Reprinted From

PSYCHIATRY

REVISED EDITION—1991

J. B. LIPPINCOTT COMPANY
Philadelphia
London New York Hagerstown

PSY-91

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Electrophysiology of Normal and Pathologic Cognition

EDITOR'S COMMENTS

Activity of the brain may be characterized biochemically, as shown throughout this text, and by means of changes in the electrical potentials exhibited by single nerve cells as well as the large populations of nerve cells that make up functional units of operation of the brain. In this chapter the authors review recent research exploring these event-related potentials. These electrical events illustrate not only where the biological manifestation of some important cognitive event might be occurring in the brain during cognitive behavior but also shed light on the temporal processing of various sensory and cognitive operations. A great deal of new research relevant to the biological substrates of psychiatric illness and its treatment has appeared only in the past few years. This is reviewed very thoroughly and with scholarship in this chapter.

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Insofar as records of the electrical activity in the scalp can help to reveal the mechanisms of our mind, they can also help unravel the mysteries of the shattered mind in various neurologic and psychopathologic syndromes. In this chapter we survey the experimental literature documenting the relationships between the perceptual and cognitive subcomponents of different tasks and the electrical responses that can be recorded at the scalp in synchrony with these mental operations. The electrical activity recorded at the scalp includes not only the ongoing electroencephalogram (EEG) but also more transient responses to specific stimuli, called the evoked (EP) or event-related potential (ERP); both are believed to represent the summation of graded postsynaptic potentials generated by the depolarization and hyperpolarization of numerous neural (and perhaps glial) elements acting in unison.

A sensory stimulus triggers a series of voltage peaks and troughs (sometimes referred to as components) lasting for several hundreds of milliseconds; this record of voltage in time is called an evoked response or an evoked potential (EP) (Fig. 1).[1] At the scalp an EP is substantially smaller in amplitude than the background EEG (5 to 10 μV versus 50 to 100 μV) and must, therefore, be extracted by an averaging procedure. This involves recording EPs to repeated stimulus presentations; it is assumed that random fluctuations will cancel each other and leave a record of the evoked or event-related activity that was time-locked to the stimulus presentation. As averaging improves the resolution of the evoked signal in proportion to the square root of the number of responses included, the number of repetitions needed for a reliable (*i.e.*, "clean") average is a function of the amplitude of the ERP component under study.

Typically, the peaks (*i.e.*, components) of an EP are labeled according to their polarity (negative [N] or positive [P]) and latency in milliseconds (*e.g.*, N100, P230, P300). On occasion, the peaks are designated by their polarity and ordinal position in the waveform (*e.g.*, N1, P1, N2). Less often, the labels refer to the hypothesized functional role (*e.g.*, readiness potential [RP]) or anatomic location of the component (*e.g.*, auditory brain-stem response [ABR]). As a general rule, the amplitudes, latencies, and scalp distributions of the earlier com-

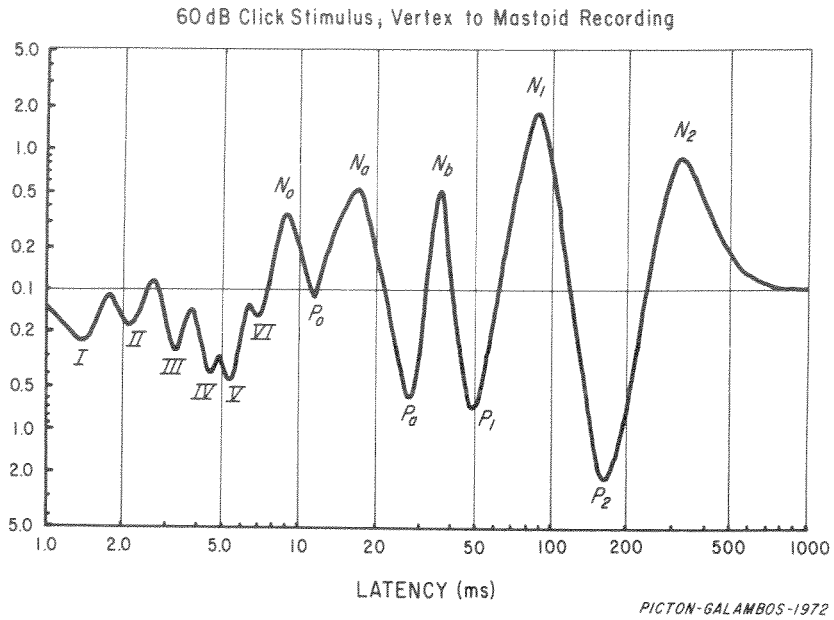


FIG. 1. The characteristic sequence of components in the human auditory evoked potential plotted on log-log coordinates. (Picton TW, Hillyard SA, Krausz HI et al: Human auditory evoked potentials: I. Evaluation of components. Electroencephalogr Clin Neurophysiol 36:179, 1974)

its (with latencies of less than 100 msec) for a ular stimulus are very consistent within an dual; that is, they are highly reproducible session to session. Moreover, systematic vari- in the physical parameters of the evoking lus (*e.g.*, intensity, frequency, duration) lead dictable changes in these early components, ing the altered activation of the sensory path- Hence, the earlier evoked components are lered to be "exogenous" or stimulus bound; re generally impervious to a subject's state of ess or attentiveness. It is this invariance in the f changing psychological state that makes the nous components an excellent diagnostic r certain sensory and neurologic disorders.[2–4] those interested in the neural bases of men- cesses, the more informative brain waves are dogenous components, which may precede ow a triggering event by many hundreds of conds. An "event" in this case refers to a us, a response, a voluntary movement, or a ive operation for which an external timing r can be specified so that time-locked electri- in activity can be examined. The relative in- vity of endogenous components to variations physical stimulus parameters contrasts to exquisite responsivity to task demands, in- ons, and the subjects' intentions, decisions, ancies, strategies, mental set, and so on. In words, endogenous ERP components are not ed" by a stimulus but are elicited by the per- l and cognitive operations that are engen- 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 stimulus. 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 neurophysiological mechanisms underlying the scalp-recorded ERPs are largely unknown, these potentials appear to be reliable manifestations of a panoply of informational transactions in the brain. However, ERPs are remote measures of the brain's electrical output and must be interpreted with caution. In most cases it has not been possible to localize the anatomic site of the intracranial generators of the scalp-recorded ERPs. Furthermore, since ERPs reflect activity of large neuronal populations acting in synchrony, cognitive acts that involve temporally dispersed processing may not produce an ERP at the scalp. 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 limitations, the ERP methodology remains one of the few techniques currently available for recording the dynamic patterns of neural activity that underlie specific cognitive acts. Over the past 5 years, the picture of neuronal activity reflected in electrical recordings at the scalp has been complemented by images provided by magnetic recordings of the same cognitive events.

A major goal of ERP research is to identify specific ERP components as markers of specific mental

operations. This is pursued through systematic study of the correlations between ERP measures, stimulus and response factors, and task performance. Once the correlations are validated, ERP results can be used in convergence with behavioral and neuropsychological 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 provide new information about the neural bases of the development, maintenance and decline of cognitive processes, including selective attention, recognition memory, decision making, and language functions.

Clinical Uses of Sensory Evoked Potentials

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 that small deviations from established norms reliably indicate neurologic or sensory dysfunction. Thus, sensory EPs are routinely used by ophthalmologists, audiologists, and neurologists to aid in confirming diagnoses of disordered sensory function, in localizing lesions among sensory pathways, in following sensorineural diseases, and in providing an objective index of the efficacy of therapeutic intervention. The EP method has proved particularly valuable in the diagnosis of clinically silent lesions (as in demyelinating diseases) that are difficult to detect in computed tomographic scans.

Because it provides an objective test of 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 from the normal range; (3) failure of the response to follow standard input-output functions in response to systematic variations in stimulus parameters such as frequency, intensity, rate of presentation, and so on; or (4) presence of an abnormal component in the waveform. For example, visual evoked potentials (VEPs) recorded to a pattern-shift stimulus in conjunction with the electroretinogram (ERG) can aid the ophthalmologist in localizing an abnormality to a specific level of the visual pathway. The early components of the auditory evoked potentials (AEPs) known as the brain-stem evoked responses (BERs) are used widely to test for hearing disorders, particularly in cases in which subjective audiometry is difficult (as with demented persons) or impossible (as with infants). Similarly, the somatosensory evoked potential (SEP) has proven valuable in diagnosing peripheral neuropathies and lesions affecting the dorsal column–medial lemniscal pathways.

Early sensory components (*e.g.*, P1, N1, P2) may eventually prove useful in distinguishing among various psychotic conditions. Several reports have documented abnormal VEP latencies in schizophrenic persons.[5,6] Those with positive symptoms (*e.g.*, thought disturbance, hostility) were characterized by reduced N1 and P2 latencies, whereas for those with negative symptoms (*e.g.*, affective blunting, anhedonia, asociality) these components were prolonged. Both animal and human studies have revealed a strong relationship between the latencies of the early VEP components and central dopamine (DA) activity levels: latencies were decreased after agents that increased central DA and delayed after administration of DA blocking agents (*i.e.*, those that decreased central DA).[7] Accordingly, increased DA activity has been implicated in the positive signs of schizophrenia and decreased arousal and DA activity have been implicated in the negative symptoms. Generally, schizophrenic patients with the shortest latency VEPs and the highest positive symptoms have very high baseline arousal levels and are thus unusually slow at habituating to sensory stimulation.

And, in fact, measures of neuronal "excitability" have been at the core of many of the investigations of early sensory components in schizophrenics. For example, Shagass[8–10] measured neuronal recovery cycles in a paradigm where ERPs were recorded to pairs of stimuli separated by varying time intervals (200 to 2500 msec). The principal measure was the speed with which the second response recovered from the refractory period induced by the first. Systematic examination of the effects of stimulus intensity, sensory modality, drugs, age, and gender led to the conclusion that psychotic patients have prolonged neural recovery times, but this effect was not pathognomonic of the different subclasses. These EPs became more normal with clinical improvement. More recently, research on the cortical excitability has employed a so-called sensory gating (double click or conditioning-test) paradigm in which the primary measure is the suppression of the P50 component of the AER to the second of a

f clicks[11,12]; other than its association with the omponent this approach is no different than covery cycle approach outlined above. Conble research with this approach has demond that diminished sensory gating is a trait r in schizophrenia but a state marker in other mental illnesses.[13] Proper sensory gatbelieved to be necessary for the ability to to important signals and to ignore extraneoises, and thus may account in part for the lty many psychopaths have with selective atn.

other aspect of early sensory components as received some attention with psychoogic groups is their trial-to-trial variability. ample, Shagass found that the variability of somatosensory ERP components was lower onic schizophrenic patients than in either l controls or other patient groups. These components tended to be of lower amplitude ressed patients and above normal in manic s. In contrast to the very short latency EP ments, the ERP components in all modaleyond 100 msec (*e.g.*, P100–N140–P200) maller and more variable in schizophrenics n normal subjects. This trial-to-trial ampliariation seemed to be more highly correlated hought disorder than any other symptom. s argued that low amplitude and high vari in the later components favored a psychotic osed to nonpsychotic diagnosis. This reducamplitude was particularly marked at rapid or high intensities of stimulation. These ended to normalize with clinical improve-

amplitude of patients' early responses to stimulation has also been examined as a e means of differentiating subtypes of psyhs along a personality dimension of "aug-g/reducing." Augmenters tend to increase jective intensity of the stimuli they receive he "reducer" strives to decrease sensory inith the use of ERP amplitudes as measures, generally found that acute, nonparanoid hrenics tended to be reducers, paranoid paended to be augmenters, and patients with affective disorders were extreme augmen-[6] The interpretation of these findings is hat clouded, however, since changes in mussion and attention also can alter the slope ugmenting-reducing function relating ERP de to stimulus intensity[17] and the nature relation seems to vary with recording

ENDOGENOUS EVENT-RELATED POTENTIALS 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 persons presumed to have deficits in these domains.[19–27] The term *cognitive* encompasses a broad range of psychological concepts, including attention, expectancy, preparation, surprise, storage and retrieval of information from memory, and linguistic processing, among others.

Endogenous Brain Potentials and Preparation

When a person prepares to process sensory information or take a motor action, specific brain wave patterns develop within the preparatory interval. The most prominent of these are the movement-related potentials and the contingent negative variation (CNV).

MOVEMENT-RELATED POTENTIALS

A characteristic series of potentials can be recorded on the human scalp both preceding and following voluntary movements (Fig. 2).[28,29] The slow negative shift, termed the *readiness potential* (RP) or *N1 component*, begins as a symmetric wave over central scalp locations 1 to 1.5 seconds prior to movement and subsequently becomes larger contralateral to the upper limb that will be moved. The RP is generally taken to be a reflection of the cortical processes associated with preparation for movement. Its amplitude is influenced by the speed, force, and duration of movement, as well as by subject handedness.[30] Eighty to 90 msec prior to movement onset a small and more variable positivity is seen (the premotion positivity [PMP] or P1). Kornhuber and colleagues[27,28] have proposed that the PMP 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 motor cortex contralateral to the responding limb; this "motor potential" or N2 component occurs near the onset of movement and

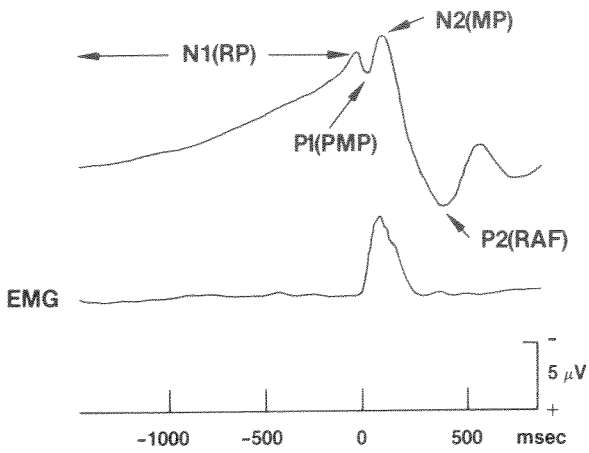


FIG. 2. Schematic illustration of movement-related potential accompanying a voluntary hand movement. The components are labeled according to the terminology of Vaughan and colleagues and Kornhuber and colleagues (in parentheses). Also shown is the integrated electromyographic (EMG) activity of the responding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

appears to reflect activation of corticospinal tract neurons in the motor cortex. Finally, following the onset of muscle contraction by 50 to 150 msec are a series of positive deflections (the P2 or reafference potential) that represents proprioceptive and kinesthetic feedback from the movement. These potentials have been localized through depth recordings from monkeys performing repetitive movements[31,32] and neuromagnetic recordings in humans.[33–35]

Most research on the movement-related potentials has focused on the effects of varying movement parameters on the amplitude, latency of onset, or lateral distribution of the elicited potentials; moreover, the great majority of these studies have concentrated on simple, voluntary movements of the hand or arm. Lately, movement-related potentials have been applied to the investigation of human information processing. In particular, the asymmetric portion of the RP has been used to index commitment to a specific motor response in choice reaction time tasks.[36–38] Such studies have demonstrated that the speed and accuracy of a subject's reaction time response is, in part, related to the degree of prior preparation manifested by the movement-related potential. In addition, recent work has included a description of potentials preceding skilled hand (*e.g.*, writing, drawing)[39,40] as well as foot movements.[41,42] ERPs preceding eye movements and speech have also been investigated; however, it has proven quite difficult to separate the brain potentials of interest from concurrent bioelectrical artifacts due to movements of the eyes, tongue, and facial musculature.[27–30]

There are only a few investigations of movement-related potentials in patients with neurologic disorders.[43,44] Both patients with hemiparesis due to unilateral cerebral lesions and with hemiparkinsonism have shown smaller amplitude RPs over the affected hemisphere (*i.e.*, contralateral to the akinetic side of the body) regardless of which hand is moved. Comparisons with data from age-matched controls for patients with parkinsonism reveal a gradual reduction in RP amplitude with age, most evident in persons who are 40 years or older.[45]

To the extent that it has been investigated, movement-related potentials appear to be abnormal in psychotic patients.[46–48] In particular, patients with psychosis display unusually 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, since such patients also showed prolongation of slow negative potentials in general (*e.g.*, CNV or postimperative negative variation [PINV]). Nonetheless, the possibility of abnormal RPs in schizophrenics is worthy of pursuit given the findings that some classes of schizophrenics have problems with both voluntary and involuntary movements; for example, they show disturbances in preparation for movement, in directional and repetitive finger movements of the dominant limb, in motor sequence programming, in lip and tongue movements, in agonist/antagonist synchrony, and in complex coordination of the extremities.[49–51] Likewise, it would be of interest to determine if depressed persons, in whom psychomotor retardation[52] is a frequently observed clinical feature, would or would not generate abnormal RPs; this finding would provide evidence on the cognitive versus motor nature of the deficit.

CONTINGENT NEGATIVE VARIATION

Grey Walter and his colleagues[53] first described a slow, negative potential shift that developed on the scalp during the interval between a warning stimulus and a subsequent imperative stimulus requiring a motor response; this potential was termed the *contingent negative variation* (CNV). Subsequently, it

bserved that the CNV could be elicited prior ceptual judgments as well as motor acts, alh its amplitude was generally larger when movements were involved.

e CNV has been implicated in processes of ion, intention, preparation, expectancy, asso- memory, arousal, alertness, motivation, efnd so on, in part, because CNV measures proven sensitive to a wide variety of task and t variables.[54,55] For example, CNV ampliwere usually enhanced when the second us of the eliciting pair was noxious (as opto innocuous) or was near threshold and lt to detect (as opposed to normal intensity). mplitudes were also enhanced under condif increased muscular effort or greater monereward. Distractions of various sorts, on the hand, decreased CNV amplitude. In sum, no ctor can account for much of the variability / amplitude. Moreover, CNV amplitudes typhave not correlated strongly with behavioral mance (such as reaction times).

ordingly, several investigators have prothat the CNV actually comprises at least two nponents,[56,57] an early phase associated with ienting properties of the warning stimulus wave) and a later phase related to the prepn of a motor response (*i.e.*, expectancy or E By this view the CNV is nothing more than nation of these separate potentials as neither nent is a reflection of the contingency be- the warning and imperative stimuli. The ude of the O wave is modulated by the mointensity, and duration of the eliciting stimn contrast, the E wave does not vary with the al parameters of the warning stimulus but with response parameters such as speed du- number of fingers used, number of discrete ients, and complexity of the response se-.[57,58] Since the effects of these movement- factors were seen primarily in potentials ere averaged time-locked to the response, t[58] proposed that the negativity prior to and ng response onset represented the formula- response-specific motor programs. Given ilarities in waveform and scalp topographies n the E wave and the RP preceding volunovements, many researchers have argued e two components are the same. Only furork will reveal whether the CNV is just the an O wave and an E wave or includes one e other subcomponents that reflect the prep- for upcoming perceptual or cognitive pro-

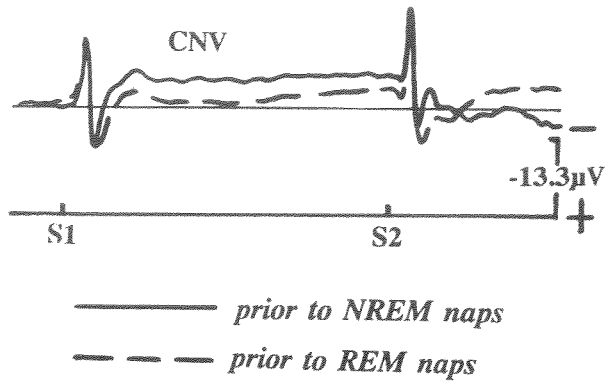


FIG. 3. Grand average (N=12) waveforms at the vertex (Cz) for narcoleptics prior to REM and NREM naps. (Adapted from Broughton RJ, Aguirre M: Differences between REM and NREM sleepiness measured by event-related potentials (P300, CNV), MSLT, and subjective estimate in narcolepsy-cataplexy. Electroencephalogr Clin Neurophysiol 67:317, 1987)

The evidence regarding age-related changes on the CNV is equivocal. Some investigators report no significant effects of aging,[59,60] whereas others have noted changes in either CNV morphology or amplitude.[61,62] Among the observed changes have been a general reduction in CNV amplitude with advancing age (65 years and older), in some cases across all scalp locations and in others confined to frontal sites.[63] Such results underscore the necessity of including age-matched controls when examining these slow negative potentials in psychiatric groups.

Although the amplitude of the CNV does not seem to be significantly different in normal controls versus patients with untreated narcolepsy-cataplexy (*i.e.*, suffering from unrelenting excessive daytime sleepiness),[64] it does differentiate between rapid-eye-movement (REM) and non–rapid-eye movement (NREM) sleepiness; REM sleepiness is characterized by almost total suppression of the CNV and a subjectively greater sense of sleepiness but equivalent speed of responding (Fig. 3).[65]

POSTIMPERATIVE NEGATIVE VARIATION

In the early 1970s, Timsit-Berthier and colleagues[66] reported that the CNV was abnormally prolonged for several seconds in most psychotics and to an intermediate degree in some neurotics. This phenomenon was called the *postimperative negative var-*

iation (PINV). Transitory PINVs have also been seen on occasion in normal subjects under stressful conditions,[67] in young children,[68,69] in narcoleptics,[65] in patients with organic brain damage, and in psychotic patients with poor prognosis.[66,70] This prolongation of the CNV has been considered an index of 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 some statistically reliable differences.[71] Although these differences lack diagnostic specificity, extremely abnormal CNV values implicate psychotic as opposed to neurotic illnesses with a fairly high probability. On the whole, psychiatric patients including schizophrenic, psychotic, depressed, and manic patients produce attenuated negativities during preparatory intervals and prolonged negativities following these intervals. This reduction in CNV amplitude is generally interpreted as due to increasing anxiety and arousal levels in combination with decreased attention.[72] The impairment in maintaining attentional set is generally ascribed to an elevated susceptibility to internal (*e.g.*, hallucinations) and external distractions. While it would be premature to conclude that these ERP abnormalities are specific to altered cognitive functioning in psychopathology, it is interesting to note that patients with lower amplitude CNVs have had a much poorer clinical and social outcome than those with CNVs in the normal range.

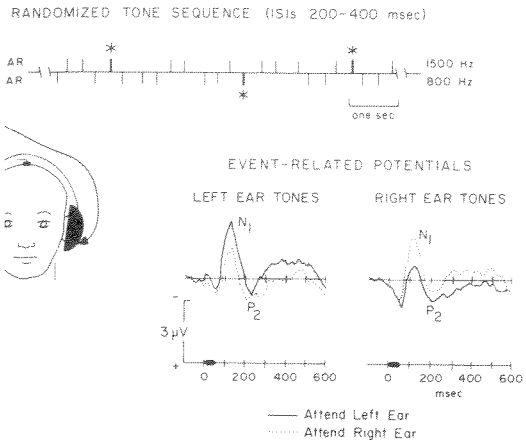
Endogenous Brain Potentials and Selective Attention

Selective attention refers to the preferential processing of some stimuli in relation to others. A central question in attention research concerns the level of the sensory systems at which stimulus selections and rejections are made. Some investigators have proposed an early stage of processing ("stimulus set") wherein stimuli that are outside an attended sensory channel are rejected after a cursory analysis,[73] while others have argued that all stimuli are processed fully before any selections are made.[74] Such questions are particularly amenable to investigation by the ERP methodology, because the ERP can provide immediate information on how stimuli are being processed not only in the attended but also in the rejected channel since the ERPs can be obtained without the need for a behavioral response.

A substantial body of evidence has accumulated demonstrating that ERPs are reliable signs of stimulus selection processes under appropriately controlled conditions.[22,25,75,76] The experimental design requirements for such experiments have been well specified.[77,78] Briefly, to show that an ERP component correlates specifically with selective attention as opposed to general changes in arousal, it is necessary to (1) ensure that across experimental conditions the physical stimulus is held constant at the sensory receptive surface (*e.g.*, retina, cochlea, skin); (2) present the attended and unattended stimuli according to a randomized sequence (*i.e.*, unpredictably); (3) use the same sequence of stimuli for the attended and unattended conditions in a counterbalanced fashion; and (4) collect behavioral measures and ERP recordings concurrently. Selective-attention experiments typically involve the presentation of two or more classes of stimuli (*i.e.*, channel) on an unpredictable basis, with attention alternated between channels through instruction. In addition, many of these experiments are designed to include both standard and target stimuli within both the attended and unattended channels; targets are differentiated from standards by their generally low frequency of occurrence and requirement for an overt response.

In auditory modality, the principal effect of attending to one channel of sounds (*e.g.*, those in one ear) and simultaneously ignoring another (*e.g.*, the other ear) is an enlargement of a negative ERP to the attended stimuli in the region of the N1 component (around 100 msec or so; Fig. 4).[79] Several studies have shown that this attention-related negativity can be dissociated from the N1 component *per se*, often extending for several hundreds of milliseconds beyond the N1 peak. This negativity is best visualized in the difference wave generated by subtracting the ERPs to stimuli in an unattended channel from the ERPs to those same stimuli when they are attended.[11] This ERP difference has been variously labeled the N1 effect, processing negativity (PN), or negative difference (Nd) wave.

Attended auditory channels differing in pitch, location, or intensity from unattended channels can elicit Nd waves when presented at very rapid rates (interstimulus intervals of 200 to 400 msec) or under conditions of increased task difficulty. Slower rates of stimulation yield an Nd wave with a delayed onset. The onset latency of the Nd wave is also influenced by the discriminability of the cue



Paradigm for demonstrating early ERP changes annel selective attention. Randomized sequences are delivered to the left (800 Hz) and right (1500 ; at intervals shown on upper time axis. Asterisks slightly deviant target tones. Subjects have to to detected targets in the attended ear; targets in ttended ear are ignored. At the bottom right are he grand average ERPs to tones in each ear as a ı of attend-left and attend-right conditions. The area represents the difference waveforms called or negative difference, wave associated with the ı-channel selection. (Hillyard SA, Simpson GV,)L et al: Event-related brain potentials and selecntion to different modalities. In Reinoso-Suarez)ne-Marsan C (eds): Cortical Integration. New aven Press, 1984)

g the attended and unattended channels; re difficult the discrimination, the later is its The functional characteristics of the Nd com- so closely correspond to the "stimulus set")f attention that the Nd has been taken as a)n of the further processing of stimuli in the d channel following an early, stimulus set n. The more prolonged portion of the Nd :n interpreted as a sign of the short-term nance of the stimulus features that define nded channel.[75]

al selective attention modulates a very dif- et of ERP components.[25,80,81] For example, ubjects attend to flashes in one visual field ore concurrent flashes in the opposite field, nded flashes are associated with ERPs with rged sequence of parieto-occipital waves, ng P130, N170, P220, and N280 peaks. The)logy of these components suggests that vi- ıtial attention acts by modulating a series of)us components of the VEP rather than by g an endogenous ERP. Selective attention to other visual cues, such as color, spatial frequency, orientation, and contour is manifested in a different ERP configuration, characterized by 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 number of early exogenous as well as endogenous components.[25,26,82]

It has been argued that the hypnotic state can be considered as one extreme of a continuum of attention, thus making hypnosis a useful tool for exploration of the neural mechanisms of focused attention. The empirical evidence on the sensitivity of ERP components to hypnotic suggestion, however, is mixed. A handful of previous reports have indicated that in hypnotizable persons the amplitude of the EP is diminished in response to the hypnotic suggestion that the stimulus is attenuated; however, just as many investigators have failed to observe any reliable effect of hypnotic suggestion. Spiegel and co-workers[83] adopted a selective attention paradigm (with color as the channel dimension and stimulus duration as the standard-target dimension) and compared ERPs in high and low hypnotizable subjects in three hypnotic conditions (stimulus enhancement, stimulus diminution, and obstructive hallucination). They found that only high-hypnotizable persons showed a significant reduction in the amplitudes of the late components (*e.g.*, N2 and P3) of the visual EP over the back of the head (occipital electrode sites) in the condition in which subjects were instructed to visualize a cardboard box that blocked viewing of the TV monitor on which the stimuli were presented. While the data patterns point to possible differences between the high and low hypnotizable subjects as a function of experimental condition, it is impossible to determine what these findings say about selective attention because the standard comparisons between nontargets in the attended and unattended channels were not analyzed and presented for visual inspection. This logic of hypnosis as a tool for studying selection attention, however, deserves pursuit.

The ERP signs of selective attention seem to be quite similar across the life span from adolescence on.[84] The robustness of the auditory Nd effect, in particular, has made it useful for evaluating patient groups with hypothesized deficits in attention such as persons designated as hyperactive[85,86] with attention deficit disorder, autism, schizophrenia, or alcoholism. Hyperactive children were found to have abnormally small amplitude N1s and Nds that approached normal following acute doses of medi-

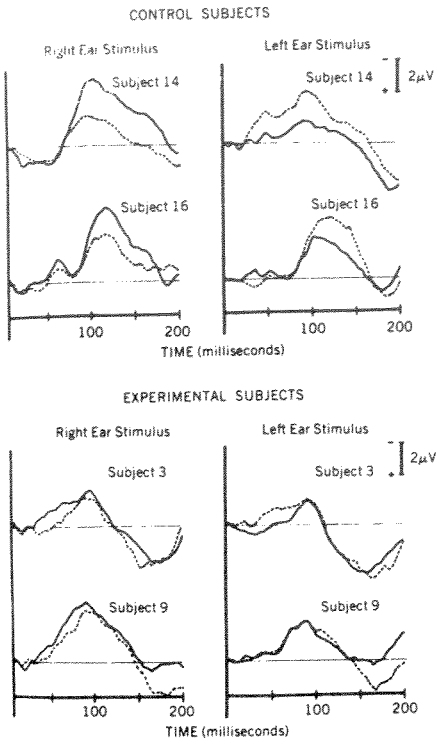


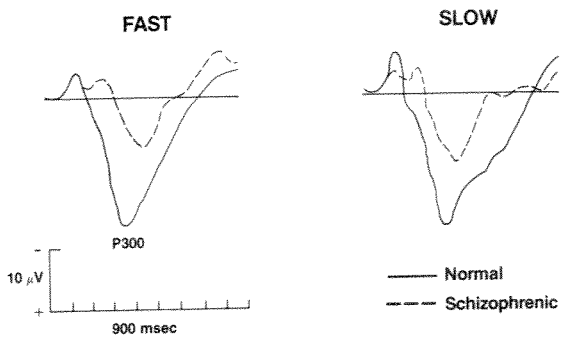
FIG. 5. Representative ERPs recorded from the vertex of two formerly hyperactive and two control adolescent males. The waveforms represent the average of ERPs to tone pips presented to the right and left ears under conditions of attending to target tones in the right (*solid lines*) versus left (*dotted 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, 1977)

cation (such as amphetamine or methylphenidate) in those children who also showed a clinical response to the drug.[87–89] These children also produced smaller than normal late positive (P300) components in response to target stimuli within an attended channel.[85,86] Other ERP characteristics have likewise been used to differentiate responders from nonresponders.[90–95] The N1 enhancement to an attended channel of tones (*i.e.*, Nd) is also reportedly below that of age-matched controls in adolescents who were formerly hyperactive but whose clinical symptoms have abated (Fig. 5).[96]

Recently it has been demonstrated that adult autistics are also characterized by grossly abnormal attention-related ERP effects (*e.g.*, Nd, N270, Nc), with the deficits being more pronounced in the auditory modality.[97] The diminution or absence of these ERP effects was interpreted as reflecting the malfunctioning of the neural mechanisms underlying the capturing, maintaining, and shifting of attention. On the basis of magnetic resonance imaging measurements, Courchesne suggested that these attentional deficits in autistic persons may be the consequence of abnormal development of the cerebellum.[98]

Abnormal selective attention effects (*e.g.*, N1 and Nd) have also been reported for adult schizophrenics[99]; the majority of these studies were conducted with patients receiving neuroleptic medication. Baribeau-Braun and associates[100] found that 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 stimuli were presented at a slower rate or the task called for dividing attention between the ears, schizophrenics showed reduced ERP signs of attention (Fig. 6). 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. Similar conclusions were drawn by Michie and colleagues[101] who examined unmedicated schizophrenics in a variant of a multidimensional attention task first used by Hansen and Hillyard.[102] In this task, channels of stimuli varied on the dimensions of location and pitch and the difficulty of discriminating the two dimensions was manipulated so that one dimen-

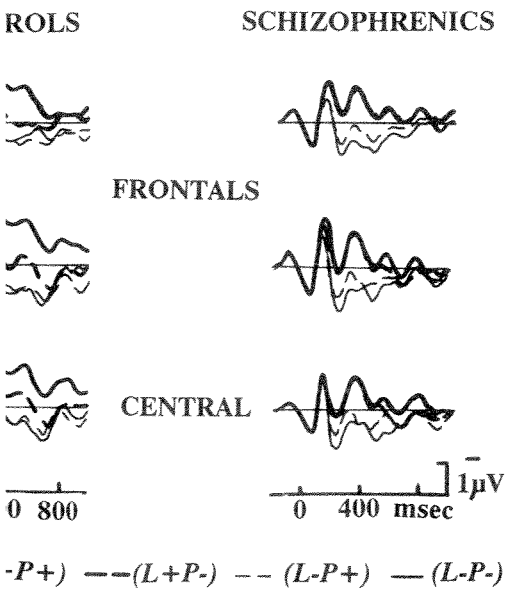
FIG. 6. ERPs from typical schizophrenic and normal subjects recorded in a focused attention experiment in which tones were presented in random order to the two ears at either a fast or a slow rate (Same task as illustrated in Figure 4). These ERPs were recorded from a midline parietal electrode in response to correctly detected targets within the attended channel. (Adapted from Baribeau-Braun J, Picton TW, Gasselin J: Schizophrenia: A neurophysiological evaluation of abnormal information processing. Science 219:874, 1983)



ocation, left versus right ear) was easy and ıer (pitch, 900 versus 960 Hz) was difficult. original as well as Michie studies, in the t pitch/easy location task, ERPs to the tones wo channels at the attended location exhib- ı early negativity (location Nd) onsetting 100 msec relative to ERPs to tones in the ıded location. This early Nd was followed by separation around 200 msec (pitch Nd) and long-lasting negativity in response to the ıat were of the appropriate pitch but only if ere in the attended location. This ERP pat- ıs taken to reflect a hierarchical pattern of n in which selection of the difficult pitch ion was subsequent to, and contingent on, n of the easy location dimension. Among attention-related ERP abnormalities, Mi- d co-workers found that schizophrenics did ›w evidence of an Nd associated with the n of pitch at the attended location (Fig. 7). ult, together with delayed Nds and reduced target tones, was taken to suggest an over- it in the planning and execution of selective listening strategies (*i.e.*, in the control functions responsible for the allocation of processing resources) by schizophrenic persons. Further elegant studies such as this with other patient populations will help determine whether or not any of these abnormalities are specific to schizophrenics.

Alcohol ingestion has also been implicated as a cause of attentional deficits in both alcoholics and nonalcoholics. Although several ERP studies have indicated smaller than normal N1 amplitudes in both alcoholics and nonalcoholics following alcohol intake, these results are of marginal interpretability.[103,104] Clearly this question is better addressed in the context of selective attention paradigms where the physical parameters of eliciting stimulus and subjects' arousal level are kept constant across comparisons of attended and unattended stimuli.

Grand average ERPs to standard stimuli at three sites for healthy controls (N=10) and unmedi- ıizophrenics (N=10). ERPs to four types of stan- nuli are superimposed: standards matching the target on location and pitch (L+P+), location -P−), pitch only (L−P+), and neither (L−P−). d from Michie PT, Fox AM, Ward PB et al: lated potential indices of selective attention and lateralization in schizophrenia. Psychophysiol- :09, 1990)



Event-Related Potentials Associated with Expectancy and Decision Making

Scalp-recorded ERPs are particularly sensitive indices of a subject's reaction to novel, surprising, and deviant events. Stimuli that deviate from 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 P3 or P300,[105] a label used to refer to late positivities with latencies anywhere from 200 to 1000 msec post stimulus, although 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 demands. Typically P300s 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 (although this has been questioned recently[106,107]), late positive wave (P3b) that is elicited maximally over the posterior scalp by task-relevant stimuli. The P3b wave was first described in a task in which subjects predicted on each trial which of a set of stimuli would occur next.[108] The amplitude of the P3 to the anticipated stimulus was an inverse function of its probability. One of the basic experimental situations in which the P3 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" or target) is typically associated with an enhanced P3 in relation to the more frequent stimulus class. The two classes of stimuli may be distinguished by simple physical cues (*e.g.*, tone frequency or light intensity) or by complex rules (*e.g.*, words belonging to different semantic categories).

Within the oddball task, P3b amplitudes have varied monotonically with the probability of the task-relevant stimuli[109] but only if the stimulus sequence was unpredictable or unknown to the subject and interstimulus intervals were less than 3 seconds. Thus, although objective or *a priori* stimulus probability has a strong influence on P3 amplitude, subjective probability or expectancy has proven to be the more critical factor. This was illustrated in studies by Squires and his co-workers,[110] showing that P3 amplitude decreased within an oddball sequence whenever a stimulus repetition occurred; repetitions were considered to raise the expectancy for further repetitions of that stimulus. In addition to event probability and sequential probability, the P3 has also been found to be sensitive to temporal, local, and response-contingent probabilities. The upshot of all these studies is that variations in P3 amplitude are determined primarily by the subject's expectancy for a task-relevant event. The notion of task relevance is important in that it underscores the need for the subject to pay attention to the stimuli to elicit a P3b component. For example, P3bs are not elicited by infrequent tones if the subject ignores them and reads a book. Likewise, target events in the unattended channel in a selective attention paradigm do not yield P3s.

On the whole, elicitation of the P3b requires active attention and engagement in a task in relation to the eliciting stimuli. Deviant or low probability events with no assigned task relevance elicit different members of the P300 family. For instance, a deviant stimulus interspersed within a monotonous auditory sequence that is not attended is associated with a "P3a" component that is earlier in latency, smaller in amplitude, and more frontally distributed than the 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.

Although earlier components such as P1, N1, and Nd provide the best indices of selective attention, the P3b in the oddball task can be used to evaluate the allocation of a subject's attentional "resources." For instance, under dual task conditions (in which counting infrequent tones is one of the tasks), P3b amplitudes to the oddball targets were found to diminish whenever the perceptual demands of the primary task were increased (*i.e.*, when more stimulus elements had to be evaluated); increasing response demands had no effect. Under these same circumstances, reaction times did not differentiate increases in perceptual load from those in response load. Subsequent studies of this type showed a clear reciprocity between the amplitudes of the P3s to the primary and secondary tasks as their respective difficulties were manipulated; this result was interpreted as an indication that the two tasks drew on a common pool of processing resources.[111] A similar logic led Daruna and associates[112] to use P3 amplitude as a test of the proposition that introverts allocate more attention to behavioral tasks than do extroverts. And, indeed they found that introverts (defined as in the top 25% of the Eysenck Personality Inventory and Sixteen Personality Factor Questionnaire) elicited larger amplitude P3s in response to low probability (25%) target in a paradigm in which subjects had to guess whether the next stimulus would be a high- or low-pitched tone; the two groups also showed different patterns of guessing, indicating use of different strategies.

The precise role of the P3 in stimulus evaluation has not been determined, but its elicitation seems to depend on a comparison of stimulus input against representations of the relevant stimuli in memory. Some evidence indicates that stimuli eliciting larger positivities in the time window generally associated with the P3 will be better remembered than stimuli with smaller positivities.[113] These findings are in line with recent suggestions

on intracranial[114–116] and neuromagnetic[117] ings that at least a portion of the P3 activity is ted in the hippocampal region, known for its ant role in stamping in and maintaining ex- ıemory. The smaller than normal amplitude P3 in chronic alcoholics,[103,118–122] persons ragile X syndrome,[123] and schizophren-),[124–128] may also reflect signs of hippocampal e.[129] At present, however, hippocampal e seems unlikely as an explanation for the d reductions in P3b amplitudes following lcohol ingestion,[122] in males at risk for alco- ,[130–134] and in depressed and manic per- ;,[136] In addition, the question has been ıs to how much of the memory-related posi- ; indeed an enhancement of the traditional There is mounting evidence that multiple reas (*e.g.*, temporoparietal junction,[138] fron- s,[116] locus coeruleus[139]) are involved in the ıtion if not generation of the P3b. There are ıtions in different patient populations that ısistent with the involvement of each of reas. For instance, the significantly smaller ıersons suffering from narcolepsy-cataplexy ıared with normal controls could reflect an ınt role for brain-stem structures (perhaps ıs coeruleus) in P3 elicitation. The contribu- the frontal lobes may be evidenced by the P3s in schizophrenics who also show fron- dysfunction by several neuropsychological ıroanatomic measures.

ıted previously, P3b latency is often consid- onger than 300 msec because increasingly mplex or difficult categorizations yield pro- ly longer latency P3s. In fact, many of the ctors that influence behavioral measures of ng time also alter P3b latencies. However, useful adjunct to RT measures because the dissociable. For example, if a subject in an task is encouraged to respond quickly, the ral response may occur before the P3b ıd the RT-P3b latency correlation may be ıall. On the other hand, if that subject re- vith an eye toward accuracy, RTs will gen- llow the P3b peak and the two measures ; highly correlated. Such results have led to ıosal that the timing of the P3b is more ied to the moment of a decision than to organization and production. For these P3b latency is presumed to provide a use- ure of the duration of stimulus evaluation s (encoding, recognition, and classifica- lependent of response processes, thus al- ıe nonmotor contributions to RT measures entangled from the motor ones.

The latency of the P3 increases systematically as a function of age, beginning at puberty and extending into the 90s. The majority of investigators[140,141] have reported a significant positive linear correlation between age and P300 latency, with slopes ranging from 1.1 msec to 1.8 msec/yr with little change in morphology across the life span. However, some reports[142,143] indicate that the relationship between P3b latency and age is more closely approximated by a curvilinear function; and under the conditions tested, this was a positively accelerating curve with a slope of 0.53 msec/yr for persons younger than 45 years of age and of 3.14 msec/yr for those older than 45. Goodin and associates[144] 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 P3 latency and RT also appears to be altered with age.[145] The elderly tend to 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 slower task performance of aged persons cannot be accounted for fully by slower sensory analyses, memory matching, or stimulus classification, but that delayed response engagement also makes a contribution. A similar interpretation has been offered for the finding that depressed persons have abnormally long reaction times together with normal latency P3s.[146] A similar logic can be used to disentangle motor and cognitive impairments in patients with parkinsonism. Several reports have suggested that N2 and P3 latencies to target tones in an oddball paradigm are delayed in patients with parkinsonism.[147–149] O'Donnell and colleagues found that P3 latency was correlated with performance on tests requiring learning or mental manipulation of information but not with measures of verbal performance or immediate memory. In addition, they noted that P3 latency prolongation was correlated with mental status decline but not with the severity of motor disturbance. In possible conflict are the findings of Starkstein and associates, who found that the P3 latencies of patients with parkinsonism were shorter in the on (*i.e.*, motor function near normal) than off (*i.e.*, severe motor disabilities) phases of the disease in the absence of concomitant changes in neuropsychological measures. Note that Starkstein and associates' patients had usually short latencies for their age (mean, 64 years); moreover, no ERPs were presented for visual inspection.

Within a given task such as the oddball paradigm, the latency of the P3 across normal subjects

of a particular age is consistent enough that it can be used in the diagnosis of organic dementia.[150,151] Demented patients typically show a P3 that is delayed in latency by more than two standard deviations beyond the mean age-matched controls.[144,152] Delays of this magnitude appear to be specific to organic dementias (Alzheimer's, Huntington's, Parkinson's) not having been observed for any other neurologic or psychiatric patient groups, although there have been occasional reports of smaller delays in P3 latencies of chronic alcoholics,[120] nondemented patients with parkinsonism,[149] and schizophrenics.[152] To date, the only group to show shorter than normal P3 latencies are nonmedicated persons suffering from obsessive-compulsive disorder (OCD).[153,154] This particular pattern of latencies across various patient populations means that the P3 can serve to help distinguish 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. Although there is some controversy as to the sensitivity and specificity of the P3 latency to dementia, it is clear that "in a patient with a 50% chance of being demented on clinical grounds, the finding of an abnormal P3 latency would increase the likelihood of true dementia to 90%)."[150] What are needed are good prospective studies that assess how well the P3 test identifies those whose later clinical deterioration and/or autopsy results confirm the diagnosis. Besides its use in diagnosing dementia, there is accumulating evidence that P3 may have a diagnostic role in tracking the clinical course of a dementing disorder, in monitoring response to treatment, and in identifying patients at risk for dementia, such as those with human immunodeficiency virus encephalopathy.[155]

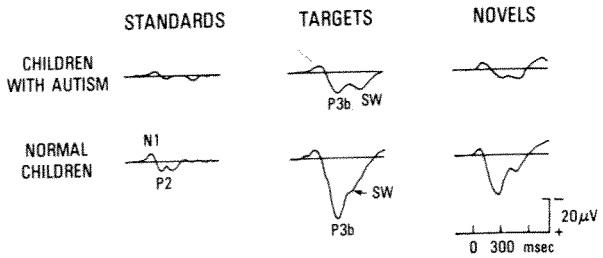
Event-Related Potentials in Children

Many of the endogenous components observed in adults have their counterparts in infants, children, and adolescents.[156,157] For instance, familiar and easily categorizable events such as the target and standard stimuli in the usual oddball task elicit similar ERPs in persons between 6 and 60 years of age with little change in morphology across the life span, although the P3s are substantially longer in latency in children than in adults under comparable conditions.

Complex visual stimuli, on the other hand, such as 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 the 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.[158–161] The most robust finding has been a reduction in the amplitudes of the P3a and P3b components, especially in the auditory modality (Fig. 8). The responses of autistics to unexpected novel and target events in the visual modality are usually not very different from those of control subjects (on occasion characterized by a somewhat attentuated Nc component). By contrast, autistics' responses in the auditory modality are substantially more variable and thus much smaller than normal on the average.[162] The pronounced auditory deficit relative to

FIG. 8. 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: Autism: Processing of novel auditory information assessed by event-related brain potentials. Electroencephalogr Clin Neurophysiol 59:238, 1984)



ıal deficit has been confirmed in a selective n task.[97]

ies of hyperactive children and those with ; disorders indicate that they, too, have di- d late positive components in target detec- discrimination tasks. Schizophrenic chil- re found to exhibit not only reduced P300 des in general but also a lack of sensitivity ges in task difficulty.[163] These ERP abnor- were associated with problems in correctly ng task-relevant stimuli. The diminished itivities in such children have generally cribed to the attentional disturbances so ristic of these syndromes.

t-Related ntials of ps at Risk

e many methodologic and theoretic advan- studying persons at risk for a disorder ıan those who show it in full clinical As the data on the different cognitive ERP ents in various patient populations accrue, oming increasingly feasible and critical to ıe whether persons (including children, nts and adults) at risk for a particular dis- ıifest any of the same abnormal electro- gic patterns despite their lack of overt ıs. At-risk populations have been defined of behavioral ratings, scores on self-report naires, or by virtue of having a positive story (FHP or FH+) for the disease. For antisocial behavior and early aggression dered risk factors for later drug abuse and utionalized nondelinquent youths with factors did show abnormal late potentials w waves) under certain conditions.[165] whether this relates to the smaller than 3s observed in adults who reported heavy ıse (*e.g.*, cocaine) is unclear given the of possible causes (Fig. 9).[166]

vhat clearer results have emerged from persons who score high on a question- luating risk for psychosis[167]; relative to vith normal scores, subjects who had high Chapman's questionnaire demonstrate al and affective symptoms. Several studies d psychophysiologic abnormalities (*e.g.*, a subset of such persons who score high of physical anhedonia (defect in pleasure and perceptual aberration experiences. In

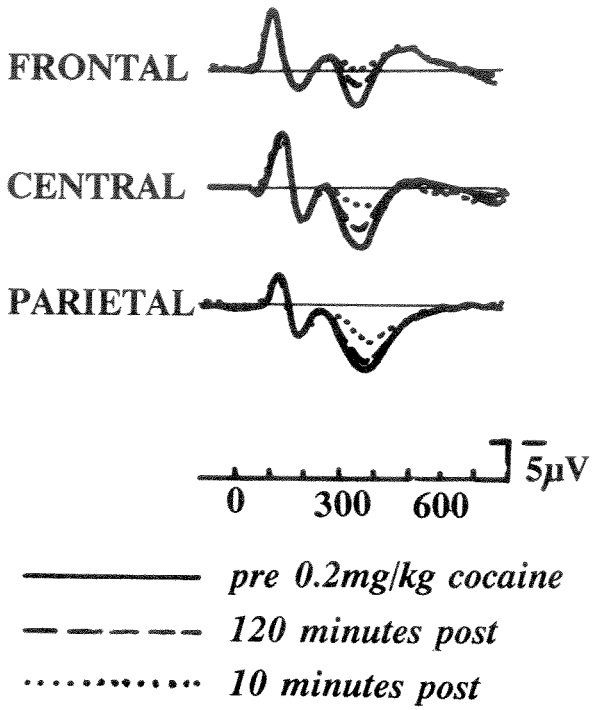


FIG. 9. Grand average ERP to infrequent tones in an oddball task before and at two times after intravenous administration of 0.2 mg/kg cocaine (Adapted from Herning RI, Jones RT, Hooker WD, Tuluna FC: Information processing components of the auditory event related potential are reduced by cocaine. Psychopharmacology 87:187, 1984)

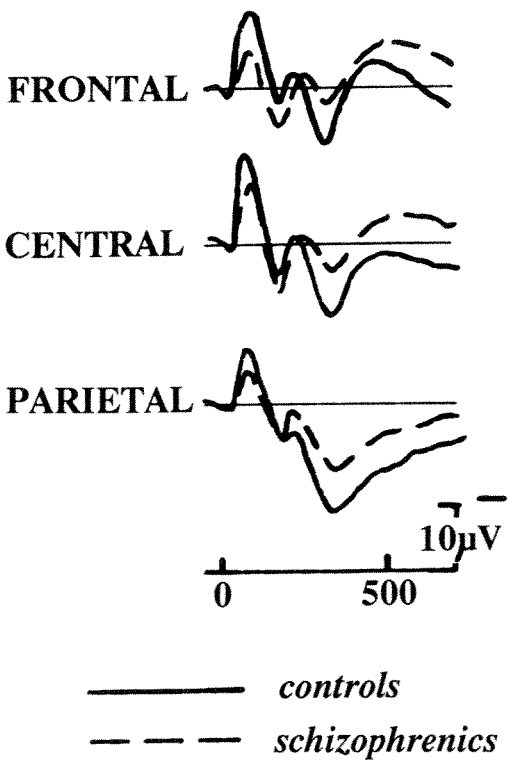
one study, unlike normal controls, anhedonics did not show larger CNVs preceding slides of human nudes than preceding more neutral slides.[168] These persons have also been found to respond to a variety of stimuli with abnormal N2, P3, and slow wave potentials.[169,170]

Two populations in which there is some evidence of genetic mediation of a disorder are children at risk for alcoholism and for schizophrenia. Studies conducted with adoptees suggest that some types of alcoholism are heritable; sons of alcoholic fathers are four times as likely to develop alcoholism than sons of nonalcoholics even when they are separated from their biological parents at birth. Although ERP signs of the genetic predisposition for alcoholism have been mixed, there does seem to be a striking similarity in the P3 responses of abstinent alcoholics and men at risk for alcoholism (namely, male offspring and relatives of those with male-limited alcoholism). In many, although not all, of the reports about young boys at risk for alcoholism, the amplitude of the P3 to a target in an oddball

task was significantly attenuated relative to age-matched controls.[131] In other cases, target P3 amplitudes were correlated with the number of drinks per occasion for the persons with a positive family history or were delayed in latency.[133,171,172] Whether the cognitive functions of males at risk for alcoholism are more or less sensitive to alcohol challenge is still at issue.[173]

The mode of inheritance of schizophrenia remains elusive.[174] The evidence of abnormal P3s in persons at risk for schizophrenia is also not very compelling. Typically, adult and child schizophrenics show reduced amplitude P3s, which by some reports are especially pronounced in the left temporal region (Fig. 10).[100,125,126,175,176] A similar reduction has been obtained for siblings of schizophrenics.[177] The most systematic longitudinal investigation of children at risk for schizophrenia has revealed no reliable differences in their ERPs relative to those of children of normal controls or persons afflicted with an affective disorder.[178] Given that there is only a small (10%–15%) probability that a child of a schizophrenic will develop the disorder, it is hardly surprising that the group as a whole does not show reduced P3s. The true test of the utility of the P3 as a reliable prognosticator will come from a prospective study of those children at risk who do indeed become schizophrenic.

FIG. 10. Grand averages at the vertex in response to target tones in an auditory detection task from 20 controls and 20 schizophrenics. (Adapted from Barrett K, McCallum WC, Pocock PV: Brain indicators of altered attention and information processing in schizophrenic patients. Br J Psychiatry 148:414, 1986)



Event-Related Potentials and Language

A substantial research enterprise has focused on the relationships between ERPs, hemispheric specialization,[179] and language.[180] Although most early studies of hemispheric specialization using electrophysiologic measures uncovered only small, inconsistent, or uninterpretable results, more recent investigations have demonstrated robust, lateralized ERP components.[25,181,182] Such lateralized ERPs have been related to hemispherically specialized modes of processing that are quite sensitive to early experience and individual differences in developmental history.[183] Few attempts have been made to link ERP lateralization with psychopathology. However, the direction of ERP asymmetry might be useful as a test of the currently popular hypothesis that schizophrenics and manic-depressives have different and opposite balances of hemispheric activation.[184] Already studies using the BEAM technique, which displays ERP topographies in a color-coded map, have suggested that the scalp distribution of the P3 differs between schizophrenic and normal persons.[175,176] In specific schizophrenics' P3s were found to be displaced anteriorly and toward the right hemisphere, whereas in the control subjects the P3s were usually bilaterally symmetric. In schizophrenics, significant correlations were obtained between the Thought Disorder Index (TDI) and the Scale for the Assessment of Positive Symptoms (SAPS) and the amplitude of the P3 in the left temporal scalp region.[185] Thus, evidence from EEG, ERP, and anatomic sources for differential hemispheric involvement in schizophrenia and mania continues to mount.[176,184–188]

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.[189,190] Words that complete sentences in a nonsensical fashion elicit much larger N400 waves than do semantically appropri-

rds or nonsemantic irregularities in a text. plitude of the N400 has been shown to be rse function of a subject's expectancy for the word (assuming that word length and fre- of occurrence in the language are held con- n addition, the N400 appears to be respon- subtle semantic relationships among words, r or not they make sense as long as some n is directed at analyzing the words (al- not necessarily the relationship[191]). These have suggested that the N400 can be a nline measure of the strength of the seman- traints imposed on a word and the time with which various factors that comprise nstraints are applied.[192]

e few studies that have examined the con- es of aging on the N400, all have found N400 is both significantly reduced in am- and delayed in latency with age.[193] Prelimi- a in our laboratory indicate such a striking in N400 amplitude in the healthy elderly e additional drop associated with Alz- s dementia seems insignificant by compari- date, none of the N400 studies have cov- broad an age range as has been employed 3. A few studies have also investigated the various schizophrenic populations with esults.

lusions

hysiologic research in psychiatry, as in psychology, has so far been largely corre- Objective ERP measures are correlated diagnostic categories of the trained psychi- ch of which is presumed to correlate with rmal physiology that underlies the mental

e moment, the ERP plays a minor role in hiatric clinic since the electrophysiologic re subject to many of the same problems e plagued behavioral investigations of psy- logy.[194] In particular, it has proven ex- difficult to match patient and control long all critical dimensions that may influ- dependent measures over and above the primary group membership. When mak- parisons among different patient groups, f age, gender, medication, and the dy- f the illness cannot be ignored as potential ling factors.

e vexing problem is the difficulty in attrib- abnormal ERP configuration to a specific cognitive dysfunction rather than to a generalized lack of task involvement. That is, patient groups may generate aberrant ERPs and generally poor performance, not because they are incapable of the task but because they are unmotivated, do not understand the task, or are otherwise preoccupied. Although there is no wholly satisfactory solution to this problem, Roth and associates[194] have suggested that behavioral measures should be recorded concurrently with the ERP and, whenever possible, performance should be matched in patient and control groups.

A final problem is the extreme vulnerability of ERP measures, particularly the late "cognitive" components to momentary changes in the subject's state. Indeed, the problem with ERPs in psychiatry has not been a lack of significant effects but rather an overabundance of nonspecific and difficult-to-interpret correlations. Tables of the ERP abnormalities that have been observed in schizophrenics, affective psychoses, personality disorders, and chronic brain syndromes abound in the literature.

In sum, ERP measures tend to reflect the presence or absence of psychopathology and to some degree its severity, rather than specific nosologic categories; that is, ERP effects observed to date are not pathognomonic. 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 persons at risk for developing them should also lead to greater diagnostic specificity.

Callaway has argued 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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Marta Kutas is supported by a Research Scientist Development Award MH3022. Some of the work cited herein was supported by grants from NIA (AG08313) and NICHD (HD22614).