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Marta Kutas and Steven A. Hillyard

Event-Related Potentials and Psychopathology

Since the initial observation that brain waves could be recorded from the human scalp, it has been assumed that these voltage oscillations would ultimately reveal something about the physiologic bases of mental states, both normal and pathologic. The scalp-recorded field potentials of the brain, which include the ongoing electroencephalogram (EEG) and the briefer evoked or event-related potentials, are generally considered to represent the summated electrical activity of large numbers of neural (and perhaps glial) elements acting in synchrony. The spontaneous rhythms of the EEG are highly responsive to changes in state of arousal, the sleep-wake cycle and a number of neurologic syndromes and have occasionally been linked with psychiatric conditions. The main emphasis of this chapter, however, will be on the phasic brain potentials that are embedded in the EEG in association with sensory, motor, and cognitive events. The evidence linking these scalp-recorded potentials with different classes of perceptual and cognitive events will be surveyed, with particular emphasis on physiologic signs of disordered information processing in association with psychopathology.

The delivery of a sensory stimulus triggers a series of voltage peaks and troughs (often referred to as "components") lasting for several hundreds of milliseconds; this voltage–time complex is called an evoked response or an evoked potential (EP) (Fig. 1).[1] An EP is usually considerably smaller in amplitude than the ongoing EEG and must, therefore, be extracted by a computerized averaging procedure. This involves recording the EPs to repeated stimulus presentations, under the assumption that those aspects of processing that are time-locked to the stimulus will summate and reveal a characteristic response waveform, while the "random" fluctuations of the EEG will tend to cancel each other. The number of repetitions needed for a reliable average depends on the amplitude of the particular EP under study, since the averaging process improves the resolution of the evoked signal in proportion to the square root of the number of responses included.

The peaks or components of an EP are typically labeled according to their polarity (negative [N] or positive [P]) and latency. In some cases the peaks are designated by their ordinal position in the waveform (*e.g.*, N1, P1, N2) and in others by their latency in milliseconds (*e.g.*, N100, P230, P300). On occasion, labels that refer to the assumed functional role or anatomic location of the EP components have been adopted. As a general rule, the earlier components (with latencies of less than 100 msec) are highly consistent within an individual for a particular type of stimulus; their amplitudes, latencies, and scalp distributions are highly reproducible from one test session to the next. Systematic variations in the physical parameters of the evoking stimulus (*e.g.*, intensity, frequency, duration) result in predictable changes in these early components in accordance with the altered activation of the sensory pathways. Thus, the earlier evoked components are considered to be "exogenous" or stimulus bound; they generally show little sensitivity to the state of alertness or attentiveness of the subject. It is this invariance in the face of changing psychological state that has made the exogenous components an excellent diagnostic tool for certain sensory and neurologic disorders.[2–4]

For the psychophysiologist interested in the neural bases of mental processes, the more inform-

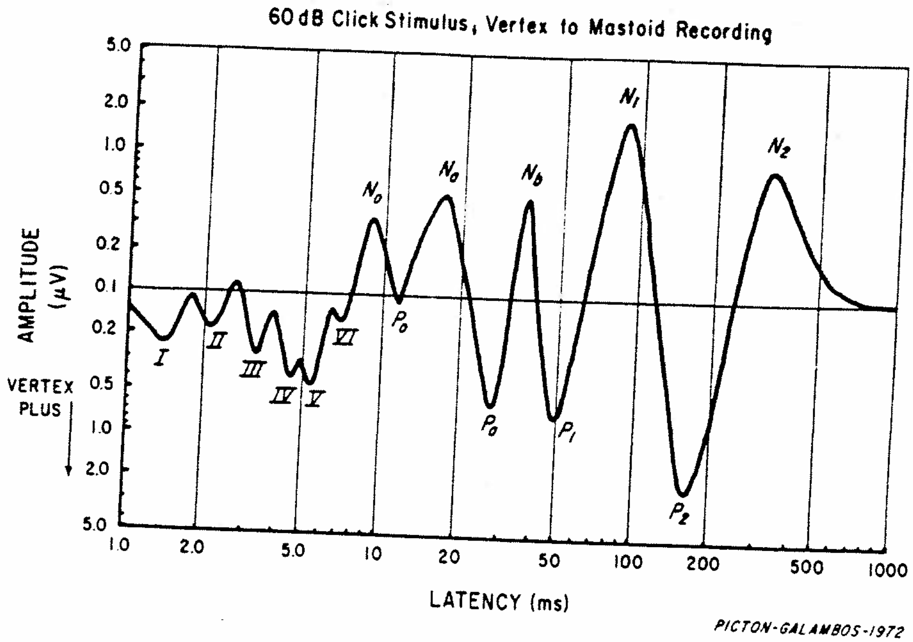

Fig. 1. The characteristic sequence of components in the human auditory evoked potential plotted on log-log coordinates. (Picton TW, Hillyard SA, Krausz HI et al: Human auditory evoked potentials: I. Evaluation of components. Electroencephalogr Clin Neurophysiol 36:179–190, 1974)

ative brain waves are the so-called endogenous components, which may precede or follow a triggering event by many hundreds of milliseconds. An "event" in this case refers to a stimulus, a response, a voluntary movement, or a cognitive process for which an external timing marker is available so that time-locked electrical brain activity (the event-related potential [ERP]) can be examined. The responsivity of endogenous components to variations in the physical stimulus parameters is relatively small in comparison with their sensitivity to experimental instructions and the subjects' intentions, decisions, expectancies, strategies, mental set, and so on. Endogenous ERP components are thus not "evoked" by a stimulus but are elicited in association with the perceptual and cognitive processing that is "provoked" by that stimulus. The same physical stimulus may or may not be followed by a particular endogenous component depending on how the subject chooses to process that information. On occasion, as in the "missing stimulus" paradigm, an endogenous ERP may be time-locked to the absence of a physical event. The term *late component* is often used interchangeably with that of *endogenous component* because most potentials in this class occur with a latency beyond 100 msec.

Although the neurophysiologic mechanisms underlying the scalp-recorded ERPs are largely unknown, these potentials appear to be reliable manifestations of a wide variety of informational transactions in the brain. It must be acknowledged, however, that ERPs are rather remote measures of the brain's electrical output and, thus, entail serious limitations. In most cases it has not been possible to pinpoint the anatomic site of the intracranial generators of the scalp-recorded ERPs. Furthermore, since ERPs reflect primarily the synchronous activity of a large neuronal population, cognitive acts that involve temporally dispersed processing may not produce a surface ERP. Finally, a visible peak or trough in the scalp-recorded ERP may represent the summation of activity from different brain sources that is related in different ways to task parameters and response requirements. Despite these difficulties, the ERP methodology remains one of the few techniques currently available for recording the dynamic patterns of neural activity that underlie specific cognitive acts.

A major goal of ERP research is to identify specific ERP components as markers of specific modes or stages of information processing. This is generally accomplished by systematic study of the correlations between ERP measures, stimulus and response factors, and task performance. Once validated in this way, ERP results can be used as converging operations with behavioral measures to clarify the timing, order, and interactions of processing events and to help choose among serial, parallel, and hierarchical mechanisms of information processing. In this way the ERPs are beginning to yield new information about the neural bases of cognitive processes, including selective attention, recognition memory, decision making, and language functions.

Clinical Uses of Sensory EPs

In several cases, the anatomic origins of sensory EP components have been identified. For example, the initial six waves of the auditory brainstem potential (ABR) originate in specific relay nuclei and pathways, including the auditory nerve (wave I) and inferior colliculus (waves IV–V). The early components of the somatosensory EP to a peripheral nerve shock have similarly been localized to specific structures in the afferent pathways and primary cortical areas. For stimuli in all modalities, the spatiotemporal configuration of the exogenous EP is determined by the integrity and organization of the mediating sensory pathways and by the physical properties of the evoking stimulus. Certain of these EP components are obtained so consistently from normal subjects that small deviations from established norms indicate neurologic or sensory dysfunction. Thus, sensory EPs are in routine use by the practicing ophthalmologist, audiologist, and neurologist for purposes that include helping to confirm diagnoses of disordered sensory function, aiding in localizing the site of lesions along the sensory pathways, following the course of the sensorineural disease processes, and providing an objective index of the efficacy of therapy. The EP method has proved particularly valuable in the diagnosis of clinically silent lesions (*e.g.*, in demyelinating diseases) that are difficult to detect in computed tomographic (CT) scan records.

Because it provides an objective method of testing sensory function, the EP technique can be used in the assessment of impaired vision, hearing, or somatic sensation. Abnormalities may manifest themselves through (1) absence of an EP component, (2) amplitudes or latencies that deviate beyond the normal range, (3) failure of the response to follow standard input–output functions, or (4) an abnormal component in the waveform. For example, the visual evoked potential (VEP) to a pattern-shift stimulus recorded in conjunction with the electroretinogram (ERG) can aid the ophthalmologist in localizing a disease process to specific levels of the visual pathway. Auditory evoked potentials (AEP) are used widely to test for hearing disorders, particularly in cases in which subjective audiometry is difficult (*e.g.*, with demented individuals) or impossible (*e.g.*, with infants). Similarly, the somatosensory evoked potential (SEP) has proven valuable in diagnosing peripheral neuropathies and lesions affecting the dorsal column–medial lemniscal pathways.

Endogenous ERPs and Cognition

ERPs recorded from the human scalp have been used to evaluate perceptual, motor, and cognitive processes in normal persons as well as in patients presumed to have deficiencies in these areas. The term *cognitive* subsumes a broad range of psychological concepts, including attention, expectancy, surprise, storage and retrieval of information from memory, and linguistic processing, among many others. The relationships between ERPs and cognition are discussed in detail in several recent books and reviews.[5–12]

ENDOGENOUS BRAIN POTENTIALS AND PREPARATION

When a person prepares to take in sensory information or to generate a motor act, specific brain wave patterns develop within the preparatory interval. Among the most prominent of these are the movement-related potentials and the contingent negative variation.

Movement-Related Potentials

A characteristic series of potentials can be recorded on the human scalp both preceding and following voluntary movements. Postmovement potentials were first reported by Bates[13] in 1951; premovement activity, however, was not observed until the early 1960s when it became possible to computer-average the ERP preceding movement by playing tape-recorded EEG data backward in time. Using this procedure, Kornhuber and Deecke,[14] in Germany, and Vaughan and his colleagues,[15] in New York, demonstrated a slow negative shift averaging from 5 μV to 15 μV and preceding movement onset by as much as 1 second. This negativity was most pronounced in electrodes overlying the motor cortex, peaked around the time of the response, and gave way to a positive-going potential after the movement.

Several distinct components were identified by these investigators within the complex of movement-related potentials (Fig. 2). The slow negative shift, termed the *readiness potential* (RP) or N1 component, begins as a symmetrical wave over central scalp locations 1 to 1.5 seconds prior to movement and then becomes larger contralaterally. The RP is generally taken to be a reflection of the cortical processes associated with preparation for move-

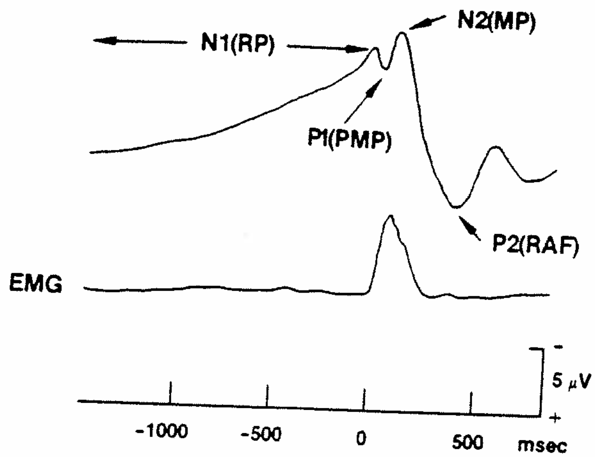

Fig. 2. Schematic illustration of movement-related potential accompanying a voluntary hand movement. The components are labeled according to the terminology of Vaughan and colleagues and Kornhuber and colleagues (in parentheses). Also shown is the integrated electromyographic (EMG) activity of the responding arm. The ERPs are averaged with respect to the onset of EMG activity at time zero.

ment. Its amplitude is influenced by the speed, force, and duration of movement, as well as by subject handedness.[16] Eighty to 90 msec prior to movement onset a small and more variable positive deflection is seen (the premotion positivity or P1). Although this positive wave is the smallest of the movement-related components, Kornhuber and colleagues have proposed that it marks the initiation of movement in a corticocerebellar–motor cortex loop. Immediately following the premotion positivity is a sharp negative wave that is localized over the precentral region contralateral to the responding limb; this "motor potential" or N2 component occurs very near the onset of movement and appears to be an expression of the activation of corticospinal tract neurons in the motor cortex. Finally, following the onset of muscle contraction by 50 msec to 150 msec are a series of positive deflections (the P2 or reafference potential) that represents the proprioceptive and kinesthetic feedback from the movement. ERP investigations with monkeys have revealed remarkably similar potentials for which cortical localization has been possible.[17,18]

Most research on the movement-related potentials has concentrated on relatively simple, upper limb movements. More recent work, however, has branched out to the description of potentials preceding skilled hand and foot movements. ERPs preceding eye movements and speech have also been reported, although it has proven very difficult to separate the brain potentials of interest from concurrent bioelectrical artifacts arising from movements of the eyes, tongue, and facial musculature.[12–16]

Only a few investigators have examined movement-related potentials in patients with neurologic disorders.[18–20] Patients with hemiparesis due to unilateral cerebral lesions tend to have smaller amplitude RPs over the affected hemisphere. Similarly, patients with hemiparkinsonism show reduced RPs over the affected side. Studies of age-matched controls for patients with parkinsonism led to observations of age-related changes in the movement-related potentials.[21] The readiness potential was reported to show a gradual reduction in amplitude with age, most evident after the fourth decade of life; a similar decline was not seen in the motor potential. Occasionally, an apparently healthy elderly individual was found to generate a positive RP across the scalp, although this pattern was characteristic of patients with bilateral parkinsonism.

To the extent that it has been investigated, movement-related potentials appear to be abnormal in psychotic patients.[22–24] In particular, patients with psychosis display abnormally prolonged RPs, an effect not seen in patients with neurotic disorders. There is some controversy as to the specificity of this finding to movement potentials *per se,* since such patients also tend to show prolongation of other slow negative ERPs, such as the contingent negative variation or postimperative negative variation.

Contingent Negative Variation

In 1964, Grey Walter and his colleagues[25] discovered that a slow, negative potential shift developed on the scalp during the interval between a warning stimulus and a subsequent imperative stimulus requiring a motor response (Fig. 3). This steady potential persisted throughout the duration of the foreperiod and was termed the *contingent negative variation* (CNV) because it depended on the subject's appreciation of the contingency (pairing) between the successive events. It was soon observed that the CNV could be elicited prior to perceptual judgments as well as motor acts, although its amplitude was generally larger when overt movements were required.

For many years, the CNV was at the center of research in cognitive psychophysiology, being implicated in processes of attention, intention, preparation, expectancy, associative memory, arousal, alertness, motivation, effort, and so on.[26,27] This re-

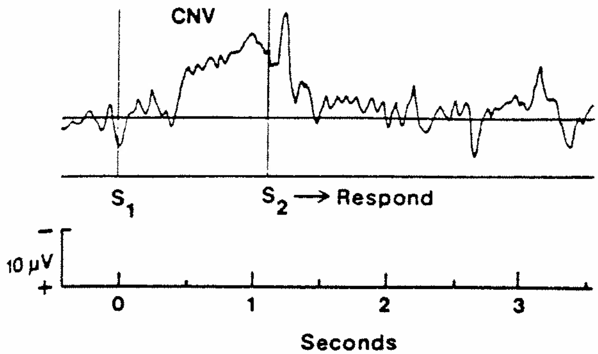

Fig. 3. The shaded area represents the contingent negative variation (CNV) arising in the interval between a warning flash (S_1) and a subsequent tone (S_2), to which a prompt motor response is required. Recordings were made from the central scalp (vertex) with direct current amplifiers.

sulted from its apparent sensitivity to a wide variety of task and subject variables. For example, CNV amplitudes were usually enhanced when the second stimulus of the eliciting pair was noxious (as opposed to innocuous) or when it was near threshold and difficult to detect (as opposed to normal intensity). CNV amplitudes were also enhanced under conditions of increased muscular effort or of greater monetary reward. Distractions of various sorts, on the other hand, tended to decrease CNV amplitude. Thus, although many task manipulations had an influence on the CNV, no one factor accounted for a great deal of its variability. Furthermore, CNV amplitudes seldom correlated strongly with subsequent behavioral performance.

As ERP researchers came to doubt the psychological specificity of the CNV, a new way of looking at it emerged.[28] Several investigators proposed that the CNV actually comprised separate subcomponents, an early phase associated with the processing of the warning stimulus and a later phase related to the preparation for a motor response. The strongest version of the two-component interpretation held that each of these waves can be elicited individually, that neither is unique to the paired stimulus situation, and that the so-called CNV is a simple summation of these separate potentials.[29]

Because of its hypothesized link with orienting processes, the early phase of the CNV has been called the O wave. Accordingly, its amplitude is responsive to changes in the modality, intensity, and duration of the eliciting stimulus. In contrast, the terminal phase of the CNV, sometimes referred to as the E wave or expectancy wave, is relatively insensitive to variations in the physical parameters of the warning stimulus. Rather, it appears to be related to the preparation for movement. This phase of the CNV is larger preceding fast than slow reaction-time responses and is greatly attenuated when no motor response is required. Since the E wave is quite similar in waveform and scalp topography to the readiness potential observed preceding voluntary movements, many researchers consider the two components to be equivalent. Further work is needed to ascertain whether the CNV can be accounted for completely by summation of an O wave and an E wave, or whether other subcomponents exist that reflect the preparation for upcoming perceptual or cognitive acts.

There is conflicting evidence regarding the effects of aging on the CNV. Some investigations report no significant age-related differences,[30,31] whereas others have noted changes in either CNV morphology or amplitude.[32,33] The changes that have been observed include a general reduction in CNV amplitude with advancing age (65 years and above), in some cases across all scalp locations and in others confined to frontal sites.[34] Such results underscore the necessity of including age-matched controls when examining these slow negative potentials in psychiatric groups.

Postimperative Negative Variation

In the early 1970s, Timsit-Berthier and her colleagues[35] reported that the CNV was abnormally prolonged for several seconds in most psychotics and to an intermediate degree in some neurotics as well. This phenomenon was called the postimperative negative variation (PINV). It has since been shown that transitory PINVs are sometimes seen in normal subjects under stressful conditions,[36] in young children,[37,38] and in patients with organic brain damage in addition to psychotic patients with poor prognosis.[35,39] This prolongation of the CNV was considered an index of the patients' failure to terminate processing and relax their attention in a normal fashion.

Most comparisons of these slow negative potential shifts (RP, CNV, PINV) between psychopathologic groups and normal controls have revealed statistically reliable differences.[40] Although these ERP differences seem to lack diagnostic specificity, it is the case that extremely abnormal CNV values indicate psychotic as opposed to neurotic illnesses with a fairly high probability. On the whole, psychiatric patients including schizophrenic, psychotic, depressed, and manic individuals are characterized by attenuated negativities during preparatory intervals and by prolonged negativities following these intervals. This reduction in CNV amplitude is generally interpreted as reflecting a combination of increased anxiety and arousal and decreased attention.[41] The impairment in maintaining attentional set is generally attributed to a heightened susceptibility to internal (*e.g.*, hallucinations) and external distractions. Given the wide range of overlapping psychological constructs with which these slow potentials have been associated, however, it would be premature to conclude that these ERP abnormalities relate specifically to altered cognitive functioning in psychopathology.

ENDOGENOUS BRAIN POTENTIALS AND SELECTIVE ATTENTION

Everyone has an intuitive feel for what it means to pay attention to something, but the concept of *selective* attention is generally defined in terms of the preferential processing of some stimulus classes in relation to others. A central question in attention research concerns the level of the sensory systems at which stimulus selections and rejections are accomplished. Some investigators have proposed an early stage of processing ("stimulus set") that rejects stimuli outside an attended sensory channel after a cursory analysis,[42] while others have argued that all stimuli are processed fully in their attributes before any selections are made.[43] Such theoretic questions are particularly amenable to investigation by the ERP methodology. The ERP is unique in providing online, immediate information of how stimuli are being processed in both the attended and rejected channels without the limitations imposed by the requirement for continuous behavioral responses.

Over the past decade a substantial body of evidence has accumulated showing that ERPs are reliable signs of stimulus selection processes under appropriately controlled conditions.[8,11,44,45] The experimental design requirements for such experiments have been detailed in several sources.[46,47] Briefly, in order to prove that an ERP component correlates specifically with selective attention rather than with general changes in arousal, it is necessary to ensure that the physical stimulus is held constant at the receptor across experimental conditions; present the attended and unattended stimuli according to a randomized sequence (*i.e.*, unpredictably); use the same sequence of stimuli for the attended and unattended conditions in a counterbalanced fashion; and collect behavioral measures concurrently with the ERP recordings. Present-day selective-attention experiments typically involve the presentation of two or more classes of stimuli on an unpredictable basis, with attention being alternated according to instructions between one class or channel and the other(s). In addition, most of these experiments are designed so that the stimuli within an attended or unattended channel consist of both standard and target stimuli; the targets generally occur infrequently and are the only stimuli that require an overt response. Experiments of this type have been carried out with auditory, visual, and somatosensory signals.

In the auditory modality, the principal effect of attending to one channel of sounds (*e.g.*, those in one ear) and simultaneously ignoring another channel (*e.g.*, the other ear) is an enlargement of a negative ERP to the attended stimuli in the region of the N1 component at a latency of 100 msec or so (Fig. 4). Several studies have shown that this attention-related negativity can be dissociated from the N1 component itself and often extends for several hundreds of milliseconds beyond the N1 peak. This negativity is best visualized in the difference wave generated by subtracting the ERP to stimuli in an unattended channel from the ERP to those same stimuli when they are being attended (Fig. 5). This ERP difference has been termed the *N1 effect, processing negativity*, or *negative difference (ND) wave*.

Attended auditory channels differing in pitch, location, or intensity from unattended channels can elicit Nd waves. These stimuli are most effective in generating an Nd wave when presented at very rapid rates (interstimulus intervals of 200 msec–400 msec) or under conditions of increased task difficulty. Slower rates of stimulation yield an Nd wave with a delayed onset. The latency of onset of the Nd wave is also dependent on the discriminability of the cue defining the attended and unattended channels; the more difficult the discrimination, the later is the onset of the Nd. The functional characteristics of the Nd component correspond closely to the "stimulus set" mode of attention. Accordingly, the Nd has been considered as a sign of the further processing of attended-channel stimuli for their task-relevant properties following the early, stimulus set selection. The more prolonged portion of the Nd has been interpreted as a sign of the maintenance in short-term memory of the stimulus features that define the attended channel.[44]

Visual selective attention affects a different set of ERP components.[11,49,50] For example, when subjects attend to flashes in one visual field while ignoring concurrent flashes in the opposite field, the

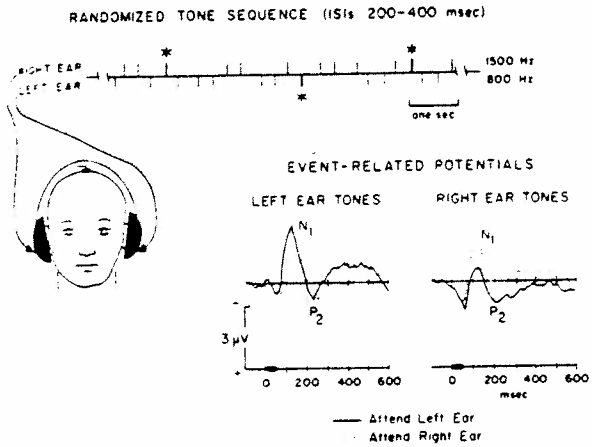

Fig. 4. Paradigm for demonstrating early ERP changes with channel selective attention. Randomized sequences of tones are delivered to the left (800 Hz) and right (1500 Hz) ears at intervals shown on upper time axis. Asterisks indicate slightly deviant "target" tones. Subjects have to respond to detected targets in the attended ear; targets in the unattended ear are ignored. At the bottom right are shown the grand average ERPs to tones in each ear as a function of attend-left and attend-right conditions. The shaded area represents the difference waveform called the Nd, or negative difference, wave associated with the between-channel selection. (Hillyard SA, Simpson GV, Woods DL et al: Event-related brain potentials and selective attention to different modalities. In Reinoso F [ed]: IBRO Conference on Neural Integration at Basic and Cortical Levels, Toledo, Spain [in press])

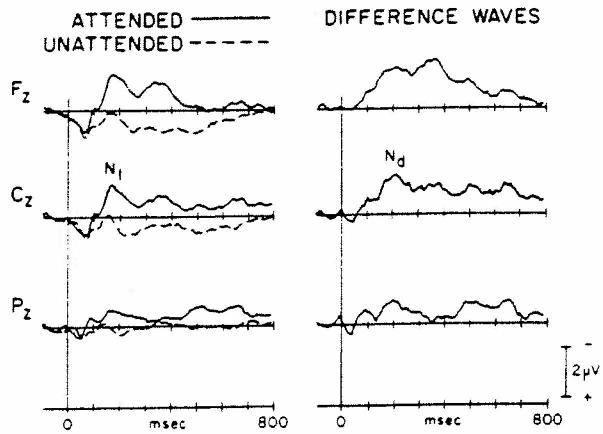

Fig. 5. ERPs associated with selective attention to one of two channels of tones distinguished by frequency cues (300 Hz vs 700 Hz). High and low frequency tones were presented in a random order at a rapid rate (three per second). Subjects attended to one channel at a time and responded to targets of longer duration therein. In the right column are shown the Nd components produced by subtracting unattended from attended ERPs. (Hillyard SA, Kutas M: Electrophysiology of cognitive processing. Annu Rev Psychol 34:33–61, 1983)

attended flashes are associated with ERPs with an enlarged sequence of parieto-occipital waves, including P130, N170, P220, and N280 peaks. The morphology of these components suggests that visual-spatial attention acts by modulating a series of exogenous components of the VEP rather than by invoking an endogenous ERP. Selective attention to other types of visual cues, such as color, spatial frequency, orientation, and contour is manifested in a different ERP configuration, which includes a broad, predominantly endogenous negativity similar to the auditory Nd wave but largest over the parieto-occipital scalp. Somatosensory selective attention also results in an enhancement of a negative component, the N140, which may or may not be wholly exogenous; this negativity tends to have a contralateral distribution over the sensorimotor regions of the cortex.[51]

The ERP signs of selective attention seem to be quite similar across the life span from adolescence to advanced age.[52] The robustness and sensitivity of the auditory Nd effect in particular has made it useful for evaluating patient groups with hypothesized deficits in attention. Research with hyperactive children has documented an abnormally small amplitude N1 component as well as a diminished attention-related negativity (Nd) during selective attention manipulations.[53] Such children also showed reduced late positive (P300) components following target stimuli within an attended channel.[54] These electrophysiologic abnormalities tended to parallel poor behavioral performance. Both ERP and behavioral indicators approached more normal values with acute doses of medication (such as amphetamine or methylphenidate) when evaluated in a subset of the subjects classified as clinical responders.[55–57] Several other ERP characteristics have been used as well to differentiate responders from nonresponders.[58–63] The N1 enhancement to attended channels of tones (the Nd effect) is also reportedly below that of age-matched controls in adolescents who were formerly hyperactive but whose clinical symptoms had subsided (Fig. 6).[64]

Abnormal selective attention effects based on the N1/Nd component have also been reported for adult schizophrenics.[65] By this electrophysiologic criterion, the schizophrenics seemed to be able to focus attention effectively on tones in one ear and ignore tones in the opposite ear when the stimuli were presented at a fairly fast rate. However, if the

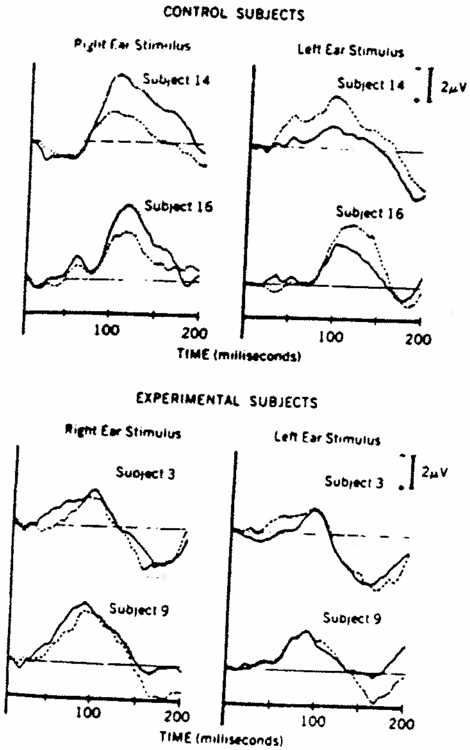

Fig. 6. Representative ERPs recorded from the vertex of two formerly hyperactive and two control adolescent males. The waveforms represent the average ERPs to of tone pips presented to the right and left ears under conditions of attending to target tones in the right (*solid lines*) versus left (*dotted lines*) ears. (Zambelli AJ, Stamm JS, Maitinsky S et al: Auditory evoked potentials and selective attention in formerly hyperactive adolescent boys. Am J Psychiatry 134:742–747, 1977)

stimuli were presented at a slower rate or the task called for dividing attention between the two ears, the schizophrenics showed reduced ERP signs of attention. These findings suggested that schizophrenia does not involve deficiencies in either stimulus set or response set aspects of attention *per se* but rather in an ability to organize and maintain an effective attentional strategy for optimal processing of the task-relevant information.

ERPs ASSOCIATED WITH EXPECTANCY AND DECISION MAKING

Scalp-recorded ERPs are particularly sensitive indicators of a subject's reaction to novel, surprising, and deviant events. Stimuli that violate expectancies elicit a prominent series of endogenous components that vary according to the context within which the deviation occurs. For example, novel or deviant events in adults may be associated with a variety of negative (N2a, N2b, N400, mismatch negativity) and/or positive (P165, P3a, P3b, P4, slow wave) components, depending on the properties of the stimuli and the state of the subject.

The best known component of this type is the so-called P3 or P300 component, a late positivity with a "typical" latency of around 300 msec.[64] However, the label P300 has been used to refer to late positivities with latencies anywhere from 200 msec to 1000 msec post stimulus, and there is good evidence that multiple positive components of differing cognitive significance can be elicited within this latency range. The members of this proliferating family of P300 waves have been associated with a variety of psychological constructs such as orienting, information delivery, uncertainty resolution, context updating, decision making, and postdecisional closure of cognitive activity, among others. This diversity reflects the fact that the generic P300 component has been recorded in a wide range of experimental situations that differ in their cognitive requirements. The P300 waves typically are elicited as part of a late wave complex that includes an earlier N200 wave and a subsequent "slow wave," both of which have been implicated in stimulus evaluation processes.

The most extensively studied member of the P300 family is a modality-independent, late positive wave that is elicited maximally over the posterior scalp by task-relevant stimuli. This component has been called the P3b to distinguish it from other late positivities, but here it will simply be designated as P300. This P300 wave was first described by Sutton and co-workers[67] in 1965 in a task in which subjects predicted on each trial which of a set of stimuli would occur next. The amplitude of the P300 wave to the anticipated stimulus was an inverse function of its probability. One of the basic experimental situations in which the P300 wave can be recorded is the "oddball paradigm," in which a random (Bernoulli) series of two classes of stimulus events is presented to a subject who must discriminate between them and make some kind of differential response. The response may involve a choice motor reaction or an updating of a mental count of the events. The less frequently occurring stimulus (*i.e.*, the "oddball") is typically associated with an enhanced P300 in relation to the more frequent stimulus class. The two classes of stimuli may be distinguished by simple physical cues (such as tone frequency or light intensity) or by complex rules (such as words that belong to different semantic categories) (Fig. 7).

In the oddball task, it has been demonstrated that P300 amplitude varies monotonically with the probability of the task-relevant stimuli.[68] However, when the stimulus sequence is predictable or known to the subject, P300 amplitudes are greatly reduced, even to highly improbable stimuli. Thus, while the objective or *a priori* stimulus probability has a strong influence on P300 amplitude, subjective probability or expectancy is the more critical factor. This was illustrated in studies by Squires and his co-workers,[69] which showed that P300 amplitude decreased within an oddball sequence when stimulus repetitions occurred; these researchers considered that repetitions raise the expectancy for further occurrences of that stimulus. In addition to event probability and sequential probability, the P300 wave has also been found to be sensitive to temporal, local, and response-contingent probabilities. The upshot of all these studies is that variations in the P300 wave are determined primarily by the subject's expectancy for a task-relevant event.

On the whole, elicitation of the P300 requires

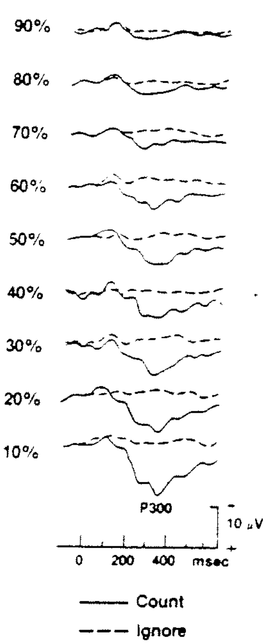

Fig. 7. Grand average ERPs (over 10 subjects) from midline parietal electrode to counted and ignored tones at nine levels of *a priori* stimulus probability. Tones of two frequencies were presented in randomized (Bernoulli) sequences. (Adapted from Duncan-Johnson CC, Donchin E: On quantifying surprise: The variation of event-related potentials with subjective probability. Psychophysiology 14:456–467, 1977)

active attention and engagement in a task in relation to the eliciting stimuli. Deviant or low probability events that have no assigned task relevance are more commonly associated with different members of the P300 family. For instance, a deviant stimulus interspersed within a monotonous auditory sequence that is not being attended typically elicits a "P3a" component that is earlier in latency, smaller in amplitude, and more frontally distributed than the usual P300 (P3b). The P3a (together with a preceding negative wave) seems to reflect a basic sensory "mismatch" operation that is a precursor to the orienting reaction toward an unexpected event in the sensory background.

The P300 in the oddball task can be used to evaluate the distribution of the subject's attentional "resources" between that and a concurrent "primary task." Under these dual-task circumstances, P300 amplitudes to oddball targets were found to be reduced when the perceptual demands of the primary task were increased (*i.e.*, when more stimulus elements had to be evaluated) but not when the response demands were made more strenuous. In this case, the ERP was more informative than the reaction time data, which failed to differentiate increases in perceptual from response load. Experiments along these lines have shown trade-offs in P300 amplitude elicited by primary and secondary task stimuli as their respective difficulties were manipulated, suggesting that the two tasks draw on a common pool of processing resources.[70]

As noted previously, the P300 latency is often considerably longer than 300 msec. Generally, the more complex or difficult the stimulus evaluation and categorization procedure, the more delayed is the P300. Many of the same factors that influence behavioral measures of processing time also alter P300 latencies. The P300 is a useful adjunct to RT measures, however, because the two are dissociable. If the subject in an oddball task is urged to respond very quickly, RTs may occur well before the P300 peaks, and the RT–P300 latency correlation may be relatively small. On the other hand, if the subject responds with an emphasis on accuracy, RTs tend to follow the P300 peak and the two are more highly correlated (Fig. 8). Such results have led to the proposal that the timing of the P300 is more closely tied to the moment of a decision than to response organization and production. Accordingly, P300 latency can be used to measure the duration of stimulus evaluation processes (encoding, recognition, and classification) independent of response processes, thereby helping to disentangle the contributions of sensory and motor factors to RT measures.

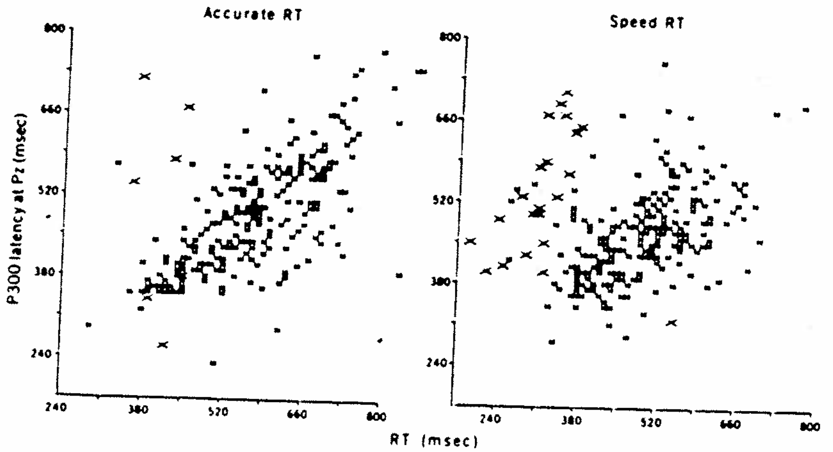

Fig. 8. Latency of the P300 component evaluated on single trials plotted against the RT on same trial. The Xs mark trials on which errors were committed. The linear regressions describing these data were y = 0.57x + 156 with $r = .66$ for the "accurate" RT condition and y = 0.38x + 276 with $r = .48$ for the "speed" RT condition. There was a greater incidence of errors when RTs were speeded and occurred earlier than the P300. (Kutas M, McCarthy G, Donchin E: Augmenting mental chronometry: The P300 as a measure of stimulus evaluation time. Science 197:792–795, 1977)

The precise role of the P300 in stimulus evaluation has not been worked out, but its elicitation seems to depend on a comparison of stimulus input against representations in memory of the relevant stimuli. There are indications that stimuli eliciting larger positivities in the region of the P300 will be better remembered than stimuli with smaller positivities. These findings are in line with recent suggestions based on intracranial[72,73] and neuromagnetic[74] recordings that at least a portion of the P300 activity is generated in the hippocampal region, known for its important role in memory functions.

The latency of the P300 wave increases systematically as a function of age, beginning at puberty and extending into the 80s. The majority of investigators[75,76] have reported a significant positive linear correlation between age and P300 latency, with slopes ranging from 1.1 msec to 1.8 msec/year. However, some reports[77,78] indicate that the relationship between P300 latency and age is more closely approximated by a curvilinear function; under the conditions tested, this was a positively accelerating curve with a slope of 0.53 msec/year for persons under 45 and of 3.14 msec/year for those over 45. Goodin and associates[79] have suggested that the general slowing of the P300 wave with age may reflect a decrease in neural conduction velocity due to decreased myelination.

The correlation between P300 latency and RT also appears to be altered with age.[80] The elderly show longer delays between the P3 peak and RT, as well as lower P3/RT correlations, than do younger subjects. These findings suggest that the slowing of sensorimotor task performance seen in aged individuals is more a consequence of delayed response engagement than of slowed sensory analyses, memory matching, or stimulus classification. A similar interpretation has been offered for the finding that depressed individuals have abnormally long reaction times together with normal latency P300s.[81]

Within a given task such as the oddball paradigm, the latency of the P300 wave across normal subjects of a particular age is consistent enough that it can be used in the diagnosis of organic dementia. Demented patients typically show a P300 wave that is delayed in latency by more than two standard deviations beyond the mean of age-matched controls.[79] Delays of this magnitude seem to be specific to organic dementias and have not been reported for any other neurologic or psychiatric patient groups. This means that the P300 wave can serve as an important diagnostic tool in distinguishing between dementia and other conditions that present similarly but are more responsive to treatment. Depression accounts for the majority of such pseudodementias, especially in the elderly, although similar syndromes can be produced by a number of psychiatric disturbances, including mania, schizophrenia, hysterical conversion reactions, and acute confusional states. The consequences of misdiagnosing an acute confusional state or depression as dementia can be tragic indeed. The clinical signs for distinguishing pseudodementia from dementia are well validated, and recordings of P300 latencies should prove valuable in diagnosing borderline patients and those with whom it is difficult to communicate.

ERPs IN CHILDREN

Many of the endogenous components recorded in adults have their counterparts in infants and children.[81–83] Studies using simple discrimination and oddball tasks that elicit P300 waves in adults have revealed similar late positivities in children and adolescents. On the whole, familiar and easily categorized events such as the target and standard stimuli in the usual oddball task tend to elicit similar ERPs in persons between 6 and 60 years of age. The complex of waves elicited by such target events changes little in morphology across the life span and includes N200, P300, and slow wave components; the P300 waves, however, are considerably longer in latency in children than in adults under comparable conditions.

On the other hand, complex visual stimuli, including meaningful pictures and novel, meaningless shapes, elicit ERPs with very different morphologies in persons of different ages. The most prominent waves in infants and children to such stimuli are frontal Nc (700 msec) and Pc (1000 msec) waves. The Nc waves decrease in latency and amplitude as a function of age until they are no longer evident in adults. The Nc elicited by pictures of known objects and scenes has been interpreted as relating to the perception of meaningful, nonverbal stimuli, while the Nc elicited by novel shapes has been related to the perception of "attention getting" events. The Pc also becomes earlier and smaller with age but is still present in adolescents and even in 50% of the adults tested.

Alterations in these late ERPs have been related to processing deficits in infantile autism.[84–87] Courchesne and colleagues[88] reported that in autistic children the ERPs to surprising and novel stimuli are markedly abnormal, in a modality-specific fashion. In the visual modality the abnormality took the form of an attenuated Nc component, whereas the major difference from normal children in the auditory modality resided in a smaller P300-like component over the central scalp (Fig. 9). These observations suggested that autistic children have differential impairments in orienting to novel auditory and visual events. Studies of hyperactive children and those with learning disorders indicate that they, too, have diminished late positive components in target detection or discrimination tasks. Schizophrenic children were found to exhibit not only reduced P300 amplitudes but also a lack of sensitivity of this positivity to changes in task difficulty.[89] These ERP abnormalities were associated with problems in correctly identifying the task-relevant stimuli. The diminished late positivities in such children have generally been attributed to attentional disturbances that are characteristic of the syndromes in question.

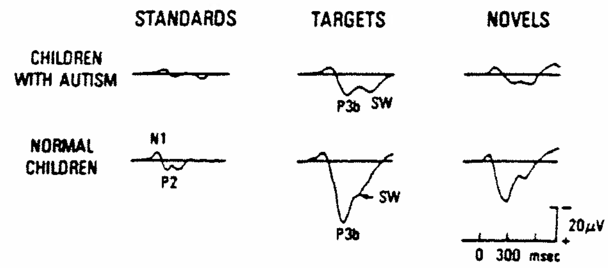

Fig. 9. ERP waveforms recorded from a midline parietal electrode from seven children with autism and seven age-matched normal children. The ERPs were elicited by auditory presentations of standards (80% the spoken word "me"), targets (10% the spoken word "you"), and novels (10%, unique complex sounds). The subjects pushed a button to the target sounds (Adapted from Courchesne E, Kilman BA, Galambos R et al: Processing of novel auditory information assessed by event-related brain potentials. Electroencephalogr Clin Neurophysiol 59(3):238–248, 1984

ERPS AND LANGUAGE

A substantial research endeavor has explored the relationships between ERPs, hemispheric specialization,[90] and language.[91] Although most early studies of hemispheric specialization using electrophysiologic measures uncovered only small, inconsistent, or uninterpretable results, more recent investigations have demonstrated that robust, lateralized ERP components can be recorded under proper circumstances.[11,92,93] Such lateralized ERPs have been related to hemispherically specialized modes of processing that are highly sensitive to early experience and individual differences in developmental history.[94] Few attempts have been made to link ERP lateralization with psychopathology. However, the direction of ERP asymmetry promises to be useful as a test of the currently popular hypothesis that schizophrenics and manic-depressives have different and opposite balances of hemispheric activation.[95]

A late negative (N400) component of the ERP has been identified as a sensitive indicator of the semantic relationship between a word and the context in which it occurs.[96,97] Words that complete sentences in a nonsensical fashion elicit much larger N400 waves than do semantically appropriate words or nonsemantic irregularities in a text. The amplitude of the N400 has been shown to be an inverse function of a subject's expectancy for the eliciting word. In addition, the N400 appears to be responsive to subtle semantic relationships among words, whether or not they make sense. These findings have been interpreted as suggesting that the N400 may reflect the priming of activation of word representations within the internal lexicon, certainly within the semantic and possibly within the phonemic and graphemic dimensions as well.

No evidence is available linking language-related ERPs to psychiatric disorders. A particularly promising area for future clinical investigations would employ the N400-type paradigm to help analyze comprehension difficulties in dementia and the organization of semantic fields in schizophrenics, who are well known for their abnormal, unpredictable word associations.

Event-Related Potentials in Psychiatry

Electrophysiologic research in psychiatry, as in cognitive psychology, has so far been largely correlational. Objective ERP measures are correlated with the diagnostic categories of the trained psychiatrist, each of which is presumed to correlate with an abnormal physiology that underlies the mental illness. Shagass[98,99] has differentiated between investigators who have adopted the psychophysiologic as opposed to the pathophysiologic approach in applying ERPs to psychiatric research. The psychophysiologic orientation assumes that deviant behavior and cognition are accompanied by aberrant physiology, and the ERP is taken as means of characterizing both. The pathophysiologic orientation, as espoused by Shagass, emphasizes the primacy of the abnormal physiologic functions that underlie the pathologic behavioral symptoms. The psychopathologic view is more concerned with localizing the malfunctioning neural structures as a marker of the disease process rather than with describing the cognitive dysfunctions. How the altered physiology gives rise to the behavioral symptomatology is of lesser concern. With either orientation, however, the psychiatrist hopes to use ERP measures as objective diagnostic indicators of the psychopathology in question.

After more than 20 years of research, the ERP still plays a minor role at best in the psychiatric clinic. Many of the same problems that have plagued behavioral investigations of psychopathology have also confounded electrophysiologic studies. In particular, it has proven extremely difficult to match patient and control groups along all pertinent dimensions that may influence the dependent measures over and above the effects of primary group membership. When making comparisons among different patient groups, factors of age, sex, medication, and the dynamics of the illness cannot be ignored as potential confounding factors.

A more vexing problem is the difficulty in attributing an abnormal ERP configuration to a specific cognitive dysfunction rather than to a generalized lack of task involvement. That is, patient groups may evince aberrant ERPs and generally poor performance, not because they are incapable of the task but because they lack motivation, do not understand what is expected, or are otherwise preoccupied. Although there is no wholly satisfactory solution to this problem, Roth and associates[100] have suggested that behavioral measures should be recorded concurrently with the ERP and, when possible, performance should be matched in patient and control groups.

A final problem area is the extreme lability of ERP measures, particularly the late "cognitive" components to momentary changes in the subject's state. As Sutton and Tueting[100] have noted:

> In comparing patient groups with each other and with normal subjects, the very sensitivity of the evoked potentials to so many psychological variables—the sensitivity of the evoked potential to every passing thought and every fluctuation of attention—is an embarrassment of riches. Given this high degree of sensitivity of the evoked potential, many of the symptoms of psychosis—delusions, hallucinations, affective states, poor attention, distractibility—create barriers to good experimental methodology.

Indeed, the problem with ERPs in psychiatry has not been a lack of significant effects but rather an abundance of nonspecific and difficult-to-interpret correlations. Extensive tables of the ERP abnormalities that have been observed in schizophrenics, affective psychoses, personality disorders, and chronic brain syndromes are supplied in the literature.[41,98,102,103]

ERPS IN PSYCHOSIS

The majority of electrophysiologic investigations in psychiatric populations have been carried out with schizophrenics. Early experiments by Buchsbaum and associates[104] attempted to differentiate subtypes of schizophrenics along a personality dimension of "augmenting/reducing"; the "augmenter" tends to increase the subjective intensity of the stimuli he receives while the "reducer" strives to decrease sensory input. Using ERP amplitudes as measures, it was generally found that acute, nonparanoid schizophrenics tended to be reducers, paranoid patients tended to be augmenters, and patients with bipolar affective disorders were extreme augmenters. The interpretation of these findings is somewhat clouded, however, since changes in muscle tension and attention also can alter the slope of the augmenting-reducing function that relates ERP amplitude to stimulus intensity.[105–107]

In studies with schizophrenics, Shagass[98,99,102] measured neuronal recovery cycles in a paradigm where ERPs were recorded to pairs of stimuli separated by varying time intervals (200 msec–2.5 sec). The principal measure was the speed with which the second response recovered from the refractory period induced by the first, a measure of neuronal "excitability." The effects of variables such as stimulus intensity, sensory modality, drugs, age, and sex were systematically examined. The principal conclusion of this work was that psychotic patients in general have reduced neural recovery, but this effect did not differentiate among diagnostic subclasses.

In other work, Shagass reported that the trial-to-trial variability of early somatosensory ERP components was lower in chronic schizophrenic patients than in either normal controls or other patient groups. These same components tended to be of lower amplitude in depressed patients and above normal in manic individuals. In contrast to the short-latency EP components, the late ERP components beyond 100 msec are smaller and *more* variable in schizophrenics than in normal subjects; this was true for the entire P100–N140–P200 complex of waves elicited by stimuli in all modalities. This trial-to-trial amplitude variation seemed to be more highly correlated with thought disorder than any other symptom category. Shagass argued that low amplitude and high variability in the later components favors a psychotic as opposed to nonpsychotic condition. This reduction in amplitude is particularly marked for rapid rates of presentation or high intensity stimulation. Moreover, these ERPs tended to normalize with clinical improvement.

The endogenous P300 component shows marked amplitude reductions in schizophrenic patients in a variety of paradigms (Fig. 10).[108–115] P300 attenuation has been a consistent finding despite the usual problems of patient compliance, medication, attentional factors, and diagnosis. Although it is difficult to generalize across the different paradigms, the reduced P300s do not appear to reflect an inability to appreciate task-relevant target stimuli so much as an indifference to their import or surprise value. In several studies, significant correlations between symptom ratings and P300 amplitude were noted. Depressed and manic patients also showed attenuated P300s in some paradigms, although not to the same degree as in schizophrenics. A P300 reduction may also be evident in children at high genetic risk for schizophrenia.

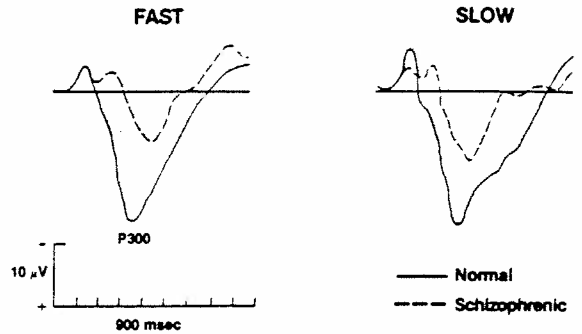

Fig. 10. ERPs from typical schizophrenic and normal subjects recorded in a focused attention experiment in which tones were presented in random order to the two ears at either a fast or a slow rate. (Same task as illustrated in Figure 4). These ERPs were recorded from a midline parietal electrode in response to correctly detected targets within the attended channel (Adapted from Baribeau-Braun J, Picton TW, Gosselin J: Schizophrenia: A neurophysiological evaluation of abnormal information processing. Science 219:874–876, 1983)

Studies using the BEAM technique, which displays ERP topographies in a color-coded map, suggests that the scalp distribution of the P300 differs between schizophrenics and normals.[116] The schizophrenics' P300 was found to be displaced anteriorly and toward the right hemisphere, whereas in normal individuals it is nearly always bilaterally symmetrical.

CONCLUSION

The main conclusion to be drawn from these electrophysiologic studies is that ERP measures tend to reflect the presence or absence of psychopathology and to some degree its severity, rather than specific nosologic categories. It has been frequently demonstrated that the ERPs of psychotic patients differ from those of nonpsychotic patients and normal subjects, but aside from a tendency for schizophrenics to have the most deviant waveforms, few links have been established between specific ERP component abnormalities and diagnostic categories. Systematic attempts to refine ERP paradigms so as to tap into specific cognitive abnormalities should help to remedy this state of affairs. The tracking of ERP changes throughout the dynamic course of an illness and in individuals at risk for developing them should also lead to greater diagnostic specificity.

Callaway[117] has proposed that the ERP technology should shed its reliance on behavioral symptomatology and classifications, against which ERP abnormalities are typically evaluated. Rather, he argues that more headway may be made if the ERP is used as an independent variable and the structured interview is used as the dependent variable. In this manner, ERPs could be used to segregate subgroups of patients, who then would be evaluated along other dimensions (*e.g.*, by clinicians, biochemists, or geneticists) to determine what characteristics these patients share. In the near future, at least, it appears that the ERP methodology will probably be most valuable as one of a battery of diagnostic tests rather than used in isolation.

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