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Author
Harrington, Margaret J.

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P300: A COMPARISON OF ACTIVE AND PASSIVE PROTOCOLS

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MARGARET J. HARRINGTON

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Dedication

This dissertation is
dedicated to my husband,
Robert B. Harrington,
without whom it would not
have been possible.

Acknowledgments

Although I can not begin to name every family member, friend, teacher, and colleague who has helped and encouraged me throughout this long process, I would like to acknowledge a few without whom my goal could not have been achieved.

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P300: A Comparison of Active and Passive Protocols

Margaret J. Harrington

Abstract

This study compares the P300 event related potential (ERP) generated by two different stimuli in two different paradigms. ERPs were collected from twenty subjects using both a passive oddball paradigm and an active three stimulus novel paradigm. In both paradigms, a 500 Hz, 100 msec tone was used as the standard. Two different rare stimuli were used: a 1500 Hz, 100 msec tone; and 100 msec novel synthesized sounds (all different). In the three stimulus novel paradigm, both rare stimuli were used. The subject was instructed to count the target 1500 Hz tone and ignore all other sounds. For the passive oddball paradigm, each of the rare stimuli was used with two separate attention controls, a reading control and a thinking control, a total of four separate passive oddball conditions. Each of the five experimental conditions was run twice in order to evaluate possible effects of habituation. The entire experiment was repeated on a second day to determine replicability.

Novel stimuli elicited a significantly larger P300 response than 1500 Hz tones, regardless of paradigm. There was no significant difference between the reading and thinking conditions; both suppressed the amplitude of the ERPs in the passive conditions compared to the attended three stimulus conditions. There was no evidence of habituation of the P300 response to either the 1500 Hz tones or the novels in either the passive or the three stimulus paradigm. The P300 response in the passive oddball paradigm was equally distributed across the midline scalp. The P300 response to both targets and novels in the three stimulus paradigm was parietal maximum.

The significantly larger amplitude P300 response produced by the novel sounds makes it a much better stimulus choice for use in clinical situations in which subject cooperation cannot be assured. The different topography of the responses is discussed in relation to previous P300 studies using both passive and active oddball paradigms and the three stimulus novel paradigm.

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CHAPTER 1

INTRODUCTION

Human brain activity can be studied by non-invasive recording of electrical potentials from small electrodes attached to the scalp. Small electrical potentials time-locked to specific external or internal events are recorded and separated from the ongoing electroencephalogram (EEG) by computer averaging over a number of trials. The resulting event-related potential (ERP) is a series of positive and negative voltage peaks, or waves. Individual peaks are termed components and are classified as either exogenous (stimulus bound obligatory responses which occur within the first 100-200 msec after a stimulus), or endogenous (which occur later and are related to the state of the subject, the meaning of the stimulus, or the demands of the task).

The first exogenous ERP was reported more than fifty years ago by P.A. Davis (1939). The change in the EEG of an awake human being to the onset of a tone, and again to the offset, was described as a negative-positive wave, largest at the vertex (center) of the scalp. This response was also elicited by the onset of light or the onset of a train of electrical pulses to the finger (Davis, Davis, Loomis, Harvey, & Hobart, 1939).

It was not until twenty years later that the field of ERP research really took off. This occurred following the development of a digital computer averager at MIT in 1959. In 1961, the Computer of Average Transients (CAT) became available at a relatively low cost, making digital averaging more affordable (Callaway & Otto, 1978). The first endogenous ERP was reported in 1965 by two separate research groups in two separate countries (Desmedt, Debecker, & Manil, 1965; Sutton, Braren, Zubin, & John, 1965). Sutton and colleagues described a large positive component at 300 msec which occurred to the second of a pair of stimuli (either sound or light). The response was larger when the subject was uncertain of the modality of the second stimulus and also when the probability of the stimulus was lower. This study was followed by a report (Sutton, Tueting, Zubin, & John, 1967) that the latency of the late positive component "is determined by the point in time at which ambiguity is resolved and the shape and amplitude are influenced by the presence or absence of an external event which delivers the information." In summary, these investigators noted "the late positive process may be initiated endogenously" which led them to interpret the late positive component "as a reflection of the information content of the stimulus."

This late positive component (LPC) was soon investigated by many groups with many different paradigms. Ritter, Vaughan, and Costa (1968) reported that a LPC occurred to unpredictable pitch changes in a habituation paradigm. The subjects were not attending to an ongoing train of tone pips (they were either instructed "to not count" or "to read"). Ritter and Vaughan (1969) reported a LPC occurred to a slight stimulus change which occurred rarely and was discriminated by the subject. The latency of the LPC was dependent on the difficulty of the discrimination.

By the early 1970's, investigators were challenging each others' interpretations and methodologies. The term LPC was gradually superseded by the term P300, or the shortened version P3, derived from the notational convention of naming components by their polarity (positive) and the average latency at which they occurred (300 msec). Many investigators looked at the P300 response with signal detection paradigms. Hillyard, Squires, Bauer, and Lindsay (1971), in a carefully controlled study, reported a close relationship of P3 amplitude to the certainty of the subject's perception of a signal having occurred. However, subjects' attention to the stimuli was not necessary. Roth (1973) and Roth and Kopell (1973) reported a P300 response to an unattended paradigm where the subject was either ignoring stimuli and/or was reading, or was ignoring stimuli while continuously pressing a switch to confirm wakefulness. The probability of a rare stimulus different from the common background stimulus was manipulated. There was an increased positivity to the rare stimulus at about 300 msec. The amplitude of all ERPs declined over time. P300 was considered a component of the orienting response by these investigators.

Over the years, P300 has continued to be one of the most studied ERP components. Investigators have still not agreed on a unitary underlying theory. Accordingly, it has been proposed that P300 represents a) the access of stimulus information to conscious or controlled processing (Woods, Courchesne, Hillyard, & Galambos, 1980); b) the revision, or updating, of memory brought about by an unexpected event (Donchin, 1981; Donchin & Coles, 1988); and c) context closure (Verleger, 1988). It is commonly considered to be an endogenous component that is an indicator of cognitive brain activity.

Although many different paradigms can be used to elicit the P300 response, by far the most common used is the oddball paradigm. In the oddball paradigm, the subject is instructed to attend to a rare target stimuli which is delivered randomly among an ongoing train of common stimuli. The recorded responses from the target stimuli, when averaged together, elicit a characteristic broad positive inflection in the ongoing brain activity at about 300 msec post-stimulus, which is largest in amplitude over parietal cortex, slightly smaller over central cortex, and smallest frontally. This broad positive component is not present in the average response to the common stimuli.

Although the latency, amplitude, and scalp topography of P300 varies depending on the paradigm and stimulus characteristics, for many years P300 was treated as a unitary phenomenon originating from common brain generators. The source of the P300 is as elusive as agreement on its functional significance.

Many methods are utilized to determine the sources of ERP potentials. These methods include intercranial recordings during surgery, lesion studies of patients with discrete brain lesions, dipole localization from magnetoencephalograms (MEG) and EEG recordings, and animal model studies. All of these methods have serious limitations. Various investigations have shown evidence for involvement of thalamus (Velasco, Velasco, Velasco, Almanza, & Olivera, 1986; Yingling & Hosobuschi, 1984), hippocampus (Halgren, Squires, Wilson, Rohrbaugh, Babb, & Cradall, 1980; Okada, Kaufman, & Williamson, 1983; Smith, Halgren, Sokolik, Baudena, Musoline, Liegeois-Chauvel et al., 1990), association cortex (Yamaguchi & Knight, 1991c), and prefrontal cortex (Wood & McCarthy, 1985).

Throughout the years, various investigators have associated particular kinds of stimuli, or paradigms, with P300 components that vary in particular ways. They identified them as variants of the P300. N. Squires, K. Squires, and S. Hillyard (1975) identified an earlier latency component with a more frontal topography which occurred to the rare auditory stimuli in an unattended, or passive, oddball paradigm. In order to distinguish it from the more parietal and later P300 component which occurred to the rare stimulus in an attended oddball paradigm, they labeled the early component to the passive oddball paradigm, P3a, and the later component to the active oddball paradigm, P3b. Courchesne, Hillyard, and Galambos (1975) identified an early latency frontal component which occurred to rare non-target visual stimuli in a three stimulus attended oddball paradigm and which was different from the component which occurred to rare target stimuli in the same paradigm. The P300 to the rare non-target stimuli, or "novel" stimuli, became known as P3 novel. P3a and P3 novel were both originally considered frontal orienting components, but since they were somewhat different in latency and topography and came from different paradigms in different modalities, they were considered to be different components. The P3b referred to in the N. Squires et al. study was synonymous with P300 and, in fact, many investigators have adopted the P3b terminology when referring to the P300. Evidence is mounting that there are multiple generators of the various P300 components. Although investigators have not agreed on an underlying theory, the P3b/P300 component is universally referred to as a cognitive component. P3a and P3 novel, on the other hand, are usually referred to as orienting components.

Because ERPs offer one of the few objective measures of functional brain activity, over the years P300 has become increasingly popular as a clinical tool. Oddball paradigms, both active and passive, have been used to assess cognitive function. For example, they have been used to assess individual differences in normals and in mentally impaired individuals, to assess cognitive decline, to indicate prognosis for patients with traumatic brain injury (TBI) or in coma, and to assess the efficacy of drug regimens and other treatments in various mental and physical disorders. In recent years, the three stimulus novel paradigm has also become increasingly utilized in clinical settings. It has been used to assess automatic operations outside the focus of attention and as a sign of distractibility in various patient populations, such as children with autism, attention deficit disorder, reading disabilities and other developmental disorders, patients with schizophrenia, Parkinson's disease, Alzheimer's disease, HIV seropositivity and AIDS, closed head injuries, and other brain lesions discussed below.

I first became interested in the two different P300 paradigms while working as a research assistant in two studies. One study was with Schizophrenic patients, the other was with coma patients. Because of these patients' inability to cooperate with instructions, the difficulty in getting good ERPs from them was a major hurdle in the investigations. We enjoyed early success in getting a P300 from a coma patient who subsequently recovered (Yingling, Hosobuchi, & Harrington, 1990). We suffered the frustration of being unable to get good ERPs from others largely because of the low amplitude of P300 in comparison to eye-movement potentials and movement potentials, in general. These experiences lead me to investigate ways of increasing P300 amplitude in active and passive paradigms and the distinction between P3a and P3b.

After an extensive review of the literature, it seems clear to me that different paradigms are being used for different theoretical reasons. Moreover, there is considerable overlap in the way components are classified and/or interpreted. For example, some studies refer to cognitive activity while using a passive paradigm and do not make a distinction between P300 and P3a. Other studies refer to the P300 generated by novel rare non-targets as P3 novel, while still others refer to it as P3a.

Considerable differences are also evident regarding how the different components are measured and defined. Some investigators measure both P3a and P3b at electrode locations over parietal scalp, some identify P3a as the component which occurs at the frontal scalp, regardless of the paradigm being used.

Since P3a, P3 novel, and P300 are increasingly utilized in clinical settings, it is important to clarify whether P3a and P3 novel are the same or different; and whether and how P3a and P3 novel may differ from P300. Some experiments have examined the difference between P3a and P3b in the passive oddball paradigm, others have investigated the difference between P3 novel and P3b in the three stimulus oddball paradigm. The purpose of this investigation is to make a direct comparison between the P3a in a passive oddball paradigm and the P3 novel in an active three stimulus oddball paradigm. This work will establish an empirical basis for the interpretation of P300 in its diverse clinical applications.

Chapter 2 describes the methods and experimental design of my study which compares the P300s from two passive oddball paradigms (one with a traditional 1500 Hz tone pip, one with all different novel stimuli) to the P300s of the three stimulus paradigm with the same 1500 Hz tone pip as a rare target and the novel stimulus as an unattended rare novel. Chapter 3 presents the results of this study. Chapter 4 presents a discussion of these results and an overview of areas for future research.

The rest of this chapter will review the literature of both P3a and P3 novel. It will begin with a brief history of each of the paradigms and immediate follow-up studies in which the original components were first identified, P3a in the passive oddball paradigm and P3 novel in the three stimulus oddball paradigm. P3a has also been identified in active oddball paradigms which produce bifurcated peaks in which the first subcomponent is identified as P3a and the second subcomponent is identified as P3b. In the section, P3a in Active Oddball Paradigms, this literature will be reviewed. The next sections, Passive P300 and Passive Oddball Paradigms, will include experimental studies of passive paradigms comparing passive and active oddball studies along with passive paradigms used to elicit P3b for use with clinical populations. How these differ from the passive paradigms which elicit P3a will be reviewed. A review of three stimulus novel paradigms and the components produced by them will follow, including both experimental and clinical literature. Brief sections covering how habituation of each component has been investigated and how components have been defined and identified will be next. In the final section, the discussion will focus on particular problems found in some of the studies reviewed and how some of these problems are addressed in this study.

How it Began

Twenty years ago, N. Squires, K. Squires and S. Hillyard (1975) differentiated two distinct late positive components of the auditory evoked response potential (ERP). For the sake of brevity (and not intending to "institutionalize" the terms), they labeled the two components "P3a" and "P3b". The two components were different from each other. P3a occurred to unattended deviant auditory stimuli, had a fronto-central scalp distribution, and had an earlier average latency (220-280 msec). P3b, on the other hand, occurred to attended auditory target stimuli, had a central-parietal scalp distribution, and a later latency (310-380 msec). The study used the basic oddball paradigm and presented 1000 Hz tones at 90 dB SPL (loud) and 70 dB SPL (soft). The ratio of loud to soft was varied from run to run with three different probabilities (0.90, 0.50, and 0.10). Subjects were told before each run to either listen and count loud tones, listen and count soft tones, or read and ignore tones. A total of 9 runs, one for each combination of attention task and probability, were recorded. The whole series was repeated in reverse order after a few minutes break. In addition to the early P3a to the unattended rare tones and the P3b to the attended target tones, some of the subjects had an additional peak at the same latency as the P3a (220-280 msec) before the P3b peak (310-380 msec).

N. Squires et al. (1975) considered P3a to be similar to the P3 component described by Ritter, Vaughan, and Costa (1968) which was elicited by shifts in non-attended trains of habituating tones and represented a physiological correlate of a shift of attention or orienting response (Ritter et al., 1968; Roth, 1973; Roth & Kopell, 1973). According to N. Squires et al., the P3a component reflected a basic sensory mechanism which registered "mismatch" to an ongoing stimulus train. P3b, on the other hand, was akin to the P300 more frequently cited which is probability dependent and occurs to rare attended target stimuli.

Shortly after N. Squires et al. (1975) published their results, Courchesne, Hillyard, and Galambos (1975) published results of a study in the visual modality that differentiated the components which occurred to rare task-relevant visual stimuli from the components which occurred to rare task-irrelevant visual stimuli. This study compared the P300 from an oddball paradigm with the number "2" as the 80% background and the number "4" as the 20% target to the P300s from a three stimulus paradigm with the "4s" as background, the "2s" as target, and rare task-irrelevant stimuli which were either "simples", easily recognizable (e.g., simple geometric shapes), or "novels", completely novel (e.g., unrecognizable colorful abstract drawings). No "simple" or "novel" was ever presented more than once to any subject. Like the N. Squires et al. study, Courchesne et al. reported two distinct varieties of P300 differentiated by latency, scalp distribution, and psychological correlates. Task-relevant counted stimuli and irrelevant simples elicited P3 waves that were largest over parietal scalp, latency 380-430 msec. Irrelevant novels elicited P3 waves largest over frontal scalp, latency 360-380 msec. This frontal component was likened to Pavlov's "what is it" reaction to novel, or unrecognizable, stimulation. In an analysis of single trials, it was found that the first P3 to the novel stimulus was very large (in the 30 μV range) but it habituated rapidly and was 50% smaller to the second stimulus and 61% smaller than the first to the third stimulus. There was no further habituation after the third or fourth stimulus.

For a number of reasons, Courchesne et al. (1975) did not believe the frontal P300 in their paradigm (originally termed "novels P3", but from here on called "P3 novel") was connected to the P3a component in the N. Squires et al. (1975) study. These reasons were:

1. P3 novel was elicited when subjects actively attended to a visual stimulus as opposed to an ignored auditory stimulus.
2. P3 novel decremented rapidly with repeated exposure and then elicited posterior P300 waves. This phenomenon was not reported for the P3a.
3. P3 novel was elicited only by complex unrecognizable stimuli. P3a was elicited by simple, easily recognized stimuli.
4. P3 novel was later and larger than P3a.

In the next few years, each of these studies was replicated and extended to other stimuli. Several investigators compared the P300 component in the active and passive oddball paradigm (Ford, Roth, & Kopell, 1976a; Snyder & Hillyard, 1976; Squires, Donchin, Herning, & McCarthy, 1977). Snyder and Hillyard (1976) replicated the N. Squires et al. (1975) experiment and showed that the same rare stimuli presented as very infrequent single stimuli (i.e. not imbedded in a train of other stimuli) did not produce large or consistent P3a components. They also showed that the amplitude of both N1 and P2 were greatly reduced by increasing the repetition rate (from one per second to three per second) but the amplitude of N2 and P3a were not affected. Courchesne and colleagues replicated and extended the three stimulus novel paradigm (Courchesne, 1977; Courchesne, Courchesne, & Hillyard, 1978). No effort was made to directly compare the two components despite the fact that many of the differences cited by Courchesne were easily tested (e.g. attend visual versus ignore auditory, no habituation data reported for P3a, and novel versus simple stimuli). In a comprehensive review of the psychophysiology of P300, Pritchard (1981) discussed the question of whether P3a and the P3 novel were the same or different components. According to Pritchard, lumping these frontal P300s together and considering them orienting correlates was tempting. However, since the P3 novel occurred to stimuli presented in an attended channel, no sudden shift of attention (orienting) seemed to occur. Pritchard also left open the question of whether P3 novel and P3b reflect different processes.

ERP literature throughout the 1980s paid little attention to the frontal P300s. The literature referred to a unitary parietal P300 as a measure of cognitive processing regardless of the paradigm which was utilized to produce it. P3a was often noted as being present in the individual averages of subjects responding to rare targets in active oddball paradigms. It was often noted as being the earlier component of a bipeaked P300 or as a bump on the ascending limb of P300. Passive paradigms were compared with active oddball paradigms in an effort to find an effective and easily administered paradigm for use with clinical populations with limited attentional or motivational capacities. The focus of most of these comparisons was P3b. The intent was to show that the passive paradigm produced equivalent P300 components to the active oddball paradigm.

P3a in Active Oddball Paradigms

Following the initial reports of P3a, the presence of a bipeaked P300 component was noted in a number of studies (Polich, 1988; Polich, Howard, & Starr, 1983; Polich, Howard, & Starr, 1985a; Polich, Howard, & Starr, 1985b). Polich et al. (1983, 1985a) identified both P3a and P3b at Cz in 88% of 93 subjects and in 82% of 104 subjects ages 5-86 years. Polich et al. (1985b) identified two separate components in 22 of 24 subjects ages 18-35. Each of these studies were active oddball studies with 1000 Hz standards and rare stimuli of either 2000 Hz, 1500 Hz, or 4000 Hz. ISI was relatively rapid (1200 msec). P3a was defined as the first positive peak after N2 between 220-280 msec. P3b was defined as the subsequent positive peak between 250-350 msec. If only one peak was present, it was labeled P3b.

In 1988, Polich reinvestigated the occurrence of bifurcated peaks. Thirty-five subjects who exhibited bifurcated peaks in a previous active oddball study were chosen out of the 100 who had participated. These subjects were divided into three groups based on the replicability of the occurrence of the two subcomponents, those whose waveforms replicated across blocks at all three electrode sites (Fz, Cz, Pz), those whose waveforms replicated across blocks at two electrodes, and those whose waveform replicated at only one electrode. The amplitude of P3a increased from Fz < Cz < Pz in the first block; in the second block the frontal amplitude decreased, but Cz and Pz remained the same. P3b amplitude increased from front to back over both blocks. Latency of both P3a and P3b increased from front to back. There were no consistent group differences in the results. Polich suggests the distribution of multipeaked P3a and P3b in some subjects and not others "is naturally asymmetric in the population". A number of differences between the earlier 1983 and 1985 studies do exist and may explain why the earlier studies had an 82% to 92 % occurrence of bifurcated peaks compared to 35% in the later study. The earlier studies were done with filters set at 1 - 30 and 3 msec/pt as compared to 0.5 - 30 and 1.5 msec/pt. The ISI of the earlier studies was 1.1 seconds compared to a 2 second ISI in the later study. The task in the early studies was to keep a silent count of the target; in the later 1988 study, it was to move the index finger to the target. The peaks of the components were picked in two separate latency windows (220-280 msec and 250-350 msec) in the earlier studies, and in one large latency window (200-400 msec) in the later study. Finally, the number of trials per block was double, forty targets per 200 in the earlier studies compared to twenty targets per 100 in the later. Any or all of these factors could contribute to the substantial difference in occurrence of bipeaked components.

Recent studies have identified separate P3a and P3b components in active oddball studies (Barrett, Neshige, & Shibasake, 1987; Bruyant, García-Larrea, & Mauguière, 1993; Sandroni, Walker, & Starr, 1992). Barrett et al. measured P3a as a separate peak, or a point of inflection on the ascending limb of the P3b component, in 24 of 28 subjects who performed an active oddball task. Auditory and somatosensory ERPs were recorded comparing both button press to target response and count target response in 27 subjects ages 20-78. P3a response (average latency 270 msec) increased with age for the auditory stimulus button press response only. Sandroni et al. compared ERPs from ten multiple sclerosis patients with ten normal controls in both an auditory oddball reaction time task and a memory probe task. N1, P2, N2, and P3b were measured at Pz. P3a was measured at Fz. Compared to controls, patients had longer latency N1 and reduced P3a and P3b components. Patients who were fatigued paradoxically had shorter latency P3a and increased P3a and P3b amplitude compared to when they were rested. Bruyant et al. replicated the results of Barrett et al. and described the presence of two separate peaks within the 250-400 msec range in a somatosensory counting oddball paradigm. P300 was defined operationally as a positive peak in the 280-500 msec latency range, with amplitude of at least 5μV, which appeared selectively to rare stimuli and was reproducible in two consecutive series. If two distinct peaks occurred with these criteria, they were labeled "early" and "late" P300. A double-peaked P300 was found in ten of seventeen subjects (59%). In the other seven subjects, there was an inflection on the ascending or descending slope of the P300. The average latency of the early component was 302 msec. The average latency of the late component was 353 msec.

Passive P300

Because there are many instances in clinical situations when attention cannot be strictly controlled, a number of studies investigated passive paradigms. Several studies compared active and passive oddball paradigms directly (Czigler, Csibra, & Csontos, 1992; Polich, 1986a; 1987b; 1989a; Rappaport, Clifford, & Winterfield, 1990; Squires, Ollo, & Sanders, 1989; Walsleben, Squires, & Rothenberger, 1989). In addition, paradigms that deliver more salient, or startling, stimuli were explored in order to acquire larger amplitude ERPs in the passive modality (Ford & Pfefferbaum, 1991; Pfefferbaum, Ford, White, & Roth, 1989; Putnam & Roth, 1987; Putnam & Roth, 1990).

Passive Oddball Paradigms

Polich (1986a) compared the ERPs from a classic oddball paradigm (1000 Hz, 50 dB common versus 2000 Hz, 65 dB rare) under three separate attention conditions, a) mentally count target, b) ignore tone pips and daydream, and c) read a book. Passively ignoring stimuli decreased the amplitude of P300 in comparison to the active count condition. The ignore read condition produced the smallest amplitude P300. These results were significant at Cz and Pz, but not Fz. Scalp distribution was the same for all conditions, increasing significantly from frontal to parietal electrode locations. In a second experiment, passive (ignore) and active (finger response) attention conditions were compared with three different probabilities of target stimuli (5%, 10%, and 20%). As in the first experiment, the amplitude of the ERP waveform was substantially reduced when no active task was required. Decreasing the probability didn't improve the amplitude substantially, although the 5% target rate did produce a measurable P300 in the passive condition. Polich concluded that, although the stimulus parameters were chosen to coerce a response from non-attending subjects, the weak amplitude of the response in non-attended conditions made passive paradigms a poor substitute for paradigms that use an active discrimination task.

Polich (1987b), in an effort to find a passive paradigm that produces a large amplitude P300 response, compared a passive tone sequence paradigm to an active oddball paradigm. In the passive tone sequence paradigm, two blocks of twenty sequences of six tones were presented. In each sequence, the first stimulus was a 2000 Hz tone pip, the remaining stimuli were 1000 Hz tone pips. The subject was instructed to ignore all tones and daydream. In the active oddball paradigm, the same stimuli were delivered in two blocks of 100 with twenty random 2000 Hz targets. Subjects were instructed to lift the index finger when the target tone occurred. In the passive sequence, the ERP was recorded to the first tone and averaged over twenty sequences. In the active oddball condition, ERPs were averaged over twenty targets. The P300 component was identified as the largest positive wave after N1-P2-N2 between 240 msec and 350 msec at Fz, Cz, and Pz. Polich reported that the P300 components from both paradigms had similar scalp distribution and latency, but the amplitude of the passive sequence was significantly reduced. Habituation was not significant for either paradigm. On the basis of these results, Polich suggested that P300 could be elicited by passive sequences and that it might be possible to enhance the amplitude of P300 by making the stimuli more salient, by increasing intensity and/or frequency separation, or by lengthening the time between tone sequences.

A difficulty with this interpretation is that, although the latency and topography of the P300 component were similar as measured in both paradigms, a look at the ERP waveforms in both the grand averages and the individual subjects' averages indicates that there was a very obvious difference in the appearance of the wave shapes. In the passive sequence, N1 and P2 are the most prominent waves and are, in fact, enhanced compared to the active oddball. P300, on the other hand, is only a bump on the downward return of P2. The morphology of the waveforms was not considered in this analysis.

Polich (1989a), in a further effort to develop a reliable passive paradigm for eliciting P300, changed the passive sequence paradigm so that the 2000 Hz rare tone, instead of occurring as the first tone, occurred randomly at position six through ten within a series of ten 1000 Hz tones. In a series of different experiments, this passive sequence (with tones ignored) was compared to a) an active oddball task (with target tones counted), b) to the same tone sequence as an active discrimination task (with rare tones counted), and c) to the same tone sequence with a distraction task (with subjects doing word puzzles). Unlike the ERPs to the passive sequence in the Polich, 1987b experiment, the ERPs to this passive sequence were morphologically quite similar to the ERPs of the active oddball paradigm and were larger than those previously reported in passive paradigms. The addition of the puzzle task decreased the amplitude of the P300 component as compared to the ignore condition. Polich believes that this passive sequence procedure offers the possibility of obtaining relatively large amplitude P3s in an easily implemented paradigm that does not require any directed attentional resources.

N. Squires et al. (1989) evaluated the P3 component in both active (count the rare target) and passive (read a book) conditions to very discrepant oddball stimuli (250 Hz, 40 dB versus 3000 Hz, 60 dB) as compared to standard oddball stimuli (1000 Hz versus 1500 Hz, both at 60 dB). The ERP waveforms of the frequent stimuli in each condition contain prominent N1 and P2 components that are maximal at Cz. However, N2 and P3 are only evident to the rare stimuli in the standard/attend condition. In both of the discrepant conditions, the N1 component was followed by a large positive component peaking at about 290 msec, and neither P2 nor N2 are discernible. The investigators attributed this to overlap of N2 with the earlier exogenous components. The latency and amplitude of N2 and P3 were, therefore, measured from waveforms derived by subtracting frequent waveforms from rare waveforms. These difference waves were used for the statistical analysis of latency, amplitude, and topography. The amplitude of the P3 component in the discrepant/attend condition was significantly larger than those in the discrepant/ignore condition or the standard/attend condition, which did not differ from each other. The ERPs to the standard/ignore (subjects reading) conditions were so small that they were not included in the analysis. The latency of both N2 and P3 were significantly longer in the standard/attend condition as compared to the two discrepant conditions (112 msec after N1 in the standard condition as compared to 34 msec after N1 in both discrepant conditions). Analysis of scalp distribution of the negative and positive difference waves showed no significant differences across conditions. N2 was maximal at Cz, and smallest at Pz. P3 was maximal at Cz, and smallest at Fz. Based on the similarities of the scalp distribution across conditions, the investigators identified these components as N2b and P3b.

In the discussion of this experiment, the investigators believed this passive procedure to have several advantages for clinical application compared to procedures previously reported in the literature. The chief advantage cited was that the exogenous and endogenous components were similar in both active and passive conditions. This was not the case in the procedures employed by Polich (1987b). This conclusion is curious since the waveforms in the discrepant conditions were quite different from the waveforms in the standard/attend condition. So different, in fact, that difference waves had to be used for analysis. Other conclusions made by N. Squires et al. (1989) that appear problematic are the conclusions that the negative and positive waveforms of the standard/ignore oddball condition represent mismatch negativity and P3a, and that the negative and positive difference waveforms in the discrepant conditions (both attend and ignore) represent N2b and P3b. These conclusions appear to have been made despite the fact that the waveforms in the standard/ignore were too small to see and were not measured or analyzed in any way. That this is the only mention in the entire paper of P3a, even though the first author was also the first author on the original P3a paper, is also remarkable. It is, however, consistent with the strong bias toward a unitary concept of P300 as a measure of cognitive processing which predominated throughout the 1980's. This is also consistent with the investigators' expressed desires to show that P300 is a useful measure of cognitive activity in clinical populations.

A different approach to increasing amplitude in a passive oddball paradigm was used by Rappaport et al. (1990). They compared active and passive attention conditions with unimodal (auditory only) stimuli and with bimodal (visual background and auditory target) stimuli. P300 amplitudes in the passive attentional state were enhanced when stimuli were bimodal as compared to unimodal. Because only a Cz-Fpz electrode pair was used, it was not possible to determine the scalp topography of the response, and thus, it also was not possible to identify it as P3a or P3b.

In a more recent study, Czigler et al. (1992) put a somewhat different focus on the question by looking at the difference between frequent and infrequent stimuli in a passive (subject reading) oddball paradigm. They compared young (average age 21.3 years) and old (average age 60.8 years) across three different ISI (800 msec, 2400 msec, and 7200 msec). Instead of focusing on the late components such as P300 and N2b, this study looked at N1, P2, and the target-minus-frequent difference waveforms, mismatch negativity (MMN) measured between 100-180 msecs, and a positive difference wave P3a measured between 220-280 msecs. The positive difference wave was identified as P3a, a correlate of the orienting of attention to stimulus deviance, because it was maximum frontally and smallest parietally. It was present in the 800 msec and 2400 msec ISI conditions in young subjects. It was not present in the 7200 msec ISI condition nor in any of the conditions with old subjects. The authors conclude that younger subjects have more sensitive orienting systems and process deviant stimuli beyond the level of automatic identification of deviance.

The passive oddball paradigm has been used in a number of studies using clinical populations. Gottlieb, Wertman, and Bentin (1991) studied different groups of demented, pseudodemented, and normal age-matched control subjects using both a passive oddball paradigm and an active oddball paradigm. Scrimali, Grimaldi, and Rapisarda (1988) compared ERPs from a passive paradigm and an active oddball paradigm in a group of schizophrenics as compared to normals. Rappaport, McCandless, Pond, and Krafft (1991) compared unimodal and bimodal passive ERPs in patients with traumatic brain injury (TBI), and a number of investigators have used a passive oddball paradigm to assess cerebral state in coma and near coma patients (De Giorgio, Rabinowicz, & Gott, 1993; Yingling et al., 1990). Plourde, Joffe, Villemure and Trahan (1993) used active and passive oddball paradigms to monitor depth of anesthesia during sufentanil anesthesia in cardiac surgery.

Efforts to enhance the response to passive paradigms have also included increasing stimulus intensity. Putnam and Roth (1987, 1989) used bursts of 105 dB white noise and 110 dB, 1000 Hz tone bursts with various durations and rise-times while subjects were passively listening. In comparing eyeblink measures and ERPs to these stimuli, Putnam and Roth concluded that P300 was different from startle but acted more like a defensive reaction to intense stimuli than like an orienting reaction. These intense stimuli were also used as the rare stimuli by Ford and Pfefferbaum (1991) to compare ERPs elicited by a group of young subjects (average age 20.2 years) and a group of old subjects (average age 72.6 years) and by Pfefferbaum et al. (1989) to compare a group of schizophrenics on and off medication to a group of controls. These stimuli produce very different waveforms and entail a different set of methodological problems. For this reason, these studies will not be dealt with further in this dissertation.

Three Stimulus Novel Paradigms

Courchesne (1983) reported having completed a normative study of changes in auditory and visual ERPs associated with development from childhood to adult. These studies used the three stimulus paradigm in both an auditory and visual form. The visual was similar to the original paradigm (Courchesne et al., 1975) described above. The auditory version used the spoken words *me* and *you* as the background and target stimuli. For the novel stimuli, bizarre, never before heard sounds were used. The novels were not described further in this report. P300 to targets in both visual and auditory modalities decreased in latency with age and reached adult values by adolescence. P300 novel, on the other hand, was different in the two modalities at all ages. The auditory P300 novel was central maximum whereas the visual was frontal maximum. The auditory component labeled A/Pcz/300 by Courchesne (auditory modality/positive at Cz/around 300 msec) was very stable in subjects from ages 4 on. It appeared to be unique to the auditory modality and was largest to previously unexperienced acoustic events. It had a rather narrow wave shape, lasting only 100 to 140 msec. These characteristics, Courchesne suggested, were reflective of an automatic detection of biologically significant acoustical deviations.

Courchesne, Kilman, Galambos, and Lincoln (1984) followed this normative study with a study of seven non-retarded autistic subjects, ages 13 to 21, and seven age-matched normal control subjects using the auditory paradigm. The novel was described as a "complex patch-work of natural sounds consisting of human vocalizations, mechanical noises and digitally synthesized nonsense sounds." Each sound lasted 200 msecs. Two experimental conditions were used, a) a passive oddball condition with subjects told to listen and the stimuli being the word *me* (90%) and the word *you* (10%) randomly mixed for three to six blocks of 50, and b) a three stimulus novel condition with subjects told to press a button to the word *you*. In these runs, the word *me* was presented 80% of the time and the novel sounds were interspersed 10% of the time. During the remaining six to nine blocks, in half of the blocks, each novel sound was different from every other novel; in the other half, all novels were the same. Subjects were not told that there would be any sounds other than the words *you* and *me*. ERPs for the normal control subjects to the passive oddball paradigm did not produce a fronto-central P300 similar to the P3a in the N. Squires et al. (1975) passive paradigm but produced a parietal maximum P300 with the typical P3b scalp distribution Fz < Cz < Pz. The latency of the passive oddball P300 was 359 msec, the amplitude was 13.7 μV. The latency of the P300 to the target in the three stimulus paradigm was 325 msec, the amplitude was 37.7 μV. The topography was the typical parietal maximum with Fz < Cz < Pz. The latency of the P300 to the novel sounds was 287 msec, the amplitude was 23.3 μV with a Cz maximum. Autistic subjects had similar responses to the passive oddball paradigm, but smaller amplitude responses to the target and novel stimuli in the three stimulus paradigm. Results indicate that both groups processed novel stimuli differently than non-novel stimuli. The smaller amplitude response of the autistic group may mean that they process this information to a lesser extent than normals.

Knight (1984) used a three stimulus paradigm similar to the Courchesne paradigms to test a group of fourteen patients with unilateral prefrontal lesions and fourteen age-matched normal control subjects. This paradigm consisted of an active oddball paradigm (stimuli were tones of 200 msec duration and intensity of 45 dB sound level (SL): 500 Hz, 91.4% common; and 375 Hz, 8.6% target) and a three stimulus novel oddball paradigm (stimuli were the same common and target stimulus with the novel stimulus being a simulated dog bark, duration 160 msec: proportions were 82.6% common, 8.6% target, 8.6% novel). P300 to the target in the control subjects was Pz maximum, latency 389 msec. The novel P300 was Fz-Cz maximum, latency 340 msec. There was a late negativity maximal at Fz at 588 msec following the P300 which was not significantly different than the late negativity following the novel P300 at 568 msec. There was no difference between the controls and the prefrontal lesioned group's P300 to target stimuli. However, the prefrontal lesioned group's novel P300 response was parietal maximum and significantly smaller at the frontal electrode than the control groups. There were no differences between groups in the late negativity for either stimulus. An analysis of single trial data shows that the amplitude of the novel P300 diminished from trial one to trial five, then remained stable in the control group. The amplitude did not diminish in the prefrontal group. Further analysis of the responses from the scalp over lesioned side versus scalp over non-lesioned side indicate that the difference in the novel P300 in the prefrontal group was not due to a simple loss of underlying cortex. Instead, a more complex role of prefrontal disinhibition of sensory and limbic circuits was proposed. The resulting habituation of these elements of the orienting system would then diminish the neural response to unexpected novel stimuli.

Knight, Scabini, Woods, and Clayworth (1989) compared a group of patients with lesions of temporal-parietal junction including the auditory association cortex, a group of patients with lesions of the lateral parietal cortex, and a control group using two different paradigms, a monaural three stimulus paradigm and the same three stimuli in a selective attention paradigm with stimuli being attended differently at each ear. Common and target stimuli were tones of 50 msec duration and intensity of 60 dB SL: 1000 Hz, 80% common; 1500 Hz, 10% target. Novel stimuli were 200 msec duration and attenuated 6 dB from the other stimuli, 10% consisting of ten computer generated complex tones and ten digitized environmental noises. In this investigation, the ERP to a correct target stimulus was operationalized as P3b, the ERP to the novel stimulus was operationalized as P3a. In experiment 1, controls generated a parietal P3b to targets (388 msec), a central P3a to novel stimuli (367 msec), and similar responses in experiment 2. Parietal lesions had no significant effect on P3 amplitude or latency. However, lesions in the temporal group abolished the target P3b and the P3a at parietal and central scalp, but not the frontal scalp. Knight et al. suggested these findings are consistent with an auditory P3 generated by a neural system involved in orientation to, and encoding of, environmental events.

Holcomb, Ackerman, and Dykman (1986) used the three stimulus paradigm to try to differentiate between four groups of children ages 8 to 12: reading disabled (RD), n = 24; attentional deficit disorder with hyperactivity (ADHY), n = 23; attentional deficit disorder without hyperactivity (ADD), n = 21; and normal control children, n = 23. Children were told to press a button as fast as possible to the target tone. Stimuli were: 2000 Hz, 70 dB, 250 msec, common 16.8%; 1000 Hz, 70 dB, 250 msec, target 66.4%; rumbling sound non-target 16.8%. ERPs to unexpected stimuli were morphologically distinct from the ERPs to the common and target stimuli. The P3a component had a mean latency of 350 msec and was largest at Pz on unexpected trials, smallest at Pz on target trials. It did not differentiate the four groups. P3b had a mean latency of 480 msec. It was largest in mean amplitude on target trials at Pz, smaller in mean amplitude on non-target trials at Cz. The control group was significantly larger than other groups.

Grillon, Courchesne, Ameli, Elmasian, and Braff (1990a) used the three stimulus paradigm to assess distraction. They measured not only the ERP responses to the target and novel stimuli but also the ERPs to the common stimuli immediately before and after the target and novels. The design of this study included three conditions: a) "Basic", an active oddball paradigm (900 Hz, 50 msec, 85% common; 1600 Hz, 50 msec, 15% target); b) "Constant", a three stimulus paradigm (900 Hz, 70% common; 1600 Hz, 15% target; and 700 Hz, 15% non-target constant deviant); and c) "Novel", a three stimulus paradigm (900 Hz, 70% common; 1600 Hz, 15% target; and 700 Hz, 15% non-target novel deviant). Novel deviants consisted of a collection of buzzes, filtered noises, and other unusual computer generated sounds delivered for 100 msec each. P3 topography to targets was parietal maximum (Fz < Cz < Pz). Amplitude was highest to the common condition in the standard oddball paradigm and was reduced more to the novel deviants than the standard deviants. P3 to deviants were central maximum (Fz < Cz > Pz). These were designated P351 for standard deviant and P299 for novel deviant. Amplitude to the novel was largest.

Assessment of distraction measured the amplitude difference between 200-400 msec to commons after targets, commons after novels, commons after standards, and commons after commons. There was a significant positive shift to commons after targets and to commons after novels, but not to commons after standards or commons after commons. It was suggested these results indicate a global effect due to the more difficult three stimulus paradigm, but also a transient effect due to distraction from novel and target stimuli.

Based on these results, Grillon, Courchesne, Ameli, Geyer, and Braff (1990b) decided that the P3a component could be used as a sign of distraction and would be a good measure of distractibility in schizophrenics. As a historical note, this was particularly interesting to me since it marked the first time I had seen the response to the deviant non-target referred to as P3a by Courchesne (Grillon et al., 1990). In fact, in their previous paper cited in their introduction to this study, the deviant ERPs were termed P351 for the constant deviant, P299 for the novel deviant. The design of the experiment was similar to the previous experiment except there were two conditions instead of three; "No Distractor", an active oddball paradigm; and "Distractor", a three stimulus paradigm. The stimuli were the same as before except a) only the novel distractors were used in the three stimulus paradigm, and b) the experiment was structured so that targets followed at least five commons, or targets followed a novel. P3b to target was reduced from the no distractor condition to the distractor condition in both schizophrenics and controls, but the effect was double in the schizophrenic group. Distractors elicited a larger P3a than the target P3b in both groups, but the difference between P3a and P3b was almost two times larger for the schizophrenic group. The control group had a high correlation between P3b and P3a, but the schizophrenic group did not. These investigators proposed that there is an imbalance in the way in which task-relevant and task-irrelevant stimuli access the brain of schizophrenics.

Nielson-Bohlman, Knight, Woods, and Woodward (1991) used the three stimulus paradigm to look at ERP responses during waking and stage II - IV sleep. P3a to novel stimuli were present in waking and stage II sleep, but not stage III or IV sleep. The latency of the P3a response (difference wave, novel versus frequent tones) increased from 322 msec, Cz maximum, to 420 msec, Pz maximum.

Friedman, Simpson, and Hamberger (1993) assessed age-related changes in scalp topography to novel and target stimuli in a three stimulus paradigm using 48 unique novel stimuli. These novel stimuli were all edited to 100-400 msec and included bird and animal calls, environmental and synthesizer sounds. Topographic distribution of the P3b was parietal for middle-age subjects (average age 50 years, n = 10) and young subjects (average age 24 years, n = 10). It was frontal for old subjects (average age 70 years, n = 9). Topographic distribution of the novelty P3 was frontal for old and middle-age subjects, equipotential Cz-Pz for the young. In general, the amplitude became larger frontally with age, as other studies found.

Yamaguchi and Knight (1991a) duplicated the three stimulus paradigm in the somatosensory modality in an elegant experiment. Stimuli consisted of mechanical taps to the finger (common 76% to the index finger, target 12% to the fifth finger, 6% rare non-target to the third or fourth finger), and 6% shock to the median nerve at the wrist. Correctly detected target stimuli generated a parietal maximal P300 (mean latency 335 msec at Pz). Infrequent tactile novel stimuli generated a centro-parietal maximal P300 (mean latency 349 msec at Cz). Shock novels generated the largest amplitude P300 maximal at Cz (mean latency 298 msec at Cz). P300 to shocks and novel habituated over the first ten single trials. P300 to target stimuli did not habituate. These results were similar to the results in the auditory and visual modalities with one exception, the topography of the novel P300 response was centro-parietal rather than fronto-central. This may have been due to the repeated presentation of the same shock during the experiment and, prior to the experiment, in a training session.

This experiment was replicated (Yamaguchi & Knight, 1991b) using thirty subjects divided into three equal groups according to age; a young group (ages 18-29), a middle-aged group (ages 30-49), and an older group (ages 50-79). Target tactile novel and shock novel P300s increased linearly with age at comparable rates to those previously reported.

Versions of the three stimulus paradigm were used to test a variety of clinical populations. In a visual three stimulus paradigm, Nasman and Dorio (1993) looked at the effect of categorically deviant targets and non-targets on twelve prefrontal tumor patients. Tachibana, Toda, and Sugita (1992) also used a visual paradigm to look at a group of patients with Parkinson's disease and a group of patients with Alzheimer's disease. Fein, Biggins, and MacKay (1995) used an auditory paradigm to look at the effects of alcohol abuse and HIV infection.

Habituation

This section will review the habituation results noted in the prior studies. It will not attempt to review habituation in general or even habituation of the human ERP. Both of these topics are beyond the scope of this dissertation. Habituation, as understood in the context of the reviewed studies, refers to a response decrement of the ERP to repeated stimulation. This has been noted most often to ERPs to unattended stimuli. The ERPs to attended stimuli, on the other hand (e.g. when the subject is counting or responding to a target stimulus), do not habituate over many trials. The distinction is made in these studies between fast habituation, which occurs to the first few stimulus presentations, and slow habituation, which occurs over a number of blocks of trials. Fast habituation is studied by investigating the decrement of each single trial (data is usually averaged over blocks and/or subjects) to the next. Slow habituation is investigated by looking at the decrement of ERP amplitude over a number of runs of many single trials.

The decrement of the ERP over repeated stimulus presentation was one of the earliest characteristics noted. Paradigms designed to study this occurrence presented stimuli at regular inter-stimulus intervals (ISI) to subjects who were either ignoring the stimuli or reading a book. In these circumstances the ERP shows slow habituation over time. Response decrement can also be due to the refractoriness of the underlying neural population when stimuli are presented at a rate faster than the recovery cycles of the ERP components under investigation. Habituation and recovery cycles of the early components were studied to see how longer or shorter ISIs effected the amplitude of a particular component.

One of the earliest reports of the LPC of the ERP resulted from a habituation paradigm (Ritter et al., 1968). Occasional unexpected dishabituating stimuli were delivered. The ERP to these stimuli showed a LPC at around 300-350 msec which was not present to ERP to the background stimuli. This LPC was seen as reflecting a shift of attention associated with the orienting response. Other paradigms also produced a LPC around 300-350 msec. This late positive component soon became known as the P300, as discussed earlier. Habituation of this P300 component varied with the salience, or task relevance, of the eliciting stimuli. In attended paradigms, when a stimulus was counted or responded to in some way, little habituation occurs to the target P300. Non-target P3s, however, showed marked amplitude reductions over time.

The importance of habituation in the distinction of P3a and P3 novel was drawn by Courchesne et al. (1975). They pointed out that the response to the novel stimuli showed marked fast habituation not shown by the target. This habituation was not described for the P3a response by N. Squires et al. (1975). Courchesne et al. measured habituation of single trials by aligning the traces from individual subjects' single trials so that the baseline measures were superimposed. Based on this rough measure, the single trial response to the first novel stimulus presented was very large (ca. 30 μV), to the second novel stimulus was 50% smaller, and to the third, 60% smaller as compared to the first. The novel stimuli in the paradigm were all at least twelve seconds apart from each other making it unlikely that refractoriness of the P3 generator could account for the large amplitude decrement.

Courchesne, Courchesne, and Hillyard (1978) investigated the effect of stimulus repetition across three consecutive trials on the P300 response to four different stimulus categories. These categories were the response to: a) the target (the letter *B*, 10% compared to an 80% background letter *A),* and then one of the following; either b) the 10% novel *other letters*; or c) the 10% novel *bright letters*; or d) the 10% novel *dim letters*. Although each of the three novel responses was equally probable, the more physically deviant *dim and bright letters* elicited much larger P300 responses on the initial three trials than the less deviant *other letters*. Continued stimulus repetition resulted in a progressive long term decrease in P3 amplitude to all novels, but not to targets.

Knight (1984) also measured single trials averaged across subjects to the P300 to the novel stimulus (a dog bark) and found most of the habituation occurred to the P300 from the first to the fifth stimulus with stable P300 amplitude measures from the fifth stimulus on. These decrements did not occur to the target P300. This pattern did not hold for the frontal lesioned subjects studied in this investigation. They showed smaller amplitude responses from the beginning and no decrement over trials. Knight (1989) collected data over four blocks, but did not report amplitude measures for each block.

Polich (1987b) compared the P300 response to twenty targets presented in two different paradigms, an active oddball paradigm and a passive sequence paradigm. In the oddball paradigms, a 2000 Hz tone was presented randomly 20% of the time and the subject was told to lift a finger as quickly as possible when that tone occurred. In the passive sequence, the subject was not attending to the tones. The 2000 Hz tone appeared as the first of a series of ten tones averaged over twenty series. Polich repeated each paradigm twice to look at the effect of repetition. No significant differences between trial blocks were obtained for either latency, amplitude, or electrode measures, although the amplitude of the P300 in the passive sequence was smaller than that of the active task and the amplitude was slightly smaller for both paradigms for the second block. Polich (1988) used the same technique to assess change due to repetition in an active discrimination task with subjects that produced two P300 peaks and reported a diminution of the P3a subcomponent's amplitude at Fz. Polich (1989c) examined habituation of the P300 response to attended target in three different ways. First, he looked at habituation over single trials. There was no evidence of amplitude decrement over fifteen single trials averaged across twenty-four subjects. Next, he looked at habituation across repeated blocks of twenty target stimulus presentations over twenty-four subjects. There was a significant effect of trial block. Amplitudes for the first four trial blocks were significantly larger than for trial blocks six through ten. In order to make sure that this habituation effect was not caused by receptor or sensory fatigue, he conducted a third experiment to see if the response could be dishabituated. After trial blocks one through nine, he reversed the target/background and presented the background as the target. Unfortunately, as so often happens in ERP habituation studies, he continued to reverse the stimuli in blocks ten through fifteen and did not return to the original stimuli, thus looking at generalization, not dishabituation (Roemer, Shagass, & Teyler, 1984). Habituation occurred on trial block nine as compared to either trial blocks one or five. P300 amplitude increased significantly from trial block nine to ten when the stimulus was first reversed, then decreased again by trial block fifteen. Polich proposed that, as long as attentional resources are engaged in the task performance, P300 amplitude remains stable. But, if the task becomes automated over time and attentional resources are less utilized, P300 amplitude declines.

Lammers and Badia (1989) also looked at habituation of the P300 to target stimuli within a block of 35 trials and across successive blocks, after which various conditions were imposed on block six to assess dishabituation. These conditions were a) no change from block five to block six (control group), b) reversal of target and background tones, c) information concerning the end of the session, and d) both (b) and (c). As in the previous experiment, no return to the original stimuli occurred, thus making assessment of dishabituation impossible. Subjects were randomly assigned to one of the four conditions for block six (ten subjects in each group). Subjects did not know how many blocks were to be presented.

Each of the six blocks lasted five minutes and contained 35 targets. Each block was divided into seven sub-blocks of five targets each. There was an inter-block interval of twenty seconds. There was a significant effect for both blocks and sub-blocks. Amplitude decreased from block one to block five. There was also a decrease across sub-blocks which became more pronounced from block one to block five. Latency increased significantly across blocks and sub-blocks. There was a significant effect of inter-block interval with P300 amplitude increasing on the first sub-block following an inter-block interval of twenty seconds. There was a significant effect for group depending on which condition was assigned to block six. The condition, knowledge plus reversal, caused the largest amplitude increase followed by the condition, knowledge only. Reversal of tones was not significantly different from the control condition.

Lammers and Badia (1989) point out that there was one difference in this study that might be responsible for habituation of target P300 which had not occurred in previous studies (Courchesne et al., 1978; Knight, 1984; Polich, 1987b). Lammers and Badia used an inter-target interval of 7.5 seconds and an inter-block interval of twenty seconds, compared to a mean inter-target interval of thirteen seconds and an inter-block interval of 180 seconds in the Courchesne et al. (1978) study, which reported no habituation for target P300. Lammers and Badia put forth several other hypotheses about the causes of habituation. A general decrease in arousal level occurred across blocks (subjects reported drowsiness and boredom) and the degree of cognitive involvement in the task may have declined as subjects were able to allocate less effort to the task (subjects reported that their mind wandered as the experiment continued).

Yamaguchi and Knight (1991a) looked at the habituation of the novelty P300 to shock novels, to tactile novels, and to target tactiles over intervals of three single trials. P300 amplitude to shock novels decreased 17% by trials four to six compared to trials one to three. It decreased 24% by trials seven through nine and ten through twelve. P300 amplitude to tactile novels diminished 29% over a similar interval, while P300 amplitude to targets showed no significant decrement.

In conclusion , most studies are consistent in showing little or no habituation of target P300, although there may be habituation of P300 elicited by rare non-targets. A few considerations of data analyses methods for habituation studies should also be noted. Petrinovich and Widaman (1984) warn that individual subject data and individual subject variability must be addressed. For example, when studying habituation only, the data from subjects showing habituation should be included in the analyses. To my knowledge, this has never been done in ERP habituation studies. Also, individual subject variability must be addressed since subjects have different amplitude responses, different signal-to-noise ratios, and different attentional levels.

Component Identification

Methods used for component identification vary from study to study. The N. Squires et al. (1975) study relied on picking peaks of individual subjects' waveforms which were verified with principal component analysis (PCA). P3a was picked in a latency range of 220-280 msec for twelve subjects. P3b was picked at a latency range of 310-380 msec for twelve subjects. P3a was originally identified in a passive oddball paradigm to the rare tone (probability 0.10). P3b, on the other hand, occurred in an active paradigm to the rare tone (probability 0.10) whether or not it was the target. P3a was also identified as occurring to the rare tone in the active paradigm along with the P3b in many of the subjects. No grand average of subjects' ERPs was obtained and statistics were computed on components identified by PCA. EOG was measured but not presented.

Courchesne et al. (1975) designated specific windows in which components should be identified. These windows were the same from condition to condition. Analysis of variance was then conducted on mean peak amplitude for different conditions. P300 was compared in a passive oddball condition (80% background, 20% rare) and an active oddball condition (80% background, 10% rare, 10% either simple or novel) which also contained rare irrelevant non-targets. These 10% rare irrelevant non-targets, depending on varying conditions, were either simple or novel. P300 data to the passive condition was not presented except to say that the infrequent rare evoked substantially larger P3 waves than the common stimulus. Individual averages were superimposed on each other to look at the replicability of the waveforms across subjects. EOG was averaged and displayed. Amplitude latency and topography were measured..

In an auditory version of the Courchesne et al. (1975) paradigm, Knight (1984) identified P300 to both targets and novels in a 250-450 msec window. P3 novel was identified with the P3 response to novel stimulus, P3b to the P300 peak which occurred to the target in the 250-450 msec window.

In the three stimulus paradigm, since novel and target are specific non-overlapping entities, component identification is fairly straightforward. The response to the target is designated P3a, the response to the novel is designated P3 novel (which is increasingly called P3a). The difficulty occurs, not in distinguishing between P3b and P3 novel, but rather in distinguishing which of several possible peaks is P3b.

The three stimulus paradigm tends to have a later and more variable P3b component. Often subjects have two P300 peaks in a designated window. Identifying these components is considerably more difficult.

Fein and Turetsky (1989) compared P300 latency measures in an active oddball and three stimulus paradigm. Thirteen of 50 subjects had very long latency P300 responses to the largest stimulus. When these responses were not included in the averages, the mean latency for the three stimulus target P300 was longer (350 msec) but in a similar range as the oddball target P300 (329 msec). When the P300 for the thirteen subjects who had very long latency responses (around 500 msec) to the target in the three stimulus paradigm were included in the average, it increased the three stimulus mean to 433 msec and increased the standard deviation from 46 to 152. This increased variability may be the result of subjects adopting different strategies of stimulus processing with the tone first classified as standard or non-standard (deviant detection), then next processing the tone as target or non-target. This may also explain the occurrence of double peaks in some subjects. A number of strategies have been used in identifying components in these subjects. Bruyant et al. (1983) operationally defined P300 as occurring between 280-500 msec with an amplitude of greater than 5 μV which appeared selectively to rare stimuli and was reproducible in consecutive runs. When two distinct peaks occurred, they were measured separately and labeled P3 early and P3 late. Polich (1988) defined P3a as the first positive peak after N2 between 220-280 msec. P3b was defined as the subsequent positive peak between 250-350 msec. If there was only one peak, it was labeled P3b.

This strategy defines how the peaks were picked but does not make clear how the peaks are handled statistically. If only a portion of the subjects have two peaks, are they analyzed with smaller N as a separate analyses and which one, if either, is combined with the subjects' P3s who have only one P300 component? A number of studies have picked P3a and P3b based on their reported topography. P3b is picked at parietal electrode Pz and P3a is picked at frontal electrode Fz.

Fein et al. (1995) measured P3a by choosing the largest peak between 260-520 msec in the subject's averaged referenced average waveform at Fz. P3b was measured in a similar manner at Pz.

García-Larrea et al. (1992) defined P250 as a positive peak at Cz which occurs between 220-280 msec and P300 was defined as the positive peak with the greatest amplitude between 280-400 msec appearing only in response to target at Pz.

Two aspects of component identification have been reviewed. In recent years, P3 novel has become considered equivalent to P3a. It is not clear, however, that the component labeled P3a in the passive oddball paradigm is the same as the component labeled P3a in the three stimulus paradigm. How and where a peak is measured is still less than an exact science. PCA was used in the early days of P3a to verify that it was a separate component. However, PCA has since been shown to have major flaws when allocating variance to overlapping components. The issue of the relationship between P3a, P3 novel, and P3b is still unresolved.

Summary

P3a and P3 novel have both been defined as orienting components. They each occur to rare deviant stimuli that are not attended. P3a, however, was originally identified in a passive auditory oddball paradigm while P3 novel was identified in an active visual three stimulus novel paradigm. As originally described, the two components had slightly different topography and different latencies. Despite the fact that stimulus differences could have accounted for most of the differences in the two components, no direct comparison of the two components was ever made. Both paradigms have since been modified and used in both normative studies and clinical testing situations. Although each has subsequently been used in both auditory and visual modalities as well as the somatosensory modality, various studies have reported conflicting findings regarding topography, latency, and habituation.

This investigation was designed to directly test whether or not the P300s produced by the two different paradigms, the passive oddball and the three stimulus novel, are equivalent. In order to test this, the same stimuli were used in both paradigms, the same subjects were used for all conditions. Two separate control conditions were used; a) a reading control, because many of the original studies were done while the subjects were reading; and b) a thinking control, because many other studies were done with subjects not reading. Each condition was run twice to evaluate habituation from run to run. Because of the large number of conditions created by having both a reading and a thinking control, it was only possible to have two runs of each condition and remain within the comfort level of most subjects for repeated testing. The entire experiment was repeated on a second day to look at replicability. Although many of the original passive oddball studies were conducted with the subject reading, none used eye-movement correction procedures. Eye-movements are known to effect frontal electrodes more than others so this study corrected all ERPs for eye-movement artifact.

The primary research question was whether the novel stimuli produced an equivalent P300 across paradigms and if this P300 was equivalent to the P300 produced with the traditional stimuli (tones of different frequencies) in the passive oddball paradigm. It was hypothesized a) that the P300 amplitude from the novel stimulus would be larger, b) that the latency would be earlier, c) that the P300 from the novel stimuli would habituate less than that of the 1500 Hz stimuli, d) that the topography of the P300 from the novel stimuli would be similar to the topography of the 1500 Hz passive oddball (fronto-central maximum), and e) it would be different from the P300 to the 1500 Hz target stimuli (parietal maximum) in the three stimulus active oddball paradigm.

CHAPTER 2

METHODS

Subjects

Twenty subjects (ten of each sex, ages 19 to 36 years, M = 27) participated in this study. Subjects were recruited by advertisement at a local college, by bulletin board notices at the university employment agency, and from among colleagues, friends, and their referrals. Subjects were selected who had no history of neurological disorders (based on self-report), and who were not taking any medication that affected their alertness. All subjects were audiometrically screened at frequencies ranging from 500 Hz to 4000 Hz, and anyone with a >15 dB difference between ears or a hearing loss of >30 dB in either ear was considered ineligible. Using this criteria, no subject was disqualified. Subjects were recruited for two recording sessions, each session approximately three hours in length. Subjects were paid eight dollars per hour plus a twenty-five percent bonus for completing both sessions. For those agreeing to participate, informed consent was obtained prior to participation.

Stimuli

Auditory stimuli consisted of 500 Hz and 1500 Hz, 100 msec tones, and a variety of synthesized 100 msec sounds. Stimuli were generated with a Roland Multi Timbral Sound Module (MT-32) controlled by a Quadra 650 computer programmed using Performer version 3.63 computer software. Performer is a musical instrument digital interface (MIDI) sequencer software program. Novel sounds were generated by using a combination of 63 different sound patches from the MT-32 sound list and a selection of notes from a keyboard. The notes had a four octave range (one octave lower than the 500 Hz tone and one octave higher than the 1500 Hz tone). This was equivalent to a 250-3000 Hz range. Sounds were chosen for novel stimuli that did not reverberate or ring and that did not sound too similar to either the 500 Hz or 1500 Hz tones. Thirteen different stimulus lists (see Appendix A for examples) were written using the Performer computer software described above. These lists were sequenced to correspond to the random lists generated by the data collection software for the thirteen different protocols used in the experiment. Seven different protocols contained novel sounds. With the exception of the control list of 100% novel sounds, most of the novel sounds were used only once. The control list contained 40 novel sounds, most of which had occurred in one of the previous protocols. Occasionally novel sounds were used in more than one protocol. As each stimulus list was played back by the computer software, it was recorded with a stereo cassette deck (Nakamichi Rx-202) onto magnetic tape. Since each stimulus list was recorded on audio tape, it was possible for each subject to receive an identical sequence of stimuli that changed for each condition. Auditory stimuli were passed through a stereo mixing console (Realistic model 32-1200c) amplified through one channel of a stereo amplifier (Denon model DRA-35V) and were delivered to the subject binaurally through small speakers (Realistic Minimus-7) placed slightly in front of and to the right and left of the subject's chair. A synch pulse recorded onto magnetic tape and amplified through the other channel triggered the beginning of a recording epoch 100 msecs before the onset of each stimulus. The inter-stimulus interval (ISI) averaged 1.5 seconds and varied randomly from 1.4 to 1.6 seconds to avoid time-locked anticipatory potentials, for example, the contingent negative variation (CNV).

Stimulus intensities were calibrated with a Realistic Sound Level Meter (Model 33-2050) midway between the two speakers. Stimulus intensities were presented at 50 dB above each subject's individual threshold for the stimuli on a representative cassette audio tape, that is, calibrated in dB sensation level (SL). Each subject's threshold for an audio presentation was determined using a method of limits procedure consisting of all 1500 Hz tones delivered at 1.5 second intervals. The amplifier control was calibrated in dB increments and used for gross adjustments. The mixer control was used for fine adjustment to determine the subject's threshold. After determination of threshold, the amplifier control, which was initially set at zero dB, was turned up to 50 dB. The audio tape was then played for a few presentations of the tones to make sure it was a comfortable level for the subject. If it was too loud, the intensity was adjusted down until it was comfortable for the subject. This occurred for only one subject.

Experimental Design

Subjects participated in two sessions, each session approximately three hours in length. In each session, the subjects completed two blocks of five conditions each and one block of three control conditions each. The conditions consisted of:

1. Three 100% control conditions: Each a block of 40 tones; tones in the first block were 500 Hz, 100 msec duration; in the second block, tones were 1500 Hz, 100 msec duration; and in the third block, tones were novel synthesized sounds, each different, 100 msec duration. During all control conditions, the subjects were instructed to ignore the tones and think about some specified topic (see discussion of topics below).
2. Two passive oddball conditions that were modified replications of the N. Squires et al. (1975) passive oddball P300 paradigm (common stimulus 85%, 500 Hz, 100 msec duration; rare stimulus 15%, 1500 Hz, 100 msec duration). During one condition, the subjects were instructed to ignore the tones and to think about some specified topic (see below). During the other condition, the subjects were instructed to read a book of their own choosing.
3. Two passive oddball conditions that were further modifications of the previous paradigm, but with different novel stimuli used as the rare stimulus (common stimulus 85%, 500 Hz, 100 msec duration; rare stimulus 15%, synthesized novel sounds, each different, 100 msec duration). As previously, during one condition the subjects were reading and, during the other, the subjects were thinking of a specified topic.
4. One condition was an auditory version of the Courchesne et al. (1975) three stimulus novel paradigm; common stimulus 75%, 500 Hz, 100 msec duration; rare target stimulus which were counted silently 12.5%, 1500 Hz, 100 msec duration; and rare novel stimulus 12.5%, synthesized sounds each

different, 100 msec duration. During this condition, the subjects were instructed to count the target tones and ignore all other sounds.

To control for inadvertent attention to auditory stimuli during passive conditions, two strategies were followed:

1. During half of the passive oddball conditions, the subjects read a book of their choice. Subjects were instructed to concentrate on the book and to ignore all sounds. Large eye-movements and blinks caused data to be rejected by the data collection program, so this was monitored closely. Subjects were given feedback after each reading block and asked if the reading material was absorbing and if the print size and the light were adequate.
2. During the other half of the passive oddball conditions and during the control blocks where the same stimulus was repeated 100% of the time, subjects were instructed to think of something of personal interest and to ignore all stimuli. A list of suggestions of absorbing topics was discussed with the subjects to help them decide on an effective strategy to ignore all auditory stimuli and to remain alert. The tasks varied according to subject interest and personality and ranged from the common (planning and listing chores which needed to be done) to the more esoteric (planning a photo shoot for a magazine article). After each passive block, the subjects were asked about the topic and their opinion of its effectiveness in absorbing the subjects' attention and keeping them awake. Different topics were used as needed throughout the recording session. See Appendix B for a list of the various thinking tasks used by each subject.

During the active three stimulus novel condition, subjects were instructed to keep a count of the target tone and to ignore the other stimuli. They were told that they would be asked the total at the end of the run. Most subjects were accurate to the exact count or off by plus or minus one. Two subjects admitted that they thought they might have lost count briefly. No subject was ever off by more than two.

All subjects received all thirteen conditions during each session. To control for order effects, the conditions, with the exception of the 100% control conditions, were assigned by Latin square design (see Table 1). The twenty subjects were broken into five groups of four, each group given a different order of conditions so that each experimental condition was the first condition for eight subjects. Each of the five experimental conditions was then repeated in the block immediately following its presentation. The 100% control conditions were always given in the same order, the 500 Hz condition first at the beginning of the session, the 1500 Hz condition next, followed by the experimental conditions as assigned by the Latin square design, and the novel control condition last. The novel control condition was given last so as not to alert the subjects to the novel tones prior to the tones being presented in the experiment. Also, the control list had many of the same novel stimuli as occurred in the experimental lists. A different counter-balanced order was assigned to each group for the second session.

Table 1. ***Latin Square Design***

	Session 1					Session 2				
	Start Position					Start Position				
Group	1	2	3	4	5	1	2	3	4	5
1	1	2	3	4	5	3	2	4	1	5
2	1	5	2	4	3	4	5	1	2	3
3	2	3	4	5	1	4	3	5	2	1
4	2	1	3	5	4	5	1	2	3	4
5	3	4	5	1	2	5	4	1	3	2

Legend:
1 Passive Oddball 1500 Hz Thinking
2 Passive Oddball 1500 Hz Reading
3 Passive Oddball Novel Thinking
4 Passive Oddball Novel Reading
5 Three Stimulus Count Target

Procedures

The first recording session began with a brief explanation of the study and ERP recording procedures. See also Appendix C for an outline of the protocols of the testing sessions. The subjects were given the opportunity to ask questions and were given an Informed Consent Document approved by the University of California, San Francisco (UCSF) Committee on Human Research to read and sign. Subjects were asked about the amount of coffee or tea consumed prior to coming to the lab and the approximate amount of sleep during the previous night. It was also ascertained if these were usual or unusual amounts. All subjects reported that their previous nights' sleep was about normal.

Hearing tests were then performed to insure that the subjects' hearing was within normal limits and to determine the subjects' pure tone threshold at each ear for the range of stimulus frequencies used in the experiment. Following the hearing tests, subjects were prepared for ERP recording. The fitting of the electrode cap and EOG electrodes and preparation of the scalp took from thirty minutes to one hour depending on subject variables such as skin impedance, amount of hair, and tenderness of scalp.

Next, the subjects were seated in a comfortable reclining chair in a sound attenuated recording chamber. Skin impedances were rechecked once the subjects' electrodes had been connected to the amplifiers and, if necessary, readjusted to 5000 Ohms or less. Subjects were instructed to remain quiet and relaxed. The importance of staying awake and alert was explained to them. Subjects were directed to choose a fixation spot at a comfortable viewing distance and to try to refrain from blinking during the actual recordings. While the experimenter checked each channel of on-going EEG, subjects had a chance to practice these instructions and to adjust to the surroundings. Subjects were next asked to make a series of blinks, then horizontal and vertical eye-movements. They then were asked to practice reading the book or material they had brought with them. Occasionally, the item brought by a subject was not satisfactory because the material required too much page turning or skipping around which caused excessive eye artifacts. In these cases and in the cases when a subject forgot to bring reading material, a selection of literature was available from which the subject could choose. During inspection of the EEG and EOG channels during the eye-movement exercises and reading, if it was determined that a subject had very large amplitude EOG potentials which saturated the A/D converters, the gain of the EOG channels was turned down from 50,000 to 20,000 amplification and the data collection system was calibrated accordingly.

Subjects' thresholds for the audio tape recorded stimuli were determined next. After the threshold for the audio presentation was found, the presentation was delivered at an intensity 50 dB higher than that threshold.

After the intensity level was set, the attention control task was explained. Subjects were told that they would be performing one of three tasks during the actual ERP recordings. The three tasks were explained and discussed with each subject: a) reading, b) thinking about a topic or task of interest to them, and c) counting a target stimulus. It was stressed that the topic should be able to keep the subject actively engaged in the task and that it should be something that the subject could report on in detail after each recording period.

Once the tasks had been discussed with the subject, the recording session began. Each recording session began with two short control runs as detailed in the design section above. This gave each subject the opportunity to get used to the recording procedures, the stimuli and the attention condition during the two short runs (approximately 1 minute 30 seconds each). The subject and experimenter communicated through an intercom. After each run, the experimenter asked each subject how things were going and confirmed that the subject was alert and following instructions. If the subject was getting drowsy or was uncomfortable, a short one to two minute break was taken. In addition to communicating via the intercom, the subject was monitored by a video camera to insure that all instructions were carried out correctly.

Before each experimental condition, each subject was told whether the attention task was reading, thinking, or counting. If the attention task was thinking, the strategy that the subject was planning to use (i.e. the task the subject would be actively concentrating on) was discussed. Each subject was reminded to be prepared to discuss the topic after the run. Before the three stimulus counting paradigm, a short excerpt of a condition list similar to the two three stimulus tapes was played for each subject so that there was no misunderstanding about which tone was the target to be counted. The subject was told to keep a silent count of the target stimuli which he/she would report at the end of each run.

Before every condition, each subject was asked if he/she was ready to begin. When they were, the experimenter indicated the recording was beginning and began the audio tape and data collection program. Frequent breaks were taken and each subject was encouraged to get up and walk around or stretch at least once during a recording session. After every break, impedances were checked and readjusted, if necessary.

ERP Recording

Electroencephalogram (EEG) and electro-oculogram (EOG) were recorded with a Grass Neurodata Acquisition System (Model 12). ERPs were recorded monopolarly from a montage of pure tin electrodes contained in a spandex-type cap (Electro-Cap International). The electrodes in the cap were placed according to the 10-20 international system. A recording montage of fourteen electrodes from the adjusted 10-20 system (American Electroencephalographic Society, 1991) was used (Fp1, Fp2, F3, F4, C3, C4, P3, P4, Fz, FCz, Cz, CPz, Pz, and Oz, with AFz ground). All scalp electrodes were referred to linked earlobes (Gonzalez Andino, Pascual Marqui, Valdes Sosa, Biscay Lirio, Machado, Diaz et al., 1990; Lutzenberger & Elbert, 1991). EOG was collected bipolarly with tin cup electrodes affixed to the face with adhesive collars. The horizontal EOG electrodes were placed at the outer canthus of each eye. The vertical EOG electrodes were placed on the supra and inferior ridges of the left eye. Impedances at all electrodes were kept at or below 5000 Ohms.

Data acquisition, stimulus presentation, and preliminary data analysis procedures were precisely programmed using ERPSYSTEM computer software (Neurobehavioral Laboratory Software). Each recording epoch was 900 msec (including a 100 msec pre-stimulus baseline) with a 4 msec sampling rate. The bandpass of the amplifiers was set to 0.1-100 Hz (with 6 dB roll-off). The signals on the EEG channels were amplified 50,000 times for all subjects. The signals on the EOG channels were amplified for each subject according to the size of their EOG potentials. For four subjects, both EOG channels were amplified by 50,000 times. For eleven subjects, both channels were amplified by 20,000 times. For three subjects, the VEOG channel was amplified by 50,000 times and the HEOG by 20,000 times. Artifact rejection was set to 80 µV baseline-to-peak on the VEOG channel (approximately 15% below A/D converter saturation ±93 μV). The HEOG channel was set so that all epochs were accepted. These extremely high settings were utilized to allow most epochs to be accepted even though contaminated by eye-movements which were expected because of the reading conditions. EOG correction procedures were implemented off-line prior to data analyses. Artifact rejection for subjects run with 20K amplification on the EOG channels was set to 200 μV baseline-to-peak on the VEOG channel (approximately 15% below A/D converter saturation ±240 μV). The HEOG channel was set so that all epochs would be accepted.

Stimulus presentation of the experimental conditions was in pairs of two runs of approximately 125 stimuli each (for each run, data was collected until sixteen good responses to targets, pre-targets, and post-targets were collected). Artifact-free trials were averaged on-line by the computer and stored in files at the end of the run. Both single trials and average files were written in a format accessible to data analysis by software available on the PC. An average evoked response was created a) for each rare, target stimulus; b) for each stimulus preceding a target stimulus; c) for each stimulus following a target stimulus; d) for each rare, novel stimulus; e) for each stimulus preceding a novel stimulus; f) for each stimulus following a novel stimulus; and g) for all other common stimuli.

Data Reduction and Analysis

Prior to further analyses, all data was subjected to eye correction procedures. This study utilized a frequency domain approach developed by (Gasser, Sroka, & Möcks, 1985). Their study and a follow-up study (Gasser, Sroka, & Möcks, 1986) showed that blinks and eye-movements have different spectral patterns and are also transferred differently to the locations on the skull. Their method also takes into account the problem that the EOG electrodes pick up EEG activity as well as EOG activity. In this implementation of Gasser et al.'s frequency domain method, a separate set of transfer functions was estimated for vertical and horizontal eye-movements for each subject. The set of vertical and horizontal transfer functions developed for a particular subject was then applied to all of that subject's data. This was based on the assumption that the amount of EOG transferred into each EEG channel should be governed by the physics of that subject's head and the placement of the electrodes on the head. EOG correction consisted of the following steps:

1. Representative epochs of high and low EOG activity were chosen from single trials which had been filtered from one to 40 Hz. At least five high and five low epochs were chosen from the HEOG channel, then separately from the VEOG channel.
2. From the representative HEOG epochs, an estimate of the horizontal transfer function between eye-movement and each EEG channel was determined.
3. Correction for horizontal eye-movements were made. For each single trial, the fast Fourier transfer (FFT) of the HEOG channel was multiplied by the horizontal transfer function and then subtracted from the FFT of each EEG channel.
4. As in Step 2, an estimate of the vertical transfer function was determined. However, this time the VEOG epochs were compared to the inverse Fourier transform of the preceding step, which is the EEG at each channel corrected for horizontal eye-movements.

Correction for vertical eye-movements were made by multiplying the FFT of the vertical EOG by the transfer function, then subtracting that quantity from the transfer function of each EEG channel. The inverse Fourier transform of each channel from the previous step is the corrected EEG. A new corrected single trial file and corrected average were written to file (the original single trial files and averages were left intact).

The eye correction program was implemented so that either a) all single trials could be corrected, or b) only trials not rejected by the data collection rejection algorithm could be corrected. Since relatively liberal rejection criteria were used, most subjects had an adequate number of good trials. Therefore, good single trials only were corrected for most subjects. For a few subjects, the option to include bad trials was chosen for some or all of the conditions.

Previous research has shown that the spectrum of eye-movements is below 7 Hz (Gasser, Möcks, Lenard, Bächer, & Verlager, 1983; Gasser et al., 1985; Matousek & Petersén, 1973). For this reason, the gain of each transfer function was truncated to zero at frequencies above 7 Hz. An EOG trace showing no activity below 7 Hz is evidence that the eye-movement program was working. Figure 1 shows an example of corrected and uncorrected single trial ERP. Figure 2 shows the averaged ERP from the single trial in Figure 1 before and after eye-movement correction.

Although data was collected from fourteen electrodes covering the entire head to make it possible to make topographic maps of the responses, this study utilized only the midline electrodes which have been used in a majority of the studies in the past. This study also only looks at the average responses to the rare stimuli and to the common stimuli which have been traditionally studied in the P300 literature. The responses to the common stimuli directly before and directly after the rare stimuli will be analyzed at a later date. For each average evoked response to the common stimuli and the rare stimuli, peak amplitude and latency were determined for three components: N1, P2, and P3 at the five midline electrode placements Fz, FCz, Cz, CPz and Pz. Individual components were measured by a computer-controlled multi-channel peak picking program of latency windows.

Latency windows were determined by inspection of the peak latencies of the components in the grand average of each of the conditions across all subjects. The N1 window was set as the largest amplitude negative peak between 52-152 msec. The P2 window was set as the largest amplitude positive peak following N1 between 124-244 msec. The P3 window was set as the largest positive peak within the latency window of 300-500 msec. This same 300-500 msec latency window was used for P300 for all conditions regardless of stimulus or paradigm. Prior to peak picking, all averages were digitally filtered with a bandpass of 1 to 15 Hz. Peak amplitude was measured relative to the mean of the pre-stimulus baseline for all components. Latency was measured from stimulus onset to the highest voltage at the electrode where the amplitude was the highest for that component. The amplitude was measured at that latency for all other electrodes.

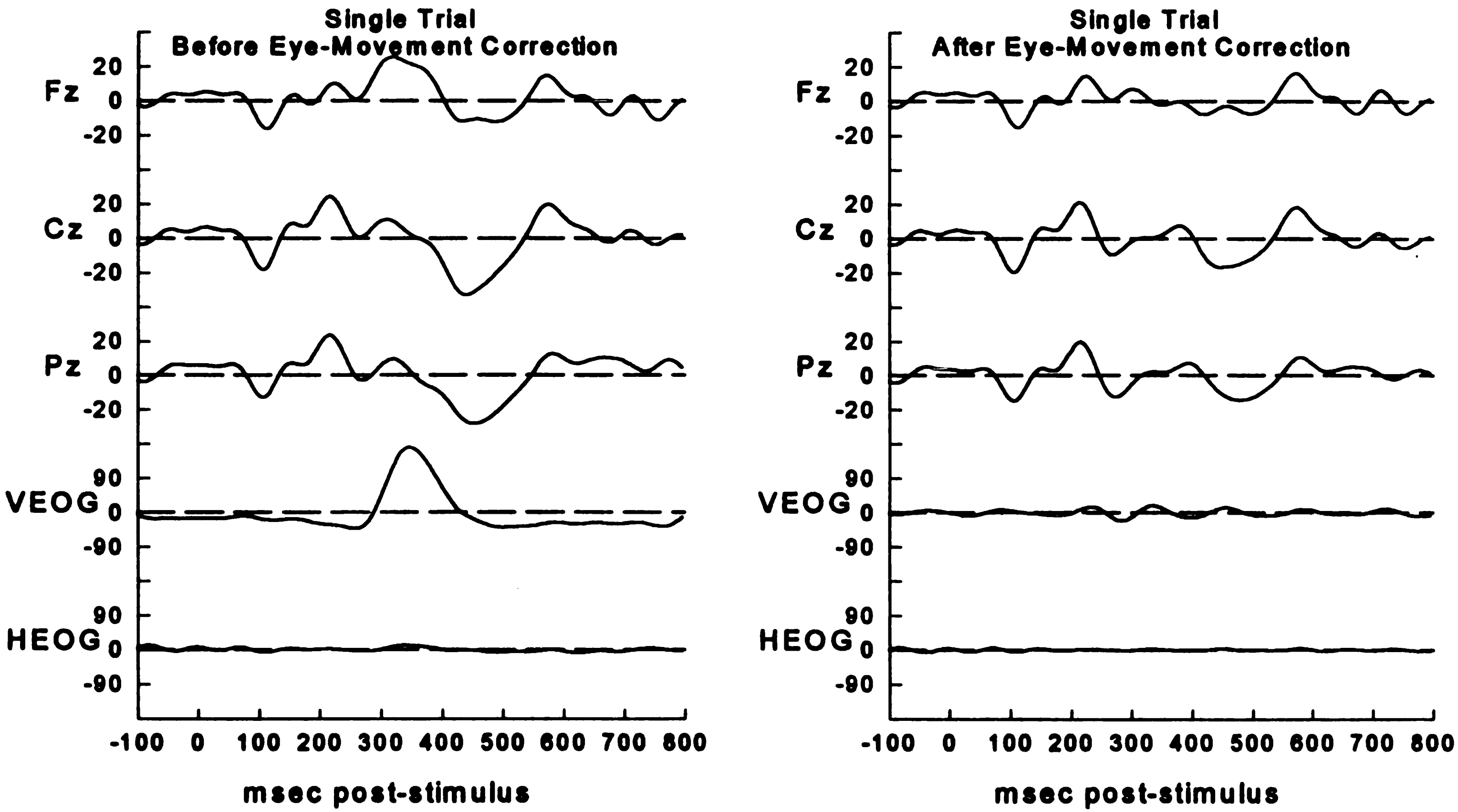


Figure 1. Illustrates a single trial with vertical eye-movement before and after eye-movement correction. The single trial is #103 from Subject 13. The paradigm is passive oddball, the stimulus is rare novel, the task is thinking. EEG channels are plotted at ±20 μV, EOG channels are plotted at ±90 μV, positive up. Data is filtered from 1-15 Hz.

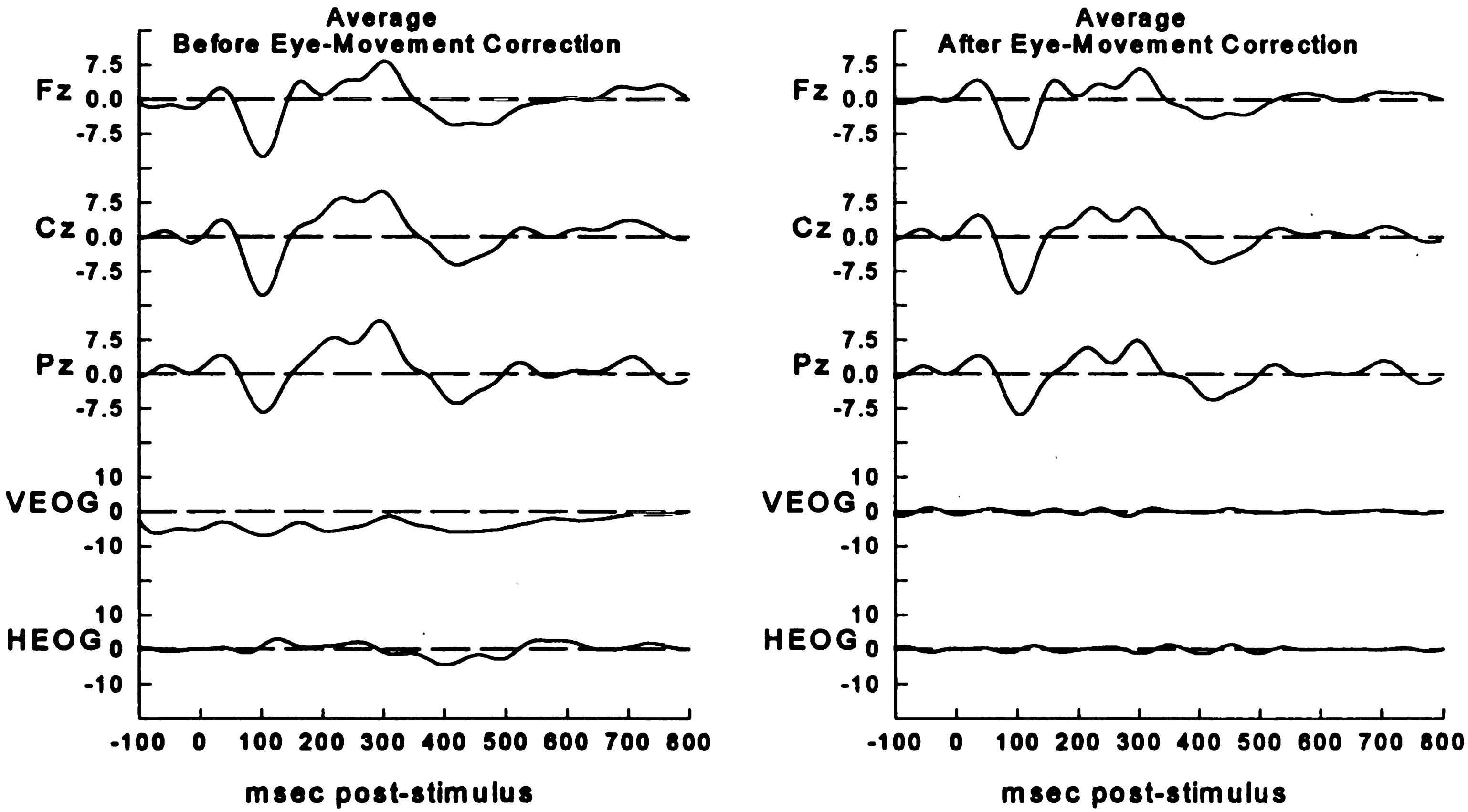


Figure 2. Illustrates averaged ERP from the same subject and the same condition as in Figure 1. EEG channels are plotted at ±7.5 μV and EOG channels are plotted at ±10 μV, positive up. Data is filtered from 1-15 Hz.

All peaks were checked and adjusted, if needed. The most frequent adjustment occurred when a peak was picked on an upward slope at the edge of the window. In the case of P2, the window was extended if the real peak fell within 20 msec and if this did not overlap the P3 peak. In the same manner, P3 was extended earlier for a number of conditions in a number of subjects. However, the earliest it was picked was 252 msec and then only if there was a clear P2 prior to that. If the P3 peaked at 500 msec, it was chosen, but the window was never extended past 500 msec. In the case of the common stimuli where there was no real P300, the amplitude was highest at 500 msec almost 30% of the time. However, for the rare condition, 500 msec was chosen fewer than ten times. Figure 3 illustrates the different peak windows and examples of computer picked peaks which were questionable and required manual repicking.

Prior to statistical analyses, two additional normalization procedures were performed:

1. An amplitude difference measure was created from run one and run two of each condition of each session for each subject so that the question of habituation from one run to the next could be viewed uncontaminated by amplitude variability across subjects. This measure, Ampdif, was derived by the formula: $\frac{amp_2 - amp_1}{\sqrt{(amp_1^2) + (amp_2^2)}}$, where amp_1 is the peak amplitude from run one of a condition and amp_2 is the peak amplitude from run two of the same condition. Habituation (indicated by a negative Ampdif score) was assessed by conducting a series of T-tests of Related Measures on the average Ampdif score for each condition. These t-tests determined whether the difference in amplitude between time 1 and time 2 for each condition was significantly different than zero.
2. The peak amplitude measures at the electrodes Fz, FCz, Cz, CPz, and Pz were normalized by vector length as recommended by McCarthy and Wood (1985). Rather than a condition specific vector length which needs to be recomputed for each condition and each analysis, each ERP measure was normalized once prior to all analyses with an individual's run specific vector

based on the SQRT of the sum of squares of all the electrodes of an individual. The specific formula used is illustrated for Fz: Fz, normalized =

$$\frac{Fz - Ex}{\sqrt{(Fz - Ex)^2 + (FCz - Ex)^2 + (Cz - Ex)^2 + (CPz - +Ex)^2 + (Pz - Ex)^2}}$$

where Ex = $\frac{Fz + FCz + Cz + CPz + Pz}{5}$ This was done for each electrode, for every average. These normalized values were used in all topographic analyses.

The dependent measures, peak amplitude, peak latency and normalized peak amplitude at five midline electrodes (Fz, FCz, Cz, CPz and Pz) were tested separately by repeated measures analyses of variance (procedure GLM of SAS). Prior to testing the primary hypotheses across paradigms, a number of preliminary analyses were conducted. Repeated measures ANOVAs were run separately for the passive oddball paradigm and for the three stimulus paradigm. For each paradigm, an overall ANOVA with the between-conditions factor of Group and the within-conditions factors of Stimulus, Session, Task, Time, and Condition (for the oddball paradigms) or the within-conditions factors of Session, Time and Condition (for the three stimulus paradigm) was run to assess the effectiveness of the Latin square design in controlling for start-order effect. If the design was effective, group should not interact with any other factor.

Overall, ANOVAs of each paradigm were also used to confirm that the common stimulus did not, in fact, produce a P300; that the Task factor (in the oddball paradigms only) did not effect one stimulus more than another; and whether or not the Session and/or Time factors were significant. Based on these ANOVAs, it was planned to collapse some of the conditions prior to testing the *a priori* hypothesis. In these ANOVAs and all subsequent ANOVAs, Greenhouse-Geisser epsilon-adjusted probability measures were used whenever sphericity assumptions were not met

The primary research question was whether the novel stimuli produced an equivalent P300 across paradigms and if this P300 was equivalent to the P300 produced with the traditional stimuli (tones of different frequencies) in the passive oddball paradigm. It was hypothesized a) that the P300 amplitude from the novel stimulus would be larger, b) that the latency would be earlier, c) that the P300 from the novel stimuli would habituate less than that of the 1500 Hz stimuli, d) that the topography of the P300 from novel stimuli would be similar to the topography of the 1500 Hz passive oddball (fronto-central maximum), and e) it would be different from the P300 to the 1500 Hz target stimuli (parietal maximum) in the three stimulus active oddball paradigm.

The hypotheses above were tested with repeated measures ANOVAs; a) P300 peak amplitude was tested with a three factor Paradigm (oddball, three stimulus) X Stimulus (1500 Hz, novel) X time (1, 2) ANOVA; b) P300 peak latency was tested with a four factor Paradigm X Stimulus X Session (day 1, day 2) X Time ANOVA; c) the habituation measure Ampdif was tested by t-test for related measures; and d) and e), the topography measures of the five normalized midline electrode positions, were tested by a four factor Electrode (Fz, FCz, Cz, CPz, Pz) X Paradigm X Stimulus X Time ANOVA.

CHAPTER 3

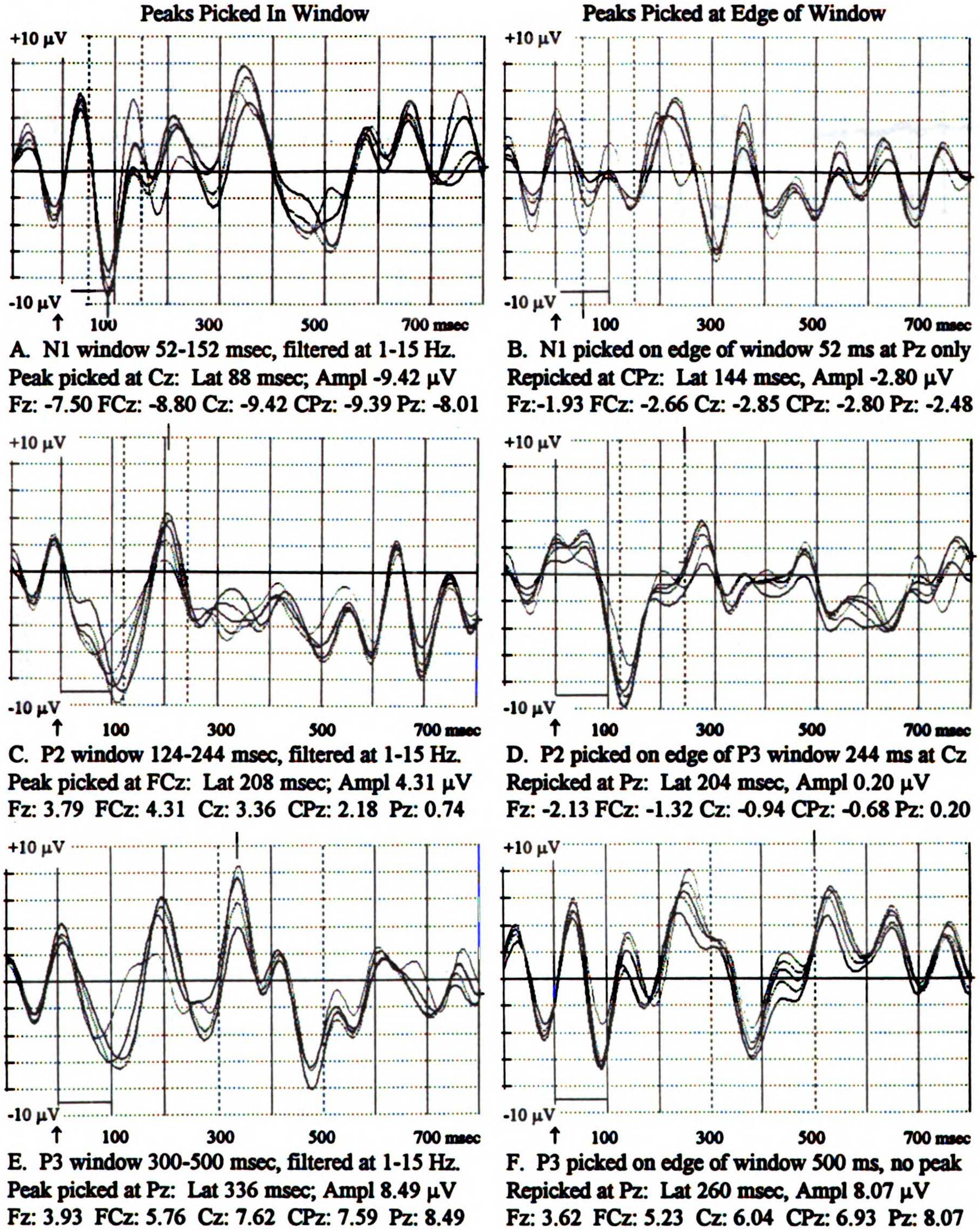
RESULTS

Group

To insure that the Latin square design assignment of subjects effectively counterbalanced the order effect of thirteen consecutive ERP runs and the possible effect of subject fatigue, peak amplitude was measured with a between-measures factor, Group (1, 2, 3, 4, 5) X within-measures factors, Stimulus (1500 Hz, novel) X Task (thinking, reading) X Session (day 1, day 2) X Time (1, 2) ANOVA for the oddball paradigm and a Group X Session X Time X Condition (1500 Hz target, novel rare) ANOVA for the three stimulus paradigm. The Group factor was not significant in either analysis. Therefore, data was collapsed across group in all subsequent analyses.

Event Related Potentials

The ERPs presented in Figures 3 and 4 are grand averages derived by point-to-point addition of the ERPs of all twenty subjects. The latency and amplitude measures used to describe the grand average ERPs were obtained by the peak picking method described in the Methods section using windows that were derived from examination of the grand averages. This experiment adopts the convention of naming ERP components by their polarity and appearance. Thus, a) P1, also known as P50, refers to the first positive component which occurs in this data set at about 44 msec; b) N1, also known as N100, refers to the negative peak which follows P1 and which occurs around 104 msecs; c) P2, also known as P200, refers to the following positivity which occurs around 224 msec, but is often considerably earlier or later; d) N2 refers to the negative peak occurring around 260 msecs; e) P3 is synonymous with P300, the largest positive peak falling between 252-500 msecs; f) P3a refers to an earlier P3 component that occurs before P300 and after P200; and g) N3 refers to the negative peak following P300,



A. N1 window 52-152 msec, filtered at 1-15 Hz.
Peak picked at Cz: Lat 88 msec; Ampl -9.42 µV
Fz: -7.50 FCz: -8.80 Cz: -9.42 CPz: -9.39 Pz: -8.01

B. N1 picked on edge of window 52 ms at Pz only
Repicked at CPz: Lat 144 msec, Ampl -2.80 µV
Fz:-1.93 FCz: -2.66 Cz: -2.85 CPz: -2.80 Pz: -2.48

C. P2 window 124-244 msec, filtered at 1-15 Hz.
Peak picked at FCz: Lat 208 msec; Ampl 4.31 µV
Fz: 3.79 FCz: 4.31 Cz: 3.36 CPz: 2.18 Pz: 0.74

D. P2 picked on edge of P3 window 244 ms at Cz
Repicked at Pz: Lat 204 msec, Ampl 0.20 µV
Fz: -2.13 FCz: -1.32 Cz: -0.94 CPz: -0.68 Pz: 0.20

E. P3 window 300-500 msec, filtered at 1-15 Hz.
Peak picked at Pz: Lat 336 msec; Ampl 8.49 µV
Fz: 3.93 FCz: 5.76 Cz: 7.62 CPz: 7.59 Pz: 8.49

F. P3 picked on edge of window 500 ms, no peak
Repicked at Pz: Lat 260 msec, Ampl 8.07 µV
Fz: 3.62 FCz: 5.23 Cz: 6.04 CPz: 6.93 Pz: 8.07

Figure 3. Illustrates the peak picking windows for N1, P2, and P3 ERP components. Left hand plots show examples of peaks correctly picked by computer, right hand plots show computer picked peaks which needed correction. In this and all following ERP figures, these standards have been adopted: ERPs are plotted on a ±10 µV scale with positive up; the horizontal axis is scaled in msec starting at -100 and going to +800 msec; stimulus onset is marked with an ↑ at zero and stimulus duration is marked by a 100 msec horizontal bar thereafter; each ERP shows Fz, FCz, Cz, CPz and Pz overplotted. Window edges denoted by vertical dashed lines. Computer picked peaks denoted by vertical line entering plot from top or bottom. All ERPs have been filtered from 1-15 Hz and corrected for eye movement artifacts.

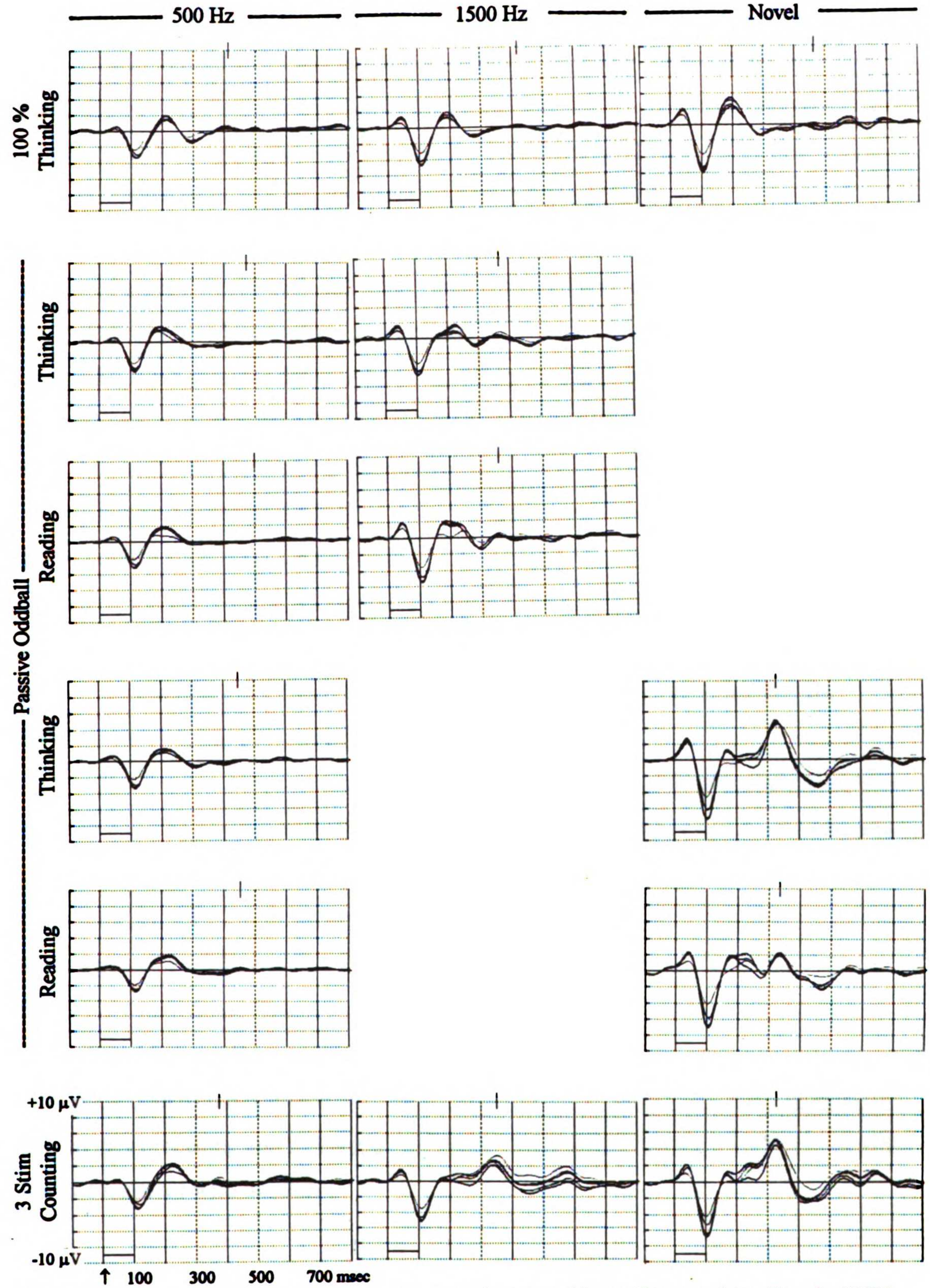


Figure 4. Grand Average ERPs for Session 1 averaged across subject and across time. Row 1: 100% Control conditions. Rows 2-5: Passive Oddball Thinking and Reading conditions. Row 6: 3 Stimulus Counting conditions. In each row, Column 1 is 500 Hz, Column 2 is 1500 Hz and Column 3 is Novel.

particularly prominent after novels, which occurs around 450 msecs. N3 is the name used because it follows P3 and also so that it not be mistaken for N400, the negative peak identified by Kutas and Hillyard (1980) which reflects semantic incongruity. Use of amplitude or latency measures to describe the grand average ERPs are for description only, no statistical inferences are meant. All statistics are based on the latency and amplitudes measured from each individual separately. In addition, each run was measured separately for each individual, then collapsed across time, task, or session in the statistical procedures, where appropriate.

Figure 4 presents the grand average ERPs for the three 100% control conditions (forty stimuli in each average) and five experimental conditions collapsed across time (32 stimuli in each rare average) for Session 1.

Figure 5 presents the ERPs for the replication conditions from Session 2. The 100% control conditions are shown in row 1. There are noticeable differences in the prominent P1, N1, P2 and N2 waves. P1 and N1 increase with 500 Hz < 1500 Hz < Novel, P2 to the 500 Hz and 1500 Hz stimuli are equal but the novel P2 increases, the N2 response was slightly different in amplitude from stimulus to stimulus but the difference was not as obvious or as large as in P2.

The Session 2 replication was consistent in every way with only slight amplitude differences. The passive oddball thinking condition is presented in row 2. A comparison of the 500 Hz common and the 1500 Hz rare shows a) an enhanced P1 and N1, b) a differently shaped P2 with latency slightly increased and amplitude slightly decreased, c) a more prominent N2, and d) a P3 that was only discernible by the preceding and following negativities. The passive oddball reading condition in row 3 was similar to the oddball thinking condition in the previous row. The P2 to the 1500 Hz rare was shaped differently than to the common, and the P3 was small, and distinguished primarily by the negativities preceding and following. For both thinking and reading conditions, Session 2 was consistent with Session 1.

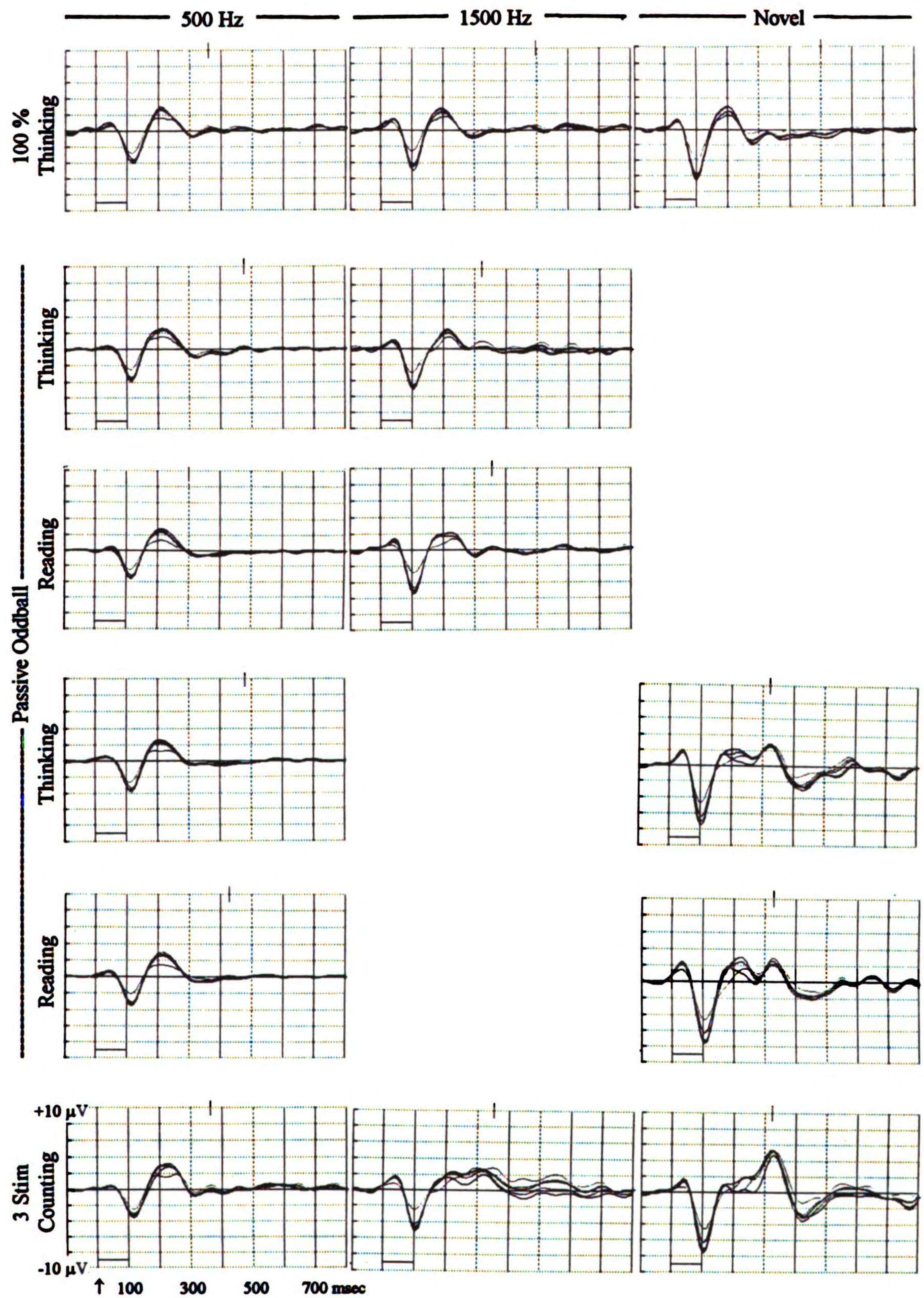


Figure 5. Grand Average ERPs for Session 2.

Row 4 and row 5 on Figure 5 show the passive oddball novel conditions, first thinking and then reading. The novel stimuli show the same enhanced P1 and N1 as the 1500 Hz, but the P2 differences are more dramatic. In the thinking condition in row 4, a) P2 was attenuated, perhaps due to an earlier N2, b) N2 (at Fz) was prominent, c) during the N2 period the other electrodes remain flat, d) P3 was a large peak (4.95 µV, 328 msec) with a FCz maximum, and e) was followed by a negative N3 wave (-3.46µ, 460 msec).

In the reading condition in row 5, a) P2 peaks earliest at Fz (1.91 µV, 180 msec) which then goes negative while the other electrodes peak later (at 2.20 µV, 224 msec), b) there was a small N2 (-0.88 µV, 276 msec) maximum at Fz, c) P3 was smaller than during the thinking condition (2.29 µV, 336 msec) with a Fz maximum, and d) P3 was followed by a negative N3 wave (-2.35 µV, 468 msec) which was not as large or as well defined as it was after the larger P3 during thinking. The waveforms in Session 2 for both thinking and reading conditions are very similar in size, shape, and latency to the P3 in the reading condition in Session 1 (thinking, 2.88 µV, 324 msec; reading, 2.90 µV, 328 msec, both Fz maximum).

The ERPs for the three stimulus paradigm are shown in row 6. The 1500 Hz target ERP looks very similar to the passive oddball novel ERPs except that the P300 to the target stimulus (3.33 µV, 352 msec) was later and parietally maximum. The target ERP in Session 2 does not have as well defined peaks. It appears to have a broad second peak arising from P2 (possibly an early P3a peak) and the parietal P3 peak (2.85 µV, 352 msec) was delayed from the rest of the underlying peak. The three stimulus novel ERP is characterized by a small P2 followed by a P3a (2.26 µV, 244 msec), and a large well defined P300 (5.11 µV, 328 msec) in Session 1 and (5.36 µV, 324 msec) in Session 2. Both target and novel P300s are followed by a negative wave which was steeper and larger to the novel; the target N3 (-1.57 µV, 456 msec), the novel N3 (-2.52 µV, 420 msec) in Session 1, the target N3 (-1.00 µV, 448 msec), and the novel N3 (-3.59 µV, 424 msec) in Session 2.

A comparison of the 500 Hz ERPs in column 1 shows that the only appreciable difference in the wave occurs in the 100% condition which has a prominent N2 that does not appear when the 500 Hz tone was the common condition in either the oddball paradigm or the three stimulus paradigms. A comparison of Session 1 with Session 2 shows that Session 2 has slightly larger amplitude. A comparison of the 1500 Hz ERPs in column 2 shows a) the enhancement of P1 and N1 seen in each of the oddball and in the three stimulus comparisons above appears to be due entirely to stimulus differences since it was not apparent when you compare the 1500 Hz rare tone responses to the 1500 Hz, 100 % condition; b) P2 was slightly changed in shape and latency and, in the 1500 Hz target, was also attenuated; and c) the only obvious P300 was to the 1500 Hz target. A comparison of the novel ERPs in column 3 show a) there was no N1 or P1 enhancement between the 100% common novel and the rare novels; b) P2 was attenuated and earlier; c) N2 was earlier, smaller, and does not include all electrodes; d) the novel P300 was large and robust in all conditions except the 100% condition, where it does not exist; e) the novel P300s (both > 5 μV) in the three stimulus paradigm was larger than the novel oddball P300s (all < 5 μV); and f) there was a prominent negative peak following the novel P300s.

The waveforms in Figure 6 are ERPs from individual subjects. Each condition was averaged across time (32 stimuli) as in the grand averages in the preceding two figures. The individual subjects are the last five subjects run in the experiment and were not chosen to represent any particular peak characteristic but to show some of the differences and similarities present in individual waveforms. Although there was a great deal of individual variation from subject to subject, the N1, P2, and P3 components can be reliably picked by eye for all but one ERP (e.g. the 1500 Hz oddball ERP for Subject 27 was predominantly alpha). In these five subjects, the novel P300 was more prominent than the 1500 Hz P300 in the same paradigm. The novel P300 was more prominent than the 1500 Hz P300 in the same paradigm in eighteen out of twenty subjects (Wilcoxon Signed-Rank Test for Matched Pairs $P < 0.005$ one-tailed).

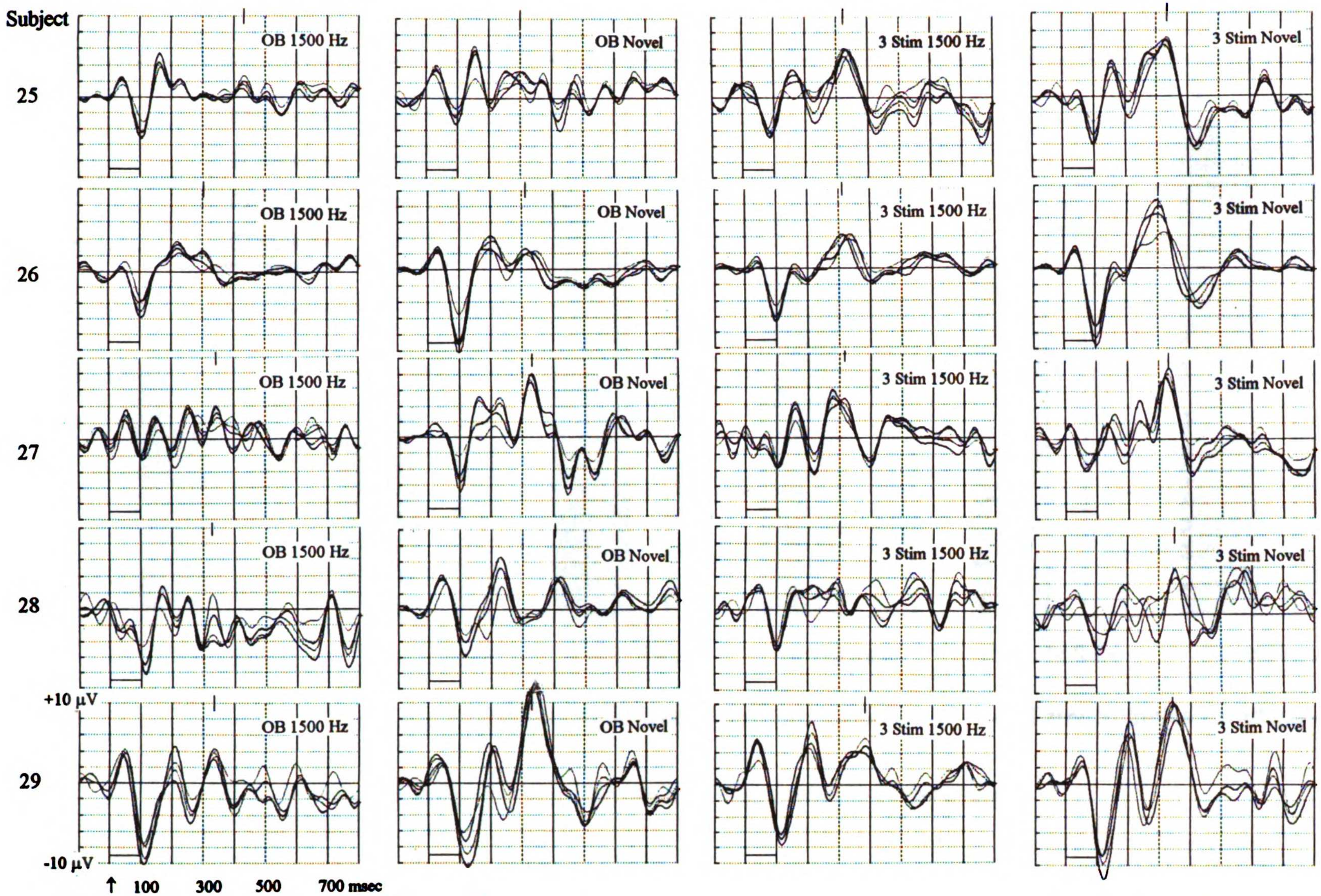


Figure 6. Representative ERPs from five different subjects.

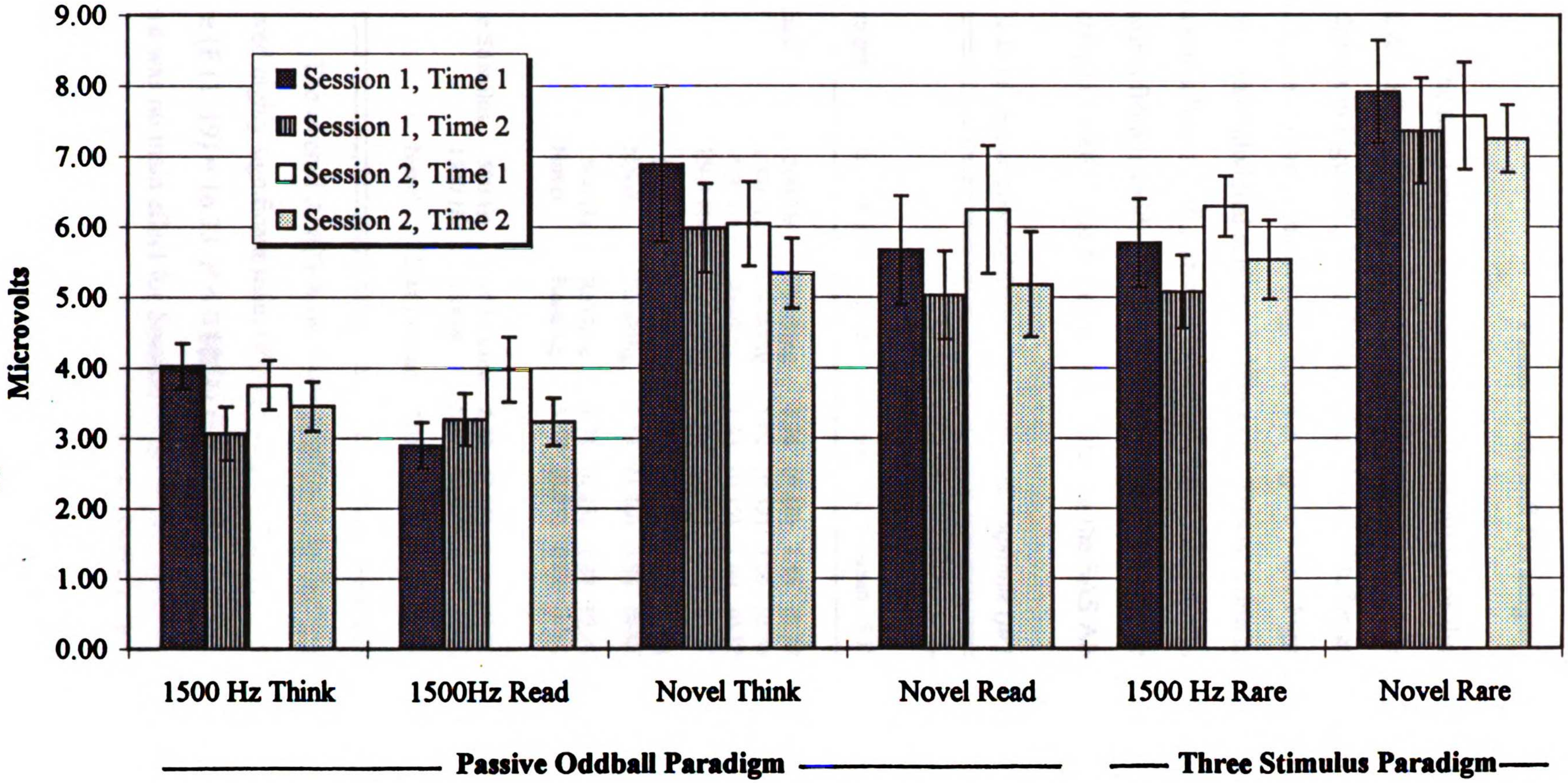


Figure 7. P300 mean peak amplitude with standard error bars for all conditions and both paradigms.

Passive Oddball Paradigm

The mean amplitudes and standard deviations of the P300 component for the passive oddball paradigms are listed in Table 2 and presented graphically for the rare conditions in Figure 7. It can be seen that the amplitudes are considerably higher than they appear in the grand average ERPs in Figure 4 and Figure 5 are more consistent with those of the individual subjects in Figure 6. This was due to the latency variability between subjects. All statistics have been done using quantified peak amplitude measures from individual subjects which were picked by the peak picking program as described in methods and then averaged during the SAS ANOVA process.

Table 2. *Mean and Standard Error of the P300 Peak Amplitude (μV)*

			Session 1				Session 2			
			Time 1		Time 2		Time 1		Time 2	
Paradigm	Stimulus	Task	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
Oddball	500 Hz	Thinking	1.76	(0.18)	1.48	(0.19)	2.00	(0.20)	1.88	(0.34)
	1500 Hz	Thinking	4.02	(0.32)	3.06	(0.38)	3.75	(0.35)	3.45	(0.35)
	500 Hz	Reading	1.43	(0.15)	1.60	(0.22)	1.25	(0.19)	1.07	(0.20)
	1500 Hz	Reading	2.89	(0.33)	3.26	(0.37)	3.97	(0.46)	3.23	(0.34)
	500 Hz	Thinking	1.71	(0.21)	2.00	(0.20)	1.70	(0.25)	1.71	(0.20)
	Novel	Thinking	6.89	(1.10)	5.98	(0.63)	6.04	(0.60)	5.34	(0.52)
	500 Hz	Reading	1.71	(0.23)	1.49	(0.24)	1.66	(0.21)	1.61	(0.19)
	Novel	Reading	5.67	(0.77)	5.03	(0.63)	6.24	(0.91)	5.18	(0.75)
Three Stimulus	500 Hz	Don't Count	2.53	(0.26)	2.47	(0.39)	2.83	(0.30)	2.63	(0.29)
	1500 Hz	Count	5.77	(0.63)	5.08	(0.52)	6.29	(0.43)	5.53	(0.57)
	Novel	Don't Count	7.91	(0.73)	7.36	(0.75)	7.57	(0.76)	7.25	(0.48)

The overall ANOVA on P300 amplitude for the passive oddball paradigm showed highly significant main effects for Stimulus (F (1, 19) = 22.92, $P < 0.0001$), Time (F (1, 19) = 16.33, $P < 0.0007$) and Condition (F (1, 19) = 135.02, $P < 0.0001$). There was no main effect for Session or for Task. There were significant interactions between Paradigm and Condition (F (1, 19) = 21.45, $P < 0.0002$) and Time and Condition (F (1, 19) = 10.57, $P < 0.005$). The Stimulus effect can be easily seen: 500

Hz (mean, 1.63 μV) <1500 Hz (mean, 3.45 μV) < Novel (mean, 5.80 μV). As hypothesized, the amplitude of the P300 to the novel stimulus was larger than that of the 1500 Hz stimulus (68% larger) and, since the common response did not vary in amplitude, the difference between common and rare was more robust, increasing from 123% larger for 1500 Hz to 256% larger for novel. There was a small but consistent difference (1 > 2) between time 1 and time 2 in all of the rare conditions (1500 Hz and novel) except one, and no consistent difference in the common conditions (500 Hz). The differences between the common and the rare apparent in Figures 4 and 5 are consistent with the P300 literature and confirmed by these statistics. Based on these results, the common condition was excluded from the other oddball analyses.

The ANOVA was rerun, without the common condition, resulting in a significant main effect for Stimulus ($F (1, 19) = 22.98$, $P < 0.0001$) and Time ($F (1, 19) = 15.25$, $P < 0.0010$). There were no significant interactions. The difference between time 1 and time 2 averaged across conditions was 0.62 μV with time 1 > time 2. This decline in amplitude was consistent across all conditions except one, the 1500 Hz reading condition. The amount of decline did not differ between the stimuli or between the thinking or reading conditions. Based on these results, the grand averages which were presented in Figures 4 and 5 were collapsed across time in order to have a larger number of responses in the average. The overall ANOVA on P300 latency for the passive oddball paradigms was significant for the main effect of Stimulus ($F (1, 19) = 27.03$, $P < 0.0001$). There were no other main effects and no interactions. Table 3 lists the mean latencies and standard errors of all conditions in both the passive oddball paradigm and the three stimulus paradigm. As hypothesized, the latency of the P300 to the novel stimuli was significantly shorter (mean latency 343 msec) than the P300 to the 1500 Hz stimuli (mean latency 381 msec).

The overall ANOVA of the P300 topography for the passive oddball paradigms produced no significant main effects. The mean normalized amplitude of the midline electrodes are in fact relatively flat (1500 Hz: Fz -0.12, FCz 0.03, Cz 0.02, CPz 0.02, Pz 0.05; and novel: Fz -0.03, FCz 0.02, Cz -0.03, CPz 0.01, Pz 0.04).

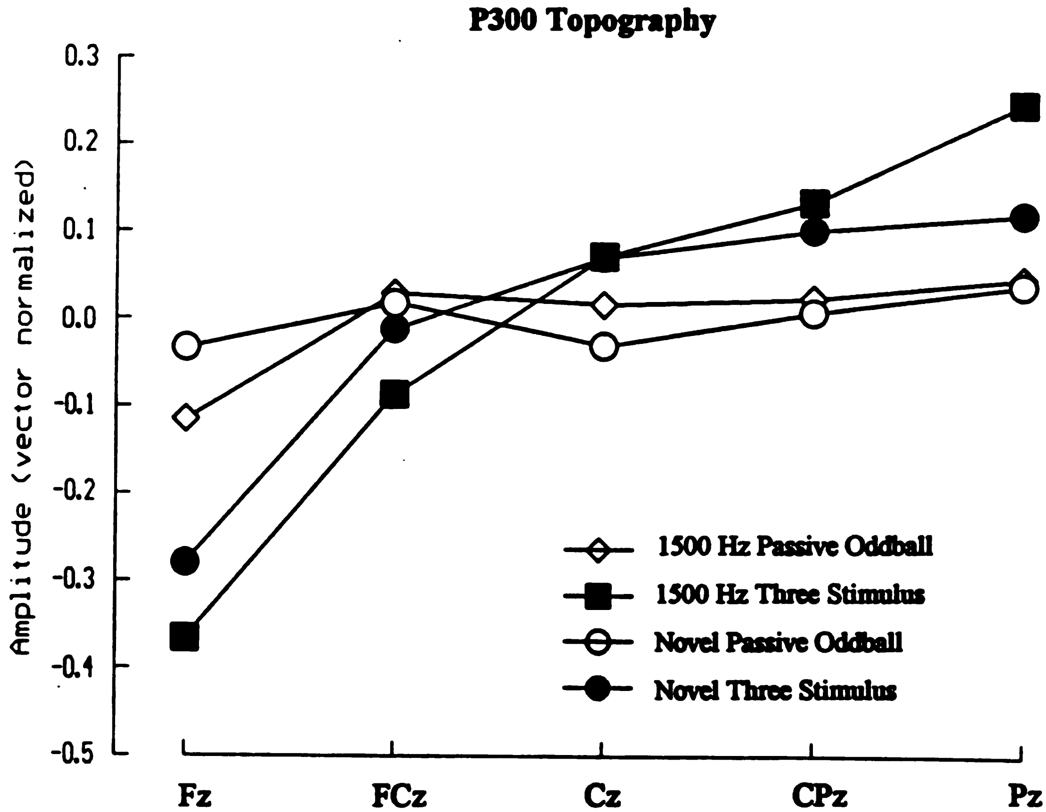


Figure 8. Normalized mean amplitude of P300 measured at five midline electrodes (Fz, FCz, Cz, CPz, Pz) for each stimulus and each paradigm (1500 Hz passive oddball, 1500 Hz target three stimulus, novel passive oddball and novel three stimulus). The Y-axis is in arbitrary units resulting from the vector normalization procedure described in Methods.

These are illustrated graphically in Figure 8, (represented by the lines with open symbols) which plots the average normalized amplitude of P300 collapsed across time and session for both paradigms and both stimuli. This does not support a fronto-central maximum as reported in many, but not all, previous studies.

Table 3. *Mean and Standard Error of the P300 Latency (msec)*

			Session 1				Session 2			
			Time 1		Time 2		Time 1		Time 2	
Paradigm	Stimulus	Task	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
Oddball	500 Hz	Thinking	402	(15.3)	397	(14.4)	423	(15.1)	406	(15.4)
	1500 Hz	Thinking	369	(10.9)	381	(11.5)	391	(12.8)	370	(12.7)
	500 Hz	Reading	381	(17.1)	394	(16.0)	401	(17.8)	402	(15.1)
	1500 Hz	Reading	384	(12.8)	389	(14.9)	378	(12.5)	383	(12.8)
	500 Hz	Thinking	403	(14.8)	394	(14.8)	403	(16.7)	411	(15.2)
	Novel	Thinking	343	(11.9)	332	(8.7)	343	(8.7)	343	(8.7)
	500 Hz	Reading	419	(15.2)	407	(17.7)	369	(15.0)	417	(16.0)
	Novel	Reading	342	(8.0)	351	(8.5)	342	(8.1)	348	(10.5)
Three Stimulus	500 Hz	Don't Count	396	(11.5)	393	(14.2)	390	(15.1)	401	(13.4)
	1500 Hz	Count	355	(10.3)	347	(10.1)	330	(10.5)	375	(14.2)
	Novel	Don't Count	332	(6.3)	324	(7.2)	332	(6.6)	329	(4.1)

Three Stimulus Paradigm

The overall ANOVA on P300 peak amplitude for the three stimulus paradigm was significant for the main effect of Stimulus ($F(2, 38) = 72.99$, $P < 0.0001$, $\varepsilon = 0.8587$). Planned contrasts confirm that P300 in the 500 Hz common condition (2.62μV) was significantly smaller ($P < 0.001$) than in the 1500 Hz target condition (5.67 μV) and also ($P < 0.0001$) than in the rare novel condition (7.52 μV). Means and standard errors are presented in Table 2. As in the oddball paradigm, the amplitude of the ERP in the 500 Hz common condition was quite small and was not affected by time. These results are also consistent with previous reports and, thus, the common condition was not considered in further analyses.

Figure 7 illustrates the mean P300 peak amplitude for the 1500 Hz rare target and the rare novel conditions in the three stimulus paradigm. Planned contrasts confirmed that the P300 to the 1500 Hz target (5.67 μV) was significantly less than to the rare novel (7.52 μV, $P < 0.001$).

The overall ANOVA on P300 latency for the three stimulus paradigm was significant for the main effect of Stimulus ($F (1, 19) = 21.09$, $P < 0.0002$), the 2-way interaction Session X Time ($F (1, 19) = 7.23$, $P < 0.02$) and Time X Stimulus ($F (1, 19) = 6.60$, $P < 0.02$) and the 3-way interaction Session X Time X Stimulus ($F (1, 19) = 4.76$, $P < 0.05$). The mean latencies and standard errors are listed in Table 3 and presented graphically in Figure 9. The mean latency of the 1500 Hz target P300 (352 msec) was 23 msec longer than the mean latency of the novel rare non-target P300 (329 msec). The difference in latency produced by the two stimuli was smaller in the three stimulus paradigm than it was in the oddball paradigms (23 msec versus 38 msec). However, both P300 latencies in the three stimulus paradigm were earlier than the latencies for the corresponding stimulus in the oddball paradigms (which were 1500 Hz, three stimulus 352 msec < oddball 381 msec; novel, three stimulus 329 msec < oddball 343 msec). All of the interactions can be attributed to the extremely early latency in the 1500 Hz target P300 Session 2, Time 1 and the extremely prolonged latency Session 2, Time 2. These interactions were not predicted and are difficult to interpret. A number of factors may have contributed and will be discussed later.

The overall ANOVA on P300 topography for the three stimulus paradigm was significant for the main effect of Electrode ($F (4, 76 = 72.99$, $P < 0.0001$, $\varepsilon = 0.4951$). There were no significant interactions. This would indicate that the topography of the target and novel were the same. It was hypothesized that the target would be parietally maximum while the novel would be fronto-central maximum. As can be seen in Figure 8 (represented by the lines with the closed symbols), both are parietally maximum (normalized mean amplitude of 0.18) with a frontal minimum (normalized mean amplitude of -0.32). The frontal minimum, however, was the characteristic which most differentiates the three stimulus P300s from the oddball P300s.

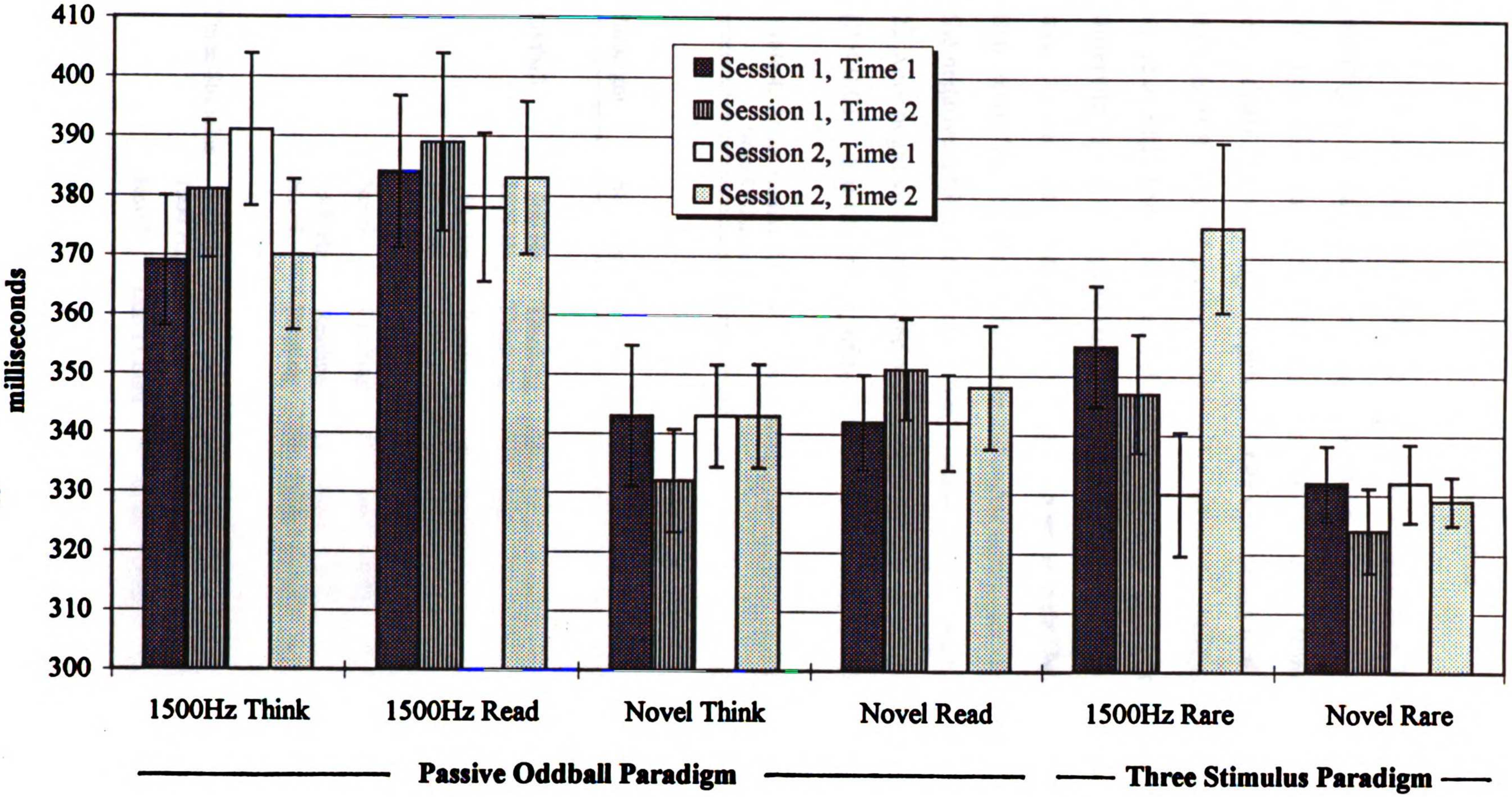


Figure 9. P300 mean peak latency with standard error bars for all conditions and both paradigms.

Habituation

The significant amplitude difference between time 1 and time 2 in the oddball paradigms, in many accounts, would be attributed to habituation. However, it was not enough to look at raw amplitude, since this may result from averaging one or two individuals with very high amplitude ERPs with others with very small amplitude ERPs. T-tests of Related Measures were conducted on the standardized amplitude difference score averaged across subjects for each condition. This tested whether the average difference score of a given condition was significantly larger than the difference which might occur by chance alone or, in other words, if the difference was significantly greater than zero. Table 4 shows the mean difference scores and the results of the t-tests. Only the negative difference scores reflect a smaller time 2 score. It can be seen that 16 out of 22 were negative but only one score (the 1500 Hz thinking condition) was significant ($P < 0.01$). For that score, fifteen out of twenty subjects had a smaller ERP time 2.

Table 4. *Mean Standard Error and Probability of the P300 Peak Amplitude Difference Score (standard units)*

			Session 1				Session 2			
Paradigm	Stimulus	Task	N*	Mean	S.E.	p	N*	Mean	S.E.	p
Oddball	500 Hz	Thinking	15	-0.13	(0.07)	n.s.	13	-0.10	(0.07)	n.s.
	1500 Hz	Thinking	15	-0.25	(0.09)	<0.01	11	-0.07	(0.08)	n.s.
	500 Hz	Reading	9	0.00	(0.13)	n.s.	10	-0.15	(0.15)	n.s.
	1500 Hz	Reading	6	0.10	(0.09)	n.s.	11	-0.15	(0.10)	n.s.
	500 Hz	Thinking	7	0.11	(0.08)	n.s.	10	0.05	(0.11)	n.s.
	Novel	Thinking	13	0.03	(0.09)	n.s.	16	-0.10	(0.06)	n.s.
	500 Hz	Reading	11	-0.10	(0.10)	n.s.	11	-0.02	(0.13)	n.s.
	Novel	Reading	12	-0.04	(0.10)	n.s.	11	-0.15	(0.09)	n.s.
Three Stimulus	500 Hz	Don't Count	11	-0.08	(0.10)	n.s.	10	-0.05	(0.07)	n.s.
	1500 Hz	Count	11	-0.07	(0.08)	n.s.	17	-0.13	(0.07)	n.s.
	Novel	Don't Count	9	-0.05	(0.06)	n.s.	11	0.01	(0.06)	n.s.

* Number of subjects (N) out of 20 demonstrating Time 2 < Time 1.

Only 250 out of 440 cells (just slightly more than half) in the Latin square design had a smaller time 2 response. This alone would indicate that, if habituation occurs, it was not a robust phenomenon. That there was no significant habituation was not too surprising because of the nature of the study. Subjects were required to sit for several hours, thirteen runs were recorded over that time. However, because each condition was assigned by Latin square design to start positions one through five, it was possible to look at only the ERPs of a condition when it was run at start time 1. Each condition was assigned to start time 1 twice. The Ampdif scores were reaveraged by group and then t-tests of related measures were done on those averages which were assigned to start time 1 to see if any significant difference occurred because of start time. There were ten possible cells (with four subjects in each) in the Latin square design with start time 1 (see Table 1 in Methods). Only one of the ten was significantly different from zero. All together, five of a possible fifty cells were significantly different from zero in the negative direction (i.e. had a smaller time 2 average). Of these, one was start time 1, one was start time 2, two were start time 3, and one was start time 4. There was, therefore, no consistent evidence for habituation of P300 in either paradigm.

Oddball Versus Three Stimulus

The three-way ANOVA of peak amplitude data from the two oddball paradigms (averaged across Task and Session) and the three stimulus paradigm (averaged across Session) showed a significant effect for Paradigm ($F(1, 19) = 32.86$, $P < 0.0001$), for Stimulus ($F(1, 19) = 58.34$, $P < 0.0001$), and for Time ($F(1, 19) = 11.18$, $P < 0.004$) with no significant interactions. Figure 10 graphically presents the means and standard errors of the oddball versus three stimulus conditions collapsed across Session and Task. The main effect for Paradigm can be seen in the 43% increase in the average three stimulus P300 response (6.6μV) versus the passive oddball average P300 response (4.63μV). In addition, the significant main effect for Stimulus can be seen in the 46% increase in the average P300 response to the novel stimulus (6.66μV) versus 1500 Hz P300 response which was 46% greater than the 1500 Hz average P300 response

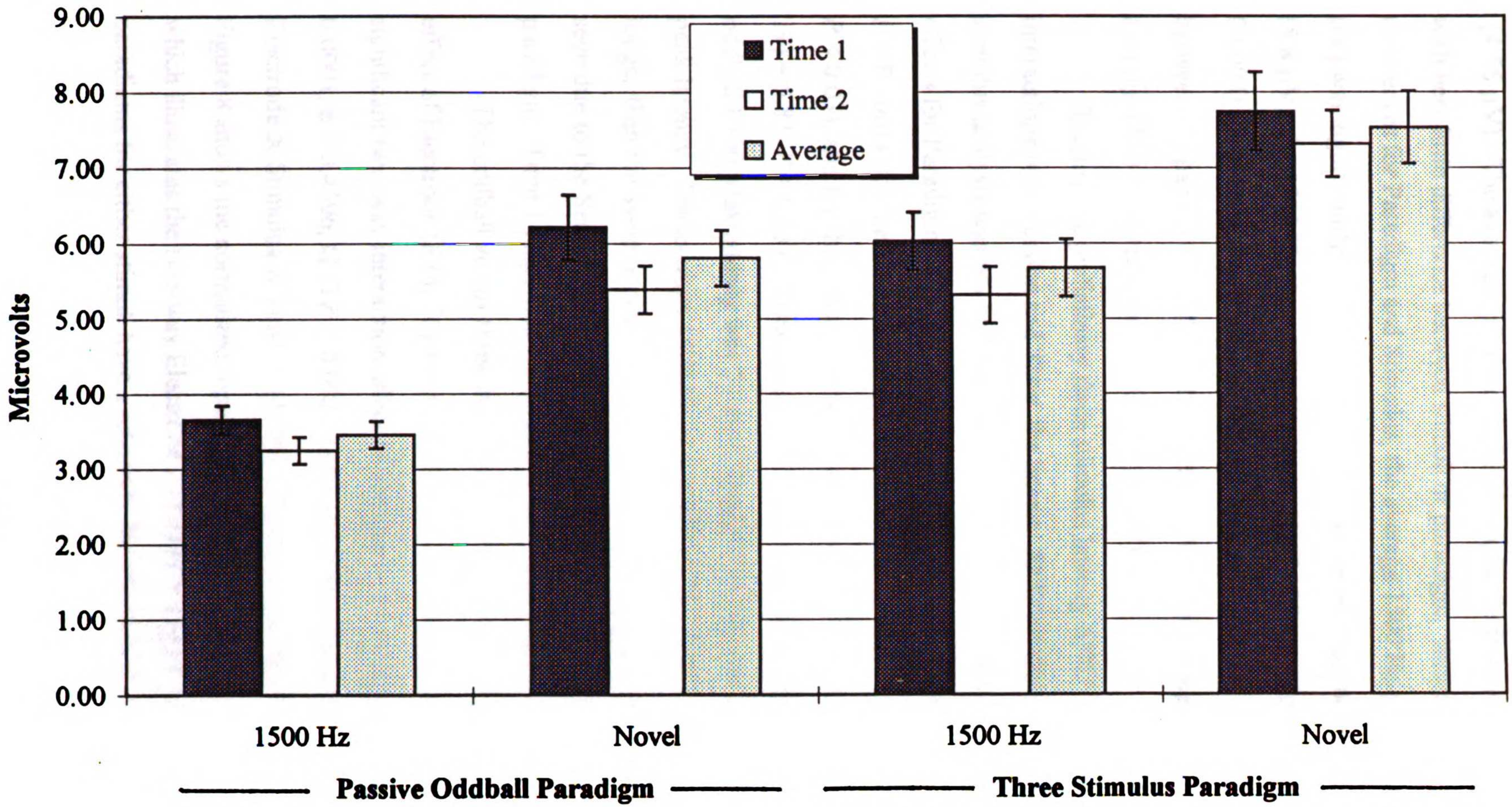
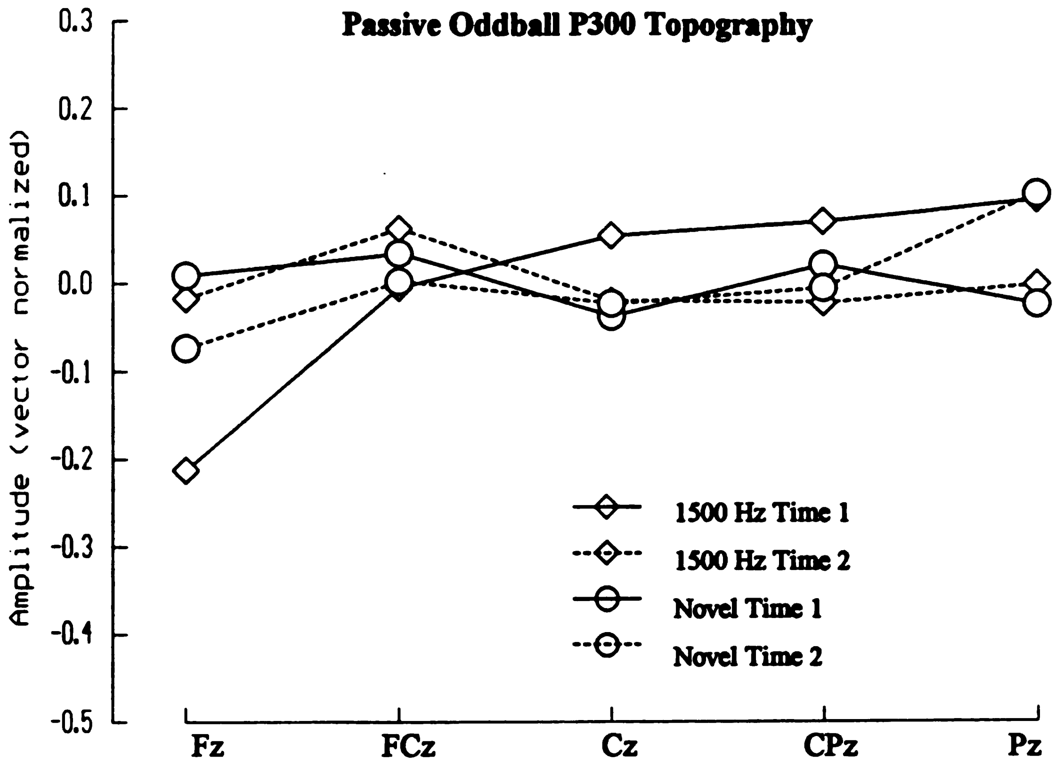


Figure 10. P300 mean peak amplitude with standard error bars for both paradigms. Time 1 and Time 2 and their average collapsed across session and task.

(4.56 μV). The average difference in P300 amplitude from time 1 to time 2 was 0.6μV with very little difference between stimuli or paradigm. Besides the overall significant differences for Paradigm and Stimulus, the average 1500 Hz passive oddball P300 (3.46 μV) was significantly smaller (P < 0.0001) than the average novel passive oddball P300 (5.8 μV), the 1500 Hz three stimulus target (5.67 μV) was significantly smaller (P < 0.0004) than the average novel three stimulus P300 (7.53 μV). The average difference between the passive oddball novel P300 (5.8 μV) was not significantly different than the average 1500 Hz three stimulus P300 (5.67 μV).

Because the preliminary three stimulus latency ANOVA showed significant interactions with Session and Time, the latency ANOVA for the oddball versus three stimulus analysis was not collapsed across Session. The ANOVA showed significant effects for Paradigm (F (1, 19) = 45.07, $P < 0.0001$), for Stimulus (F (1, 19) = 24.27, $P < 0.0001$), for the 3-way interaction Stimulus X Session X Time (F (1, 19) = 5.79, $P < 0.03$), and for the 4-way interaction Paradigm X Stimulus X Session X Time (F (1, 19) = 5.81, $P < 0.03$). These results are illustrated graphically in Figure 9. The average oddball P300 peak latency was 21 msec longer than the average three stimulus P300 peak latency. The average 1500 Hz stimulus P300 latency (366 msec) was 30 msec longer than the average novel stimulus latency (336 msec). All the interactions can be seen due to the Session 2 target ERPs which were described for the three stimulus paradigm. Time 1 responses are unusually fast, time 2 responses are unusually slow.

The oddball versus three stimulus topography ANOVA shows a significant main effect of Electrode (F (4, 76) = 8.42, $P < 0.0001$, ε = 0.4428, G-G $P < 0.002$), a significant two-way interaction effect of Electrode X Paradigm (F (4, 76) = 8.71, $P < 0.0001$, ε = 0.4596, G-G $P < 0.002$), and a significant three-way interaction effect of Electrode X Stimulus X Time (F (4, 76) = 5.14, $P < 0.001$, ε = 0.5170, G-G $P < 0.01$). Figure 8 shows the normalized topography of both paradigms collapsed across time which illustrates the two-way Electrode X Paradigm interaction. The passive oddball paradigms for either stimuli have a relatively flat topography whereas the three stimulus paradigm has a Fz minimum, Pz maximum topography for both stimuli.



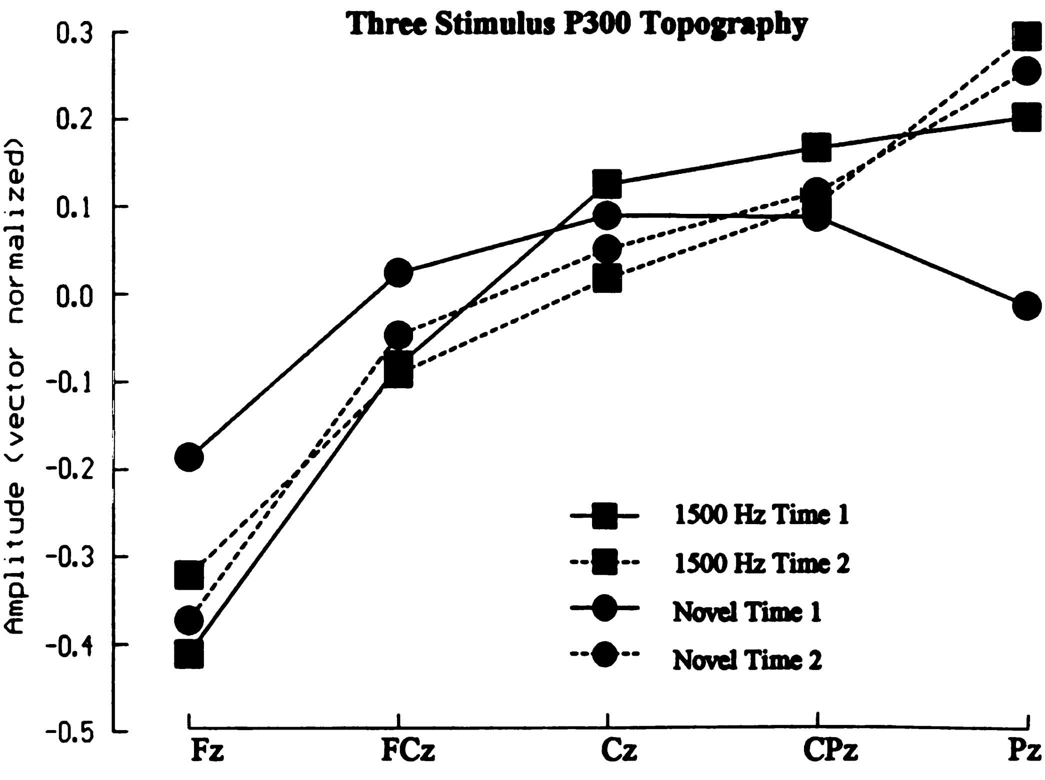


Figure 11. Normalized mean amplitude of P300 measured at five midline electrodes for each paradigm and stimulus collapsed across session, but not time.

Figure 11 shows the normalized topography of both paradigms collapsed across session but not collapsed across time. This illustrates the three-way interaction Electrode X Stimulus X Time. The interaction can be located at the electrodes CPz and Pz in the novel stimuli. At time 1, CPz was more positive than Pz. At time 2, Pz was more positive than CPz. All of the other electrode amplitudes are similar across times. Both figures illustrate the basically flat nature of the passive oddball paradigm for either stimulus and the prominent Fz minimum, Pz maximum topography of the three stimulus paradigm. The novel stimulus in the three stimulus paradigm time 1 was not parietal maximum, but it was not frontal-central, either. It was hypothesized that the topography of the novel stimuli would be the same across paradigms. This was not confirmed.

CHAPTER 4

DISCUSSION

The main objective of this investigation was to compare the P300 components produced by the passive oddball paradigm and the P300s produced by the three stimulus novel paradigm. The amplitude of the P300 response to the novel stimulus was larger in all conditions in comparison to the 1500 Hz stimulus. The latency of the P300 response to the novel stimulus was a) earlier in the passive oddball paradigm than the P300 produced by the 1500 Hz tone in the passive oddball paradigm, b) earlier in the three stimulus paradigm than the P300 produced by the 1500 Hz target, and c) equal in the passive paradigm to the P300 produced by the 1500 Hz target in the three stimulus novel paradigm. Although P300 declined slightly in amplitude from time one to time two in each condition in all paradigms, there was little evidence of substantial habituation in any of the conditions. The amplitude was still large enough to be easily identified. The topography of the P300 in the passive oddball paradigm was relatively flat across all midline electrodes for both the novel and the 1500 Hz stimulus. The topography of both 1500 Hz target and novel P300 in the three stimulus paradigm were maximum parietally. Results obtained clearly show that the P300 produced by the novel stimuli used in this study produce a robust P300 component regardless of the paradigm employed. A direct consequence of this investigation may be a more effective way of eliciting P300 in clinical populations who can not cooperate.

Previous attempts to find a robust passive paradigm have included using stimuli which stand out because of their position in a train of stimuli, or because they are very discrepant from the common, or because they are very different in intensity (Ford and Pfefferbaum, 1991; Polich, 1987b; Polich, 1989a; Pfefferbaum, Ford, White, & Roth, 1989; Squires et al., 1989). In the auditory modality, for instance, stimuli which were either louder or softer than the background stimuli were used. In some paradigms, loud startling noise bursts were used. In the somatosensory modality, shock has been used in contrast to tactile stimulation (Yamaguchi & Knight, 1989a, 1989b). In the visual modality, contrasting bright and dim light stimuli have been used (Courchesne et al., 1978). Other studies have used meaningful stimuli such as a dog bark (Knight, 1984), the subject's name, or environmental noises such as bird and animal calls (Friedman et al., 1993). Often these stimuli have been of relatively long duration (up to 400 msec), thus overlapping the time of the response.

This experiment used novel sounds, each different, which were the same intensity and duration as the background stimuli and which did not overlap the response. The exact order of the stimuli was set in advance and could be repeated for all subjects. Other experiments have delivered bits of random sounds from an audio tape (Knight et al., 1989; Fein et al., 1995; Grillon et al., 1991) which resulted in different sequences being presented to each subject.

The novel stimuli produced a response that was equally robust under several conditions, a) while subjects were doing a thinking task, b) while subjects were reading, and c) while subjects were counting a different stimulus. This suggests that, in addition to laboratory settings, such stimuli may be preferable for use in clinical populations where subjects can be physically and/or cognitively impaired and, thus, less able to comply with task instructions.

The P3a has generally been defined as fronto-central. While in most published studies the amplitude is central maximum, in reality the amplitude is nearly equipotential across the entire midline. Comparison of topography of the P300s in the passive oddball and the three stimulus oddball shows that the passive P300, often called P3a, has a very different topography than the attended P300 in the three stimulus paradigm. Amplitude of P300 to both the novel stimulus and the 1500 Hz stimulus in the passive oddball paradigm was relatively flat across the midline. In contrast, in the attended three stimulus paradigm, the amplitude of the P300, both to target and novel stimuli, increased from frontal to parietal. This topography is most often described as parietal because it is parietal maximum. When topography is plotted using normalized amplitude, the direction of the amplitude differences can be evaluated without complication of differences in the actual amplitude. In plots of the three stimulus topography, two things are clear, a) there is a prominent parietal maximum, and b) there is a frontal minimum. In the passive paradigm, neither is so.

The novel stimuli used in this paradigm produced a robust P300 in both the passive oddball paradigm and the three stimulus paradigm. The 1500 Hz stimulus did not. These findings are consistent with previous studies reported in the literature. Although the rare tones in the N. Squires et al. (1975) study produced a robust P3a, only individual subject's data was shown and no grand averages were made as is the common practice today. Data analyses relied on PCA for verification. Although mean amplitudes were not given in the N. Squires et al. report, they were plotted and can be estimated. From the plots, it can be seen that the unattended rare tone P300 was under 5 μV. Approximate values were Fz 4 μV $<$ Cz 5 μV $>$ Pz 3 μV in the ignore condition and Fz 4 μV $<$ Cz 7 μV $>$ Pz 6 μV in the count condition. Mean P3b amplitude in the count condition was in the 8 to 12 μV range (Fz $<$ Cz $<$ Pz). Mean peak amplitude in the present study for the 1500 Hz tone ranged from 3 to 4 μV in the passive conditions and 5 to 6 μV in the three stimulus condition. While the Courchesne et al. (1975) study had much greater amplitude P3 responses, the study was in the visual modality which typically produces a higher amplitude response than the auditory modality. A three stimulus paradigm in the auditory modality produced P300 responses which are comparable with the responses in the present study. Grillon, Courchesne, Ameli, Elmasian, and Braff (1990) plotted mean P3 amplitude 8 to 10 μV (700 Hz rare deviant stimulus), 12 to 16 μV (rare novel stimuli) and 5 to 10 μV (1600 Hz target). This last condition is directly comparable to the 1500 Hz target in the present study and, although larger, it is in the same range and can most likely be accounted for by stimulus or data collection differences.

This study produced a consistent difference in amplitude from time 1 to time 2. However, the average decline was only 0.62 μV and there were no differences between either stimuli or paradigms. Although amplitude decline from one run to another is usually considered to reflect habituation, it is questionable whether this decline reflects a significant habituation effect. When individual subjects' data is taken into consideration, only little over half of the subjects in any one condition showed an amplitude decline. This would seem to indicate that habituation was not a general phenomenon across all subjects. It is possible that the lack of amplitude decline in some subjects was a result of the Latin square design which assigned subjects to conditions. However, when the difference scores of the subjects who had been assigned to a given condition in start time one were analyzed, there was still no evidence of habituation. Given the facts that the amplitude decline was less than 1 µV and that it was the same across all conditions, any habituation effect has to be considered of little consequence.

Latency of the P300 to novel stimuli was significantly earlier than the latency of the P300 to the 1500 Hz stimulus, as was the latency of the three stimulus paradigm significantly earlier than the passive oddball paradigm. These latencies were all > 300 msec which is considerably later than the Squires et al. (1975) range. This was a function of the peak windows used in this investigation. In order to not overlap with P2, the P3 window was picked from 300-500 msec with the window extended as early as 252 msec if a peak was picked on its following slope. There were instances where an earlier P3 peak occurred, but it was smaller. In an effort to be consistent, only one peak was picked within the same window for all conditions. Recent studies have handled this differently. No consistent method has been adopted. PCA, which was widely used in the late 70's and early 80's, has been shown to be weak in exactly the area which this problem occurs, overlapping components. The latencies in this study are similar to those in many studies in the current literature.

There was a significant three-way (Stimulus X Session X Time) and four-way (Paradigm X Stimulus X Session X Time) interaction which was the result of a very early P300 to the 1500 Hz target Session Two, Time One and very delayed latency Time Two. P300 to the target in the three stimulus paradigm is often variable (Fein & Turetsky, 1989) possibly due to subjects using different stimulus selection strategies. In this study, subjects reported having great difficulty in staying alert during the three stimulus paradigm. It was also the condition which caused the most difficulty in peak picking with peaks falling on the edges many more times than for other conditions. All of these factors probably contributed to these interactions.

There were no significant effects for task. This would indicate that reading and listening were equally as effective in controlling subjects attention. It is difficult to prove definitively whether a subject is not attending to stimuli. One indication that they were effective is that both tasks suppressed the ERP response as compared to the three stimulus paradigm. Both tasks have positive and negative aspects. If reading is employed as a control, eye-movement correction must be used. This adds another step to data processing, but this function can be automated to some extent. There are many clinical populations in which a reading control cannot be used.

To this point, the primary hypotheses regarding amplitude and latency have been confirmed. P300 amplitude is significantly larger and earlier to the novel stimulus. The hypothesis that there would be less habituation to the novel stimulus was not confirmed. Fast habituation within the first few single trials was not analyzed, however. This is an area for further analyses.

Regarding the hypothesis about topography, it was hypothesized that the topography of both stimuli in the passive oddball paradigm would be fronto-central maximum and it would be similar. The topography was similar for both stimuli but, rather than fronto-central, it would be more accurate to say it was equipotential across the midline. There was relatively little difference in mean amplitude at any of the electrode locations. This appears to differ from the Squires et al. (1975) results. However, a number of differences exist. In the Squires et al. investigation, only individual subjects' data was looked at and no eye-movement corrections were done, even though subjects were reading. It should also be noted that in the topography plots of mean amplitude, the distribution is central maximum and there is only a 1 μV difference between electrode sites.

It was also hypothesized that the topography of the novel stimulus in the three stimulus paradigm would be different than the topography of the 1500 Hz target stimulus. It was expected that the target stimulus would produce the usual parietal maximum P300 and that the rare novel stimulus would produce a central maximum

P300. This was not confirmed. Instead, the P300 topography to the novel stimulus was parietal maximum and looked very similar to the target P300. Topography of the novel stimulus in Session One was central maximum. This has been noted in several other three stimulus paradigms. However, it has never been illustrated or quantified. In reexamining data from the present study and the investigations reviewed earlier, it became very clear that, although all were central maximum most had a frontal minimum. In fact, it is this characteristic which stands out. This frontal minimum characteristic seems to be present as a result of attending to the stimuli. This result was perhaps the most surprising of the investigation.

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APPENDIX A

100% Novel Stimulus List

	Click			Novel		
Click Onset	Patch #	Key	Stim Onset	Patch #	Key	Description
0:01.52	47	G1	0:01.62	01	Db5	Acoustic Piano 1
0:03.07	47	G1	0:03.17	07	Db3	Electric Piano 4
0:04.64	47	G1	0:04.74	65	C3	Acoustic Bass 1
0:06.18	47	G1	0:06.28	22	Db3	Clavi 3
0:07.78	47	G1	0:07.88	16	C2	Accordian
0:09.35	47	G1	0:09.45	37	C2	Soundtrack
0:10.79	47	G1	0:10.89	30	Db5	Synthesized Bass 1
0:12.32	47	G1	0:12.42	39	Db4	Warm Bell
0:13.91	47	G1	0:14.01	79	B3	Sax 1
0:15.50	47	G1	0:15.60	15	Db5	Pipe Organ 3
0:17.08	47	G1	0:17.18	87	C3	Bassoon
0:18.50	47	G1	0:18.60	44	Db5	Echo Pan
0:19.98	47	G1	0:20.08	94	C2	French Horn 2
0:21.39	47	G1	0:21.49	42	Db5	Ice Rain
0:22.98	47	G1	0:23.08	51	C1	String Section 3
0:24.50	47	G1	0:24.60	19	Db5	Harpsichord 3
0:25.91	47	G1	0:26.01	89	C4	Trumpet 1
0:27.43	47	G1	0:27.53	70	Db4	Slap Bass 2
0:28.84	47	G1	0:28.94	62	C3	Electric Guitar 1
0:30.25	47	G1	0:30.35	95	Db5	Tuba
0:31.75	47	G1	0:31.85	82	Db3	Sax 4
0:33.25	47	G1	0:33.35	08	Db4	Honkytonk
0:34.72	47	G1	0:34.82	110	Db5	Whistle 2
0:36.26	47	G1	0:36.36	115	Db5	Deep Snare
0:37.72	47	G1	0:37.82	77	Db5	Recorder
0:39.19	47	G1	0:39.29	118	C2	Taiko
0:40.68	47	G1	0:40.78	53	Db4	Violin 1
0:42.09	47	G1	0:42.19	91	C2	Trombone 1
0:43.61	47	G1	0:43.71	111	Db5	Bottleblow
0:45.20	47	G1	0:45.30	76	F#6	Piccolo 2
0:46.76	47	G1	0:46.86	66	Db5	Acoustic Bass 2
0:48.21	47	G1	0:48.31	02	Db3	Acoustic Piano 2
0:49.63	47	G1	0:49.73	98	Db4	Vibe 1
0:51.17	47	G1	0:51.27	25	Db5	Synthesized Brass 1
0:52.70	47	G1	0:52.80	113	C2	Timpani
0:54.14	47	G1	0:54.24	85	C4	Oboe
0:55.60	47	G1	0:55.70	75	Db3	Piccolo 1
0:57.03	47	G1	0:57.13	48	Db5	Square Wave
0:58.58	47	G1	0:58.68	120	C3	Cymbal
1:00.01	47	G1	1:00.11	88	C4	Harmonica

1:01.54	47	G1	1:01.64	92	C3	Trombone 2
1:03.13	47	G1	1:03.23	81	Db4	Sax 3
1:04.65	47	G1	1:04.75	71	C2	Fretless 1
1:06.08	47	G1	1:06.18	114	C4	Melodic Tom
1:07.62	47	G1	1:07.72	107	Db5	Sho
1:09.12	47	G1	1:09.22	68	C3	Electric Bass 2
1:10.58	47	G1	1:10.68	106	C4	Koto
1:12.13	47	G1	1:12.23	96	C3	Brass Section 1
1:13.72	47	G1	1:13.82	122	B3	Triangle
1:15.15	47	G1	1:15.25	69	C2	Slap Bass 1
1:16.61	47	G1	1:16.71	84	C4	Clarinet 2
1:18.18	47	G1	1:18.28	64	C3	Sitar
1:19.77	47	G1	1:19.87	53	C2	Violin 1
1:21.18	47	G1	1:21.28	49	Db5	String Section 1

APPENDIX B

Description of Tasks Chosen by Subjects During Thinking Conditions

During the three 100% control conditions and the thinking half of oddball conditions, subjects were instructed to concentrate on a specific thinking task. Each subject (twenty subjects, numbered 10 through 29) was told that the tasks should be of personal interest and structured such that the subject's thoughts could be later discussed with the experimenter. Topics were changed during the experiment as needed to maintain subject interest and help the subject stay mentally alert. Listed below are descriptions of some of the subjects' thinking tasks.

Subject 10. Making a mental list of favorite children's books, planning a trip to New York City with a five year old, listing pros and cons of archeology versus psychology as a college major.

Subject 11. Making mental lists of things subject can't do without, list of favorite musical groups, list of favorite books as a child, list of favorite films.

Subject 12. Making a mental list of changes to a computer software program.

Subject 13. Making mental lists of favorite children's books, favorite vacations, favorite restaurants, things to learn to cook, foods hated as a child and which are now liked or still hated, five favorite desserts.

Subject 14. Replaying a rugby game, visualizing good plays, making a mental list of things to do to prepare a car for sale.

Subject 15. Making a lesson plan for an English-as-a-second-language class, making a mental list of things to do later in the day.

Subject 16. Making mental lists of 10 favorite ballads, 10 best movies, 10 worst westerns, 10 best independent films, good TV sitcoms, places to eat, celebrities who would make the best dates, classifying marine mammals, desirable domestic travel destinations, reasons not to go to Malaysia.

Subject 17. Budgeting next paycheck, planning a sightseeing excursion around San Francisco while hosting a visiting friend.

Subject 18. Composing musical lyrics and melodies, list of things needed to finish before in-laws visit, planning trip to Dallas by car, prioritizing things to do in Dallas, mentally listing favorite books read during past two years.

Subject 19. Thinking of things necessary to do in order to move out of parents' home into place of own, thinking about staging and performance of Cirque du Soleil at the Mirage Hotel in Las Vegas.

Subject 20. Planning a shopping trip for baseball caps, reworking the plot of a recently seen movie, planning a weekend, designing a weight lifting regimen for the experimenter, listing different job possibilities.

Subject 21. Making a mental list of chores needed to be done, planning an exercise routine, planning an outing with a five year old and a 16 month old, planning a Monday work schedule, thinking of ways to prepare oldest child to start kindergarten in fall, planning Christmas gift list.

Subject 22. Thinking of favorite CD with mellow progressive sound, thinking of list of things needed from kitchen back home in Florida, visualizing every detail about that kitchen, making a mental list of people to whom the subject should write, listing places already visited and adding to a "want to visit" list, list of movies that subject would like to see.

Subject 23. Mentally preparing a list of photos that subject plans to print, planning the photo shoot of a rave that evening.

Subject 24. Recalling words of a song, planning how to spend financial aid money, planning weekend, listing people recalled from the past starting with the subject's second grade teacher, foreign countries and capital cities lists.

Subject 25. Making a mental list of things needed to do at work, list of TV shows subject likes to watch, list of foods in a grocery store, how to spend a hypothetical $500 windfall, list of groceries to buy for six with $25, planning a balanced meal with no junk food for six on $50 budget, $3-$5 desserts containing no chocolate, coconut or eggs.

Subject 26. Mentally deriving mathematical equations.

Subject 27. Planning a list of things to make during the next year, list of words that rhyme with "eight", visualizing all books on subject's bookshelf, making a mental list of things to sew.

Subject 28. Thinking about details of recording session, mentally preparing dinner for grandmother that evening, listing hardware needed for house.

Subject 29. Mentally writing a novel, reviewing a historic topic, compiling a list of all past teachers.

Protocol Design by
M. J. Harrington
Version 3.0
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APPENDIX C

Passive Oddball vs. Three Stimulus Novel Protocol

Approximate Time in Minutes	Approximate Elapsed Time	Session One - Part One Day 1 Procedures
:10	:10	Explain study and procedures to subject. Answer any questions. Obtain signed UCSF Human Research Committee-approved Informed Consent Document.
:15	:25	Perform hearing test to determine subject's pure tone threshold at each ear for each frequency to be used as stimuli. Calibrate SL values.
:20	:45	Apply electro-cap and EOG electrodes, check impedances.
:15	1:00	Have subject sit in reclining chair in recording chamber. Connect electrode cables. Recheck impedances on Grass amplifier. Help subject get comfortable and explain the importance of remaining relaxed throughout the session. Show the subject how to keep eyes straight ahead looking at a fixation spot. Ask the subject to refrain from blinking during the recording. Do EEG, EOG, and artifact calibration.
:05	1:05	Determine subject's threshold for the taped stimuli. Check intensity level at 50 dB above that threshold to make sure it is a comfortable level for the subject. Explain attention control task (have subject think of something of interest). Have subject practice the control task and reading with little eye movement while recording EEG to a series of tones. Check data from all channels.
:02	1:07	1 block of 40 PASSIVE CONTROL: 100% at 500 Hz, 100 msec, ISI 1.5 sec. Subject is instructed to ignore stimuli and to perform control task. Subject will be asked about it at the break.
:02	1:09	1 block of 40 PASSIVE CONTROL: 100% at 1500 Hz, 100 msec, ISI 1.5 sec. Subject is instructed to ignore stimuli and to perform control task. Subject will be asked about it at the break.
:02	1:11	BREAK. See if subject has any questions and is comfortable.

1500 Hz Oddball Paradigm	Three Stimulus Novel Paradigm	Novel Oddball Paradigm
85% at 500 Hz, 100 msec 15% at 1500 Hz, 100 msec Average ISI 1.5 sec Intensity, below startle eye-blink 2 blocks of ~120, 3 min ea. block (16 good trials each condition)	75% at 500 Hz, 100 msec 12.5% at 1500 Hz, 100 msec 12.5% novel sounds, 100 msec Average ISI 1.5 sec Intensity, below startle eye-blink 2 blocks of ~120, 3 min ea. block (16 good trials each condition)	85% at 500 Hz, 100 msec 15% Novel sounds, 100 msec Average ISI 1.5 sec Intensity, below startle eye-blink 2 blocks of ~120, 3 min ea. block (16 good trials each condition)

Approximate Time in Minutes	Approximate Elapsed Time	Session One - Part Two 1500 Hz Oddball, Three Stimulus Novel, Novel Oddball, and Novel Control Conditions
:08	1:19	2 blocks of 120 each PASSIVE *. Subject is instructed to ignore stimuli and to perform control task. Subject will be asked about it at the break.
:02	1:21	BREAK. Write Data from E: to D:

Passive Oddball vs. Three Stimulus Novel Protocol (continued)

:08	1:29	2 blocks of ~120 each READ *. Subject is instructed to read a book, minimizing eye movements, and ignore any stimuli.
:02	1:31	BREAK.
:08	1:39	2 blocks of ~120 ACTIVE *. Subject is instructed to count target tones (1500 Hz) and report number after each block. Play a sample of a Three Stimulus Novel audio tape.
:05	1:44	BREAK. Have subject stretch and move around. Ask if subject wants to use restroom. Write data on E: to D:
:06	1:50	If subject has left the recording booth, have subject go back into booth, reconnect electrode cables and check impedances.
:08	1:58	2 blocks of ~120 PASSIVE *. Subject is instructed to concentrate on control task, reporting results at the break.
:02	2:00	BREAK.
:08	2:08	2 blocks of ~120 READ *. Subject is instructed to read book with as few eye movements as possible, ignore any stimuli.
:02	2:10	BREAK. Write data from E: to D:
:02	2:12	1 block of 40 PASSIVE CONTROL: 100% Novels, 100 msec, ISI 1.5 sec. Subject is instructed to concentrate on control task, reporting results at the break.
:18	2:30	Debrief subject while removing electro-cap and electrodes. Set up appointment for second recording session.

* Subjects will be assigned to groups and conditions according to Latin Square Design.

Approximate Time in Minutes	Approximate Elapsed Time	Session Two - Part One Day 2 Procedures
:55	:55	Repeat shortened version of preliminary procedures from Session One. Ask subject if he/she has any questions from the previous session, skip hearing test, apply electro-cap etc., redo EEG, EOG, and artifact calibrations, discuss the control task and reading procedures, and have subject practice until comfortable with the recording situation.
:05	1:00	Rerun 500 Hz, 1500 Hz Passive Controls, one block of 40 each; followed by break.

Approximate Time in Minutes	Approximate Elapsed Time	Session Two - Part Two 1500 Hz Oddball, Three Stimulus Novel, Novel Oddball, and Novel Control Conditions
1:12	2:12	The entire Session One - Part Two will be replicated in the order assigned to subjects by the Latin Square Design in Session One. As before, 100% Novels Passive Control is last.
:18	2:30	Debrief subject while removing electro-cap and electrodes. Pay subject and obtain receipt. Ask if subject would like to have any follow-up information sent to him/her.