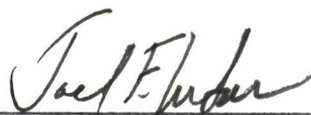


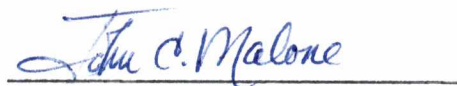
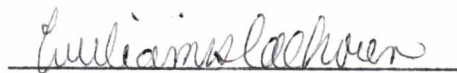
To the Graduate Council:

I am submitting herewith a thesis written by Steven M. Satterfield entitled "P300 in the Rat Evoked by Unpredictable and Task Relevant Stimuli." I have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Arts, with a major in Psychology.



Joel F. Lubar, Major Professor

We have read this thesis and
recommend its acceptance:



Accepted for the Council:



Vice Provost
and Dean of The Graduate School

STATEMENT OF PERMISSION TO USE

In presenting this thesis in partial fulfillment of the requirements for a Master's degree at The University of Tennessee, Knoxville, I agree that the Library shall make it available to borrowers under rules of the Library. Brief quotations from this thesis are allowable without special permission, provided that accurate acknowledgment of source is made.

Permission for extensive quotation from or reproduction of this thesis may be granted by my major professor, or in his absence, by the Head of Interlibrary Services when, in the opinion of either, the proposed use of the material is for scholarly purposes. Any copying or use of the material in this thesis for financial gain shall not be allowed without my written permission.

Signature

Steven M. Lattin

Date

22 Feb '85

P300 IN THE RAT EVOKED BY UNPREDICTABLE
AND TASK RELEVANT STIMULI

A Thesis
Presented for the
Master of Arts
Degree
The University of Tennessee, Knoxville

Steven M. Satterfield

March 1985

ABSTRACT

Evoked potentials were recorded from rats under four experimental conditions, so that the waveforms could be compared. The P300 was present in each condition except for the "habituation" schedule of stimulus presentation. Moreover, the morphology of the P300 was markedly different for each rat in the "task relevant" condition than in the baseline conditions. These results are discussed in relation to the development of the rat as an animal model for P300 abnormalities associated with Alzheimer's-like cognitive deficits.

TABLE OF CONTENTS

CHAPTER	PAGE
I. INTRODUCTION	1
II. METHODS	17
Subjects	17
Materials	17
Procedures	19
III. RESULTS	21
IV. DISCUSSION	27
REFERENCES	30
VITA	34

LIST OF FIGURES

FIGURE	PAGE
1. AEP Under the Initial Baseline Conditions	22
2. AEP Under the Habituation Condition	24
3. AEP After Return to Initial Baseline Conditions	25
4. AEP Under "Task Relevant" Conditions	26

CHAPTER I

INTRODUCTION

In 1963, E. Roy John observed changes in what he called "labeled potentials" in the averaged evoked potential of the cat (John, 1963). He noted that the changes were a function of alterations in the initiating stimulus. John hypothesized, on the basis of this observation, that changes in the electrical potential of the cortex can reflect cognitive processes as well as responses to sensory stimulation. He, and many others, have since turned to the human as a more appropriate subject for experimentation that focuses on variables which effect cognition. Over the years since John's 1963 experiment, the measurement of amplitude and latency shifts of cortical "evoked potentials" have lent credence to his hypothesis.

An evoked potential (EP) may be generally defined as the observed change in the electrical potential of the cortex, as measured by electroencephalogram (EEG) recordings, following some physical stimulus or psychological event. Because there is a problem with background noise in the ongoing EEG, such as interference with the cortical signal by electrical potentials generated by muscular movement, it is necessary to average several EP signals together to obtain a more favorable signal to noise ratio, and thus more easily distinguish the EP waveforms.

Signal averaging is based on the assumption that the background noise is going to be random in time, regarding the presentation of the

evoking stimulus. Therefore, over several trials, this random "noise" should average to near zero in amplitude (Peters, 1973). So evoked potentials are more often referred to as averaged evoked potentials (AEP).

The evidence suggests that AEP's may be separated into two sets of components. Those occurring up to 150-200 msec after presentation of the initiating stimulus are often referred to as sensory-related potentials. Those occurring later than 200-250 msec after presentation of the stimulus are the event-related potentials (ERP). The latter appear to reflect the information content of the stimulus (Sutton, Braren, Zubin, & John, 1965; Ritter Simson, & Vaughan, 1972). The P300 ERP component ranges in latency from 250-550 msec after stimulus presentation. This component is called the P300 because it occurs on the average at about 300 msec after stimulus presentation, and the waveform is traditionally positive. The P300 is one of the most intensively studied ERP components today.

The measurement of amplitude and latency shifts of the P300 have shown tremendous potential as a diagnostic tool for specific dementias (Syndulko et al., 1982). A dementia disorder which is currently the focus of much research in the United States is Alzheimer's disease (AD). The symptomatic manifestation of AD, which may be noticeable as early as age 45, is characterized by the insidious onset and steady progression of a global loss of intellectual abilities, with associated deterioration of personality and behavior, which eventually renders the individual completely incapacitated and dependent upon others

for survival. There was once a diagnostic distinction between senile dementia and dementia of the Alzheimer's type (presenile onset). However, postmortem examinations of the brains of both senile and presenile onset dementia patients have revealed such similar specific cortical abnormalities that both are now widely believed to reflect the same disease process; Alzheimer's (Coyle et al., 1983). It would appear, then, that the vast majority of the estimated 1½ million cases of dementia in the United States alone are of the Alzheimer's type. Syndulko et al. (1982) demonstrated the potential of the P300 as a means of differentially diagnosing AD from other psychiatric disorders which may also exhibit similar cognitive deficits.

Most available research of the P300 component in humans supports the hypothesis that it is a manifestation of the changes in the cortical electrical field which reflect information processing. The P300 was first described (Sutton, Braren, Zubin, & John, 1965) following an experiment in which the subject was required, immediately after a cueing stimulus, to state his guess as to the sensory modality of the next (test) stimulus. There were two kinds of pairs of stimuli, one of which allowed for certainty as to the nature of the test stimulus, and another which allowed for uncertainty. The P300 was observed in both the certain and uncertain conditions, but was greater in amplitude for the uncertain condition in 100% of the 36 experiments with 8 subjects. In the same paper, Sutton et al. described another set of experiments which demonstrated that stimuli with a lower probability of occurrence evoked a P300 of greater amplitude than those with higher probabilities. Prior to these observations, evoked potentials were all referred

to as sensory evoked potentials. This set of experiments corroborated John's (1963) hypothesis that evoked potentials could be influenced not only by exogenous factors, such as the physical parameters of the stimulus, but also by endogenous factors related to the subject's cognitive processing of the event.

Sutton, Tueting, & Zubin (1967) cited the results of the aforementioned experiments as evidence that the amplitude and latency of the P300 component of the human ERP are a function of the significance of the stimuli for the subject. In other words, these measures are related to the amount of information which the stimulus conveys to the subject. They also observed that only the latency of P300 appears to be effected by changes in the sensory modality of the stimulus, while the amplitude remains constant across modalities.

Although given different labels by different authors; i.e., P3, P300, late positive component (LPC), the P300 component of the ERP in humans became subject to much research following the publication of the article in which it was initially described by Sutton et al. (1965). However, whereas Sutton and his associates immediately converged on the general notion of the amount of information conveyed to the subject by the stimulus as the principle source of variation in the waveform of P300, later researchers began to examine more specific factors contributing to the overall information content of the stimulus. Tueting, Sutton, & Zubin (1971), for example, designed an experiment, using human subjects, consisting of three sets of conditions, each of which examined the effect of only one independent variable on the P300.

These variables were: a priori relative probability of the occurrence of the initiating stimulus; the sequential probability of stimulus occurrence (i.e., the probability of a different or like stimulus following each presentation); and the degree of the subject's uncertainty regarding the physical parameters of each ensuing stimulus. These results suggest that although manipulating each of these variables does effect the P300 waveform independent of the other variables, the interaction of all three variables produces a much greater effect on the amplitude of the component. Specifically, a low probability stimulus (.20 or less), randomly presented to a subject who is uncertain regarding the physical parameters of each anticipated stimulus correlates with an increase in amplitude, and a slight decrease in latency, of the P300.

Tueting et al. performed two separate analyses of the effects of variations in sequential probability; one for alternated stimuli, and another for repeated stimuli. The results of these analyses show a definite trend toward increased P300 amplitude with decreased (.20 or less) sequential probability for the alternated stimuli. There was no clear relationship between P300 amplitude and sequential probability for the repeated stimuli. This finding is consistent with their conclusion that P300 amplitude seems to be determined by the subject's degree of unexpectedness regarding the physical parameters of each in a series of stimuli. However, the observation that low relative probability stimuli correlated with increases in the amplitude of the P300 even when the subject was certain of the physical nature of each ensuing

stimulus is inconsistent with their conclusion. Tueting et al. suggest that the slight increase in the P300 under this condition could be attributed simply to the novelty of the infrequent stimulus; as it were, a relief from boredom.

Other researchers have suggested that increased amplitude of the P300 under such conditions reflects an orienting response, or shift in attention, to the infrequent, and thus novel, stimulus (Roth & Kopell, 1973; Ritter, Vaughan, & Costa, 1968).

The selective attention of the subject to the initiating stimulus is another factor which contributes to the amount of information conveyed by the stimulus to the subject. Many researchers have examined this factor within the context of P300 sensitivity. Sheatz and Chapman (1969) designed an experiment which allowed them to quantify such selective attention by human subjects. They obtained such quantification by making one of the stimuli "task relevant." Specifically, they alternately assigned either a noise-like hiss, or a pure tone, the status of "relevant" stimulus. They then assigned their subjects the "task" of comparing the two "relevant" stimuli in each series of four sequentially alternating stimuli. By comparison the subject then determined which of the two relevant stimuli was lower in frequency. Their results show an increase in P300 amplitude for the relevant stimuli, regardless of which stimulus (noise or tone) was "relevant." Sheatz and Chapman also consistently observed that the second relevant stimulus in each series correlated with greater increases in P300 amplitude than did the first. They suggested that this difference

could be a result of the subject only having to "store" the information conveyed by the first relevant stimulus, while the second relevant stimulus initiated the more complex function of problem solving.

Sheatz and Chapman, then, provided us with a methodology for quantifying selective attention to specific stimuli by making them "task relevant." Moreover, their results not only demonstrated the effect of selective attention on P300, but of problem solving as well. All of which corroborates the general notion that the P300 is a manifestation of cortical information processing, increasing in amplitude as the complexity of the cortical processes increases.

Paul and Sutton (1972) took this "task relevance" methodology a bit further. They were able to manipulate, using a somewhat complex system of reward and penalty for right or wrong answers, not only the level of attention to the initiating stimulus, but also the significance, or meaningfulness, of the relevant stimulus to the subject. They also eliminated stimulus change as a possible variable by using a signal detection paradigm. In a signal detection paradigm, only one type of stimulus is necessary. The stimulus is the detection of the signal against a constant white noise background. The subject's task here was to press either a "yes" or "no" button after each specific time interval, indicating whether or not he had detected a signal, or stimulus presentation. Paul and Sutton used two experimental conditions. In one condition, the independent variable was the a priori probability of the occurrence of a signal, with three levels of probability ($P = .25$; $P = .50$; $P = .75$), and the reward/penalty factor

remained constant. In the other condition, the independent variable was the reward/penalty factor, with three levels of "significance" (cautious, unbiased, liberal), and the probability of occurrence remained constant at .50. Paul and Sutton were thus able to examine the effect of the level of significance, or meaning, of the stimulus to the subject, independent of the level of probability of occurrence. In the experiment in which the degree of reward or penalty for correctly or incorrectly indicating that a signal had occurred was the independent variable, they observed that the amplitude of the P300 was much higher when the reward and penalty values were highest (cautious), than when these values were either moderate (unbiased) or low (liberal). Similarly, they observed that the amplitude of the P300 was highest in the other experimental condition when the probability of occurrence was lowest. So it appears that both variables (probability of occurrence, and level of significance) may be very similar in their effects on the P300, and thus, hypothetically, contribute similarly to the overall information content of the stimulus.

These data indicate that the various factors to which the P300 is sensitive are each sufficient to produce changes in the waveform, but that it is unlikely that any one of these factors is necessary, given the presence of any of the others. In other words, the P300 is most likely a manifestation of overall changes in cortical electrical potentials during information processing, and the more factors which contribute to the total information conveyed to the subject by the stimulus, the more complex and widespread the necessary cortical processes, and thus the greater the amplitude of the P300.

This hypothesis is consistent with the findings of Vaughan & Ritter (1970), that, although P300 diminished somewhat in amplitude as the recording distance from the vertex of the skull increased, the waveform was consistently present over the entire cortex. The early, sensory-related AEP components, on the other hand, not only diminished more markedly in size with increasing recording distance from the cortex, but actually reversed polarity (i.e., positive going waveforms became negative) at specific distances from the vertex. The recording electrodes were distributed, equally spaced, in two chains; one following the midline from the front to the back, the other extending from temple to temple such that the vertex of the skull was the point of intersection with the midline chain.

Hillyard, Krausz, & Picton (1974) similarly reported that the P300 was consistently distributed over the cortex, but was greater in amplitude on recording sites Cz and Pz (specific reference areas for EEG recording from the human scalp which are part of an international standard; C refers to central areas, P to parietal, and z designates the midline). They also observed a much broader zone of maximal amplitude for P300 as opposed to the earlier, sensory related, AEP components. Hillyard et al. regarded such a consistent distribution of the P300 over the cortex as evidence for the hypothesis that a substantial portion of each P300 is generated by a common cerebral system. Hillyard et al. expanded this hypothesis to include a unitary psychological correlate for the P300, regardless of the physical parameters or sensory modality of the initiating stimulus, or the psychological variables manipulated in the experimental condition.

Karis, Fabiani, & Donchin (1984) recently proposed such a correlate. Karis et al. observed that the items which elicit the Von Restorff (isolation) effect (a term which refers to the enhanced learning of an "isolated" event), are very similar in certain attributes to stimuli which evoke the P300. Specifically, they are novel and task relevant. They then hypothesized that the P300 is a physiological manifestation of "context updating," a metaphorical model to describe the cortical processes by which the working memory is revised in the presence of novel, relevant incoming sensory data, or by cognitive processes which may be affected by the impingement of such data upon the consciousness. On the basis of this hypothesis, they designed an experiment to determine if the amplitude of the P300 evoked by specific items could be correlated to the ability to recall that item on a subsequent test. The items were words which were in lists of 15. Each list contained one word, located somewhere between position 6 through 10, which was "isolated" by changing its size relative to the rest of the list. The Von Restorff effect occurs when the subject recalls these "isolated" words more often than other words in the same position.

Their results did indeed indicate that the words which caused the Von Restorff effect also evoked larger amplitude P300's than did the other words. They further observed that subjects who reported using simple (rote) mnemonic strategies remembered few words, showed a high Von Restorff effect, and also greater amplitude P300's evoked by the isolated words, which were correlated then with later recall ability.

Conversely, subjects who reported using complex mnemonic strategies not only remembered a higher percentage of words, but also showed no Von Restorff effect. Although these latter subjects showed a larger amplitude P300 following presentation of the "isolated" words, the many other words which they were able to recall evoked no significantly larger P300 than did the other words on the list. Thus no relationship was found between P300 amplitude following initial presentation of an item, and later ability to recall that item, for those subjects who used complex mnemonic strategies. If something analogous to "context updating" is reflected by P300, and is induced by novel, relevant data introduced through the nervous system, it would very likely involve much of the cortex. Karl Pribram (1971) described some of his earlier research in which he demonstrated that lesioning or removal of cortical areas impairs only memory which has not yet been "consolidated" into long term memory. He suggested, therefore, that a memory for any specific event is probably not restricted to any single neural location. Given the evidence that much rehearsal is necessary for most people to remember novel information, Pribram suggests that during such rehearsal, the information is being distributed throughout the cortex. As it spreads throughout the cortex, it becomes linked to the extant assortment of previously stored experiences and information.

On the basis of Pribram's model, one would expect the initial cognitive processes which follow the experience of a novel, significant stimulus to involve widespread changes in the electrical potential of the

cortex. This would be reflected then in the P300. The absence of a greatly increased P300 in subjects reporting the use of complex mnemonic devices implies the possibility that these complex mnemonic devices are capable of linking novel information (words) to a significantly large portion of the extant body of stored experiences much more quickly. These devices bypass, as it were, the necessity of the substantial changes in the electrical potential which are manifest in the P300.

The experiments described above are but a representation of the large body of research which demonstrates that many factors, both independently and in combination, are capable of altering the waveform of the P300 in the human ERP. All of the data discussed above support the argument that these factors are all related to the information content conveyed by the stimulus to the subject. Moreover, they support the early description of P300 (Sutton, Braren, Zubin, & John, 1965) as a manifestation of endogenous cortical processes set in motion by the information content of the evoking stimulus.

While much research has been designed purely to examine the nature of the P300 ERP component, and the factors to which it is sensitive, a more recent body of research has been developed in an effort to determine the clinical utility of the P300. Kutas, McCarthy, & Donchin (1977), for example, found that the latency of P300 corresponds to stimulus evaluation time, in that there is a large positive correlation between decreases in P300 latency and shorter reaction time (RT). Moreover, the correlation is much higher under conditions in

which accuracy rather than speed of response was stressed. Kutas, McCarthy, & Donchin suggested the clinical use of the P300 as a tool for mental measurement, as it seems to temporally reflect certain cognitive processes.

Goodin, Squires, & Starr (1978), having observed that the P300 is sensitive to many factors which influence cognition, and that its measurement has apparent clinical utility, hypothesized that neurological disorders characterized by cognitive deficits might be associated with alterations in the P300 waveform. Specifically, they were interested in dementia, as the demented individual has deficits in attention, memory, and the processing of sensory stimuli; all of which are factors to which the morphology of the P300 has been shown to be sensitive. They used three groups of subjects: normals, nondemented psychiatric patients, and demented psychiatric patients. Their initial observation, interestingly, was that within the normal and nondemented psychiatric patient groups (ranging in age from 15-78), the P300 shifted to longer latencies and decreased in amplitude as a function of increasing age. Previous research (Ohlrich & Barnet, 1972) had demonstrated that P300 does not become a prominent ERP component in human infants until about one year of age. Having observed this effect of age on the ERP, Goodin et al. then had to compare individuals within groups, and between groups, who were approximately the same age. The results were that the P300 was an average of 50 msec more latent for the demented patients, while the latency for nondemented patients was approximately the same as for normal subjects.

So, even though P300 latencies increase with age, the demented patients showed latencies far in excess of those of all other subjects of the same age.

Having used a control group of nondemented patients with such diagnoses as multiple sclerosis, depression, and schizophrenia, Goodin et al. demonstrated that the latency and amplitude of P300 might be used clinically to specifically diagnose dementias from other psychiatric disorders which may manifest functional, rather than organic, cognitive deterioration.

Goodin et al. also observed that, despite the fact that both the sensory-related components (specifically P200) and the event-related components (particularly P300) of the AEP increase in latency with increasing age in normal subjects and nondemented psychiatric patients, only the P300 showed greater latency within age groups for the demented patients. They suggested the implications of this observation as an argument against an hypothesis that presenile dementia is due to an accelerated aging process.

Syndulko et al. (1982) designed a partial replication of the above experiment. Based on the observed changes in P300 latency as a function of dementia described by Goodin et al., they used P300 latency abnormality as a diagnostic criterion for dementia, and correctly classified 83% of the demented patients. Their experiment thus confirmed the utility of the P300 as a diagnostic tool for dementia disorders.

Since John (1963) decided that humans would be more appropriate subjects for experiments in which variables affecting cognition were

manipulated, most ERP research has involved human subjects. There is now a need, however, for the development of an animal model with which to study more specifically the etiology of Alzheimer's disease. Since it has been demonstrated that abnormalities in P300 are associated with AD such that they can actually confirm a diagnosis, a logical step toward the development of such a model would be to demonstrate an effect on the P300. Wilder (1981) has demonstrated the presence of P300 in the cat AEP, and suggested its potential as an animal model for manipulation of this ERP component. Cats, however, are relatively expensive to purchase for experimental purposes. Moreover, due to legislation which regulates their housing and care in the laboratory, they are quite costly to keep. The rat, however, is relatively inexpensive to purchase and house.

O'Brien (1982) has demonstrated the presence of the P300 in the rat AEP. However, his methodology was far removed from that of human studies. Specifically, prior to obtaining the AEP's, O'Brien injected the rats with Nembutal, 50 mg/kg intraperitoneally (IP), the usual recommended anesthetic dose. He then presented the infrequent (evoking) stimuli in a different sensory modality than that for the frequent (background) stimuli. The frequent stimulus was visual (a light flash), while the infrequent stimulus was somatic (three 0.1 msec subcutaneous shocks of 250 Hz and 5 volts to the hindpaw of the sleeping rat).

The purpose of the present experiment was to demonstrate the presence of the P300 component in the rat AEP under conditions much

more similar to those in which it is found in human subjects. The experiment was designed to examine the P300, in each rat, under four different conditions. In the first condition, naive rats were presented with randomly distributed infrequent (evoking) stimuli, with an a priori relative probability of .10. The same rats were then presented the evoking stimulus with a priori relative and sequential probabilities of .50. The third experimental condition was a return to the .10 relative probability, random presentation schedule. Finally, in the fourth condition, ERP's were recorded after selective attention had been quantified by making the evoking stimulus "task relevant."

In each of these four conditions, the physical parameters of the infrequent stimulus were different than those of the frequent stimulus, although both were in the auditory sensory modality (albino rats having poor visual acuity). Kaufmann et al. (1982) described the ability of an infrequent stimulus with different physical parameters than those of the frequent stimulus, to increase the amplitude of the P300 independent of any other variables. Roth (1973) had observed that the pairing of random presentation with a low a priori relative frequency of the infrequent stimulus correlated with a greater increase in amplitude of P300 than either variable alone. He attributed this observation to an overall increase in "unpredictability" of the evoking stimulus.

CHAPTER II

METHODS

Subjects

The subjects were four mature male Sprague-Dawley rats, weighing between 500-600 g, housed singly in the animal facility, with free access to food and water. One of the subjects died the day after surgery, and so is not represented in the results.

Materials

Equipment consisted of a Grass S-88 electrical stimulator for generating stimuli and shocks, a Grass 7D polygraph for EEG recording, and Apple II Plus computer with printing capabilities and a video monitor, and a shuttle box with a .75 inch high hurdle, protruding from the grid floor, at the "border" separating the box equally into two ends. Alternate rods were electrified across the grid floor, and a switch attached to the Grass S-88 stimulator allowed an electrical impulse to be delivered to only one end of the box at a time.

The Grass S-88 stimulator presented stimuli to the subject of 0.3 sec duration, with a consistent interstimulus interval (ISI) of 1.5 sec. An electrical impulse from the Grass S-88 stimulator to a piezoelectric tone generator initiated the frequent stimulus--a tone of approximately 3500 Hz. Switching the output from the Grass S-88 to activate a solenoid operated electro-mechanical buzzer initiated

the infrequent "evoking" stimulus. Both the tone generator and the buzzer were mounted on the table on which the shuttle box was placed. During all experimental conditions, while the rat was in the shuttle box for both training and recording, an effort was made to control for environmental variables in the posttraining AEP.

A trigger stimulus, generated from the Grass S-88 to the Apple II Plus, began a recording interval lasting 1.08 seconds. The S-88 produced the stimulus impulse 180 msec after the onset of the recording interval.

The Apple II Plus averaged each recording interval, using the Signal Averaging program from Apple II Software, and updated the video display as each "evoking" stimulus was presented. Although the initial baseline AEP's consisted of 20 trials, the return to baseline condition (Figure 3) consisted of only 12, since the ERP's were observed to diminish in amplitude after this number of presentations of the infrequent stimulus, thus making it difficult to distinguish the waveform. The number of EP's averaged in the posttraining condition was 12 for each subject.

Using Channel 1 of the Grass 7D polygraph for EEG recording, the parameters were as follows:

amp. lo freq: 1.0 Hz

Sensitivity: 30 μ V/mm

amp. hi freq: 0.1 Hz

Pens: 30 Hz

60 Hz filter: In

Procedures

In preparation for EEG recording, two stainless steel screws, attached by soldering to electrode plugs, were chronically implanted in the skull of each rat. One electrode was for actual recording, the other served as a reference, or ground electrode. The recording electrode was implanted approximately over the interaural line, and just lateral to the midline, in an effort to position it as close to the vertex as possible. The reference electrode was implanted more frontally, and contralateral to the midline regarding the recording electrode. The rats were anesthetized with intraperitoneal (IP) injections of Xylazine (17.5 mg/kg) followed 10 minutes later by Ketamine (45 mg/kg), also IP. Each rat then recovered from the surgical procedure for at least 5 days before the actual recording was done.

In the first experimental condition (in which the infrequent tone, randomly presented, had an a priori relative probability of .10), the Apple II Plus recorded three initial baseline AEP's from each subject.

In the second condition (an "habituation" schedule in which the "evoking" stimulus had both relative and sequential a priori probabilities of .50), the computer recorded one average of 100 presentations of the "evoking" stimulus from each subject.

In the third experimental condition, the computer obtained three more baseline recordings from each subject immediately after the "habituation" schedule was presented. As in the first condition, the

infrequent tone had an a priori relative probability of .10, and was randomly presented.

Then, with each subject in turn placed in the shuttle box, the Grass S-88 stimulator paired the infrequent stimulus with an electrical pulse of 80 volts to whichever end of the box the rat was on at the time. At least 30 seconds separated each pairing of the infrequent tone with the foot shock. This interval insured that overall increased physiological arousal would not interfere with learning of the avoidance task. After several such pairings, each rat learned to avoid the foot shock by jumping to the other end of the box immediately upon presentation of the infrequent stimulus. The infrequent stimulus thus became "task relevant," allowing for observation and quantification of selective attention.

All subjects met the criterion for being fully trained in the avoidance task, which was 5 consecutive avoidances of the shock. Although each rat learned the avoidance task at a different rate, all were presented with 200 pairings of the infrequent stimulus with the foot shock. The computer then obtained three posttraining recordings from each rat within 2 hours of the training session. Again, as in the baseline conditions, the infrequent stimulus had an a priori relative probability of .10, and was randomly presented.

CHAPTER III

RESULTS

The data presented here represent those AEP's in which the waveforms were more easily observable. The program which averaged the signals of each session was not capable of then averaging all signals across sessions. In each of the figures presented, the vertical line at 180 msec marks the time at which the stimulus was presented to the subject. The positive peaks are labeled, the third one representing P300. On each graph, the distance between each dot on the horizontal lines represents 30 msec, so that the distance between each dotted vertical line represents 120 msec. The point which represents 300 msec after the stimulus presentation is marked, so that latency shifts can be more readily observed. Amplitude changes may be observed relative to other peaks. No statistical analysis of the data was necessary, given the small number of subjects, other than signal averaging.

Figures 1a, 1b, and 1c below represent the AEP under the initial baseline conditions. The independent variables were randomness of presentation, low a priori relative probability (.10) of occurrence of the infrequent stimulus, and change in the physical parameters of the infrequent stimulus. The P300 is present in each of these subjects under these conditions. The latencies vary, however, between subjects.

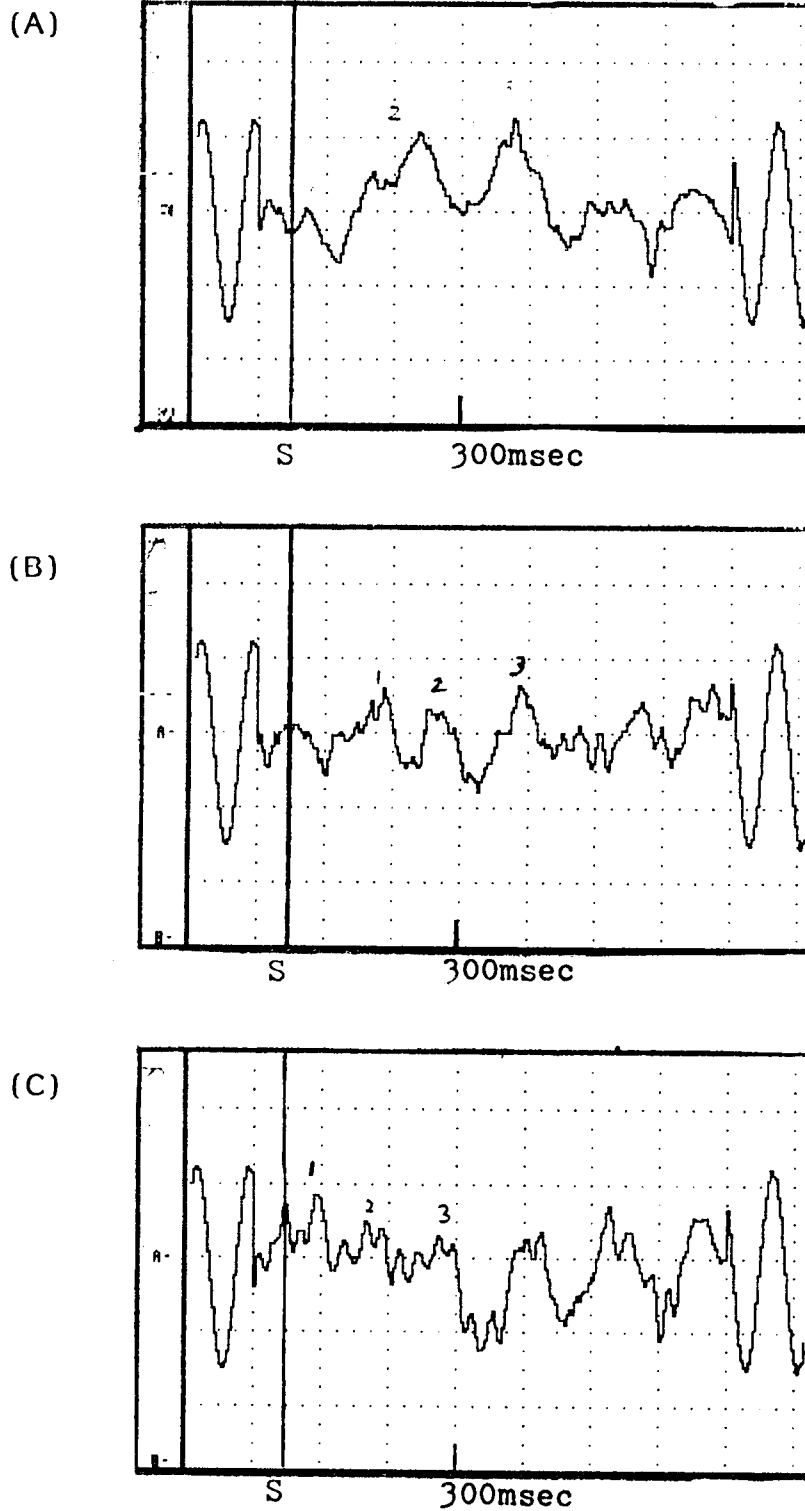


Figure 1. AEP under the initial baseline conditions. Probability of the occurrence of the evoking stimulus is 10%, with and average of 20.

Figures 2a, 2b, and 2c below represent the AEP when both the relative and sequential a priori probabilities for each stimulus were .50. The P300 is absent under these conditions, with 100 presentations of the "evoking" stimulus.

Figures 3a, 3b, and 3c below represent the results of a return, immediately following the "habituation" schedule, to the conditions under which the first set of baseline recordings (1a, 1b, 1c) were obtained. The P300 returned immediately under these conditions, although it is not quite so prominent as in the first set of baseline recordings.

Figures 4a, 4b, and 4c below represent AEP recordings obtained within 2 hours after each rat successfully performed the avoidance task at least 5 times consecutively. Rats #1 and #2 (Figures 4a and 4b) show markedly decreased latencies under these conditions, compared to the baseline recordings. There were also two distinct peaks in the P300 under the posttraining condition, the P3a and P3b (Squires, Squires, & Hillyard, 1975). The significance of these will be addressed in the discussion section. Although P300 for rat #3 demonstrates no shift in latency between baseline and posttraining recordings, there is a marked increase in amplitude in the latter condition. Rat #2 also shows an increase in P300 amplitude under posttraining conditions, while the same conditions for rat #1 actually show a decrease in amplitude compared to the initial baseline recording.

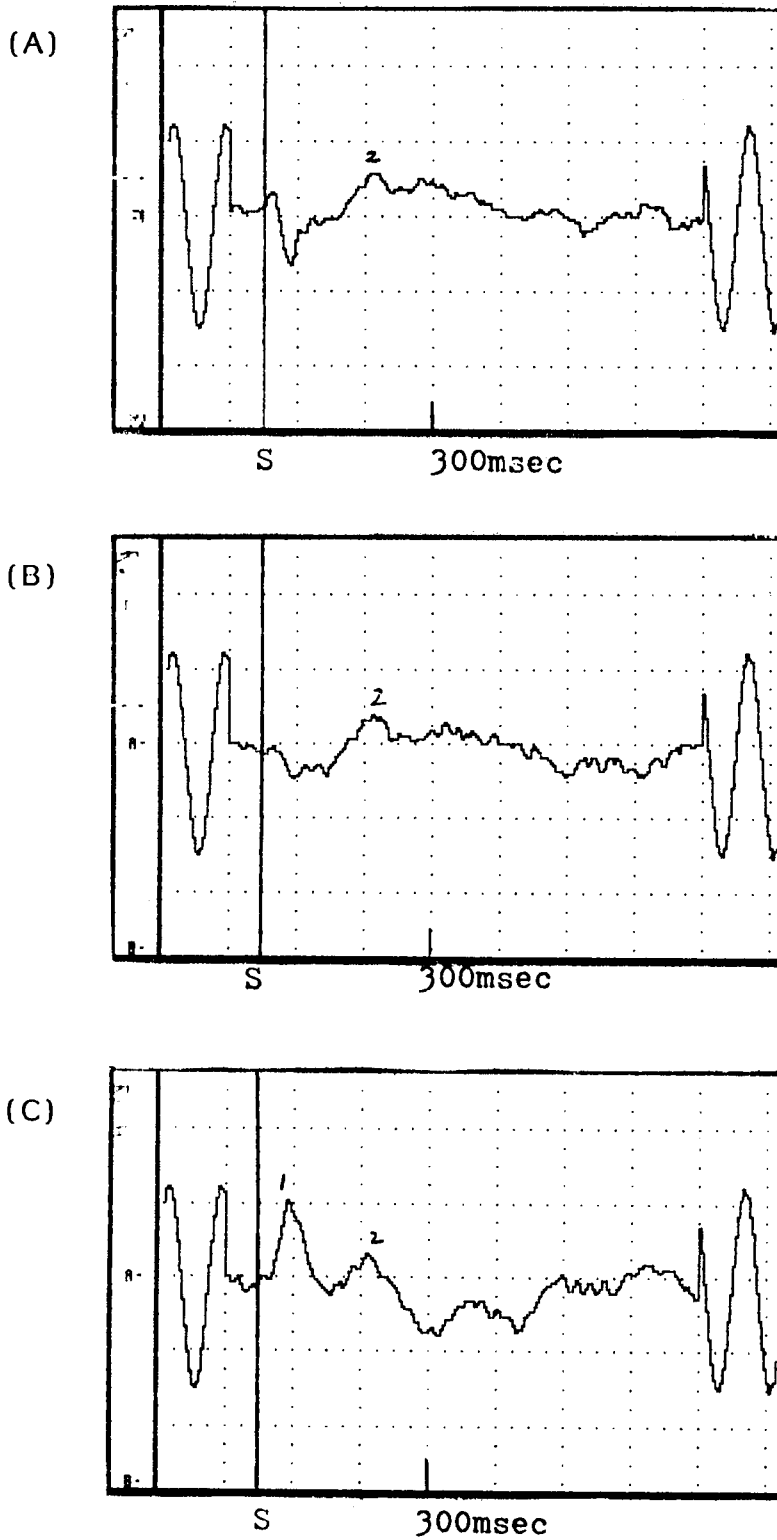
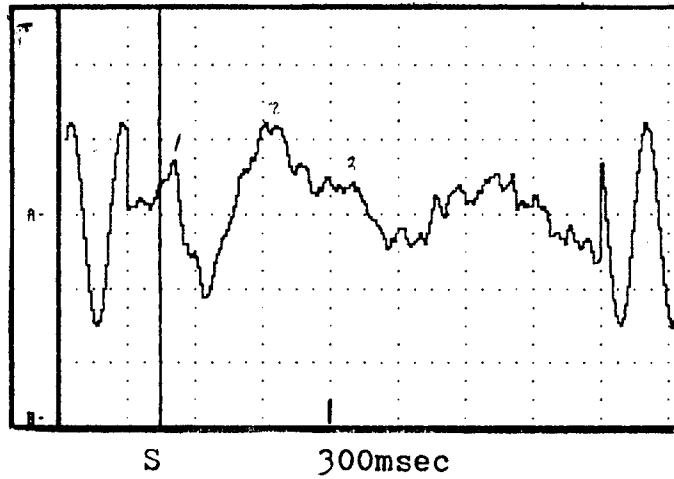
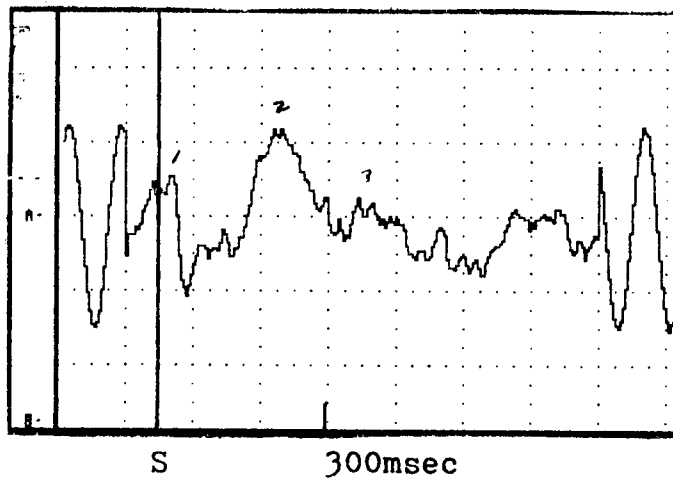


Figure 2. AEP under habituation condition. Probability of the occurrence of the evoking stimulus is 50%, with an average of 100.

(A)



(B)



(C)

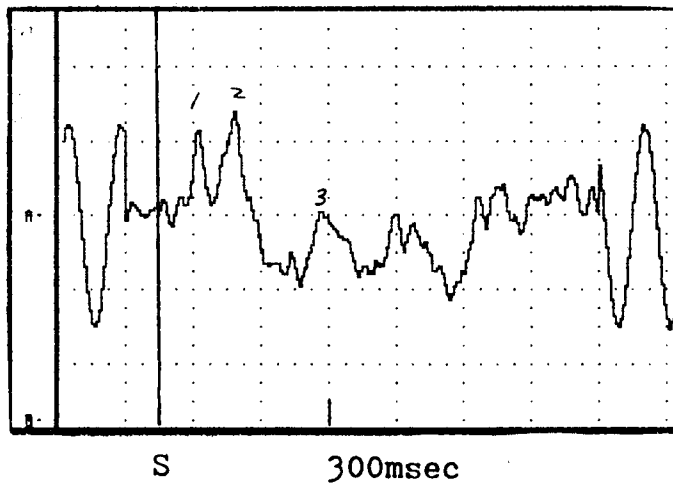
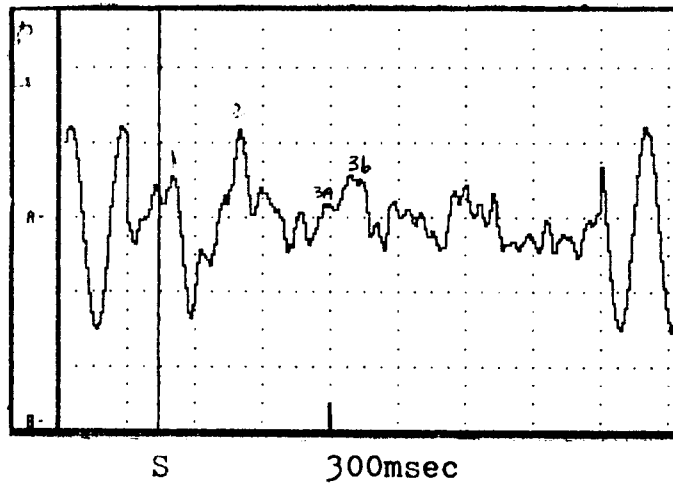
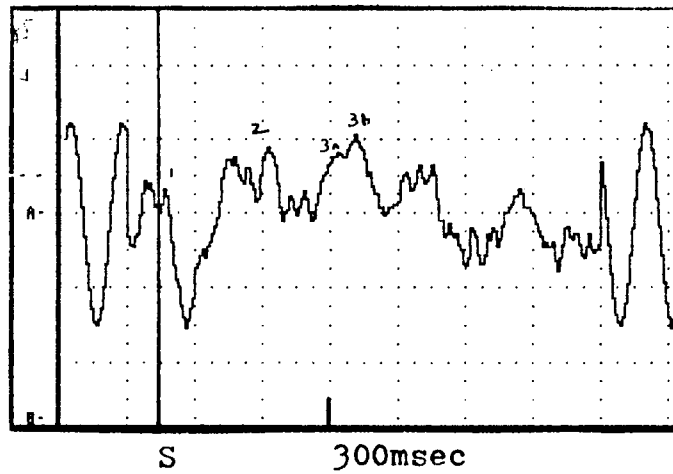


Figure 3. AEP after return to initial baseline conditions. Probability of the occurrence of the evoking stimulus is 10%, with an average of 12.

(A)



(B)



(C)

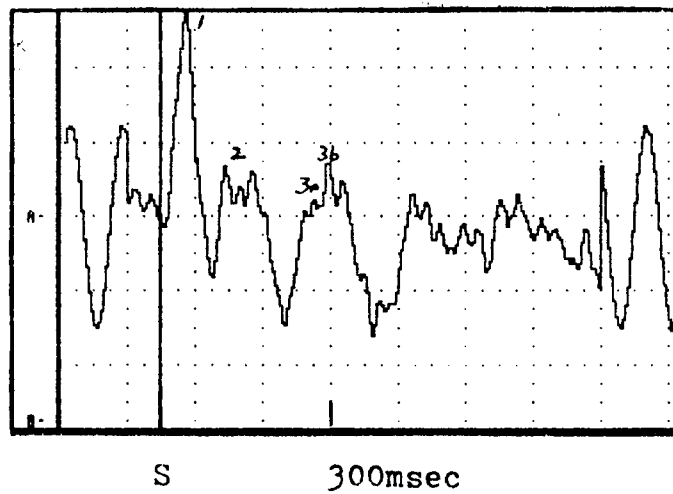


Figure 4. AEP under "task relevant" conditions. Probability of the occurrence of the evoking stimulus is 10%, with an average of 12.

CHAPTER IV

DISCUSSION

These results, although far from conclusive due to the small number of subjects, strongly suggest that the P300 is present in the rat AEP under conditions similar to those which have been used in human studies. They also suggest that the rat P300 may be manipulated by independent variables such as randomness of presentation, a priori probability, and significance of the initiating stimulus.

The most promising evidence for such manipulation present in these data is the easily observable differentiation of the P300 waveform into the P3a and P3b components after having trained the rats to perform the "task" of avoiding a shock upon hearing the "relevant" infrequent stimulus, thereby attaching some significance to it. Squires, Squires, & Hillyard (1975), compared the P300 waveforms in human subjects under conditions of active attention and nonattention. They observed a P300 waveform of only one major component under nonattention conditions, elicited by infrequent, unpredictable stimuli. Under conditions in which the subject actively attended to the infrequent, unpredictable stimuli, however, they observed similar differentiation of the P300 into two distinctive peaks. These they labeled P3a and P3b, noting that P3b manifests itself only in relation to active attention.

Donchin (1977) discussed the tendency of many researchers to regard the ERP as merely a global representation of the cortical

electrical potential, and suggested instead that the various components of an ERP be examined, as each possibly represents electrical activity in different groups of neurons.

These data, as suggestive of the presence and manipulability of P300 in the rat under these conditions, should be quite well received by those researchers who are interested in localizing specific groups of neurons which may contribute differentially to the P300 waveform. There is very little opportunity to conduct the type of research necessary for such localization with human subjects. A notable exception was an experiment conducted by Yingling and Hosobuchi (1984), in which they obtained AEP recordings from electrodes chronically implanted in the somatosensory area (Ventrobasal complex) of the Thalamus in a chronic pain patient. They found a negative ERP with the same latency as the P300 which was present in AEP's concurrently recorded from the scalp, using the same reference, or ground, source. There is general consensus that ERP's recorded from the scalp, although consistent over the entire cortex, are at greatest amplitude over the parietal and central regions (or, as some have observed, simply at the vertex of the skull). The observation of this subcortical polarity inversion of P300 led Yingling and Hosobuchi to suggest the possibility of localizing the generation of the signal within the cortex. They have also provided a reasonable method by which to proceed, using an animal model.

Perhaps more importantly, these data hold great promise for Alzheimer's disease research. For example, current research by

Brian J. Hurlbut, in the laboratory of Dr. Joel F. Lubar, at The University of Tennessee, Knoxville, has been designed to produce cognitive deficits, similar to those of AD, in rats by destroying a group of cells (Nucleus basalis of Meynert) in the basal forebrain, which show selective degeneration in AD patients (Whitehouse et al., 1983). The preliminary results are promising. Should the experiment now in progress demonstrate these cognitive deficits, these data offer the possibility of then examining the effects of such deficits on the P300 in similar rats.

Certainly, then, the results of this experiment indicate its replication on a larger scale, and the continued development of the rat as an animal model for ERP correlates of the cognitive deficits associated with Alzheimer's disease.

REFERENCES

REFERENCES

- Coyle, J. T., Price, D. L., & DeLong, M. R. (1983). Alzheimer's disease: A disorder of cortical cholinergic innervation. Science, 219, 1184-1189.
- Donchin, E. (1977). Event-related brain potentials: A tool in the study of human information processing. In H. Begleiter (Ed.), Evoked brain potentials and behavior (pp. 13-88). New York: Plenum Press.
- Goodin, D. S., Squires, K. C., & Starr, A. (1978). Long latency event-related components of the auditory evoked potential in dementia. Brain, 101, 635-648.
- Hillyard, S. A., Krausz, H. I., & Picton, T. W. (1974). Scalp distributions of the late positive wave (P3) in six different decision tasks. Electroencephalography and Clinical Neurophysiology, 36, 211.
- John, E. R. (1963). Neural mechanisms of decision making. In W. S. Fields & W. Abbot (Eds.), Information storage and neural control (pp. 243-277). Springfield, Ill: Charles C. Thomas.
- Karis, D., Fabiani, M., & Donchin, E. (1984). "P300" and memory: Individual differences in the Von Restorff effect. Cognitive Psychology, 16 177-216.
- Kaufmann, F., Kaufmann, R., & Salapatek, P. (1982). The effect of change in a stimulus sequence on P300. Neuropsychologia, 20, 439-445.
- Kutas, M., McCarthy, G., & Donchin, E. (1977). Augmenting mental chronometry: The P300 as a measure of stimulus evaluation time. Science, 197, 792-795.
- O'Brien, J. H. (1982). P300 wave elicited by a stimulus-change paradigm in acutely prepared rats. Physiology & Behavior, 28, 711-713.
- Ohlrich, E. S., & Barnett, A. B. (1972). Auditory evoked responses during the first year of life. Electroencephalography and Clinical Neurophysiology, 32, 161-169.
- Paul, D. ., & Sutton, S. (1972). Evoked potential correlates of response criterion in auditory signal detection. Science, 177, 362-364.

- Peters, J. F. (1973). Signal averaging: some considerations. American Journal of EEG Technology, 14, 40.
- Pribram, K. H. (1971). Languages of the brain: Experimental paradoxes and principles in neuropsychology (pp. 26-47). New Jersey: Prentice-Hall.
- Ritter, W., Simson, R., & Vaughan, H. G., Jr. (1972). Association cortex potentials and reaction time in auditory discrimination. Electroencephalography and Clinical neurophysiology, 33, 547-555.
- Ritter, W., Vaughan, H. G., Jr., & Costa, L. D. (1968). Orienting and habituation to auditory stimuli: A study of short term changes in average evoked responses. Electroencephalography and Clinical Neurophysiology, 25, 550-556.
- Roth, W. T. (1973). Auditory evoked responses to unpredictable stimuli. Psychophysiology, 10, 125-137.
- Roth, W. T., & Kopell, B. S. (1973). P300--An orienting reaction in the human auditory evoked response. Perceptual and Motor Skills, 36, 219-225.
- Sheatz, G. C., & Chapman, R. M. (1969). Task relevance and auditory evoked responses. Electroencephalography and Clinical Neurophysiology, 26, 468-475.
- Squires, N. K., Squires, K. C., & Hillyard, S. A. (1975). Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalography and clinical neurophysiology, 38, 387-401.
- Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. Science, 126, 1187-1188.
- Sutton, S., Tueting, P., & Zubin, J. (1967). Information delivery and the sensory evoked potential. Science, 155, 1436-1439.
- Syndulko, K., Hansch, E. C., Cohen, S. N., Pearce, J. W., Goldberg, Z., Montan, B., Tourtellotte, W. W., & Potvin, A. R. (1982). Long-latency event-related potentials in normal aging and dementia. In J. Courjon, F. Mauguiere, & M. Revol (Eds.), Clinical applications of evoked potentials in neurology (pp. 279-285). New York: Raven Press.
- Tueting, P., Sutton, S., & Zubin, J. (1971). Quantitative evoked potential correlates of the probability of events. Psychophysiology, 7, 385-394.

- Vaughan, H. G., Jr., & Ritter, W. (1970). The sources of auditory evoked responses recorded from the human scalp. Electroencephalography and Clinical Neurophysiology, 28, 360-367.
- Whitehouse, P. J., Hedreen, J. C., White, C. L., III, & Price, D. L. (1983). Basal forebrain neurons in the dementia of Parkinson disease. Annals of Neurology, 13, 243-248.
- Wilder, M. B., Farley, G. R., & Starr, A. (1981). Endogenous late positive component of the evoked potential in cats corresponding to P300 in humans. Science, 211, 605-607.
- Yingling, C. D., & Hosobuchi, Y. (1984). A subcortical correlate of P300 in man. Electroencephalography and Clinical Neurophysiology, 59, 72-76.

VITA

Steven Michael Satterfield was born February 20, 1954, in Chicago, Illinois. He received a B.A. in psychology from The University of Tennessee, Knoxville, in 1982 and the M.A. in psychology from The University of Tennessee, Knoxville, in 1985. He is currently employed at Overlook Mental Health Center as a Crisis Intervention Specialist.