

EVENT-RELATED POTENTIALS AND MAGNETIC FIELDS IN THE HUMAN BRAIN

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To uncover the neural bases of a cognitive process it is important both to identify the participating brain regions and determine the precise time course of information transmission within and among those regions. Although neuroimaging techniques based on cerebral blood flow or metabolism (e.g., positron emission tomography [PET] and functional magnetic resonance imaging [fMRI]) are providing increasingly detailed pictures of the anatomic regions activated during cognitive activity, these methods lack the temporal resolution to reveal the rapid-fire patterning of neuronal communication. Noninvasive recordings of the electrical and magnetic fields generated by active neuronal populations, however, can reveal the timing of brain activity related to cognition with a very high, msec-level resolution. This chapter gives an overview of how these temporally precise recording techniques have been used to analyze perceptual and cognitive mechanisms in the human brain.

The changes in field potentials that are time-locked to sensory, motor, or cognitive events are known as event-related potentials (ERPs) and the corresponding magnetic field changes are termed event-related fields (ERFs). Both ERPs and ERFs consist of precisely timed sequences of waves of varying field strength and polarity (Fig. 32.1). These observed peaks and troughs in the waveform are often referred to as "components." Some authors, however, prefer to use the term component to refer to portions of the waveform that originate from particular neural structures, whereas others consider ERP/ERF components to be those waveform features that are associated with a particular cognitive process or manipulation (2). Both ERPs and ERFs are generated primarily by the flow of ionic currents in elongated nerve cells during synaptic activity. Whereas synaptic currents flowing across nerve cell membranes into the

extracellular fluid produce ERPs, the flow of synaptic current through neuronal processes produce ERFs, thereby giving rise to concentric magnetic fields surrounding the cell. When a sufficient number of neurons having a similar anatomic configuration are synchronously active, their summated fields may be strong enough to be detectable at the scalp.

When ERPs or ERFs are recorded from the surface of the head, the locations of the active neural generators can only be estimated rather than visualized directly. The calculation of generator locations from surface field distributions is known as the inverse problem, which typically has no unique solution. However, the validity of inverse source estimations can be considerably improved by using algorithms and models that take into account the geometry of the cortical surface, biophysical properties of the intervening tissues, constraints from neuroimaging data, and statistical likelihood of alternative source locations (3,4). In general, the localization of active neural populations is more straightforward with surface recordings of ERFs than with ERPs, because magnetic fields, unlike electrical fields, are minimally distorted by the physical properties of the intervening tissues.

ERP and ERF recordings have been used extensively to investigate the spatiotemporal patterns of brain activity associated with a variety of perceptual, cognitive, and linguistic processes. The general research strategy has been to discover the mapping between the components of the waveform and specific cognitive processes that are engaged by a particular task. When an ERP/ERF component can be shown to be a valid index of the neural activity underlying a cognitive operation, that component can yield valuable information about the presence or absence of that operation and its timing with respect to other cognitive events. In many cases, such data have been related to psychological models of the underlying processing operations and used to test alternative theoretical positions. In addition, by localizing the neural generators of such components, inferences can be made

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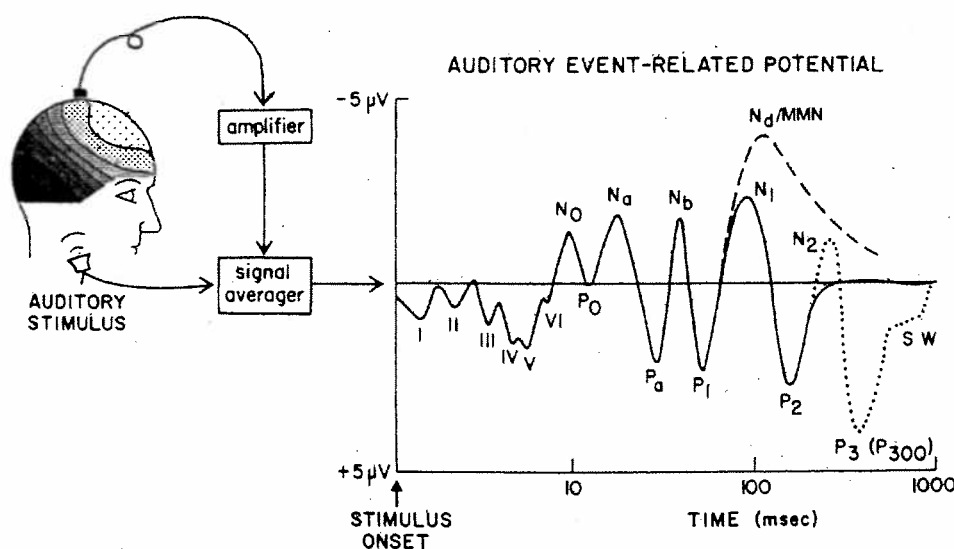


FIGURE 32.1. The characteristic waveform of the auditory event-related potential following a brief stimulus such as a click or tone. The individual components (peaks and troughs) are evoked with specific time delays (latencies) after stimulus onset. Note the logarithmic time base, which makes it possible to visualize the earliest waves (I–VI) generated in the auditory brainstem pathways. Longer latency negative (N) and positive (P) components are generated in different cortical areas. Dashed line shows increased negativity elicited by attended sounds (negative difference) or by deviant sounds (mismatch negativity), and dotted line shows N2 and P3 components to task-relevant target stimuli. Adapted from Münte TF, Schiltz K, Kutas M. When temporal terms belie conceptual order. *Nature* 1998;395:71–73.

about the participating anatomic circuits that can be interfaced with neuroimaging and neuropsychological data. This chapter describes recent advances made using this approach for analyzing the neural and cognitive mechanisms of preattentive sensory processing, selective attention, mental chronometry, memory storage and retrieval, and language comprehension and production. The use of ERP/ERF recordings to evaluate cognitive disorders associated with neurobehavioral and psychopathologic syndromes also is reviewed.

PREATTENTIVE SENSORY PROCESSING

Much of the early ERP waveform, and some later components as well, represent sensory-evoked neural activity in modality-specific cortical areas. These evoked components vary with the physical parameters of the stimuli and in many cases are associated with the preattentive encoding of stimulus features. In the visual modality, for example, the early C1 component (onset latency 50 to 60 msec) originates in retinotopically organized visual cortex (5) and varies in amplitude according to the spatial frequency of the stimulus (6). Similarly, the early auditory cortical components P50 and N100 (and their magnetic counterparts, M50 and M100) arise in part from generators in tonotopically organized supratemporal auditory cortex and reflect the encoding of perceived pitch (7).

In general, ERP amplitudes decrease when the time between successive stimulus presentations is made shorter than the refractory or recovery period of the component under study. Although the neural processes underlying ERP refractory effects are not well established, some candidate mechanisms include synaptic fatigue, active inhibition, and the

persistence of sensory memory for the preceding stimulus. In line with this latter idea, the refractory period of the auditory M100 has been found to have a similar time course to that of sensory or “echoic” memory for stimulus loudness (8).

The P50 and Sensory Gating

The refractory properties of the auditory P50 (P1) component have been studied extensively over the past 20 years as a possible marker of abnormal sensory input control in schizophrenia (9–12). In the standard paradigm, pairs of auditory stimuli are presented with an ISI of 0.5 sec, and the amplitude ratio of the P50 evoked by the second stimulus (S2) relative to the first stimulus (S1) is calculated. In general, schizophrenic subjects do not show as large a reduction in the P50 amplitude to S2 relative to S1 as do normal controls. This refractory reduction of P50 amplitude to S2 has been interpreted as a sign of preattentive sensory gating, which occurs because the initial S1 automatically activates an inhibitory system that suppresses responsiveness to S2 (9, 10). This inhibitory system presumably prevents irrelevant information from ascending to higher levels of cortical processing. The abnormally large S2/S1 amplitude ratio for P50 seen in schizophrenics was thus considered evidence for impaired sensory gating, which was suggested to be the principal sensory deficit of the disease process.

This pattern of more rapid P50 recovery in schizophrenia has been widely reported, but there have been some notable exceptions that raise questions about the exact conditions needed to produce the effect (13–15). A more serious question, however, is whether existing studies have, in fact, demonstrated a reliably abnormal S2/S1 ratio of the auditory P50 in schizophrenics. This concern stems from the way the

P50 has typically been measured—as the maximal positive amplitude within a time window (e.g., 40 to 80 msec) that encompasses the P50 peak. Such peak measures may be artificially inflated by increased levels of background noise in the EEG recordings, originating from either intracranial or extracranial sources. Thus, if a patient group has higher EEG noise levels, then the measured P50 amplitudes tend to be greater because the noise peaks are at times mistaken for the actual peak of the P50. This type of error is more pronounced when measuring the P50 to S2, because its amplitude is diminished relative to the noise owing to refractory effects. Reports of increased variability and lower reliability of P50 measures in schizophrenics (12,16) suggest that background noise levels are indeed higher in the patient groups. Several studies, however, have reported that the P50 evoked by S1 is smaller in schizophrenics (11,12,16), which suggests that overall response amplitudes may be lower and/or response latencies more variable in these patients. Further studies are needed to determine whether the actual S2/S1 amplitude ratio is reliably higher in schizophrenics, or whether this reported effect is a product of noise-sensitive measurement procedures.

Even if the S2/S1 ratio for P50 were determined to be greater in schizophrenia, there would still be some question about its functional interpretation. There is little evidence that refractory reductions of ERP amplitudes to stimuli repeated at 0.5 sec ISIs are associated with any reduction in the perceptual information reaching higher centers. Nor does it appear that the amplitude of P50 to S2 is reduced only when S2 is irrelevant (17), calling into question the hypothesis that the P50 refractory effect reflects the selective gating of irrelevant versus relevant sensory inputs. In addition, it has been reported that schizophrenic patients showing the most severe perceptual anomalies did not differ from normals in their P50 refractory effects (15). Thus, there seems to be scant evidence that reduced P50 refractoriness in schizophrenia, if such exists, is related to the selective gating or filtering of irrelevant sensory information in the auditory cortical pathways.

Auditory Feature Encoding

The preattentive coding of auditory features is indexed with considerable precision by the mismatch negativity (MMN) component and its magnetic counterpart, the MMNm. The MMN is a scalp-negative component with a latency of 120 to 250 msec that is specifically elicited by a deviant sound in a repetitive auditory sequence (18–20). The MMN can be triggered by any discernible change in the ongoing sounds, such as deviations in frequency, intensity, duration, rise-time, timing, and spatial location. MMNs also have been recorded to changes in more complex sound properties such as the phonetic structure of speech sounds and the patterning of tone sequences (20,21). Näätänen (22) has proposed that the MMN is generated by an automatic com-

parator process that contrasts current auditory input against a multidimensional trace of the previous repeating sound's features held in preperceptual sensory memory. This mismatch detection process may represent an early stage in the alerting and orienting of the organism toward novel and potentially important changes in the acoustic environment.

The MMN provides a window on auditory sensory or "echoic memory" because it is initiated by a mismatch with the memory traces of the preceding sounds (23). Indeed, the maximal interstimulus interval (ISI) at which the MMN can be maintained is of the order of 10 sec, corresponding well with behavioral estimates of the duration of echoic memory (19,20). The MMN also can be used to study more permanent auditory memory traces, such as those for the phonemic characteristics of one's native language (19) as they emerge during the first year of life (21).

It has been proposed that a supratemporal component of the MMN originating in auditory cortex reflects the preattentive sensory store and automatic change detection process, whereas a frontal component indexes the involuntary orienting of attention to the deviant event (24,25). For speech sounds, however, the MMN/MMNm appears to arise from sources in auditory cortex of the left hemisphere, in accordance with proposals that the left posterior temporal cortex is the locus of language-specific auditory traces (19).

Given that the MMN may be elicited with minimal cooperation from the subject, it has found wide applicability for the diagnosis and evaluation of a variety of neurobehavioral and psychiatric disorders (24,26). Schizophrenic patients have reduced or prolonged MMNs to pitch or duration deviants, with the degree of abnormality depending on the specific parameters of the stimulus deviance (24,27,28). These findings provide clear evidence for a deficit in preattentive auditory processing in schizophrenia, although there is some debate about whether the impairment is primarily in temporal processing (28) or auditory encoding and trace formation (27). A different pattern of abnormality has been observed in Alzheimer's disease, with MMN amplitude reductions becoming more prominent at longer ISIs (29), suggesting a more rapid decay of auditory sensory memory traces. MMN abnormalities indicative of auditory processing deficits have also been reported in cases of learning disorders, language and speech impairments, depression, autism, parkinsonism, and HIV infection. (See refs. 19, 21, 24, and 29 for reviews.) Drugs that interfere with NMDA-receptor mediated neurotransmission also disrupt the MMN, which is consistent with models of schizophrenia that posit a disturbance in glutamergic/NMDA functioning (27).

SELECTIVE ATTENTION

The brain's attentional systems include a central control network with projections to the sensory pathways of the different modalities that enable the selective modulation of

incoming information. A good deal of research on attention over the past few decades has been aimed at determining whether incoming sensory information is selected at "early" or "late" levels of processing—that is, before or after stimulus properties are fully analyzed (30). Current evidence from both behavioral and physiologic studies indicates that attention can select stimuli at different levels of the sensory pathways, depending on the features being attended and the task requirements.

Auditory Attention

In the auditory modality, ERPs have demonstrated that attentional selection occurs at early levels of cortical processing, but not in the brainstem pathways (31). In dichotic listening tasks with rapidly presented tones to the left and right ears, the earliest ERP component that is reliably influenced by paying attention selectively to one ear is a small positive wave with a latency of 20 to 50 msec (termed the P20–50), which has been localized using magnetoencephalography (MEG) to sources in or near primary auditory cortex. This short-latency modulation provides evidence for an attentional mechanism of sensory gain control at the earliest levels of cortical processing. A much stronger attentional modulation of auditory input takes place at 50 to 70 msec after stimulus onset in the form of a negative difference (Nd) potential that augments the amplitude of the evoked N1 wave to attended-channel sounds (Fig. 32.1). This N1/Nd attention effect also has been localized to auditory cortex by MEG recordings and is considered to be an index of further processing of attended sound information, or alternatively, of the closeness of match between incoming stimuli and the acoustic features that define the attended channel (30). These negative ERP modulations indicate the precise timing with which different auditory features are attended or rejected (32) and provide strong evidence for early selection theories of attention. Schizophrenic subjects reportedly show abnormally reduced Nd amplitudes when attending to multiple sound features, suggesting a deficit in their control functions for allocating attentional resources during selective listening (33).

In recent studies, auditory ERPs have been used to study how attention is allocated in a noisy environment with multiple, competing sound sources (34). When subjects listened selectively to sounds coming from one loudspeaker in a free-field array, the spatial focusing of auditory attention took place in two distinct stages: an early, broadly tuned input selection occurring over the first 80 to 180 msec (indexed by N1/Nd) was followed by a more sharply focused selection of target sounds that began at around 250 msec (indexed by the late positive P3 component). These findings indicate that auditory spatial attention is deployed as a sharply tuned gradient around an attended sound source in a noisy environment. Under these conditions congenitally blind persons were found to have sound localization capabilities superior

to those of sighted control subjects (35). ERP data indicated that this enhanced capability of blind persons is mediated at least in part by an attentional tuning mechanism that operates within the first 100 msec after sound onset.

Visual Attention

Covertly directing attention to a specific location in the visual fields typically results in faster and more accurate detections or discriminations of stimuli at that location. Recordings of brain activity in both humans and animals have identified a number of sites along the visual pathways where afferent information is modulated under the influence of visual-spatial attention. Neurophysiologic studies in monkeys demonstrated strong influences of spatial attention on neural activity in extrastriate cortical regions, including retinotopic areas V2, V3A, and V4 and higher areas of both the ventral (inferior temporal lobe) and dorsal (area MT, posterior parietal lobe) processing streams (36). These findings are congruent with human ERP studies showing that stimuli at attended locations elicit enlarged P1 (70 to 130 msec) and N1 (150 to 190 msec) components (Fig. 32.2), which have been localized to generators in extrastriate visual cortex (37). This amplitude enhancement of the P1 and N1 waves occurs with little or no change of the component latencies, suggesting that spatial attention exerts a gain control or selective amplification of attended inputs within the visual-cortical pathways in the interval between 70 and 200 msec after stimulus onset (38).

In experiments that combined PET neuroimaging and ERP recordings, the calculated dipolar sources of the P1 attention effect were found to correspond closely with regions of increased blood flow in retinotopically organized extrastriate areas, including areas V3/V4 and the posterior fusiform gyrus (37). Significantly, however, the earlier C1 component (onset at 50 msec), which appears to originate from generators in primary visual cortex (area V1), was found to remain invariant with changes in the direction of spatial attention. These findings suggest that spatial attention modulates the flow of visual information at a higher level than the primary cortex.

Recent studies in monkeys, however, reported that stimulus-evoked activity in area V1 may be affected by spatial attention when competing stimuli are present in the visual field (39). The participation of V1 in spatial attention has also been inferred from recent fMRI studies in humans (40). In a study combining fMRI with ERP recordings, Martínez and colleagues (41) observed focal increases in blood flow (BOLD signal) in area V1 as well as areas V2, V3/VP, and V4 at sites corresponding to the retinotopically mapped position of the attended stimulus; however, the amplitude of the C1 component again remained invariant (Fig. 32.2). The earliest influence of attention was on the P1 component (75 to 130 msec), which was localized through dipole modeling to dorsal and ventral extrastriate sources. It was sug-

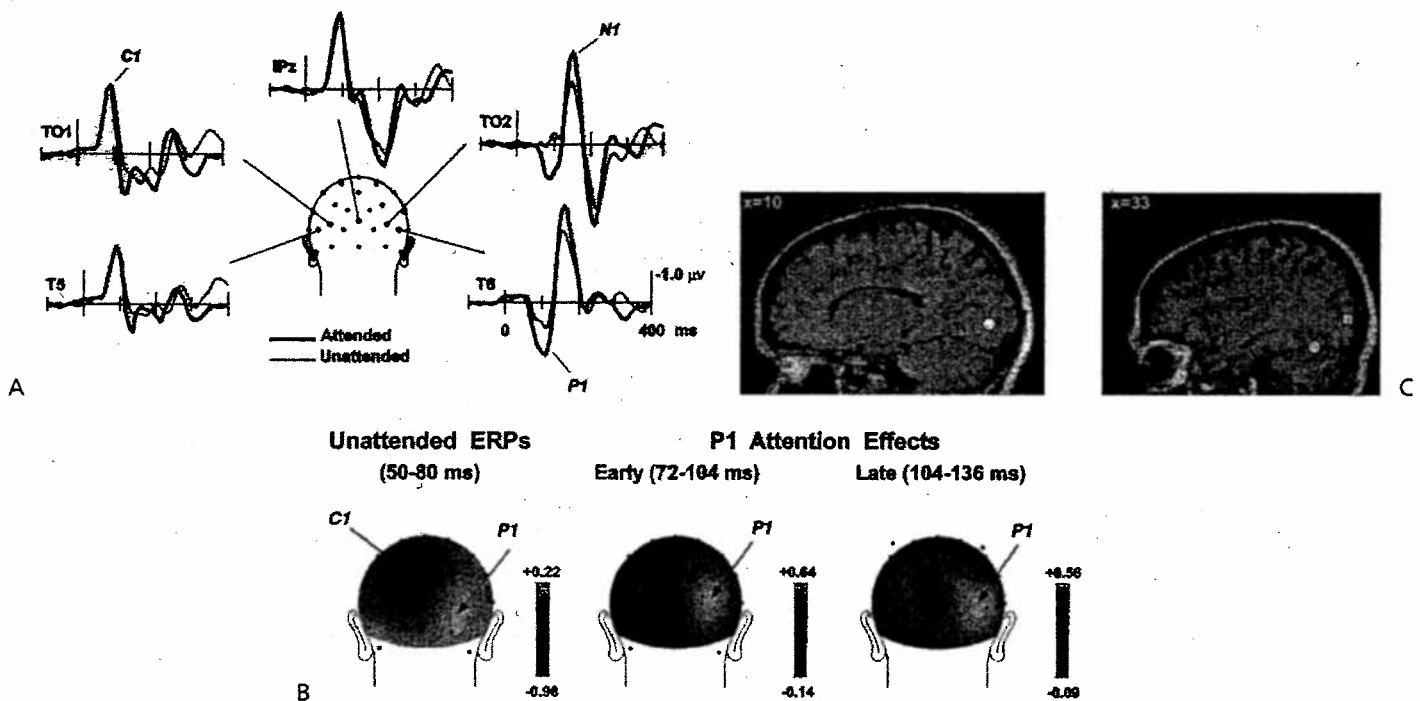


FIGURE 32.2. A: Visual event-related potential waveforms from several scalp sites in response to stimuli in left visual field in study by Martínez and colleagues (41). Subjects were required to attend to one field at a time while randomized stimulus sequences were presented concurrently to left and right fields. Note increased amplitude of P1 and N1 components when stimuli were attended and lack of change in C1 component. B: Voltage topographies of C1 component and of the P1 attention effect (increased positivity with attention) in two different time ranges. C: Locations of dipolar sources calculated for the C1 component (in primary cortex of calcarine fissure, left) and the early and late P1 attention effects (dorsal and ventral extrastriate cortex, respectively, right).

gested that the attentional modulation of V1 activity revealed by fMRI may take place at a latency longer than the initial geniculostriate response represented by the C1 and is consequent on delayed feedback of enhanced visual signals back to V1 from higher extrastriate areas. Such long-latency modulations in V1 have been observed in animals and may enhance figure/ground contrast in attended regions of the visual field (39).

The spatial allocation of attention has also been studied with the steady-state visual evoked potential (SSVEP), which is the oscillatory response of the visual cortex evoked by regularly repeating stimuli such as a light that flickers at a rate of 8 Hz or more (42). The amplitude of the SSVEP elicited by such a flickering stimulus is substantially increased in amplitude when attention is directed to its location, thereby indexing amplification of visual inputs within the spotlight of attention. The continuous nature of the SSVEP as a measure of cortical facilitation makes it suitable for measuring the time course of attention shifts among stimuli in the visual fields.

In contrast with spatial attention, when stimuli are selected on the basis of nonspatial features such as color, shape, or spatial frequency, a different pattern of ERP com-

ponents is observed. Stimuli having the attended feature elicit a prominent "selection negativity" (SN) over the posterior scalp that begins at 120 to 220 msec and may extend for several hundreds of msec (37). The onset of the SN provides a precise measure of the time point at which a particular feature is discriminated and selectively processed, and localization of its neural generators points to the brain regions involved in the selection. When stimuli are selected on the basis of two or more features concurrently, recordings of the SN can indicate whether the features are selected independently or in an interactive, contingent manner (43).

MENTAL CHRONOMETRY

Motor preparation, execution, and evaluation are indexed by a series of electric (and magnetic) components both preceding and following movement onset. Prime among the ERPs indexing preparation is the readiness potential (RP), which is a slowly ramping negativity that starts about 1 s before the onset of a voluntary or self-paced movement and peaks around movement onset (44). The initial, bilaterally symmetric portion of the RP is generated in the supplement-

tary motor area (SMA). Approximately 200 to 500 msec before movement onset the RP becomes asymmetric, being maximal over central scalp contralateral to the active musculature. This lateralized portion of the RP has a somatotopic distribution over the motor cortex and has been localized to the primary motor cortex (45). This asymmetric portion of the RP can be seen in stimulus-locked averages (46) and serves as the basis for an index of differential motor preparation termed the lateralized readiness potential (LRP). Subtracting for each hand separately the activity over the ipsilateral from that over the contralateral central site, and then averaging the activity for the two hands together derive the LRP.

The LRP has proven especially useful in studies of mental chronometry aimed at answering questions about the dynamics of information processing. For example, LRP data have shown that whether a person responds quickly and accurately is in large part a function of whether he or she is prepared to do so before the stimulus appears. Appropriate preparation leads to fast and correct responses, whereas inappropriate preparation leads to fast but wrong responses, and no preparation at all leads to slow but accurate responses. More important, LRP data revealed that people develop biases that influence how they prepare to respond. (See refs. 47 and 48 for review.)

In a number of sensory-motor discrimination tasks, LRP recordings have provided strong support for "continuous flow" models that specify that transmission of perceptual information to the response system occurs continuously rather than in discrete, all-or-none stages. Such studies have revealed partial transmission of perceptual information (e.g., about letter identity) to the response system and have provided a means of tracking the time course of the extraction of various types of information. The LRP also has been used to determine the timing of "the point of no return," that is, the time in the course of response preparation beyond which response execution cannot be stopped (47).

Readiness potentials have been examined in a number of patient populations. They are abnormal in a large majority of individuals with Parkinson's disease (PD), presumably because of abnormal activation of the SMA by the basal ganglia (49,50). Because the early part of the RP is sensitive to attention, it has been suggested that motor performance in PD patients might be improved by having them attend to movements that they might otherwise try to execute automatically (51). Individuals with tardive dyskinesia (TD) also show abnormal RPs that are larger in amplitude than those of normal controls and schizophrenic patients without TD (52). Unlike voluntary leg movements, involuntary myoclonic leg movements in patients with restless leg syndrome do not elicit an RP, suggesting that these involuntary movements have a subcortical or spinal origin (53).

Purposeful movements are generally monitored and evaluated so that remedial action may be taken if an error is committed. Performance monitoring of this sort is indexed

by an ERP known as the error-related negativity (ERN), which peaks about 100 msec after the onset of the electromyographic activity associated with an erroneous response. ERN amplitude covaries with the perceived inaccuracy of a response (54) and is influenced by how similar the given response is to the correct one. An ERN is also elicited by a feedback stimulus that lets the subject know an error was made. ERN generators have been localized to the anterior cingulate gyrus and are modulated by lateral prefrontal cortex (55). Patients with lateral prefrontal cortical damage are impaired in correcting their behaviors and produce equal-sized ERNs for correct and incorrect responses. ERN amplitude is sensitive to mood and personality variables (56), especially when correct responses are rewarded and/or incorrect responses are punished (57).

MEMORY

Working Memory

Unexpected events typically require us to revise or update our current working mental model of the environment. Donchin and colleagues (58) proposed that this updating of the working memory (temporary, limited capacity) system is indexed by the P3 (also known as the P300 or P3b) component. (See refs. 59 and 60 for alternative views.) The P3b is a positive, broadly distributed component with a centroparietal maximum and peak latency between 300 and 800 ms. It is elicited by infrequent target events in a sequence of higher probability nontarget events that are being attended, although irrelevant stimuli that draw attention may also trigger a P3. In general P3 amplitude grows with the relevance, salience, and utility of the target or "oddball" stimulus. The P3 can be elicited by many different simple and complex events, including the occasional absence of a predicted stimulus. (See ref. 61 for review.) The differences in the distribution and timing of P3s in various modalities are consistent with the proposal that there are multiple working memory stores.

P3 amplitude is inversely related to the overall probability of the target events, and varies with the fine structure of event sequences. The more difficult the categorization of the target events, the longer the P3 latency. P3 latency is not correlated with the variance in reaction time that is caused by response execution, thereby making it a rather pure measure of stimulus evaluation/categorization time. The combined sensitivity of the P3 to attention and stimulus evaluation makes it a good index of the availability and allocation of capacity-limited perceptual resources. Measurements of P3 latency and RT together can be used to pinpoint the processing locus of individual differences in performance, as was done, for example, to analyze cognitive slowing with normal aging (62). Similarly, P3 data have demonstrated that the prolongation of response time for the second of two decisions made in rapid succession ("psy-

chological refractory period") is owing to interference at a stage that follows perceptual categorization, presumably that of response selection (63).

Updating working memory has consequences for an individual's subsequent performance. For example, the relative amplitude of the P3 on a trial when a subject commits an error is predictive of the performance (accuracy and response speed) on the next trial; moreover, the larger the P3 to an item, the greater the likelihood that it will be remembered subsequently. (See ref. 64 for review.) Intracranial recordings in individuals with epilepsy have revealed P3-like potentials in the hippocampal region of the medial temporal lobe (65). The scalp-recorded P3, however, primarily reflects activity in a number of neocortical (frontal, central, parietal, temporal-parietal junction) and perhaps subcortical generators and is mediated by several neurotransmitter systems (66). Not surprisingly, therefore, many patient populations show abnormally small or delayed P3bs including schizophrenic patients, individuals at risk for alcoholism, patients with probable Alzheimer's dementia, and individuals with attention deficit and hyperactivity disorder, among others (61,66).

The storage of information in working memory may be modulated by attention and appears to be strongly suppressed during the "attentional blink" that follows detection of the first of two target stimuli presented in a rapid sequence. Luck and colleagues showed that the P3 was absent in response to targets that went undetected during the attentional blink, suggesting that no updating of working memory occurred. (See ref. 67 for review.) However, undetected target words did elicit late negative ERPs, indicating that they had been identified at the level of lexical/semantic processing. Thus, the ERP data provided strong evidence that the attentional blink acts at the postperceptual stage of working memory storage.

A frontally distributed late positivity (P3a) is elicited by rare and unexpected stimuli for which there is no memory template readily available. It appears to reflect an orienting response to stimulus novelty and is reduced in patients with prefrontal cortical injury (68). Maintenance of information in working memory is also reflected in sustained ERPs lasting on the order of seconds. These potentials vary in their scalp distribution as a function of the information being held in working memory, consistent with proposals of independent short-term buffers for verbal and nonverbal information, among others (69).

Long(er)-Term Memory

Encoding

Encoding processes (transforming sensory input into a lasting representation) are associated with an increased positivity between 200 and 800 msec that spans several components. Items that call for preferential processing because they

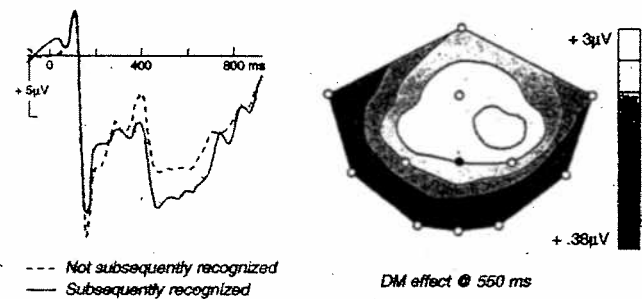


FIGURE 32.3. Averaged event-related potentials (ERPs) from midline parietal site (filled in circle in map on the right) sorted as a function of subsequent memory in a cued recall test. The responses to words subsequently recalled (solid line) are overlapped with those subsequently not recalled (dashed line). Participants were presented the first three letters of a word and asked to use this stem as a clue for verbally recalling the words they had just studied. The voltage map of this difference related to memory (Dm) effect at 550 ms was computed by subtracting the ERPs to words subsequently not recalled to ERPs from those subsequently recalled. **A:** Semantically anomalous word. **B:** Unexpected word. Adapted from Paller KA. Recall and stem-completion priming have different electrophysiological correlates and are modified differentially by directed forgetting. *J Exp Psychol Learn Mem Cogn* 1990;16:1021–1032.

stand out, for example, are better recalled and elicit larger P3 components (70). Likewise, the more deeply (semantically) an item is analyzed, the more likely it is to be remembered, and this is reflected in greater late positivity (71). Even among items that are all deeply processed, those that will in fact be remembered later elicit a larger positivity during encoding than those that will be forgotten (Fig. 32.3). These late components produced during encoding that are predictive of subsequent memory performance are collectively termed Dm effects (71).

Dm effects are larger in semantic than in nonsemantic tasks and are not seen for items that have no preexisting representation in long-term memory. Van Petten and colleagues (73) suggested that this positivity indexes the richness of associative elaboration engendered by the to-be-remembered event. Consistent with this proposal, the Dm effect varies with the encoding task and information retrieved from long-term memory and shows substantial variability in onset latency, duration, and scalp topography (74).

Retrieval

Retrieval processes are indexed by several ERP effects that vary with whether or not the rememberer is in a retrieval mode, whether memory is queried directly or indirectly, what aspect of the memory is being queried, and whether or not the retrieval attempt is successful (75,76). Retrieval itself is indexed by slow potentials sustained over several seconds with an amplitude determined by the difficulty of the retrieval and a scalp topography determined by the na-

ture of the information retrieved (77). These results fit with the notion that the brain areas involved in explicit memory are the same as those carrying out the initial encoding and perception and argue against the concept of a single, amodal memory store.

In a typical retrieval paradigm items are presented twice, and ERPs to the first and second (i.e., repetition) presentations are compared. When subjects are asked to recognize and detect the repeated items, the task is considered to probe memory directly or explicitly. By contrast, when the old or new distinction is irrelevant, as in tasks involving lexical decision, semantic judgment, or identification of visually degraded words, the stimuli may only tap memory indirectly or implicitly and may not produce actual recollection. In both implicit and explicit memory tasks, stimulus repetition produces large and reliable ERP effects. The first is a reduction in the amplitude of negativity between 250 and 500 msec (N400) that is associated with semantic processing (76). The N400 is reduced by repetition, whether or not the task explicitly calls for detection of repeated items, even in amnesic individuals with damage to the medial temporal lobes (78). Some authors have linked a frontal subcomponent of the N400 to repetition independent of recognition (79).

Another ERP consequence of word repetition is a change in the amplitude of a late positive component (LPC), which typically begins around 400 to 500 msec, and is somewhat larger over the left than right scalp. There is mounting evidence that this LPC reflects conscious recollection. Factors that influence perceptual priming do not modulate LPC amplitude (80), whereas factors that influence recognition memory do. There is an LPC repetition effect whether

memory is tested implicitly or explicitly. When participants are asked to indicate whether an item is old or new, correctly recognized old items elicit larger LPCs than do unrecognized old items or correctly recognized new items, although its distribution across the scalp varies somewhat with the materials (81). The LPC to correctly recognized old items is larger for confident than less confident decisions, and for items that participants actually "remember" (82).

When a subject attempts to remember some aspect of the context in which an item was studied or some attribute of the item that it shared with others in the study task, a large, late, frontally distributed (sometimes right lateralized) positivity is elicited (83). This large positivity over prefrontal sites occurs in addition to the standard LPC effect. The prefrontal locus of this ERP source retrieval effect fits with the known impairments that patients with frontal lobe damage have in retrieving source information about items that they recognize (84).

LANGUAGE

Semantic Analysis

The semantic analysis of verbal and nonverbal stimuli is indexed by the N400 component (85). The N400 is a broadly distributed component, with a negative-going peak over centroparietal sites often with a slightly right predominance; in young adults, it has an onset around 200 msec and a peak around 400 msec. The largest N400s are elicited by unexpected, semantically anomalous words in a sentence (Fig. 32.4). However, all *potentially* meaningful items (e.g., words and pseudowords, environmental sounds, pictures,

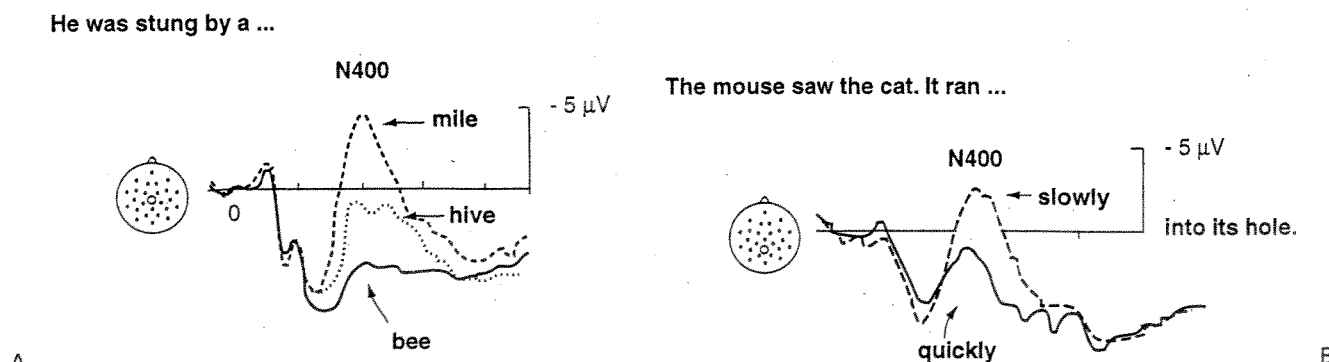


FIGURE 32.4. A: A prototypical N400 recorded at the vertex in response to a semantically anomalous word (dashed line) at the end of a sentence, compared with the ERP to the expected ending (solid line), and an anomalous ending that is semantically related to the expected ending (dotted line). Note reduced N400 for nonsensical ending ("hive") that is semantically related to expected ending. B: The N400 recorded at a midline parietal site elicited by a word that fits with the ongoing discourse context (solid line) versus that to a word that is less expected and does not fit as well with the ongoing discourse context (dashed line). Data taken from van Berkum JJA, Hagoort P, Brown CM. Semantic integration in sentences and discourse: evidence from the N400. *J Cog Neurosci* 1999;11:657-671.

faces) can elicit some N400 activity with an amplitude that is determined by a variety of factors. With little or no contextual constraint, N400 amplitudes are inversely related to the frequency of the eliciting word in the language (86).

The N400 is typically considered an ERP index of semantic processing or contextual integration because its amplitude is modulated by its relation and fit to the ongoing context, be it a single word, a sentence, or a multisentence discourse. (See refs. 87 and 88 for review.) N400 amplitudes are enlarged to a word in unrelated word pair or in an incongruous or weak context relative to the response to the same word in a related pair or strong congruous sentence. The N400 in these cases is almost identical in timing and distribution over the head, indicating that by 400 msec at the latest, lexical, sentential, and discourse processes all converge to influence language comprehension in a similar manner. Visual half-field studies of the N400 show that the left hemisphere, in particular, uses the organization of semantic memory tapped by context words to aid in its online predictions, whereas the right hemisphere waits and integrates (89).

As would be expected of an index of semantic processing and contextual integration, N400 amplitude is greatly attenuated and its latency delayed in aphasic patients with moderate to severe comprehension deficits (90). N400 latency is also prolonged with normal aging and various dementias. Although ERP evidence for a differential organization of semantic memory in schizophrenia is equivocal, a delay in N400 latency has been reported. (See ref. 87 for review.) Intracranial recordings from patients with epilepsy show potentials functionally similar to the scalp N400 in the anterior fusiform gyrus (91).

Syntactic Analysis

The processing of language at a syntactic level is indexed by a several ERP components, both negative and positive. Many, although not all, syntactic violations elicit a late positivity variously called the P600 or the syntactic positive shift (SPS) (92–94). The P600 is typically elicited when some aspect of sentence structure violates the rules of the language—for example, if the subject of the sentence does not agree with its verb in number or if a word in a phrase is out of order. The P600 also may be elicited when processing difficulties arise at a structural level (87). Some researchers have proposed that the P600 belongs to the family of P3 waves (95). In addition to the P600, many syntactic violations also elicit a left anterior negativity (LAN), which some researchers have interpreted as an index of working memory usage (96,97).

The fact that an N400 or P600 is elicited shortly after a semantically anomalous or grammatically incorrect word, respectively, regardless of its ordinal position in a sentence, is most consistent with those models of sentence processing that emphasize the immediate and online nature of compre-

hension (98). That is, the language processing system seems to use all information as it becomes available, often to predict what words or ideas are likely to come next (89,99). That processing at a semantic and syntactic level yields different patterns of electrophysiologic activity suggests that the processes differ, if not the representations. Further, the presence of different ERP patterns to various syntactic violations indicates that syntax is not a unitary phenomenon mediated by a single neural generator. Many aspects of sentence processing at semantic, syntactic, referential, thematic, prosodic, and discourse levels are indexed by transient ERP effects and/or slow potentials that encompass the entire sentence (100,101). In short, the reported patterns of ERP effects are inconsistent with a view of language comprehension that gives syntactic analysis precedence over semantic analysis or a system wherein syntactic processes are isolated from all other processes. Instead, ERP data provide considerable evidence for parallel processing, interaction, and top-down effects during language processing. The brains of readers and listeners work very much online using all information as it becomes available to anticipate upcoming items, concepts, and schemas to achieve the aim of an efficient and error-free understanding of the incoming language (even if at times these predictions may lead to misunderstanding).

Language Production

As in language comprehension, many of the controversies in language production revolve around the issue of the relative timing of the different levels of processing that are engaged. Although there is a general consensus that producing a coherent utterance involves information at the levels of meaning, syntax, and phonetics there is no agreement as to whether meaning comes first and then phonologic form (i.e., a serial model), these processes overlap somewhat in time (i.e., a cascade model), or they unfold in parallel (102). Two ERP measures—the LRP and N200—can be used to track the time course of information availability as people prepare to speak, even if they never actually utter a word. In studies using a two choice go/no-go paradigm, subjects were shown a picture of an item on each trial about which they were asked to make two decisions (Fig. 32.5). Across experiments, decisions were based on semantic, syntactic, and phonologic aspects of the pictured item and its name. The timing of the N200 and LRP on no-go trials indicated that semantic information becomes available before syntactic information (by about 80 msec), which is in turn available before phonologic information (by about 40 msec) (103,104). Electrophysiologic data from the scalp thus support a serial model of speech production, indicating that people first figure out what they want to say and then choose exactly how to say it.

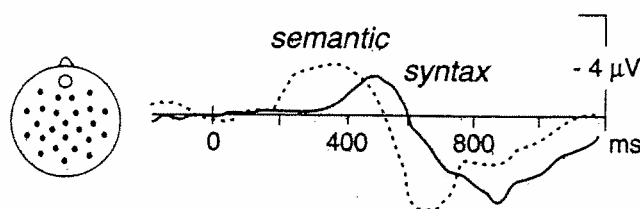


FIGURE 32.5. Overlapped are the N200 difference waves (no-go minus go event-related potentials) recorded at a midline prefrontal site (as marked on head icon) when the decision to respond or not (go/no-go) was contingent on a semantic (dashed line) versus a syntactic (solid line) attribute of the pictured object. Note that the N200 effect contingent on the semantic analysis peaks around 380 ms, whereas that contingent on syntax peaks around 500 ms. Data from Schmitt B, Münte TF, Kutas M. Electrophysiological estimates of the time course of semantic and phonological encoding during implicit picture naming. *Psychophysiology* 2000 Jul;37(4):473–484.

CONCLUSION

Specific components of ERPs and ERFs recorded from the surface of the head are sensitive to a wide range of sensory, perceptual, motor, mnemonic, and linguistic processes. It appears that many cognitive acts engender synchronous neural activity patterns that produce electrical and magnetic fields precisely time-locked to informational transactions in the brain. Recordings of ERPs/ERFs thus provide critical information about the timing and neural substrates of the processing stages that underlie cognitive activity. These physiologic data are being used increasingly to test alternative functional models and to constrain psychological theories (2,64,105).

Considerable progress has been made in demonstrating reliable associations between ERP/ERF components and a wide range of psychopathologic syndromes. In no case, however, is a single ERP/ERF component absent or abnormal in such a way as to be diagnostic. Rather, a given syndrome (e.g., schizophrenia) usually manifests abnormalities in one or more parameters of several different ERP components, and a given component (e.g., the P3) appears abnormal across a range of neurobehavioral syndromes. This is to be expected, except in the unlikely (and perhaps nonexistent) case in which the psychopathology would only affect a single, isolated cognitive subprocess that had a unique ERP/ERF marker. Thus, instead of seeking a single ERP marker, it seems more likely that various patient populations will be distinguished by different profiles of ERP effects across a number of different tasks (much like the approach taken in neuropsychological testing). Many of the same interpretational issues that are of concern with neuropsychological testing may become relevant for testing with an ERP battery, together with some that are specific to these physiologic measures. For example, the considerable synaptic plasticity of the neocortex suggests that even normal individuals' com-

ponent amplitudes and latencies are likely to show considerable variability, depending on their life experiences. Such variability within the normal population clearly exacerbates the difficulty of uniquely identifying ERP/ERF markers of specific clinical syndromes. Further progress in achieving diagnostic specificity and sensitivity may require comparing ERPs/ERFs across multiple tasks in each patient to reveal reliable abnormalities that are related to specific cognitive manipulations. Such ERP/ERF abnormalities will become increasingly informative about the specific processing mechanisms that are dysfunctional in patient groups as the cognitive specificity of the distinctive components is sharpened through studies in normals and as better methods are developed for measuring and isolating those components. These developments should make it possible to incorporate ERP/ERF data into multimeasure diagnostic batteries to aid in classifying and subtyping psychopathologic syndromes.

Recent technical advances have made it possible to obtain more accurate information about the neural bases of ERPs/ERFs and their relationships with cognitive and behavioral variables. The neural generators of surface recorded ERP/ERF activity can be localized with increased precision using algorithms that exploit more accurate bioelectric models of the head and constrain the generators to lie within the cortical mantle as reconstructed from MRI scans. (See ref. 105 for review.) Source localizations can be further improved by incorporating functional imaging data (e.g., from fMRI) into the inverse calculations, thereby providing a more veridical picture of the spatiotemporal patterning of cognitive-related brain activity (3,4,106). New approaches also have been developed for decomposing these complex patterns of brain activity arising from multiple, concurrently active generators into functionally meaningful subcomponents. Among these, the technique of Independent Component Analysis (107) has shown considerable promise for decomposing ERP data sets from multiple task conditions into temporally independent and spatially localizable components that may be related to cognitive operations on the one hand and to fMRI activation patterns on the other. Newer spatiotemporal filtering procedures (e.g., wavelet filtering) have improved our ability to extract the ERP/ERF signal from ongoing brain activity and other background noise. (See ref. 105 for review.) These methods ultimately may allow reliable detection of event-related signals on a single-trial basis without relying on the usual computer averaging procedure. Single-trial analyses are important not only for achieving a closer correspondence between brain activity and behavioral performance but also for ascertaining the degree of trial-to-trial variability that may characterize different clinical syndromes. All of these techniques will substantially increase the utility of ERP/ERF recordings for analyzing the neural bases of both normal and disordered cognition.

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