

AGE RELATED CHANGES IN P300

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***An Independent Project submitted as part fulfilment of First
Year M.Sc., (Speech and Hearing), Mysore.***

All India Institute of Speech and Hearing, Mysore

May 1997

DEDICATED

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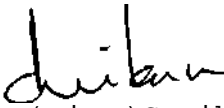
My Dear Thatha

*"An Human Dynamo, whose
Zest and zeal for life
Never cease to surprise"*

CERTIFICATE

This is to certify that this Independent Project entitled **AGE RELATED CHANGES IN P300** is the bonafide work in part fulfilment for the degree of Master of science (Speech and Hearing) of the student with Register No.M9617.


Mysore
May, 1997


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CERTIFICATE

This is to certify that this Independent Project entitled **AGE RELATED CHANGES IN P300** has been prepared under my supervision and guidance.

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DECLARATION

This Independent Project entitled **AGE RELATED CHANGES IN P300** is the result of my own study under the guidance of Mrs.Vanaja C.S. Lecturer in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysore and has not been submitted earlier at any University for any other diploma or degree.

Mysore
May, 1997

Reg. No.M9617

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I am thankful Dr.(Miss) S. Nikam, Prof. and Director, All India Institute of Speech and Hearing, Mysore, for allowing to take up this project.

I express my deep and sincere indebtedness to my guide Mrs.Vanaja, C.S, Lecturer in Audiology, All India Institute of Speech and Hearing, Mysore, for her invaluable help, suggestion and guidance at every phase of this project.

Dear Mom, Dad, Vinayak and Visa - no language has words to represent the love you have showered on me. I just feel like standing on the highest point of the world and shouting "Hey, I've got the Best".

"There is always room for improvement, it is the biggest room in the house" - Dad and Mam, its these words of yours that carry me against all the odds I face.

A friend - is a person who sings with you at the top of the mountain and walks quietly beside you in the Valley.

My beloved friends, It would be a meek attempt to repay your love by just mentioning your names in this piece of paper. It's you people who have opened a whole new world of happiness, fun, love and affection to me. Thanks a ton, yaar.

Finally, I'd like to thank Rajalakshmi Akka for her indispensable work of typing this Independent Project and giving its final shape.

TABLE OF CONTENTS

	PAGE No .
I INTRODUCTION	1 - 10
II REVIEW OF LITERATURE	11 - 53
III METHODOLOGY	54 - 60
IV RESULTS AND DISCUSSION	61 - 76
V SUMMARY AND CONCLUSIONS	77 - 79
VI REFERENCES	80 - 95

INTRODUCTION

"The attempt to identify electrophysiological correlates of attention in man may appear as a rather empty exercise. Indeed one could ask, what can possibly be gained by linking up ill-defined, hypothetical events on the psychological level with diffuse and unreliable electrophysiological phenomena having unknown brain origins?. Our reply is that the scalp Recorded Event Related Potentials (ERPs) are virtually the only means that current technology provide to evaluate the physiological events of the normal human brain, as it performs its spectacular feats of information processing".

Hillyard and Picton (1979)

Concentration on the short latency or auditory brainstem response (ABR) by the field of audiology clearly stemmed from the needs for an objective measure of hearing. Psychology on the other hand focussed on the late or long-latency. ERPs since these are associated with perceptual and cognitive processes. Recently there are signs, however, that the interest of the field of audiology and hearing sciences are expanding beyond identification -the "Does the patient hear the tone/question?" to measures of auditory speech discrimination, processing and cognition i.e., the "How does

the patient hear the tone/question?". This growing interest recognizes the association that is steadily being strengthened between various auditory event-related-potentials and subtle forms of neuro-developmental disorders of hearing (McPherson, 1994).

An evoked-potential (EP) refers to a series of electrical changes occurring in the peripheral and central nervous systems, usually related to the sensory pathways. When these electrical changes are caused by sensory stimulation of the end-organs, for examples the auditory systems. They are referred to as sensory evoked potentials (SEPS). Depending on which sensory systems is being stimulated, evoked potential may be referred to as an Auditory-evoked-potential (AEP), visual evoked potential (VEP) or somato sensory evoked potential (SSEP). Each of these a SEP's may be further categorized according to specific usage. For example in the auditory systems, further categorization may include the brainstem auditory evoked potential (BAEP), the middle latency auditory evoked potential (MAEP) and the long latency auditory evoked potential (LAEP).

The BAEP, MAEP and LAEP are primarily elicited by some external event related to the dimensions of the stimulus and as such are considered EXOGENOUS. There are also changes in the brain electrical activity that occur in response to internal events such as cognition or perception and are referred to as event-related potentials (ERPS). ERPS are considered to be ENDOGENOUS in nature.

While clinical interest in the long latency potentials, particularly the exogeneous potentials, preceded interest in the short-latency potentials, the acceptance of their utility has vacillated over time (Squires and Hecox, 1983). One of the reasons for their waning popularity is undoubtedly that they are more affected by change in patient state than are the earlier auditory potentials. In contrast, Endogeneous (Event -Related) potentials occur in proximity to the stimuli, but are relatively invariant to changes in the physical parameters of the eliciting stimulus (Desmedt and Debecker, 1979a ; Donchin et al., 1978).

One of the most popular and widely employed Event -related potential is the P300. The response is so named because it is a vertex positive wave component occurring from 250-600 msec. post-stimulus. It is thought to result from cognitive processes related to relevant stimuli. As such,

the same stimulus way or may not result in a P300 waveform in an individual, depending on the relevance of the stimulus to the individual. In addition, the P₃₀₀ may be elicited by an absence of a stimulus, if that absence is task-relevant (Donchin et al., 1978). Picton et al., (1977) stated that "They are the best evoked potential measurements available, if they can be reproducibly recorded as their presence indicates the complete integrity of the auditory pathway in the Central-Nervous-System (CNS)".

While the origin of the stimulus-related potentials (SRPs) is cortical with probable generator sites in the auditory cortex of the superior temporal lobe, parietal and frontal association areas (Picton, et al., 1972; Mason and Meller, 1984), the P₃₀₀ ERP originates from non-specific, unknown neural generators and is felt to be an electrophysiological manifestation of strategies used by the CNS in selective attention activities, including frontal cortex (Courchesne, 1978), Centro-parietal cortex (Simpson, et al., 1977), and auditory cortex of superior-temporal lobe (Kilany, 1985), hippocampus and associated brain sites (Okade, et al., 1983).

The P₃₀₀ or P₃ components can be obtained with a number of stimulus presentations (Auditory, visual and somatosensory stimuli), in which the subject processes task relevant information. The P₃₀₀ component is considered to reflect aspects of cognitive processing. Its latency is thought to reflect the time taken to evaluate stimuli according to a number of factors including salience (Pritchard, 1981).

P₃₀₀ is theorized to be relatively independent of evoking stimulus (Polich and Starr, 1983; Picton, and Fitzgerald, 1983; Weinberg, et al., 1984). The response occurs when an individual relates the incoming sensory information to memory updating processes (Donchin, 1981), and is considered to be unaffected by exogeneous influences (Kilney and Kripal 1987; Sponberg and Decker, 1990).

The amplitude of the P₃₀₀ is about 15 microvolts and under certain recording and stimulus conditions may be bimodal (i.e., P_{300a} and P_{300b}). The "a" component seems to have a frontal distribution, whereas the "b" component appears to have a parietal distribution (Squires, Squires and Hillyard, 1975). The P_{300a} occurs around 275 msec. and the P_{300b} around 300 msec. (Polich, et al., 1986b). The P₃₀₀ response is enhanced when the subject is attending to "target" or "odd

ball" stimuli, which is a low probability stimuli presented against a background of higher probability non-target stimuli (Polich, et al., 1986b).

Current Applications

The late components are not used routinely in clinical hearing assessment. A number of studies have considered P₃₀₀ latency and amplitude as useful measures of assessing the cognitive function in both normals and neuro-physiological disordered patients, as P₃₀₀ responses is directly related to the neuropsychological state of the individual (Musiek, et al., 1988). P₃₀₀ latency increase also reflects the degree of cognitive decline in dementing illness (Polich, et al., 1986) and mental retardation (Squires et al., 1980). P₃₀₀ has been used to differentiate cognitive disorders such as depression from the Alzheimer's type i.e., organic vs. functional type.

In children, longer P₃₀₀ latency and low P₃₀₀ amplitude has been reported in hyperactivity and attention deficits, schizophrenia, autism, cluttering, central auditory disorders

and reading disability populations (Finley, Faux, Hutcheson and Amstutz, 1985).

NEED TO STUDY

The recent reports of the clinical utility of the P300 Event-Related potential in the diagnosis of less profound cognitive deficits, autism, mental retardation, behaviour disorders such as hyperactivity - Attention deficits, reading disability and cluttering give promise of an expanding role for clinical event-related potentials.

However, in order to use the late components of the ERP as a clinical tool, the alterations due to normal development must be well established. Several studies have examined P₃₀₀ latencies over continuous age range (Goodin, et al., 1978b; Squires et al., 1980; Syndulko, et al., 1982). These studies have all described a linear increase in P₃₀₀ latency scanning puberty and extending into the eighth decade. These studies report significant positive linear correlations with slope ranging from 1.1 msec./year (Syndulko, et al. 1982) to 1.8 m.sec./year (Goodin, et al., 1978 b). However there are studies (Beck, et al., 1980, Brown, Masch and Bharve, 1982) who report of a curvilinear relationship between P₃₀₀ latency and developmental aging.

The precise form of age/P300 latency regression is of clinical importance. If the function is assumed to be linear and is in fact non-linear, this assumption has potential consequences for the recognition of deviant P₃₀₀ latency and the use of this result in the detection of clinical populations. Hence there is a need to replicate similar experiments in an attempt to resolve the discrepancy.

Another important consideration in the application of P₃₀₀ response to clinical audiology is the task assigned to the subject. Clearly if the aim is to obtain optimal responses, selection of the appropriate task is important. Moreover the response strategy selected should be applicable to a wide range, especially suit younger children in order to compare the results.

Butcher (1983) compared the P300 responses obtained using three response types, specifically subjects were instructed to (i) mentally acknowledge, (ii) silently count or (iii) silently count and press a button in response to rare stimulus presentations. Their result indicated that the changes in the response mode had a significant impact on P300 amplitude. No difference were noted between the two counting conditions while a large amplitude reduction was present in

the first condition . Brown, et al., (1982) also had suggested differences in the response task as a possible reason for the discrepancies seen in P300 latency between his study and Goodin, et al., study.

Although the P300 is considered to be an "Endogeneous potential" with its amplitude, latency and scalp distribution independent of the physical attributes of the evoking stimulus, a few studies have shown that there are changes in the P300 with variations in the stimulus parameters. Butcher (1983), utilized a oddball paradigm and found that changes in the intensity of the rare stimulus had a significant effect on the latency of the P300 response. When the stimulus was increased from 10 dBSL to 50 dBSL, there was an average reduction of 29.3 msec the latency of P₃₀₀ . Though he reported that changes in stimulus frequency had no significant effect on the P₃₀₀ response. Polich (1989b) reported that both the latency and amplitude of the response were affected significantly by changes on the frequency, and the P₃₀₀ latency was affected by an interaction of stimulus intensity and duration. Further more, a study by Polich , Howard and Starr (1985) reported that increased target tone frequency yielded decreased P₃₀₀ latency. They also reported that use of masking resulted in an increase in P₃₀₀ latency.

Thus the review of literature shows that stimulus and response strategies do affect the P₃₀₀ response, and hence every clinical/research setup needs to develop their own normative data for different age groups with a fixed testing procedure, stimulus parameters and response strategies.

The present study was undergone with the following objectives:-

- 1) To check if there is any age-related variation in the latency of P₃₀₀ on comparing paediatrics (7-10 years) and young adults (18-35 years).
- 2) To check if there is any age-related variation in the amplitude of P₃₀₀ on comparing paediatrics (7-10 years) and young adults (18-35 years).
- 3) To check if there is any significant difference between the latency and amplitude of the response obtained from vertex electrode placement (Cz) and parietal electrode placement (Pz) in the different age groups studied.

REVIEW OF LITERATURE

First discussed by Davis in 1964, and beginning with a report by Sutton, Baren, Zubin and John (1965), it has been demonstrated that a component of the human AEP existed that did not reflect the physical parameters of the eliciting stimuli. Rather this component appears to reflect active cognitive processing of stimulus information on the part of the subject. This same brain component is elicited in certain experimental contexts regardless of the sensory modality of stimulus presentation (Squires, Squires and Donchin, 1977). The most common designation given to this component is 'P₃₀₀' referring to its polarity (positive) and approximate latency (about 300 msec) following stimulus presentation. Other designations include P3 referring to the prominent positive component following stimulus presentation or otherwise called late positive component (Price and Smith, 1974).

The amplitude of the P₃₀₀ is about 15 microvolts, and under certain recording and stimulus conditions may be bimodal (i.e. P_{300a} and P_{300b}). The "a" component seems to have a frontal distribution, whereas the "b" component appears to have a parietal distribution (Squires, Squires and Hillyord, 1975). The P_{300a} occurs around 275 msec. and the

P_{300b} around 325 msec. Squires et al. (1975) described an early vertex maximal P_{300a} that might be related to the registration of sensory changes, and a later parietal maximum P_{300b} that might be related to the active cognitive processing of the registered information.

The P_{300a} decreases in amplitude with age or more likely not increasing in amplitude/latency with age, as much as P_{300b} (Squires, et al., 1975). Polich, et al., (1983) have attempted to record separate P_{300a} and P_{300b} components across different ages, and have reported that the P_{300a} latency does change less with age than the P_{300b} latency.

Whether a given stimulus serves as a task relevant target/non-target is a function of the instructions given to the subject, and not of something intrinsic to the stimulus itself. Since the same stimulus may/may not result in P₃₀₀ depending on the experimental context, it is more accurate to speak of P₃₀₀ as being "Invoked" by the stimulus than as "Evoked". Hence the term Event-Related Potential (ERP) is beginning to replace evoked potential in the literature.

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NEUROANATOMICAL AND PHYSIOLOGICAL ORIGINS OF P₃₀₀

The P₃₀₀ ERP originates from nonspecific unknown neural generators and is felt to be an electrophysiological manifestation of strategies used by the central nervous system in selective attention activities, including frontal cortex (Courchesene, 1978), auditory cortex of superior temporal lobe (Kilany, 1985), Hippocampus and associated brainsites (Okade, et al., 1983).

Buchwald (1990) has suggested that although the generator sites of the P₃₀₀ are still unknown, the maturation of the P₃₀₀ provides some insight into the ontogeny of the developing brain for cognitive versus sensory brain systems. Infact, the auditory brainstem evoked potentials (sensory, exogeneous) are mature by about 60 months (McPharson, Horesufi and Starr, 1985; Starr et al. 1981) whereas the P₃₀₀ (cognitive, endogenous) is not mature until about 14 years of age (Buchwald, 1990).

The P₃₀₀ latency has been found to decrease with increase in cognitive development stemming from maturation in children (Courchesne, 1984; Howard and Polich, 1985).

Adult aging (Goodin and Squire, 1978; Brown, Marsh and Larue, 1983; Polich, Howard and Starr, 1983) and neurological impairment (Pfefferbaum et al. 1980; Lai et al., 1983; Reich, et al., 1986) have been correlated with increases in P₃₀₀ latency. In addition P₃₀₀ amplitude variations have been associated with individual differences in memory function (Polich et al., 1984; Davis, Donchin and Fabiani, 1984), differentiated inheritability of alcoholism (Neville et al. 1982; Begleister et al., 1984; Polich, 1986) and the residual effects of alcohol consumptions. Thus the P₃₀₀ ERP is beginning to provide electrophysiological index of the cognitive processes that co-vary with physiological changes.

Endogenous electrical potentials like P₃₀₀, appear at the scalp when a subject is engaged in tasks requiring judgements about the properties of a stimulus. Typically the components of task related potentials appear between about 200 and 600 m.sec, after the onset of the stimulus. The strengths of these components depend mainly on the relevance of the stimulus to the task, and less on the sensory modality being stimulated or on the particular sensory property of the stimulus (Sutton et al., 1965). Thus these components are believed to reflect non-sensory, cognitive processes carried out by the human-brain (Donchin, et al., 1978).

Gordon, Rennie and Collins (1990), using MEG have shown that the source of the auditory P300 is in either the temporal cortex or the Hippocampus, Paller et al. (1988), however have disputed the origin of the P300 as being in the temporal lobe. In his study using monkey's, Paller et al. recorded P300 responses following bilateral lesions in the medial temporal lobe. They concluded that the medial temporal brain structures "are not critical for P300 generation". This was similarly true when the association cortex in cat's was ablated (Harrison, et al., 1990). The P300 response was intact, thus suggesting that the P300 is probably not generated by the poly-sensory association cortex.

Knight, et al., (1989) were able to record the P₃₀₀ in patients with "extensive" lateral parietal cortical lesions in patients with focal cortical lesions of lateral parietal cortex and the temporal cortex. The P₃₀₀ was absent in patients with unilateral lesions centered in the posterior superior temporal plane, suggesting that the temporo-parietal function is important to the generation of the P₃₀₀ in humans. The results of a study by Pineda, et al., (1989) on monkey showed a correlation between the extent of damage of locus coeruleus cell bodies and reduction of the P₃₀₀ response. They concluded that the nucleus coeruleus plays a

major role in the "Modulation" and "Generation" of the P₃₀₀ response.

In a series of epileptic patients chronically implanted with electrodes in the frontal, temporal and parietal regions. Reicher, et al. (1989) observed a biphasic potential similar to the P₃₀₀ response. The potential completed a 180 degree phase shift from the posterior-temporal area to the frontal area. Reicher. et al. (1989) stated that this was consistent with a dorso-frontal oriented posterior-temporal generator for the P300.

Velesco, et al. (1981) examined the vertex potentials in patients with surgically implanted electrodes. They activated both the specific sensory system, and non-specific system by stimulation with depth electrodes. Based on their results, they concluded that the P300 was considered to be generated from sequential generators for the N2-P3-N4 sub-components of the P₃₀₀ with N₂ and N₄ from the non-specific sensory system, and subcomponents P₃ from the specific auditory system.

Although the precise generators are still not fully resolved, there is evidence of a sub-thalamic and medial

geniculate origin, with other activity noted in the gyrus orbitalis, rostral thalamus and anterior commissure. Intra-cranial recordings from epileptic patients revealed large extra-cellular potential gradients and increased single unit firing in or near the hippocampal formation and amygdale while the patients were performing tasks elicited the endogenous potentials at the scalp (Helgren et al. 1980; Wood, et al., 1980, 1983).

Genetic studies have shown marked similarity in P300 waveform between monozygotic twins (Buchbaum, 1974). Comparison of monozygotic and dizygotic twins have suggested a strong genetic basis for this similarity (Polich and Burns, 1987). The morphological similarity in the twin waveform compared to the control pairs ERP suggest that the individual differences in the P300 components are determined by the underlying neurophysiological structures associated with its generation (Polich and Burns, 1987).

Thus it can be seen that the identification of sources of the P300 is a difficult task, and can be considered to be from multiple, sequential and overlying sources. Put into the simplest form, the P300 includes responses from frontal cortex, centeroparietal cortex and hippocampus.

ELICITING P₃₀₀

One test approach or paradigm commonly used in recording the P300 responses involves the presentation of an "oddball" stimulus.

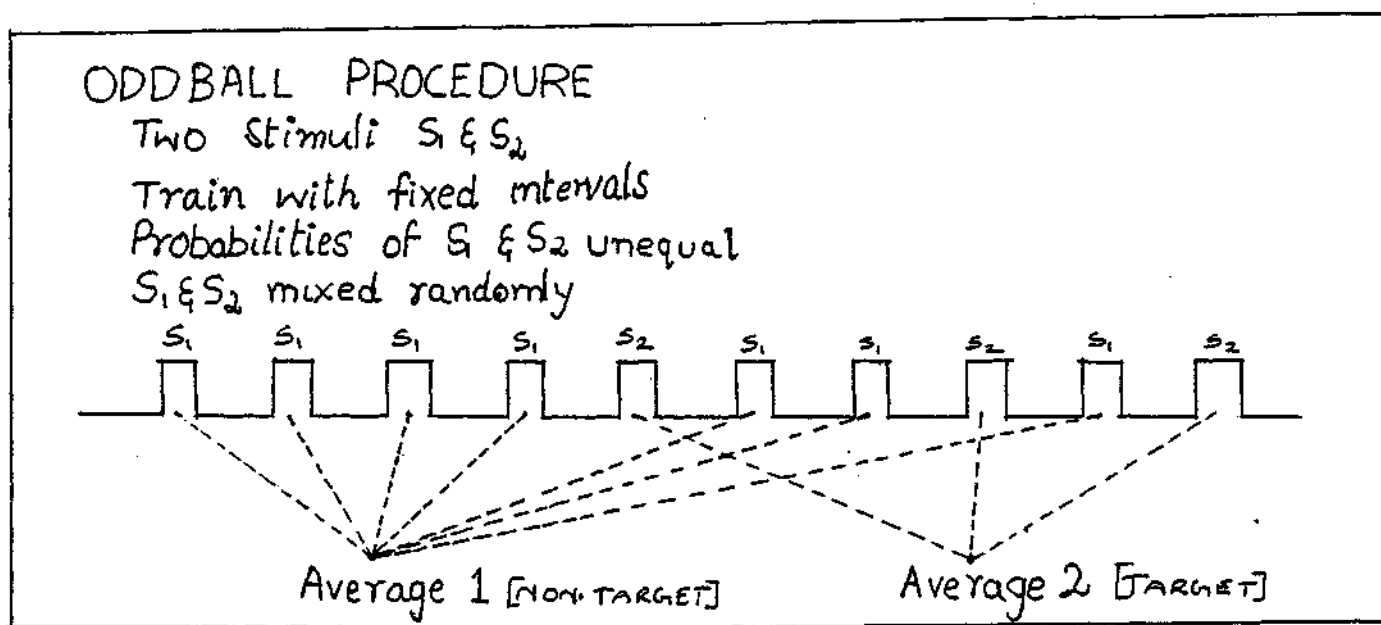


Fig.1. Schematic diagram of oddball stimulus presentation paradigm for P300 measurement (from Squires and Hecox, 1983). Responses are averaged separately for stimulus type 1 i.e. the frequent stimulus and stimulus type 2 i.e. the rare or oddball stimulus.

The stimulus used in the frequent condition is presented, most of the time i.e. frequently, but occasionally a different stimulus is presented, instead. That is, a series of about 5 or 6 identical and then, unpredictably a different or oddball stimulus e.g., 2000 Hz is presented.

The oddball stimulus may differ in its frequency, or in some other parameter such as intensity or duration.

While the target tone is physically different from the standard tones, it is not the physical difference which produces the large positive going component but rather the information supplied to the subject with relevant target tones (Sutton, et al. 1965; 1967). This is evident by the fact that the same response can be obtained by omitting a stimulus in a series of tones and having the subjects count the number of omissions (Picton, et al. 1974).

The P₃₀₀ can be elicited by other strategies like semantic priming tasks, using verbal stimuli (Holcomb, 1988), visual stimuli and somato sensory stimuli (Donchin, 1979; Sutton, 1979; Snyder, et al. 1980).

Semantic Priming Tasks - Verbal Stimuli

The elicitation of ERPs by linguistic stimuli has become more common due in large part to the pioneering research of Kutas, et al., (1980, 1982, 1983, 1984). The great majority of these studies have used visual stimuli. Spoken words, being more difficult to present with consistent

stimulus quality and reliable time locking to the EEG, have rarely been used in ERP studies. Spoken words have appeared substantially the same as those obtainable in similar paradigms using tones or visually presented words.

Neville, Kutas and Schmidt (1982) in their ERP study of cerebral specialization during reading reported that the amplitude of P_{450} and subsequent positive shift at the occipital regions was larger over the hemisphere ipsilateral to the unilateral word presentations. The P_{450} is similar in some respects to P_{300} elicited by infrequent, unexpected stimuli (Donchin, Ritter and McCallum, 1978).

Very reliable alterations in the N_{100} and P_{300} components were observed, elicited by word's (Neville et al. 1978; Neville, 1980) and found to be greater in left-hemisphere than right.

Neville, Kutas and Schmidt (1982) investigated intra- and inter hemispheric specialization in congenitally deaf adults during a word reading task. They found that the deaf subjects were as accurate as the hearing subjects in identifying word's however, they did not display visual field assymetry.

Wood word, Owen's and Thompson (1990); Friedman, Simpson, Ritter and Rapin (1975) reported that P300 elicited by spoken word's were small/absent when subjects "merely listened", but much larger when the word's were low probability task relevant oddball's. Such enhancement of P₃₀₀ amplitude by reduced temporal probability and task relevance is a common finding in ERP studies across a wide range of stimuli.

Cohort Model (Merslen-Wilcon and Welsh, 1978; Merslen-Wilson, 1980; Grosjeen, 1980; Tyler, 1962) made strong predictions regarding time course of word recognition which suggested that listener identifies a word precisely as soon as he or she has sufficient information.

And thus further study of the timing of word recognition processes may benefit from the ability of ERP to augment mental chronometry (Kutas, McCarthy, and Donchin, 1977). In particular the latency of the P300 has been considered an index of stimulus evaluation time (Pritchard, 1981; Dunchan-Johnson and Donchin, 1982}.

Johson, Pfefferbaum and Kopell (1985) observed that markedly broadened P₃₀₀ components consistent with word to

word P₃₀₀ latency variability were elicited by visually presented word's in a memory paradigm.

Kutas and Hillyard (1980) recorded ERP from subjects as they silently read 160 different seven word sentences presented one word at a time. Substantial inter subject variability was observed in the ERP wave shapes following the words. More than half of the subjects generated P₃₀₀ components to word stimuli which was greater in left hemisphere than right. One quarter of the sentences at random, ended with a word printed in a Type-Force that was different from preceding word's which elicited P₃₀₀ to greater extent.

In studies of language functioning, the ERP's have reported to index perceived meaning of words (Brown, Marsh and Smith, 1973, 1976), different linguistic categorization (Kutas and Donchin, 1979) and has been applied to the study of the development of speech perception (Molfese, Freeman and Palerino, 1975), the study of semantics (Tatcher, 1977) and study of reading (Kutas and Hillyard, 1980). Further more P₃₀₀ has been suggested as a tool for quantifying hemispheric asymmetries and in detecting dichotic deficits (Jerger et al., 1955), and is reported that the N₂-P₃ complex accurately

reflects the phonemic categorization of speech stimuli (Maiste et al., 1955).

The ERP's have hence been proven to reliably index neuro-physiological events associated with human language and cognitive functions.

Once the spatial and temporal distribution of language-related ERP has been described in particular paradigm's in normal adults, the comparison of similar paradigm's from brain damaged adults may suggest way's in which the flow of language information is altered in aphasia and in recovery from aphasia. Similar developmental studies may indicate neurophysiological changes that accompany normal and abnormal developmental of language abilities (Neville, 1980).

Analysis of the acoustic structures of word's must precede identification of its meaning. These phases of speech processing are associated with ERP components that differed in their timing. Posner and Snyder (1975) suggested that ERP changed when the task was automatic during lexical decision task's. Dunchin, Johnson and Donchin (1982) recorded P₃₀₀ latency and Reaction time (RT) in a task where target letter's were preceded by either a matching letter,

neutral stimulus or a mismatching letter. RT and P300 were not delayed in the first two conditions but delayed in the mismatched letter.

A number of studies have reported the existence of ERP components that temporarily overlaps the P300 but which has a later peak (0-400 msec after P300). In a systematic series of studies, Ruchkin and Colleagues have demonstrated that P300 reflects initial stimulus evaluation and a component they referred to as slow-wave (SW) to a later more "depth" or reevaluation process that varies to task demands (Ruchkin, Sutton and Stag, 1980).

VISUALLY EVOKED ERP AND SOMATOSENSORY EVOKED ERP

Picton, et al., (1984) who studied the age related changes of the visually evoked P₃₀₀ reported that the P₃₀₀ component showed a similar change in latency with age, to the evoked by the auditory stimulus. However, the P₃₀₀ evoked was delayed by approximately 90 msec than that obtained with the auditory signal. Most of this delay was explained by the differences in transmission time to the cortex. The initial response at the human primary -auditory-cortex occurs with a latency of about 15 msec, whereas the initial response in the primary visual cortex has a latency of about 40-60 msec.

According to Squires, et al., (1950); Pfefferbaum et al., (1983), the visually evoked P300 is reported to increase in latency more rapidly with age, than the auditory evoked P300.

The P₃₀₀ component evoked by the somatosensory signal was delayed and larger than the of auditory and visual signal (Picton et al., 1984), and this was related to the subjects finding the somatosensory task more difficult than the auditory task, since this delay could not be explained by delayed transmission time.

AUDITORY STIMULUS EVOKED ESP

Following the germinal studies of Sutton and his colleagues (Sutton et al., 1965, 1967), it has been frequently demonstrated that the vertex potential evoked by a task-relevant stimulus that delivers, significant information is characterized by an augmented late positive wave at about 300 msec in latency (the P₃ or P₃₀₀ component).

In one class of studies, it has been shown that an enhanced P300 component is elicited by a specific anticipated

"target" signal that occur's unpredictably with in a series of non-target stimuli and demand a special cognitive or motor response.

In the auditory modality which has received the most study, the P_{300} wave would be elicited selectively upon the detection of target signals of various types including:

- 1) Pitch changes (Ritter et al., 1972; Wilkinson and Lee, 1972; Hillyard., 1973)
- 2) Intensity shifts {Ritter and Vaughen, 1969; Picton and Hillyard, 1974)
- 3) Threshold level tone pips (Mast and Watson, 1968; Hillyard et al., 1971)
- 4) Clicks among speech sounds (Smith et al, 1970)
- 5) Noise bursts among clicks (Ford et al, 1973)
- 6) Omissions from a train of clicks (Picton and Hillyard, 1974).

Several authors have emphasized the need for active attention towards the targets as a prerequisite for P_3 enhancement and have shown that ignoring the stimulus resulted in a elimination or absence of P_{300} (Hillyard et al., 1971; Squires et al., 1973; Picton and Hillyard., 1974)

The P300 wave which follows the detection of an attended auditory target has a widely distributed scalp topography with maximum amplitude at central and parietal regions (Ritter, et al., 1972; Picton and Hillyard., 1974; Hillyard et al., 1975).

P₃₀₀ can also be elicited when the subjects attention is diverted from the auditory stimuli to read a book (Ritter et al., 1965), perform a concurrent manual task (Roth and Kopell., 1973) or simply to "Ignore the sound bursts as much as possible "(Roth., 1973; Roth et al., 1973).

As mentioned earlier, P300 can be elicited by omissions from a train of clicks (Picton and Hillyard., 1974). However this P₃₀₀ is reported to be different from the auditory evoked P₃₀₀, in that it should no age related changes. This difference has been interpreted in several ways. One interpretation is that the positive peak that occurs during the detection of an omitted stimulus is not the same as the P₃₀₀ that occurs during the detection of a target stimulus. However, the similarities in morphology and scalp distribution suggest that the 2 waves represent the same cerebral process. A second interpretation is that the age related increase in the latency of the P₃₀₀ to a sensory

signal is related to difficulties in sensory discrimination, and that when the P300 is elicited by a non-sensory event, there is no age related delay. A third explanation is related to uncertainty. It is possible that older subjects might make decision about sensory signals as quickly as younger subjects but delay their P₃₀₀ response because of residual uncertainty about their decision. When detecting an omitted stimulus, there would be little if any residual uncertainty. After the decision has been made, the subject becomes more and more certain that it was correct, and there is no delay in the P300.

PSYCHOLOGICAL CORRELATES OF P₃₀₀

The results obtained from various studies on the P₃₀₀ have posed difficulties for any simple theoretical interpretation of the P₃₀₀ phenomenon. There has been no general agreement upon how best to formulate the psychological correlates of the P₃₀₀. On one hand, the evidence that P₃₀₀ is evoked by shifts in a non-attended train of habituating tones has led to suggestions that it is a cerebral component of the orienting response (Ritter, et al., 1968; Roth, 1973; Roth and Kopell, 1973). On the other hand, the P₃₀₀ that follows attended and task relevant stimuli has been interpreted in terms of decision making

(Hillyard, 1969; Smith et al., 1970) and information delivery (Sutton, et al., 1967).

Salience or significance (Sutton, 1971), cognitive evaluation (Ritter and Vaughen, 1969), reduction of arousal (Karlin, 1970), change in preparatory set (Kerlin and Martz, 1973) and "Response set" selective attention (Hillyard, et al., 1973) are other proposed explanations.

A further unresolved question concerning the P300 wave concerns its latency of occurrence. Most reports place its latency within 300-450 msec. post-stimulus, but some have found it as early as 210-220 msec. (Roth, 1973; Roth et al., 1973), and others as late as 450-550 msec. (Ritter and Vaughen, 1969). Particularly puzzling are the wide discrepancies between the latencies reported for the P₃₀₀ evoked by shifts in pitch of an irrelevant train of bursts; Ritter, et al., (1965) obtained a latency of about 350 msec. in all subjects, while Roth and Kopell (1973) determined a value of 300 msec. and Roth (1973) found a mean latency of 217 msec.

Squires and Hillyard (1975) found two distinct late positive components of the scalp recorded auditory evoked

potential which differed in their latency, scalp topography and psychological correlates. The earlier component called the 'P_{300a}' (latency about 240 msec.) was elicited by infrequent, unpredictable shifts of either intensity or frequency in a train of tone-pips, whether the subject was ignoring (reading a book) or attending to the tones (counting). The later component called 'P_{300b}' (latency about 350 msec.) occurred only when the subject was actually attending to the tones. It was evoked by the infrequent, unpredictable stimulus shifts regardless of whether the patient was counting the target stimuli or frequent stimuli.

VARIABLES AFFECTING P₃₀₀

A) ATTENTION

Polich (1986) noted that attention was a necessary factor in the generation of P₃₀₀ component and a decrease in attention is related to a decrease in response amplitude. This effect of attention is reported to be similar across all sensory modalities-Auditory, visual and somatosensory (Hohnobain, Falbenstein, Hoormann and Blanke, 1991).

According to McPherson (1996), P₃₀₀ may be viewed in essentially three attention conditions: (1) Active attention

in which the traditional oddball paradigm is used and the subject must perform some mental or response task to the rare i.e., target stimuli; (2) A passive attention condition in which the subject is not instructed to respond to the rare i.e., oddball stimuli; and (3) an ignore condition whereby the subject is told to ignore the rare stimuli (the subject is given some other task such as reading). The P_{300} is most robust in the oddball paradigm, showing the greatest amplitude and shortest latency. In the passive condition, there is a reduction in amplitude of the P_{300} , but latency shows no changes relative to the oddball paradigm. Finally, in the ignore condition, the P_{300} is either greatly reduced or in some instances, absent (although the alter infrequently occurs) (Pfefferbaum, Ford, Weller and Kopell, 1985).

A fourth paradigm, which has been termed a 'go'/'No go' response task, is an active discrimination task similar to the oddball paradigm (Pfefferbaum, et al., 1985), used in eliciting the P_{300} and produces similar results. This paradigm uses a warning stimulus, that indicates as to whether or not the subject is to respond to the imperative stimulus. Often, there are two warning tones; one that requires a response and one that does not require response, hence the term 'go'/'no go'. This paradigm is also reported

to produce similar waveform as obtained in the attention condition.

B. INTENSITY

P₃₀₀ is considered to be an 'endogenous' component since its amplitude, latency and scalp distribution does not depend upon the physical attributes of the evoking stimulus (Donchin, Ritter and McCallum, 1978). However this generally accepted invariance of at least the amplitude of the P₃₀₀ to stimulus intensity has been challenged by Roth and its associated in a series of 3 papers demonstrating the dependence of P₃₀₀ amplitude on the intensity of the evoked stimulus (Roth, et al., 1930). Although these studies did not employ the most frequently used 'oddball' paradigm, the results raise serious doubt as to the P₃₀₀ amplitude invariance in general.

Butcher (1983), utilized a oddball paradigm and reported that changes in the intensity of the rare stimulus, had a significant effect on the latency of the P₃₀₀ response. When the stimulus intensity was increased from 10 dB SL to 50 dB. SL, the average reduction in P₃₀₀ latency was 29.3 msec.

Papanicoleau et al., (1985) reported that P_{300} amplitude was not significantly affected by the intensity of the stimulus. However a statistically significant increase in P_{300} latency contingent on reduction of stimulus intensity was noted. Hence it is important to ascertain with both normal subjects and with clinical population, the effective stimulus intensity remains constant across the groups which are compared.

C) FREQUENCY

Butcher (1983) utilized a oddball paradigm, and reported that changes in the stimulus frequency had no significant effect on the P_{300} response.

Polich, Howard and Starr (1985) studied the frequency separation effects of target tone frequency/presence of masking stimulus and subjects sex on the auditory ERP using a oddball paradigm. P_{300} latency become shorter (about 15 msec.) as the difference between the standard (1000 Hz) and target tone frequency increased (1500 Hz, 2000 Hz and 4000 Hz), but become longer (about 10 msec.) with the presence of a white noise masking stimulus and found this true with both P_{300a} and P_{300b} subcomponents of P_{300} .

Polich (1989) reported that both the latency and amplitude of the response were affected significantly by changes in frequency, and P₃₀₀ latency was affected by an interaction of stimulus intensity and duration.

D) PROBABILITY

According to Picton et al. (1984), the probability of the signals eliciting the P₃₀₀ shows significant effects on the P₃₀₀ amplitude and latency. These effects do not change with age, suggesting that the probability-determinants of the P₃₀₀ remain constant across the life-span. Their study showed that P₃₀₀ latency was significantly longer in a long inter-stimulus interval condition (3.1 sec) than in a 1.1 sec. condition.

In a study by Fitzgerald and Picton (1981), the amplitude of the P₃₀₀ was significantly reduced when the probability of the signal was increased from 10% to 30% and the inter-stimulus interval maintained at 1.1 sec. They suggested that at higher sequential probabilities and longer inter-stimulus-intervals, the subjects may employ a different cognitive strategy. Thus there is a need to determine an optimal paradigm for recording P₃₀₀, for clinical use, and it

is probably better to record using a lower signal probability.

E) TASK

In experimental designs in which a subject either predicts prior to a trial whether/not a stimulus will be presented is a Guess task, and in which he reports after the trial whether or not stimulus was presented, is a Detect task. Both have been reported to elicit P_{300} and no significant effect due to task is noticed on P_{300} (Ruchkin, Sutton and Stage, 1980).

Butcher (1983) compared the P_{300} responses obtained using three response types. Specifically, subjects were instructed to: (1) Mentally acknowledged (2) silently count or (3) silently count and press a button in response to rare stimulus presentations. Results indicated that the changes in response mode had a significant impact on P_{300} amplitude. No differences were noted between the two counting conditions, a large amplitude reduction was present when the subjects were only mentally acknowledging the tones. No latency effects were seen as a function of response mode.

Polich (1987) examined the effect on P300 by changes in response mode, across three conditions during a discrimination task. The three conditions were silent counting, tapping an index finger, and pressing a button in response to a target stimuli. Results indicated that the P₃₀₀ amplitude was greater when subjects counted the targets than for the other conditions, and there was an increase in P₃₀₀ latency when subjects counted.

Thus it can be seen that an important consideration in the application of the P₃₀₀ response to clinical audiology is the task assigned to the subject. Clearly if the aim is to obtain optimal responses, selection of the appropriate task is important.

F) TASK DIFFICULTY

Another factor affecting the P₃₀₀ is the task difficulty. This factor specifically becomes important if the response is to be utilized with patients having suspected cognitive or auditory processing deficits.

Polich (1987) examined P₃₀₀ responses obtained for 'easy' and 'hard' auditory discriminations, and concluded

that processing difficulty does affect the latency and amplitude of P_{300} responses. Results also suggest that the effects are independent of stimulus probability unless differences in task requirements affect the encoding of the stimuli employed.

G) SEX

Most of the studies report of no difference among males and females, in the evoked P_{300} (Polich et al., 1985; Spongberg and Decker, 1990; Fernandez and Torres, 1988). Polich, et al., (1985) reported no significant differences between 50 males and 50 females in either latency or amplitude of the P_{300} responses. However, a study by Picton, et al., (1984) reported a smaller amplitude of the P_{300} component in male subjects when compared to female subjects. The difference was quite small when compared to the general variability of the P_{300} latency. They interpreted this difference to some physical difference in head size or skull thickness rather than any cognitive differences between the sexes.

H) AGE

Age is an important factor affecting the P_{300} latency and amplitude (Brown, Marsh and Larue, 1983) and will be discussed in detail, later.

I) ELECTRODE SITE PLACEMENT/SCALP DISTRIBUTION

Another factor that has been found to influence the waveform is the electrode site placement.

The P₃₀₀ is a positive potential that is broadly distributed with a maximum amplitude observed at the midline over the centro-parietal areas. The maxima moves slightly depending on the task. For example, in a signal detection paradigm, the maxima is largest at the vertex, and in discrimination tasks, it is largest just posterior to the vertex (Simpson, Vaughen, and Ritter, 1977). Likewise, Snyder, Hillyard and Galambos (1980) observed an amplitude maxima for the P₃₀₀ just anterior of the vertex for the "oddball" paradigm. Thus, electrodes should be placed minimally at Fz, Cz and Pz for optimum recordings and referenced to linked mastoids (or lobes) (McPherson, 1995).

Several experiments have reported of a change in the scalp distribution of the P₃₀₀ with aging (Pfefferbaum, et al., 1980; Smith, Michelewski, Brent and Thompson, 1981; Pfeffferbaum, et al., 1984). At the two most posterior sites (Oz and Pz), young children and adolescents had large targets

P₃₀₀'s. In the older subjects the P₃₀₀ is relatively larger at the mid-frontal electrode compared to the vertex than in the younger subjects. Both Pfefferbaum (1980, 1984) and Smith (1980) have interpreted this as being due to an age related decrease in the amplitude of an overlapping frontal negative slow wave.

J) DEFICITS IN MEMORY

Deficits in short-term as well as overall memory performance are associated with both increased P₃₀₀ latency and variability (Howard and Polich, 1985; Polich, et al. 1986).

K) COGNITIVE PROCESSING

P₃₀₀ latency is felt to be directly related to speed of information processing (Mullis, Holcomb, Diner and Dyken (1985). Difficulties in these areas would be reflected by longer P₃₀₀ latencies.

L) RELATION WITH OTHER EXOGENOUS POTENTIALS

Spongberg and Decker (1990) studied the relationship for latency and amplitude between exogenous auditory potentials

arising at the level of cranial nerve VIII and continuing through the level of the cortex (ABR, MLR and LLR), with the auditory P₃₀₀ endogenous potential. Their results revealed that there was no significant positive correlations for individual latency or amplitude differences between ABR, MLR and LLR (exogenous responses), and the latency or amplitude of the endogenous P₃₀₀ response. Subjects those had demonstrated large amplitude and/or short-latency exogenous responses did not demonstrate P₃₀₀ responses that were correspondingly larger in amplitude or shorter in latency. However, it was observed that components Pa (of MLR) and P₃₀₀ were negatively correlated for latency and amplitude, though the neurophysical basis of this interaction is unexplained by the above researchers.

M) OTHER FACTORS

Prietchard (1981) cited selected attention, feedback, orienting response, language, decision confidence as other factors affecting the P₃₀₀ response.

Thus in summary, it can be stated that although the P₃₀₀ response is considered to be an endogenous potentials and is therefore less sensitive to the physical attributes of the

stimuli employed, than the exogenous responses, it is clear from the above literature that stimulus and response characteristics do have reliable effects on the P300 latency and amplitude of the P300 response.

P₃₀₀ AS A CLINICAL TOOL

P₃₀₀ has been used in the assessment of cognitive functions as it is thought to reflect stimulus evaluation and classification processes. Initial applications found that latency of the P₃₀₀ becomes longer with an increase in adult age (Goodin et al., 1978b; Syndulko, et al., 1982; Brown, et al., 1983; Pfefferbaum, et al., 1984a; Picton, et al., 1984; Polich, et al., 1985a). It also increases substantially with mental dysfunction such as mental retardation (Squire, et al., 1979) and dementing illnesses (Brown, et al., 1982; Goodin et al, 1978a; Hansch, et al., 1982; Pfefferbaum, et al., 1984b; Polich, et al, 1986). Additional studies have suggested that shorter P₃₀₀ latencies are associated with relatively superior memory performance in neurologically normal subjects (Polich, et al., 1983; Howard and Polich, 1985).

Studies have also reported that changes in P₃₀₀ component can originate from fluctuations in cognitive state

(Goodin et al. 1983) amount of alcohol typically consumed (Polich, 1984; Polich and Bloom, 1986) and individual differences in memory retrieval (Kevis, et al., 1984). The P₃₀₀ has been employed to differentiate children with attention deficit and hyperactivity disorder (ADHD) from normal children (Satterfield, et al, 1990; McPherson and Davis, 1995). The typical findings are an increased latency (by approximately 30 msec) of the P₃₀₀ and decreased amplitude of the P_{300b}. Satterfield, et al., (1984) working with hyperactive and normal boys, observed significant latency and amplitude differences between these groups using auditory ERPS. They noted that younger hyperactive subjects exhibited longer peak latency and smaller amplitude, while the older clinical subjects showed shorter latency and longer amplitude. Satterfield, et al., (1987) conducted a longitudinal investigation of both delinquent and non-delinquent hyperactive boys as well as normal age and gender matched controls, and reported that the latency measures of the auditory P₃₀₀ response were sensitive to abnormal maturational changes in the non-delinquent group when compared to both the delinquent and normal subjects.

AUDITORY PROCESSING DISORDERS

Children with central auditory processing disorders (CAPDs) present a unique challenge for the audiologist. Such children usually do not present with a peripheral hearing problem which can be assessed through the traditional test battery approach. In an effort to enhance the objectivity in the assessment of central processing difficulties, interest has been focussed on the use of event-related potentials (Musiek and Baran, 1988). Jirsa, et al., (1990) compared the P₃₀₀ ERP of confirmed CAPD and age-matched children. Their results indicated that the patients either failed to generate an P₃₀₀ or produced a P₃₀₀ component that was significantly longer in latency and reduced in amplitude compared to the normal control group. Moreover, when the clinical group was subdivided into four subgroups on the basis of the degree of central auditory involvement, those subjects in the group with most severe involvement exhibited the longest P₂-P₃ interval. Thus P₃₀₀ can be used as a clinical tool to predict the severity of the processing disorder also.

Nevilles, et al. (1984) studied P₃₀₀ and related long latency components and various learning and developmental processes in adults and children (using both normal hearing and hearing-impaired subjects). They examined the intra

and inter hemisphere specialization during reading activities and found that visual P300 ERP were sensitive to cortical activities occurring during the processing of written language material. Furthermore they demonstrated that P₃₀₀ ERPS were useful in defining differences in cortical organization occurring between the normal hearing and hearing-impaired subjects during reading activities.

COGNITIVE FUNCTIONS

Auditory ERPS were employed by Finley, et al., (1985) to study children with cognitive disorder. They found that compared to normal controls, children with organically confirmed cognitive problem had significantly delayed P₃₀₀ latency. In addition, they reported that children with organic disorders could be differentiated from those with functional disorders or psychiatric disorders on the basis of P₃₀₀ latency.

In addition to aiding in the diagnosis of dementia (Goodin et al., 1978; Lappler and Greenberg 1972), in predicting the degree of cognitive decline in dementing illness (Polich, et al., 1986), and in distinguishing pseudodementia from dementia, the P₃₀₀ ERP seems to provide a

sensitive indicator of fluctuations in mental state experienced by individual patients, as a result of changes in underlying illness (decrease in P300 latency with clinical improvement in mental functions and increase in P₃₀₀ latency in clinical deterioration).

Studies on traumatic head injury cases, (Campbell, et al., 1986) have reported that appearance of the P₃₀₀ response may coincide with resolution of post-traumatic amnesia, and return of orientation and memory. A study by Hall and Harris (1990) on 50 brain injury rehabilitation patients at various stages of cognitive recovery ranging from coma to near premorbid function, revealed that for patients at more advanced stages of recovery, the P₃₀₀ response appears to be related to cognitive functioning level.

Ruchkin, et al., (1994) compared the P₃₀₀ between multiple sclerosis patients and age matched normal as a means of evaluating their working memory impairment. Their results indicated that the P₃₀₀ amplitude tended to be smaller in the multiple schelerotic patients, and there was no indication of any latency differences between the groups. Newton, et al., (1989) found that abnormal P₃₀₀ tended to be associated with higher plaque counts and longer disease duration.

LANGUAGE AND MOTOR SPEECH DISORDERS

Studies have reported that the P₃₀₀ can be used as a tool for quantifying hemispheric asymmetries and in detecting dichotic deficits (Jerger et al., 1995). Mason and Meller (1984) on evaluating children with either confirmed language or motor speech disorders, reported significant intra and inter hemispheric amplitude differences in the auditory long latency response and P₃₀₀ when compared to normal controls. They speculated that these findings may prove beneficial in the examination of various factors involved in normal language development.

The P₃₀₀ is reported to be reduced in amplitude (Martineau, et al., 1989; 1992) and delayed in latency (Courchesne (1984) in autistic subjects when compared to normal subject. Dawson, et al., (1988) using phonemes observed a greater reduction of amplitude of P₃₀₀ over the left hemisphere than over vertex or the right hemisphere in autistic subjects. In a similar study using "high functioning autistic children, differences in the vertex P₃₀₀ was not observed (Erwin, et al., 1991). According to Barrett (1993), the reduced P₃₀₀ amplitude reflects "either a less on inefficient processing of the stimuli".

Musiek (1989a) speculated that the P300 would be beneficial in the evaluation of individuals with aphasia or related communication disorders. Since the generation of the P₃₀₀ requires that an individual understands the task at hand, Musiek reports that the observation of the ERP gives important information regarding receptive capabilities which would be useful in planning a therapeutic program.

In general, an advantage of using the later auditory potentials is that a wide variety of stimuli can be used to obtain the response. Longer tones (upto 200 msec), short-segment speech stimuli and clicks can be used. Another advantage is that the large amplitude of these potentials allow's for testing very close to behavioural threshold and for still seeing an identifiable wave form. Clinically, late potentials such as the P₃₀₀ can be used to examine the function of more rostral components of the auditory pathway. An evoked potential test battery examining ABR, MLR and late potentials can be of value in delineating the general site of auditory dysfunction.

A few other applications of P₃₀₀ are - Maiste et al (1995) employed the P₃₀₀ to determine whether there are any physiological correlates of categorical perception . They reported that the N₂-P₃ complex was formed to accurately

reflect the phonemic categorization of speech-stimuli.

- Attias et al., (1996) studied a group of chronic tinnitus patients with the P₃₀₀ ERP. They reported that their findings point to a cortical information processing dysfunction in the chronic tinnitus patients, associated primarily with auditory stimuli and that ERP'S may provide an objective electro-physiological tinnitus measure.

EXPONENTIAL ELECTROPHYSIOLOGICAL AGING - P₃₀₀ LATENCY

All of the late potentials are influenced by neuromaturational factors with N₁ , P₂ and N₂ thought to stabilize by about 10-15 years of age (Kilney, 1985; Moson and Meller, 1984; Musiek, et al., 1988).

The P₃₀₀ component appears to mature somewhat later than the earlier waves with several studies showing a decrease in latency and an increase in amplitude from age 5-16, followed by an progressive decrease in amplitude and an increase latency throught adulthood (Courchesne, 1978; Goodin, Squires and Henderson, 1978; Pfefferbaum et al, 1980; Polich, Howard, Starr, 1985)

ERPs have been recorded while performing stenberg's paradigm of memory retrieval task by young (Roth et al., 1975, 1977, 1978; Gomer et al., 1976; Adam and Collins, 1978), and young and old subjects (Marsh, 1978; Ander et al., 1972; Anders and Fozzer, 1973; Ford et al., 1979), and found that P₃₀₀ increased with increasing memory sets and age and thus P₃₀₀ reflects the time taken to encode the test stimulus. They also found a same relation with rise time (RT), but this included response processes also. These results were consistent with other researchers (Kutas et al., 1977; Squires et al., 1977; Duncan-Johnson, 1978; Roth et al., 1978) indicating that generation of P₃₀₀ is related to the processes associated with stimulus evaluation and that the latency of P₃ reflects the relative time taken to evaluate stimulus sufficiently to perform the task.

Recent reports have shown that the P₃₀₀-ERP has clinical utility in the diagnosis of conditions like Autism (Martineau et al., 1989, 1992), children with attention deficits and delinquent children (Satterfield et al., 1984), with central auditory processing deficits (Jirsa, et al., 1990) and other disorders. However in order to use the P₃₀₀ ERP as a clinical tool, the alterations due to "normal" development must be well established.

The latencies of AEP components occurring after 150 msec. (P_2 , N_2 , P_3) have all been shown to increase as a function of age (Marsh and Thompson, 1972; Brent, et al., 1977; Goodin, et al., 1978b; Ford, et al., 1979; Pfefferbaum, et al., 1979b). In contrast components occurring before 150 msec. show little or no latency change with age (Goodin, et al., 1978b; Pfefferbaum, et al., 1979b). Goodin, et al., (1978b) demonstrated that the later the evoked potential component with regard to stimulus onset time, the more it is prolonged with age i.e., P_{300} is prolonged more than P_2 , which is prolonged more than N_1 . They calculated the slope of the regression line for the latency of the various components on age to be 1.8 msec./year for P_{300} , 0.7 msec./year for P_2 and 0.1 msec./year for N_1 .

Holcomb, Diner and Dykinan (1985) studied visual stimuli to elicit ERP on 108 normal subjects ranging in age from 8-90 years. Age related inferences were found for both P_{300} latency and amplitude. Children and elderly adults were found to have latest P_{300} , and earliest P_{300} were found in subjects in their twenties. A curvilinear function best described P_{300} latency-age relation. P_{300} decreased in amplitude at posterior site and increased in frontal locations with increasing age.

Kurtzberg, et al., (1986) reported of recording P₃₀₀ response to speech sounds in awake infants. Stimuli used were stop consonant vowel (CV) syllables such as /ta/ /da/ and /ba/ presented, in a oddball paradigm. A distinct P₃₀₀ response was reported, with changes in morphology, with development. Initially, it was reported to be a -negative peak in a preterm infant, progressively becomes a positive peak, although morphology may differ as a function of the speech sound stimulus, and the developmental course may vary, depending on electrode site (Midline vs. Lateral temporal).

Martin, Barajas and Fernandez (1988) studied P₃₀₀ response development, using a tone burst oddball stimulus paradigm in 68 normal hearing subjects ranging in age from 6 through 23 years. The results revealed a significant correlation between age and latency was defined by a P₃₀₀ latency/age slope upto age 15 years. Pearce, et al., (1989) examined age related changes in P₃₀₀ latency in children ranging in age from 5-13 years. These authors reported significant age trends in P₃₀₀ latency which appeared to be linear in nature. The slope of the curve reported was approximately 20 msec, which is in good agreement with 19 msec. slope reported by Martin et al., (1988) for children aged 15 years, and younger.

An extensive study by McPherson, et al., (1989) reported the following latency values for the different age groups 5-12 years = 241-396 msec, 17-30 years = 225-365 msec, 30-50 years = 290-380 msec, and in 50-70 years = 350-427 msec. Barajas (1990) has shown that the P_{300} reaches its shortest latency at about 18-24 years of age and then increases at a rate of approximately 1.25 msec. per year upto 78 years of age.

A single exception to age vs. P_{300} latency increase was reported by Michaelleski, et al., (1982) for the omitted P_{300} , to mixing clicks in which no age differences were seen for N_2 and P_3 for traditional or latency corrected average.

In addition to the variations in the latency, there seems to be an interaction between age and scalp topography in P_{300} measurements. Young adults had a pronounced parietal distribution, whereas P_{300} becomes distributed from the parietal region (Pz) to the frontal region (Fz) as a function of advancing age (Pfefferbaum, et al., 1980; 1984). Harbin, Marsh and Harvey (1984) evaluated the effect of age on late ERPs elicited by semantic vs. non-semantic tasks. ERPs were generated by the last word in a string of 5 words, which was either in the same semantic category as the other words or in

a different category. Young subjects showed a larger potential for matched words (vs. mismatched), while the older subjects showed just the opposite pattern.

Because of its relationship to information processing the P₃₀₀ has been studied extensively across the life span in order to evaluate the neurophysiological basis of the changes in cognition that occur with aging. Normal increase/decrease with age in P₃₀₀ latency/cognitive processing time might be due to a decrease/increase in neural conduction velocity caused by an age related decrease in myelination.

However, further studies of the relationship between P₃₀₀ latency and age development are needed to clarify whether these interpretations are right and to establish reliable normative P₃₀₀ data.

METHODOLOGY

The present study was undertaken to investigate the following objectives

1. To check if there is any age related variation in the latency of P₃₀₀ on comparing children (7-10 years) and young adults (18-35 years)
2. To check if there is any age-related variation in the amplitude of P₃₀₀ on comparing children (7-10 years) and young adults (18-35 years)
3. To check if there is any significant difference between the latency and amplitude of the response obtained from vertex electrode placement (Cz) and parietal electrode placement (Pz), in the different age groups studied.

Subjects

Two groups of subjects were included in the study. Group I consisted of 30 normal young adults between age-range of 18-35 years (15 males and 15 females).

Group II consisted of 30 children with normal hearing in the age range of 7-10 years.

Criteria for selection of subjects

1. All subjects had volunteered for the study.
2. None of the subjects had presented with any past history of otological/neurological/or psychological disturbances.
3. None of the subjects reported of any medical or neurological impairment such as Tremors, cerebral palsy etc.
4. The subjects were able to relax in the presence of electrodes placed for the duration of testing and impedance values were within normal limits.
5. All subjects had no cognitive impairment and had normal intelligence as evidenced by their teachers report and school/college performance.

Instrumentation

The entire experiment was conducted in a specially designed electrically isolated, sound treated room using Biologic-Evoked Potential System (EP Navigator). TDH-39 earphones with MXH-41/OR cushions were used to deliver the

alternating tone burst stimuli (both target and non-target) of 2 KHz for the target tone and 1 KHz for the non-target standard tone, presented at 75 dB nHL binaurally at a probability ratio of 20/80 for target/non-target. The tones were presented in a random series at a rate of 1.1/sec. with 300 stimuli in each run. Each stimuli had a rise and fall time of 2 msec. and a plateau of 20 msec. The amplifier filter was set to a band pass of 1 Hz - 30 Hz, with a 12 dB/octave roll-off.

The equipment set-up, patient record and test selection were done as given in the instrument manual.

TEST PROCEDURE

(1) Patient set-up

The subjects were seated in a comfortable posture, with the head fully supported to ensure noise-free recordings. Neck and jaw muscles were relaxed to ensure a minimum rejection rate.

(2) Electrode placement

The electrode site for the two channel mapping recordings were selected as Cz and Pz as positive, the FPz as

common and A1 (left ear mastoid) and A2 (right ear mastoid) as negative.

The electrode were plugged into the following jacks of the electrode box.

Site	Headbox connection
Fore head (FPz)	Common
Vertex (Cz)	Channel 1, input 1
Parietal (Pz)	Channel 2, input 1
Left ear (A1)	Channel 1, input 2
Right ear (A2)	Channel 2, Input 2

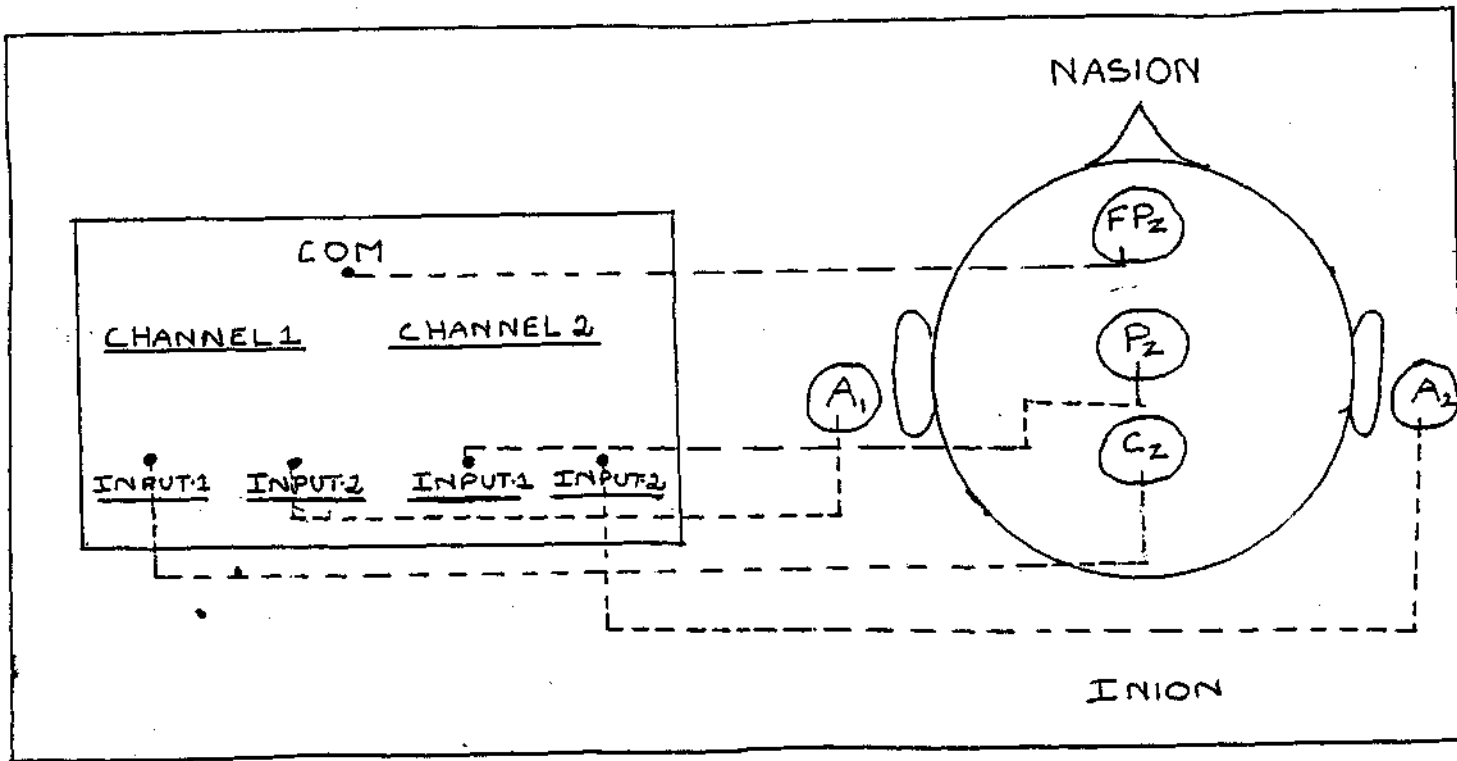


Fig.2 Electrode connection for a P₃₀₀ response

Silver-cup electrodes were fixed at the sites given in Fig.2 after thorough skin surface cleaning with surgical spirit and a skin preparing solution, and later filled with standard EEG electrode paste, suitably secured in place with surgical tape.

3. Measuring Impedance

The impedance of the electrodes were measured for each electrode for the two channels. The impedance values for the positive and negative electrodes were referenced to the common electrode. All electrode impedance were less than 5 K.ohms, and within 3 K ohms of each other. If the impedance increased beyond 5 K ohms, the electrodes were removed, the sites properly cleaned again, the patient was asked to relax and resettled with the electrodes secured in their respective sites again.

The negative electrodes A1 and A2 were linked together by means of a jumper to obtain a clear P₃₀₀ wave form.

4. Instructions to the subjects

1. The subjects were instructed to be alert but relaxed throughout the recording.

2. The subjects were asked to keep his/her eyes open and to fixate his/her vision to one spot to minimize alpha interference.
3. The subjects were asked to relax all neck and jaw muscles.
4. The subjects were told they would hear two stimuli. The difference between the rarely occurring stimulus and frequently occurring stimulus was described i.e., a low-pitch tone burst would occur frequently and a high-pitch tone burst would occur rarely.

A trial run was given to ensure that they understood the instruction.

5. The subjects were asked to make a mental count of the number of rarely occurring target stimuli, and to ignore the frequently occurring non-target stimuli. In the case of the paediatric subjects, to facilitate the task, they were allowed to count with their fingers, if they wished to.

At the end of the stimulus run, the subjects were required to report the number of target stimuli, they had counted.

6. The subjects were cautioned to avoid time locked physical responses such as eye-blinks with each presentation of the rare stimulus.

(5) Procedure of recording

1. The earphones were placed on the subjects ear, being careful not to dislodge any electrodes.
2. The blue ear phone was over the left ear and the red earphone over the right ear. The center of the earphone diaphragm was placed directly over the ear canal opening. This is not always the most comfortable earphone placement, but this placement is critical for the delivery of accurate stimulus intensity level.

The electrode leads and electrode head box were as far away from the earphones as possible. The earphones and head box cables did not overlap.

Identification of the P₃₀₀ wave form

The P₃₀₀ waveform was identified by visual inspection. The first positive peak following the N₂₀₀ was considered as v The P₃₀₀ amplitude was measured as the amplitude difference between N₂₀₀ and P₃₀₀ peak.

ANALYSIS, RESULTS AND DISCUSSION

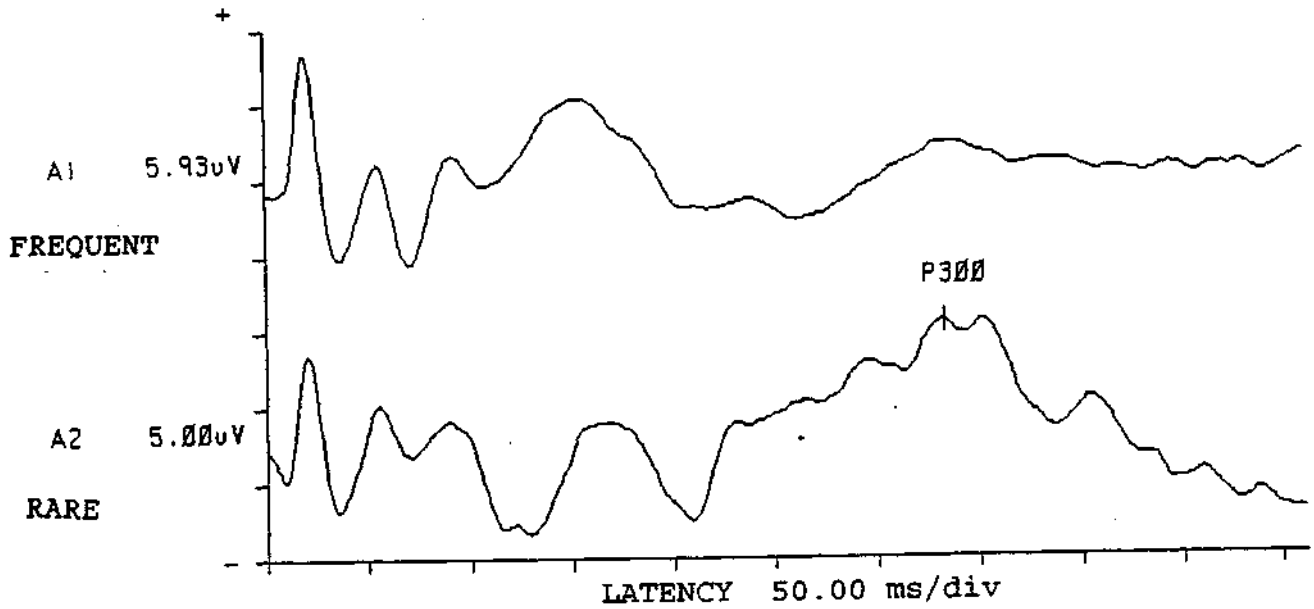
Out of the 30 adults (15 males and 15 females) a P300 waveform could be Identified for 29 subjects (15 males and 14 females). P₃₀₀ was obtained for both Pz and Cz electrode placements in the 29 subjects. For 5 subjects, a double peak (P_{3a} and P_{3b}) was recorded.

Such a bimodel P₃₀₀ has been reported by Squires et al. (1975), Polich, et al., (1983) and McPherson (1996).

Out of the 30 children (15 males and 15 females, 10 each in the 3 different age groups), a P₃₀₀ waveform could be identified for 22 children (7 in the age group of 7-8 years, 6 in the age group of 8-9 years, and 9 in the age group of 9-10 years). In general, the P₃₀₀ was less distinct in the children's group, particularly in the younger age group (7-8 years). This may be due to the higher number of artifact recorded and the inability of the younger group to sustain their attention.

Only one subject showed a bimodel P₃₀₀ waveform.

A Bimodal P₃₀₀ waveform of a subject aged 22 years



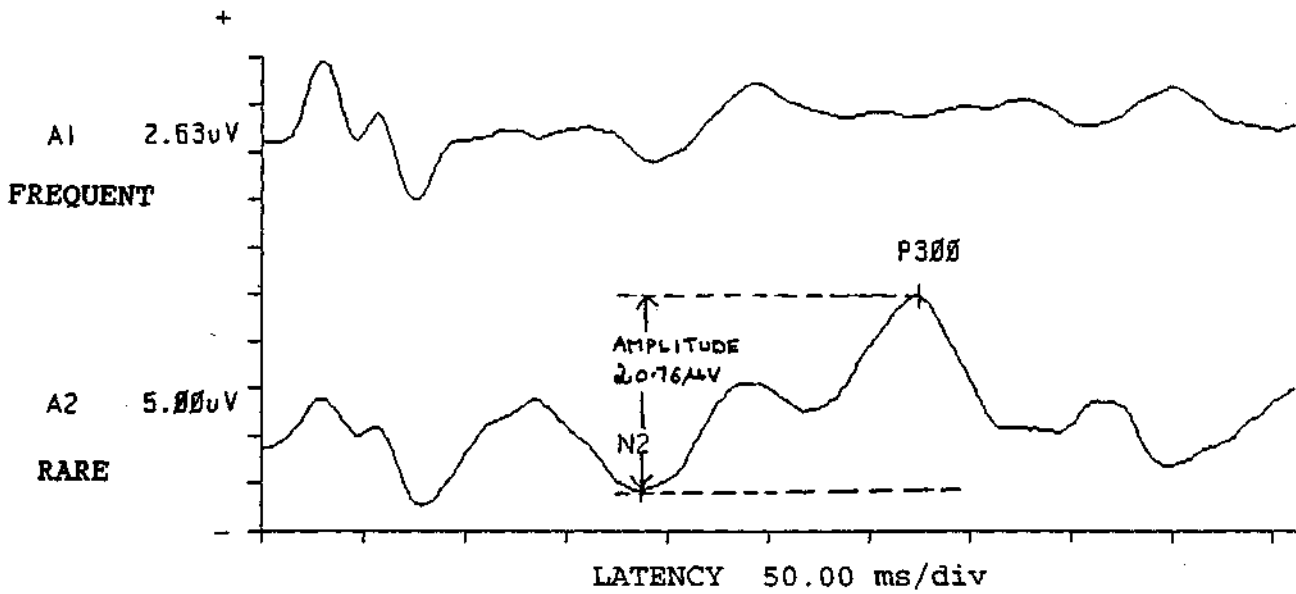
P₃₀₀ LATENCY = 333 msec. P₃₀₀ AMPLITUDE = 12.81 μ V

The data obtained was subjected to statistical analysis.

Table-1: Latency of P₃₀₀

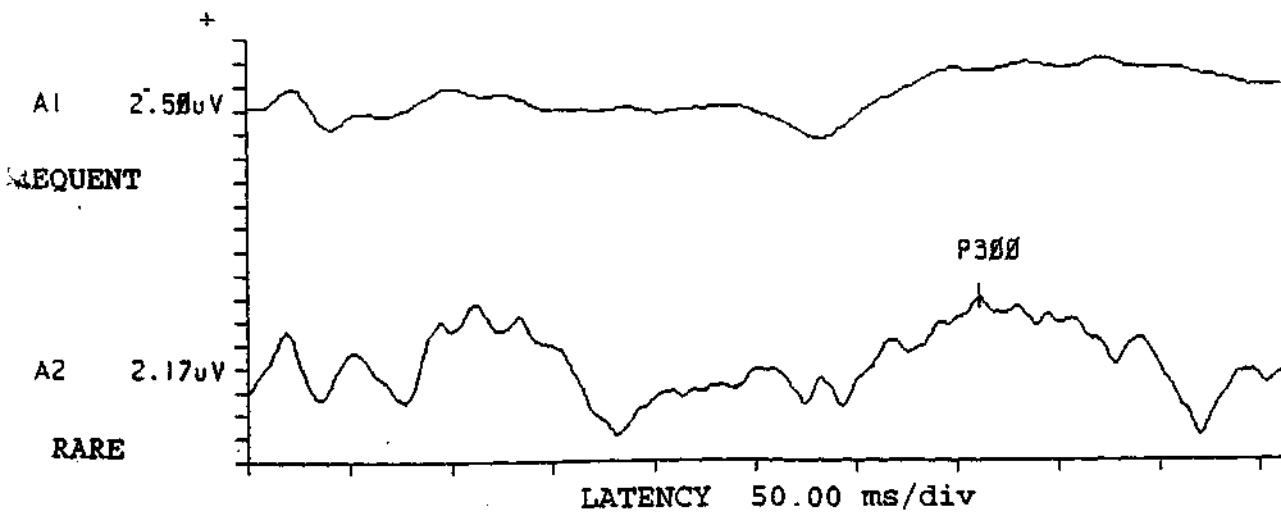
S.No	Age group (in years)	Electrode site	NO.	Mean msec	Median msec	SD msec	Min. msec	Max. msec
1.	Adult (18-35)	Cz	29	315.14	318	36.99	252	401
		Pz	29	313.62	317.5	40.24	241	409
2.	Children (7-10)	Cz	22	342.23	343	28.07	272	386
		Pz	22	342.18	346.5	32.65	266	386
3.	Children Sub-group I (7-8)	Cz	7	356.28	363	22.22	327	386
		Pz	7	363	365	23.20	327	386
4.	Children Sub-group II (8-9)	Cz	6	345.66	362	36.84	272	366
		Pz	6	333.17	363	49.79	266	369
5.	Children Sub-group III (9-10)	Cz	9	329	333	21.70	283	357
		Pz	9	332	334	16.96	303	354

P₃₀₀ waveform of a subject aged 23 years, recorded at Pz electrode site.



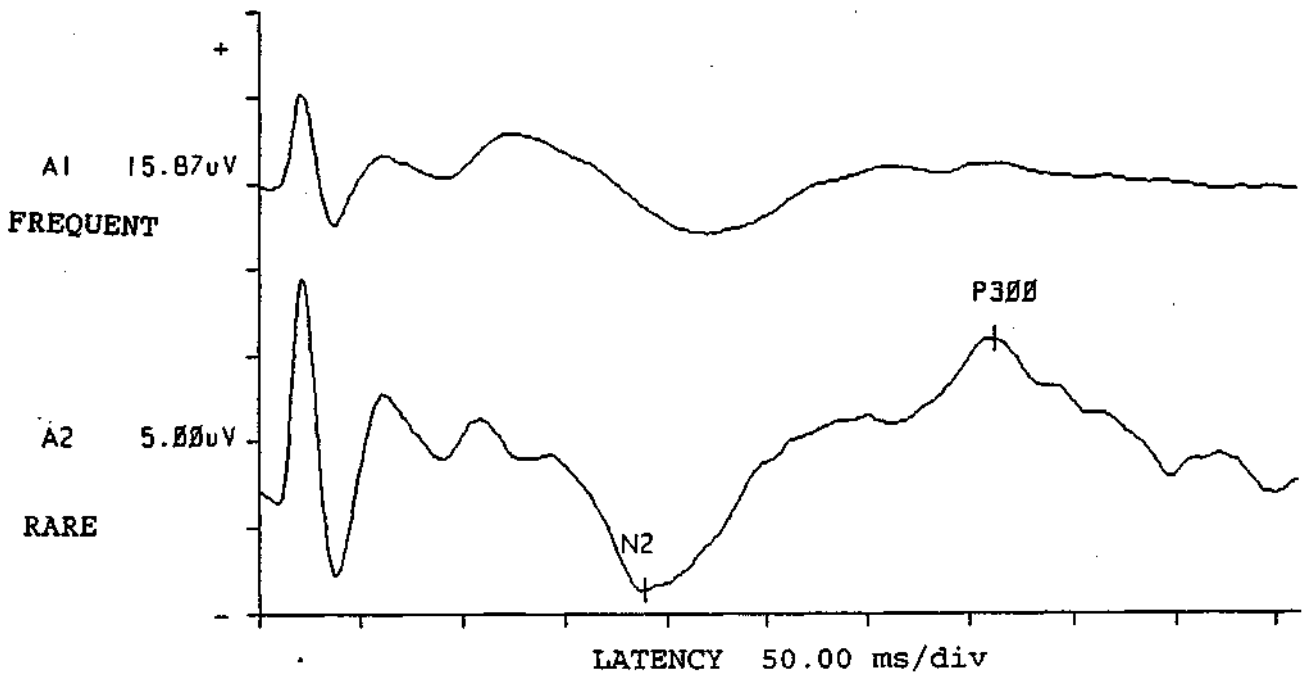
P₃₀₀ LATENCY = 323 msec.

P₃₀₀ waveform of a subject aged 7 years, recorded at Cz electrode site.



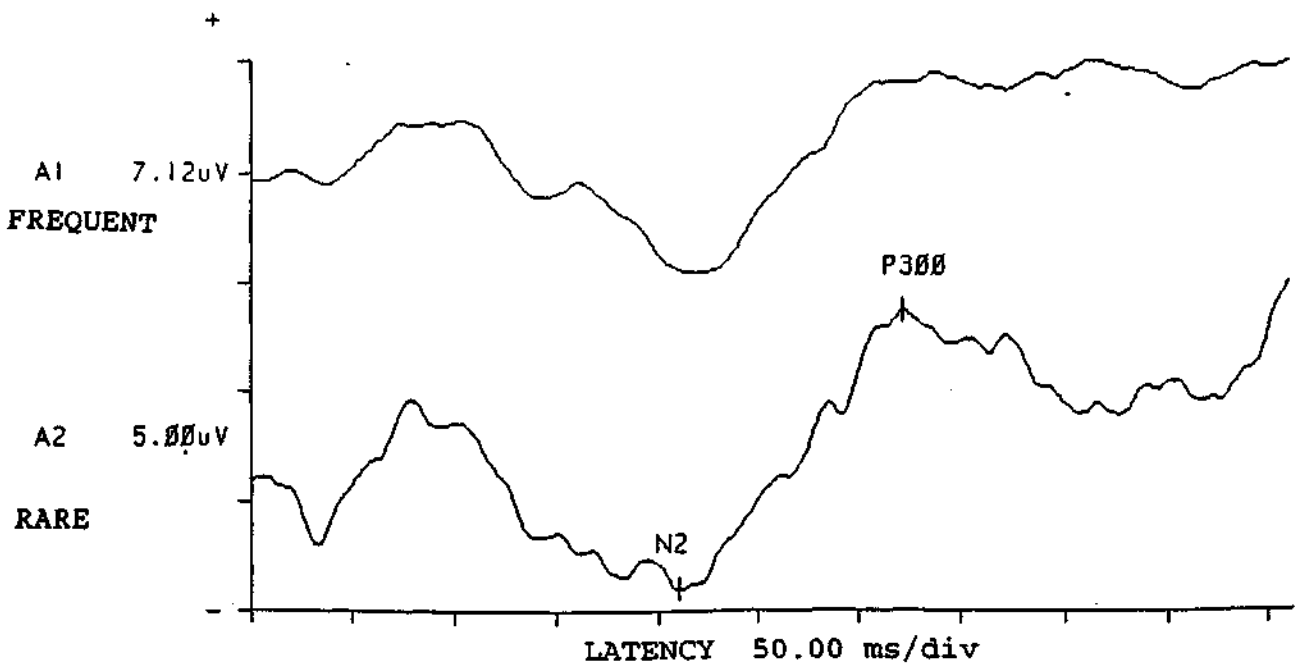
P₃₀₀ LATENCY = 363 msec. P₃₀₀ AMPLITUDE = 9.74 μ V

P₃₀₀ waveform of a subject aged 8 years, recorded at Cz electrode site.



4 P₃₀₀ LATENCY = 362.6 msec. P₃₀₀ AMPLITUDE = 14.39 μ V

P₃₀₀ waveform of a subject aged 9 years, recorded at Pz electrode site.



P₃₀₀ LATENCY = 343 msec. P₃₀₀ AMPLITUDE = 12.70 μ V

As shown in Table-1, there was a clear developmental trend in the P_{300} latency, with the adult group having the least latency and the 7-8 years children group having the longest latency, for both Cz and Pz electrode placements. In comparison to the children group, the adult group P_{300} latency was more variable (SD for Cz = 36.99, SD for Pz = 40.24).

Table-2: Latency of P_{300} : Comparison between the adult group and children group (2 sample 'T' Test).

S.No	Variable	N	Mean msec.	SD msec.	F-ratio	Probabi-N lity level
1.	Cz latency adult	27	360.37	33.11	1.3914	0.4320
	children	22	342.23	28.07		
2.	Pz latency adult	27	307.96	35.13	1.1580	0.7265
	children	22	342.18	32.65		

As shown in Table 2, there was no significant difference on 2 sample 'T' test between the young adults group (18-35 years) and children group (7-10 years) for P_{300} latency in both Pz and Cz electrode placements (For Cz, probability level= 0.4320; for Pz, probability level=0.7265).

Table-3: Latency of P_{300} : comparison between adult group and each separate children group (Mann-Whitney 'U' Test)

Variable	N	Mean (msec)	'U' value	Probability level
Cz Latency adults	8	305.88	7	0.007
Children (7-8 years)	7	356.28		
Pz Latency adults	8	310	5	0.003
Children (7-8 years)	7	342.18		
Cz Latency adults	8	305.88	6	0.010
Children (8-9 years)	6	345.66		
Pz Latency adults	8	310.88	4	0.004
Children (8-9 years)	6	333.17		
Cz Latency adults	8	305.88	22	0.164
Children (9-10 years)	9	329		
Pz Latency adults	8	310	26	0.578
Children (9-10 years)	9	332		

Mann-Whitney 'U' test was carried out to compare the latency of adults with each of the 3 children groups. As the

number of children tested, in each group was less, a random sampling was done to select 8 adult subjects. As seen in Table 3, the results showed that :

- i) There was a significant difference between the sampled adult group and the 7-8 years children group for both Pz and Cz electrode placements, at 0.01 level (probability level for Cz = 0.007, probability level for Pz = 0.003).
- ii) There was a significant difference between the sampled adult group and the 8-9 years children group for both Pz and Cz electrode placements at 0.01 level (probability level for Cz = 0.010; probability level from Pz = 0.004).
- iii) There was no significant difference between the sampled adult group and 9-10 years children group, for both Pz and Cz electrode placements at 0.05 level (probability level for Cz = 0.164; probability level for Pz = 0.578).

Table-4 : Latency of P₃₀₀ : Comparison of latency within the children age groups (Mann-Whitney Test)

S.No.	Variable	N	Mean	'Z' value	Probability level
1.	Cz Latency children (7-8 years)	7	356.28	0.2857	0.7751
	Children (8-9 years)	6	345.66		
2.	Pz Latency children (7-8 years)	7	363	1.1429	0.2531
	Children (8-9 years)	6	333.17		
3.	Cz Latency children (7-8 years)	7	356.28	1.9053	0.0567
	Children (8-9 years)	9	329		
4.	Pz Latency children (7-8 years)	7	363	2.3287	0.0199
	Children (8-9 years)	9	333		
5.	Cz Latency children (8-9 years)	6	345.66	2.0035	0.0451
	Children (9-10 years)	9	329		
6.	Pz Latency children (8-9 years)	6	333.17	1.0607	0.2888
	Children (9-10 years)	9	332		

As seen in Table-4, comparison of P300 latency within the children age groups, using Mann-Whitney 'U' test, showed that :

(i) There was no significant difference in P_{300} latency at 0.05 level, between the 7-8 years children group and 8-9 years children group, for both Cz and Pz electrode placements.

(ii) There was a significant difference in P300 latency at 0.05 level for Pz electrode, between the 7-8 years children group and 8-9 years children group (probability level = 0.0199) .

Cz electrode showed no significant difference between the above 2 groups.

(iii) There was a significant difference in P_{300} latency at 0.05 level for Cz electrode between the 8-9 years children group and 9-10 years children group (probability level= 0.0451).

There was no significant difference in P_{300} latency for Pz electrode between the above 2 groups.

Thus the above results are in concurrence with earlier studies in showing a decrease in P_{300} latency with maturation of the auditory nervous system. Holcomb et al., (1985) studied 108 normal subjects in the age group 8-9 years using visually evoked P_{300} and reported of a age-related change in P_{300} latency, with a decrease in latency with age upto early adulthood. Martin, et al., (1989) studied 68 normal subjects in the age range of 6 to 23 years, and reported of a significant correlation between age and latency upto age 15 years. Similar results have been reported by Pearle, et al., (1989) who studied normal subjects in the age range of 5-13 years, McPherson et al., (1989) who studied the age range of 5-12 years and Barajas et al., (1990), who studied the age range of 6-24 years.

The lack of a statistically significant difference for the P_{300} latency between the adult group and children group may be explained by the large variability in the latency (large SDs) obtained within each group. Such large SDs have been reported in earlier studies also (Brown, et al., 1983); Polich, et al., 1985; Pearce, et al., 1989; Barajas, et al., 1990). The finding of a significant difference between the adult group and the 7-8 and 8-9 years children group and the lack of a significant difference between the adult group and the 9-10 years children group suggests that the difference in

latency between the adult group and children group decreases with increase in age.

Thus these findings provide a normative data for P₃₀₀ latency for the children age group (7-10 years) and young adults (18-35 years). This is especially important for the study of clinical populations such as learning disability, mental retardation, central-auditory disorders etc, as the major alteration seen is a variation of P₃₀₀ latency, which is also seen in normal development, but to a lesser degree, as shown by this study.

Table-5: Amplitude of P₃₀₀

S.No	Age group (in years)	Elec-trode	No.	Mean (micro volts)	Median	SD	Min.	Max.
1.	Adult (18-35)	Cz	29	12.28	12.43	5.44	4.11	24.17
		Pz	29	12.40	12.96	4.97	5.11	25.05
2.	Children (7-10)	Cz	22	11.64	11.73	3.82	4.5	19.33
		Pz	22	11.54	10.97	4.63	3.21	22.31
3.	Children Sub-group I (7-8)	Cz	7	11.08	12.46	3.20	6.19	14.88
		Pz	7	10.36	10.72	3.96	6.34	15.16
4.	Children Sub-group II (8-9)	Cz	6	10.43	10.34	3.84	4.5	14.39
		Pz	6	9.31	9.46	2.80	3.21	11.23
5.	Children Sub-group III (9-10)	Cz	9	12.87	11.54	4.29	7.91	19.33
		Pz	9	14.35	14.35	4.86	7.07	22.31

Table-6: Amplitude of P_{300} : Comparison of adult and children group (2 sample 'T' test).

S.No	Variable	N	Mean (micro- volts)	SD (micro- volts)	F-ratio	Probabi-N lity level
1.	Cz amplitude adult	27	12.21	5.37	1.9726	0.1086
	children	22	11.64	3.82		
2.	Pz amplitude adult	27	12.65	4.95	1.1404	0.7542
	children	22	11.54	4.63		

As shown in Table 5, there was lots of variability in amplitude of P_{300} and there was no systematic change in amplitude with increase in age.

As shown in Table-6, when the 2 groups were compared with 2 sample 'T' test, there was no significant difference between the adult group (18-35 years) and children group (7-10 years) for P_{300} amplitude in both Cz and Pz electrode placements (For Cz, probability level = 0.1086; for Pz, probability level = 0.7542).

This finding is in concurrence with earlier studies (Goodin et al., 1978, Brown, et al., 1983; Polich, et al., 1985; Martin, et al., 1988; Barajas, et al., 1990) who also report of no significant variation of the P_{300} amplitude

with an increase in age. Such a finding may be explained by the presence of a large inter subject variability in P_{300} amplitude across all age groups. It has been reported in literature that intra-subject and intersubject variability is more for amplitude of P_{300} (Brown, et al., 1983; Polich, et al., 1985; McPherson, et al., 1989).

Thus the above study reveals that the P_{300} amplitude does not show any developmental trend and has high intersubject variability or even within the same age group. This suggests that it is difficult to study developmental changes or maturation of the auditory nervous system by recording amplitude of P_{300} . Also the amplitude of P_{300} when in clinical population should be interpreted with caution.

Table-7: Latency of P300 : Comparison of Pz and Cz electrode placements in the different age groups.
(Mann-Whitney Test)

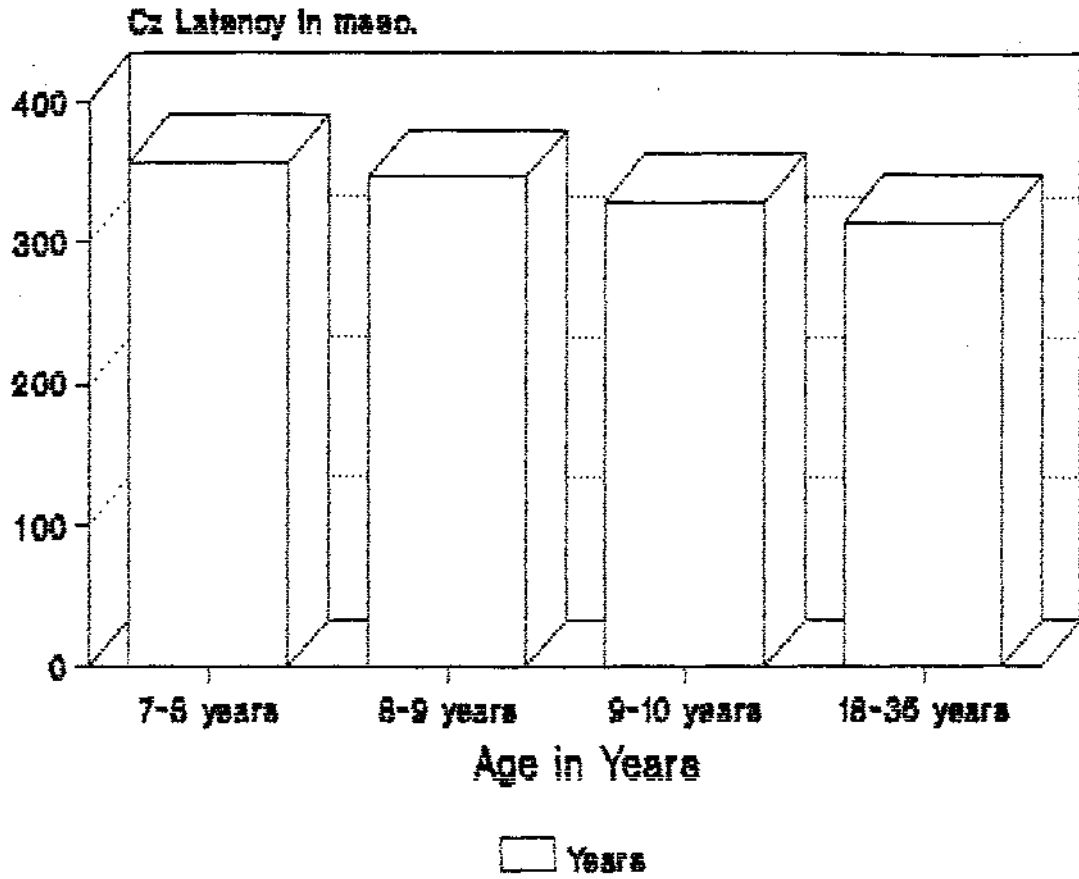
S.No	Variable	N	Mean msec.	Z-value	Probability level
1.	Adults				
	Cz	27	310.37	-4.3249	0.9655
	Pz	27	307.96		
2.	Children (7-8 years)				
	Cz	7	356.28	-0.5111	0.6093
	Pz	7	363		
3.	Children (8-9 years)				
	Cz	6	345.66	-0.2401	0.8102
	Pz	6	333.17		
4.	Children (9-10 years)				
	Cz	9	329	-0.3090	0.7573
	Pz	9	332		

As seen in Table 7, there was no significant difference in the P300 latency between the Pz and Cz electrode placements, in both the adult and children groups. This finding suggests that there is no shift in the prominent P₃₀₀ electrode site.

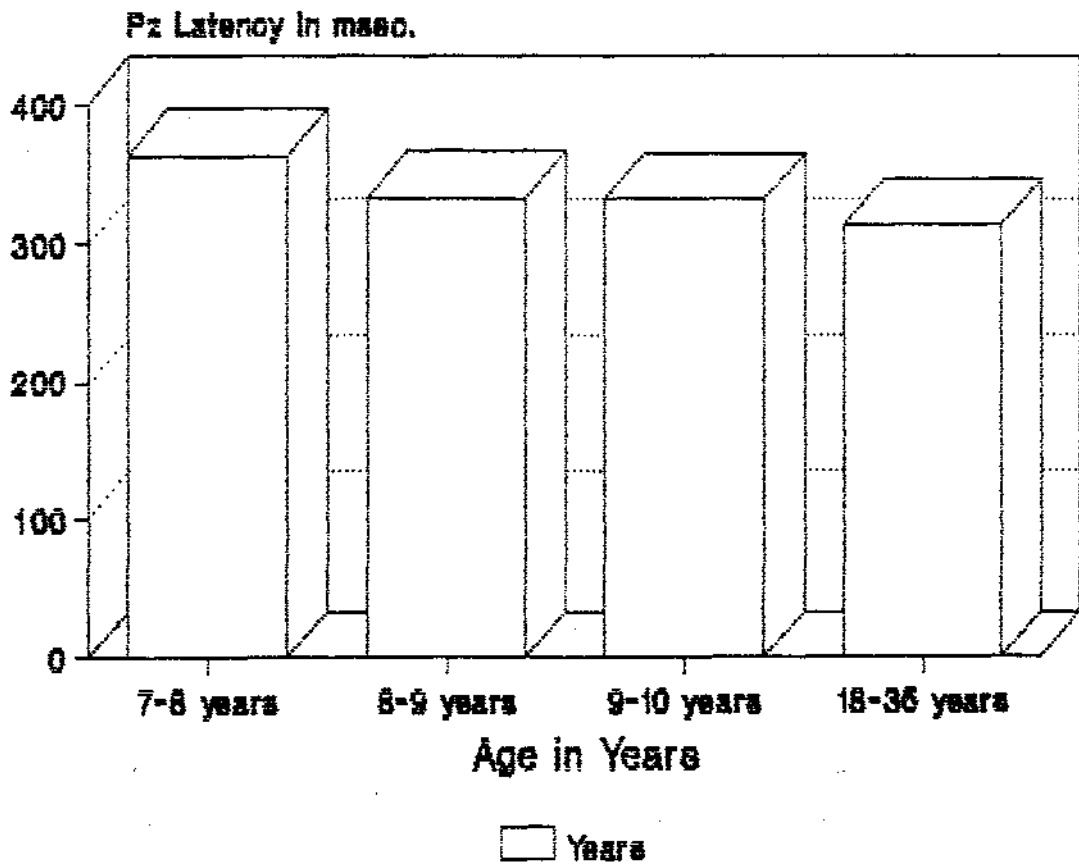
This finding is in contrast to earlier studies. Holcomb, et al., (1985) reported of a shift in the dominant

P₃₀₀ waveform (shorter latency and larger amplitude) from a posterior site (Cz) to a more anterior site (Pz) with increase in age. Similar results have been reported by Pfefferbaum, et al., (1980), Smith, et al., (1980) Pfefferbaum, et al., (1984). The present studies result is inconcurrence with Snyder's study (1980) which reported of no age related changes in the P₃₀₀ electrode site.

Cz latency vs age



Pz latency vs age



SUMMARY AND CONCLUSION

The P₃₀₀ is a positive response recorded at 300 msec, and is an endogenous cognitive event-related potential (ERP). The amplitude of the P₃₀₀ is about 15 microvolts, and under certain recording and stimulus conditions may be bimodal i.e., P_{300a} and P_{300b}. The P₃₀₀ is broadly distributed with a maximum amplitude observed at the midline over the centro-parietal areas, and is best recorded with a auditory "odd-ball" paradigm. The P₃₀₀ is greatly influenced by attention, alerting, arousal, subject psychological state and varies with development/aging of the subject.

The current study was undertaken to investigate if there was any age related significant variation in the latency of P₃₀₀ and its amplitude on comparing normal children (7-10 years) and normal young adults (18-35 years). It was also designed to determine whether there was any significant variation in P₃₀₀ on comparing frontal (Cz) and parietal (Pz) electrode placements.

The 2 groups were studied on an auditory 'odd-ball' paradigm, in which a infrequently occurring target tone (2 KHz, 20% of the trials) was used to elicit the event-related P₃₀₀ potential against a background of a frequently occurring

non-target tone (1 KHz, 80% of the trials). The subjects were instructed to keep a cumulative count of the rare tones and to ignore the frequent tones. P300 was recorded at Cz and Pz electrode sites.

The mean P₃₀₀ latency was Cz = 315.14, Pz = 313.62 msec. and Cz = 342.23, Pz 342.18 msec. for the adult and children group, respectively. The 3 children age groups had a mean latency of Cz = 356.28; Pz = 363 msec. (7-8 years); Cz = 345.66 msec, Pz = 333.67 msec. (8-9 years) and Cz = 329 msec, Pz = 332 msec. (9-10 years).

The results revealed that

1. There was clear developmental trend in the P₃₀₀ latency (the latency decreased from the children to adult age group) seen, but no statistical significant difference was seen between the 2 groups.

There was a significant difference in terms of P₃₀₀ latency between the adult group and the children age groups 7-8 years and 8-9 years, but no significant difference was found between the adult group and 9-10 years children group.

2. There was no developmental trend in the P300 amplitude, and no significant difference was found between the 2 groups (adults vs. children).
3. There was no significant difference in the P₃₀₀ latency between the Pz electrode placement and Cz electrode placement.

The results of this study, thus reaffirms the importance of aging as a contributing factor to changes in the latency of event-related potential P₃₀₀.

Limitations of the present study

1. The number of subjects included in each group, was not large enough, to reliably extend the results to all subjects of the same age group.
2. The present study included children in the age group of 7-10 years, only and thus did not study the variation in the P₃₀₀ latency over the whole children population.
3. The present study employed a fixed stimulus parameters and response strategies, and did not study the influence of a varied stimulus parameters and response strategies on the P₃₀₀ latency.

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