

The P300 Wave of the Human Event-Related Potential

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Summary: The P300 wave is a positive deflection in the human event-related potential. It is most commonly elicited in an "oddball" paradigm when a subject detects an occasional "target" stimulus in a regular train of standard stimuli. The P300 wave only occurs if the subject is actively engaged in the task of detecting the targets. Its amplitude varies with the improbability of the targets. Its latency varies with the difficulty of discriminating the target stimulus from the standard stimuli. A typical peak latency when a young adult subject makes a simple discrimination is 300 ms. In patients with decreased cognitive ability, the P300 is smaller and later than in age-matched normal subjects. The intracerebral origin of the P300 wave is not known and its role in cognition not clearly understood. The P300 may have multiple intracerebral generators, with the hippocampus and various association areas of the neocortex all contributing to the scalp-recorded potential. The P300 wave may represent the transfer of information to consciousness, a process that involves many different regions of the brain. **Key Words:** Event-related potentials—P300—P3—Late positive component.

The P300 wave is a parietocentral positivity that occurs when a subject detects an informative task-relevant stimulus. The "P300" name (Smith et al., 1970) derives from the fact that its peak latency is about 300 ms when a young adult subject makes a simple sensory discrimination. It has also been called the "P3" wave because it is the third major positive peak in the late sensory evoked potential (Ritter et al., 1968) and the "late positive component" (Sutton et al., 1965, 1967).

In 1965, several papers reported late positive waves evoked by meaningful, task-relevant stimuli (Desmedt et al., 1965; Sutton et al., 1965; Walter, 1965). The clearest of these was that of Sutton et al. (1965), who described a late positive component in the evoked potential to visual and auditory stimuli that confirmed or disconfirmed a subject's guess about

their modality. The component was larger when the stimulus was less probable. It was also larger when the subject was guessing than when he or she knew which stimulus would occur next. The authors proposed that the late positive component was "endogenous," related to the psychological reaction of the subject to the stimulus rather than to the physical characteristics of the stimulus.

Within the next 5 years, the essential characteristics of the P300 were described. Sutton et al. (1967) showed that the P300 wave could be elicited by the omission of a stimulus if this omission was informative. The P300 wave occurred only when the subject attended to the stimuli, whether this attention was required for the task (Donchin and Cohen, 1967; Sheatz and Chapman, 1969) or demanded by the intrusiveness of the stimulus itself (Ritter et al., 1968). Ritter and Vaughan (1969) first used the "oddball" paradigm, wherein a subject detects occasional target signals randomly interspersed among more frequent standard stimuli. The pari-

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etocentral scalp distribution of the P300 wave was first described by Vaughan and Ritter (1970).

Since these early days, we have learned much more about the P300 wave. As often happens, the more we know the less we understand. This paper reviews our present knowledge and suggests some directions for future research. The hugeness of the literature has led to a selectivity that at times verges on the idiosyncratic. This review concentrates on oddball paradigms because of their popularity in clinical situations. For simplicity, the figures are adapted from their original published form and all plotted with the same polarity.

TECHNICAL ASPECTS OF P300 RECORDINGS

Time Constants

The recent literature has worried a little about the high-pass filters used to record the P300 wave (Duncan-Johnson and Donchin, 1979; Ebmeier et al., 1992; Goodin et al., 1992). Analog filters with high-pass cutoffs greater than 0.5 Hz significantly distort the P300 wave: the P300 amplitude is reduced and the later portions of the P300 wave become negative because of phase distortion. The P300 is best recorded with an analog high-pass filter set at 0.1 Hz or less (a time constant of 1.5 s or more). Further filtering can be performed off-line using digital filters designed to maintain phase information and minimize distortion.

Ocular Artifacts

Electrical potentials generated by eye movements and blinks are a major problem when recording the P300 wave. These ocular potentials are large and easily entrained by the stimuli that evoke the P300. There are two main approaches to this problem.

First, one can reject from analysis any trials wherein eye movements or blinks occur. The electro-oculogram (EOG) is monitored using peri-ocular electrodes (e.g., above and below the eyes), and trials are rejected if the EOG exceeds some criterion (e.g., $\pm 100 \mu\text{V}$). The EOG should nevertheless be recorded and averaged simultaneously with the EEG to ensure that small eye movements (e.g., less than $100 \mu\text{V}$) do not become time-locked to the stimuli. This approach has two main drawbacks. First, rejecting trials decreases the efficiency of the recording. In the worst possible case, all trials might be rejected due to ocular artifacts. In order to prevent

this, one usually urges subjects not to blink or move their eyes unless absolutely necessary. This leads to the second drawback of the rejection procedure. By asking the subject to limit their eye movements, one has changed the nature of the task. Subjects must now divide their attention between their eyes and the stimuli. This can significantly affect the P300 wave (Verleger, 1991).

Second, one can subtract the ocular artifacts from the EEG. The signals recorded on the scalp are a combination of the true EEG and some fraction of the EOG. If one can properly characterize the eye movements and calculate the propagation factors for each type of eye movement, the effect of the ocular artifacts on the EEG can be subtracted from the recordings (Gratton et al., 1983; Elbert et al., 1985). Unfortunately, the subtraction will also remove some portion of the frontal EEG signals that are recorded from peri-ocular electrodes together with the EOG. This is not a problem with a recent technique that calculates ocular "source components" at the same time as estimating the intracerebral sources for the event-related potentials (Berg and Scherg, 1991; Lins et al., in preparation).

Multi-Channel Recording

By the time the P300 wave occurs, many different regions of the brain are actively processing the information provided by the stimulus. Many of these regions can generate electrical fields at the scalp. The proper identification and measurement of the P300 wave therefore require its differentiation from these other electrical fields. One important parameter that is very helpful in identifying the P300 wave is its scalp distribution. The P300 wave is maximally recorded from the midline centroparietal regions (Fig. 1). In order to recognize the P300 wave, the minimum recording montage would therefore involve at least three scalp locations (Fz, Cz, and Pz) referred to a distant reference and an EOG recording. More electrodes would provide more information. The event-related potentials are every bit as complex as the spontaneous EEG, and most electroencephalographers are not satisfied with less than 16 channels.

Averaging

The amplitude of the P300 wave is about $10 \mu\text{V}$. The P300 is usually measured in alert subjects with their eyes open after averaging between 30 and 100 trials and the reliability of the results demonstrated

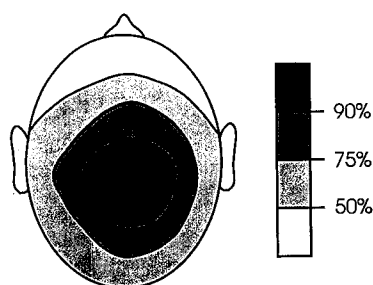


FIG. 1. Scalp distribution of the P300 wave. This shows the average data from seven subjects when they detected an omitted auditory stimulus. This version of the P300 was chosen because there are no superimposed sensory evoked potentials. The potentials were recorded from the scalp using a sternovertebral reference. These data are adapted from Picton and Hillyard (1974).

by replicated tracings. Although it is usually recorded by averaging, the P300 wave does not always obey the assumptions of the averaging process, since it may vary in amplitude and latency from trial to trial.

One can usually recognize the P300 in single-trial recordings particularly if they are low-pass filtered at 3–5 Hz (McCarthy and Donchin, 1981; Ruchkin, 1988). Single-trial analysis of the P300 wave can serve two purposes. First, it can show trial-to-trial fluctuations. A classic question has considered how closely the P300 latency relates to the simultaneously recorded reaction time (Ritter et al., 1972). Second, the analysis can allow one to compensate for the trial-to-trial latency variability (“jitter”) when averaging. Given an estimate of the peak latency of the P300 wave on each recording, one can line up these recordings prior to averaging (Ruchkin, 1988).

Component Identification and Measurement

The P300 wave is usually identified as a parieto-central positive deflection in the ERP waveform that varies with the probability of the eliciting stimulus or event (Fabiani et al., 1987). The P300 wave is usually measured in terms of a peak amplitude relative to a prestimulus baseline and a peak latency relative to the stimulus onset. The peak is usually identified as the most positive point in the waveform between 200 or 250 ms and some later time (e.g., 400 ms if the stimulus is easy to discriminate or 800 ms if it is difficult). Superimposed wiggles on the P300 wave can be attenuated by low-pass filtering (3–6 Hz cutoff) prior to peak identification or, if amplitude is the main measurement, by taking the mean amplitude value over a period of time (e.g., 200–400 ms). The measurements are usually taken at one electrode lo-

cation, typically either Cz or Pz. The latency of the P300 wave varies from one electrode location to the next, usually being earlier at more frontal locations. The information from multiple electrode locations may be combined in measurements such as “global field power” (Rodin, 1991).

Unfortunately, these approaches to identifying and measuring the P300 do not take into account the possibility that multiple processes may be occurring at the time of the P300 wave. These processes may generate fields that overlap the scalp-recorded P300 wave. It is beyond the limits of this article to consider these processes beyond a rather simplistic listing: a “mismatch negativity” that occurs at the beginning of the P300 when a repeating auditory stimulus changes, an N2 wave that may represent the perceptual registration of this change, an Nd wave or processing negativity that occurs during the processing of an attended stimulus, a P3a wave that occurs when a stimulus is noticed but not attended, a slow wave that relates to further processing of stimulus information, and an N400 wave that reflects the activation of memory processes when an unexpected or incongruous stimulus occurs (Hillyard and Picton, 1987).

These different “components” of the response can be differentiated by their distinct relationships to experimental manipulations. Donchin et al. (1978) defined a component as “a source of controlled, observable variability.” For example, three positive waves overlap during the P300 latency range: P3a peaking near 250 ms, P3b peaking near 350 ms, and a positive slow wave (Squires et al., 1975; Ruchkin et al., 1990). They can be considered as different components because they have distinct relationships to the experimental variables. The P3a is more frontal in its scalp distribution than the P3b, whereas the slow wave is more parietal (Fig. 2). Although all three components vary with stimulus probability, they are differentially sensitive to the information provided by an improbable stimulus. The P3a is not affected by whether the subject is attending to the stimuli, whereas the P3b and slow wave are larger with attention.

How does one distinguish such components? One approach is to perform a principal component analysis (PCA) (Fabiani et al., 1987). This provides a set of waveforms that most efficiently explains the variance of the recordings made under different experimental conditions. PCAs have been used extensively in the study of the P300 and related components and have provided a great deal of information. However, these analyses are not without problems.

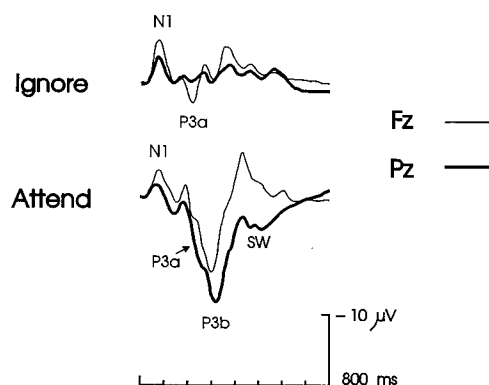


FIG. 2. Overlapping components in the P300 wave. These waveforms show the response in one subject (K.S.) to improbable target stimuli when the subject was either attending to the stimuli or ignoring them. There is a small P3a wave in response to the ignored target stimulus. When the target is actively attended, a P3b and slow wave (SW) are superimposed on this P3a component. These data are adapted from Squires et al. (1975).

The first is that the resultant waveforms may not be easily interpreted in physiological terms. A second problem is that a PCA attempts to explain all of the variance in the data including any residual noise. To perform a PCA on noisy data is to court disaster. A third problem is that the PCA cannot easily handle components that vary in latency with the experimental manipulations.

A second approach is to perform a source analysis (Scherg, 1990; Scherg and Picton, 1991). Like the PCA, this attempts to interpret multichannel scalp recordings in terms of a smaller set of components. However, source analysis uses physiological rather than statistical constraints to derive these components. It attempts to model the surface waveforms in terms of patterns of activity at different intracerebral locations. Most work with source analysis has concerned event-related potentials earlier than the P300 wave. A source analysis of the P300 wave is a daunting task because multiple processes overlap to generate the scalp waveform and because the essence of the P300 is how it varies with experimental manipulations. Future developments may include this experimental variance in the source analysis (Turetsky et al., 1990; Scherg and Picton, 1991).

PSYCHOLOGICAL ASPECTS OF THE P300 WAVE

Some Introspective Comments

Introspection suggests that the amplitude of the P300 wave varies with the amount of conscious at-

tention paid to a stimulus. Subjects are able to categorize the amplitude of their own P300 waves at above-chance levels, indicating some consciousness of the P300 wave or the conditions under which it occurs (Sommer and Matt, 1990). These subjects were instructed that "variations in the amount of attention paid to an event, in the certainty with which it is expected, in the surprise which it elicits, or in the clarity with which it is perceived might relate to the amplitude of the P300." My largest P300 waves have occurred on days when I perceived the target with a vividness and intensity more appropriate for a visiting divinity than a simple tone. My smallest P300 waves occurred when I was tired and preoccupied with other matters. At those times, I felt that I had been given only so many P300 waves and that they should not be so foolishly squandered on insignificant tasks.

Attention and Task Relevance

When competing trains of stimuli are presented, the P300 wave is most prominent in response to stimuli that the subject is attending to. The direction of attention is usually controlled by the experimenter who requires the subject to perform a task that involves some stimuli and not others. The P300 wave generally occurs only in response to task-relevant stimuli. The perverse desire of subjects to attend to irrelevant stimuli can be prevented by making the assigned task sufficiently difficult in terms of complexity or speed that attention to irrelevant stimuli is not possible. When a subject attends to auditory stimuli in one ear and ignores auditory stimuli in the other ear, an improbable target only elicits a P300 if it occurs in the attended ear (Hillyard et al., 1973; Donald and Little, 1981).

There are limits to how much a human brain can process. These limits are generally considered in terms of attentional resources that can be allocated to different tasks. Studies of the P300 waves in dual-task paradigms show that as the perceptual demands of a secondary task increase, the amplitude of the P300 evoked by the detection of targets in the primary task decreases in amplitude (Wickens et al., 1983). The amplitude of the P300 is relatively unaffected by increasing the motor demands of the secondary task (Israel et al., 1980). These results suggest that perceptual and motor resources are separate, and that the P300 wave is mainly related to resources of the perceptual kind.

Hillyard et al. (1973) associated the P300 wave with "response set" levels of attention. By means of "stim-

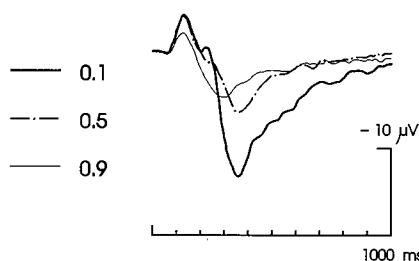


FIG. 3. Effects of probability. This figure represents the grand-mean waveforms from seven subjects recorded from Pz for detected auditory target stimuli in an oddball paradigm at three different levels of target-probability. These data are adapted from Johnson (1986).

ulus set," a subject attends to one of several incoming sensory channels defined in terms of relatively simple physical attributes such as sensory modality or spatial location. By means of "response set," a subject can facilitate the perception of particular kinds of stimuli that require particular responses.

Probability, Expectancy, and Information

The P300 wave is larger when the stimulus is more improbable. Duncan-Johnson and Donchin (1977) recorded event-related potentials (ERPs) as subjects listened to a randomized sequence of two tones and counted one of them. They found that the amplitude of the P300 wave was inversely proportional to the probability of each tone (Fig. 3). The P300 for the counted tones was slightly larger than that elicited by the uncounted tones, but this effect was much smaller than the probability effect.

This effect depends on the probability of the category in which a stimulus is perceived rather than the probability of the individual stimulus. Courchesne et al. (1977) asked subjects to detect the letter "B" occurring with a probability of 15% in a train of other visual stimuli. In one condition ("homogeneous") the background stimuli were all "As" and in another condition ("heterogeneous") they were randomly any other letter except "B." In both conditions, the response to the target stimulus contained a large P300 wave, and the response to the background stimuli contained little, if any, P300. The P300 wave, therefore, varied with the probability of the target-background categories rather than with probability of the individual stimuli, which in the "heterogeneous" condition was smaller for the background stimuli than for the targets.

Exactly how stimuli are categorized will depend as much on the attentional strategy of an individual subject as on the instructions given by the experi-

menter (Nasman and Rosenfeld, 1990). If a sequence of stimuli contains two distinct types of improbable stimuli and the subject is asked to respond to only one of these, both improbable stimuli will generally elicit a P300 wave (Pfefferbaum et al., 1984a). The subject probably classifies the improbable nontarget separately from the more probable nontarget. This would not have been possible if, as in the Courchesne study, there were 25 rather than 2 nontarget stimuli.

Probability can be considered in terms of time—how often a particular stimulus occurs within a period of time—or in terms of stimuli—how many stimuli are of a particular kind. Fitzgerald and Picton (1981) suggested that the P300 wave was more closely related to "temporal probability" than to "stimulus probability." (They termed the latter "sequential probability," but this can easily be confused with other sequence effects.) They maintained the probability of the target stimulus at 0.2 but changed the interstimulus interval (ISI) from 0.5 s to 4 s, thereby decreasing the temporal probability from 1/2.5 s to 1/20 s. The amplitude of the P300 increased monotonically with decreasing temporal probability. Polich (1990) found that the P300 amplitude did not increase when target probability was maintained at 0.2 and ISI varied between 2 s and 10 s (temporal probabilities between 1/10 s and 1/50 s). Polich found that the amplitude of the P300 to targets occurring with a stimulus probability of 0.8 increased in amplitude when the ISI was increased from 2 to 10 s, thereby decreasing the temporal probability from 1/2.5 s to 1/12.5 s. These data therefore suggest that, in the oddball paradigm, the P300 amplitude increases with decreasing temporal probability until reaching a maximum amplitude at about 1/10 (Fig. 4).

The effects of probability on the P300 can occur independently of subjective awareness. If one changes the probability of the stimulus, but does not tell the subject, the P300 amplitude changes even though the subject may not be aware of the experimental manipulation (Johnson and Donchin, 1982; Dalbokova et al., 1990).

Other effects of probability also play a role in determining the amplitude of the P300. Squires et al. (1976) maintained the global probability of a target stimulus over a block of stimuli but examined the responses to targets separately according to the exact sequence of preceding stimuli (the "local" probability). The P300 in response to the target stimulus was larger when the target followed a series of stan-

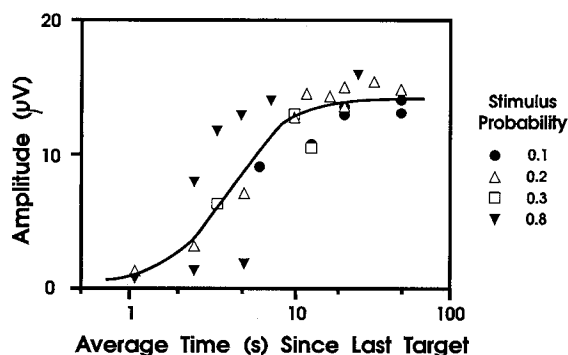


FIG. 4. Temporal probability. This figure plots the P300 amplitudes at Pz versus the temporal probability of the target stimulus. Temporal probability is measured as the average time between the target stimuli and plotted using a logarithmic scale. The figure combines data from four different studies (Fitzgerald and Picton, 1981; Perrault and Picton, 1984; Polich, 1987, 1990). All studies involved the detection of an auditory target stimulus in a simple oddball paradigm. The stimulus-probability of the target stimulus varied from experiment to experiment. The P300 amplitude varies with the temporal probability of the target stimulus over the range 1/1s to 1/10s.

dard stimuli than when it followed a series of other targets.

It is possible that P300 varies in amplitude with time, since it was last evoked by a particular category of stimulus. This hypothesis might explain both the global and local probability effects. It will not explain everything, since there are particular sequence effects with alternations (Squires et al., 1976). However, it might explain most of the variance in P300 amplitude with probability.

Several studies, however, have shown that large P300 waves can be recorded in response to targets presented at rapid rates. Woods and Courchesne (1986) used a task wherein subjects had to decide whether one, two, or three targets occurred in a brief 1,200-ms period. When three targets occurred, they each evoked large P300 waves. Verleger and Berg (1991) asked subjects to count the number of times that three targets occurred in a row in an oddball paradigm with targets occurring at a probability of 0.5 (the "waltzing oddball"). The P300 increased in amplitude over a sequence of three adjacent targets. In both these experiments, it is probable that the subject separately categorized events as single, double, or triple. Each category might involve a different P300 system, each system having its own temporal characteristics.

Difficulty, Confidence, and Uncertainty

When the task of discriminating the target stimulus from the standard stimulus becomes difficult,

the amplitude of the P300 wave becomes smaller and its latency longer (Fig. 5). The decrease in amplitude has been explained in terms of the confidence with which the subject discriminates the target (Squires et al., 1973). However, when the task becomes too easy, the mind may stray to other matters and the P300 decreases in amplitude (Hillyard et al., 1971). Given the same amount of attention that is allocated to a task, however, the certainty of the decision and the P300 amplitude covary. Ruchkin and Sutton (1978) suggested that the P300 amplitude reflected the amount of information transmitted during perception. This would be the amount of information presented by the stimulus less the amount lost through "equivocation" in its processing. Another related possibility is that the P300 amplitude may represent the amount of useful information (Johnson and Donchin, 1978). This takes into account the task relevance of the information as well as its reliability.

Johnson (1986, 1992) has proposed a "triarchic" model to explain the amplitude changes of the P300 wave under different experimental conditions. Two factors are additive in their effect on P300 amplitude: the improbability of the stimulus and the meaning of the stimulus. The "improbability" factor appears to combine both global and local expectancies. The "meaning" factor also has several sub-components: the complexity of the task (how much is entailed when a particular stimulus is recognized), the complexity of the stimulus (how many features must be discriminated), and the value of the stimulus (how much is it worth to detect it). The

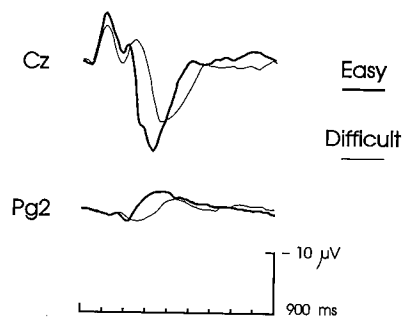


FIG. 5. Nasopharyngeal recordings. This figure shows the P300 wave recorded from the vertex and right nasopharyngeal (Pg2) electrodes during the detection of a target stimulus during an auditory oddball task. The waveforms are the grand mean of 10 subjects who performed the tasks when the frequency difference between the target and the standard stimuli was easy or difficult to discriminate. The auditory P300 wave recorded from the vertex is smaller and later when the task becomes more difficult. At the nasopharyngeal electrode, a negative wave is recorded at about the same latency as the scalp-recorded P300 wave.

sum of the improbability and meaning factors are multiplied by a third "transfer" factor that represents the proportion of the stimulus information received. This will depend on equivocation in the evaluation of the stimulus information and the amount of attention paid to the task. The model provides an intriguing review of many experimental findings. Some of the details can be debated, such as the subcomponents of the probability and meaning factors and whether the transmission factor differs between these subfactors. However, the model is important, since it suggests that the P300 process is not unitary but represents the sum of several (and perhaps many) different processes.

The latency and the amplitude of the P300 wave may be differentially affected by experimental variables. For example, if the stimulus is used as a feedback stimulus rather than just being counted, the P300 amplitude is much larger, although there is no clear change in the latency (Picton et al., 1978; Johnson, 1986). Prolonging the time necessary to evaluate the stimulus can increase the latency of the P300 wave, but if the evaluation can be made as confidently for the complex as for the simple task, the amplitude of the P300 wave does not change. Kutas et al. (1977) recorded P300 waves under three different conditions: detecting the name "Nancy" appearing 20% of the time when all the other stimuli were "David"; detecting female names in a sequence of different male names; detecting words that were synonymous with the word "prod" in a series of other words. The latency of the P300 increased systematically with the complexity of the semantic categorization, but there was no clear change in the amplitude of this wave.

Relations to Reaction Time

Ritter et al. (1972) demonstrated that, if one records the reaction (RT) time simultaneously with the P300 in a simple oddball task, the reaction time occurs about 50 ms before the peak of the P300. Similar results were obtained by Picton et al. (1976) in the omitted stimulus paradigm. Because of the time required for impulses to travel from the brain out to the muscles, it is therefore impossible for the P300 to represent the decision process that invokes the response. Ritter et al. (1979) suggested that the preceding N2 wave may index this decision. However, Goodin et al. (1986), who recorded changes in the EMG prior to the response, suggest that even the N2 wave may follow the decision process.

Kutas et al. (1977) examined the relationship be-

tween the latency of the P300 wave and RT when subjects were asked to respond as quickly or as accurately as possible. When accuracy was emphasized, the reaction time tended to follow the peak latency of the P300 peak and the measurements were highly correlated. The slope of the regression was 0.6, indicating that the P300 latency increased less than RT. When speed was emphasized, the RT could occur well before the peak latency of the P300, and the correlation between RT and P300 was reduced. Many of the early responses were incorrect. These results suggested that, when responding as quickly as possible, the subjects initiated their response before the stimulus was fully evaluated. Kutas et al. suggested that the P300 might index the completion of stimulus evaluation. Under speed instructions, subjects might take a chance on being wrong and respond prior to full evaluation of the stimulus.

McCarthy and Donchin (1981) independently manipulated the complexity of stimulus evaluation and the complexity of response selection. The time for stimulus evaluation was varied by embedding the target (either "RIGHT" or "LEFT") in visual noise that made the target more or less difficult to detect. The time for response selection was manipulated by changing the compatibility between the target and the responding hand. Both visual noise and response incompatibility increased the reaction time. However, only visual noise had any effect on the P300 latency. The P300 wave in the "noise" condition was much broader in amplitude than in the "no noise" condition. This might have been due to several overlapping waves during the decision process or due to latency variability of the P300 waves from trial to trial. Latency correction methods resulted in a narrowing of the P300 wave in the "noise" condition, thereby supporting the interpretation that the broadness of the response was due to latency jitter (Magliero et al., 1984).

PHYSIOLOGICAL CHARACTERISTICS OF THE P300 WAVE

Scalp Distribution

Vaughan and Ritter (1970) recorded the P300 wave from multiple scalp electrodes using a reference on the nose. In an auditory oddball task the scalp distribution of the P300 was widespread with a maximum amplitude over the midparietal region. Unlike the earlier waves of the auditory response, the P300 showed no change in polarity over the scalp. Vaughan and Ritter interpreted these results as in-

dicating a bilateral source for the P300 wave in the parietal association areas. Simson et al. (1976, 1977a) showed that the P300 wave for omitted stimuli was similar to that for target stimuli and that the P300 wave elicited by targets in different modalities was similar in its scalp distribution, despite "subtle" differences between experimental conditions.

Later studies have confirmed these differences. Barrett et al. (1987) found that the somatosensory P300 was significantly more central than the auditory P300. Naumann et al. (1992) have found significant differences between the P300 wave elicited by targets in different sensory modalities but suggested that these might be due to overlapping modality-specific sensory responses.

Hillyard et al. (1976) recorded the P300 wave under several different experimental conditions. Although the scalp distributions of these P300 waves were very similar, there were some clear differences. In a task in which the subject responded to one stimulus and not to another equiprobable stimulus, the "no go" P300 was significantly more fronto-central and less parietal than other P300 waves. This has been confirmed by other studies (Simson et al., 1977b; Jodo and Inoue, 1990; Verleger and Berg, 1991). Stapleton et al. (1987b) found that the P300 was similar in scalp distribution for different tasks. However, they also found that the P300 was slightly larger over the right hemisphere than over the left. Goodin et al. (1985) reported that the P300 wave was larger over the left hemisphere when subjects discriminated either words or shapes, and symmetrical when they discriminated the size of a visual stimulus.

One of the most striking differences in the scalp topography of the P300 wave was reported by Courchesne et al. (1975). In response to a totally unexpected or "novel" stimulus, the P300 wave was maximally recorded from the frontal regions, unlike the parietal P300 wave that occurred in response to detected targets in the same block of stimuli. Similar frontal P300 waves have been recorded following novel sounds (Knight, 1984) and novel somatosensory stimuli (Yamaguchi and Knight, 1991a).

Johnson (1992) has recently reviewed many different studies of the scalp distribution of the P300 wave. He concludes that the scalp distribution of the P300 wave varies significantly from experiment to experiment. There are two ways to handle this information. One can maintain that there is a basic P300 wave upon which different experimental conditions may superimpose other potentials, or one

can relinquish the idea of an underlying unitary P300 and consider multiple different generators for the scalp-recorded P300 wave.

Intracerebral Recordings

Recordings from intracerebral electrodes in patients who are being evaluated for surgery have provided important information about the intracerebral origins of the scalp-recorded P300 wave. Halgren et al. (1980) recorded large potentials from electrodes in the hippocampus and amygdala at the same time as the scalp-recorded P300 wave. These potentials changed in polarity over short distances, indicating a local origin in the limbic system. These results were confirmed in other patients (Squires et al., 1983; Stapleton and Halgren, 1987) and in other laboratories (McCarthy et al., 1989; Puce et al., 1989; Smith et al., 1990). The limbic potentials are reduced on the side most affected by pathology (Squires et al., 1983; Puce et al., 1989).

McCarthy et al. (1989) have described the spatial distribution of these limbic potentials. Negative waves are recorded when the electrodes are in hippocampus or immediately medial to it. Positive waves are recorded posterior, superior, anterior, and lateral to the hippocampus. The coronal section through the hippocampus shows a C-shaped structure with the convexity of the C pointing laterally. The P300 potentials are negative inside the C and positive outside.

The limbic system is not the only area of the brain that is active when a P300 wave occurs at the scalp. It is, however, an area of the brain that is prone to epileptic discharge and one that is extensively investigated when epilepsy becomes intractable and surgery is considered. Depth electrodes are also inserted into the thalamus for the treatment of tremor and into the midbrain for the control of pain. Yingling and Hosobuchi (1984) recorded activity in the midbrain region at the same latency as the scalp P300. Several reports (Velasco et al., 1986; Kropotov and Ponomarev, 1991) have recorded similar activity in various regions of the thalamus and basal ganglia.

Recent studies of the neocortex have indicated a clear inversion of polarity across the parietal association cortices at the latency of the scalp-recorded P300 wave (Kiss et al., 1989; Smith et al., 1990). Occasional inversions also occur across regions of the frontal cortex. Smith et al. (1990) have extensively reviewed the intracerebral distribution of the po-

tentials recorded concomitantly with scalp-recorded P300 waves. They suggest that, although they may be active during the scalp P300 wave, regions of the thalamus and midbrain probably do not contribute significantly to the scalp recording. Both the medial temporal lobe and the inferior parietal lobe probably contribute to the scalp-recorded P300, with the parietal generator being predominant.

There have not been extensive recordings of the P300 wave from subdural electrode arrays as yet. Neshige and Lüders (1992) recorded a large P300 wave from one electrode over the temporal lobe when adjacent electrodes in the array showed no clear positivity. They also recorded negative waves over the anterior and inferior surfaces of the temporal lobe in the same latency region as the scalp P300.

Nasopharyngeal and Sphenoidal Recordings

The intracerebral recordings from the limbic system triggered several studies of the P300 wave using nasopharyngeal and sphenoidal electrodes. These studies have unfortunately provided somewhat contradictory data, perhaps because different reference electrodes were used. Using a sternovertebral reference, Perrault and Picton (1984) reported a small negative wave occurring slightly later than the P300 wave recorded from the scalp (Fig. 5). This negativity was affected by experimental manipulations in the same way as the scalp-recorded P300. Perrault and Picton therefore proposed that the nasopharyngeal electrode might be recording from beneath a dipole source located somewhere between the nasopharynx and the centroparietal scalp. Using a mastoid reference, Schellenberg et al. (1990) found a small positive wave in the nasopharynx rather than a negative wave. This discrepancy might be explained by the report by Neshige and Lüders (1988), which described a large negative wave with a latency a little later than the surface P300 wave recorded from the ear when using a sternovertebral reference. The Schellenberg et al. montage would subtract this large ear (or mastoid) negativity from the small nasopharyngeal negativity. All is not perfectly clear, however, since Neshige and Lüders also recorded an N300 wave from their T3 and T4 electrodes, and this has not been observed in other studies (e.g., Perrault and Picton, 1984). Rugg et al. (1990) reported no clear response from sphenoidal electrodes (relative to a sternovertebral reference) at the latency of the scalp-recorded P300 wave, al-

though some of their figures show a small negative wave.

Magnetic Recordings and Current Sources

Magnetoencephalography (MEG) has several advantages over electrical recordings. Most importantly, magnetic fields are relatively unaffected by the conductance of the tissues between the source and the detector. The main disadvantage of MEG is that, although it can accurately detect and localize current sources that are oriented tangentially to the scalp, it is relatively blind to radially oriented current sources. The main localizing pattern for the MEG is dipolar with the field entering the scalp in one location and exiting from another. The current source is located midway between the line joining the two extrema, at a depth that varies with the length of this line, and with an orientation perpendicular to the line.

Okada et al. (1983) recorded the magnetic fields when subjects performed a visual oddball task. At the same time as the scalp-recorded P300 wave, they found an outgoing magnetic field over the anterior left temporal region, an ingoing field over the anterior right temporal region, and small and variable fields over the occipital regions. They suggested that these patterns could be explained by two vertically oriented current dipoles located in the hippocampus. The fields at the occiput deriving from these two dipoles would tend to cancel each other, being outward for the right hemisphere dipole and inward for the left hemisphere dipole.

Recent MEG studies of the P300 wave during an auditory oddball task (Rogers et al., 1991) have suggested that the generator of the P300 may be located in the auditory regions of the cortex. However, some of these data (their Table 1) do not fit at all with the scalp-recorded electrical fields. The current dipole points directly toward the occiput rather than toward the centroparietal region, where the electrical fields of the P300 are maximally recorded. There may be activity in the auditory cortex at the time of the P300 wave, and this may generate magnetic fields. However, such activity is not the major source of the scalp-recorded P300 wave.

Two problems must be considered when evaluating the present MEG evidence for the intracerebral origins of the P300 wave. First, MEG does not pick up radially oriented current sources and may not detect such sources in the inferior parietal lobe.

Second, the analysis of MEGs does not at present consider the possibility of multiple overlapping sources. It is difficult to evaluate bilateral hippocampal sources if the ingoing and outgoing fields at the occiput do indeed cancel.

Published source analyses for the electrical P300 wave are subject to the same criticism that they have not evaluated multiple-dipole solutions. Single-dipole solutions show a centrally located source oriented toward the centroparietal regions (Lukas et al., 1990; Sidman et al., 1990). This probably has little meaning, since there are almost certainly multiple sources for the P300. Three-channel Lissajous trajectory analyses of the P300 wave show a trajectory oriented toward the centroparietal region (Attias and Pratt, 1991; Clifford and Williston, 1992). This type of analysis makes an *a priori* assumption that the generators are located in the center of the head. It therefore cannot provide anything more than a very abstract representation of the scalp fields.

Animal Studies

There have been three different kinds of research on the P300 wave in animals. The goal of the first kind of research is to demonstrate that the P300-like waves can occur in animals under conditions that are similar to those of human studies. Experimental paradigms have to be modified, since animals are generally trained to perform rather than instructed to respond. A typical approach is to use the oddball paradigm together with some reinforcement of the oddball stimulus with electrical shock (O'Connor and Starr, 1985) or a juice-reward (Paller et al., 1988). However, some studies have not attempted to involve the animal's attention in this way and have simply used a passive oddball paradigm (Pineda et al., 1989). The key characteristic for an animal homologue of the P300 wave is the dependence of this component on the probability of the stimulus. In studies using both active and passive conditions (Wilder et al., 1981; Paller et al., 1988), the P300-like wave evoked by the improbable stimulus was larger in the active condition.

As previously discussed, the passive paradigm in human subjects evokes a P3a wave that is smaller and more frontal in its scalp distribution than the P300 wave that occurs when the subject is actively attending to the target stimuli. However, if the improbable stimuli are intense (Roth et al., 1982) or if there are long intervals between the targets (Polich, 1989) the P300 wave recorded in a passive paradigm

may become very similar to the larger response obtained when the subject is actively attending.

A second type of animal research determines which areas of the brain are active during the scalp- (or skull-) recorded P300 wave. Animal studies are much less limited than human studies, in which the decisions concerning the electrode locations are made on the basis of the patient's clinical condition rather than on the basis of hypotheses concerning the P300 generators. However, there are problems in determining homologies between animal and human brains, particularly when considering the association cortices. Other problems involve the different geometric arrangements of different brain regions among the different species.

Event-related potentials can be recorded from many different regions of the animal brain during both active and passive P300 paradigms. In the cat, activity has been shown in the thalamus, hippocampus, auditory cortex, and association cortex (Katayama et al., 1985; O'Connor and Starr, 1985; Basar-Eroglu et al., 1991). In the monkey, activity has been recorded in the hippocampus (Paller et al., 1992). Although most studies have used awake animals, P300-like activity has been recorded in anesthetized animals (O'Brien, 1982). Even more intriguing is the finding of long-latency potentials evoked by oddball (or omitted) stimuli in the tectum and retina of fish (Bullock et al., 1990).

A third type of animal study evaluates the effects of lesions to different brain regions. These studies can indicate the cerebral generators of the P300 wave or regions that significantly interact with these generators. Most lesion studies have been negative. In the cat, the auditory P300 response does not seem to be affected by bilateral lesions to the auditory cortex, by extensive lesions to the association cortices or by bilateral hippocampal lesions (Buchwald, 1990). The P300 wave was still present in monkeys with bilateral lesions to the medial temporal lobe (Paller et al., 1988). The only lesions that have significantly reduced the P300 wave have involved the septal area (Harrison et al., 1988) and the locus coeruleus (Pineda et al., 1989). It is highly unlikely that these regions generate the scalp-recorded P300 wave. However, they may modulate or activate the generators. The septal area is a region of the limbic system with close connections to the hippocampus. It sends cholinergic fibers to both hippocampus and neocortex. The locus coeruleus in the pons sends noradrenergic fibers to many different areas of the forebrain.

INDIVIDUAL DIFFERENCES

Age

Goodin et al. (1978a) reported that the latency of the P300 wave in an auditory oddball paradigm was significantly related to age for subjects between 18 and 76 years. These results have been confirmed extensively by many other studies, which have been recently reviewed by Bashore (1990) and by Polich (1991). Rather than repeat their review, I shall highlight some of the issues in this field of research.

The P300 latency in adults shows a significant linear regression on age with a slope of about 1.3 ms/year and a standard error of the regression estimate of about 31 ms (Fig. 6). These numbers represent the average results from Table 5 in Polich's review. Occasional studies have suggested a curvilinear relationship with the slope increasing with increasing age. However, this effect has not been generally found. The age-related changes are similar for auditory, visual, and somatosensory modalities.

The relationships among the P300, RT, and age are quite complex. For simple tasks, age increases the latency of the P300 more than it does the reaction time. For more complex tasks, the reaction time is more affected by age than the P300 wave. These findings may relate to differences in response strategy with older subjects being more conservative on more difficult tasks. However, the interactions between age and task difficulty are variable. Picton et al. (1986) reported that task difficulty had the same effect on the P300 latency in both young and old subjects, whereas Squires et al. (1980) found that increasing task difficulty had a larger effect in older subjects than in young. There seems to be no

significant age-related change in the latency of the P300 wave evoked by an omitted stimulus (Michalewski et al., 1982; Picton et al., 1984). It is possible that this finding and the task difficulty results are related to uncertainty. When a stimulus is omitted, there is little or no uncertainty.

In general, the amplitude of the P300 is smaller in older subjects than it is in younger subjects. It is possible that some of this may be due to latency-variability. Pfefferbaum et al. (1984a) showed that correcting the waveforms for latency-variability prior to averaging removed the age-related amplitude differences in the P300 wave.

Several authors have found that the scalp distribution of the P300 wave changes significantly with age. Pfefferbaum et al. (1984a) and Smith et al. (1980) found that the P300 became more frontal in older subjects. Picton et al. (1984) suggested that this might be due to the P300 wave becoming significantly smaller at the vertex rather than larger over the frontal regions. The age-related changes in the P300 scalp distribution may be caused by age-related changes in waves that overlap the P300 or they may be due to differential effects of age on the different positive waves that make up the P300 wave complex.

Several studies have related these aging data on the P300 latency to neuropsychological tests of cognitive ability. There are three main findings. First, there is little, if any, relationship between the P300 latency and tests of long-term memory such as those that evaluate vocabulary. Second, there is a definite negative correlation between the P300 latency and measures of the capacity of short-term memory such as the digit span (Polich et al., 1983; Verleger et al., 1991). Third, the P300 latency is negatively correlated with performance on timed tasks involving simple problem-solving (Picton, 1988; Emmerson et al., 1989).

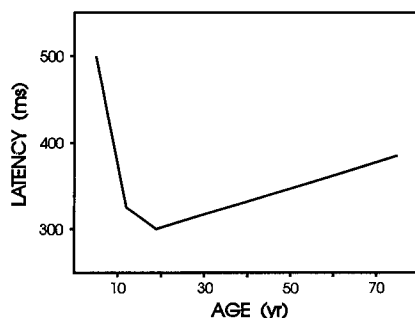


FIG. 6. The effects of age on the P300 latency. This figure presents a diagrammatic summary of the results from many papers. There is a very rapid decrease in the peak latency of the P300 wave from age 5 to 12 years, a somewhat slower decrease in latency until the age of about 18 years and thereafter a slow increase in latency as subjects get older.

Developmental Changes

Determining how the P300 wave develops as children grow up to become adults is very difficult. Artifacts are common and children may have difficulty in sustaining their attention. Once reliable recordings are obtained, one finds that the component structure of the response is often quite different from that recorded in adults (Courchesne, 1990). A large frontocentral negative wave (Nc) may overlap the P300 wave. The Nc is usually evoked by novel stimuli, but in younger children it may also be elicited by simple oddball stimuli. It is difficult

to determine whether the late parietal positive wave recorded in children is homologous to the P300 or to the positive slow wave recorded in adults (Ollo and Squires, 1986; Courchesne, 1990).

From the age of 5 years, this parietal positive wave can be recognized during oddball paradigms. This decreases in latency with increasing age (Taylor et al., 1988; Pearce et al., 1989; Polich et al., 1990; Barajas, 1991). This decrease in latency is most marked between the ages of 5 and 12 years when the P300 latency decreases at a rate of about 25 ms/year (Fig. 6). Between the ages of 12 and 20 years, there is a further decrease in latency of 1–5 ms/year. Minimum latency values occur somewhere between the ages of 15 and 20 years. The changes in the latency of the P300 wave are very similar to the developmental changes in digit span (Polich et al., 1990). Children show more variable data than adults. Some of this may be related to confusion between the P3b and the slow wave. Other differences may be caused by attempting to combine data over two different periods of development—before and after 12 years. Johnson (1989b) found significant differences between the auditory and visual modalities in the development of the P300 latency. The annual rate of change for the auditory modality was approximately twice that of the visual modality.

The amplitude of the P300 increases with increasing age until about age 13, after which it may decrease slightly to normal adult values (Polich et al., 1990). In tasks that involve a great deal of effort, the P300 may be larger in children than in adults (Taylor, 1988). The effects of probability on the P300 wave in children appears similar to the effects noted in adults (Ladish and Polich, 1989).

The scalp distribution of the P300 changes significantly as children grow older. In younger children, the P300 is associated with a simultaneous negativity in the anterior head regions (Fig. 7) (Taylor, 1988). Johnson (1989b) found that the scalp distributions of the P300 wave associated with auditory and visual stimuli were quite different in children. Unlike in adults, in whom the scalp distributions are similar, the visual P300 was larger in frontocentral regions than the auditory P300 wave.

Intelligence and Personality

Studies of the effects of age on the P300 wave have suggested that the latency of this wave is related to the ability of a subject to solve simple problems.

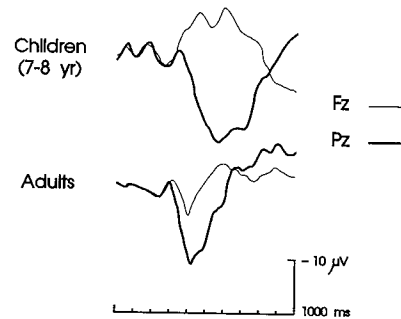


FIG. 7. P300 waves in childhood. These waveforms represent the data recorded from midfrontal (Fz) and midparietal (Pz) electrodes during a visual oddball task wherein the subjects discriminated between different alphabetic characters. The response in the adult subjects shows a P300 wave peaking at approximately 450 ms in the midparietal electrode. At the midfrontal electrode, there is a smaller and slightly earlier positive peak. The children show a large parietal positive wave that is much later than in the adults. At the same time as the parietal positivity there is a large frontal negative wave. These data are adapted from Taylor (1988).

This leads to an important question concerning whether the P300 latency is related to intelligence independently of age. Recently, McGarry-Roberts et al. (1992) evaluated the P300 wave in several tasks of varying complexity in a group of 30 women between the ages of 18 and 25. The subjects pressed a “home” button until making a decision, at which time they moved their finger to press one of two other buttons. This allowed two measurements of response time: reaction time (RT) between the onset of the target and the release of the home button and movement time (MT) between the release of the home button and the final discriminative response. The latency and amplitude of the P300 wave were both negatively correlated with intelligence in this group of subjects. McGarry-Roberts et al. therefore suggested the P300 wave indexes some cognitive process that is related to the general mental ability measured on IQ tests.

Stelmack et al. (1992) looked at these data from the point of view of personality factors as well as IQ. Three main relationships showed up. Extroversion was negatively related to MT, perhaps because of impulsivity on the part of extroverted subjects. Neuroticism was negatively related to P300 latency. Psychoticism appears to be negatively related to the amplitude of the P300 wave. Other studies have reported that extroverts have smaller P300 waves than introverts (Daruna et al., 1985; Pritchard, 1989). This probably relates to the difficulty that extroverts have in maintaining attention for long periods of time (Ditraglia and Polich, 1991).

Absolute Pitch

Individuals with absolute pitch are able to identify the pitch of a sound without having to compare it to a standard stimulus. Klein et al. (1984) studied the P300 wave in subjects with absolute pitch and found that the auditory P300 wave was very small in an oddball paradigm wherein the target differed in frequency from the standard stimulus. The visual P300 wave, when discriminating between H and S, was quite normal. The authors suggested that the P300 wave represents the updating of templates in short-term memory. Since subjects with absolute pitch do not need to use such short-term memory templates they do not need to generate P300 waves to maintain them. However, although the P300 wave is reduced during the auditory oddball task in these subjects, it is still clearly present (Wayman et al., 1992). It is possible that subjects with absolute pitch may not need to pay as much attention to the auditory stimuli as normal subjects.

PHARMACOLOGICAL ASPECTS OF THE P300 WAVE

Alcohol

Many studies have shown that alcohol reduces the amplitude of the P300 wave and increases its latency (Campbell et al., 1984; Rohrbaugh et al., 1987; Lukas et al., 1990). This effect occurs concomitantly with decreases in the size of earlier waves, suggesting that it may be related in part to some generalized depression of cerebral function.

There are intriguing interactions between attentional strategy, task-difficulty, and alcohol. The P300 wave may not be attenuated by alcohol when the task is difficult (Campbell et al., 1984). It is possible that the subject tries to overcome the effects of alcohol when the difficulty of the task requires it. When both targets and distracting stimuli are presented to a subject who has taken alcohol, the P300 wave was reduced to the distracting stimuli but not to the targets (Campbell and Lowick, 1987). Perhaps the inebriated subjects concentrated their limited resources on the task-relevant stimuli and decided not to attend to the distracting stimuli.

Anticholinergic Drugs

The anticholinergic drug scopolamine may significantly reduce the amplitude of the P300 wave and increase its latency (Callaway, 1984; Hammond et al., 1987; Meador et al., 1989). There may be an

almost complete absence of the P300 wave in an auditory oddball task even though the subject can still keep a running mental count of the targets. However, the ability to remember items over short periods of time was significantly decreased during the same period that the P300 amplitude was reduced. Physostigmine, a cholinergic antagonist, could partially reverse the effects of the scopolamine on both the P300 wave and the memory impairment.

The effects of scopolamine are more complex than suggested by these findings in simple oddball tasks (Brandeis et al., 1992). Scopolamine may affect earlier components of the evoked potential as well as the P300. The P300 results may therefore partly reflect disordered sensory processing. Furthermore, the effects of scopolamine are less when the task is more difficult. As with alcohol, subjects may attempt to compensate for the drug effects.

Other Drugs

Callaway (1984) showed that the adrenergic drug methylphenidate does not consistently affect the P300 wave, although it can speed up the RT. Clonidine, another adrenergic drug, attenuates the amplitude of P300, but it is possible that this may be related to its indirect anticholinergic effect (Joseph and Sitaram, 1989). Antiserotonergic drugs do not affect the P300 wave (Meador et al., 1989). L-Dopa decreases the latency of the P300 wave in patients with Parkinson's disease (Stanzione et al., 1991), suggesting that dopaminergic fibers can play some role in the generation of the P300 wave. However, dopaminergic fibers are not absolutely necessary for the P300, since toxic lesions to these fibers do not affect the monkey P300 wave (Glover et al., 1988). Benzodiazepine derivatives reduce the amplitude of the P300 wave (Samra et al., 1988; Milligan et al., 1989; Reinsel et al., 1991). These effects are probably related to the sedative rather than to the amnesic effects of these drugs, since similar results can be obtained with barbiturates and the time course of the P300 reduction was not the same as the time course of the drug-induced amnesia. Antihistamines can reduce P300 amplitude (Loring and Meador, 1989). This effect appears to vary with the sedative effect of the antihistamines.

Anesthetics

Unintentional intraoperative awareness is an important problem in anesthesia. A patient's level

of consciousness is particularly difficult to assess when the patient is paralyzed by neuromuscular blockers. ERPs may become useful in monitoring the level of consciousness during anesthesia (Plourde and Boylan, 1991; Plourde and Picton, 1991). In general, the N100 and P300 waves to an auditory target stimulus are present when a patient detects the target before induction and during recovery from the anesthetic. However, when emerging from the anesthetic, the patient can sometimes respond appropriately to signals without displaying clearly recognizable N100 or P300 waves.

THE P300 IN CLINICAL DISORDERS

Schizophrenia

Schizophrenic patients have been widely studied with the event-related potentials (Pritchard, 1986). All studies agree that the amplitude of the P300 is reduced in schizophrenia (Pfefferbaum et al., 1984b, 1989; Blackwood et al., 1991; Ward et al., 1991) (Fig. 8). This reduction does not seem to be related to lack of attention (Baribeau-Braün et al., 1983) or to medication (Pfefferbaum et al., 1989). The amplitude of the P300 is inversely related to the severity of the patient's symptoms, particularly those considered "negative," such as flattened affect, apathy, and alogia (Pfefferbaum et al., 1989; Ward et al., 1991).

Some recent papers have suggested that the P300 wave is asymmetrical in schizophrenic patients with a reduced amplitude over the left temporal region (Faux et al., 1988). These findings are compatible with other studies suggesting temporal lobe

abnormalities in schizophrenic patients. However, they have been difficult to replicate. Pfefferbaum et al. (1989) found that the P300 in schizophrenics was less parietal in its scalp distribution than the P300 in normal subjects, but they could not detect any significant asymmetries.

Epidemiological evidence suggests a significant genetic predisposition for schizophrenia. Several studies have investigated the event-related potentials in children at risk for developing schizophrenia with the goal of finding a neurophysiological marker for the disease. Although the P300 is reduced in at-risk children with cognitive disorders (Schreiber et al., 1991), there is no clear differentiation between children at risk for schizophrenia and other children (Friedman et al., 1988).

Autism

The P300 wave is reduced in amplitude in patients with autism (Dawson et al., 1988; Oades et al., 1988; Cieselski et al., 1990). Recently, Courchesne et al. (1992) have shown that a late parietal positive wave in response to stimuli that requires a change in attentional strategy may be particularly reduced in autism. This work provides some intriguing information about the pathophysiology of autism, since normal social interactions require constant shifting of attention. Moreover, it suggests that we should perhaps look at behavioral disorders using more specific paradigms than the simple oddball task. In this way, we may be able to find specific cognitive deficits rather than just a general indication of abnormal function.

Other Psychiatric Disorders

The amplitude of the P300 wave is reduced in patients with severe depression (Pfefferbaum et al., 1984b; Diner et al., 1985). In these cases, it is very difficult to evaluate the effects of motivation. The P300 generator may be normal, and the patient may just lack any attentional engagement in the task. The latency of the P300 wave may be increased slightly, but this is usually not as much as in patients with dementia (Squires et al., 1980; Pfefferbaum et al., 1984b).

In some types of psychiatric patients, the P300 may be larger or faster than normal. In obsessive-compulsive patients, the latency of the P300 wave may be reduced (Towey et al., 1990). These patients may suffer from some hyperactivity of their perceptual systems. Psychopathic patients have a larger

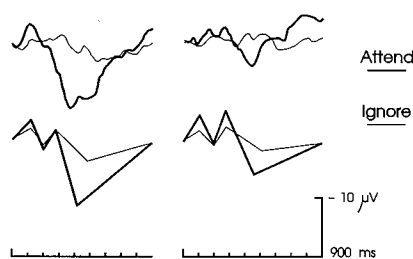


FIG. 8. Schizophrenia. The upper tracings in this figure are the vertex-responses of a typical normal subject (left) and a typical schizophrenic patient (right) during a task involving selective attention to the stimuli presented to one ear in a dichotic listening task. Only those targets to which the subjects responded accurately and rapidly were included in the averages. The lower waveforms represent the mean peak measurements in the experimental groups after removing medication effects. Schizophrenic patients show a smaller P300 wave than the normal subjects. These data are adapted from Baribeau-Braün (1981).

and more prolonged P300 than normal subjects (Raine and Venables, 1988). This suggests some greater allocation of attentional resources to task-relevant events and may relate to the sensation-seeking behavior of these patients.

Dementia

Goodin et al. (1978*b*) reported that the P300 wave was delayed in latency and decreased in amplitude in patients with dementia. These findings have been extensively replicated and are reviewed by Goodin and Aminoff (this issue, pp. 521–525) in this issue. Several aspects of this work are worth emphasizing. First, because of the normal variability in P300 latency, there is overlap between normal subjects and demented patients. Although the P300 can therefore provide helpful information, it cannot always distinguish normal from abnormal findings. Second, the P300 is delayed in many different cognitive disorders. Although a delayed P300 can indicate abnormal cognition, the diagnosis of the type of cognitive disorder will depend on other clinical findings. Third, other ERP waves may also be affected by cerebral disorders. Therefore, one should not concentrate solely on the P300 wave but should measure other components as well. Different patterns of ERP waveforms may distinguish different types of cerebral disorder. Fourth, longitudinal studies of the P300 wave may help in following the course of the dementia (St. Clair et al., 1988) or in monitoring treatment.

Cognitive Disorders in Children

The P300 is abnormally small and delayed in children with various kinds of cognitive dysfunction (Finley et al., 1985; Olo and Squires, 1986). Children with attention deficit disorder have smaller P300 waves than normal children (Holcomb et al., 1986; Robaey et al., 1992). Children with dyslexia have P300 waves that are later and smaller than normal children (Taylor and Keenan, 1990). This is particularly true in younger children with dyslexia. Interestingly, the P300 was reduced when discriminating simple visual shapes as well as letters or words.

Encephalopathy

P300 measurements may be helpful in demonstrating a mild encephalopathy. In metabolic disorders, one is never certain whether mild cognitive

symptoms are caused by metabolic dysfunction in the brain or by anxiety. Although blood tests can demonstrate a metabolic disorder, they do not correlate well with the degree of encephalopathy. The P300 wave can be delayed by hepatic encephalopathy (Davies et al., 1990), renal failure (Cohen et al., 1983), or hemodialysis (Tennyson et al., 1985). The P300 may also be helpful in demonstrating the encephalopathy associated with human immunodeficiency virus (Goodin et al., 1990; Grotemeyer et al., 1992; Olo et al., 1991) and the abnormal cognitive processing that occurs following closed head injury (Deacon and Campbell, 1991).

Alcoholism and Korsakoff's Syndrome

In general, alcoholics have P300 waves that are delayed in latency and reduced in amplitude (Pfefferbaum et al., 1979, 1991). However, these changes may vary with task requirements. For example, the auditory P300 but not the visual P300 waves were delayed in chronic alcoholics. There is some suggestion that the P300 amplitude reduction may be related more to positive family history for alcoholism than to the amount or duration of alcohol intake. If this is so, the amplitude of the P300 wave may be a marker for the genetic predisposition to alcoholism (Pfefferbaum et al., 1991; Whipple et al., 1991). However, these findings are not consistent from one group of subjects to another (Polich, et al., 1988).

Blackwood et al. (1987) found that a group of patients with Korsakoff's amnesic syndrome had normal P300 waves. These patients were quite different from patients with Alzheimer's disease who had small and delayed P300 waves. The patients with Korsakoff's syndrome had been abstinent for more than 6 months, and it is possible that these patients, therefore, differed from the chronic alcoholics examined in other studies. Nevertheless, the most important finding in this study was that the patients showed normal P300 waves despite severe memory impairments.

Lesions of the Limbic System

The recording of P300-like waves in the human hippocampus raised the possibility that this region of the brain might generate the scalp-recorded P300 wave. However, the majority of patients who have had temporal lobectomies for epilepsy do not show any significant difference from normal subjects in their scalp-recorded P300 waves (Stapleton

et al., 1987a; Johnson, 1988; Scheffers et al., 1991). Some studies, however, have shown small reductions in the amplitude of the P300 wave over the side of the lobectomy (McCarthy et al., 1989; Daruna et al., 1989). Auditory and visual P300 waves appear to be differentially affected by temporal lobectomy (Johnson 1989a). Left temporal lobectomy significantly reduced the auditory P300 wave, and right temporal lobectomy significantly reduced the frontal extent of the visual P300 wave.

The P300 wave has also been studied in patients with nonsurgical lesions of the temporal lobe. Rugg et al. (1991) reported a normal P300 in a patient with extensive damage to the left medial temporal lobe caused by an infiltrating glioma. Onofrij et al. (1991) found normal P300 waves in an amnesic patient with bilateral damage of the limbic system following encephalitis. The P300 wave was small, but definitely present. The scalp distribution was different from the scalp distribution of the normal P300 with the waveform being negative over the frontotemporal regions.

Cortical Lesions

The effects of different cortical lesions on the P300 wave have been recently reviewed by Knight (1990). Their findings concerning the auditory P300 wave (Knight et al., 1989) have been extended to the P300 waves evoked by somatosensory stimuli (Yamaguchi and Knight, 1991a,b, 1992). Four major findings from this work can be highlighted. First, the P300 wave to target stimuli is selectively reduced by lesions to the temporoparietal junction, but not by lesions to more superior regions of the parietal cortex. This suggests that the temporoparietal region most likely generates at least some part of the target P300 wave. Second, in patients with unilateral lesions of the temporoparietal region, the target P300 was reduced over both hemispheres. This suggests facilitatory connections between the two hemispheres during the generation of the normal P300 wave. Third, frontal lobe lesions caused a slight reduction in the target P300 wave. This suggests that the frontal cortex may contribute to the generation of the wave or may have a modulatory influence on the generator in the temporoparietal region. Fourth, the P300 to novel stimuli was selectively reduced by lesions to the frontal lobe. This P300 wave was not affected by lesions to the temporoparietal region.

Section of the Corpus Callosum

Kutas et al. (1990) showed that the oddball P300 wave persisted in patients after sectioning of the corpus callosum. However, the disconnection of the hemispheres brought up some asymmetries that were not present in normal subjects. Tones delivered bilaterally elicited a P300 wave that was significantly greater over the right parietal region than over the left. For visual targets, the P300 wave showed a similar asymmetry to stimuli in the left visual field but not to stimuli in the right visual field. Interhemispheric disconnection, therefore, appears to isolate generators of the P300 wave that are concurrently activated in normal subjects. For relatively simple discriminations, a right-sided P300 generator may be the dominant activity.

Thalamic Lesions

Onofrij et al. (1992) have recently demonstrated that unilateral thalamic hemorrhages can delay the P300 but not reduce its amplitude or change its scalp distribution. The lesions were in the posterior superior part of the thalamus. It is tempting to suggest that this region projects to a P300 generator in the temporoparietal cortex.

Multiple Sclerosis

There have been several recent reports of delayed P300 waves in patients with multiple sclerosis (Newton et al., 1989; Geisser et al., 1992; Honig et al., 1992). These delays occur in about half of patients with definite multiple sclerosis. They correlate with subcortical demyelination on imaging and cognitive dysfunction on neuropsychological testing. Deans, Picton, and Nelson (unpublished observations) studied the P300 wave in 16 patients with definite multiple sclerosis who performed a visual oddball task to discriminate whether a small foveal rectangle was vertical or horizontal. The recordings showed several patterns (Fig. 9). The most common abnormality was a delay in both the occipital visual EP and the P300. In other patients, the P300 was delayed with a normal visual evoked potential. In some patients, the P300 showed a normal latency despite a delayed visual evoked potential. This suggests that the P300 and the visual evoked potential are initiated in parallel.

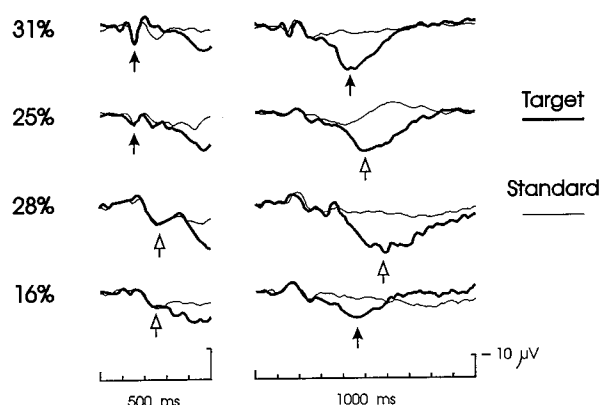


FIG. 9. Multiple sclerosis. This figure shows the evoked potentials from four different patients with multiple sclerosis, chosen to illustrate the different patterns of response during a visual oddball task, wherein the patients discriminated a small vertical rectangle from a horizontal rectangle. In the left column are shown the responses recorded from the occiput (Oz). In the right column are shown (on a longer time scale) the responses recorded from the midparietal electrode (Pz). The percentages on the left of the figure indicate the incidence of these different types of pattern in a group of 16 patients with definite multiple sclerosis (32 eyes). The filled arrows indicated normal peak latencies; the open arrows indicate abnormally delayed peaks. These waveforms are taken from unpublished data of Deans, Picton, and Nelson.

UNANSWERED QUESTIONS

What Generates the Scalp-Recorded P300 Wave?

The present literature provides no clear statement concerning the intracerebral origin of the P300 wave. Perhaps the P300 wave is not generated in one place. It may represent concurrent activity in multiple regions of the brain. The regions of the brain most involved in this interactive process would be the polymodal association areas of the frontal, parietal, and temporal lobes and the limbic system.

However, the P300 wave probably does not represent a widespread nonspecific process. More likely, it represents a multifocal rather than a generalized process. One reason for proposing this derives from the variability in the scalp distribution of the P300 wave. Multiple separate regions specifically activated by various aspects of a particular task would explain these different scalp distributions more easily than a nonspecific process. It is possible that the different areas of cortex contributing to the P300 wave may be quite focal. This is suggested by the epidural recordings of Neshige and Lüders (1992). Activity at several such focal areas could at a distance look very similar to activity over a large area.

What is the role played by subcortical structures

such as the locus coeruleus and the septal area? They are probably not the source of the scalp-recorded waves, since their structures do not generate large fields at a distance. They might serve to "connect" regions of the cortex by modulating or facilitating their activity.

What Is the Function of the P300 Wave?

Over the past quarter century many different ideas have been suggested, but none has clearly explained what the P300 wave does in the brain. We know that the P300 wave has something to do with cognition but we are not sure exactly what.

Initial studies suggested that the P300 wave was associated with the decision that something important had occurred. It was generally referred to as the "Aha" wave. The major problem with this proposal was that a subject could accurately press a button before the peak of the P300 wave. The decision leading to the button-press must therefore have preceded the process that generates the P300 wave. It is possible that the button-press might occur before the subject is aware of the decision to press the button. However, one was left with the fact that the P300 follows the decision.

The search then turned to cognitive processes that might follow cognitive decisions. One suggestion was cognitive or perceptual "closure" (Desmedt, 1980; Verleger, 1988). Exactly what this "phasic physiological deactivation" (Verleger, 1988) means in either cognitive or physiological terms is not obvious, perhaps the erasing of processed information or the resetting of perceptual analyzers. It is doubtful that the brain would use a specifically inhibitory process for this, since adaptation is the usual way of allowing new information to be processed.

Nevertheless, several studies have suggested a decrease in cerebral processing at the time of the P300 wave. When an oddball stimulus is detected, the speed of response in a secondary RT task slows down (Woodward et al., 1991), and the background EEG simplifies itself in terms of its chaotic dimension (Skinner et al., 1992). However, these phenomena do not always follow the same time course as the P300 wave. Studies of the perception of simple tunes have shown that the P300 does not always occur at the end of the tune, a time when one would predict perceptual closure (Besson and Macar, 1987; Verleger, 1990).

Another possibility is that memory might be updated after incoming information has been evalu-

ated (Donchin, 1981; Donchin and Coles, 1988). Although several studies have shown that the amplitude of the P300 wave evoked by a stimulus varies with the ability to recall that stimulus later, other studies do not (reviewed by Verleger, 1988). The relation might therefore be through some other variable such as "distinctiveness." If this is so, the P300 may not be tightly related to memory updating, particularly in situations in which distinctiveness is not as important as other factors (Fabiani et al., 1990).

The updating of memory requires more than just the fixing of a new pattern in a specific cerebral store. Human memories are probably represented in a composite trace with many different memories superimposed on an extensive neuronal network (Metcalf, 1992). Such a composite memory trace must be monitored and controlled to ensure that it does not "explode" or become so active that it cannot code anything. Updating must strengthen patterns for new information while not enhancing the activity of old patterns. Metcalf (1992) has suggested that the P300 wave may represent the control of this updating process, perhaps as a signal from neocortex to the hippocampus. Hippocampal lesions would not affect the P300 but would affect memory updating because the P300 message is not received.

The problem with any memory-updating theory is that the P300 occurs in situations wherein one would not think that updating is necessary. In the usual oddball task, the brain should quickly develop a memory model that incorporates the possibility of an occasional target stimulus. Updating this model should not be necessary each time the target occurs.

Cognitive theory suggests that information is processed in two different ways. Most information is processed automatically using fast, efficient, unchecked parallel processing. Controlled processing is a different type of processing that is slow, effortful, conscious, and serial. Posner et al. (1973) initially suggested that the P300 might relate in some way to controlled processing. Rösler (1983) pointed out that the P300 wave occurs whenever an event requires controlled processing. The latency of the P300 is related to the termination of automatic processing. Some of the discussions at the first Carmel Conference on Cognitive Psychophysiology raised the possibility that the P300 might reflect the transfer of information to controlled processing or consciousness (Picton et al., 1984). Once the information is in consciousness, a variety of responses may

be initiated: memories may be updated if necessary, hypotheses may be tested, behavior may be initiated. All of these consciously controlled responses would occur after the P300 wave. However, simple responses may occur automatically prior to the P300 and prior to awareness.

Evidence against this hypothesis might come from several studies in which consciousness is dissociated from behavior. P300 waves have been recorded in patients with blindsight who are not conscious of the stimuli (Shefrin et al., 1988). Furthermore, in a patient with prosopagnosia, the P300 differentiated between familiar and unfamiliar faces even when they were not recognized by the patient (Renault et al., 1989). Normal subjects may sometimes show a P300 for somatosensory stimuli that are below the threshold for conscious detection (Barrett et al., 1979). In all these cases, one might suggest that some information reached consciousness but was not sufficient to be recognized.

Another difficulty with the hypothesis is that we have little idea of the nature of conscious processing. It probably involves the concomitant and connected activity of many different regions of the cortex. The pattern of the connections would vary with the content of consciousness. This vague concept would fit with a P300 wave generated in multiple regions of the cortex. However, vague concepts are not easily tested.

The proposal by Donchin and colleagues that the P300 represents context-updating in "working memory" may not be very different from the suggestion that the P300 represents the transfer of information to consciousness. Working memory is where the contents of consciousness are located if they are located at all. However, much of the information that reaches consciousness may not need to be incorporated into the individual's model of the world. Updating of models is not a necessary concomitant of conscious processing.

What Is the Clinical Usefulness of the P300 Wave?

Since we are uncertain about the cerebral origin of the P300 wave and since we do not know the exact role that it plays in cognitive processing, the clinical usefulness of this wave is limited. However, it may provide a general index of cognitive processing.

A normal P300 wave may therefore indicate that a subject is cognitively processing the evoking stimulus. This may be helpful in demonstrating the

brain's ability to discriminate between stimuli in cases of functional sensory impairment. It may also be helpful in suggesting that a subject is conscious during anesthesia.

If the P300 wave is abnormally small or delayed, there is probably some abnormality of cognitive processing. Latency is a much more reliable indicator than amplitude, since latency is difficult to alter with attention. Furthermore, the normal limits for latency are less broad than the normal limits for amplitude. The use of the P300 latency to demonstrate cognitive dysfunction is important in such conditions as early dementia or the cognitive dysfunction that occurs with metabolic disorders.

Because of the wide limits of normal variability, measurements of the P300 often cannot provide specific diagnostic information. Rather, they can be used to shift the probability of a diagnosis in one direction or the other. As such, they must not be used in isolation but only together with other assessments of the patient.

Where Do We Go from Here?

Probably the most important question concerning the P300 wave is the nature of its origin within the brain. Since the P300 wave is probably generated at multiple locations within the brain, and since these locations may vary from task to task and from individual to individual, it will not be easy to demonstrate the sources. The new techniques of source analysis will have to be refined so that they can consider experimental manipulations as well as different electrode locations. In order for this problem to be tractable, certain constraints will be necessary. These can come from imaging techniques and from magnetoencephalography.

There is a great need for further studies in animals. One thing that is totally missing from our present information is what might be happening in the cortex during the generation of a P300-like wave. Is the P300 wave related to glial activity or to neuronal activity? If it is related to neuronal activity, which neurons are being activated or inhibited?

Our understanding of the function of the P300 process will require more detailed hypotheses concerning the nature of consciousness. A network of neurons can automatically process complex information. This processing may be associated with event-related potentials even in fairly simple systems. What determines that such processing is conscious? Is it a different mode of activity requiring connections through large distances? Does the P300

just represent the information transmitted to consciousness from multiple automatic analyzers, or does some part of the P300 reflect the actual activation of conscious processing?

This review has been limited to the P300 wave. Our evaluation of cerebral function should not be limited in this way. There are multiple overlapping processes in the scalp-recorded event-related potentials. To look at one and not the others is to put on blinkers.

In all clinical studies, there is a tension between the need for a standard clinical test and the relevance of that test for a particular patient. It is always necessary to understand the limits of normal, and these are far easier to determine for a simple test than for one that has many parameters. However, a simple test may miss the abnormality or be so nonspecific that it is unhelpful. I think we have reached this state with the oddball P300 wave. We need better paradigms. We need to adjust our tests so that they can evaluate a specific hypothesis about a patient or a disorder (Kutas, 1991). Many different paradigms are available (Fabiani et al., 1987). When evaluating patients with memory disorders, we should use paradigms that involve memory (Starr and Barrett, 1987). When evaluating patients with attentional disorders, we should use paradigms that involve different levels of attention (Baribeau-Braün et al., 1983; Ward et al., 1991). This will require close collaboration between clinicians who know the patients and neurophysiologists who know the different tests that are available.

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