83
Picture completion	10.94	2.13	N.S.	9.70	1.61
Block design	12.82	2.69	*	10.70	2.22
Picture arrangement	12.41	1.83	**	9.41	2.91
<b>Memory tests</b>					
Logical memory	11.52	2.64	***	5.55	2.04
Immediate recall	8.29	2.37	***	3.50	1.73
Delayed recall	15.55	3.18	***	9.79	4.13
Paired associate learning					
Benton Visual Retention test					
Correct responses	7.41	1.17	***	5.47	1.28
Error scores	3.11	1.53	***	7.52	2.60
Recognition memory test					
Words	48.23	1.60	*	45.00	5.61
Faces	43.94	4.65	**	39.23	3.49

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

of the data (Jennings and Wood, 1976). Separate MANOVAs were run for the amplitude and latency of each component, RT and error scores were analysed separately with one between-subject factor (Group) and two within-subject factors (Set size and Probe).

Those variables which showed significant main effects or significant interactions were subjected to *post-hoc* tests (Scheffé) using an  $\alpha$  level of less than 0.05.

Differences between the psychological data obtained from patients and controls were compared using the Student's unpaired *t*-test (two-tailed).

Correlations between ERP amplitudes and latencies and either RT or IQ were carried out with multiple linear regressions (Pearson's product moment coefficient) using a significance level of  $p < 0.01$  to reduce the risk of chance associations.

## RESULTS

### Psychological data

With the exception of the WAIS subtest "picture completion", the patients generally performed less well than the healthy subjects (Table I). The patients'

scores on IQ tests were lower than controls, but still fell within the average range for a normal population (Wechsler, 1955) and were either within, or close to 1.5 S.D. of the healthy control means. By contrast, the patients' mean scores on the memory tests differed markedly from those of the controls. Their scores for immediate and delayed recall on the Wechsler memory scale were between 2 and 2.5 S.D. from the control means, i.e. below average for a normal population (Table I). Other tests, including estimates of "digit span", were less markedly compromised (Table I).

There were no consistent correlations between FSIQ and ERP parameters in either patients or controls.

### Behavioural data

**Reaction time.** RTs were significantly longer in the patients [main effect of Group;  $F(2,32) = 28.42$ ,  $p < 0.0001$ ] (Fig. 1). Both patients and controls showed an increase in RT with increasing set size, but the increase was significantly larger in the patients [Group  $\times$  Digit:  $F(2,64) = 10.5$ ,  $p < 0.0001$ ]. The slope for the patients was 123 ms/digit, and for the

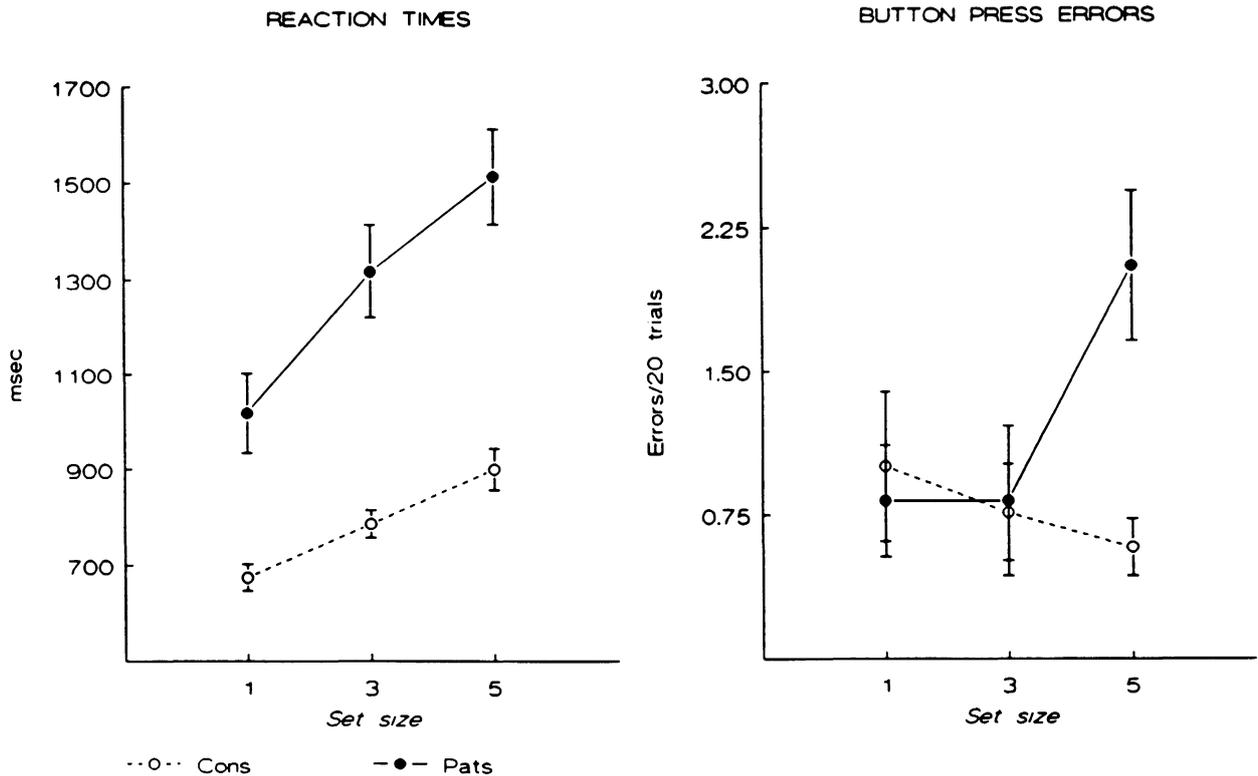


FIG. 1. Reaction times and error scores for patients ( $n = 17$ ) and controls ( $n = 17$ ) by memory set size. Error bars = standard error of the means. In left graph, note the steeper slope for the patients and their longer RTs at all set sizes. For errors (right graph) note significant group differences occur only for five digit sets.

controls was 56 ms/digit. Significant correlations between RT and the amplitude or latency of components were not consistent across electrode sites and stimulus conditions.

**Errors.** The error rates were significantly higher for the patients overall [main effect of Group:  $F(1,32) = 8.58, p < 0.01$ ] and only the patients made more errors as set size increased [Group  $\times$  Digit;  $F(2,64) = 3.56, p < 0.05$ ]. *Post-hoc* analysis showed that the significant differences occurred between sets of three and five digits (Fig. 1).

## ERPs

**Response waveform in healthy controls.** The major components are shown in the group average responses in Fig. 2. The effects on the ERP waveform of increasing the size of the memory sets include a prolongation of the N290 latency and a reduction of the P250, N290 and P400 waves. In addition, the negativity (N640) which followed the P400 was reduced or partially replaced by the late positive wave P560, particularly at Cz and Pz (Fig. 2). The effects of memory loading in healthy subjects have been described in detail in a previous paper (Pelosi *et al.*, 1992a).

**Response waveform in patients.** The group average responses in the patients showed essentially the same waveform with all the major components present (Fig. 2). The first main wave, the N170, was, for all set sizes and all electrode positions, markedly reduced in amplitude relative to the control responses (Fig. 3). The N290 wave in the responses to single digits was reduced and delayed (Fig. 3, left column); for sets of three and five digits this component appeared to be bifid, or was replaced or overlaid by two small negative peaks, particularly at Pz (Fig. 3, right column). The major positivity, the P400 wave, was delayed in the responses to single digits, but relatively preserved in amplitude, whereas in the responses to sets of three and five digits, it was either attenuated with an ill-defined peak, or overlaid or replaced by negative-going activity (Fig. 3).

**Individual response analysis.** A MANOVA on the patient and control data (see Methods) revealed no significant effects of, or interactions with probe type. Nevertheless, as there are significant behavioural (RT and error scores) as well as ERP differences between probe types in healthy subjects (Pelosi *et al.*, 1992), all further analysis was carried out on the correct responses to positive probes.

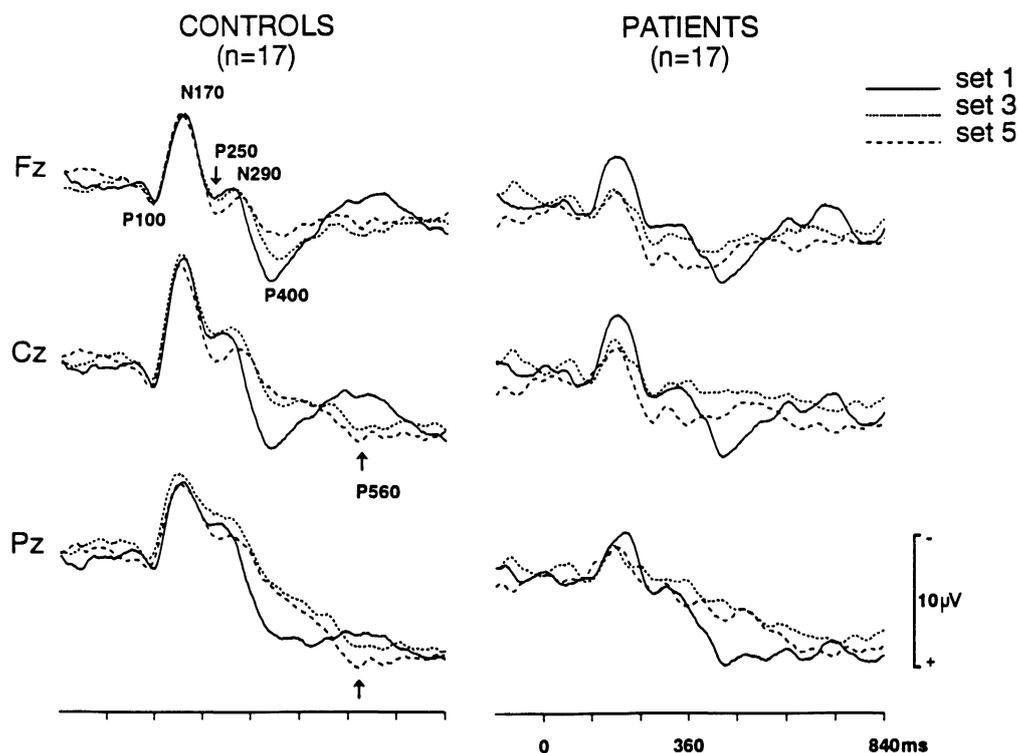


FIG. 2. Superimposition of group averages of positive probes of controls and patients by memory set size. The major components are labelled according to their polarities and approximate mean latencies. Note the changes with set size and topography in controls (left column): P400 reduces with increasing set size and a second positive wave (P560) appears in responses to larger sets, particularly at Cz and Pz. In the patients' responses, all components can be identified, but with increasing set size the N170 is reduced. In this and the following figure, probe presentation is at time zero and the time divisions and pre-stimulus epoch are 120 ms.

The majority of the latency measurements were inside the limits set for each component and stimulus condition, and only a small percentage of the components included were identified "equivocally" (see Methods) in the patients' responses (i.e. N170, 0.6%; P250, 6.5%; N290, 15%; P400, 1%; and P560, 12%).

Apart from P560, the prevalence of missing values was low for all stimulus conditions and electrodes (i.e. from 0% of the early components to 14% for P400) and comparable in patients and controls. The low frequency of the P560 in the response to single digits in healthy subjects has been described previously (Pelosi *et al.*, 1992a).

#### Differences between patients and controls.

**Baseline-to-peak amplitudes.** The N170 wave was significantly reduced in patients [Group:  $F(1,32) = 15.1$ ,  $p < 0.001$ ] for all set sizes (Table II, Fig. 3). The reduction of N170 amplitude with increasing set size was slight in the controls and marked in the patients [Group  $\times$  Digit:  $F(2,64) = 3.73$ ,  $p < 0.05$ ] (Fig. 2, Table II). The significant reduction of N170 in the patients' responses occurred on moving from

single digits to three digit sets; the further attenuation that occurred between the responses to sets of three and five digits was not significant. The P250 wave was significantly larger [Group:  $F(1,32) = 6.94$ ,  $p < 0.05$ ], and the N290 significantly smaller, in the patients [Group:  $F(1,32) = 3.30$ ,  $p < 0.05$ ]. The subsequent positive waves, P400 and P560, were not significantly altered.

**Peak-to-peak amplitudes.** This method gave similar results for the N170 wave, i.e. a significant amplitude reduction in the patients [Group:  $F(1,32) = 23.8$ ,  $p < 0.001$ ] and a significant difference between patients and controls in the effects of set size [Group  $\times$  Digit:  $F(2,64) = 3.15$ ,  $p < 0.05$ ]. By contrast, for the later components, this method of measurement gave results which differed from the baseline-to-peak analysis. There were no significant group differences for the P250 and N290 waves, whereas the P400 wave was significantly smaller in the patients' responses [Group:  $F(1,22) = 4.49$ ,  $p < 0.05$ ] (Table II).

**Latencies.** The latencies of the N290 [Group:  $F(1,32) = 13.1$ ,  $p < 0.001$ ] and P560 [Group:

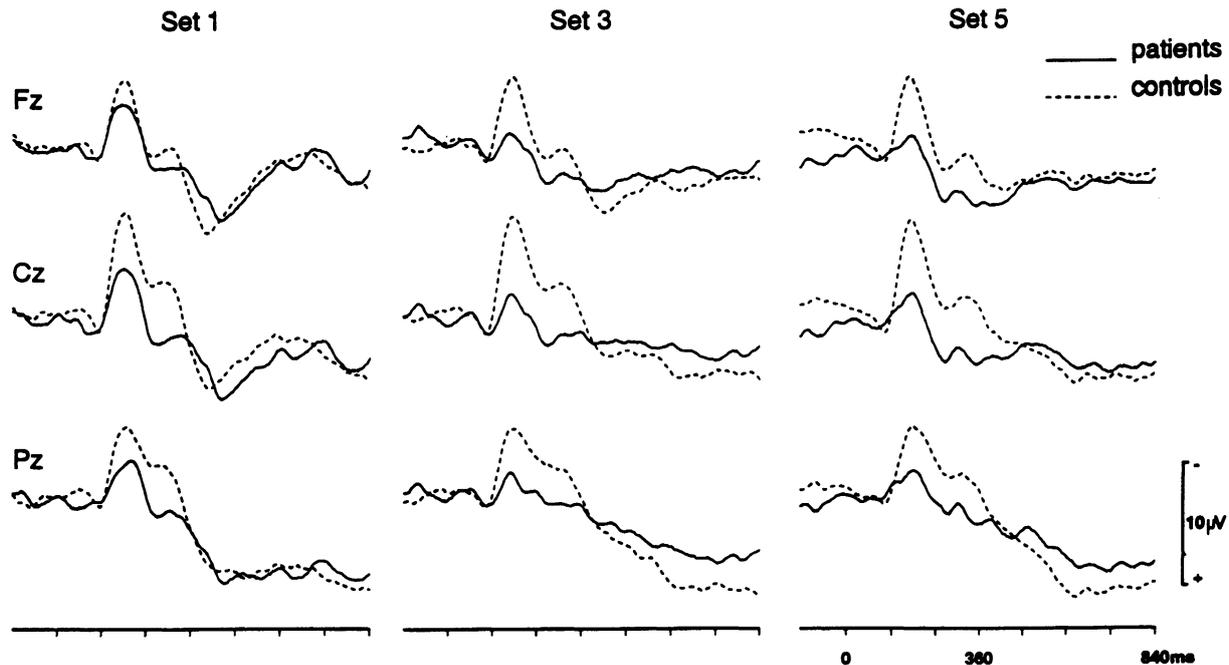


FIG. 3. Superimpositions of group averages of positive probes of patients ( $n = 17$ ) and controls ( $n = 17$ ) by set size. Amplitude differences in the early section of the waveform (N170, P250 and N290) can be seen across all set sizes. Note that whereas N290 and P250 are shifted with respect to baseline, they are relatively well preserved peak-to-peak. By contrast, the P400 is relatively unchanged with respect to baseline, but its amplitude is reduced when measured from the preceding N290 peak.

$F(1,19) = 4.35, p < 0.05$ ] waves were significantly prolonged in the patients (Table II).

## DISCUSSION

We have found significant abnormalities of the ERPs generated by a digit-probe identification-matching task in patients with temporal lobe epilepsy. In previous reports of ERPs (mostly elicited by the auditory "oddball" task) in patients with epilepsy, investigators have concentrated on the major positive waves and the earlier short-latency components have seldom been investigated. Similarly, in studies using other paradigms, most analyses have been restricted to the activity after 300 ms (e.g. Rugg *et al.*, 1991b). Nevertheless, changes in earlier waves have occasionally been reported, including delays of an "N2" wave (Drake *et al.*, 1986; Triantafyllou *et al.*, 1992).

The significant changes in the responses of our patients were the amplitude reduction of the N170 wave, and its further attenuation by increasing memory load (Group  $\times$  Digit interaction), and a prolongation of the N290 latency (and to a lesser extent the P560). The other changes depended on the method of analysis; with a baseline-to-peak analysis the N290 and P250 waves were significantly reduced

and the P400 relatively preserved, but with peak-to-peak measurements these results were reversed.

It could be argued that the reduction of the early N170 wave in our patients simply reflects a reduction in their levels of attention (Hillyard and Kutas, 1983) and/or increase in their distractibility (Bornstein *et al.*, 1988b). Indeed, these factors, which can result in faulty encoding (Delaney *et al.*, 1982), appear to have an important effect on performance testing in epilepsy (Bornstein *et al.*, 1988b). However, our behavioural data provide no evidence to support reduced levels of attention in our patients during the task. The ratio of correct hits to errors at low levels of task difficulty was similar in patients and controls; the error scores in the patients differed significantly only for the five digit sets. Further, the additional attenuation of the N170 in the patients on increasing the memory load from one to three digits was not associated with an increase in errors, and finally, the increase in errors from set three to set five was not accompanied by a further reduction of the N170 amplitude. Therefore we think it is unlikely that the amplitude attenuation of this wave with memory loading can be attributed solely to an increasing effect of impaired concentration or attention at higher levels of task difficulty. It has been hypothesized on the basis of pooled evidence from studies

TABLE II. F values for repeated measures MANOVA of latencies and amplitudes including between-subjects factor Group (controls, patients) and within-subjects factors Digit (1, 3, 5) and Electrode (Fz, Cz, Pz)

	Component				
	N170	P250	N290	P400 <sup>1</sup>	P560 <sup>2</sup>
<b>Latencies</b>					
Group	N.S.	N.S.	13.17***	N.S.	4.35*
Digit	N.S.	N.S.	4.53**	N.S.	N.S.
Group × Digit	N.S.	N.S.	N.S.	N.S.	N.S.
Electrode	N.S.	N.S.	5.82**	N.S.	N.S.
Group × Electrode	3.69*	N.S.	4.44*	N.S.	N.S.
Digit × Electrode	N.S.	N.S.	N.S.	N.S.	N.S.
Group × Digit × Electrode	N.S.	N.S.	2.54*	N.S.	N.S.
<b>Amplitudes (baseline-to-peak)</b>					
Group	15.17***	6.94*	3.30*	N.S.	N.S.
Digit	3.49*	5.31**	N.S.	5.95**	N.S.
Group × Digit	3.73*	3.42*	N.S.	N.S.	N.S.
Electrode	22.10***	30.50***	25.91***	N.S.	17.00***
Group × Electrode	4.61*	5.51**	N.S.	N.S.	N.S.
Digit × Electrode	N.S.	N.S.	N.S.	5.04**	N.S.
Group by Digit by Electrode	N.S.	4.45**	3.30*	N.S.	8.58***
<b>Amplitudes (peak-to-peak)</b>					
Group	23.85***	N.S.	N.S.	4.49*	N.S.
Digit	3.72*	N.S.	3.88*	9.93***	N.S.
Group × Digit	3.15*	N.S.	N.S.	N.S.	N.S.
Electrode	29.22***	29.33***	6.51**	9.15***	46.00***
Group × Electrode	7.53**	N.S.	N.S.	N.S.	N.S.
Digit × Electrode	N.S.	N.S.	N.S.	N.S.	N.S.
Group × Digit × Electrode	N.S.	N.S.	N.S.	N.S.	N.S.

<sup>1</sup>Only 24 cases.

<sup>2</sup>For within-subjects factor Digit only two levels (3 and 5).

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

of different auditory paradigms, that certain subcomponents of the “N1” wave may reflect the formation of memory traces to the eliciting stimulus, whereas others are related to the matching of traces from current and preceding stimuli (Näätänen and Picton, 1987). Our findings support the concept of endogenous components in the early response and suggest that the endogenous contribution to the N170 wave of the Sternberg paradigm is sensitive to memory load. It is of relevance that Begleiter and colleagues (1993), who admittedly used a different paradigm and recorded potentials to non-matching stimuli (cf. our matching probes), recently demonstrated a potential at approximately 170 ms which appears to index visual short-term memory.

The amplitude reduction of the N170 wave in our patients appeared to be mainly if not entirely responsible for the “positive shift” of the early part of the response waveform. As a result, the significant reduction of the P250, N290 and P560 waves in our

patients, when measured with respect to baseline, needs to be cautiously interpreted. The peak-to-peak analysis showed that these waves were relatively unaffected, and simply shifted with respect to baseline. Similarly, the higher order interactions (Group × Digit × Electrode) for these components were not significant with a peak-to-peak analysis. By contrast, the P400 waves in the patients seemed relatively preserved with respect to baseline and their significant amplitude reduction was revealed only on peak-to-peak analysis. This illustrates the importance of allowing for pathological or physiological modulation of sections of the ERP waveform which may shift some potentials with respect to baseline while leaving others unchanged. Under certain circumstances, baseline-to-peak (or peak-to-peak) may lead to erroneous interpretations, and preferably both methods should be used in ERP studies.

All our patients were complaining of memory difficulties and had evidence of reduced memory function,

and to a lesser extent intellect, on psychological tests. They had markedly prolonged RT and we can assume that their steeper RT slope reflects their slowed cognitive processing time. The significantly delayed N290 wave may be the ERP correlate of this cognitive slowing, perhaps representing different stages in the processing of the task. In addition, the relationship between N290 latency and memory load suggests that this wave is involved in stimulus processing. However, the ERP and behavioural data do not coincide; N290 latency is at best weakly correlated with RT and the increase in latency of N290 with set size (approximately 10% of the RT slope) cannot fully account for the RT difference between patients and controls. Furthermore, the effects of memory load on the N290 latency in patients and controls is at least partially dependent on the recording site with maximal differences in fronto-central electrodes (Group  $\times$  Digit  $\times$  Electrode). Perhaps the N290 prolongation with memory load simply reflects one aspect of the multiple steps necessary for the successful completion of the task. The other component whose latency was significantly prolonged in the patients was the late positivity, the P560. Why this should be so is uncertain as the latency of this wave does not appear to be sensitive to memory load in healthy controls (Pelosi *et al.*, 1992a, 1994).

As far as we are aware, this is the first demonstration of the pathological alterations of early "memory-scanning" potentials in patients with cognitive difficulties. Studies in healthy subjects have demonstrated a modulation of a similar early section of "memory-scanning" ERPs according to the subject's performance of intelligence tests (Pelosi *et al.*, 1992a,b); subjects with higher cognitive performance show a negative shift of all the waves which follow the peak of the N170. In the present study we matched for age and education years, but our patients nevertheless had significantly lower scores on tests of intellect than the controls. The small numbers involved did not allow a retrospective analysis with IQ matching. Further studies are under way in a larger group of patients in order to control for IQ. However, we do not think that the differences between our controls and patients can be accounted for by the differences in, for example, IQ or vocabulary scores, as the significant ERP differences begin earlier (i.e. between 100 and 170 ms) than the IQ-related changes seen in healthy subjects (Pelosi *et al.*, 1992b). In addition, we found no correlations between FSIQ and any of the components which distinguished patients from controls. Future studies could perhaps identify more precisely the electrophysiological markers of memory dysfunction by comparing patients

with or without quantified memory deficits who have been matched for IQ.

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