Chapter 9

# ELECTROPHYSIOLOGIC METHODS AND TRANSCRANIAL MAGNETIC STIMULATION IN BEHAVIORAL NEUROLOGY AND NEUROPSYCHOLOGY*

Leon Y. Deouell
Richard B. Ivry
Robert T. Knight

Electrophysiologic recording techniques are widely employed to study cognitive processing in normal and clinical populations.[1–3] Frequency analysis of the ongoing electroencephalogram (EEG) and extraction of event-related potentials (ERPs) embedded in the ongoing EEG provide information on tonic and phasic changes in brain activity during cognitive processing. Analysis of EEG frequencies is particularly valuable for the study of alterations in regional neural activity in a time domain extending from one to several seconds, approximating the time scale of blood-flow–based physiologic techniques described in Chap. 7, such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). Metabolic techniques such as PET and fMRI currently provide better spatial resolution of cognitive activity, but their temporal resolution is limited to the second (fMRI) or minute (PET) range.

ERP methods can extract stimulus, response, or cognition-related neural activity from the ongoing EEG in the millisecond-to-second range, providing a method for real-time assessment of changes in neural activity during cognitive processing. Recent efforts to record EEG and fMRI simultaneously represent a promising approach to linking neuronal and regional blood-flow changes during mental activity.[4–8] Converging data from ERP, PET, and fMRI will likely provide the strongest insights into the neural regions and mechanisms involved in mental activity. This review focuses predominantly on the use of event-related potentials in behavioral neurology (for discussions of frequency-based methods, see, for example, Refs. 9 to 15).

While metabolic and electrophysiologic measurements allow researchers to "eavesdrop" on neural activity, it has long been recognized that an alternative physiologic approach to understanding the function of specific brain regions would be to manipulate neural activity directly. By applying an electrical current, neural discharge can be induced, and the effects of this stimulation can be observed in the resulting behavior. The classic example of this approach is Penfield's work in the 1950s, in which the somatotopic organization of sensorimotor cortex was revealed through direct cortical stimulation applied during the course of neurosurgery.[16] The direct stimulation of human neural tissue is naturally limited to relatively rare situations, however—surgical situations in which the individuals suffer from neurologic conditions such as epilepsy, Parkinson's disease, or tumors.

Transcranial magnetic stimulation (TMS) allows either activation or disruption of activity in neural tissue through the intact skull, providing a more widely applicable method. Rapid improvements in the methodology and safety of these methods provide an exciting way for testing the integrity of neural pathways[17] and for testing hypotheses regarding the role of cortical areas in sensory, motor, and higher cognitive functions.[18] By

* **ACKNOWLEDGMENTS:** Special thanks to Clay C. Clayworth for skillful technical assistance. Supported by NINDS Grants NS21135, NS30256, and NS33504.

producing brief deactivation of cortical areas, TMS results in highly selective "virtual lesions" within healthy brains. It thus has the potential to pinpoint the critical areas responsible for specific functional deficits found in patients with naturally occurring (and permanent) lesions.

## EVENT-RELATED POTENTIALS

Neural activity in axonal pathways and inhibitory (IPSPs) and excitatory (EPSPs) postsynaptic potentials on the soma and dendrites of active neurons contribute to scalp-recorded field potentials, with the brunt of scalp EEG activity due to summed IPSPs and EPSPs. A major limitation of scalp electrical and (to a lesser degree) magnetic recording is uncertainty about the precise brain locations of the signal sources. However, intracranial source localization is improved by using mathematical dipole modeling constrained by information obtained from intracranial recordings in surgical patients, event-related fMRI studies, the study of brain-damaged patients, and animal models (see Refs. 19 to 21 for reviews).

ERPs are classified as either exogenous (sensory) or endogenous (cognitive). The latency and amplitude of exogenous responses are determined predominantly by stimulus parameters such as intensity and rate. Examples of exogenous responses include the brainstem auditory evoked response (BAEP), the pattern shift P100 visual evoked potential (VEP), and primary somatosensory evoked potentials (SEP). Since these responses are largely resistant to cognitive influences, they are widely employed in a variety of neurologic conditions to measure neural activity in sensory pathways.

In contrast, endogenous potentials are sensitive to the cognitive parameters of the task. The degree of attention [P300 (P for positive, 300 for latency in milliseconds)], effort [contingent negative variation (CNV)], movement preparation [movement-related potentials (MRPs)], and linguistic analysis [N400 (N for negative, 400 for latency in milliseconds)] are examples of cognitive factors determining the amplitude, latency, and scalp distribution of different types of endogenous brain potentials (see Refs. 22 to 24 for reviews). Since endogenous potentials reflect mental processes not immediately evoked by an external stimulus, the term *evoked potentials* has been replaced by the term *event-related potentials* in describing these signals. However, the borderline between a truly exogenous (presumably sensory, data-driven, hard-wired, and automatic) response and one involving higher cognitive functions is frequently blurred, as several "exogenous" components are modulated by top-down processes (see below). Moreover, some potentials may be regarded as being "exogenous" in some respects and "endogenous" in others [e.g., the mismatch negativity (MMN); visual N170]. Therefore the term *event-related potential* (ERP) may be used for all time-locked scalp potentials, as is done in this chapter.

### General Technical Considerations

The local intracranial geometry of intracranial neural sources places an important constraint on scalp or extracranial EEG or magnetoencephalography (MEG) recording. Neural sources must have an open-field configuration to generate dipole sources recordable at a distance.[19,25] Simply put, an open-field geometry occurs when neurons assume a local organized cellular structure wherein neurons are oriented in the same direction. Examples of open-field geometry would include the laminar structure of the cortex or the hippocampus where electromagnetic fields of synchronously active pyramidal neurons are aligned and sum to produce a dipole field recordable at the scalp. A closed-field geometry occurs when a neuronal structure lacks a clear local cellular anatomic substructure (e.g., the intralaminar thalamic nuclei). In this situation, neurons may fire synchronously but the local extracellular fields are not well aligned, and the dipoles will cancel out locally and not generate a summed dipole field recordable at a distance.

This constraint of open-versus closed-field geometry is shown schematically in Fig. 9-1. On the left are two neurons that are aligned in the same direction in an open-field configuration. If these neurons fire synchronously, their extracellular fields will sum and this activity can be propagated by volume conduction and recorded at a distant site such as the scalp. On the right are the same two neurons firing synchronously but aligned 180 degrees out of phase in a closed-field configuration. In this situation their extracellular fields

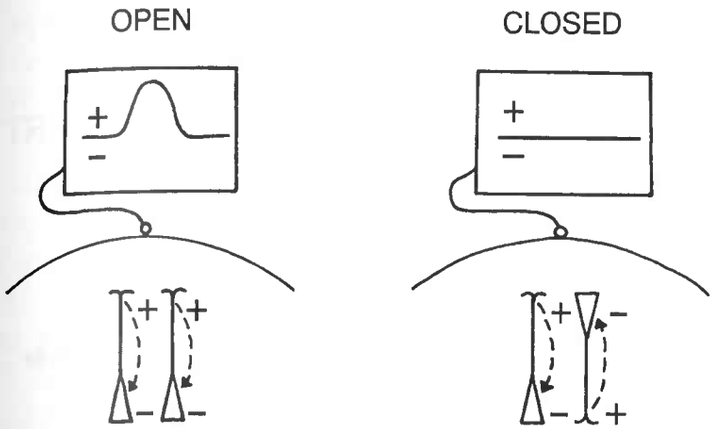



**Figure 9-1**

*Schematic of an idealized open- and closed-field neuronal configuration. In the open-field situation, extracellular fields sum and can be recorded at a distance. In the closed-field condition, the extracellular fields of the two synchronously active neurons cancel and no evoked field is recorded at a distance.*

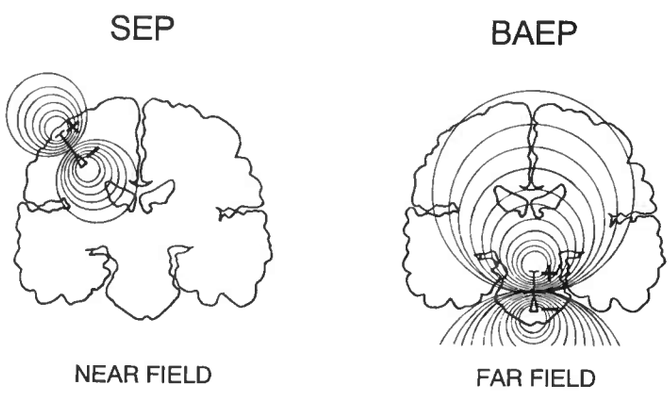



**Figure 9-2**

*On the left is the near field of the primary SEP. The evoked field changes rapidly over small distances on the scalp. On the right is an example of the far-field response of the BAEP. Note that the field is broadly distributed over the scalp, since the neural source is deep in the brainstem. See text for details. (Modified from Knight,[53] with permission.)*

would cancel and no electrical field would be recorded at a distance. A single-unit recording electrode would record equivalent activity in both the open- and closed-field condition, and metabolic techniques would also record comparable activity in each situation.

The distance of an active neuronal source from the recording site has a major influence on the strength of the signal recorded at the scalp. This is due to the fact that electric and magnetic fields drop in amplitude as an inverse power function of the distance of the active neuronal elements from a recording site. Intracranial neuronal generators can be classified as near- or far-field sources. An example of a near-field source would be the primary SEP generated in the depths and crown of the postcentral gyrus. Since this neuronal source is on the surface of the hemisphere, the scalp field will be strong and focally distributed in parietal scalp electrodes situated over the postcentral gyrus (Fig. 9-2). A classic far-field source would be the BAEP. The BAEP is generated by sequential activity of auditory structures located in the brainstem extending from the eighth nerve to the inferior colliculus. The dipole field of these generators is broadly distributed over the scalp and small in amplitude due to its distance from the scalp (Fig. 9-2). Because of this biophysical constraint, the brunt of electrical activity recorded at scalp sites arises in near-field generators in neocortical regions. This selectivity for near-field sources may be sharpened using scalp current-density (SCD) derivations of scalp potentials.[26] The SCD is calculated by taking the second spatial derivative (the Laplacian) of the potential distribution over the scalp. Therefore it reflects the rate of change of potential between nearby electrodes. Since far-field sources will not result in large differences between adjacent electrodes (Fig. 9-2), their contribution will be effectively filtered out, providing a finer resolution of more superficial (cortical) sources. Figure 9-3 provides a demonstration of potential maps and SCD maps from the same data set.[103] Whereas the potential maps reveal a broad frontocentral negativity and posterior positivity which is quite similar across conditions, the SCD maps reveal more localized foci of activity, highlighting differences between the conditions (see legend for Fig. 9-3).

Event-related potentials range in amplitude from 0.5 $\mu$V for the exogenous BAEP to 10 to 20 $\mu$V for longer-latency endogenous potentials such as the P300, N400, and CNV. These signals are buried in the ongoing EEG, which typically varies from 10 to 200 $\mu$V, depending in large part on the arousal state of the subject. In order to extract these signals from the ongoing EEG, the event-related response to a discrete sensory stimulus or cognitive manipulation must be averaged over multiple trials. Since the background EEG can be approximated as random noise, the average of repetitive EEG epochs will approximate zero.

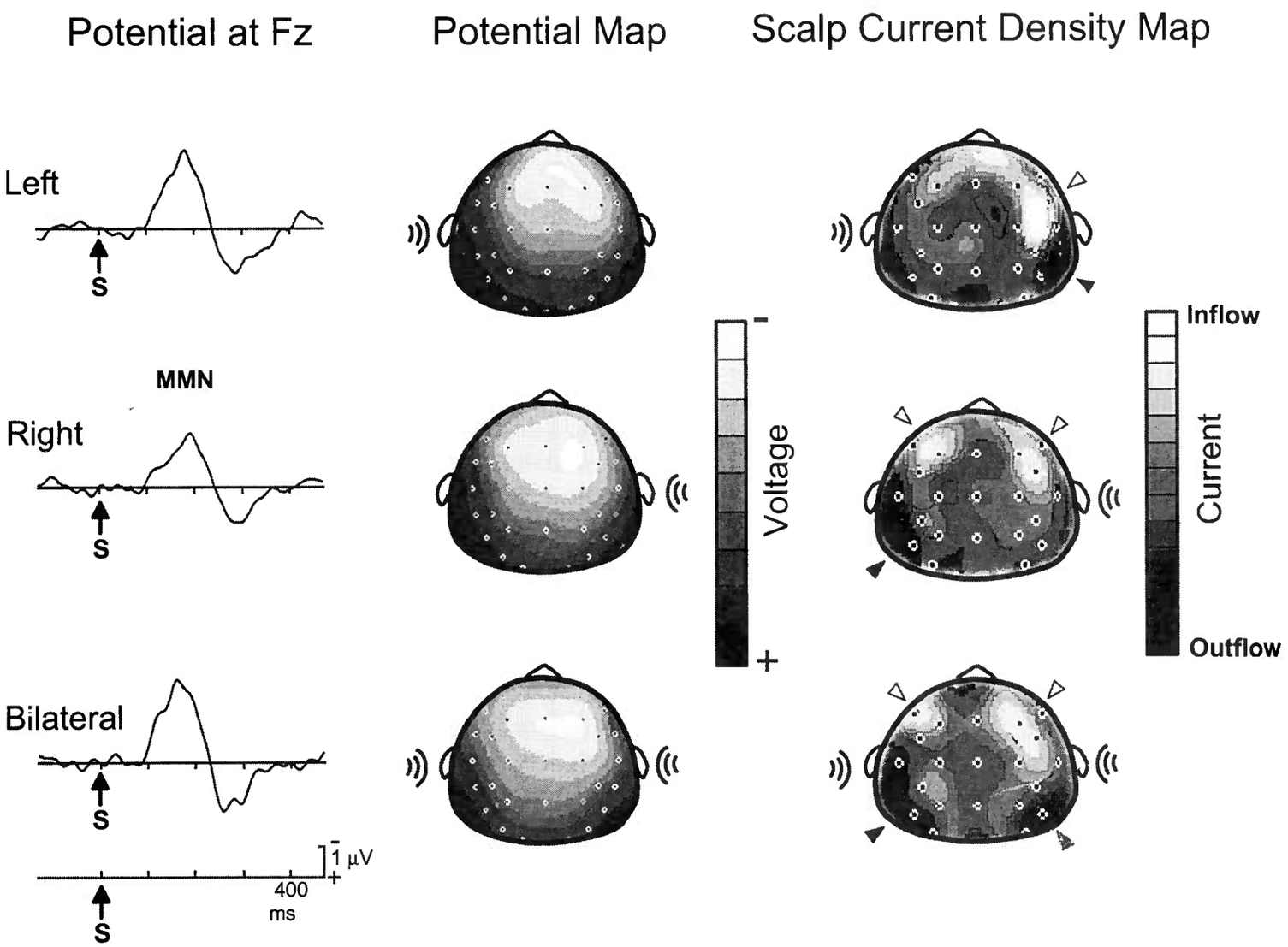



**Figure 9-3**

*Waveforms, potential maps, and scalp current density (SCD) maps for the same data. Fifteen subjects heard sequences of two different tones presented simultaneously, one to each ear. The waveforms show the difference, at the Fz site, between the event-related potential (ERP) elicited by a standard pair and the ERP elicited by a change in the pitch of the left, right, or both tones. The deviants elicited the typical mismatch negativity. The potential maps around the peak of the MMN for each condition show a broad frontocentral negativity, skewed rightward, regardless of the side of deviation, and a bilateral temporal positivity. The SCD maps, which are the laplacian derivations of the same data, show more circumscribed foci of activity with different patterns dependent on side of deviation. The temporal foci (black arrowheads) were significantly stronger contralateral to the side of deviation (symmetrical for the bilateral condition). The frontal scalp foci (open arrowheads) were significantly right lateralized in the left-deviant condition but were symmetrical when the deviant was on the right or bilateral (see Deouell et al.[103] for details).*

Conversely, the event-related response, time-locked to a specific stimulus or response, is assumed to repeat itself across trials and therefore emerges by averaging from the background EEG. The signal-to-noise ratio, which can be viewed as a measure of the ability to confidently identify the evoked signal in the background EEG "noise," is proportional to the square root of the number of epochs averaged. Consequently, smaller signals require many more trials before a reliable potential is seen. The effects of signal averaging for the small, far-field, exogenous BAEP is shown in Fig. 9-4. Note that no signal is apparent in the evoked potential

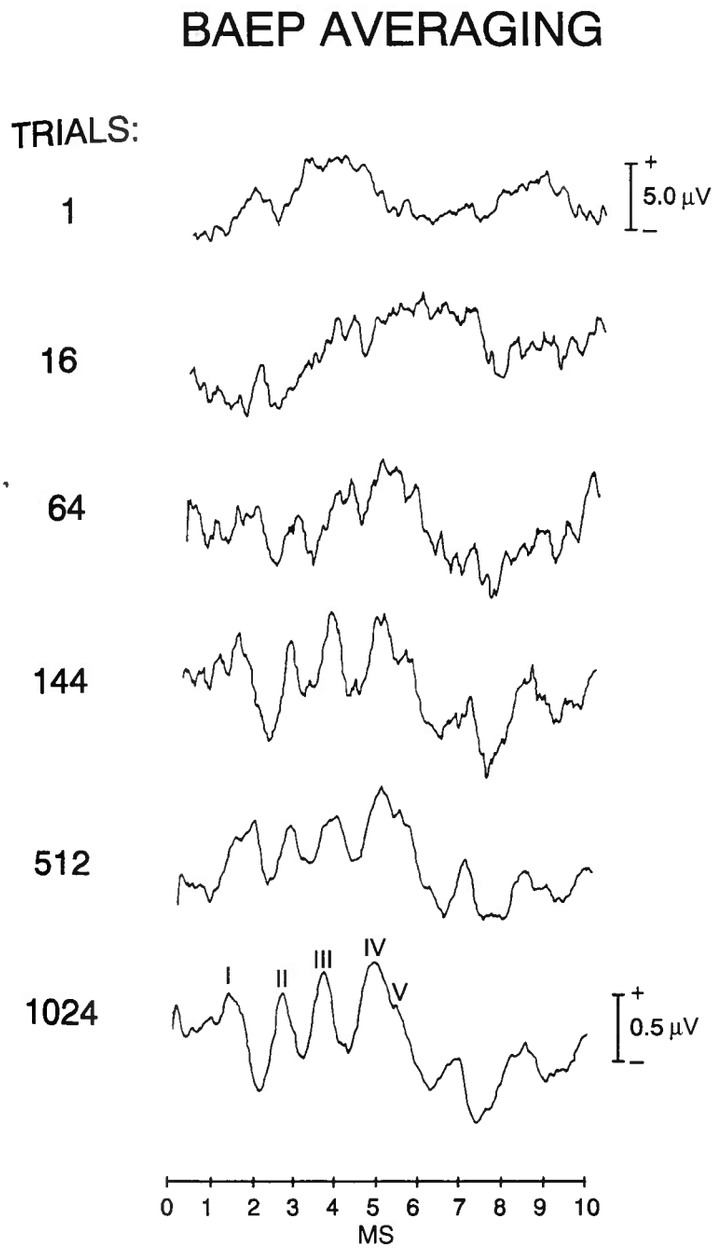



**Figure 9-4**

*The signal averaging of the BAEP. Note that a clear signal is not observable for at least 144 trials, since the BAEP is small (~0.5 μV) and buried in the background EEG activity.*

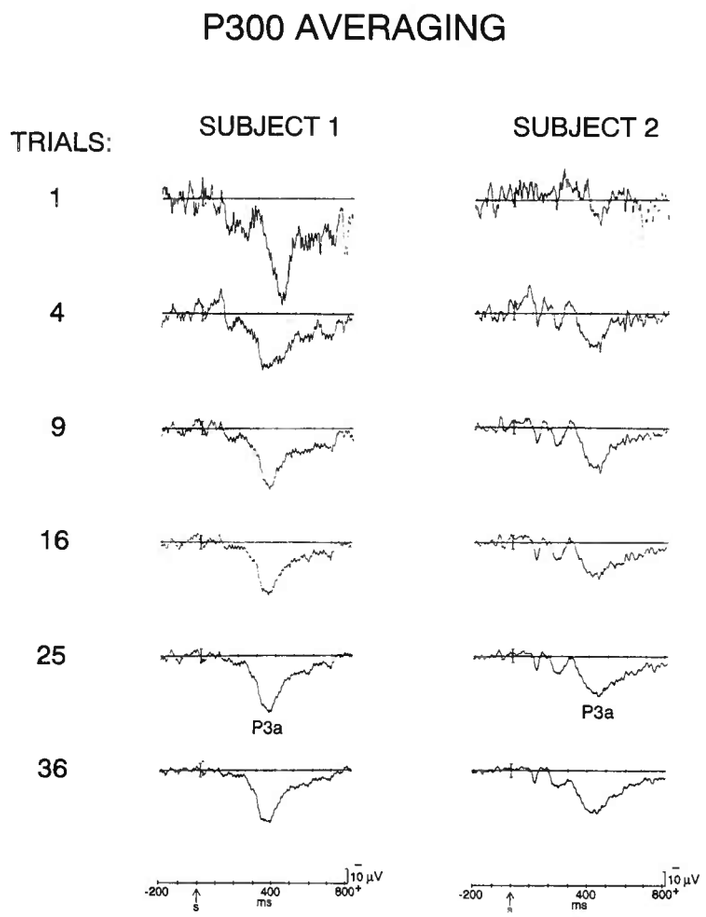



**Figure 9-5**

*The signal averaging of novelty P3a responses in two subjects. Since the P3a amplitude is large (~10 μV), the signal is well seen in only a few trials.*

average of the first 16 trials. A clear but noisy signal is seen after 144 trials. By 1024 trials, a clean signal is obtained, revealing the principal five components of the BAEP as well as two additional potentials that reflect thalamocortical activity projecting from the inferior colliculus to primary auditory cortex. A different pattern is seen in Fig. 9-5, which shows the averaging of a P300 response to unexpected novel sounds over 1 to 36 trials in two subjects. Since the P300 to these unexpected sounds is in the range of 10 to 30 μV for a single stimulus, it can be readily distinguished from the background EEG noise after just a few trials. Indeed, it can be seen after a single trial in subject 1 and after four trials in subject 2. Note that the superimposed EEG noise continues to flatten out with repetitive trials, especially apparent in the prestimulus epoch. Several techniques have been developed to extract single trials from the ongoing EEG during cognitive tasks that generate large responses (see Refs. 19 and 27 for reviews of signal processing techniques).

## Special Considerations in Studying Brain-Damaged Patients with ERPs

Chapter 8 reviews some of the advantages and special challenges of functional neuroimaging with brain-damaged patients. Many of these special considerations

arise with the use of ERPs with neurological populations, along with others unique to electrophysiologic methods.

The recording of ERPs requires considerable cooperation from the subject, both in minimizing artifacts and, in some cases, in complying with the task requirements. These limitations may be especially pronounced for brain-damaged patients, particularly when studied in relative proximity to the onset of their illness. The difficulties result from several factors. First, it is often difficult to make sure that the patient fully understands the procedure, aim, and significance of the test, especially when he or she manifests language disturbances (aphasia), disorientation, or confusion. Under these circumstances, the environment and equipment used in an ERP study may also be particularly intimidating. Second, with or without psychoactive medications, patients frequently undergo significant fluctuations in their arousal. This may cause both problems in performance and interference from slow waves (in the alpha band or slower) in the EEG. Third, patients with motor weakness may have difficulty sitting quietly in their chairs for the entire test duration, causing excessive artifacts of muscular activity. Fourth, patients may suffer from general attention deficits, making it difficult for them to stay alert, focused, and compliant throughout a prolonged testing session. The last problem is especially evident in patients with right hemisphere damage (RHD).

The above difficulties require the adjustment of experimental paradigms to shorten the testing sessions as much as possible and to minimize the patient's discomfort and apprehension. Alternatively, patients can be tested in a more chronic phase, when many of the above concerns are alleviated. However, if the goal is to correlate ERPs with behavioral deficits that may subside with time (e.g., unilateral neglect or aphasia), one must attempt to deal with the problems inherent in studying acute patients. Unfortunately, even if these precautions are taken, patients are occasionally excluded a priori from ERP studies because of failure to cooperate fully, and considerable amounts of data may often have to be discarded because of excessive noise (cf. Ref. 28). Of course, this procedure increases the risk of a selection bias toward less severely affected patients.

An additional problem (not unique to ERPs) is that the comparison of patients with normal controls is confounded by many factors other than the phenomenon under investigation. Such factors are, for example, the hospitalization, the use of medications, concomitant affective components such as depression, and the level of alertness. In fact, even the comparison between patients is complicated by inescapable variability in lesion sites and volumes, general medical condition, and uncontrolléd premorbid differences. A possible partial remedy is to prefer designs in which each patient serves as his or her own control ("within subject" designs; see, for example, the studies of neglect patients below).

A major methodologic concern involves the interpretation of scalp-recorded ERPs in brain-damaged patients. The amplitude and spatial distribution of the ERP signals may be altered by the lesion in at least three ways: (1) there may be direct damage to the electrical source generating the ERP, (2) the damaged area may modulate the activity of an electrical source distant from the lesion, and (3) altered electrical conduction in the damaged tissue may diminish or augment the amplitude of scalp-recorded potentials over the damaged hemisphere even if the underlying generators are functioning normally[29] (Fig. 9-6). There is no simple solution to these problems, and the best approach (as is the case in almost any method in neuroscience) may be awareness of these potential caveats and reliance on converging information from several methodologies.

Despite these difficulties, ERPs have been applied to the study of almost every functional problem covered in this volume, providing invaluable data in many cases. This endeavor has benefited from the convergence of better understanding of the cognitive correlates and anatomic substrate of different ERP components (e.g., Refs. 20, 22, and 30), improved localization of lesions with the advent of MRI and computerized reconstructions (e.g., Refs. 31 to 33), and increasingly refined neuropsychological methods. This combination of ERPs, lesion analysis, and cognitive neuropsychology is informative in at least two complementary ways. First, by examining the effect of discrete lesions on specific components of ERPs, it is possible to discern the neural elements of large-scale networks controlling, for example, attention and memory in the healthy brain.[34] Second, by using electrophysiologic components whose correlation with specific cognitive operations is reasonably clear, it is possible to shed light on the cognitive, anatomic, and physiologic mechanisms

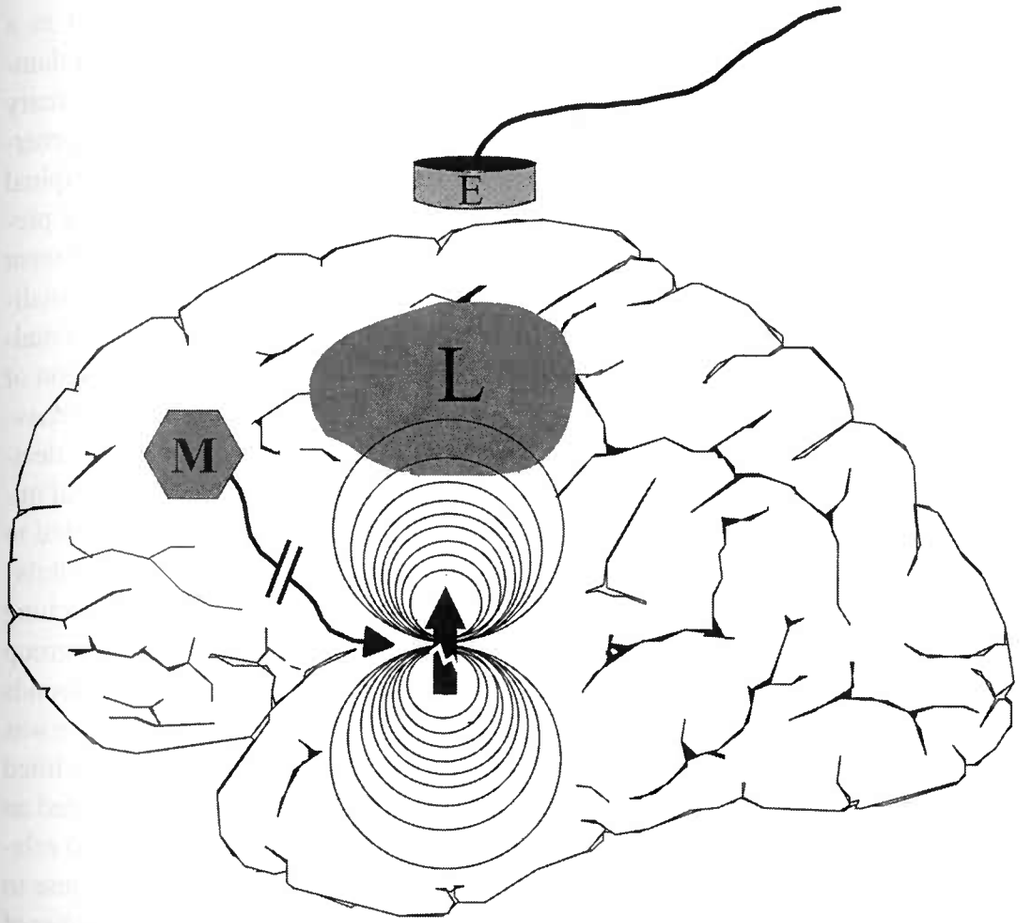



**Figure 9-6**
*Schematic model depicting three possible ways in which a lesion can change the pattern of a scalp recorded potential: (1) The lesion destroys the neural generator (broken arrow); (2) the conductivity of the damaged parenchyma (L) is altered, distorting the amplitude recorded at the scalp electrode (E); (3) The lesion is remote from the neural generator of the recorded potential, but it disrupts modulatory input (M) to the generator by ablating the source of the modulatory input or by disconnection.*

of specific functional deficits, information that cannot be obtained by traditional behavioral methods.[35,36]

In the following, we attempt to demonstrate some of these insights through examination of three cardinal neurobehavioral domains—prefrontal damage, unilateral neglect following right hemisphere damage, and aphasia following left hemisphere damage.

## Prefrontal Damage and Executive Control

As discussed in Chaps. 32 and 33, prefrontal cortex is crucial for executive control and efficient goal-directed activity. Through its attentional, inhibitory and/or working memory functions, prefrontal cortex enables us to suppress irrelevant information and facilitate the processing of relevant information. These functions may be bound under the headings of sustained and selective attention. For attention to be flexible, we must also be able to respond to potentially important events (e.g., a threat) outside the focus of attention and to detect and further process targets within the focus of attention (phasic attention). Lateral prefrontal cortex is crucial for the control of sustained and phasic attention to environmental events, as well as to novelty and target detection.[37,38] Attention and orienting ability have been studied using ERP techniques in neurologic patients with damage centered in Brodmann's areas 9 and 46 and in patients with posterior cortical and mesial temporal damage. Both the electrophysiologic and behavioral data from these patients have indicated that problems with inhibitory control of sensory inputs, reduced facilitation of processing of relevant information (sustained attention), and abnormalities in the detection of novel events are central concomitants of prefrontal disease.[39] At the same time, these data reveal the dynamic interaction between bottom-up and top-down processes that is necessary for normal function.

### Inhibitory Modulation and Sensory Gating

The attention deficits of patients with prefrontal lesions and the behavioral phenomena of perseveration in advanced prefrontal disease have been linked to problems with inhibitory control of posterior sensory and perceptual mechanisms.[40,146] Inability to inhibit internal representations of previous responses that are now incorrect, coupled with random inappropriate shifts of

attention, contributes to the poor performance of patients with prefrontal damage on the Wisconsin Card Sorting Task and on the Stroop task.[41,77] Problems with tasks involving "working memory" (operationally defined as the holding of information needed for the execution of action over short delays) may be due to intrusion of irrelevant information coupled with failures to sustain neural activity in distributed task-dependent neural circuits.[43] Physiologic data indicates that this lack of inhibitory control may extend to early sensory processing in primary cortical regions.

Neural inhibition by prefrontal regions has been reported in a variety of mammalian preparations. A net inhibitory output to both subcortical[44] and cortical regions has been documented.[45] Cryogenic blockade of a prefrontal-thalamic gating system in cats results in enhancement of amplitudes of primary sensory cortex evoked responses.[46,47] This system is modulated by an excitatory lateral prefrontal projection to the nucleus reticularis thalami, although the precise course of anatomic projections between these structures is not well understood. The nucleus reticularis thalami, in turn, sends inhibitory GABAergic projections to sensory relay nuclei, providing a neural substrate for selective sensory suppression.[48]

This prefrontal-thalamic inhibitory system provides a potential mechanism for modality-specific suppression of irrelevant inputs at an early stage of sensory processing. Support for a similar mechanism in humans has been obtained from the observation of patients with prefrontal damage due to stroke.[49,50] Task-irrelevant auditory and somatosensory stimuli were delivered to patients with damage to lateral prefrontal cortex (PFC) and to others with comparably sized lesions in the temporoparietal junction or the lateral parietal cortex. Evoked responses from primary auditory and somatosensory cortices were recorded in these patients and in age-matched controls (Fig. 9-7). The stimuli consisted of either monaural clicks or brief electric shocks to the median nerve, eliciting a small opponens pollicis twitch.

Lesions of the posterior association cortex invading either the primary auditory or somatosensory cortex reduced early latency (20 to 40 ms) evoked responses generated in these regions. Lesions in posterior association cortex, sparing primary sensory regions, had no effects on the amplitudes or latencies of the primary cortical evoked responses; such patients served as a brain-lesioned control group. Lateral prefrontal damage resulted in enhanced amplitude of both the primary auditory and somatosensory evoked responses generated from 20 to 40 ms poststimulation.[43,49–51] Spinal cord and brainstem potentials were unaffected by prefrontal damage, indicating that amplitude enhancement of primary cortical responses was due to abnormalities in either prefrontal-thalamic or direct prefrontal-sensory cortical mechanisms. Chronic disinhibition of sensory inputs may contribute to many of the behavioral sequelae of prefrontal damage. For instance, decision confidence is decremented by a noisy internal milieu, and the orienting response would be expected to habituate.[52,53] A direct correlation between disinhibition and decreased performance in a delayed matching to sample task has been now demonstrated in a group of prefrontal patients, required to compare two sounds separated by a 5-s delay.[43,54] Patients' performance was significantly degraded when the delay period was filled with tone pips, and these tone pips, in turn, elicited an augmented primary auditory potentials (Na, Pa) relative to normals. The enhancement of Pa in response to the distracting tones also correlated with the number of delay errors. Similarly, in patients with right prefrontal damage, sounds presented to an unattended ear in a dichotic paradigm reduce the attentional enhancement (see next section) of subsequent to-be-attended sounds. The unattended sounds have no such effect in healthy controls.[55]

**Attentional Facilitation** In addition to suppressing irrelevant information, normal function involves facilitation of processing of relevant information. A "biased competition" model suggests that excitatory signals to neurons result in inhibition of nearby task-irrelevant neurons, resulting in a sharpening of the attentional focus.[56] Selective attention to a sensory channel such as an ear, a portion of the visual field, or a finger increases the amplitude of evoked potentials generated to all stimuli delivered to that region[57–60] and induces a slow negative potential spanning several hundreds of milliseconds following the presentation of the stimulus [known, in different contexts, as negative difference (Nd), selection negativity (SN), or processing negativity (PN)].[22] There is evidence that attention reliably modulates neural activity at early sensory

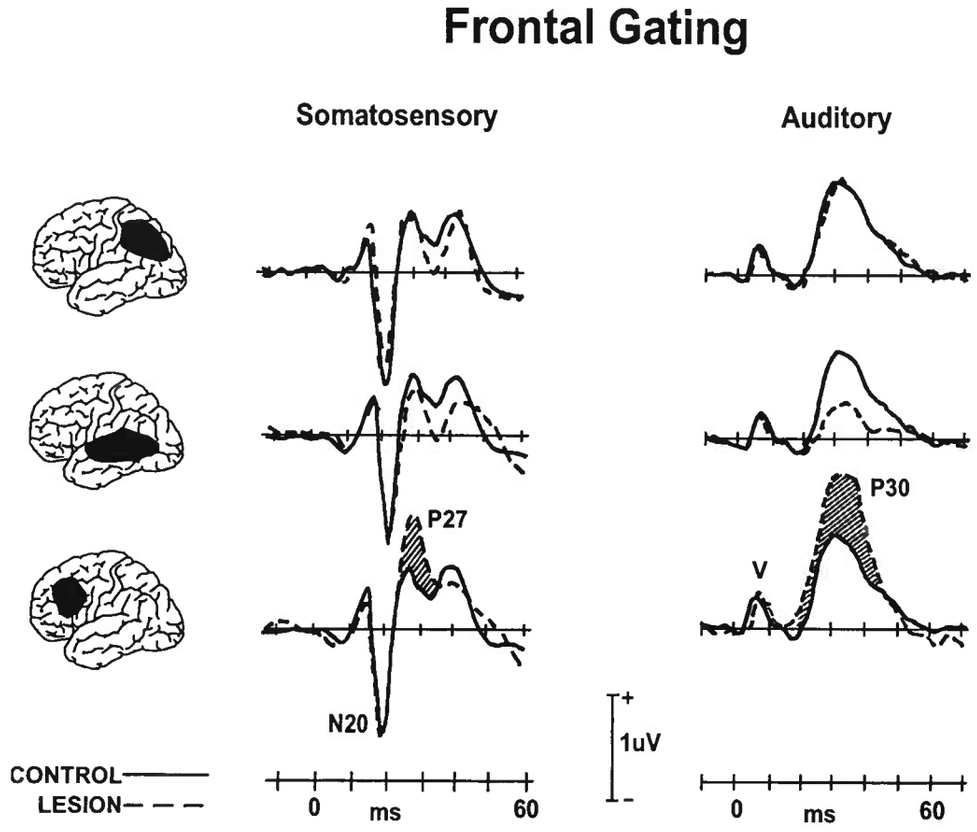



**Figure 9-7**

*Primary cortical auditory and somatosensory event-related potentials are shown for controls (solid line) and patients (dashed line) with focal damage in the lateral parietal cortex (top, n = 8), temporoparietal junction (middle, n = 13), or dorsolateral prefrontal cortex (bottom, n = 13). Reconstructions of the center of damage in each patient group are shown on the left. Somatosensory event-related responses were recorded from area 3b (N20) and areas 1 and 2 on the crown of the postcentral gyrus (P26). Stimuli were square-wave pulses of 0.15 ms duration delivered to the median nerve at the wrist. Stimulus intensity was set at 10 percent above opponens twitch threshold, and stimuli were delivered at a rate of 3/s. Damage in posterior cortical regions sparing primary somatosensory cortex had no effect on the N20 or earlier spinal cord potentials. Prefrontal damage resulted in a selective increase in the amplitude of the P26 response (hatched area). Auditory stimuli were clicks delivered at a rate of 13/s at intensity levels of 50 dB HL. Unilateral damage in the temporoparietal junction extending into primary auditory cortex reduces P30 responses. Lateral parietal damage sparing primary auditory cortex has no effect on P30 responses. Dorsolateral prefrontal damage results in normal inferior collicular potentials (wave V) but an enhanced P30 primary cortical response (hatched area). The shaded area in each modality indicates the area of event-related potential amplitude enhancement.*

cortices, including secondary and perhaps primary sensory cortex.[61–65] Visual attention involves modulation in the excitability of extrastriate neurons through descending projections from hierarchically ordered brain structures.[66] Single-cell recordings in monkeys,[67,68] lesion studies in humans[34,39,42] and monkeys,[69] and blood-flow data[70–76] have linked PFC to control of extrastriate cortex during visual attention.

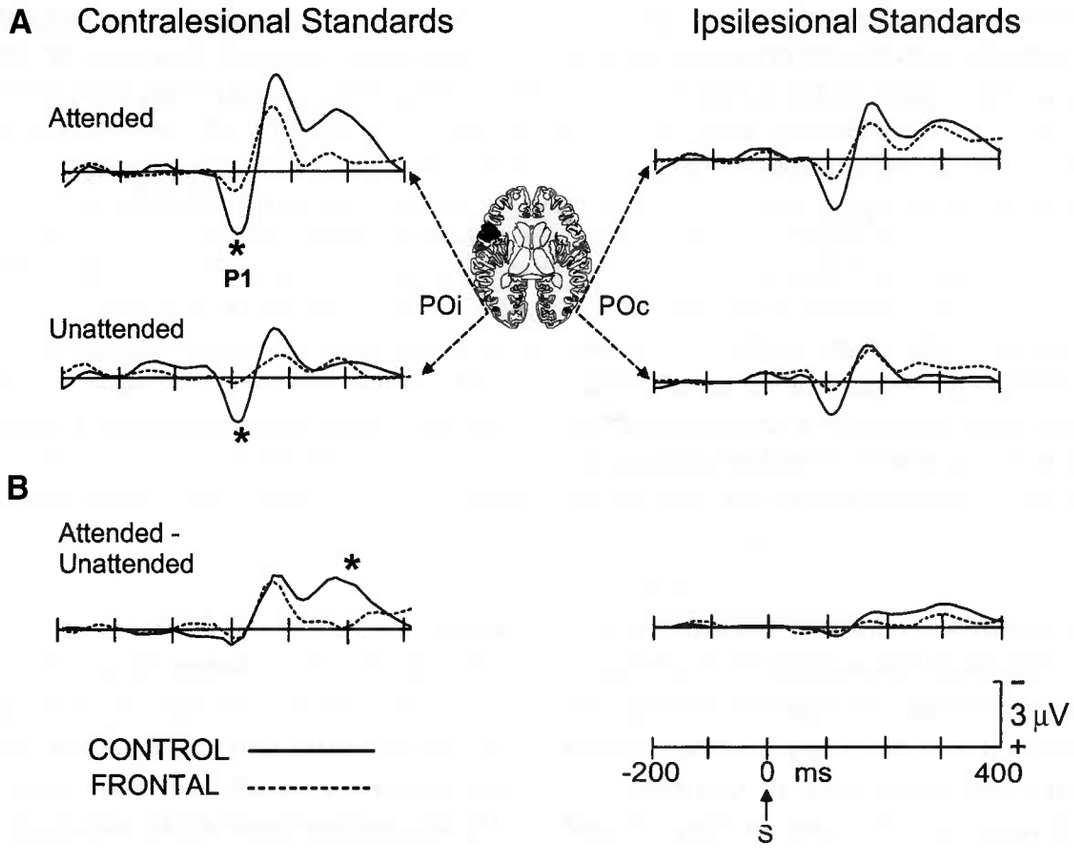
ERP studies in patients with lateral PFC damage suggests that human lateral PFC regulates extrastriate neural activity through three distinct mechanisms: (1) by enhancement of extrastriate cortex response to

attended information; (2) through a tonic excitatory influence on ipsilateral posterior areas for all sensory information, including attended and nonattended sensory inputs; and (3) by a phasic excitatory influence of ipsilateral posterior areas to correctly perceived task relevant stimuli. In a series of ERP studies, patients with unilateral PFC lesions (centered in Brodmann's areas 9 and 46) were required to detect inverted triangles (targets) among a series of upright triangles (distractors). In one experiment, patients and age-matched controls were asked to press a button whenever a target appeared at fixation.[34] In another, the target appeared in either visual field[42] while both visual fields were similarly attended. In a third experiment, subjects were instructed to attend to only one visual field.[79]

An interesting pattern of results emerged from these experiments (Figs. 9-8 and 9-9). First, the experiments revealed that lateral PFC provides a tonic excitatory influence to ipsilateral extrastriate cortex. When the stimuli appear centrally the PFC patients showed a significant reduction of the extrastriate N1 component (with a latency of 170 ms).[34,78] When the

**Figure 9-8**

*Visual event–related potentials in patients with lateral frontal lobe damage and healthy controls. Patients with dorsolateral prefrontal cortex lesions and controls had to detect upright triangles in a series of inverted triangles (standards, 70 percent), upright triangles (targets, 20 percent), and novel stimuli (10 percent) presented one at time to either side of fixation. Patients (n = 8) and controls (n = 11) were instructed to attend and respond to targets on the left or on the right of fixation.* **A:** *The ERPs elicited by the contralesional standard stimuli elicited significantly reduced P1 responses in the patients whether the standards were in the attended or the unattended side.* **B:** *The attention effect (extracted by subtracting the response to unattended standards from the response to the attended ones) reveals a significantly smaller effect for contralesional standards in patients relative to controls, starting around 200 ms postonset. POi = The ipsilesional of P7 and P8. POc = The contralesional of the two. For controls POi/POc = P7/P8, respectively. (Modified from Yago and Knight.*[79])



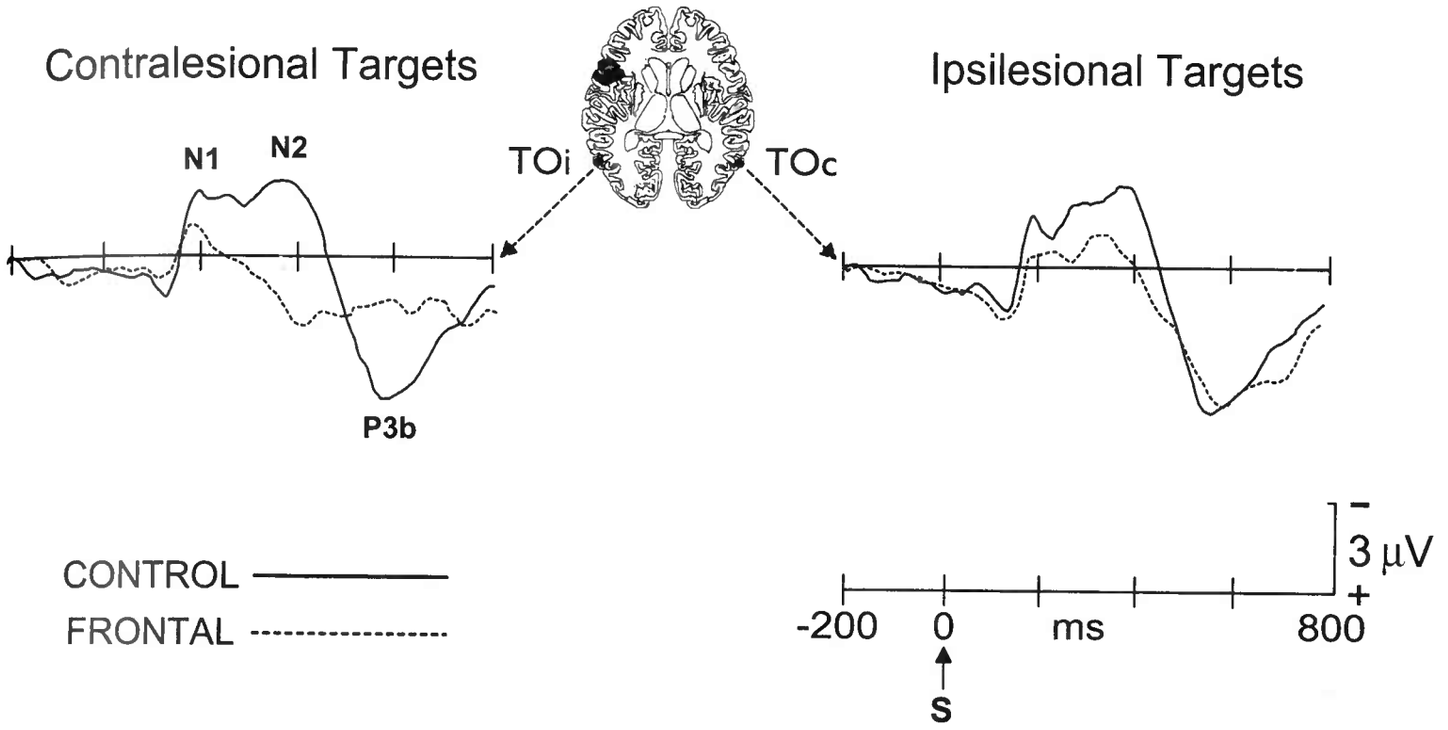



**Figure 9-9**

*Same paradigm as Fig. 9–8, only that the patients (n = 10) and controls (n = 10) were attending to both right and left sides in this case. The N1, N2, and P3b peaks, seen in the controls' waveform, were significantly reduced in the patients in response to contralesional targets but not for ipsilesional targets (see Ref. 42 for more details). TOi = T5 or T6, the one ipsilateral to the lesion in patients; T5 in controls. TOc = T5 or T6, the one contralateral to the lesion in patients, T6 in controls.*

stimuli were lateralized, the P1 component of the visual ERP was markedly reduced in amplitude for all stimuli presented to the contralesional field.[42,79] Importantly, this tonic influence was attention-independent, since a reduced P1 potential in extrastriate cortex was found ipsilateral to PFC damage for all visual stimuli (attended and nonattended targets and nontargets) presented to the contralesional field (Fig. 9-8a.).[79] This tonic component may be viewed as a modulatory influence on extrastriate activity. In the auditory modality, the patients elicited a reduced N1 component peaking 100 ms after the onset of the stimulus.[43] The auditory N1 has several sources in the superior temporal plane[20] providing additional evidence or prefrontal modulation of early sensory processing. Second, when the attention was directed to only one visual field, attention effects on extrastriate cortex were normal in the first 200 ms for the PFC patients and severely disrupted after 200 ms (Fig 9-8b).[79] This finding suggests that other cortical areas, possibly the posterior parietal cortex, are responsible for attention-dependent regulation of extrastriate cortex in the first 200 ms. The PFC facilitation appears to begin after 200 ms. It is conceivable that inferior parietal cortex is responsible for the early reflexive component of attention, whereas PFC is responsible for more controlled and sustained aspects of visual attention beginning after the parietal signal to extrastriate cortices.

Third, in addition to the observation of channel-specific enhancement, another distinct electrophysiologic event (including the N2-P3b complex) was observed when a relevant target event was detected in an attended channel (Fig. 9-9).[79] The latency of this top-down signal was about 200 ms after a correct detection, and it extended throughout the ensuing 500 ms, superimposed on the channel-specific ERP attention enhancement.[80] Damage to lateral PFC results in marked decrements in the top-down signal, accompanied by behavioral evidence of impaired detection ability.[42] The N2, a component which is generated in

the inferior temporal lobe in response to targets and which is therefore assumed to reflect postselection processing, was abolished over the lesioned hemisphere for targets in both visual fields. Behaviorally, the patients reacted more slowly to targets in the contralesional visual field and missed more targets than the controls did. The frontal patients also showed reduced P3b over the temporooccipital electrodes, but not at parietal sites.[42]

The P3b has been proposed to underlie a range of cognitive processes. One proposal is that the P3b is generated during closure of a perceptual task.[81] According to this theory, the P3b represents inhibition of a discrete epoch of stimulus processing. More precisely, this theory posits that the P3b is generated by inhibition of regional negativity in activated neocortex or mesial temporal sites associated with the termination of voluntary processing of an expected stimulus.[82,83] Alternatively, the P3b may index the updating of information in working memory.[84] Other proposals, such as those linking P3b and template matching, may be subsumed under the concept of context updating in working memory.[85] Most likely, the P3b includes contributions from multiple intracranial sources and processes (for reviews see Refs. 30, 86, and 87), which may include also modality-specific components.[88] This is highlighted by the fact that, in the PFC patients, the parietal P3b was intact, but at the same latency positivity was reduced over ipsilateral occipitotemporal sites.

Auditory selective attention capacity has also been examined in patients with lateral PFC lesions. In dichotic selective attention tasks, normal subjects generate an enhanced ("selection") negativity to all stimuli in an attended channel with onset from 25 to 50 ms after delivery of an attended auditory stimulus. Prefrontal patients generated reduced attention effects depending on the side of the lesion. Patients with left hemisphere lesions showed a reduced attention effect regardless of which ear was attended. In contrast, patients with right prefrontal damage showed reduced enhancement effect mainly when the contralateral ear was to be attended, consistent with the symptoms of unilateral neglect (see below).[89] Posterior association cortex lesions in the temporoparietal junction have comparable attention deficits for left- and right-sided lesions.[90] This suggests that some aspects of hemineglect subsequent to temporoparietal damage may be due to remote effects of disconnection from asymmetrically organized prefrontal regions.

The CNV is a negative-polarity brain potential maximal over frontal-central scalp sites generated during a delay period initiated by a warning stimulus. The CNV is terminated by a behavioral response that is contingent on information delivered in the warning stimulus.[91] The behavioral structure of tasks that generate a CNV shares attributes with paradigms associated with working memory in monkeys and humans.[92,93] The CNV potentials are focally reduced by discrete prefrontal damage, supporting a generator of the CNV in prefrontal cortex[94–96] (Fig. 9-10). These data provide a further link between prefrontal regions and sustained attention and working memory capacity.

**Novelty Detection** The earliest brain potential directly reflecting the detection of deviance is the mismatch negativity (MMN). The MMN[97] is elicited in response to small deviations from regularities in the acoustic environment (e.g., a pitch change in a series of tones). The MMN can be observed for events outside the focus of attention and peaks 100 to 250 ms following the deviant event. It reflects an "error signal" generated automatically by a neural mechanism comparing a perceived stimulus to a sensory "memory trace" formed by the standard stimuli[98] or the updating of the existing model of the environment.[99] The mismatch response is presumed to trigger an involuntary reorientation of attention.[98,100] The MMN is generated mainly in the secondary auditory cortex (see Ref. 101 for review) but may have a second frontal generator, presumably related to the triggering of an attention switch.[102,103] The distribution of this frontal generator is reminiscent of the distribution of the visual attention mechanism, whereby the left frontal generator is active in response to contralateral deviancies while the right frontal generator responds to events on either side (Fig. 9-3).[103,104]

The MMN in response to pitch and pattern changes[51,105] is reduced in patients with prefrontal lesions, indicating an early deficit in automatic detection of deviance outside the focus of attention. Whereas temporoparietal lesions caused an MMN reduction

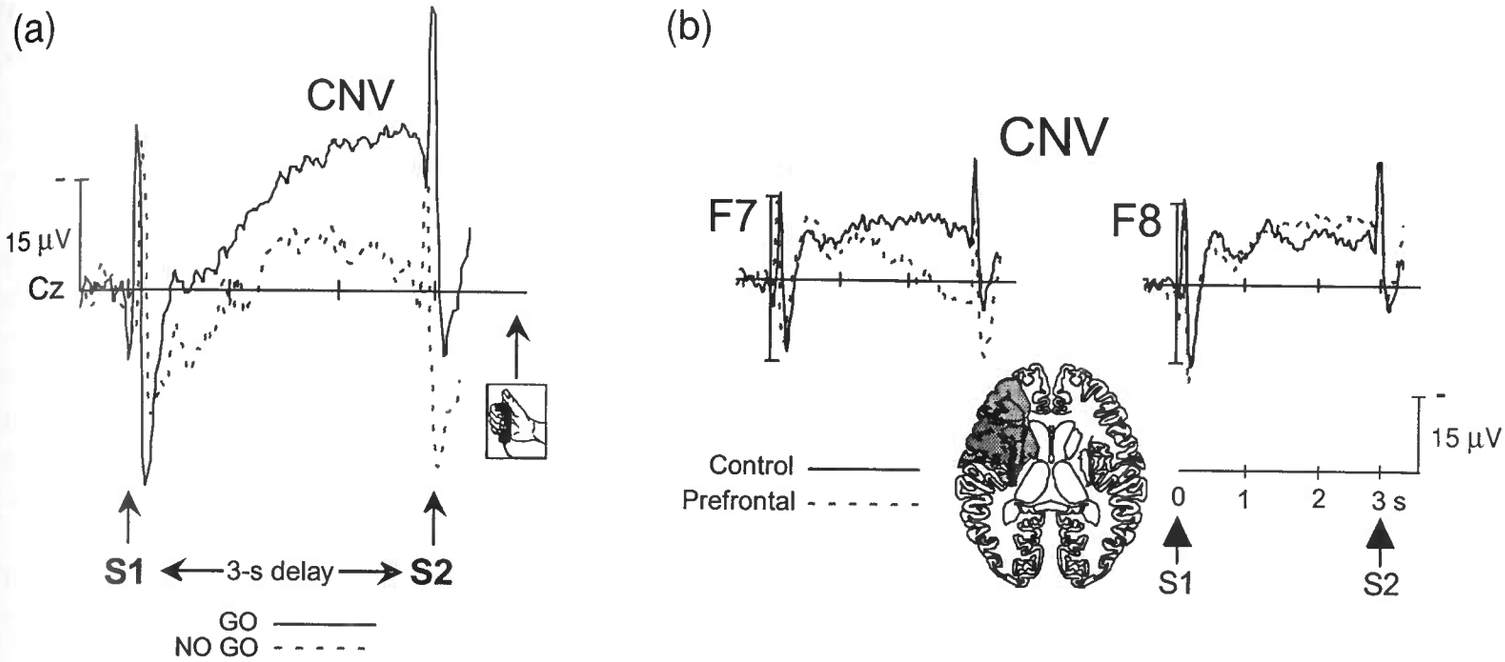



**Figure 9-10**

*This figure shows the results of a classic auditory contingent negative variation (CNV) experiment in patients with focal prefrontal (PFCx) damage. On the left (a) are the results of a CNV task in normals. A warning stimulus (S1) triggers either a GO or NO/GO trial, which is terminated by the imperative S2 stimulus. GO trials generate a large DC shift maximal over frontocentral scalp sites, referred to as the CNV. Damage to the PFCx results in severe attenuation in the CNV over lesioned cortex (b), reductions observed throughout the lesioned hemisphere (see Rosahl and Knight[95] for details). On the bottom right are the group-averaged lesion reconstructions in 10 patients with prefrontal damage. Posterior lesions focally reduce the CNV over lesioned cortex but do not result in widespread hemispheric declines. These data provide evidence of PFCx involvement in sustaining distributed neural activity during delay periods.*

mainly to contralesional stimuli, dorsolateral prefrontal lesions elicited comparable deficits regardless of stimulus side in one study[105] and more to ipsilesional sounds in another.[51] In addition, there was a tendency for right prefrontal lesions to be associated with larger MMN reductions than left frontal lesions, while no such asymmetry was found for the temporoparietal lesions.[105] These results suggest different contributions of the temporoparietal region and the prefrontal region to the MMN. It is yet to be determined whether reduced MMN following prefrontal damage reflects a weakened memory trace of the previous regularity due to disinhibition of irrelevant information, reduced frontal facilitation of a comparator mechanism in the secondary auditory cortex, a failure to initiate an attention switch following the detection of the change, or a damage to the postulated frontal generator of MMN.

Delivery of an unexpected and novel stimulus generates a P300 response (P3a) that is observed over widespread anterior and posterior scalp sites. The P3a potential has an earlier latency and a more frontocentral scalp distribution than the P3b in all sensory modalities and has been proposed to be a central marker of the orienting response.[52,53,106,107] Intracranial recordings in the visual, auditory, and somatosensory modalities have shown that multiple neocortical and limbic regions are activated during tasks that generate scalp novelty-dependent P3a potentials.[108–111] Intracranial P3a activity has been recorded in widespread areas of frontal and posterior association cortex in addition to cingulate and mesial temporal regions.[112] These intracranial novelty-related P3a potentials have been proposed to reflect neural activity in a distributed multimodal corticolimbic orienting

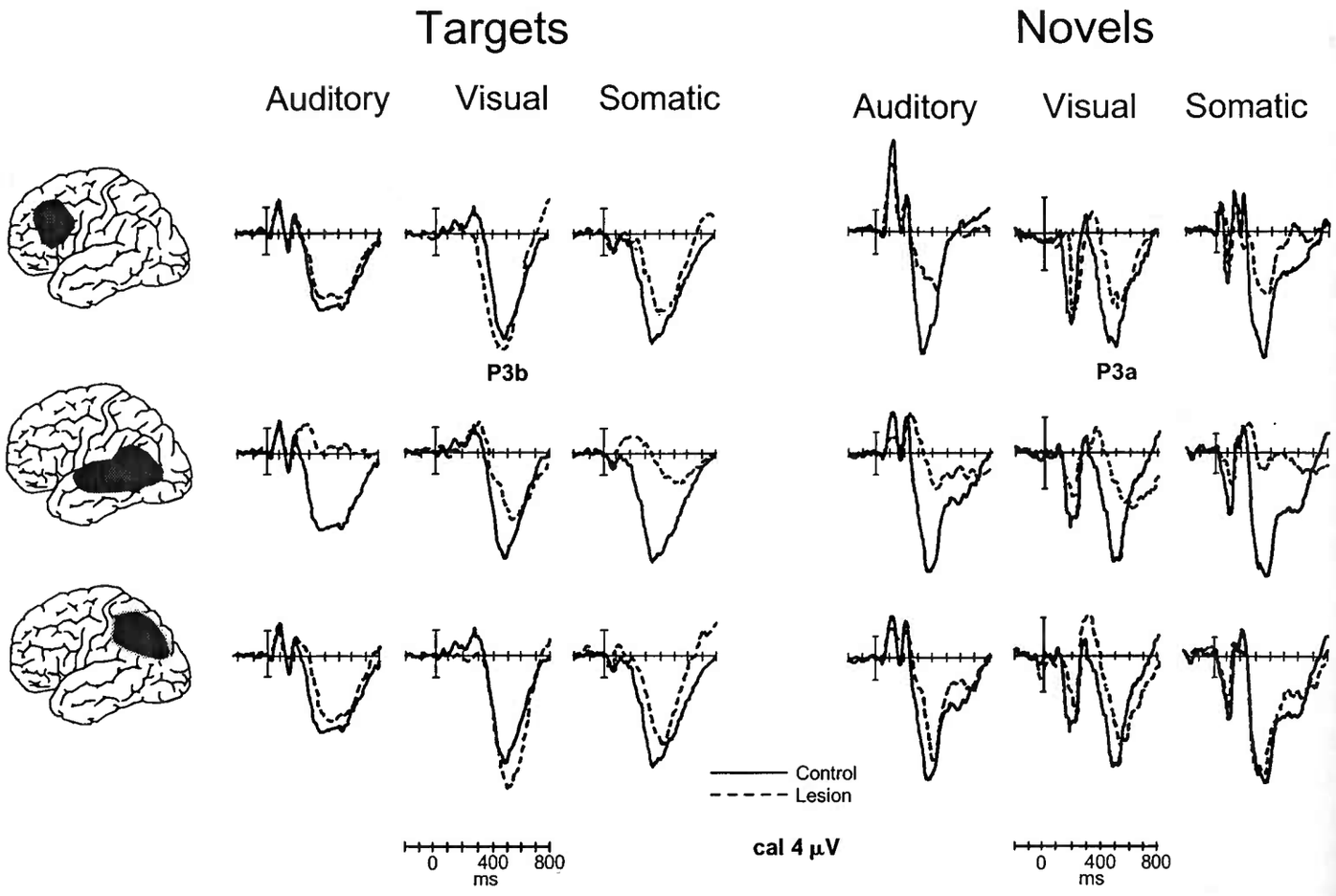



**Figure 9-11**

*Summary of the target P3b and novelty P3a effects in controls and three patient groups with focal cortical damage. The center of the damage in each group is shown on the left. The waveforms from selected electrodes with maximal response amplitude (Pz for targets, Fz for novels) are shown for both target and novel stimuli in the auditory, visual, and somatosensory modalities in patients and controls. Prefrontal and lateral parietal lesions had no significant effect on the latency or amplitude of the target P3b generated in this simple detection task in the auditory, somatosensory, or visual modalities, implying that substantial regions of dorsolateral, prefrontal, and parietal association cortex are not critical for the parietal maximal P3b. Conversely, focal infarction in the temporoparietal junction resulted in marked P3b reductions in the auditory and somatosensory modalities and partial reductions in the visual modality. On the right are the results of the novelty experiments. Lateral parietal damage again had no significant effect on the P3 to novel stimuli and served as a brain lesioned control. Both prefrontal and temporoparietal damage resulted in multimodal reductions of the novelty P3a.*

system. Similar theories have been suggested for the scalp P3a response.[53,106,113] fMRI studies using both blocked and event-related designs indicate distributed regions of activation during novelty and target detection, including the inferior frontal gyri, inferior parietal regions, the insula, the lateral temporal lobe,[114,115] and, in certain paradigms, also in the hippocampus.[116]

Novelty P3a responses generated over prefrontal scalp sites to unexpected novel stimuli are reduced by prefrontal lesions, with reductions observed throughout the lesioned hemisphere.[34] Comparable P3a decrements have been observed in the auditory,[53,117] visual,[34] and somatosensory modalities in humans with prefrontal damage[118] (Fig. 9-11). Reductions appear to be more severe after right prefrontal damage.[119]

Galvanic skin response (GSR), a peripheral marker of the orienting response, is also reduced by damage to the prefrontal and posterior association cortex.[120] These findings support a prefrontal source for the frontal scalp component of the novelty P300 and converge with both clinical observations and animal experimentation supporting a critical role of prefrontal structures in the detection of novel stimuli.[121,122] The combination of data from patients with lesions in anterior and posterior lesions suggest distributed interaction between prefrontal and posterior regions during both voluntary and involuntary attention and working memory,[123,124] with a special role for the right prefrontal region.[2]

Unilateral damage centered in the posterior hippocampal region has no effect on parietal P3b activity generated to auditory, visual, and somatosensory stimuli but reduces frontocentral P3 activity to both target and novel stimuli in all modalities. Reductions are most prominent over frontal regions and for novel stimuli[87,126] (Figs. 9-12 and 9-13). These reductions are comparable in amplitude to those observed after focal prefrontal damage. However, unilateral hippocampal damage reduces P300 potentials over both prefrontal cortices, whereas prefrontal damage results in predominantly unilateral reductions over the lesioned hemisphere. Studies with PET have also documented frontal hypometabolism in patients with medial temporal amnesia.[127] These observations support involvement of a prefrontal-hippocampal system in the detection of deviancies in the ongoing sensory stream and indicate that the hippocampal formation has bilateral facilitatory input to prefrontal cortex. Reciprocal pathways coursing through the caudomedial lobule of the mesial temporal lobe provide a potential anatomic substrate for prefrontal-hippocampal interactions during sensory and mnemonic processing.[128]

These results, in conjunction with the data from intracranial and functional imaging studies, provide further evidence that the P300 phenomenon is not a unitary phenomenon but represents distributed neural activity in corticolimbic regions engaged during both voluntary and involuntary response to discrete environmental events. Although this view is more complicated than initial proposals of a unitary nature of P300 activity, it strengthens the potential utility of scalp ERP recording, since it provides a means for the measurement of neural activity in distributed brain regions in the time domain of cognitive processing.

## Unilateral Neglect and Extinction after Right Hemisphere Damage

Unilateral neglect (UN) is a frequent sequel of right hemisphere damage. As reviewed in Chaps. 25 and 26, patients suffering from neglect following right hemisphere damage fail to orient and respond to stimuli and events occurring on the left side of their personal or extrapersonal space.[129] In extinction, a related disorder, the failure to notice a contralesional stimulus occurs only when a competing stimulus is simultaneously presented more toward the side of the lesion.[130–132] Unilateral neglect (UN) may manifest itself in the visual, auditory, or tactile modalities.[133–135] Examination of UN patients has been widely used to explore mechanisms of attention and awareness. Yet, despite the ubiquity of such patients and the grave implications for their recovery after stroke, the cognitive and anatomic underpinnings of UN are not clear (see Chaps. 25 and 26). Since UN and extinction may occur in the absence of primary sensory deficits, theoretical accounts of UN have emphasized higher-order processes associated with the allocation of attention, representation of space, or motor preparation. These theories are based almost exclusively on clinical observations and studies employing behavioral methods. Recently, functional neuroimaging methods including ERP and fMRI have begun to provide new insights that might necessitate modification of current theories.

A major question in neglect research is still whether early perceptual processes are really unaltered, as suggested by theories that emphasize higher-order deficits in neglect. Normal SEPs (including N9, N13, P15, N20, and P25) were observed in three UN patients with lesions in the right frontotemporo-parietal regions and in one patient with damage in the right occipital periventricular region, even though the patients were not aware of the electrical shocks applied to the left median nerve.[136,137] Moreover, in two of the patients whose primary visual cortex was largely spared, the visual evoked potentials (VEPs) including N75, P100, and N145 were within normal range.[136] In contrast, SEPs and VEPs were absent or reduced in patients suffering from hemianesthesia or hemianopsia,

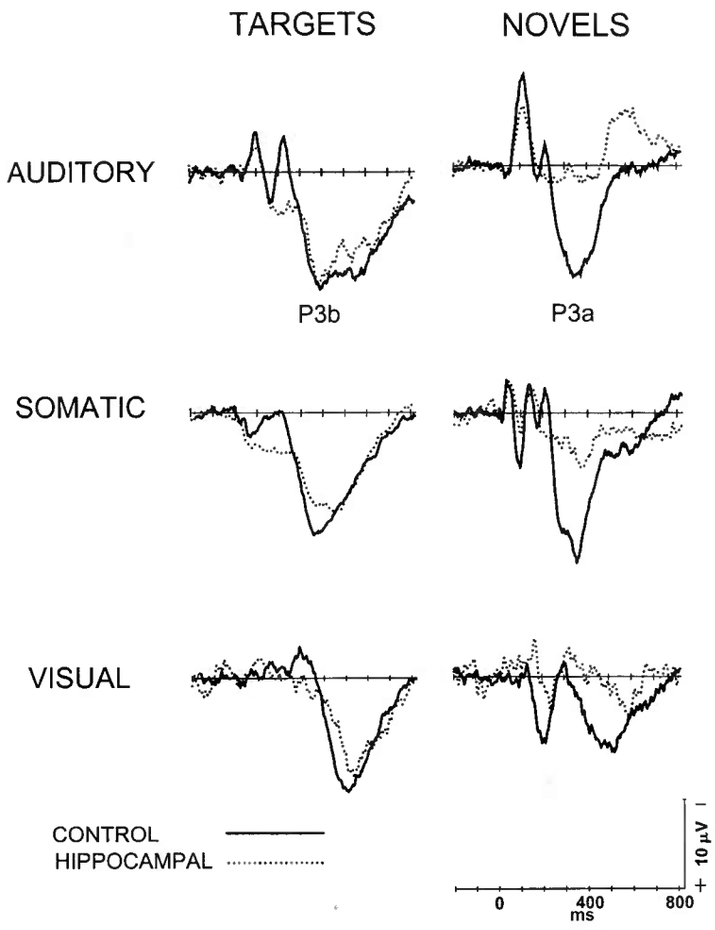



**Figure 9-12**

*Group-averaged event-related potential (ERP) data from controls and patients with hippocampal lesions (n = 7) for auditory, visual, and somatosensory target and novel stimuli. Subjects were seated in a sound-attenuated booth and instructed to press a button upon detection of a designated target stimulus during each experiment. Auditory stimuli consisted of blocks of repetitive standard 1000-Hz monaural tone bursts (60 dB HL; 50 ms duration, 1 s ISI). Tone bursts of 1500 Hz occurred randomly on 10 percent of the trials and served as targets. Unexpected novel tones consisting of complex computer-generated sounds, and environmental noises such as bells or barks were randomly delivered on 10 percent of the trials. A similar paradigm was employed in the visual modality. Visual stimuli consisted of repetitive presentation of triangles. On 10 percent of the trials, inverted triangles served as target stimuli. On an additional 10 percent of trials, random line drawings or pictures of irrelevant stimuli served as novel events. Somatosensory stimuli consisted of repetitive taps to the index finger, with targets being random taps to the ring finger that occurred on 10 percent of the trials. Novel stimuli consisted of brief random shocks to the median nerve on 6 percent of the trials. The ERPs shown are from the electrode where maximal responses were recorded (Pz for targets; Fz for novels). The novelty P3a is markedly reduced at prefrontal sites in all three modalities, and the target P3b is spared.*

respectively—syndromes that resulted from damage to the left primary somatosensory and visual cortices, respectively. Analogous results were reported by Viggiano and colleagues, who recorded steady-state VEPs in 10 neglect patients, 10 brain-damaged patients without neglect, and 6 healthy subjects.[138] No differences in right-left amplitude were observed in the neglect patients. These data support the view that the impairment in neglect stems from "defective access of the output of *preserved* primary sensory analyses to successive processes involved in conscious perception and in overt verbal response" (Vallar et al.,[137] p. 1921, our italics). However, more recent findings suggest that early sensory analysis may not be completely intact.

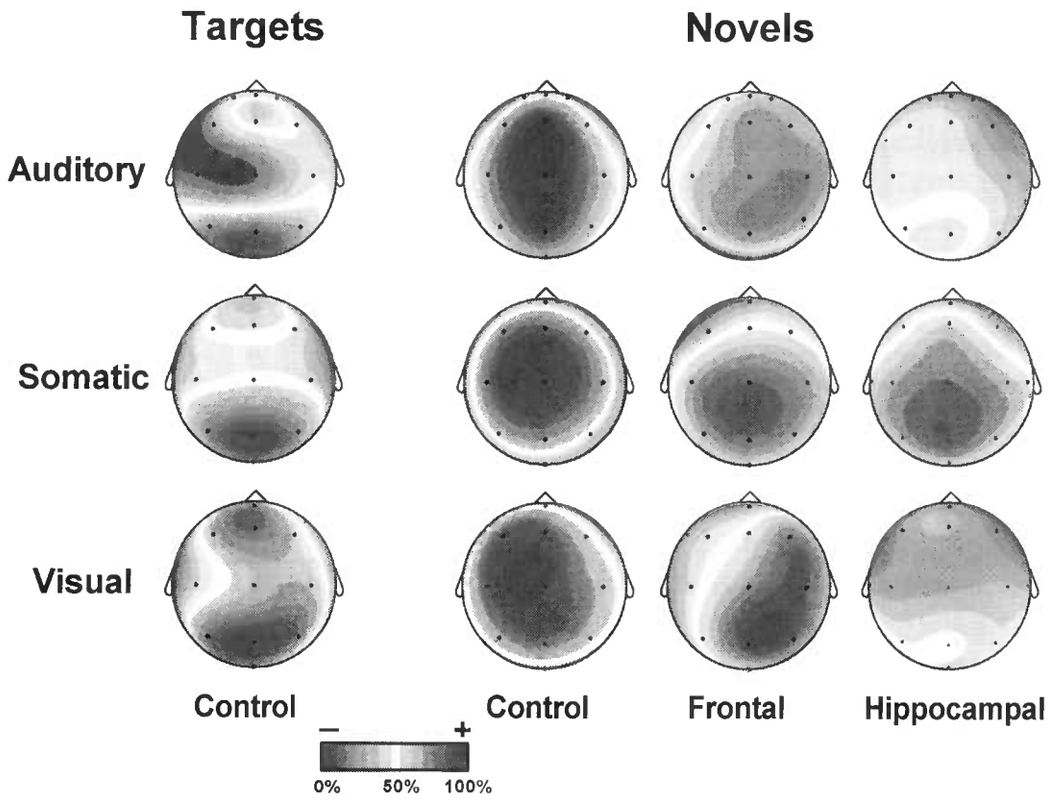



**Figure 9-13**

*This figure shows the scalp voltage topographies for target and novel stimuli in controls. Note the marked increase in prefrontal activity to the novel stimuli in all sensory modalities. The effects of prefrontal or hippocampal lesions on the brain novelty response are shown on the right. Unilateral prefrontal damage results in multimodal decreases in the novelty response. Unilateral hippocampal damage results in severe bilateral reductions in the novelty response, maximal at prefrontal sites. These findings implicate a prefrontal-hippocampal network in the detection of perturbations in the environment (see text for details).*

Abnormal sensory function in neglect was found in studies reporting that the visual and auditory N1 components are smaller over the damaged relative to the intact hemisphere of neglect patients regardless of the side of stimulation.[35,139] In contrast, the N1 in normal subjects is larger over the hemisphere contralateral to the stimulus side.[140] The enhanced left hemisphere (relative to right hemisphere) auditory N1, irrespective of the side of the stimuli, may contribute to the tendency of patients with left-side auditory neglect to err localizing auditory stimuli as coming more to the right of their true source.[141]

Drawing from the putative association between the N1 and the orienting response,[142] it has been suggested that the N1 reduction over the damaged hemisphere reflects the patients' difficulty in orienting toward the contralesional side of space.[139] This is consistent with two single-case studies in which the visual N1 and P1 components were reduced in trials in which the left-sided stimulus was extinguished, but not when it was recognized[143,144] (see also Ref. 145). Recent fMRI studies comparing detected versus extinguished stimuli revealed reduced activation in right occipital cortex (as well as in bilateral fusiform and left parietal sites) when stimuli were extinguished in patients with right hemisphere damage.[144,145] The fact that in these fMRI studies extinguished faces seemed to activate the so-called fusiform face area suggests that the lack of awareness may not result from a breakdown of the object recognition pathway of the visual system but from a failure of its interaction with parietal and frontal mechanisms.[35,144,146,147]

Steady-state VEPs revealed an intriguing pattern in neglect patients. Latencies are increased for steady-state VEPs elicited by stimulation in the neglected side compared with those elicited by similar stimulation in

the intact side.[28,148–150] This delay was absent in brain-damaged patients who did not show signs of neglect. Even more revealing is the fact that the latency increase was found with relatively high frequency luminance-contrast gratings but not with chromatically modulated contrasts,[151] suggesting a specific deficit related to the magnocellular system (luminance sensitive but color blind) and sparing the parvocellular part of the visual system.[152] The possibility of a feature specific deficit in preattentive processing has also been investigated in the auditory modality using the MMN.

As noted previously, the MMN is an electrical brain manifestation elicited by infrequently occurring oddball stimuli interspersed among repetitive stimuli. Several characteristics of the MMN make it an especially interesting measure in the study of UN and extinction. First, the MMN is assumed to reflect an automatically elicited preattentive process.[153–155] Second, the process underlying the MMN has a potential role in triggering an involuntary attention switch,[98,156–158] and such a process is likely disrupted in UN. Third, the MMN paradigm allows one to examine separately the feature-specific processing of auditory stimuli[159–162] (see Ref. 163 for a discussion of the feature-specificity). Fourth, elicitation of the MMN does not require the subject to perform a task or impose any attentional requirements. Therefore it is an ideal probe for comparing preattentive processing of left- and right-sided stimuli and for evaluating the processing of different dimensions of the auditory stimulus.

In a study of 10 patients with auditory and visual UN, deviations on either side of space were examined, with the stimulus differences defined in terms of spatial location, duration, or the pitch of sounds presented from loudspeakers.[35] The most robust finding was that the MMN elicited by deviation in sound-source location was considerably reduced when the stimuli were on the left (neglected) compared to the right side. Pitch deviance also tended to exhibit right-side advantage, but this effect was not as robust as for location. In contrast, no right-left difference was found for the MMN elicited by duration deviance (Fig. 9-14). Since the magnocellular visual pathway is the main contributor to the dorsal stream of the visual system, which is involved with the processing of spatial information, the results from the studies in vision[151] and audition[35] suggest a specific, preattentive deficit in encoding spatial attributes of sensory events. A possible reason for the lack of awareness in UN despite implicit processing of the neglected stimuli is that perceived events cannot be placed in a spatial framework, which is necessary for conscious awareness and for adequately shifting attention towards the stimuli.[35]

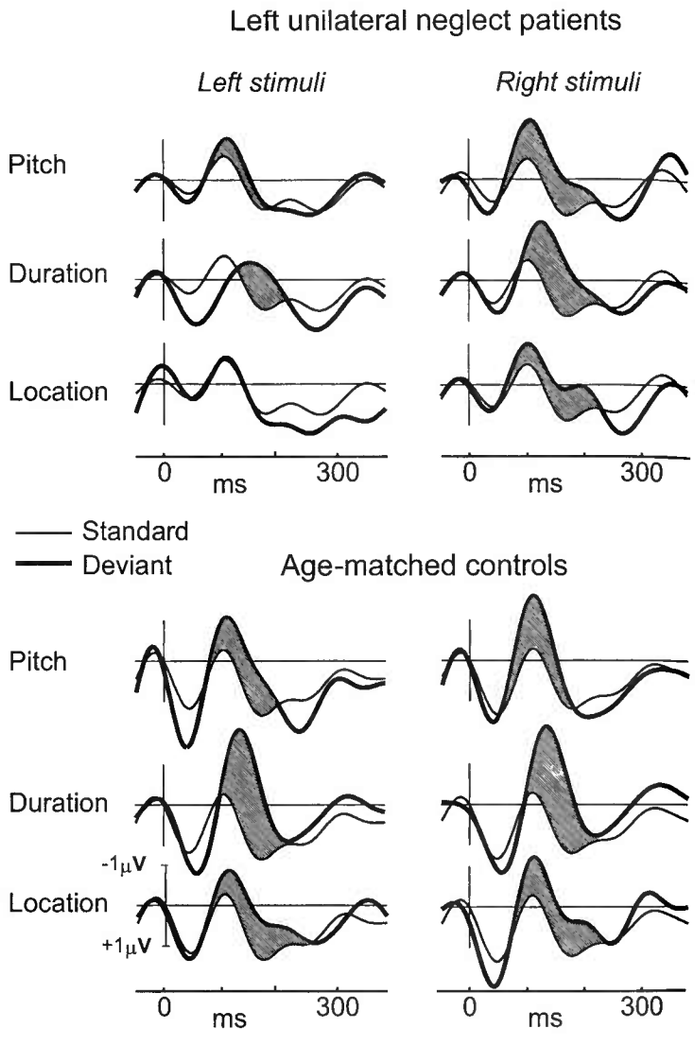



**Figure 9-14**

*Mismatch negativity (hatched area) to deviation in pitch, duration, and location of stimuli in 10 patients with damage to the right hemisphere and with unilateral left visual and auditory neglect and 10 age-matched controls. Stimuli were presented in different blocks 60 degrees to the right or to the left of the subjects through loudspeakers. Standard stimuli were 75-ms-long harmonic tones (600-Hz fundamental). The probability of the pitch deviants (60 Hz lower), duration deviants (50 ms shorter), and location deviants (30 degrees more medial) was 0.1 each. Data presented are for Fz electrode referenced to averaged mastoids. There was a significant decrement in MMN to left location deviants (comparing within patient to the response to right side stimuli). The decrement approached significance for pitch and was not significant for duration (see Ref. 35 for details).*

The "Posner paradigm"[164] was used to explore the effect of neglect on the allocation of attention as reflected by the P3 and Nd.[139] It has been previously shown that in right temporoparietal patients, a misleading (invalid) cue on the ipsilesional side dramatically slows down the reaction time to contralesional targets more than the normal effect of such a cue and more than the effect of a contralesional invalid cue on the reaction time to an ipsilesional target,[164,165] suggesting that patients with these lesions fail to "disengage" from stimuli (e.g., the invalid cue) on the ipsilesional side. This conjecture was corroborated by the finding that in right parietal patients the Nd, an ERP manifestation of selective attention, was significantly smaller following right-sided (invalid) cues than any other cue-target combination.[139] This effect was evident as early as 200 ms after target onset, suggesting that even if the underlying deficit may originate in the higher-order attention mechanism, it affects "the very processing of perceptual input" (Verleger et al.,[139] p. 455).

A more complex pattern of results was obtained regarding the patients' P3 component in the Posner paradigm.[139] The late positive potential (LAP or P3f, denoting a P3 recorded at Fz[166]) was largest for the critical combination of right cue and left target. This pattern resembles the enhanced P3 observed in monkeys with frontoparietal damage and signs of UN.[167] Post hoc, the P3f enhancement was interpreted as reflecting the patients' attempt to reorient attention toward the left-side target following late detection. Direct tests of this hypothesis are needed. In contrast to the P3f, the P3b (recorded at a central parietal site) was reduced in patients irrespective of the cue and target location, corroborating earlier observations.[125] This general reduction was ascribed to damage to P3 generators, especially those centered in the temporoparietal junction.

The use of electrophysiological and hemodynamic functional imaging sheds new light on intact and impaired processes in UN. The extant studies show that the lesion may induce specific impairments in an early stage of processing to which behavioral methods may be blind.

## Linguistic Processing in Aphasic Patients

Whereas language deficits following brain damage are traditionally classified into crude clinical syndromes such as Broca's or Wernicke's aphasia, advances in neurolinguistics suggest that a finer-grain analysis, based on individual symptoms, may be more fruitful (see Chap. 12). Distinct ERP components have been linked to stages of language comprehension including (1) early left anterior negativity (ELAN), a marker of syntactic violations[168,169]; (2) The N400, related to lexical/semantic integration (N400)[170]; and (3) the "late positivity" or P600, which has been attributed to reprocessing of linguistic information (P600).[171] The N400 was first described by Kutas and Hillyard as being elicited by violations of semantic expectancies at the end of sentences ("She takes her coffee with cream and *dog*" rather than ". . . cream and *sugar*").[170] The N400 amplitude is modulated by the extent to which a word is related to its prior context ("N400 effect"), being more negative the more unexpected the word is.[172] The effect is not limited to sentences but can be seen both when comparing words primed or not primed by a previous semantically related or associated word[173] or when a word in a sentence is incompatible with the general context of a discourse.[174] In fact, even nonverbal stimuli such as faces,[175] pictures,[176–178] and environmental noises[85] (but not endings of melodies[179,180]) have been reported to elicit N400-type components, suggesting a link to lexical access[181] or postlexical integration of a stimulus into the semantic context.[182] It is conceivable that multiple intracranial regions contribute to the scalp N400 with different subcomponents related to various aspects of cognitive processing, as has been suggested for P300 phenomena.[183] The N400 amplitude was reduced in patients with lesions of the left temporoparietal cortex exhibiting symptoms of Wernicke's aphasia. Conversely, N400 amplitudes were reported to be less affected in patients with frontal lesions exhibiting symptoms of Broca's aphasia.[184] Intracranial recordings in the anterior medial temporal lobe (MTL) have revealed potentials resembling the scalp N400 in verbal recognition memory, lexical decision, semantic priming, and picture-naming tasks.[183,185,186] MTL-N460 amplitudes have been reported to be largest in the left MTL following new words, while an MTL-P620 potential was largest to repeated words and was reduced in a passive condition. Puce and colleagues[187] found similar MTL potentials to both verbal stimuli and abstract "nonverbalizable" patterns during recognition memory. These data suggest that a posterior

cortical-mesial-temporal network is engaged during N400 generation.

Elderly controls and patients with Broca's aphasia demonstrated semantic and associative priming effects, manifest by a decreased N400 to related targets versus unrelated targets, while patients with Wernicke's aphasia failed to show this priming effect.[184] However, the N400 effect was found to correlate significantly with the degree of comprehension in a group of aphasic patients irrespective of their diagnosis as Broca's or Wernicke's aphasia.[36,184] Whereas the hallmark of Broca's aphasia is an expressive problem, it is now believed that these patients also have some problems with comprehension. For example, agrammatic nonfluent aphasics have difficulty in understanding sentences involving atypical syntactic constructions.[188] An interesting double dissociation was found between a "Broca" patient with a frontal lesion including the frontal operculum and the insula, and a "Wernicke" patient with posterior-temporal/inferior-parietal lesion.[189] The patient with the frontal lesion failed to elicit the "early left anterior negativity" (ELAN) effect following a phrase structure (grammatical) violation but showed a normal N400 effect for a semantic violation of the sort outlined in the previous paragraph. The patient with the posterior lesion showed the opposite result. This supports the existence of distinct mechanisms for grammatical parsing and lexical-semantic integration, with the former dependent on the inferior frontal and insular cortex and the latter dependent on posterior parietotemporal cortex. Patients with anterior lesions fail to exhibit a differential ERP response to closed-class (e.g., pronouns) and open-class (e.g., nouns) words, possibly reflecting a deficit in the rapid categorization of words into their syntactic roles.[190] However, the semantic processing in patients with anterior lesions may not be completely intact. When an ambiguous word (e.g., *bank*) is placed as the last word in a sentence, the sentence may disambiguate the word in one direction (e.g., "the man called the bank"). In normal controls, a target word (e.g., *river*) following the disambiguated word elicits a smaller N400 if it is associated with the selected meaning than if it is unrelated or is related to the alternative meaning (the N400 effect). The same result was obtained in a group of patients with frontal lesions and Broca's aphasia as long as the time between the disambiguated word and the target word was long (1250 ms).[190] When this gap was short (100 ms), the alternative meaning primed the target word significantly (although to a smaller degree than the selected meaning). Age-matched controls showed the normal pattern for both gaps. This has been interpreted as a slowing of lexical integration in the aphasic patients, with both meanings of the ambiguous word remaining "active" for a longer time and thus hampering comprehension. In addition to higher-order linguistic deficits, ERP studies using the MMN component revealed a lower level deficit of phonetic discrimination in patients with comprehension deficits following left posterior temporal lesions, including Wernicke's area, but not in patients with anterior lesions and signs of Broca's aphasia.[159,191–193] Thus, some of the deficit in comprehension may reflect difficulty in deciphering the phonetic stream, resulting in degraded input to higher-order linguistic processes.

Although the results of these pioneering studies of language impairment may be open to different interpretations based on competing theories of language processing, they nevertheless demonstrate the potential benefits of using ERPs to investigate normal and impaired language processes. Initial attempts have also been made to use ERPs as a diagnostic aid in examining the comprehension of patients with global aphasia, which cannot be examined behaviorally.[194,195]

## TRANSCRANIAL MAGNETIC STIMULATION

Merton and Morton provided the first demonstration of transcranial electrical stimulation (TES) in 1980.[196] By applying a brief, high-voltage electric shock to the scalp over motor cortex, they were able to elicit focal muscle activity, or what has come to be called the motor evoked response (MER). This technique had obvious utility for clinicians, offering a tool for measuring the integrity of efferent pathways in a manner analogous to that provided by the somatosensory evoked potential. However, TES had one serious drawback: the shocks were very painful because the stimulus also activated pain receptors in the scalp. Transcranial magnetic stimulation (TMS) was developed as a painless alternative to TES[197] (for recent reviews, see Refs. 198 and 199).

## Technical Considerations

The TMS device consists of a tightly wrapped wire coil that is encased in an insulated sheath and connected to a power source of electrical capacitors. When triggered, the capacitors send a large electric current through the coil, resulting in the generation of a large yet compact magnetic field (up to 3 tesla) with lines of flux perpendicular to the plane of the coil. The magnetic field peaks within about 150 $\mu$s and decays within 1 ms. This rapid change induces electric eddy currents in conductive tissue. The skull presents low impedance to magnetic fields of this frequency; thus there is minimal current induction in extracerebral tissue, including pain receptors. However, eddy currents are produced within the brain, thus stimulating neural tissue. The exact mechanism is unknown. It may be that the current leads to the generation of action potentials in the soma; alternatively, the current may directly stimulate axons or involve a mixture of cell body and axonal stimulation.

The current generated is strongest under the edges of the coil; it become weak near the center. Thus, with circular coils, the area of activation is dispersed and not homogenous across the region spanned by the coil. To obtain more focal stimulation, figure-eight coils are commonly employed, with the current strongest at the point where the two circles intersect (Fig. 9-15). With such coils, the primary activation can be restricted to an area of about 1 to 1.5 cm. The extent and intensity of the induced neural activity varies with the intensity of the generated current and falls off fairly rapidly as the distance from the coil increases. As such, TMS is primarily targeted at cortical areas that lie along the gyri, although deeper structures such as the supplementary motor area have been successfully stimulated.[200] In addition, the resistance of white matter is greater than that of gray matter, further reducing the likelihood that TMS can be targeted to deep structures of the cortex or subcortical nuclei.

## Applications of TMS

TMS has become a relatively standard clinical tool for evaluating the speed of conduction in motor pathways. For example, activation of the abductor digiti minimi muscle (fifth finger) can be elicited by placing the stimulator over the ulnar nerve at the wrist, at the C7 level of the spinal cord, or over the contralateral motor cortex.[17] In this manner, it is possible to determine if abnormal latencies arise from central or peripheral pathology in a disease such as multiple sclerosis or when monitoring corticospinal function during spinal cord surgery. While clinical uses of this kind are primarily diagnostic, TMS has also been studied as a possible therapeutic device. Preliminary studies have indicated that repetitive TMS (rTMS; with rates varying from 0.5 Hz for 10 s to 10 Hz for 5 s) applied over prefrontal cortex may prove effective for treating major depression.[201,202] The mechanism of such treatment is unclear, but it may offer a more focal and less debilitating treatment than electroshock therapy for patients with resistant mood disorders.

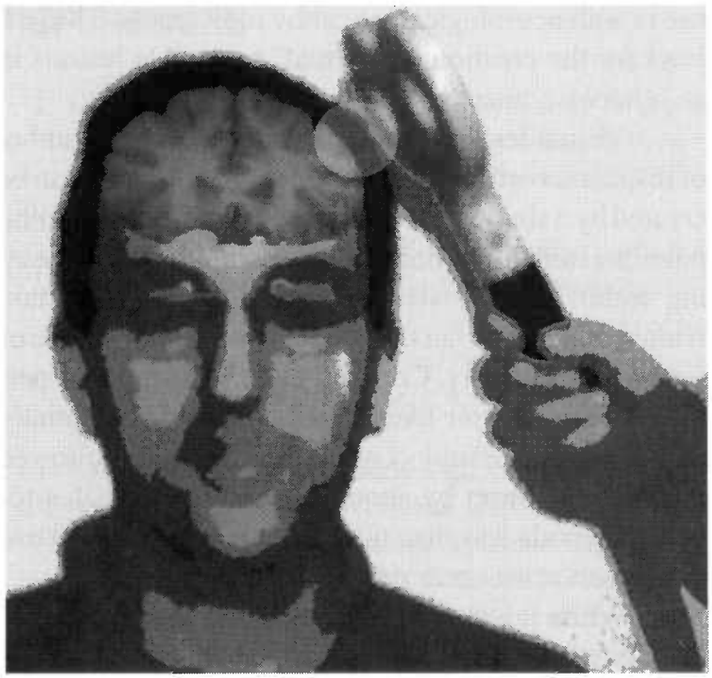


**Figure 9-15**
*Transcranial magnetic stimulation (TMS). The figure shows a figure-eight-shaped TMS stimulator applied to the head; the region of stimulated cortex is indicated schematically.*

TMS offers a new experimental approach for cognitive neuroscience. With this method, an experimenter can disrupt neural function in a selected region of the cortex and, as with lesion studies, the resulting changes in behavior can shed light on the normal function of the targeted tissue. What makes this method appealing is that, appropriately applied, the technique is safe and noninvasive. Moreover, since the principal

use is with neurologically healthy individuals, TMS allows for the creation of "virtual" reversible lesions in an otherwise intact brain.[18]

Virtual lesions have been created over a number of disparate cortical areas. A functional scotoma can be created by a single TMS pulse applied over the occipital pole, presumably reflecting the disruption of processing within primary visual cortex.[203,204] An important feature of TMS is that the effect shows a high degree of temporal specificity. Corthout et al.[205] found that performance on a letter-identification task was essentially abolished for one subject when the TMS pulse followed the stimulus onset by about 100 ms. For stimulus-to-TMS intervals less than 60 ms or greater than 140 ms, performance was near perfect.

While it is tempting to conclude that the critical activity within primary visual cortex for letter identification occurs about 100 ms after stimulus presentation, it is also possible that there is a delay between the onset of the TMS-induced activity and the actual neural disruption in task performance. For example, it is quite possible that a silent period follows the TMS volley, and it may be that this silent period is what leads to the scotoma. Nonetheless, TMS can be useful for examining the relative timing of processing within different visual areas. For example, Beckers and Zeki[206] reported that stimulation over either V1 or V5 (MT) impaired performance on a motion discrimination task. Interestingly, the disruptive effects in V1 occurred with much longer stimulus-to-TMS intervals than found for V5, a result that would seem at odds with conventional notions that processing proceeds in a serial manner from V1 to higher visual areas. The TMS results would suggest that back projections from V5 to V1 might be an important part of the discrimination process (see also Ref. 207).

A second example of the use of TMS for exploring functional connectivity comes from a study in which subjects were trained to perform sequential finger movements.[200] When the coil was centered over the hand area of motor cortex, the next response in the sequence was frequently disturbed, either because the movement was halted in midstream or because the wrong key was pressed. The subjects perceived the problem as a temporary loss of coordination, commenting that the finger suddenly seemed to jerk in the wrong direction. In contrast, when the coil was targeted to affect the supplementary motor area (SMA), the effects were delayed, occurring about three key presses after the TMS pulse. Here, the subjects reported that they lost track of their place in the sequence or that they temporarily forgot the order of responses. Thus, TMS demonstrated the differential role of supplementary motor area and primary motor cortex in motor planning and execution, respectively. It is important to note that TMS pulses in this study were applied in a rapid series (3 Hz). It is unclear whether measurable effects on higher-level aspects of cognition such as motor programming can be obtained with single-pulse TMS. Unfortunately, there have been a few reported cases of induced seizure activity with rapid TMS (>1 Hz), thus limiting the use of this method.[216]

There have recently been a number of impressive reports in which TMS and functional neuroimaging have been used in combination. A long-standing debate in cognitive neuroscience has centered on the question of whether visual imagery requires the engagement of neural regions involved in visual perception. Evidence in favor of a shared medium for imagery and perception comes from imaging studies; as measured by PET, activation in visual areas including primary visual cortex have been reported when subjects were asked to image visual patterns and then make judgments about properties such as length and orientation.[208]

However, as with all imaging studies, the evidence is correlational, making it difficult to draw conclusions about causation. Connections from higher-order visual areas (or even nonvisual areas) to primary visual cortex due to long-term perceptual experience may have led to the activation of primary visual cortex even though this activity was not essential for task performance. To test this possibility, Kosslyn and colleagues used a novel TMS method. Prior to performing a second session on the imagery task, 1-Hz TMS was applied over the occipital pole for 10 min.[208] Previous studies had shown that the efficacy of neural activity is depressed for an extended period after such repetitive TMS, allowing performance to be assessed under conditions in which the nonspecific effects such as the noise from the stimulator or muscle twitches are not present.[209] Indeed, performance on the imagery task was impaired following this stimulation in comparison to a sham TMS control condition in which the coil was oriented perpendicular to the skull. Thus it appears that

disruption of normal activity in primary visual cortex can impair imagery, providing experimental evidence that converges with the correlational results obtained in the PET phase of the study. In a similar way, TMS over visual cortex has been shown to disrupt tactile perception of shape in both sighted[210] and blind individuals,[211] indicating that the activation observed in these areas during neuroimaging studies[212,213] is not an epiphenomenon.

TMS has recently been used to reproduce phenomena naturally observed after brain damage. The line bisection task is a common test for unilateral neglect (see above and Chap. 25). In a variant of this task known as the landmark task, subjects are asked to judge whether a line is correctly bisected into two equal segments. Single-pulse TMS applied within 200 ms following the stimulus over posterior parietal area of healthy volunteers slowed down reaction times when the bisecting landmark was to the right of the midline[214] and biased perception toward underestimating the left segments.[215] Left-sided pulses or sham pulses did not alter performance. Notably, patients with right parietal lesions bisect lines to the right of the midline. Thus, the posterior parietal region stimulated (corresponding to Brodman's area 7 and the intraparietal sulcus) may indeed have a critical role in this task. In addition, this procedure suggests the possibility of a human model for studying some visuospatial deficits found in unilateral neglect.

## CONCLUSIONS

The use of event-related potentials to study patients with localized brain damage and with specific behavioral dysfunctions continues to provide invaluable information on the underlying mechanisms of normal and pathologic cognition and its neural mechanism. TMS provides a new and promising method of inducing virtual lesions in healthy subjects, thus providing a method to test functional hypotheses regarding the contribution of targeted neural areas to particular tasks. The combination of these methods with traditional neuropsychological and hemodynamic imaging methods is likely to transform our understanding of brain function. Hopefully, this will yield better diagnostic as well as restorative procedures for neurologic patients.

## REFERENCES


1. Hillyard SA, Picton TW: Electrophysiology of cognition, in Plum F (ed): *Handbook of Physiology: The Nervous System.* Baltimore: American Physiological Society, 1987, pp 519–584.
2. Knight RT: Attention regulation and human prefrontal cortex, in Thierry AM, Glowinski J, Goldman-Rakic P, Christen Y (eds): *Motor and Cognitive Functions of the Prefrontal Cortex: Research and Perspectives in Neurosciences.* Berlin and Heidelberg: Springer-Verlag, 1994, pp 160–173.
3. Egan MF, Duncan CC, Suddath RL, et al: Event-related potential abnormalities correlate with structural brain alterations and clinical features in patients with chronic schizophrenia. *Schizophr Res* 11:259–271, 1994.
4. Bonmassar G, Schwartz DP, Liu AK, et al: Spatiotemporal brain imaging of visual-evoked activity using interleaved EEG and fMRI recordings. *Neuroimage* 13:1035–1043, 2001.
5. Goldman RI, Stern JM, Engel J, et al: Acquiring simultaneous EEG and functional MRI. *Clin Neurophysiol* 111:1974–1980, 2000.
6. Allen PJ, Josephs O, Turner R: A method for removing imaging artifact from continuous EEG recorded during functional MRI. *Neuroimage* 12:230–239, 2000.
7. Kruggel F, Herrmann CS, Wiggins CJ, et al: Hemodynamic and electroencephalographic responses to illusory figures: Recording of the evoked potentials during functional MRI. *Neuroimage* 14:1327–1336, 2001.
8. Lazeyras F, Zimine I, Blanke O, et al: Functional MRI with simultaneous EEG recording: Feasibility and application to motor and visual activation. *J Magn Reson Imaging* 13:943–948, 2001.
9. König P, Engel AK: Correlated firing in sensory-motor systems. *Curr Opin Neurobiol* 5:511–519, 1995.
10. Basar-Eroglu C, Strüber D, Schürmann M, et al: Gamma-band responses in the brain: a short review of psychophysiological correlates and functional significance. *Int J Psychophysiol* 24:101–112, 1996.
11. Llinas R, Ribary U, Contreras D, et al: The neuronal basis for consciousness. *Philos Trans R Soc Lond B Biol Sci* 353:1841–1849, 1998.
12. Pfurtscheller G, Lopes da Silva FH: Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clin Neurophysiol* 110:1842–1857, 1999.
13. Sannita WG: Stimulus-specific oscillatory responses of the brain: A time/frequency-related coding process. *Clin Neurophysiol* 111:565–583, 2000.

14. Tallon-Baudry C, Bertrand, O, Peronnet F, et al: Induced gamma-band activity during the delay of a visual short-term memory task in humans. *J Neurosci* 18:4244–4254, 1998.
15. Herrmann CS, Knight R: Mechanisms of human attention: event-related potentials and oscillations. *Neurosci Biobehav Rev* 25:465–476, 2001.
16. Penfield W. Jasper H: *Epilepsy and the Functional Anatomy of the Human Brain*. Boston: Little, Brown, 1954.
17. Brunholzl C, Claus D: Central motor conduction time to upper and lower limbs in cervical cord lesions. *Arch Neurol* 51:245–249, 1994.
18. Pascual-Leone A, Bartres-Faz D, Keenan JP: Transcranial magnetic stimulation: Studying the brain-behaviour relationship by induction of "virtual lesions." *Philos Trans R Soc Lond B Biol Sci* 354:1229–1238, 1999.
19. Picton TW, Lins OG, Scherg M: The recording and analysis of event-related potentials, in Boller F, Graffman J (eds): *Handbook of Neuropsychology*. New York: Elsevier, 1995, pp 3–73.
20. Picton TW, Alain C, Woods DL, et al: Intracerebral sources of human auditory-evoked potentials. *Audiol Neurootol* 4:64–79, 1999.
21. Swick D, Kutas M, Neville HJ: Localizing the neural generators of event-related brain potentials, in Kertesz A (ed): *Localization in Neuroimaging in Neuropsychology*. New York: Academic Press, 1994, pp 73–121.
22. Näätänen R: *Attention and Brain Function*. Hillsdale, NJ: Erlbaum, 1992.
23. Knight RT: Electrophysiology in behavioral neurology, in Mesulam M-M (ed): *Principles of Behavioral Neurology*. Philadelphia: Davis, 1985, pp 327–346.
24. Picton TW: Human event-related potentials, in *Handbook of Electroencephalography and Clinical Neurophysiology*. Philadelphia: Elsevier, 1987, vol 3.
25. Klee M, Rall W: Computed potentials of cortically arranged populations of neurons. *J Neurophysiol* 40:647–666, 1977.
26. Pernier J, Perrin F, Bertrand O: Scalp current density fields: Concept and properties. *Electroencephalogr Clin Neurophysiol* 69:385–589, 1998.
27. Gevins A, Smith ME, McEvoy LK, et al: Electroencephalographic imaging of higher brain function. *Philos Trans R Soc Lond B Biol Sci* 354:1125–1133, 1999.
28. Angelelli P, De Luca M, Spinelli D: Early visual processing in neglect patients: A study with steady-state VEPs. *Neuropsychologia* 34:1151–1157, 1996.
29. Aboud S, Bar L, Rosenfeld M, et al: Left-right asymmetry of visual evoked potentials in brain-damaged patients: a mathematical model and experimental results. *Ann Biomed Eng* 24:75–86, 1996.
30. Knight RT, Scabini D: Anatomic bases of event-related potentials and their relationship to novelty detection in humans. *J Clin Neurophysiol* 15:3–13, 1998.
31. Damasio H, Damasio AR: *Lesion Analysis in Neuropsychology*. New York: Oxford University Press, 1989.
32. Fiez JA, Damasio H, Grabowski TJ: Lesion segmentation and manual warping to a reference brain: Intra- and interobserver reliability. *Hum Brain Mapp* 9:192–211, 2000.
33. Brett M, Leff AP, Rorden C, et al: Spatial normalization of brain images with focal lesions using cost function masking. *Neuroimage* 14:486–500, 2001.
34. Knight RT: Distributed cortical network for visual attention. *J Cogn Neurosci* 9:75–91, 1997.
35. Deouell LY, Bentin S, Soroker N: Electrophysiological evidence for an early (pre-attentive) information processing deficit in patients with right hemisphere damage and unilateral neglect. *Brain* 123:353–365, 2000.
36. Swaab T, Brown C, Hagoort T: Spoken sentence comprehension in aphasia: Event-related potential evidence for a lexical integration deficit. *J Cogn Neurosci* 9:39–66, 1997.
37. Knight RT, Stuss DT: Prefrontal cortex: the present and the future, in Stuss DT, Knight RT (eds): *Principles of Frontal Lobe Function*. New York: Oxford University Press, 2002, pp 573–597.
38. Knight RT, D'Esposito M: The lateral prefrontal syndrome: A deficit in executive control, in D'Esposito M (ed): *Neurological Foundations of Cognitive Neuroscience*. Cambridge, MA: MIT Press. In press.
39. Knight, RT, Staines WR, Swick D, et al: Prefrontal cortex regulates inhibition and excitation in distributed neural networks. *Acta Psychol* 101:159–178, 1999.
40. Lhermitte F: Human autonomy and the frontal lobes: Part II. Patient behavior in complex and social situations: The "environmental dependency syndrome." *Ann Neurol* 19:335–343, 1986.
41. Shimamura AP: Memory and the frontal lobe, in Gazzaniga M (ed): *The Cognitive Neurosciences*. Cambridge, MA: MIT Press, 1994, pp 803–813.
42. Barcelo F, Suwazono S, Knight RT: Prefrontal modulation of visual processing in humans. *Nat Neurosci* 3:399–403, 2000.
43. Chao LL, Knight, RT: Contribution of human prefrontal cortex to delay performance. *J Cogn Neurosci* 10:167–77, 1998.

44. Edinger HM, Siegel A, Troiano R: Effect of stimulation of prefrontal cortex and amygdala on diencephalic neurons. *Brain Res* 97:17–31, 1975.
45. Alexander GE, Newman JD, Symmes D: Convergence of prefrontal and acoustic inputs upon neurons in the superior temporal gyrus of the awake squirrel monkey. *Brain Res* 116:334–338, 1976.
46. Skinner JE, Yingling CD: Central gating mechanisms that regulate event-related potentials and behavior, in Desmedt JE (ed): *Progress in Clinical Neurophysiology.* Basel: Karger, 1977, vol 1, pp 30–69.
47. Yingling CD, Skinner JE: Gating of thalamic input to cerebral cortex by nucleus reticularis thalami, in Desmedt JE (ed): *Progress in Clinical Neurophysiology.* Basel: Karger, 1977, vol I, pp 70–96.
48. Guillery RW, Feig SL, Lozsadi DA: Paying attention to the thalamic reticular nucleus. *Trends Neurosci* 21:28–32, 1998.
49. Knight RT, Scabini D, Woods DL: Prefrontal cortex gating of auditory transmission in humans. *Brain Res* 504:338–342, 1989.
50. Yamaguchi S, Knight RT: Gating of somatosensory inputs by human prefrontal cortex. *Brain Res* 521:281–288, 1990.
51. Alho K, Woods DL, Algazi A, et al: Lesions of frontal cortex diminish the auditory mismatch negativity. *Electroencephalogr Clin Neurophysiol* 91:353–362, 1994.
52. Sokolov EN: Higher nervous functions: The orienting reflex. *Annu Rev Physiol* 25:545–580, 1963.
53. Knight RT: Decreased response to novel stimuli after prefrontal lesions in man. *Electroencephalogr Clin Neurophysiol* 59:9–20, 1984.
54. Chao L, Knight RT: Human prefrontal lesions increase distractibility to irrelevant sensory inputs. *Neuroreport* 6:1605–1610, 1995.
55. Woods DL, Knight RT: Electrophysiological evidence of increased distractibility after dorsolateral prefrontal lesions. *Neurology* 36:212–216, 1986.
56. Desimone R: Visual attention mediated by biased competition in extrastriate visual cortex. *Philos Trans R Soc Lond B Biol Sci* 353:1245–1255, 1998.
57. Hillyard SA, Hink RF, Schwent UL, et al: Electrical signs of selective attention in the human brain. *Science* 182:177–180, 1973.
58. Heinze HJ, Mangun GR, Burchert W, et al: Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature* 372:543–546, 1994.
59. Mangun GR: Neural mechanisms of visual selective attention. *Psychophysiology* 32:4–18, 1995.
60. Martínez A, Anllo-Vento L, Sereno MI, et al: Involvement of striate and extrastriate visual cortical areas in spatial attention. *Nat Neurosci* 2:364–369, 1999.
61. Woldorff MG, Gallen CC, Hampson SA, et al: Modulation of early sensory processing in human auditory cortex during auditory selective attention. *Proc Natl Acad Sci U S A* 90:8722–8726, 1993.
62. Grady CL, Van Meter JW, Maisog JM, et al: Attention-related modulation of activity in primary and secondary auditory cortex. *Neuroreport* 8:2511–2516, 1997.
63. Somers DC, Dale AM, Seiffert AE, et al: Functional MRI reveals spatially specific attentional modulation in human primary visual cortex. *Proc Natl Acad Sci U S A* 96:1663–1668, 1999.
64. Steinmetz PN, Roy A, Fitzgerald PJ, et al: Attention modulates synchronized neuronal firing in primate somatosensory cortex. *Nature* 404:187–190, 2000.
65. Roelfsema PR, Lamme VAF, Spekreijse H: Object-based attention in the primary visual cortex of the macaque monkey. *Nature* 395:376–381, 1998.
66. Hillyard SA, Anllo-Vento L: Event-related brain potentials in the study of visual selective attention. *Proc Natl Acad Sci U S A* 95:781–787, 1998.
67. Fuster JM, Bodner M, Kroger JK: Cross-modal and cross-temporal association in neurons of frontal cortex. *Nature* 405:347–351, 2000.
68. Funahashi S, Bruce CJ, Goldman-Rakic PS: Dorsolateral prefrontal lesions and oculomotor delayed-response performance: Evidence for mnemonic "scotomas." *J Neurosci* 13:1479–1497, 1993.
69. Rossi AF, Rotter PS, Desimone R, et al: Prefrontal lesions produce impairments in feature-cued attention. *Soc Neurosci Abstr* 29:2, 1999.
70. McIntosh AR, Grady CL, Ungerleider LG, et al: Network analysis of cortical visual pathways mapped with PET. *J Neurosci* 14:655–666, 1994.
71. Büchel C, Friston KJ: Modulation of connectivity in visual pathways by attention: Cortical interactions evaluated with structural equation modeling and fMRI. *Cereb Cortex* 7:768–778, 1997.
72. Chawla D, Rees G, Friston KJ: The physiological basis of attentional modulation in extrastriate visual areas. *Nat Neurosci* 2:671–676, 1999.
73. Rees G, Frackowiak R, Frith C: Two modulatory effects of attention that mediate object categorization in human cortex. *Science* 275:835–838, 1997.
74. Kastner S, Pinsk MA, de Weerd P, et al: Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron* 22:751–761, 1999.

75. Corbetta M: Frontoparietal cortical networks for directing attention and the eye to visual locations: Identical, independent, or overlapping neural systems? *Proc Natl Acad Sci U S A* 95:831–838, 1998.
76. Hopfinger JP, Buonocore MH, Mangun GR: The neural mechanisms of top-down attentional control. *Nat Neurosci* 3:284–291, 2000.
77. Barcelo F, Knight RT: Both random and perseverative errors underlie WCST deficits in prefrontal patients. *Neuropsychologia* 40:349–356, 2001.
78. Swick D: Effects of prefrontal lesions on lexical processing and repetition priming: An ERP study. *Brain Res Cogn Brain Res* 7:143–157, 1998.
79. Yago E, Knight RT: Tonic and phasic prefrontal modulation of extrastriate processing during visual attention. *Soc Neurosci Abstr* 30:8397, 2000.
80. Suwazono S, Machado L, Knight RT: Predictive value of novel stimuli modifies visual event-related potentials and behavior. *Clin Neurophysiol* 111:29–39, 2000.
81. Verleger R: Event-related potentials and cognition: A critique of the context updating hypothesis and an alternative interpretation of P3. *Behav Brain Sci* 11:343–356, 1988.
82. Heit G, Smith ME, Halgren E: Neuronal activity in the human medial temporal lobe during recognition memory. *Brain* 113:1093–1112, 1990.
83. Schupp HT, Lutzenberger W, Rau H, Birbaumer N: Positive shifts of event-related potentials: A state of cortical disfacilitation as reflected by the startle reflex probe. *Electroencephalogr Clin Neurophysiol* 90:135–144, 1994.
84. Donchin E, Coles MGH: Is the P300 component a manifestation of context updating? *Behav Brain Sci* 11:357–427, 1988.
85. Chao L, Nielsen-Bohlman L, Knight RT: Auditory event-related potentials dissociate early and late memory processes. *Electroencephalogr Clin Neurophysiol* 96:157–168, 1995.
86. Soltani M, Knight RT. The neural origins of P3. *Crit Rev Neurobiol*. In press.
87. Knight RT, Nakada, T: Cortico-limbic circuits and novelty: A review of EEG and blood flow data. *Rev Neurosci* 9:57–70, 1998.
88. Verleger R, Heide W, Butt C, Kompf D: Reduction of P3b potentials in patients with temporo-parietal lesions. *Cogn Brain Res* 2:103–116, 1994.
89. Knight RT, Hillyard SA, Woods DL, et al: The effects of frontal cortex lesions on event-related potentials during auditory selective attention. *Electroencephalogr Clin Neurophysiol* 52:571–582, 1981.
90. Woods DL, Knight RT, Scabini D: Anatomical substrates of auditory selective attention: behavioral and electrophysiological effects of temporal and parietal lesions. *Cogn Brain Res* 1:227–240, 1993.
91. Walter WG, Cooper R, Aldridge V, et al: Contingent negative variation: An electrical sign of sensorimotor association and expectancy in the human brain. *Nature* 203:380–384, 1964.
92. Levy R, Goldman-Rakic PS: Segregation of working memory functions within the dorsolateral prefrontal cortex. *Exp Brain Res* 133:23–32, 2000.
93. McCarthy G, Puce A, Constable RT, et al: Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. *Cereb Cortex* 6:600–611, 1996.
94. Chao LL, Knight RT: Age related prefrontal changes during auditory memory. *Soc Neurosci Abstr* 20:1003, 1994.
95. Rosahl S, Knight RT: Prefrontal cortex contribution to the contingent negative variation. *Cereb Cortex* 5:123–134, 1995.
96. Zappoli R, Versari A, Zappoli F, et al: The effects on auditory neurocognitive evoked responses and contingent negative variation activity of frontal cortex lesions or ablations in man: three new case studies. *Int J Psychophysiol* 38:109–144, 2000.
97. Näätänen R, Gaillard AW, Mäntysalo S: Early selective-attention effect on evoked potential reinterpreted. *Acta Psychol* 42:313–29, 1978.
98. Näätänen R: The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. *Behav Brain Sci* 13:201–288, 1990.
99. Winkler I, Karmos G, Näätänen R: Adaptive modeling of the unattended acoustic environment reflected in the mismatch negativity event-related potential. *Brain Res* 742:239–252, 1996.
100. Schröger E: A neural mechanism for involuntary attention shifts to changes in auditory stimulation. *J Cogn Neurosci* 8:527–539, 1996.
101. Alho K: Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. *Ear Hearing* 16:38–51, 1995.
102. Giard M-H, Perrin F, Pernier J, et al: Brain generators implicated in the processing of auditory stimulus deviance: A topographic event related potential study. *Psychophysiology* 27:627–640, 1990.
103. Deouell LY, Bentin S, Giard M-H: Mismatch negativity in dichotic listening: Evidence for interhemispheric differences and multiple generators. *Psychophysiology* 35:355–365, 1998.
104. Kaiser J, Lutzenberger W, Birbaumer N: Simultaneous bilateral mismatch response to right- but not leftward sound lateralization. *Neuroreport* 11:2889–2892, 2000.

105. Alain C, Woods DL, Knight RT: Distributed cortical network for sensory memory in humans. *Brain Res* 812:23–37, 1998.
106. Courchesne E, Hillyard SA, Galambos R: Stimulus novelty, task relevance, and the visual evoked potential in man. *Electroencephalogr Clin Neurophysiol* 39:131–143, 1975.
107. Yamaguchi S, Knight RT: P300 generation by novel somatosensory stimuli. *Electroencephalogr Clin Neurophysiol* 78:50–55, 1991.
108. Paller KA, McCarthy G, Wood CC: Event-related potentials elicited by deviant endings to melodies. *Psychophysiology* 29:202–206, 1992.
109. Halgren E, Baudena P, Clarke JM, et al: Intracerebral potentials to rare target and distractor auditory and visual stimuli: I. Superior temporal plane and parietal lobe. *Electroencephalogr Clin Neurophysiol* 94:191–220, 1995.
110. Smith ME, Halgren E, Sokolik ME, et al: The intracranial topography of the P3 event-related potential elicited during auditory oddball. *Electroencephalogr Clin Neurophysiol* 76:235–248, 1990.
111. Scabini D, McCarthy G: Hippocampal responses to novel somatosensory stimuli. *Soc Neurosci Abstr* 19: 564, 1993.
112. Halgren E, Marinkovic K, Chauvel P: Generators of the late cognitive potentials in auditory and visual oddball tasks. *Electroencephalogr Clin Neurophysiol* 106:156–164, 1998.
113. Squires N, Squires K, Hillyard SA: Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. *Electroencephalogr Clin Neurophysiol* 38:387–401, 1975.
114. Opitz B, Mecklinger A, Friederici AD, et al: The functional neuroanatomy of novelty processing: integrating ERP and fMRI results. *Cereb Cortex* 9:379–391, 1999.
115. Kiehl KA, Laurens KR, Duty TL, et al: Neural sources involved in auditory target detection and novelty processing: An event-related fMRI study. *Psychophysiology* 38:133–142, 2000.
116. Zeineh MM, Engel SA, Bookheimer SY: Application of cortical unfolding techniques to functional MRI of the human hippocampal region. *Neuroimage* 11:668–683, 2000.
117. Scabini D, Knight RT: Frontal lobe contributions to the human P3a. *Soc Neurosci Abstr* 15:477, 1989.
118. Yamaguchi S, Knight RT: Anterior and posterior association cortex contributions to the somatosensory P300. *J Neurosci* 11:2039–2054, 1991.
119. Scabini D: Contribution of anterior and posterior association cortices to the human P300 cognitive event related potential. PhD dissertation. University of California, Davis: University Microfilms International, 1992.
120. Tranel D, Damasio H: Neuroanatomical correlates of electrodermal skin conductance responses. *Psychophysiology* 31:427–438, 1994.
121. Kimble DP, Bagshaw MH, Pribram KH: The GSR of monkeys during orienting and habituation after selective partial ablations of the cingulate and frontal cortex. *Neuropsychology* 3:121–128, 1965.
122. Knight RT, Grabowecky M: Escape from linear time: Prefrontal cortex and conscious experience, in Gazzaniga M (ed): *The Cognitive Neurosciences.* Cambridge, MA: MIT Press, 1995, pp 1357–1371.
123. Mesulam MM: A cortical network for directed attention and unilateral neglect. *Ann Neurol* 10:309–325, 1981.
124. Friedman HR, Goldman-Rakic PS: Coactivation of prefrontal and inferior parietal cortex in working memory tasks revealed by 2DG functional mapping in the rhesus monkey. *Neuroscience* 14:2775–2788, 1994.
125. Lhermitte F, Turell E, LeBrigand D, et al: Unilateral neglect and wave P300. A study of nine cases with unilateral lesions of the parietal lobes. *Arch Neurol* 42:567–573, 1985.
126. Knight, RT: Contribution of human hippocampal region to novelty detection. *Nature* 383:256–259, 1996.
127. Perani D, Bressi S, Cappa SF, et al: Evidence of multiple memory systems in the human brain: A 18F FDG PET metabolic study. *Brain* 116:903–919, 1993.
128. Goldman-Rakic PS, Selemon LD, Schwartz ML: Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. *Neuroscience* 12:719–743, 1984.
129. Heilman KM, Watson RT, Valenstein E: Neglect and related disorders, in Heilman KM, Valenstein E (eds): *Clinical Neuropsychology,* 3d ed. New York: Oxford University Press, 1993, pp 279–336.
130. Rapcsak SZ, Watson R, Heilman KM: Hemispace-visual field interactions in visual extinction. *J Neurol Neurosurg Psychiatry* 50:1117–1124, 1987.
131. De Renzi E, Gentilini M, Pattacini F: Auditory extinction following hemispheric damage. *Neuropsychologia* 22:733–744, 1984.
132. Heilman KM, Pandya DN, Geschwind N: Trimodal inattention following parietal lobe ablations. *Trans Am Neurol Assoc* 95:259–261, 1970.
133. De Renzi E, Gentilini M, Barbieri C: Auditory neglect. *J Neurol Neurosurg Psychiatry* 52:613–617, 1989.
134. Soroker N, Calamaro N, Glickson J, et al: Auditory inattention in right-hemisphere-damaged patients with and without visual neglect. *Neuropsychologia* 35:249–256, 1997.

135. Gainotti G, De Bonis C, Daniele A, et al: Contralateral and ipsilateral tactile extinction in patients with right and left focal brain lesions. *Int J Neurosci* 45:81–89, 1989.
136. Vallar G, Sandroni P, Rusconi ML, et al: Hemianopia, hemianesthesia, and spatial neglect: a study with evoked potentials. *Neurology* 41:1918–22, 1991.
137. Vallar G, Bottini MD, Sterzi R, et al: Hemianesthesia, sensory neglect, and defective access to conscious experience. *Neurology* 41:650–652, 1991.
138. Viggiano MP, Spinelli D, Mecacci L: Pattern reversal visual evoked potentials in patients with hemineglect syndrome. *Brain Cogn* 27:17–35, 1995.
139. Verleger R, Heide W, Butt C, et al: On-line correlates of right parietal patients' attention deficits. *Electroencephalogr Clin Neurophysiol* 99:444–457, 1996.
140. Näätänen R, Picton TW: The N1 wave of the human electric and magnetic response to sound: A review and an analysis of the component structure. *Psychophysiology* 24: 375–425, 1987.
141. Bisiach E, Cornacchia L, Sterzi R, et al: Disorders of perceived auditory lateralization after lesions of the right hemispheres. *Brain* 107:37–52, 1984.
142. Luck SJ, Heinze HJ, Mangun GR, et al: Visual event related potentials index focused attention within bilateral stimulus arrays: II. Functional dissociation of P1 and N1 components. *Electroencephalogr Clin Neurophysiol* 75:528–542, 1990.
143. Marzi CA, Girelli M, Miniussi C, et al: Electrophysiological correlates of conscious vision: Evidence from unilateral extinction. *J Cog Neurosci*, 12:869–877, 2000.
144. Vuilleumier P, Sagiv N, Hazeltine E, et al: Neural fate of seen and unseen faces in visuospatial neglect: A combined event-related fMRI and ERP study. *Proc Natl Acad Sci U S A* 98:3495–3500, 2001.
145. Driver J, Vuilleumier P, Eimer M, et al: Functional magnetic resonance imaging and evoked potential correlates of conscious and unconscious vision in parietal extinction patients. *Neuroimage* 14:S68–S75, 2001.
146. Lhermitte F, Pillon B, Serdaru M: Human anatomy and the frontal lobes: Part I. Imitation and utilization behavior: A neuropsychological study of 75 patients. *Ann Neurol* 19:326–334, 1986.
147. Driver J, Vuilleumier P: Perceptual awareness and its loss in unilateral neglect and extinction. *Cognition* 79:39–88, 2001.
148. Pitzalis S, Spinelli D, Zoccolotti P: Vertical neglect: Behavioral and electrophysiological data. *Cortex* 33:679–88, 1997.
149. Spinelli D, Burr DC, Morrone MC: Spatial neglect is associated with increased latencies of visual evoked potentials. *Vis Neurosci* 11:909–18, 1994.
150. Spinelli D, Di Russo F: Visual evoked potentials are affected by trunk rotation in neglect patients. *Neuroreport* 7:553–556, 1996.
151. Spinelli D, Angelelli P, De Luca M, et al: VEP in neglect patients have longer latencies for luminance but not for chromatic patterns. *Neuroreport* 7:815–859, 1996.
152. Doricchi F, Angelelli P, De Luca M, et al: Neglect for low luminance contrast stimuli but not for high colour contrast stimuli: A behavioural and electrophysiological case study. *Neuroreport* 31:1360–1364, 1996.
153. Alho K, Sams M, Paavilainen P, et al: Event related potentials reflecting processing of relevant and irrelevant stimuli during selective listening. *Psychophysiology* 26:514–528, 1989.
154. Alho K, Woods DL, Algazi A, et al: Intermodal selective attention: II. Effects of attentional load on processing of auditory and visual stimuli in central space. *Electroencephalogr Clin Neurophysiol* 82:356–368, 1992.
155. Näätänen R: Mismatch negativity outside strong attentional focus: A commentary on Woldorff et al (1991). *Psychophysiology* 28:478–484, 1991.
156. Alho K, Escera C, Diaz R, et al: Effects of involuntary auditory attention on visual task performance and brain activity. *Neuroreport* 8:3233–3237, 1997.
157. Novak G, Ritter W, Vaughan HG Jr: The chronometry of attention-modulated processing and automatic mismatch detection. *Psychophysiology* 29:412–430, 1992.
158. Schröger E: A neural mechanism for involuntary attention shifts to changes in auditory stimulation. *J Cogn Neurosci* 8:527–539, 1996.
159. Aaltonen O, Tuomainen J, Laine M, et al: Cortical differences in tonal versus vowel processing as revealed by an ERP component called mismatch negativity (MMN). *Brain Lang* 44:628–640, 1993.
160. Deacon D, Nousak JM, Pilotti M, et al: Automatic change detection: does the auditory system use representations of individual stimulus features or gestalts? *Psychophysiology* 35:413–419, 1998.
161. Deouell LY, Bentin S: Variable cerebral responses to equally distinct deviance in four auditory dimensions: A mismatch negativity study. *Psychophysiology* 35:745–754, 1998.
162. Schröger E: Processing of auditory deviants with changes in one versus two stimulus dimensions. *Psychophysiology* 32:55–65, 1995.
163. Ritter W, Deacon D, Gomes H, et al: The mismatch negativity of event-related potentials as a probe of transient auditory memory: A review. *Ear Hear* 16:52–57, 1995.

164. Posner MI, Walker JA, Friedrich FJ, et al: Effects of parietal lobe injury on covert orienting of visual attention. *J Neurosci* 4:1863–1874, 1984.
165. Friedrich FJ, Egly R, Rafal RD, et al: Spatial attention deficits in humans: A comparison of superior parietal and temporal-parietal junction lesions. *Neuropsychology* 12:193–207, 1998.
166. Donchin E, Ritter W, McCallum WC: Cognitive psychophysiology: The endogenous components of the ERP, in Callaway E, Tueting P, Koslow SH (eds): *Event-Related Potentials in Man.* New York: Academic Press, 1978, pp 349–442.
167. Watson RT, Miller BD, Heilman KM: Evoked potential in neglect. *Arch Neurol* 34, 224–227, 1977.
168. Neville H, Nicole JL, Barss A, et al: Syntactically based sentence processing classes: Evidence form event related brain potentials, *J Cogn Neurosci* 3:155–170, 1991.
169. Friederici AD, Pfeifer E, Hahne A: Event-related brain potentials during natural speech processing: Effects of semantic, morphological and syntactic violations. *Brain Res Cogn Brain Res* 1:183–192, 1993.
170. Kutas M, Hillyard SA: Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science* 207:203–205, 1980.
171. Osterhout L, Holcomb PJ: Event-related brain potentials elicited by syntactic anomaly. *J Mem Lang* 31:785–806, 1992.
172. Van Petten C, Kutas M: Influences of semantic and syntactic context on open- and closed-class words. *Mem Cognit* 19:95–112, 1991.
173. Bentin S, McCarthy G, Wood CC: Event-related potentials, lexical decision and semantic priming. *Electroencephalogr Clin Neurophysiol* 60:343–355, 1985.
174. van Berkum JJ, Hagoort P, Brown CM: Semantic integration in sentences and discourse: Evidence from the N400. *J Cogn Neurosci* 11:657–671, 1999.
175. Barrett SE, Rugg MD, Perrett DI: Event-related potentials and the matching of familiar and unfamiliar faces. *Neuropsychology* 26:105–117, 1988.
176. Nielsen-Bohlman LC, Knight RT: Rapid memory mechanisms in man. *Neuroreport* 5:1517–1521, 1994.
177. Friedman D: Cognitive event-related potential components during continuous recognition memory for pictures. *Psychophysiology* 27:136–148, 1990.
178. Nigam A, Hoffman JE, Simons RF: N400 to semantically anomalous pictures and words. *J Cogn Neurosci* 4:15–22, 1992.
179. Paller KA, McCarthy G, Roessler E, et al: Potentials evoked in human and monkey medial temporal lobe during auditory and visual oddball paradigms. *Electroencephalogr Clin Neurophysiol* 84:269–279, 1992.
180. Besson M, Macar F: An event-related potential analysis of incongruity in music and other nonlinguistic contexts. *Psychophysiology* 24:14–25, 1987.
181. Deacon D, Hewitt S, Yang C, et al: Event-related potential indices of semantic priming using masked and unmasked words: evidence that the N400 does not reflect a post-lexical process. *Brain Res Cog Brain Res* 9:137–146, 2000.
182. Brown C, Hagoort P: The processing nature of the N400: Evidence from masked priming. *J Cogn Neurosci* 5:34–44, 1993.
183. Nobre AC, McCarthy G: Language-related ERPs: Scalp distributions and modulation by word type and semantic priming. *J Cogn Neurosci* 6:233–255, 1994.
184. Hagoort P, Brown CM, Swaab T: Lexical-semantic event-related potential effects in left hemisphere patients with aphasia and right hemisphere patients without aphasia. *Brain* 119:627–649, 1996.
185. Smith ME, Stapleton JM, Halgren E: Human medial temporal lobe potentials evoked in memory and language tasks. *Electroencephalogr Clin Neurophysiol* 63:145–159, 1986.
186. McCarthy G, Nobre AC, Bentin S, et al: Language-related field potentials in the anterior-medial temporal lobe: I. Intracranial distribution and neural generators. *J Neurosci* 15:1080–1089, 1995.
187. Puce A, Andrewes DG, Berkovic SF, et al: Visual recognition memory: neurophysiological evidence for the role of temporal white matter in man. *Brain* 114:1647–1666, 1991.
188. Berndt RS, Mitchum CC, Haendiges AN: Comprehension of reversible sentences in "agrammatism": A meta-analysis. *Cognition* 58:289–308, 1996.
189. Friederici AD, Hahne A, von Cramon DY: First-pass versus second-pass parsing processes in a Wernicke's and a Broca's aphasic: Electrophysiological evidence for a double dissociation. *Brain Lang* 62:311–341, 1998.
190. ter Keurs M, Brown CM, Hagoort P, et al: Electrophysiological manifestations of open- and closed-class words in patients with Broca's aphasia with agrammatic comprehension. An event-related brain potential study. *Brain* 122:839–854, 1999.
191. Swaab TY, Brown C, Hagoort P: Understanding ambiguous words in sentence contexts: Electrophysiological evidence for delayed contextual selection in Broca's aphasia. *Neuropsychologia* 36:737–761, 1998.
192. Auther LL, Wertz RT, Miller, et al: Relationships among the mismatch negativity (MMN) response, auditory

comprehension and site of lesion in aphasic adults. *Aphasiology* 14:461–470, 2000.
193. Wertz RT, Auther LL, Burch-Sims GP, et al: A comparison of the mismatch negativity (MMN) event-related potential to tone and speech stimuli in normal and aphasic adults. *Aphasiology* 12:499–507, 1998.
194. Connolly JF, D'Arcy RC, Lynn Newman R, et al: The application of cognitive event-related brain potentials (ERPs) in language-impaired individuals: review and case studies. *Int J Psychophysiol* 38:55–70, 2000.
195. Revonsuo A, Laine M: Semantic processing without conscious understanding in a global aphasic: Evidence from auditory event-related brain potentials. *Cortex* 32:29–48, 1996.
196. Merton PA, Morton HB: Stimulation of the cerebral cortex in the intact human subject. *Nature* 285:227, 1980.
197. Barker AT, Jalinous R, Freeston IL: Noninvasive magnetic stimulation of human motor cortex. *Lancet* 1:1106–1107, 1985.
198. Hallett M: Transcranial magnetic stimulation and the human brain. *Nature* 406:147–150, 2000.
199. Walsh V, Cowey A: Transcranial magnetic stimulation and cognitive neuroscience. *Nat Rev Neurosci* 1:73–79, 2000.
200. Gerloff C, Corwell B, Chen R, et al: Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. *Brain* 120:1587–1602, 1997.
201. Loo C, Mitchell P, Sachdev P, et al: Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *Am J Psychiatry* 156:946–948, 1999.
202. Menkes DL, Bodnar P, Ballesteros RA, et al: Right frontal lobe slow frequency repetitive transcranial magnetic stimulation (SF r-TMS) is an effective treatment for depression: a case-control pilot study of safety and efficacy. *J Neurol Neurosurg Psychiatry* 67:113–115, 1999.
203. Amassian VE, Cracco RQ, Maccabee PJ, et al: Suppression of visual perception by magnetic coil stimulation of human occipital cortex. *Electroencephalogr Clin Neurophysiol* 74:458–462, 1989.
204. Kastner S, Demmer I, Ziemann U: Transient visual field defects induced by transcranial magnetic stimulation over human occipital pole. *Exp Brain Res* 118:19–26, 1998.
205. Corthout E, Uttl B, Ziemann U, et al: Two periods of processing in the (circum)striate visual cortex as revealed by transcranial magnetic stimulation. *Neuropsychologia* 37:137–145, 1999.
206. Beckers G, Zeki S: The consequences of inactivating areas V1 and V5 on visual motion perception. *Brain* 118:49–60, 1995.
207. Pascual-Leone A, Walsh V: Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science* 292:510–512, 2001.
208. Kosslyn SM, Pascual-Leone A, Felician O, et al: The role of area 17 in visual imagery: Convergent evidence from PET and rTMS. *Science* 284:167–170, 1999.
209. Pascual-Leone A, Tormos JM, Keenan J, et al: Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol* 15:333–343, 1998.
210. Zangaladze A, Epstein CM, Grafton ST, et al: Involvement of visual cortex in tactile discrimination of orientation. *Nature* 401:587–590, 1999.
211. Cohen LG, Celnik P, Pascual-Leone A, et al: Functional relevance of cross-modal plasticity in blind humans. *Nature* 389:180–183, 1997.
212. Deibert E, Kraut M, Kremen S, et al: Neural pathways in tactile object recognition. *Neurology* 52:1413–1417, 1999.
213. Sathian K, Zangaladze A, Hoffman JM, et al: Feeling with the mind's eye. *Neuroreport* 8:3877–3881, 1997.
214. Pourtois G, Vandermeeren Y, Olivier E, et al: Event-related TMS over the right posterior parietal cortex induces ipsilateral visuo-spatial interference. *Neuroreport* 12:2369–2374, 2001.
215. Fierro B, Brighina F, Piazza A, et al: Timing of right parietal and frontal cortex activity in visuo-spatial perception: a TMS study in normal individuals. *Neuroreport* 12:2605–2607, 2001.
216. Wasserman EM: Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalogr Clin Neurophysiol* 108:1–16, 1998.