EVENT RELATED EVOKED POTENTIAL RESPONSES IN EPILEPTIC PATIENTS

O. P. TANDON* AND PRAVEEN DUHAN

*Department of Physiology,
University College of Medical Sciences & GTB Hospital,
Shahdra, Delhi – 110 095*

Abstract : The effect of epilepsy on cognitive functions has been investigated in this study. The P300 auditory event related potentials (AERP), Wechsler Adult Performance Intelligence Scale (WAPIS – Indian Adaptation) & Digit Span Test (DST) have been used to assess the cognitive status. Twenty primary generalised epilepsy patients and 20 normal controls were subjected to WAPIS & DST testing and their AERP recorded. On comparative statistical analysis, epileptic subjects were found to have significantly higher N2 & P300 latencies and lower P300 amplitude, WAPIS-IQ scores & DST scores. These findings suggest that there is a general decline of cognitive functions in epileptics especially the memory, attention, concentration and speed of mental processing and as also corroborated by P300 and that P300 can be used as an additional sensitive parameter to assess the cognitive status.

Key words : epilepsy   cognitive functions   P300   AERP

INTRODUCTION

Alteration of cognitive functions in epilepsy received particular attention from the 19th century physicians who implied that intellectual deterioration was an inevitable part of epilepsy. Since that time there has been fairly extensive discussion of intellectual changes in epilepsy. A number of investigators have examined specific deficits in patients with epilepsy including abnormalities of memory (1, 2, 3), perceptuomotor skills (4,5), speed of mental processing (6, 7) and attention (2, 8, 9) as well as overall impairments (as reflected by IQ scores etc.) of cognitive abilities (10, 11, 12).

In recent years, the P300 event related potential has been used to assess cognitive processing (13, 14). P300 latency reflects stimulus evaluation time (15) and is affected by task difficulty (16). P300 amplitude is related to decision making, memory processing and task relevance (17). In this study, the P300 Auditory Event Related Potential has been used as the electrophysiological tool to assess the cognitive status in epileptics and in addition, psychometric testing with Wechsler Adult Performance Intelligence Scale (Indian adaptation of Wechsler Adult Intelligence Scale {WAIS} by P. Ramalingaswamy) (18) and the Digit Span Test has been carried out.

METHODS

Subjects : Twenty male patients of primary generalised epilepsy (newly diagnosed clinically) of age 18–30 yrs were subjects of this study. Inclusion criteria were : a) No

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*Corresponding Author

evidence of progressive brain or systemic disease, b) No previous exposure to antiepileptic drugs. All patients had two or more unprovoked seizure attacks. Seizures were classified according to the revised International Classification of Epileptic Seizures (19). The control group consisted of age and sex matched 20 healthy volunteers. The controls and patients had comparable level of education (average : middle school passed) and socioeconomic status. Both patients and controls were administered the WAPIS & DST and their AERP recorded. Each subject was included after a detailed physical & ENT examination.

P300 (AERP) : The subject was briefed about the test procedure. He was made to sit on a comfortable chair in a soundproof air conditioned room. SMP4100 auditory/visual stimulator and MEB5200 NeuropackII evoked potential recorder were used for AERP recording. Standard auditory 'Odd Ball' paradigm was used. In this paradigm, the subject was presented binaurally, through headphones, a sequence of two distinguishable sound click stimuli with different characteristics. One occurred frequently (non target stimulus) and the other infrequently (target stimulus). The subject was asked to respond by pressing a button using his preferred hand whenever a rare stimulus was presented. The cerebral response obtained was recorded on the screen of the evoked potential recorder.

The electrode recording sites on the scalp were cleaned with spirit and skin pure. Electrolyte paste (Elefix) was applied and Ag/AgCl disc electrodes were anchored as per 10–20 International system of electrode placement :

Active electrode (–): Vertex (Cz), Midline Parietal (Pz)

Reference electrode (+): Both ears connected (A1 + A2)

Grounding electrode: Forehead (Fpz)

The input impedance was kept below 5 Kohms. Using shielded headphones, alternating tone bursts, with a starting condensation phase of 10 msec rise/fall time, 100 msec duration (plateau time), intensity 70 dB NHL and rate 1 every 2 sec were used as target stimuli. 80% of total 160 tones were 1 KHz (frequent) and 20% were 2 KHz (rare). Stimulus sequence was random. The signals were in phase at two ears. The MEB–5200 setting were properly selected and evoked responses to frequent and rare stimuli were filtered with a band pass 5–30 Hz and averaged simultaneously for 32 responses. Data obtained were stored, analysed and averaged by the computer. The latency of N2, P300 and amplitude of P300 (recorded from Cz) for target stimulus was calculated. During the recording session, the subject was asked to fix his eyes on a particular spot on the ceiling in order to avoid electro-oculographic artifacts due to eye movements and improve his concentration and attention to the stimuli presented. The method used for recording P300 was similar to the reported in our laboratory (13).

Psychometric tests: The Indian adaptation of WAIS by P. Ramalingaswamy and the DST were administered to all patients and controls. The original WAIS consists of eleven subjects viz., information, comprehension, arithmetic, similarities, digit span, vocabulary, digit symbol, picture completion, block design, picture arrangement and object assembly. Out of these, first six form the verbal scale and the last five form the performance scale. Due to the multilingual society in India and large illiterate population, the utility and applicability of verbal scale is

limited, therefore, the Indian adaptation of WAIS by P. Ramalingaswamy consisting of the performance scale of WAIS with slight modifications to make it applicable to the Indian population was used. The performance scale IQ is a more sensitive indicator of higher function deficit than the verbal part. The DST was included in the battery of psychometric tests as it is a very sensitive test for immediate retention and recall, attention and concentration. Both forward and backward digit span tests were administered. WAPIS-IQ (intelligence quotient) scores and Digit Span scores were computed for each subject. A stop watch was used to keep time during WAPIS and DST administration.

Data analysis: IQ scores for WAPIS, Digit Span scores, Latencies of N2 & P300 and P300 Amplitude were calculated for each subject. Comparisons of these variables between the epileptics and control groups were made. The relationship between IQ scores, Digit Span scores, N2 latency, P300 latency amplitude was measured (Pearson's correlation test). Scatter diagrams were plotted showing correlation between these values.

RESULTS

On comparative statistical analysis, following results were obtained :

TABLE I: Showing comparative data in two groups.

| Variable	Controls (n = 20)		Epileptics (n = 20)		P-value (T-test)	Significance
	Mean	SD	Mean	SD		
Age (yrs)	23.92	3.70	22.83	3.95	0.496	Not Significant
N2 (Lat) (ms)	204.00	44.80	271.83	19.17	0.000	Significant
P300 (Lat) (ms)	282.75	23.96	348.17	22.05	0.000	Significant
P300 (Amp) (µV)	12.72	3.56	8.33	1.73	0.001	Significant
WAPIS Score (IQ)	109.33	8.51	95.67	5.18	0.000	Significant
Digit Span Score (max 28)	23.08	1.08	18.67	1.07	0.000	Significant
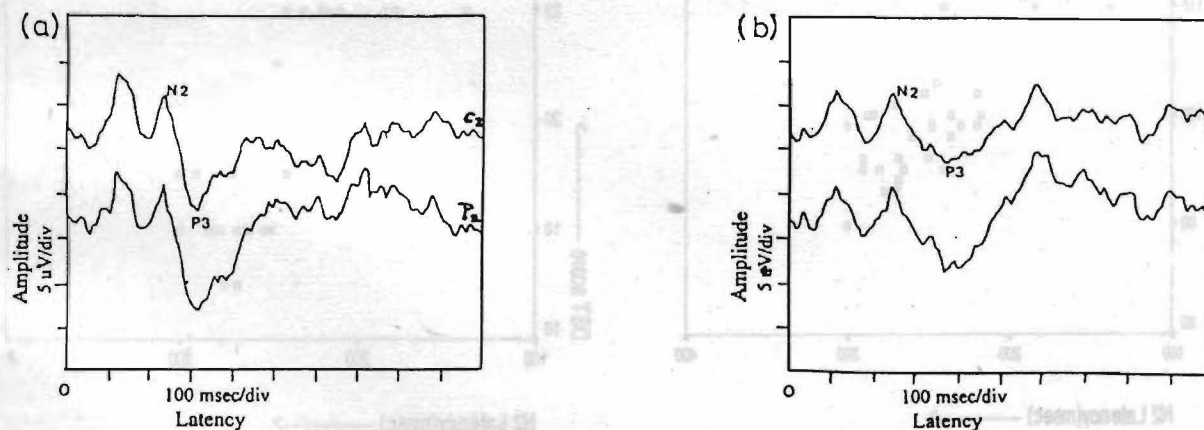
Fig. 1: Auditory event related potentials (P300) obtained from a representative subject from each group (a) Control Group (b) Epileptic Group. P300 recorded using auditory 'odd ball' paradigm. In (b), N2 and P300 latencies are higher and P300 amplitude is lower.
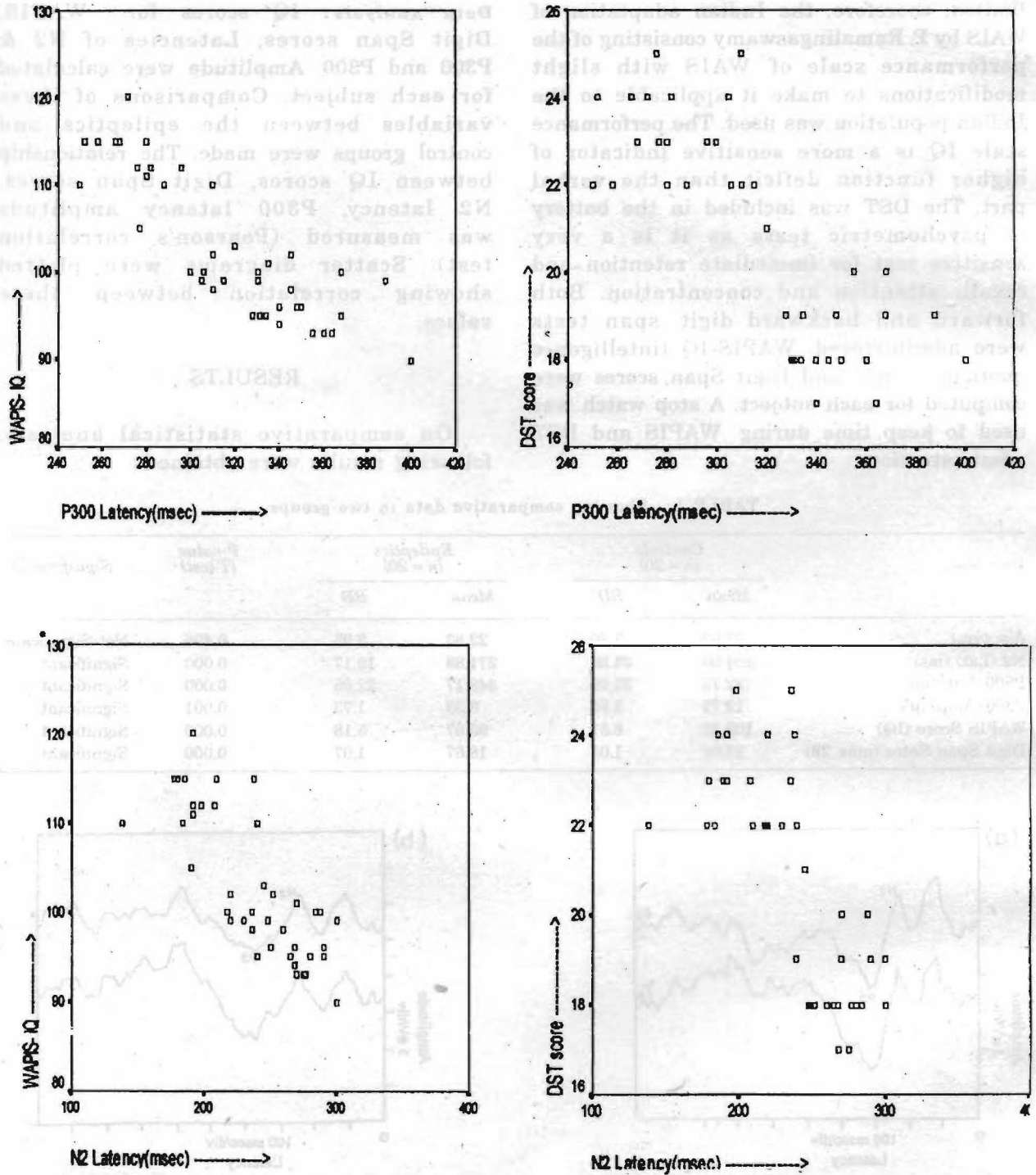
Fig. 2 : Scatter diagrams showing relationship between P300 latency, WAPIS IQ & DST scores and N2 latency, WAPIS IQ & DST scores.

The mean P300 amplitude in controls was $12.72 \pm 3.56\,\mu V$ and in epilepsy patients was $8.33 \pm 1.73\,\mu V$, a difference of $4.39\,\mu V$, which is significant. The mean P300 latency in epileptics $(348.17 \pm 22.05\,msec)$ was significantly higher than the mean P300 latency in the control group $(282.75 \pm 23.96\,msec)$. The mean IQ scores (95.67 ± 5.18) and mean DST scores (18.67 ± 1.07) of epilepsy patients are significantly lower than the mean IQ scores (109.33 ± 8.51) and mean DST scores (23.08 ± 1.08) of controls (Table I). Figure 1 shows the actual representative records of P_3 of control (a) and epileptic patients (b). The latter clearly depicts increased N_2, P_3 latency and decreased amplitude.

A significant negative correlation was found between IQ scores & P300 latency, DST scores & P300 latency, IQ scores & N2 latency and DST scores & N2 latency (Fig. 2).

DISCUSSION

Several groups of investigators have studied the cognitive changes in epilepsy and the results generally indicate (apart from inter-study variations) that there is a decline of cognitive functions in epileptics, especially the memory, attention, concentration and speed of mental processing. Our results are in consonance with these observations. The IQ scores and Digit Span scores of epileptics in our study were significantly lower than the scores of control group.

The N2 & P300 latencies were significantly higher in epileptics than in controls and they were negatively correlated with IQ and DST scores. These results are also in agreement with those of other similar studies (20, 21, 22). Prolonged N2 & P300 latencies may

indicate disturbed information processing in the brain as these cortical evoked potentials are sensitive indices of cognitive functions. Much work has been done on P300 potentials (23, 24, 25), but N2, potentials have not received as much attention. N2 is a long latency event related potential, normally having a latency of ~200 msec. It reflects processes that play a causal role in detection and discrimination. It is a sign of mismatch between an infrequent stimulus and a preceding series of background stimuli. N2 actually consists of two separate components, one reflecting controlled processing i.e. occuring only for attended stimuli, and the other being a manifestation of automatic processing referred to as Mismatch Negativity (MMN) to emphasise its dependence on mismatch of a deviant stimulus and a homogeneous background. P300 is a measure of controlled processing, i.e. processing that is intentional and capacity limited. It reflects subsequent memory storage processes that enable the subject to use current information to prepare for future events.

There are marked changes in EEG activity of primary generalised epilepsy patients. High amplitude spikes and sharp waves of 10/sec or higher frequency are seen during seizures and in interictal period. The epileptogenic foci must be interacting with generators of P300 residing in limbic areas of temporal lobe, changing P300 characteristics, however exact mechanism of this interaction remains to be worked out.

The P300 amplitude did not correlate with IQ scores or with DST scores (although the mean P300 amplitude of epileptic group was significantly lower than the control group), so P300 latency is more sensitive to cognitive changes than the P300 amplitude.

From this study it can be concluded that epilepsy does affect cognitive processing and causes decline of higher functions especially recent memory and recall, attention, concentration and speed of mental processing.

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