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PROJECT REPORT

NAME : Dr. SREEKANTASWAMY

PROGRAMME : D.M. Neurology

MONTH AND YEAR OF SUBMISSION : October 1993

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LIST OF PROCEDURES DONE
PROJECT REPORT

TITLE OF THE PROJECT: EVENT RELATED POTENTIAL (P_{300})
NORMAL VALUES FOR HEALTHY
ADULT POPULATION

NAME ..... Dr. SREEKANTASWAMY

PROGRAMME : RESEARCH PROJECT FOR D.M. NEUROLOGY

MONTH & YEAR
OF SUBMISSION : OCTOBER 1993

CERTIFICATE

I, Dr....SREEKANTASWAMY.....hereby declare that I have actually performed all the procedures listed / carried out the project under report.

Signature.....

Place :

Name in... Dr. ...SREEKANTASWAMY.....
capital letters

Date :

Forwarded. He has carried out the minimum requirement of procedures / etc.

Signature 15/10/93

Head of the department

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM 695 011

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Dr.SREEKANTASWAMY

PLACE: TRIVANDRUM

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CONTENTS

EVENT RELATED POTENTIAL (P_{300})

NORMAL VALUES FOR HEALTHY ADULT POPULATION

INTRODUCTION

Electrophysiology is one of the important branches of Neurology which has a significant role in the diagnosis and management of various neurological disorders. Among the available methods in the field of electrophysiology, evoked potentials have an important place in the field of neurosciences. An evoked potential is an electrical manifestation of brain's reception of and response to an external stimulus.

Long latency evoked potentials related to the aspects of cognition processing are referred to as cognitive evoked potentials, or endogenous potentials. Among the various endogenous potentials P_{300} (P_3) is the best known and widely studied which is a large positive wave occurring around 300 MS. The other endogenous potentials are N_1,P_2,N_2, slow wave (SW) and the contingent negative variation (CNV).

There is lot of interest grown in these potentials in the recent years, because of growth of cognitive psychology, and greatly increased interest in

neurocognitive disorders. These event related potentials (ERP) and in particular, P_{300} wave are accepted research tools for the study of cognitive neurosciences. They are being increasingly used in the diagnosis of Neurocognitive disorders. Since these components are subjected to various variables, including the laboratory conditions, each electrophysiology lab should have its own normative data of the control healthy population, for the meaningful application of this test for various disorders.

Most laboratories engaged in the field of neurocognitive disorders, psychiatry, and behavioral neurology have their own established normal values for population. In India, various neurosciences and psychiatry institutes, are employing this test in their laboratories, especially in the field of psychological medicine. They have their own lab values for control population. Hence, this prospective study was undertaken to establish the normal values of the healthy population attending our institute.

OBJECTIVES:

1. To establish the normal data for P_{300} of the adult healthy population for the laboratory.

2. To compare the latency and amplitude changes between male and female population at various age groups.

3. To find out changes of P_{300} of people with various educational and occupational standards.

REVIEW OF LITERATURE

Evoked potentials are being increasingly used as an objective tests of afferent function in patients with neurological diseases. (6)

The concept of usefulness of brain waves in the assessment of mental events dates back to 1938, when Woodworth in his survey of experimental psychology, ventured to hope that brain waves might be used in the timing of mental events. (17). The presence of normal, or near normal sensory evoked potentials does not guarantee that the sensory information is actually utilised, like for example a perfectly normal BAEP may be recorded from individuals who are behaviouraly blind. There are certain components of evoked potentials, however, that seems to have an association with the cognitive processes.

Cerebral evoked potentials can be largely divided into two categories, stimulus related and event related potentials. The stimulus related potentials usually have short latency (less than 50 MSSec) and are evoked by specific stimulus. They are also called exogenous potentials. The event related potentials (also called endogenous potentials, cognitive potentials) are usually nonspecific for the kind of stimulus presents, and are

not localised to any specific cortical sensory areas, but instead they are predominantly recorded over the midline centroparietal scalp locations, regardless of the modalities of stimulus. They usually occur after 250 MSec, are mostly susceptible to psychological influences, like the psychophysiological state of subject, his alertness, attention, memories of relevant past experiences, expectancy and motivation.

The credit of exposing this cognitive potential to the field of neuroscieces goes to Sutton et at (40). Various authors define P_{300} in different ways. According to Dochin et al (8) "It is a component with a latency longer than 275 MSe, positive in polarity at all mid line electrode locations (in comparison with a neutral reference), with maximum positivity at parietal and central locations, elicited by task relevant stimulus and whose amplitude is affected by subjective probability and task relevance of the stimulus." Douglas S. Goodin (6) defined P_{300} as an electropositive wave that occurs approximately 300 m.Sc after an infrequently occurring stimulus to which the subject is attending. J.Polich defined it as a large (5-15 Microvolts) positive going waveform that occurs with a modal latency of about 300 M.Se in normal young adults (28).

P_{300} is a prominent electropositive wave that occurs with latency that varies from 250 to 600 m.se, depending on stimulus parameters. The maximum amplitude is over the midline central and parietal regions. It can be elicited with stimulus of any modality (4.5). The various modalities of stimulation like, auditory, visual and somato-sensory can be used. The most commonly employed method is the auditory odd ball paradigm, because it is easy to administer and reliably produces readily identifiable P_{300} component (32). This method involves presentation of unexpected or infrequent stimuli randomly interspersed among more frequent stimuli. The infrequent stimuli differs from the frequent only in terms of frequency or intensity. The person is required to be attentive to the infrequent stimuli, and ignore the frequent ones. After averaging few (usually 20-30) infrequent stimuli, the latency and amplitude are analyzed. Indeed the P_3 amplitude is so large that the P_3 response can be identified in a single trial. The percentage of rare stimuli to regular ones ie, normally 10-30%.

The two parameters of the stimulus, the attention of task relevance and frequency operate independently. The infrequency is supposed to elicit the P_{3a} which

occurs slightly earlier and has a more frontal distribution than the parietal maximum P_{3b} component, which is elicited by attending to a task relevant stimulus. The routinely elicited P_{300} represents presumably a sum of these two components (3). To name some of the other paradigms are the omitted stimulus paradigms, feed back and guessing paradigm. The P_3 is normally preceded by a negative component called N_2 component. The amplitude of P_3 is quite large as compared to the other evoked potentials, and hence an average of few responses of rare stimuli is usually sufficient. The responses are usually recorded from a minimum of four channels i.e. FZ, PZ, Cz referenced to an indifferent scalp location (eg: linked mastoid or ear lobule). The eye movement artifact usually contaminate the P_{300} peak, hence they are monitored by fourth channel (6).

There are reports where in two subcomponents of P_{300} are observed, P_{3a} and P_{3b} which are elicited by both auditory and visual stimuli.(41) (30). The P_{3a} preceeds P_{3b}. The P_{3a} is usually larger in amplitude over the frontal and central electrode sites, appear to reflect the manifestation of an early alerting process (4,5,19,36). Later peak has been labelled the P_{3b} and corresponds to the memory updating and attentional

allocation processes. (7,8). The appearance of these two peaks some times results in difficulty in locating the exact peak and measuring the latency accurately. It is suggested that the largest peak, having central parietal maximum amplitude occurring with in the latency range, appropriate for the age of the subject be employed as a given individual's P_3 component. This so called PMAX approach has been evaluated and found to produce consistent overall data (28,30). Few of the studies take the average of these two peaks. However the origin of these two subcomponents of P_{300} is not definitely known (30).

Most studies have employed the auditory odd ball paradigm for eliciting P_{300}, which requires patients attention to concentrate on the odd stimuli. However few studies have shown that P_{300} can be elicited even without the attention of the subject (32)(31),A small per cent of otherwise healthy population do not generate P_{300} wave, inspite of repeated trials. Most authors report a failure rate of five per cent or less (6,31,29), the reason for which is not known.Majority of the studies take P_{300} as the positive component occurring after about 300 (MSe). The upper limit of the latency varies from author to author, excepting for few studies, most agree that it lies

between 400-500 m.se. (28,29,33). In few studies the upper limit is mentioned up to 700 - 750 MSe (1).

The latency is the important aspect of P_{300}, as it is this part, which is of clinical utility mostly, because it reflects the speed of stimulus classification resulting from the discrimination of one event from another, when updating of the memory context occurs (21,22). A variety of normative reports have found that the individual differences in P_3 latency from normal subjects correlates with general cognitive function as assessed by neuropsyhological as well as experimental procedures.

The latency is subjected to various variables, apart from the stimulus parameters, like, intensity of stimulus (Shorter latency with increasing intensity) (33). The subject parameters are many, including the time of test conducted, temperature, etc. (33). There is a tendency for the latency to be prolonged as the age advances. In general the latency increases by 1.4 M.Se/Yr from adults to the old age (6.32) (34). The amplitude is also variable depending on the above parameter. It varies depending on the amount of information providing by the given stimulus (38). For both latency and amplitude the important factor is the attention of the subject. In

general the amplitude decreases with advancing age, at a rate of 0.2 microvolt/yr (6). No significant change in latency is noted between males and females, although slightly increased amplitude is seen in males as compared to the females, mostly because of skull thickness and head size.(33).

As far as the site of origin of P_{300} is concerned, there is a lot of difference of opinion between the various authors. Many areas of brain have been postulated to be the source of generation of P_3 wave, these include diencephalon, medial temporal lobe structure, and various neocortical areas. According to Michel Smith et al (19) it is the inferior parietal lobule that generates P_3 component. Helgren et al (17) proposed that P_3 was generated in hippocampus. Yingling et al (45) while stimulating the subcortical structures for chronic pain, recorded P_3 from thalamus. Desmedt et al (6) proposed that P_3 reflects transient inhibition of reticulothalamic cortical activating mechanism.

Applications of P_{300}: Since Sutton et al (41) first described the P_{300} potential, the clinical application of this in the diagnosis of various cognitive disorders are increasing. Because P_3 appears to reflect memory and

decision making processes, it has been applied as an index of information processing in a wide range of normal and cognitively impaired subjects (28). Douglas et al (6) reported that in dementia of various etiologies 80 per cent had abnormally prolonged P_3 latency compared to the age controlled subjects, since then there is a great interest in the use of this coponent in the diagnosis of dementia. It helps to differentiate the pseudo dementia from true dementia, as only 4 per cent of patients of various psychiatric illness had prolonged latency in Douglas study.

Goodin et al (8) showed that the prolonged P_3 latency reverted back to normal in some neurological conditions where the cause of dementia could be treated. The P_3 may be useful in differentiating subcortical from cortical dementias.(13,14,40). Rosenberg et al (40) suggested that P_3 can be utilised to evaluate the relative risk of dementia in Huntington's chorea. The latency was found to be prolonged in one fourth of the relatives of Huntington's chorea who were at risk. (35). P_{300} has been increasingly employed in the assessment of effect of psychotropic substances. (20,21) It has been studied in the assessment of early hepatic encephalopathy.(44).

It is employed in assessing the alcoholic subjects, and subjects with family history of alcoholism by Pfefefferbaum et al (35), and by Belgleiter et al (2), and found to have altered P_3 compared to the control groups.

It is utilised to investigate the pathophysiology of various neurobehavioral syndromes, like in assessing prosopognosia (3), in attention following prefrontal lesions (19) and anosognosia (3).

In a study by Marsia et al (26), it was shown that in narcolepsy, the latency was normal, where as the amplitude was significantly reduced. P_3 is used in epileptic patients on antiepileptic drugs to assess the effects of these drugs on cognition (7) It is employed as a tool to predict the outcome of nontraumatic coma (36). It may have a role in following the clinical course of a dementing illness, monitoring response to treatment, and identifying patients who are at a risk of developing dementia (15,27).

It is also utilised to know the efficacy of drugs like benzodiazepines (43)

MATERIALS AND METHODS

The material for this study comprised 100 healthy subjects of different age groups from 21 to 60 yrs and above. These subjects included staff of our institute like, unit helpers, staff nurses, doctors, and friends and relatives of the patients who visited the hospital. All these subjects were of different education-al standard, socioeconomic status and profession. All the test subjects were enquired about any neurological illness in the past, mental illness, memory deficits of any kind, head injury and drug intake (drugs that are supposed to have effect on neurocognitive aspect). Only those who had none of the above problems were recruited for the study. Those subjects who had significant hearing problems were not taken for the study. All the subjects were explained the purpose and the test procedure. The whole population was divided into five age groups. Gr.I contained subjects from 21-30 yrs. Gr.II 31-40, Gr.III 41-50 Gr.IV: 51-60 Gr: V 61 and above. In each group, ten males and ten females were taken. The three subjects who failed to record any P_3 potentials were excluded in the final analysis. Excluding these three subjects, the total were one hundred.

All the subjects were made to sit comfortably in a chair, and asked to close the eyes, and listen to the stimulie which were delivered through the headphone. The frequency and intensity of stimuli for both ears was same. Most of the tests were conducted two hours after the intake of major meal. The room temperature was kept constant at 25^0c during the test procedure. The machine used was Dantec 4000 evomatic. A total of four channels were used i,e FZ,CZ,PZ, referenced to the linked mastoids, and the fourth channel for monitoring the extra ocular movements, by keeping one electrode above the upper eye lid and one below the lower lid. The ground was placed on the forehead. Two click stimuli, one non target at a tone frequency of 1000 HZ and another the target at a tone frequency of 2000 HZ were delivered at 80 per cent and 20 per cent ratio. The duration of each stimulus was kept at 50 M.Sc. the raise and fall time at 10 M.Se, and intensity was 60 dl spl above the minimum hearing threshold. The rate of click delivered was 1 per second. The band pass was 0.3 to 2 HZ high pass and 30-100 HZ low pass. Sweep speed was kept at 750 M.Se. The skin and scalp impedance was kept below 10.k.om. The subjects were requested to close their eyes, and concentrate on the target stimuli, and to raise the index finger whenever they heard the

click. A total of 3 trials were done for each subject, first trial was discarded to allow the subjects to accommodate to the test procedure. The second and third trials were considered for analysis. The P_3 potential was identified as the most prominent positive wave occurring after 250 M.Se., and with-in 750 M.Se. in all the three electrode sites. After averaging twenty target stimuli for each trial, the automatic averager displayed the mean of these twenty stimuli. The mean potential of each trial was super-imposed on one another, and when super imposable, it was considered for analysis, and measurement of latency and amplitude was done. The time from the stimulus artifact to the peak of the prominent positive wave was taken as latency. If ~~whenever~~ the peak was not clear, or if there were two peaks, the average of these was taken as latency. The amplitude was taken from base line to peak. After 3-4 trials, if the subject did not produce any P_3 potential, it was considered not elicited.

After analyzing the latency and amplitude for each age group, all the subjects were grouped into two groups, based on their educational level - those who had education upto tenth standard were grouped as group I, and those who had beyond tenth standard as gr.II. Similarly, based on the nature of profession, the whole

population was divided into two groups, gr. I included unskilled (House wives, labourers, unemployed subjects) and skilled (Nurses, doctors, engineers and teachers). Also, based on whether the subject came from urban and rural background, they were grouped into two groups. The mean latency for the whole population, for each age group, and amplitude for each sex was calculated, in each age group, the lowest and highest latency was identified.

RESULTS

A total of 103 subjects participated in this study. Among them no response (P_3) could be elicited in three, after repeated trials. These three were not considered for the final analysis. At the end of substracting these three non responders there were 100 subjects for final analysis. The non responders constituted 2.9 percentage of the participated subjects. The mean latency and amplitude for the entire population at different electrode sites is given in table-I. The amplitude at Pz was on the whole greater than the other electrode sites. The minimum latency recorded for the entire population of 100 was 258 M.Se, in a 43 yr old male, and the max. latency was 468 M.Se in a 48 yr old male subject. (Table.II).

Table.III(a) and (b) shows the mean latency and amplitude for various age groups at the various electrode sites. However the mean lower latency was seen in the age group between 21-30 yrs and the maximum was in 61 and above group. The oldest subject in this study was 74 yr old, who had the mean latency of 368 M.Se.

The mean latency for the entire population irrespective of age, sex and electrode site was 341.8 M.Sec. and amplitude was, 8.65 microvolts. The mean latency for all male subjects was 338.6 M.Sec with an amplitude of 10.03 Microvolts (Table IV) for females it was (344.95) M.Sec and amplitude of 8 Microvolts.

There were seventy one subjects who had their education upto tenth class (gr.I) and twenty nine who had above tenth class (gr.II). The later age group included highly qualified doctors, engineers, staff nurses and, teachers. The mean latency at the three electrode sites was 341.46 M.Sec.(SD.31.40) for group.I, and 343.18 M.Sec (Sd:40.34) for gr.II. There were 32 subjects with skilled profession and 68 with unskilled profession. The mean latency for skilled professionals was 344.17 (SD 42-17) and for unskilled it was 340.53 M.Sec (SD: 29.97). There was difference of latency and amplitude between urban and rural population. (Table.V)

TABLE I

MEAN LATENCY AND AMPLITUDE FOR THE 100 SUBJECTS

	FZ	CZ	PZ
Amplitude (Microvolts)	8.7691 (4.8158)	8.6548 (5.0822)	9.8008 (4.8628)
Latency (MS)	341.1100 (34.0600)	341.5000 (34.2193)	342.7680 (33.9739)

TABLE II

SHOWING MINIMUM AND MAXIMUM LATENCY AND AMPLITUDE AT VARIOUS AGE GROUPS

Age (Yrs)	Latency (M.Sec)		Amplitude (Microvolts)	
	Minimum	Maximum	Minimum	Maximum
21-30	290.60	370.00	2.41	23.00
31-40	269.30	400.00	3.44	22.50
41-50	258.00	465.33	1.50	18.10
51-60	302.00	431.33	2.41	16.43
61 above	312.00	444.66	2.08	16.21

TABLE - III (a)

SHOWING MEAN LATENCY AND AMPLITUDE FOR VARIOUS AGE GROUPS

Age Group	Latency(M.Sec)			Amplitude (Microvolts)		
	FZ	CZ	PZ	FZ	CZ	PZ
21-30	316.000	316.000	319.000	8.415	8.430	8.430
31-40	334.000	337.000	337.000	10.250	11.200	11.200
41-50	332.000	332.000	334.000	8.715	8.120	9.400
51-60	358.000	356.000	356.000	7.180	5.930	9.800
61 and above	358.000	356.000	356.000	7.8000	7.8000	8.430

TABLE - III(b)

TABLE SHOWING MEAN LATENCY (MS) AND AMPLITUDE (MICROVOLTS) IN VARIOUS AGE GROUPS

	21-30	31-40	41-50	51-60	61 and above
MALE					
F	330.00	326.20	325.60	353.60	355.80
Z	(12.49)	(12.48)	(8.29)	(7.15)	(9.05)
C	330.00	326.40	325.20	355.00	354.70
Z	(12.39)	(13.59)	(7.73)	(6.56)	(6.28)
P	330.00	328.40	326.40	365.09	366.66
Z	(13.21)	(13.45)	(9.54)	(10.26)	(9.17)
FEMALE					
F	313.10	335.00	340.60	365.09	366.66
Z	(6.52)	(9.01)	(7.99)	(7.79)	(6.76)
C	312.90	336.00	343.80	364.54	366.66
Z	(6.77)	(8.89)	(8.61)	(8.55)	(6.96)
P	313.80	336.60	349.00	364.90	365.77
Z	(7.36)	(8.97)	(10.04)	(10.26)	(8.23)

TABLE - IV

SHOWING MEAN LATENCY AND AMPLITUDE FOR MALE AND FEMALE SUBJECTSAT DIFFERENT AGE GROUPS

Age Group (Yrs)	Latency(M.Sec)		Amplitude (Microvolts)	
	Male	Female	Male	Female
21-30	312.9 (21.6654)	313.266 (21.665)	12.7043 (6.2026)	6.889 (3.1416)
31-40	326.933 (22.669)	335.866 (32.492)	13.13 (5.9312)	8.9596 (5.066)
41-50	325.8 (24.9586)	344.000 (44.889)	8.8721 (5.2914)	8.8856 (4.4127)
51-60	354.5333 (42.3248)	364.8455 (19.0466)	7.2146 (2.7932)	8.8632 (4.3212)
61 above	356.1666 (35.6834)	366.3704 (31.4581)	8.1733 (4.3452)	7.3222 (3.4649)

TABLE V

SHOWING MEAN LATENCY AND AMPLITUDE FOR URBAN AND RURAL POPULATION

Population	Latency (M.Sec.)	Amplitude (Microvolts)
Urban	345.44 (37.46)	9.16 (4.88)
Rural	339.84 (29.42)	8.99 (4.96)

DISCUSSION

This study included population at random irrespective of age, sex, education and social background. The grand mean latency of the all one hundred subjects is in accordance with most studies (3,1,28,7,8). The mean latency and amplitude for various age groups are with-in the normal range. However there was no linear increase within the increasing age groups as seen in table-3. Most of the available studies mention about the linear increase of latency and decrease of amplitude with age. In this study also, the mean lowest latency was in the younger age group, and highest mean latency was in older age group, except that the latency in the age group of 41-50 yrs. which was lower than the age group below it. The latency in our female subjects was slightly higher than the males, but it was not significant, and it is similar to the observation of others (1,3,28,33). The amplitude was higher in younger age group as compared to older age; There was a suggestion of higher amplitude in male subjects, similar to the observation of J.Polich (33). The overall amplitude of P_{300} was slightly lower as compared to other studies (1.5,3). The amplitude at

various sites as noted in Table-III is similar to other studies. The maximum amplitude of P_3 was obtained at parietal region, however there was no proportionate increase of amplitude when compared to FZ and CZ sites. There was no significant variations in the latency between the different sites. None of our subjects had latency beyond 468 M.Se. which is similar to most of the studies.

The latency and amplitude were analyzed separately for skilled and unskilled population. The unskilled population had slightly shorter latency than the skilled ones. Among the four subjects older than 70 yrs. the latency was with in 380 M.Se. and had the mean amplitude lower than the other age groups, except for one who was 73 yrs. old who recorded an amplitude of 15.60 micro volts at PZ. However, the mean highest amplitude was recorded in subjects between 21-30 yrs. Majority of these subjects who recorded higher amplitude were males, even in the older age this difference was observed. The latency of older male subjects was shorter than the age matched females.

When the two groups of educational standard were compared for the latency and amplitude, no significant difference was observed. None of our subjects were

uneducated. Most of them had their primary education, The whole population in this study was from Kerala state which has been declared with hundred percent literary. The results of this study needs to be compared in terms of latency and amplitude with the populations of the other states in India, to asses whether the population in Kerala as a whole have a basic higher level of intelligence.

CONCLUSIONS:

1. This study was undertaken to establish the normal data for P_{300} among the healthy population. 50 male and 50 female age matched subjects were studied.
2. There was slight difference interms of latency and amplitude - between different professions, education standard and social background.
3. There was longer latency with lower amplitude in female subjects as compared to male subjects.
4. The mean latency of the whole population was 341.8 M.Sec.

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