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P 300 EVENT RELATED POTENTIAL IN DEPRESSION

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ABSTRACT

P300 component of the event related potential (ERP) provides one neurophysiological index of cognitive dysfunction in depression. Forty subjects fulfilling DSM-III criteria for depression were compared to 40 age and sex matched normal controls. The P300 was recorded using the auditory odd-ball paradigm. Depressives had a significantly prolonged P300 latency and reduced P300 amplitude as compared to the controls. The P300 latency showed a significant positive correlation with age of the patient and severity of depression while P300 amplitude showed a significant negative correlation with age. The clinical subcategory of depression, duration of illness and sex did not show any relationship with P300 abnormality. Twelve out of 40 depressives (30%) had an abnormal P300. The mean Hamilton Rating Scale for Depression (HRSD) score was significantly high in those with an abnormal P300.

Key words : Event related potentials, P300, depression

Depression is the most prevalent psychiatric condition. Several areas of research suggest that depressed subjects exhibit deficits in cognitive functioning. Among these are self reported concentration problems (Watts & Sharrock, 1985), memory deficits (Golinkoff & Sweeney, 1989) and signal detection difficulties (Dunbar & Lishman, 1984). Impairment of cognitive function in depression could be evaluated more objectively by neurophysiological tests. Event related potentials (ERPs) are important non-invasive measures of brain function. The 'early' ERP components (those occurring within the first 100 msec post-stimulus) are thought to reflect the activity in sensory nerves, brainstem, thalamus and primary sensory cortex (Allison,1986). The 'late' ERP components (those occurring more than 100 msec post stimulus) are thought to reflect aspects of information processing such as attention and decision making (Pritchard,1981). The most widely studied of these late ERPs is the P300 component which consists of a positive wave recorded over the centro- parietal area occurring approximately 300 msec after delivery of a task relevant stimulus (Sutton,1965). It is thought to be elicited by salient events that would lead a subject to revise future strategies. Donchin (1979) has proposed a context updating model of the P300 component. They suggest that a subject engaged in monitoring a sequence of stimuli continuously and automatically forms a hypothesis about the nature of the next stimulus in the sequence. P300 is generated if the stimulus violates that contextual hypothesis and produces updating of the neuro-cognitive model (Pritchard, 1981). Cognitive theories have postulated that one key defect in depression may be an inability to update predictive cognitive schemata

A small number of studies have examined the P300 component in depression with variable results with some studies showing a reduction in P300 amplitude (Baribeau-Braun & Lesevre, 1983; Pfefferbaum et al.,1984; Diner et al.,1985; Thier et al.,1986; Blackwood et al.,1987, Brown et al.,1991; Gangadhar et al.,1993) and others have reported no change (Roth et al.,1981; Giedke et al.,1981; Brown et al.,1982; Patterson

et al.,1988; Sara et al.,1994). In contrast to P300 amplitude, P300 latency has consistently been reported to be normal in depressed subjects. A recent exception to this is the study of Bruder et al. (1991) who reported that subjects with major depression with melancholia had abnormally prolonged P300 latency during spatial but not temporal discrimination tasks, and a reversal of normal hemispheric asymmetry with prolonged P300 latencies for stimuli in the right hemifield.

As the results of various studies are inconclusive so the present study has been undertaken to evaluate the P300 latency and amplitude in patients with depression.

MATERIAL AND METHOD

Depressive patients attending the Psychiatry OPD of the Gandhi Memorial & Associated Hospitals, King George's Medical College, Lucknow on certain specified days formed the sample for the present study. The diagnosis of depression was based on the ICD-10 criteria (F 32 & 33). Out of the 53 patients screened 40 depressives fulfilling the following selection criteria were included.

Inclusion criteria :

(i) Patients fulfilling the diagnostic criteria of depression according to ICD-10,

(ii) A score of 17 or more on the first 17 items of Hamilton Rating Scale for Depression (HRSD).

Exclusion criteria :

(i) Presence of any co-morbid psychiatric and/ or neurological illness,

(ii) Patients on anti-convulsants and any other physical disease requiring active medication, e.g. hypertension, diabetes mellitus, ischaemic heart disease,

(iii) ECT during previous 6 months.

Forty controls were selected (out of the 55 subjects evaluated) from the normal healthy relatives of patients admitted in psychiatry with neurotic diseases. All the controls included in the study had no psychiatric and/or organic disease and had a score of less than 10 on M-R section of Cornell Medical Index (CMI).

The inclusion criteria common to both the study and control groups were a total score of 25 or more on Mini Mental State Examination (MMSE) and consent to participate in the study. Subjects having alcohol and/or any other psychoactive substance dependence, severe deafness and contamination of the P300 waveform were excluded from both the groups. All the subjects included in the study were right handed.

The various reasons for which patients and controls were not included in the study are given in table 1. The subjects fulfilling the selection criteria for depression and controls were given appointment on future date for a detailed workup. The following tools were used for evaluation.

1. Semi-structured proforma.
2. ICD-10 classification of mental and behavioural disorders. Clinical description and diagnostic guidelines (WHO, 1992).
3. MMSE (Folstein et al., 1975)
4. HRSD (consisting of 17 items) (Hamilton, 1960)
5. CMI (Broadman et al , 1949)

The semi-structured proforma includes patients identification, socio-demographic variables, history of present illness, past history, family history, personal history, premorbid personality, complete physical examination, mental status examination, and diagnostic formulation. Sixteen patients in the study group were receiving antidepressant drugs (Fluoxetine + Alprazolam 8, Imipramine + Diazepam 5, Imipramine + Lithium 2, Amineptine 1) for a period ranging from 1 to 4 weeks prior to inclusion in the study while 24 patients were drug naive.

The auditory odd-ball paradigm was used for P300 recording on Neuropack - 4 evoked potential machine (Nihon Kohden) in a quiet, air conditioned room with the subject lying comfortably on a couch. EEG was recorded between 0.1 Hz and 50 Hz from Fz and Cz sites (International 10-20 system, Jasper, 1958) referred to linked ears (A1+A2) with ground electrode on forehead (Fpz). Disc electrodes were applied using conducting jelly. The electrode impedance was kept below 5 kOhms by rubbing the scalp with a special abrasive cream. Stimuli were presented binaurally at 70db SPL. Pure tones of 1000 Hz (80%) and 2000 Hz

(20%) were presented in a pseudorandom order. The rise time and fall time of the tones were 10 ms while plateau time was 100ms. The subjects were expected to detect the infrequent tone (2000 Hz) by raising the right index finger. Subject was asked to lookup straight, avoid eye movements, and keep his eyes closed but keep awake. Experimenter observed the subject to ensure that he/she does not sleep off and detected the targets correctly. Correct detections were counted. The accuracy of the subjects response was checked by noting the difference between the number of target stimuli actually presented and those to which the subject responded by lifting his index finger. A correct detection rate of 80% or more was considered adequate. A pre-stimulus baseline of 100 ms was obtained before the stimuli (frequent and rare) were delivered and thirty responses were averaged for both non-target and target stimuli. Two sequential recordings were done to ensure reproducibility. Automatic artifact rejection facility was used. A 50 Hz notch filter was not used. Smoothening of the response was done. The data was stored on a floppy.

The latency and amplitude measurement were done by placing cursors on the screen by a person who did not know about the subject identification. The various peaks of the waveform were identified by visual inspection. The P300 is usually followed by a slow negative wave and is recognised as the positive wave after N1-P2-N2 complex and between 265 and 600ms. None of the recordings had a bifid P300. Latency was measured by moving a cursor to the peak and amplitude from a superimposed isoelectric line. The measurements were made on Cz site. The criteria for labeling a waveform as abnormal were based on the regression equation for P300 latency and age obtained in the laboratory. The P300 latency was considered abnormal if it exceeded the predicted value for that age plus 2 standard deviations.

The 't' test was used to compare the means between the patient and control groups. Correlation of coefficient (r) was calculated for age, duration of present episode, HRSD score and P300 latency and amplitude. Relationship of P300 latency and amplitude with various clinical features were analysed by one way analysis of variance and using Scheffe's test for inter-group differences. The level of significance was chosen at $p<0.05$.

RESULTS

The demographic data for the subjects in the study is given in table 2. The patients and the controls were age and sex matched.

TABLE 1
REASONS FOR NON-INCLUSION IN STUDY

Reasons	Patients (n=13)	Control (n=15)
Organic brain disease	3	-
Seizure disorder	2	3
Alcohol and/or other psychoactive substance dependence	3	6
ECT in last 6 months	2	-
Hearing impairment	1	2
Contamination of waveform	2	4

TABLE 2
AGE AND SEX DISTRIBUTION

Variables	Control Group n	%	Study Group n	%
Sex				
Male	23	57.5	21	55.0
Female	17	42.5	19	45.0
	X^2 =0.05; df=1; p=NS			
Age (in years)				
< 40	19	47.5	17	42.5
41-60	10	25.0	12	30.0
>60	11	27.5	11	27.5
Range	21-70		20-70	
Mean±SD	44.8±15.2		46.2±15.9	
	X^2 =0.29; df=2; p=NS			

The mean P300 latency was significantly prolonged (Fig. 1a & b) and P300 amplitude significantly lower in depressives (Fig. 2). There was no significant difference in the P300 latency and amplitude amongst treated (391.81±51.53 ms; 5.95±2.13 uv) and untreated (383.58±50.35 ms; 6.32±3.21 uv) patients. Depressive patients above 40 years and those with a severe depression had a significantly greater prolongation of P300 latency as compared to those 40 years or younger and those with a mild

or moderate depression respectively. The P300 amplitude was significantly lower in the depressives above 60 years as compared to patients 60 years or younger. The sex of the patient, clinical subtype (depressive episode, recurrent depressive disorder, bipolar affective disorder-current episode depression) and duration of present episode did not have any significant relationship with P300 latency and amplitude (Table 3). There was a significant positive correlation between P300 latency with age and HRSD score (Fig. 3), while there was a significant negative correlation between P300 amplitude and age (Table 4). The P300 was abnormal in 12 patients with depression (30%).

TABLE 3
RELATIONSHIP OF P300 LATENCY AND AMPLITUDE TO VARIOUS CLINICAL FEATURES

Clinical features	n	P300 Latency (msec)	P300 Amplitude (μv)
Age (years)			
≤ 40	17	363.1±63.3	7.32±2.54
41-60	12	404.8±63.3*	7.07±3.27
>60	11	406 4±54.4*	4.43±2.03**
Sex			
Male	21	387.3±48.5	6.29±2.94
Female	19	389.2±57.5	6.56±2.63
Clinical subtype			
A	23	370.0±59.0	6.02±2.61
B	8	404.8±59.8	4.78±2.28
C	9	383.7±48 3	6.83±3.63
Severity			
Mild	12	359.8±53.1	5.82±2.78
Moderate	16	367.3±53.0	6 49±3.01
Severe	12	432.6±42.6***	5.52±2.50
Duration of present episode (months)			
≤ 3	21	387.5±51.6	5.82±2.90
>3	19	389 8±54.7	6 10±2.72

*p<0.05 as compared to ≤ 40 years
**p<0.05 as compared to ≤ 40 years and 41-60 years
***p<0.01 as compared to mild and moderate severity

TABLE 4
CORRELATION BETWEEN P300 LATENCY AND AMPLITUDE WITH VARIOUS CLINICAL FEATURES

Clinical features	Correlation coefficient (r) P300 latency	P300 amplitude
Age	0.52*	-0.42**
HRSD score	0.68*	-0.11
Duration of present episode	-0.07	-0.21

*p<0.001; ** p<0.01

HRSD score was significantly higher in those with abnormal P300 as compared to those with a normal P300 (Table 5).

TABLE 5
COMPARISON OF DEPRESSION WITH NORMAL AND ABNORMAL P300

Clinical features	Normal P300 (n=28)	Abnormal P300 (n=12)
Age (in years)	46.9±16.3	44.0±15 5
Sex (m:f)	15.13	6·6
Duration of present episode (in months)	4.13±4.60	4.17±3.76
Family history positive	5	-
HRSD score	20.6±3.4	26 4±4.7*

*p<0.01

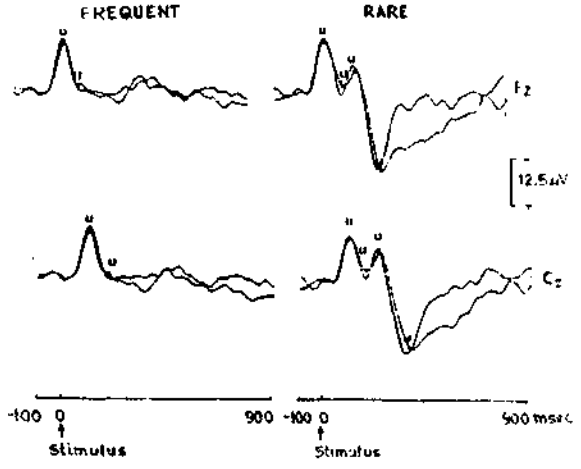

Fig. 1A Normal P300 in a healthy control

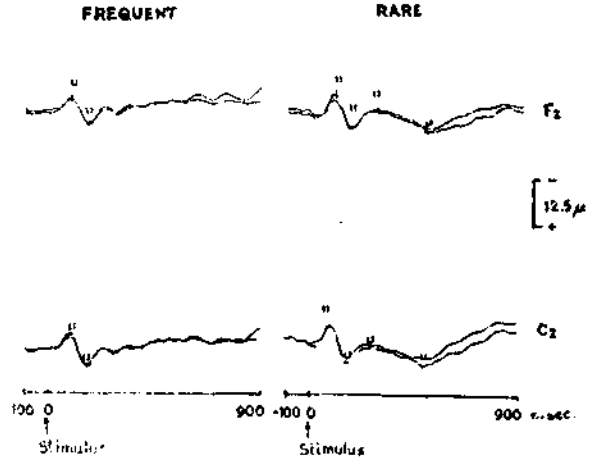

Fig. 1B Abnormal P300 in a patient with depression showing prolonged latency

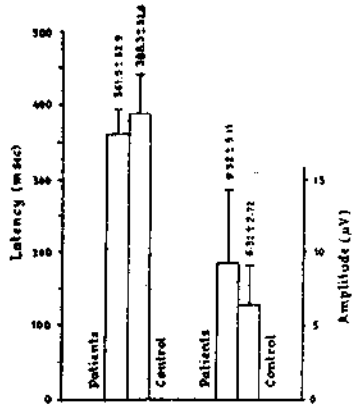

Fig. 2 P300 latency and amplitude showing a significant increase in latency (t=2.72; p<0.01) and decrease in amplitude (t=3.62; p<0.01) in study group

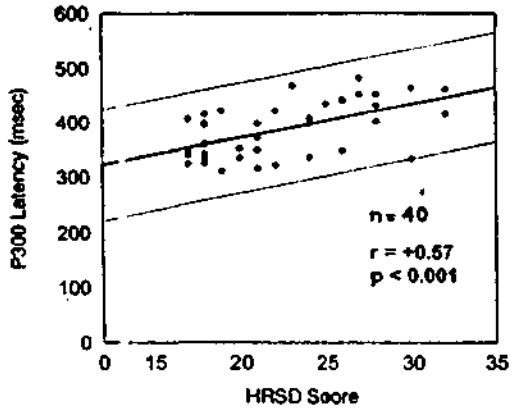

Fig. 3 Scattergram showing the correlation between P300 amplitude and HRSD score

DISCUSSION

ERPs are potentials that are produced when information is processed by the living brain. They are derived from internal processes that are not dependent on external stimuli, that is they are believed to reflect "post decision closure" in preparation for the processing of a new stimulus and involve stimulus evaluation and context updating after a stimulus has been assessed and acted upon (Beck & Clark, 1988).

One of the major findings in the present study was that the mean latency of P300 in depressive patients was significantly prolonged than that of age and sex matched healthy controls (p<0.01). This was consistent with the study of Bruder et al. (1991) who examined P300 latency to auditory temporal and spatial discrimination tasks in patients of major depression with melancholia. On the other hand Blackwood et al. (1987), Gangadhar et al. (1993) and Sara et al. (1994) failed to find significant prolongation of P300 latency. Probably the most important factor affecting P300 latency is aging. Another variable is task difficulty. It has been shown that making stimuli less discriminable leads to prolongation of P300 latency (Squires, 1976). The depressive patients in the present study showed a statistically significant correlation of latency of P300 with age and severity of depression as measured by total score of HRSD. On the contrary, Schlegl et al. (1991) reported that the P300 latency in depressives is correlated with the retardation items of the Bech-Raefelsen Melancholia Scale but not on the total HRSD score.

The mean amplitude of P300 in depressive patients was found to be significantly lower than normal controls (p<0.01). This was consistent with the studies of Levit et al. (1973), Roth et al. (1981), Shagass et al. (1985), Baribeau-Braun and Lesevre (1983), Diner et al. (1985), Thier et al. (1986), Brown et al. (1991) and Gangadhar et al. (1993). However, Sara et al. (1994) did not find any change in P300 amplitude of depressed patients as compared to normal controls although the depressives performed the experimental task significantly less accurately than normal controls. The amplitude of P300 is increased by many factors, including the subjects attentiveness and the unpredictability of the oddball stimulus. The reduced amplitude of P300 suggests that patients with depression fail to extract fully the available information from a stimulus possibly because of the inability to allocate attention to

the ERP task. The P300 amplitude has been shown to predict response to electroconvulsive therapy in patients with melancholia. The P300 amplitude is normal in rapid responders as compared to slow responders (Ancy et al.,1996).

No significant difference was observed in mean latency and amplitude of P300 among different diagnostic subcategories of depression like depressive episode, recurrent depressive disorder and bipolar affective disorder- current episode depression. Similarly duration of current episode of depression had no effect on latency and amplitude of P300.

The P300 has a bilateral, mid parietal distribution. However, a single generator for the potential cannot be defined, the wave is likely to reflect activity in multiple areas of the brain (Picton, 1992). The hippocampus and adjacent areas of the limbic system are active at the time of scalp recorded P300 (Halgren, 1980). It is possible that the P300 represents activity generated in both the limbic system and the parietal association area. Positron emission tomography (PET) scan studies have reported global or local reductions in cerebral blood flow and metabolism in depression (Gur et al.,1984; Baxter et al.,1985).

Altered P300 is found in association with schizophrenia, infantile autism, childhood attention defect disorder and alcoholism (Barrett, 1993), so P300 is unlikely to serve as a biological markers for depression. However, one can speculate that all the above disorders, may in common with depression have structural and/or functional abnormalities of limbic/hippocampal function.

P300 abnormalities in depression may be considered to reflect abnormalities of cognitive processing. The exact usefulness of P300 in patients with depression is still uncertain as the changes lack sensitivity and disease specificity. The procedure itself requires a considerable understanding and cooperation by the subjects. One of the main problems for the clinical application of ERPs is their wide variability in the healthy population. It may be more fruitful, therefore, to concentrate on within patient studies e.g. studying depressives before and after drug treatment. Gangadhar et al. (1993) have shown that rapid responders had larger (normal or near normal) P300 amplitude than the slow responders. Murthy et al.(1997) have reported normalisation of P300 amplitude following treatment in dysthymia. Further analysis of sub - components of P300 is warranted as cognitive functions are expected to vary from moment to moment. P300 may be slightly different from stimulus to stimulus thus single trial evoked potentials might be useful for recording P300 if the technique is established.

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