Chapter 4

# Localizing the Neural Generators of Event-Related Brain Potentials

Diane Swick, Marta Kutas, and Helen J. Neville

## I. INTRODUCTION

A major approach to neural localization has been inferring the location of cognitive operations within "normal" brains from the behavioral deficits and brain damage observed in neurological patient populations (Caramazza, 1992; Kosslyn & Intriligator, 1992). Years of research attest to the difficulty of this enterprise and underscore the need for converging evidence from multiple techniques. This chapter focuses specifically on describing how recordings of the electrical activity of the brain (in particular, transient responses to various events) in patients and in control subjects can enrich our understanding of neuropsychological issues. Although the imaging methods currently available for investigating neural and psychological function in awake humans have improved markedly over the last decade, the nature of the inferences that can be drawn is constrained by the limits inherent in each technique. Generally, the trade off is between precision in space and time. At present, no technique provides both very high spatial and very high temporal resolution; however, within 5-10 years we are likely to have developed a technique that does.

The measurement of brain electrical activity from the scalp is noninvasive, has very high temporal resolution (on the order of tenths of milliseconds), and can provide an on-line record of brain function at the level of large neuronal populations. The electroencephalogram (EEG) consists of continuous voltage fluctuations caused by the summation of graded postsynaptic potentials from thousands of neurons and has long been used by clinicians to monitor behavioral state. (For discussions of neuronal electrogenesis, see Freeman, 1975; Nunez, 1981; Wood & Allison..1981; for clinical use of the EEG, see Niedermeyer & Lopes da Silva, 1987.) In contrast to its fine temporal resolution, the spatial resolution of scalp-recorded electrical

activity is relatively poor. However, recently implemented techniques (discussed subsequently) have improved localization accuracy and have increased our knowledge of the underlying physiological mechanisms and anatomical substrates.

Event-related potentials (ERPs) are brain potentials that are time-locked to the occurrence of sensory, motor, or cognitive events and extracted from the ongoing EEG by signal averaging techniques (Fig. 1; see Coles, Gratton, Kramer, & Miller, 1986; Hillyard & Kutas, 1983; Hillyard & Picton, 1987, for reviews). The resultant waveform consists of a series of overlapping peaks and troughs that have been separated into relatively distinct components on the basis of polarity, latency, scalp distribution, and experimental manipulation. Although labeled peaks offer a convenient shorthand, it is important to note that component effects need not

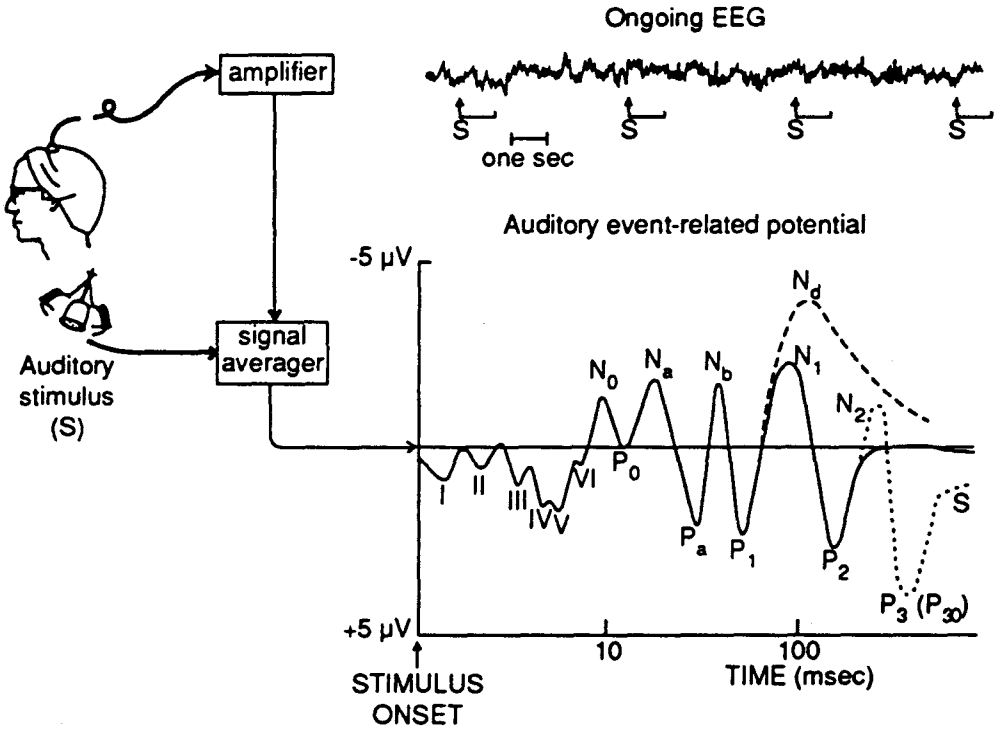


**Figure 1** Idealized waveform of the computer-averaged auditory event-related potential (ERP) to a brief sound. The ERP is generally too small to be detected in the ongoing EEG *(top)* and requires computer averaging over many stimulus presentations to achieve adequate signal-.noise ratios. The logarithmic time display allows visualization of the early brainstem responses (Waves I-IV), the midlatency components ($N_o$, $P_o$, $N_a$, $P_a$, $N_b$), the "vertex potential" waves ($P_1$, $N_1$, $P_2$), and task-related endogenous components ($N_d$ , $N_2$, P300, and slow wave). Reproduced with permission from Hillyard & Kutas (1983).

map directly onto peaks and troughs, especially if the component is defined in terms of experimental manipulation. A direct mapping is most evident in the case of short latency "exogenous" components, which are primarily responsive to the physical parameters of the evoking stimulus (although attention effects have been noted as early as 20 msec[1]). In contrast, longer latency "endogenous" components, which are most sensitive to the psychological variables surrounding an event, often span multiple peaks and troughs. ERPs can provide a useful index of the timing of covert sensory, cognitive, and linguistic processing in humans to complement the traditional behavioral measures of cognitive psychology. By also providing a measure of the activity of neuronal ensembles, ERPs can help narrow the huge conceptual gap between psychological theories and cellular neurophysiology.

One of the most intensely investigated endogenous ERP components is the P300 or P3, a positive potential that is maximal at centro-parietal scalp sites, peaking 300-600 msec after infrequent target stimuli that are detected within a repetitive series of background events (the "oddball" paradigm; see Squires, Squires, & Hillyard, 1975). This P300, or P3b, can be elicited by stimuli of different modalities (Snyder, Hillyard, & Galambos, 1980) and even by missing or omitted stimuli (Simson, Vaughan, & Ritter, 1976). Its amplitude is responsive to stimulus probability (Fig. 2),

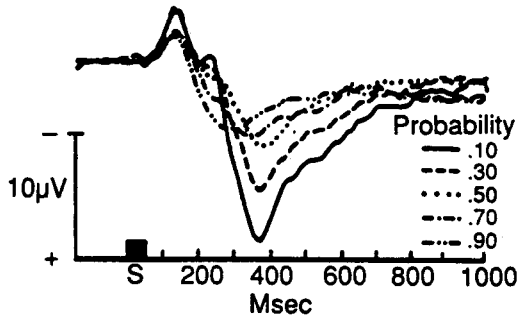


**Figure 2** Grand-mean waveforms from Pz for auditory stimuli in an oddball paradigm under RT instructions at five levels of a priori probability. In this and subsequent figures, negative voltages are plotted as upward deflections. Stimulus presentation is indicated by the filled rectangle on the time scale. Reproduced with permission from Johnson (1986).

[1]In a dichotic listening experiment, Woldorff and Hillyard (1991) demonstrated that an early auditory component peaking just after the Pa wave, the P20-50, was enhanced when subjects attended to rapidly presented tones in one ear relative to when the same tones were ignored. However, another laboratory (Woods & Alain, 1993) has failed to replicate this finding.

subjective probability, temporal probability, stimulus meaning, and task relevance (see Donchin & Coles, 1988; Fabiani, Gratton, Karis, & Donchin, 1987; Johnson, 1988a; Pritchard, 1981, for reviews). The cognitive processes associated with P300 have been described by a number of psychological constructs including context updating, information delivery, stimulus categorization, and cognitive closure, although no consensus has been reached (for discussion, see Donchin & Coles, 1988; Verleger, 1988). In part, this disagreement may reflect the fact that there exists a family of late positivities with similar, albeit not identical, characteristics. For example, the P3a subcomponent, largest at fronto-central sites, is elicited by rare task-irrelevant stimuli and has been associated with orienting, arousal, and response to novelty (Courchesne, Hillyard, & Galambos, 1975; Ritter, Vaughan, & Costa, 1968; Squires et al., 1975). Finally, late positivities have been obtained under conditions other than those of the oddball task, including signal detection paradigms (Paul & Sutton, 1972) and the repetition of words in lists, sentences, and text (Besson, Kutas, & Van Petten, 1992; Rugg & Nagy, 1989; Van Petten, Kutas, Kluender, Mitchiner, & McIsaac, 1991). Whether all these positive components can be considered P300s per se is an unresolved question.

The context-updating hypothesis (Donchin, 1981; Donchin & Coles, 1988) is currently one of the most prevalent explanations for P3b and suggests that surprising or unexpected events interrupt ongoing cognitive processing and cause the subject to revise the current model of the environment. The relationship between late positive potentials and memory has been demonstrated in incidental learning paradigms. Words that were later remembered by the subjects elicited larger late positivities than words that were not remembered (Fabiani, Karis, & Donchin, 1986; Neville, Kutas, Chesney, & Schmidt, 1986; Paller, Kutas, & Mayes, 1987). Some groups have proposed a relationship between P300 and subsequent recall/recognition of words (Fabiani et al., 1986; Karis, Fabiani, & Donchin, 1984); whereas others have suggested that, although a memory-related positivity exists, it can be distinguished from P300 on the basis of its scalp distribution (Paller et al., 1987). Localizing the neural substrates of P300 and other ERPs (such as Nd, MMN, and N400) would clarify the distinctions between related subcomponents and would contribute to a better understanding of which brain regions are performing various information processing functions.

In principle, the problem of locating the generator(s) of scalp-recorded electrical activity from that activity alone is insoluble, since there is no axiomatic method for choosing among the many possible solutions that account for equal amounts of the variance (Balish & Muratore, 1990; van Oosteram, 1991; Wong, 1991; Wood, 1982). Unless additional constraints

are applied, the "inverse problem" (i.e., obtaining the number and configuration of sources from the scalp potential field) has an infinite number of solutions. Hence, researchers have attempted to winnow the list of candidate sources for various ERP components by adding further restrictions to the localization problem (e.g., Vaughan, 1982). Among the various approaches used to localize ERP components are (1) developing animal models of a component that then can be evaluated using invasive techniques (lesioning, pharmacological intervention, intracranial recording); (2) analyzing recordings from various patient populations with naturally occurring lesions (strokes), surgical removals of brain tissue, or intracranial electrodes implanted for clinical purposes; (3) combining electrical with magnetic recording; (4) topographically mapping gradients of current, as in current source density analyses; and (5) dipole modeling methods such as brain electric source analysis. The remainder of this chapter provides illustrations of how these procedures have been employed in the localization of various ERP components. P300 is emphasized as a case study because it has been investigated for a longer period of time than most other cognitive components and therefore exemplifies the different approaches to localization. Additional components will be reviewed briefly as they arise in the text.

## II. ANIMAL MODELS

Animal models have illuminated a range of issues relevant to the localization of ERPs by utilizing the techniques of lesioning, pharmacology, and intracranial recording (Galambos & Hillyard, 1981). One limitation of animal models is the difficulty of proving the equivalence of an ERP component across species. Similarities in the anatomical, physiological, and behavioral correlates of the component must be demonstrated. The assumption of phylogenetic continuity is problematic, particularly when comparing ERP recordings from species such as the rat with those from humans. Differences in brain organization due to, for example, the rat's greater reliance on olfactory and tactile cues and the expanded number of visual cortical areas in humans raise questions of homology. Moreover, animal models cannot reveal information about the generators of the several ERP components that have been hypothesized to reflect syntactic processing and other linguistic dimensions that are not applicable to animal communication (Kluender, 1991; Neville, Nicol, Barss, Forster, & Garrett, 1991; Osterhout & Holcomb, 1993).

Animal models of P300-like activity have been developed in rats, cats, rabbits, and monkeys to examine possible neural substrates more

systematically (Arthur & Starr, 1984; Buchwald & Squires, 1982; Ehlers, Wall, & Chapin, 1991; Gabriel, Sparenborg, & Donchin, 1983; Glover, Ghilardi, Bodis-Wollner, Onofrj, & Mylin, 1991; Glover, Onofrj, Ghilardin, & Bodis-Wollner, 1986; Paller, Zola-Morgan, Squire, & Hillyard, 1988; Pineda, Foote, & Neville, 1987; Pineda, Foote, Neville, & Holmes, 1988; Wilder, Farley, & Staff, 1981). Some of these studies, however, have used paradigms that bear little resemblance to paradigms used to elicit P300 in humans. For example, Wilder et al. (1981) demonstrated late positive potentials sensitive to stimulus probability and signal meaning in cats, but the subjects were paralyzed, artificially respired, and exposed to an aversive conditioning paradigm. On the other hand, awake cats exposed to an auditory oddball paradigm showed a P300-like potential in response to rare loud clicks or to omitted stimuli (Buchwald & Squires, 1982). This "cat P300" has a smaller amplitude and longer latency in old cats, similar to the P300 changes seen in aged human subjects (Harrison & Buchwald, 1985).

Neville and Foote (1984) recorded a broad positive complex in squirrel monkeys that began ~300 msec after infrequent tones and decreased in amplitude with repeated presentations. This component was largest over frontal and temporal electrodes of the left hemisphere. In a second block of trials, an occasional "dog bark" also elicited a large P300-like component that was largest parietally and at lateral temporal electrodes. Pineda and associates (1987) further demonstrated that monkey P300 was sensitive to stimulus probability and trial-to-trial changes in stimulus sequence and largest over lateral parietal sites. A subsequent experiment examined the role of task relevance and behavioral response in a group of squirrel monkeys trained to press a lever after target tones were presented in an oddball paradigm (Pineda et al., 1988). A long-latency positive component (LPC), also inversely related to stimulus probability, was elicited by the targets (Fig. 3). This LPC showed a broader scalp distribution and had a greater amplitude when response rates were high. Arthur and Star (1984) also reported a P300-like component in macaque monkeys trained to release a lever within 600 msec of target tone offset. This potential, maximal over sensorimotor and parietal cortices and negligible over frontal and temporal areas, was not present when the lever was removed in the no-task condition.

Glover et al. (1991) recorded ERPs from monkeys who were being trained on a visual oddball task. Target probability was 0.5 in early sessions; the monkeys correctly discriminated on 55-60% of the trials. The ERP responses to targets and standards were not different at this stage of training but, as the monkeys improved their performance to 75-80%, a P300-like potential emerged over the following 2-4 wk. As the monkeys

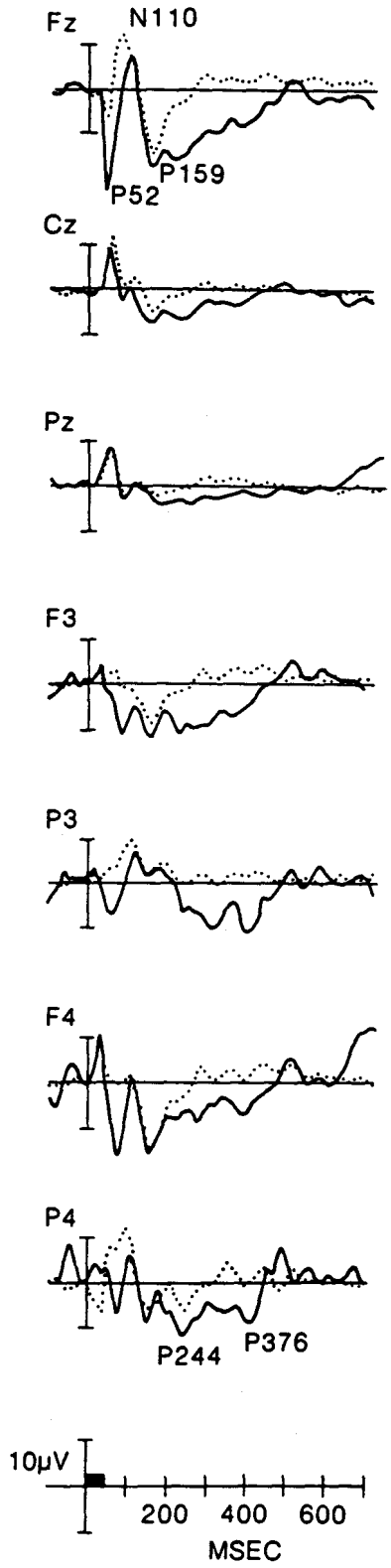


**Figure 3** Grand average (across all monkeys) ERPs in the 90-10 oddball paradigm at all electrode sites in response to target (--------) and background (••••••••) tones. Black rectangle on the time scale represents the onset and duration of tone stimuli. Note the enhanced positivity occurring in the 200-600 msec latency interval following target presentations. Reproduced with permission from Pineda, Foote, Neville, & Holmes (1988).

continued to show behavioral progress, the amplitude of the P300-like component increased and its latency decreased. P300 amplitude also increased when target probability was decreased to 0.3.

Hence, there are several instances in nonhuman animals of P300-like activity that behaves like the human component in response to manipulations of probability, task relevance, and so on. A reasonable premise, therefore, is that these examples are valid animal models of P300, and that hypotheses about its loci can be tested by lesioning, pharmacological manipulation, and intracranial recording.

### A. Lesions

One test of the postulated relationship between memory and P3a/P3b is damaging the brain regions involved in memory function in monkeys. Paller and colleagues (1988) presented both improbable pure tones and rare complex tones to untrained and trained macaques. Bilateral ablations of the medial temporal lobe (MTL) which included hippocampus, amygdala, and adjacent cortical areas did not abolish either passive (Fig. 4) or active P300-like waves. These results coincide with findings in human temporal lobectomy patients (reviewed subsequently) and suggest that MTL structures are not essential in generating P300 (at least P300 recorded at midline electrode sites).

Lesions of other brain regions have been performed in the cat model. Bilateral ablations of primary auditory cortex (Harrison, Buchwald, & Kaga, 1986) or polysensory association cortex (Harrison, Dickerson, Song, & Buchwald, 1990) did not significantly reduce the amplitude of the epidurally recorded cat P300. The association cortex lesions-which included either pericruciate cortex, anterior lateral and medial suprasylvian gyri, or all three areas-substantially diminished two earlier components: a 30- to 35-msec negativity (wave $N_A$) and a 50- to 75-msec positivity (wave C). Although polarity-reversing potentials have been recorded from these regions at latencies of 200-300 msec, they are apparently unnecessary for the generation of vertex P300-like potentials in the cat.

Another line of work has examined how neurotransmitter systems might modulate the neuronal activity that generates ERPs, particularly cortical slow potentials (reviewed by Marczynski, 1978; Pineda, Swick, & Foote, 1991). Cell groups containing norepinephrine, acetylcholine, dopamine, and serotonin comprise four major subcortical transmitter systems that modulate neocortical function and behavioral state (Foote & Morrison, 1987). These extrathalamic nuclei innervate widespread areas of primate neocortex with regional and laminar specificities. Their neurons have slow spontaneous firing rates, their action potentials can take tens or

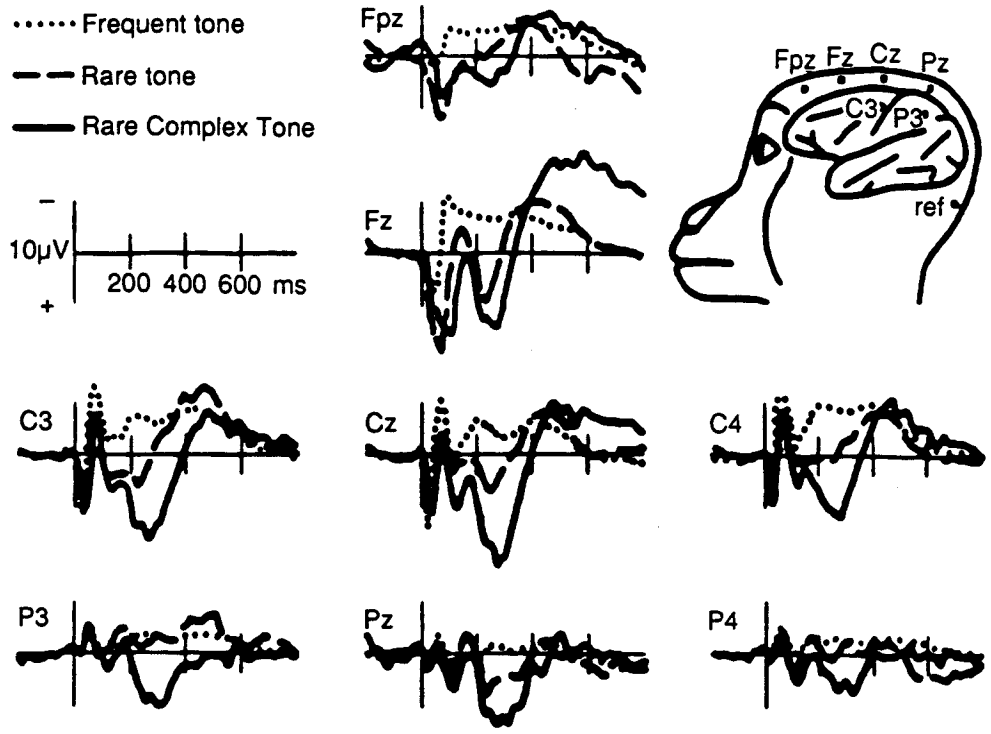


**Figure 4** Event-related brain potentials elicited during the passive condition from a group of five monkeys with bilateral medial temporal lobectomies. Ref, Reference electrode. Reproduced with permission from Paller, Zola-Morgan, Squire, & Hillyard (1988).

even hundreds of milliseconds to reach target areas, and their neurotransmitters have long-duration effects on postsynaptic target cells. Halgren and Smith (1987) suggest that the EEG is largely dominated by the effects of these systems; some ERP components might not be "generated by the synapses active in specifically processing the stimulus, but rather are generated by a diffuse synaptic network that modulates the specific information processing" (p.131).

In fact, evidence exists for specific modulation of various ERP components following disruption of neurotransmitter function by lesions or neuropharmacological interventions. Bilateral lesions of the medial septal nucleus and the vertical limb of the diagonal band, the major cholinergic projections to hippocampus, resulted in a transient increase followed by a progressive decrease and disappearance of P300-like activity in cats (Harrison, Buchwald, Kaga, Woolf, & Butcher, 1988). Lesions of the noradrenergic (NA) nucleus locus coeruleus (LC) in squirrel monkeys produced a significant reduction of P300-like potentials recorded in a passive auditory

oddball paradigm (Pineda, Foote, & Neville, 1989). Extensive damage to cell bodies in the nucleus and knife cuts disrupting ascending axons in the dorsal bundle (DB) were both necessary since DB damage alone produced no changes. There was a significant correlation between the size of lesion and percent reduction in P300 area.

### B. Pharmacology

In addition to eliminating the intended neurons, electrolytic lesions can damage areas along the microelectrode track, fibers of passage, and areas adjacent to the nucleus. Pharmacological manipulations have the advantage of being reversible and more selective for a particular transmitter system. The alpha-2 adrenergic agonist clonidine, for example, suppresses LC unit activity by binding to autoreceptors on these neurons (Cedarbaum & Aghajanian, 1977). A preliminary study in squirrel monkeys demonstrated that systemic administration of clonidine produced dose-related decreases in the area of P300-like potentials, with recovery to control levels in post-drug sessions (Swick, Pineda, Holmes, & Foote, 1988). The highest dose was the most effective in reducing P300-like waves and was chosen for a subsequent investigation with a larger number of subjects (Swick, Pineda, & Foote, 1993). In this experiment, clonidine specifically increased the latency and decreased the area of a P300-like potential elicited in response to rare tones (Fig. 5).

In contrast to these alterations in the auditory modality, the same dose of clonidine did not affect the latency, amplitude, or area of a visual P300-like potential in squirrel monkeys (Pineda & Swick, 1992). This finding suggests that the LC-NA system makes a modality-dependent contribution to the generation of P300-like potentials. Variations in the distribution of NA fibers across different neocortical regions may result in distinct influences on the processing of signals from different sensory modalities. Lesion data from human patients suggests that P300 has modality-specific generators (Johnson, 1989a; Knight, Scabini, Woods, & Clayworth, 1989; see subsequent discussion). Differential NA innervation patterns could contribute to such effects.

The neurotoxin 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), which produces parkinsonian symptoms by depleting dopamine and norepinephrine, initially abolished P300-like potentials in a group of 5 monkeys (Glover, Ghilardi, Bodis-Wollner, & Onofrj, 1988). Acute administration of a dopamine precursor did not restore P300, although tremor and rigidity were improved temporarily. P300 returned 30-40 days later in 2 monkeys that showed partial behavioral recovery. Whereas dopamine systems remain chronically suppressed after MPTP treatment,

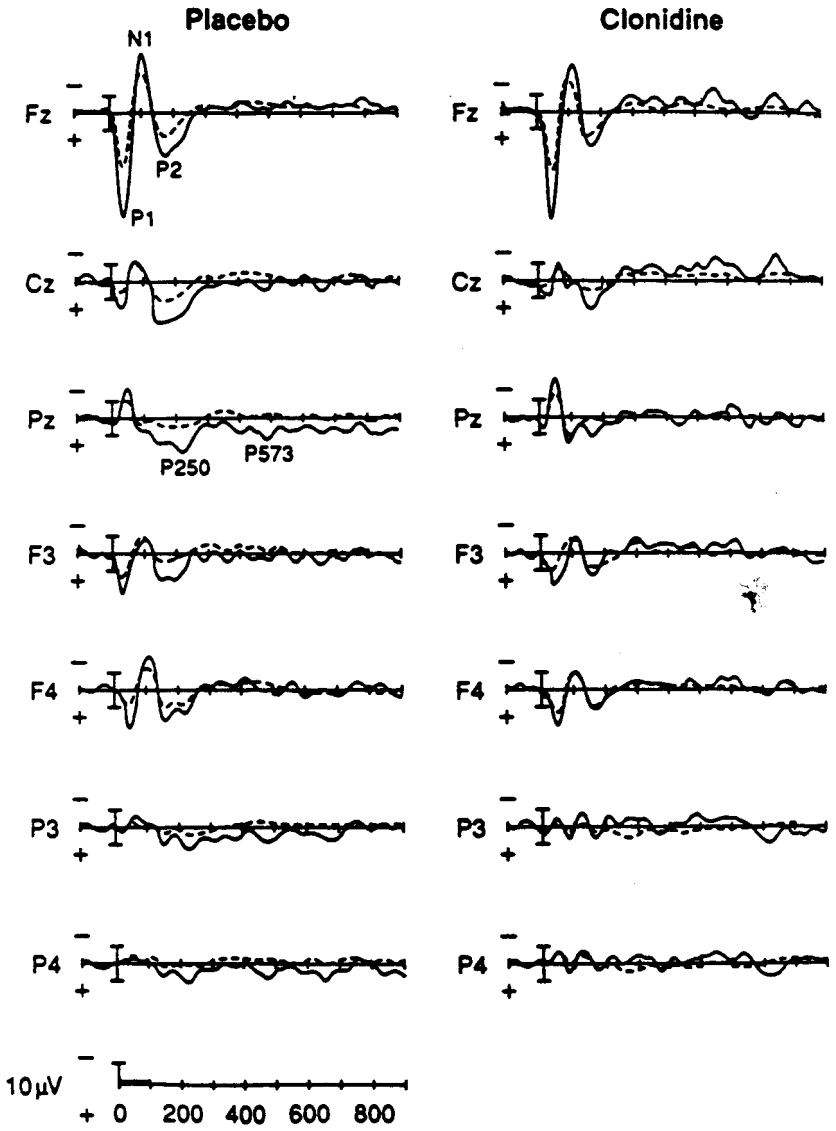


**Figure 5** (*Left*) Grand average ERPs across 6 squirrel monkeys following placebo administration. ERPs were recorded in response to background (dashed lines) and target (solid lines) tones presented in the 90-10 oddball paradigm. (*Right*) Grand average ERPs for the same 6 monkeys following administration of clonidine (0.1 mg/kg IM). ERPs were recorded 15 min post-drug; placebo and drug sessions were separated by at least 3 weeks. Note the dramatic decrease in the magnitude of P250 and P573, whereas the earlier potentials are unchanged. Reproduced with permission from Swick, Pineda, & Foote (1993).

norepinephrine (NE) systems recover, perhaps accounting for the return of P300 in some animals. Partial depletions of dopamine and serotonin in rats did not affect a late positive potential recorded from dorsal hippocampus and amygdala (Ehlers et al., 1991), but these lesions may not have been substantial enough to produce alterations. Ethanol, which may produce some of its effects through endogenous opioid systems and the benzodiazepine/gamma-aminobutyricacid (GABA) receptor complex, significantly decreased NI and P3 amplitudes in squirrel monkeys (Ehlers, 1988). Diazepam, which enhances activity of the GABA., receptor with no known actions on opioid systems, reduced only N1 amplitude (Ehlers, 1988). Utilizing the same passive auditory oddball paradigm, the opiate antagonist naloxone was found to decrease P300 latency in squirrel monkeys (Ehlers, 1989).

Neurons in the nucleus basalis of Meynert (NBM) comprise the major cholinergic projection to amygdala and neocortex in primates (Mesulam, Mufson, Levey, & Wainer, 1983). Pirch, Corbus, Rigdon, and Lyness (1986) demonstrated that NBM lesions, pharmacological depression of NBM neurons, and blockade of muscarinic cholinergic receptors in cortex reduce the low frequency negative potentials recorded from rat frontal cortex during an associative conditioning paradigm. These potentials were elicited by a 2-sec light cue that preceded rewarding stimulation of the medial forebrain bundle. This general type of paradigm, in which a warning stimulus (S1) precedes an imperative stimulus (S2) that requires a motor response, elicits the "contingent negative variation" (CNV), slow negative potentials that are largest over frontal-central sites, during the interval between S1 and S2 (Borda, 1970; Rohrbaugh, Syndulko, & Lindsey, 1976; Walter, Cooper, Aldridge, McCallum, & Winter, 1964).

A summary of drug effects on P300 and other potentials is presented in Table 1. These studies suggest that neurotransmitter systems, particularly the monoaminergic and cholinergic systems, are critical in modulating the synaptic events that give rise to ERP components. For instance, these systems alter the signal-to-noise processing characteristics of postsynaptic neurons, either enhancing or diminishing a cell's response to other inputs. Additionally, these systems are capable of providing a synchronizing input to anatomically distinct generators, the activity of which sums to produce an ERP component that is recorded as a single entity from the scalp.

### C. Intracranial Recordings

A major advantage of recording within the brain rather than from the scalp or even the brain surface is, of course, the ability to get closer to the neural sources generating ERPs. Field potentials and single or multi-unit

activity can be recorded from the same electrode in some cases. Additionally, it is possible to observe inversions of polarity, which are considered signs of local generation of the component in question. The majority of intracranial recordings has focused on somatosensory, auditory, and visual evoked potential responses. Locating the generators of these potentials, particularly those in brainstem and thalamic relay centers, is of clinical interest and can assist in diagnosing patients with sensory deficits.

Arezzo and co-workers (Arezzo, Legatt, & Vaughan, 1979; Arezzo et al., 1981) mapped the surface and depth components of the somatosensory evoked potential (SEP) in rhesus monkeys exposed to median nerve stimulation. Field potentials and multi-unit activity were recorded from the same intracranial electrodes. The earliest surface waves were thought to reflect activity of primary somatosensory neurons ascending in the dorsal columns, the summation of synchronized action potentials traveling along the medial lemniscus to the thalamus, and the thalamocortical radiations. The first cortical components recorded at precentral surface sites were the P10-N20 complex, analogous to the human P20-N30 which inverts across the central sulcus. The simian P10-N20 was generated in the posterior bank of the central sulcus, inverting in polarity across the deep layers of areas 3a and 3b of primary somatosensory cortex. The P12-N25 complex, recorded at surface sites posterior to the central sulcus and analogous to the human P25-N35, displayed a transcortical polarity inversion within areas 1 and 2. The monkey P20 was generated in area 5 and is probably analogous to a human peak recorded at 45-50 msec over parietal areas contralateral to stimulation. The monkey P40 had a bilateral source in area 7b and may be comparable to the human P80.

Similarly, the sources of auditory evoked potentials (AEPs) were mapped with depth recordings in monkeys (Arezzo, Pickoff, & Vaughan, 1975). The earliest cortical waves, P12 and P22, were generated in the posteromedial region of the supratemporal plane (STP) within primary auditory cortex. The sources of N38, N60, and N100 were more anterior in the STP, whereas P73 and N140 were generated in a broader posterior region of the STP Some potentials also showed polarity inversions in motor cortex, summating with STP potentials to produce the surface-recorded peaks.

More recently, a few researchers have searched for the intracranial correlates of long-latency surface-recorded ERPs such as P300. Depth recordings in cats demonstrated polarity-reversing potentials in the marginal and suprasylvian gyri and hippocampus at 200-350 msec in response to a rare stimulus (O'Connor & Starr, 1985). Other investigators have found polarity-reversing potentials at 200-500 msec in the medial septal area, hippocampus (primarily the pyramidal cell layer), entorhinal cortex, and amygdala but not in auditory cortex (Harrison & Buchwald, 1987; Kaga,

**Table 1** Summary of the Effects of Pharmacological Manipulations on P300 Potentials and Other Selected Components in Animals and Humans[a]

| Drug | Actions | Species | Effects on P300h | Reference |
|---|---|---|---|---|
| Clon | Suppresses LC firing and NE release | Squirrel monkey | aud: eliminated in passive and active oddball<br>vis: no effect in passive oddball | Swick et al. (1988,1993)<br>Pineda & Swick (1992) |
| | | Human | aud: reduced in oddball task | Duncan & Kaye (1987); Joseph & Sitaram (1989) |
| MP | Increases release and blocks reuptake of CA | Human | vis: no effect on latency in detection task (amplitude not reported); RT decreased | Naylor et al. (1985) |
| Amph | Increases release and blocks reuptake of CA | Human | vis: no effect on latency in detection task (amplitude not reported); RT decreased | Halliday et al. (1987) |
| Coke | Blocks reuptake of CA | Human | aud: reduced amplitude in oddball task, N1 and P2 amplitude reduced<br>aud target detection following cue: no effect on amplitude or latency to target, enhanced N1 and CNV amplitude to cue | Herning et al. (1985)<br>Herning, Hooker, & Jones (1987) |
| MPTP | Depletes DA, NE | Macaque monkey | aud classical conditioning: initially abolished, returned 30-40 days later | Glover et al. (1988) |
| 6-OHDA in VTA | Depletes DA | Rat | aud: no effect in passive oddball (depth potential in dorsal hippocampus & amygdala) | Ehlers et al. (1991) |
| PCPA | Depletes 5-HT | Rat | aud: no effect in passive oddball (depth potential in dorsal hippocampus and amygdala) | Ehlers et al. (1991) |
| Mths | 5-HT antagonist | Human | aud: no effect on latency or amplitude in oddball task | Meador et al. (1989) |

*continues*

**Table 1** (*Continued*)

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|---|---|---|---|---|
| Scop | Cholinergic antagonist | Human | aud: increases latency and decreases amplitude in oddball task; reversed by Phys, an ACNE inhibitor | Hammond et al. (1987); Meador et al. (1987) |
| | | | Altered hippocampal P3s: increases amplitude in epileptic hemisphere, increases latency in normal hemisphere | Meador et al. (1988) |
| | | | vis: increases latency and RT in detection task (amplitude not reported) | Callaway et al. (1985) |
| Atrp | Cholinergic antagonist | Rat | Reduced CNV recorded from frontal cortex | Pirch et al. (1986) |
| Etoh | Possibly at BDZ/ GABA, opioid, other sites | Squirrel monkey | aud: reduced in passive oddball, N1 amplitude also reduced | Ehlers (1988) |
| DZP | Enhances activity of $GABA_A$ receptor | Squirrel monkey | aud: no effect in passive oddball, but N1 amplitude reduced | Ehlers (1988) |
| Nalox | opiate antagonist | Squirrel monkey | aud: decreases latency in passive oddball | Ehlers (1989) |
| | | Human | selective listening: increases Nd amplitude in selective attention but not in single channel or divided attention conditions | Amsten et al. (1984) |

[a]Abbreviations: AChE, acetylcholinesterase; Amph, amphetamine; Atrp, atropine; BDZ, benzodiazepine; CA, catecholamine; Clon, clonidine; Coke, cocaine; DA, dopamine; DZP, diazepam; Etoh, ethanol; 5-HT, 5-hydroxytryptamine (serotonin); GABA, y-aminobutyric acid; LC, locus coeruleus; MP, methylphenidate; MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; Mths, methysergide; Nalox, naloxone; NE, norepinephrine; PCPA, parachlorophenylalanine; Phys, physostigmine; Scop, scopolamine; 6-OHDA, 6-hydroxydopamine; VTA, ventral tegmental area.

[b]aud, auditory; vis, visual; RT, reaction time; CNV, contingent negative variation.

Harrison, Butcher, Woolf, & Buchwald, 1992). Rabbits previously trained in a discriminative avoidance task showed large positive potentials in cingulate cortex and anterior thalamus 150-300 msec after the infrequent CS+ (conditioned stimulus) (Gabriel et al., 1983). No polarity inversions were reported.

Negative potentials with 210-msec latency (50 msec later than a positive-going epidural potential recorded in response to rare tones[2]) were recorded in medial MTL structures of two macaque monkeys during a passive auditory oddball paradigm (Paller, McCarthy, Roessler, Allison, & Wood, 1992). A steep potential gradient was located in the hippocampal region. In a visual oddball task, negative MTL potentials that followed correct responses peaked 50-100 msec after an epidural positivity at about 250 msec. Recordings from human patients were similar in that negative potentials in the MTL peaked 50-100 msec later than scalp P300s (see also Halgren et al., 1980; McCarthy, Wood, Williamson, & Spencer, 1989). No polarity reversals were noted in either paradigm. The depth electrodes, located medial to the hippocampus in most cases, had 8 contacts spaced 1 mm apart (from thalamus dorsally to subiculum and entorhinal cortex ventrally). However, a transcortical polarity inversion was observed in the posterior parietal cortex following exposure to visual targets.

Another strategy has been to record from single cells in regions hypothesized to generate or modulate a component. Since one hypothesized function of the LC-NA system is a role in the control of attention, arousal, and response to novel events (Aston-Jones, Chiang, & Alexinski, 1991; Foote, Berridge, Adams, & Pineda, 1991), this system might also modulate P300 activity by providing a synchronizing input to the generators, thereby producing signal-to-noise enhancements in the neuronal ensembles that generate these potentials. An initial attempt to record LC unit activity in monkeys exposed to a passive auditory oddball paradigm failed to find evoked responses following presentation of either oddball or frequent stimuli (Grand, Aston-Jones, & Redmond, 1988). Louder, more alerting tones, all of the same frequency, did produce a phasic enhancement of firing. The work of Aston-Jones and colleagues (1991) suggested that tentatively identified LC cells respond more vigorously to a rare visual stimulus than to a highly probable one. Macaques were trained to discriminate two colors in a visual oddball paradigm. Cell firing was significantly higher in response to the targets. When the color of the infrequent stimulus was switched, the cells also showed a reversal in firing patterns. Although LC cells respond to alerting stimuli of all modalities,

[2]The epidural peak at 160 msec is probably too early to be a P300 analog; a smaller positivity between 200 and 300 msec is a more likely candidate.

some differences between modalities and between active and passive paradigms may exist.

Another group recorded LC unit activity and ERPs concurrently in monkeys exposed to an auditory oddball paradigm to determine whether the activity of individual LC neurons is enhanced during the occurrence of P300-like potentials (Swick, 1991). Some LC cells (25%) showed a phasic activation after presentation of infrequent tones. Like the P3a, cellular responses were heterogeneous, related to stimulis sequence, and influenced by the subjects' behavioral state. The occurrence of a P3a-like component was not necessarily correlated with a phasic LC response to infrequent tones in the passive condition. In one trained monkey, LC cells tended to show a tonic elevation in firing after presentation of target tones. This tonic activation ws enhanced when the monkey performed the task; a phasic activation was related to behavioral response rather than to stimulus presentation. Collectively, the lesion data, the pharmacological evidence, and the single unit data suggest a link between the LC-NA system and the generation of P300.

## III. HUMAN PATIENTS

Determining the neural structures involved in generating ERP components in human patients with focal brain lesions has been suggestive of specific generator sites, although problems with localization and interpretation can make these results somewhat inconclusive. If a lesion abolishes an ERP component, it may not necessarily be because the neural substrate itself has been destroyed, but rather because of damaged input to the generators. Lesions also may act indirectly by altering behavioral state or through nonneural mechanisms (see Wood et al., 1984, for discussion). For instance, the removal of skull in temporal lobectomy patients presumably alters intracranial conductivity and surface ERP topography (Vaughan, 1987). Likewise, it is difficult to determine whether a particular intracranial potential contributes to a potential recorded concurrently on the scalp. Late positive potentials resembling P300 have been recorded in the MTL, for example (Halgren et al., 1980; McCarthy et al., 1989), but MTL lesions do not alter scalp-recorded P300 in a manner consistent with an MTL primary generator (Johnson, 1988b; Stapleton, Halgren, & Moreno, 1987). A final complication is the fact that most depth electrodes are placed in the abnormal compromised tissue of neurological patients; brain pathology may affect these intracranial potentials. Nevertheless, studies in brain-damaged patients have limited the range of possible sources for a given ERP component. Particular attention has been devoted to P300, which is discussed in detail in the following sections.

**Table 2** Summary of Lesion Effects on P300 in Human Patients

| Lesion | Modality | Effects on P300 | Reference |
|---|---|---|---|
| Prefrontal cortex | Auditory | P3a to novels reduced bilaterally, P3b to targets normal | Knight (1984) |
| | | P3a to novels decreased over lesioned hemisphere, with greater reduction for right lesions | Scabini et al. (1989) |
| | Visual | P3a to novels decreased over lesioned hemisphere, P3b to targets normal | Knight (1990) |
| | Somatosensory | P3a to novels decreased bilaterally, slight decrease in P3b to targets (only at frontal site ipsilateral to lesion) | Yamaguchi & Knight (1991) |
| Lateral parietal | Auditory | No change in P3a or P3b | Knight et al. (1989) |
| | Visual | No change in P3a or P3b | Knight (1990) |
| | Somatosensory | P3a decreased to contralateral shock novels, normal P3b to targets | Yamaguchi & Knight (1991) |
| Temporal-parietal junction | Auditory | P3a to novels and P3b to targets abolished posteriorly | Knight et al. (1989) |
| | Visual | P3a to novels reduced, lesser reductions for P3b to targets | Knight (1990) |
| | Somatosensory | P3a to novels & P3b to targets reduced bilaterally, both contralateral and ipsilateral to lesion | Yamaguchi & Knight (1991) |
| Anterior temporal lobe (unilateral) | Auditory | P3b to targets normal, P3a to novels reduced in left ATL patients | Stapleton et al. (1987) |
| | | P3b to targets normal in right ATL, slightly reduced in left ATL; no left-right asymmetries in either group | Johnson (1988b) |
| | | P3b to targets normal in patient with left MTL damage | Rugg et al. (1991) |
| | | P3b reduced at parietal site ipsilateral to right temporal lesion | Daruna et al. (1989) |
| | | P3b to targets normal at parietal sites, decreased at frontal sites for left ATL | Johnson (1989a) |

*continues*

**Table 2** (*Continued*)

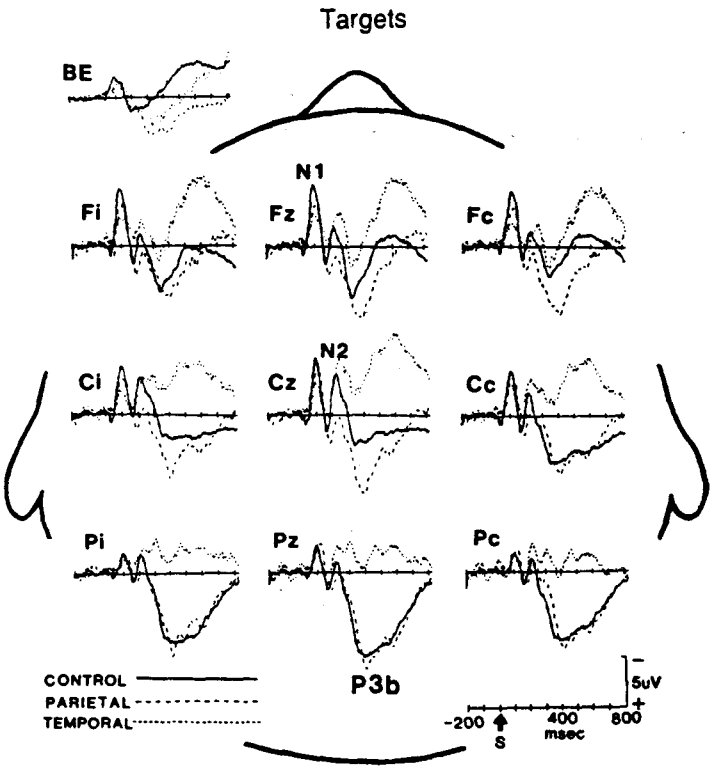
| | | | |
|---|---|---|---|
| | Visual | P3b to targets normal | Stapleton et al. (1987); Scheffers et al. (1991) |
| | | P3b to targets normal in patient with left MTL damage | Rugg et al. (1991) |
| | | P3b to targets normal at parietal sites, decreased at frontal sites for right ATL | Johnson (1989x) |
| Posterior hippocampus and inferior temporal cortex | Auditory | P3a to novels decreases frontally but not parietally, P3b to targets normal | Knight (1991) |
| | Visual | Same | Knight (1991) |
| | Somatosensory | Same | Knight (1991) |
| Anterior and midlemporal lobes (bilateral) | Auditory | P3b to targets normal at F3/4, C3/4, T5/6, P3/4, and O1/2 and at midline sites, but reduced al Fp1/2, F7/8, and T3/4 | Onofrj et al. (1992) |
| Commissurotomy | Auditory | Binaural targets: P3 amplitude greater over right hemisphere | Was et al. (1990) |
| | Visual | Bilateral targets: P3 amplitude greater over right hemisphere | |
| | | LVF targets: greater over right hemisphere | |
| | | RVF targets: equal over both hemispheres | |

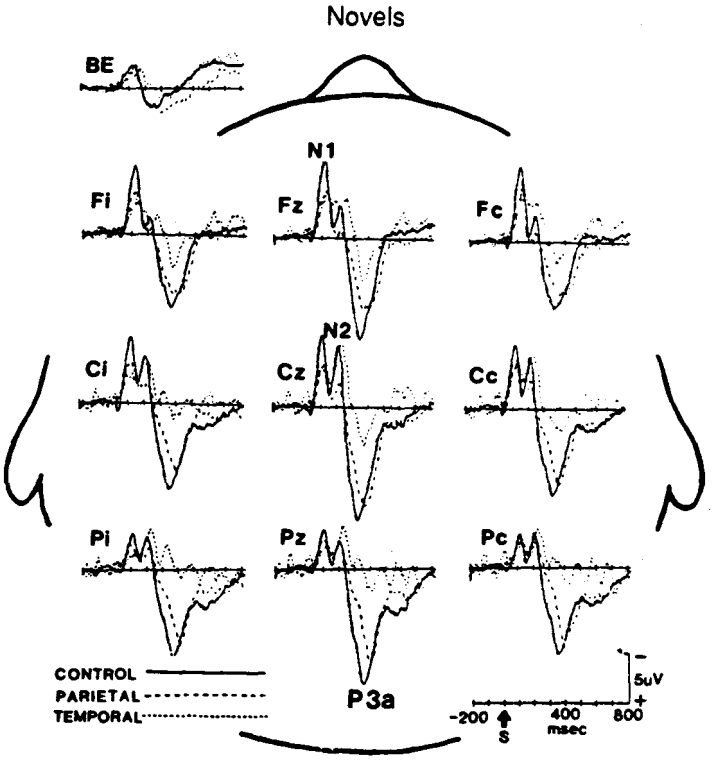
**A. Lesions**

Substantial lesion and intracranial evidence has implicated a number of brain regions in P300 electrogenesis, including portions of frontal, temporal, and parietal cortices, as well as several subcortical areas (Halgren et al., 1980; Knight, 1984; Knight, Scabini, Woods, & Clayworth, 1989; McCarthy et al., 1989; Smith et al., 1990; Yingling & Hosobuichi, 1984). Table 2 summarizes the effects of different brain lesions on P3a and P3b. Patients with unilateral lesions of prefrontal cortex showed normal, parietally distributed P300s in response to targets in an auditory discrimination task (Knight, 1984). Responses to unexpected "novel" stimuli (rare nontarget stimuli) at fronto-central sites were reduced and instead exhibited a more parietal distribution, resembling the P300 elicited by targets. A lateralized decrease over lesioned cortex was not observed, however, leading the author to conclude that the prefrontal cortex, although not the primary generator of P3a, modulates its activity. A more recent preliminary study by Scabini, Knight, & Woods (1989), however, indicated that P3a is reduced over lesioned prefrontal cortex, maximally for right hemisphere lesions. Somatosensory P3as to "novel" tactile stimuli and shocks were decreased by lesions of dorsolateral prefrontal cortex, particularly at frontal sites (Yamaguchi & Knight, 1991); P3b to tactile targets showed only slight reductions.

In the auditory modality, the P3b to targets was abolished and P3a to novels was reduced substantially at central and parietal sites in patients with unilateral lesions that included both caudal inferior parietal cortex and superior temporal gyrus (Fig. 6; Knight et al., 1989). Patients with lesions including only lateral parietal cortex exhibited normal P3a and P3b potentials. Similar results were seen in the somatosensory modality (Ya-. maguchi & Knight, 1991). Lesions of the temporal-parietal junction eliminated the visual P3a but had lesser effects on the amplitude of the visual P3b (Knight, 1990, personal communication). In contrast, auditory and somatosensory P3bs were abolished by temporal-parietal lesions (Knight et al., 1989; Yamaguchi & Knight, 1991). One likely explanation is that P300 has multiple generators, some of which are modality specific. For instance,

**Figure 6** Group-averaged ERPs recorded to target (above) and novel (below) stimuli in the monaural tone detection task The arrows (S) denote stimulus onset. Solid lines show ERPs from controls, dotted lines from temporal patients, and dashed lines from patients with parietal lesions. Data are shown from the midline and parasagittal scalp sites. Scalp sites are shown ipsilateral (i) and contralateral (c) to the lesioned hemisphere for patients, or on the left and right for controls. Lesions in the temporal-parietal junction abolished the P3a and P3b responses at all posterior scalp sites. ERPs are grand averages over 6 patients in each group. Reproduced with permission from Knight, Scabini, W oods, & Clayworth (1989).


Targets
BE
N1
Fi
Fz
Fc
N2
Ci
Cz
Cc
Pi
Pz
Pc
CONTROL
PARIETAL
TEMPORAL
P3b
5uV
-200
S
400
msec
800


Novels
BE
N1
Fi
Fz
Fc
N2
Ci
Cz
Cc
Pi
Pz
Pc
CONTROL
PARIETAL
TEMPORAL
P3a
5uV
-200
S
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msec
800

the temporal-parietal junction is critical for P3a in all modalities and for P3b in the auditory and somatosensory modalities; this region makes a significant but smaller contribution to visual P3b. These results also support previous suggestions that P3a and p3b are distinct subcomponents with different neural sources. Prefrontal cortex, for example, is necessary for the generation of P3a but not P3b.

In oddball-type paradigms, the modality-specific N200 component precedes P3a and P3b (Simson, Vaughan, & Ritter, 1977; Squires et al., 1975). Naatanen (1988, 1990, 1991) has divided N200 into two subcomponents: an earlier N2a or mismatch negativity (MMN) that reflects an "automatic" process and a later N2b that precedes P3b and is related to the shifting of attention toward a target. Woldorff, Hackley, and Hillyard (1991), however, reported that the MMN in unattended channels was suppressed under conditions of highly focused attention and suggested that it may be only "weakly automatic." These authors interpreted this effect as an attentuation of early sensory processing in the unattended channels. An alternative explanation contends that overlap from the N2b contributed to the larger negativity observed in attended channels, accounting for most of the MMN attention effect (Naatanen, 1991).

In the same groups of temporal-parietal patients discussed earlier, lesions of lateral parietal cortex significantly reduced N200 in response to target and novel stimuli in both auditory (Knight et al., 1989) and somatosensory (Yamaguchi & Knight, 1991) modalities. Lesions of the temporal-parietal junction, conversely, did not affect N200 amplitude in either modality. The dissociation between N200 and P300 observed in these studies suggests that the two potentials have different neural sources. Additionally, lesions of dorsolateral frontal cortex reduced the amplitude of somatosensory N200 to novels and targets (Yamaguchi & Knight, 1991) and auditory N200 to novels only (Knight, 1984).

Since P300 has been proposed to be a reflection of memory encoding (Donchin & Coles, 1988), temporal lobe structures have been considered primary sources of this potential. Contrary to the prediction of this hypothesis, unilateral temporal lobectomies that included removal of hippocampus, amygdala, and anterior temporal lobe did not significantly affect scalp-recorded P3b in auditory or visual oddball tasks (Johnson, 1988b; Stapleton et al., 1987). No hemispheric asymmetries were observed in these patients, as would be expected if MTL structures were major contributors to the P3b recorded on the scalp. Additionally, P300s from anterior temporal lobectomy (ATL) patients did not differ significantly from those of normal controls when stimulus quality in a visual discrimination tasks was reduced, although the right-lesioned group made significantly more errors (Scheffers, Johnson, & Ruchkin, 1991). A patient with

a glioma affecting the entire left MTL exhibited unimpaired performance and symmetrical P300s of normal amplitude in response to both auditory and visual oddball stimuli, but a large negativity was evoked by visual targets at frontal sites (Rugg, Pickles, Potter, & Roberts, 1991). Slightly dissimilar results were obtained in another experiment that used an auditory oddball paradigm with longer and variable interstimulus intervals. Patients with right temporal lobe lesions exhibited smaller P300 amplitudes at the parietal site ipsilateral to the lesion in this paradigm (Daruna, Nelson, & Green, 1989).

Although ATL did not affect the P3b to auditory targets in the study of Stapleton et al. (1987), these investigators did observe a reduction in the P3a to novel auditory stimuli in the group with left ATLs. A similar report indicated that posterior hippocampus and adjacent inferior temporal cortex may make a modality-independent contribution to the frontal P3a (Knight, 1991). Lesions of these areas had no effect on the parietal P3b to targets or the parietal P3a to novel stimuli in auditory, visual, and somatosensory modalities. Patients with bilateral damage of anterior and medial temporal lobes and severe anterograde amnesia showed reductions in P3b amplitude recorded in an auditory oddball task (Onofrj et al., 1992). These decrements were significant at lateral frontal and midtemporal sites but not at midline, posterior temporal, lateral parietal, or occipital electrodes. In addition to demonstrating once again that intact MTLs are not necessary for generating the P300 that is maximal at Cz and Pz, this finding suggests that MTL contributes to the positivity recorded at other scalp sites and strongly implies multiple P300 sources.

Johnson (1989a) provides additional evidence for modality-dependent generators. Auditory P300 amplitude was reduced at frontal sites in patients with left temporal lobectomies, whereas visual P300 was normal at all electrodes. Conversely, patients with right temporal lobectomies showed normal auditory P300s but reduced visual P300s at frontal electrodes. Additionally, studies of the developmental changes in P300 recorded from children have demonstrated differences between auditory and visual P300s (Johnson, 1989b).

Unilateral stimuli elicit a bilaterally symmetric P300 in control subjects, whereas split-brain patients show an asymmetric distribution for both the auditory and visual modalities (Kutas, Hillyard, Volpe, & Gazzaniga, 1990). Targets in the left visual field and bilateral visual targets elicited an LPC that was larger over the right than over the left hemisphere. Targets in the right visual field produced an LPC of approximately equal amplitude over both hemispheres. Binaurally presented tones also produced a P300 that was greater in amplitude over the right hemisphere. This interesting pattern of results suggests that P300 arises from neither a diffuse

bilateral source (since laterality in the visual task depended on which hemisphere was stimulated) nor from totally independent cortical generators (since separate lateralized generators would yield predictable, reversed asymmetries). Intact subcortical systems, however, are probably important in generating or modulating P300 activity, as discussed earlier.

### B. Pharmacology

Pharmacological studies in humans also have contributed to an increasing awareness of the importance of neurotransmitters in various aspects of information processing and their ERP indices (Table 1). The stimulant drugs methylphenidate and amphetamine, which increase release and block reuptake of catecholamines, decreased reaction time (RT) but did not affect P300 latency, suggesting that stimulants act on response selection processes but not on stimulus evaluation (Halliday, Naylor, Callaway, Yano, & Walton, 1987; Naylor, Halliday, & Calloway,1985). Herning, Jones, Hooker, and Tulunay (1985), conversely, reported that cocaine reduced not only P300 amplitude but also the amplitudes of N100 and P200 in an auditory oddball task, indicating that stimulants may influence both earlier processes such as those related to selective attention as well as later stimulus evaluation processes.

Scopolamine, a cholinergic antagonist acting at muscarinic receptors, increased both P300 latency and RT in a visual discrimination task (Callaway, Halliday, Naylor, & Schechter, 1985). Scopolamine also interacted with stimulus complexity, increasing P300 latency and RT for more easy "pop out" visual stimuli than for complex stimuli that required a serial search (Naylor, Brandeis, Halliday, Yano, & Callaway, 1988). Another group reported that scopolamine not only increases P300 latency but also decreases P300 amplitude and impairs recent memory (Hammond, Meddor, Aung-Din, & Wilder, 1987; Meador et al., 1987). These effects were partially reversed by physostigmine, an anticholinesterase. Depth electrodes placed in the hippocampi of epileptic patients showed polarity-inverting potentials that were altered by scopolamine (Meador et al., 1988). In another experiment, scopolamine was compared with methysergide, an antiserotonergic drug (Meador et al., 1989). Both drugs impaired recent memory, but only scopolamine had effects on P300, implying that serotonergic systems are not essential in generating P300.

A preliminary report by Duncan and Kaye (1987) showed that clonidine decreased P300 amplitude in an auditory discrimination task, to the greatest extent for the easiest discrimination. After placebo administration, P300 amplitude increased as discriminability increased, but the opposite effect was observed with clonidine. Joseph and Sitaram (1989) also

reported that clonidine reduced P300 amplitude in an easily discriminable auditory paradigm.

The opiate antagonist naloxone was administered to subjects performing an auditory selective attention task (Arnsten, Neville, Hillyard, Janowsky, & Segal, 1984). Tones were presented in three different spatial locations, and subjects had to detect longer-duration targets in one of these channels. Typically, an enhanced negativity is elicited by tones in the attended channels compared with those in unattended channels (Hillyard, Hink, Schwent, & Picton, 1973). Naloxone increased this attention effect in the selective attention condition but not in undistracted or divided attention conditions, suggesting that endogenous opiates can influence ERP measures of selective attention. Pharmacological manipulations in humans, as well as in animals, are thus capable of altering the output of neural groups generating ERPs recorded from the scalp.

### C. Intracranial Recordings

Intracranial recordings in human patients have demonstrated steep potential gradients and polarity inversions in P300-like activity recorded from a number of different cortical and subcortical regions, including hippocampus and medial temporal lobe structures (Halgren et al., 1980; McCarthy et al., 1989; Stapleton & Halgren, 1987), frontal lobe (Smith et al., 1990; Wood & McCarthy, 1986), parieto-occipital junction (Kiss, Dashieff, & Lordeon, 1989), inferior parietal lobe (Smith et al., 1990), and thalamus (Kropotov & Ponomarev, 1991; Velasco, Velasco, Velasco, Almonza & Olivera, 1986; Yingling & Hosobuichi, 1984). Very large positive potentials were elicited by auditory (Fig. 7), visual, or somatosensory targets in regions anterior and posterior to the hippocampus, inverting in polarity within the hippocampus (McCarthy et al., 1989). These potentials were task relevant, sequentially dependent, and could be elicited by omitted stimuli, demonstrating similarities to scalp-recorded P300 although they may not be a major source of its activity. In another study, stimulus omissions evoked typical late potentials from temporal but not from frontal or parietal depth electrodes, suggesting that P300 has both endogenous and exogenous sources (Alain, Richer, Achim, & Saint Hilaire, 1989).

A negative component with the same latency as the vertex P300 was recorded in the somatosensory thalamus and periaqueductal gray of a chronic pain patient, implying that the hippocampal activity is not volume conducted to the scalp (since positive potentials should be recorded dorsal to the hippocampus; Yingling & Hosobuichi, 1984). Polarity reversals were not observed in this experiment, but Velasco et al. (1986) found polarity inversions between subthalamus and dorsal thalamus. Further, they

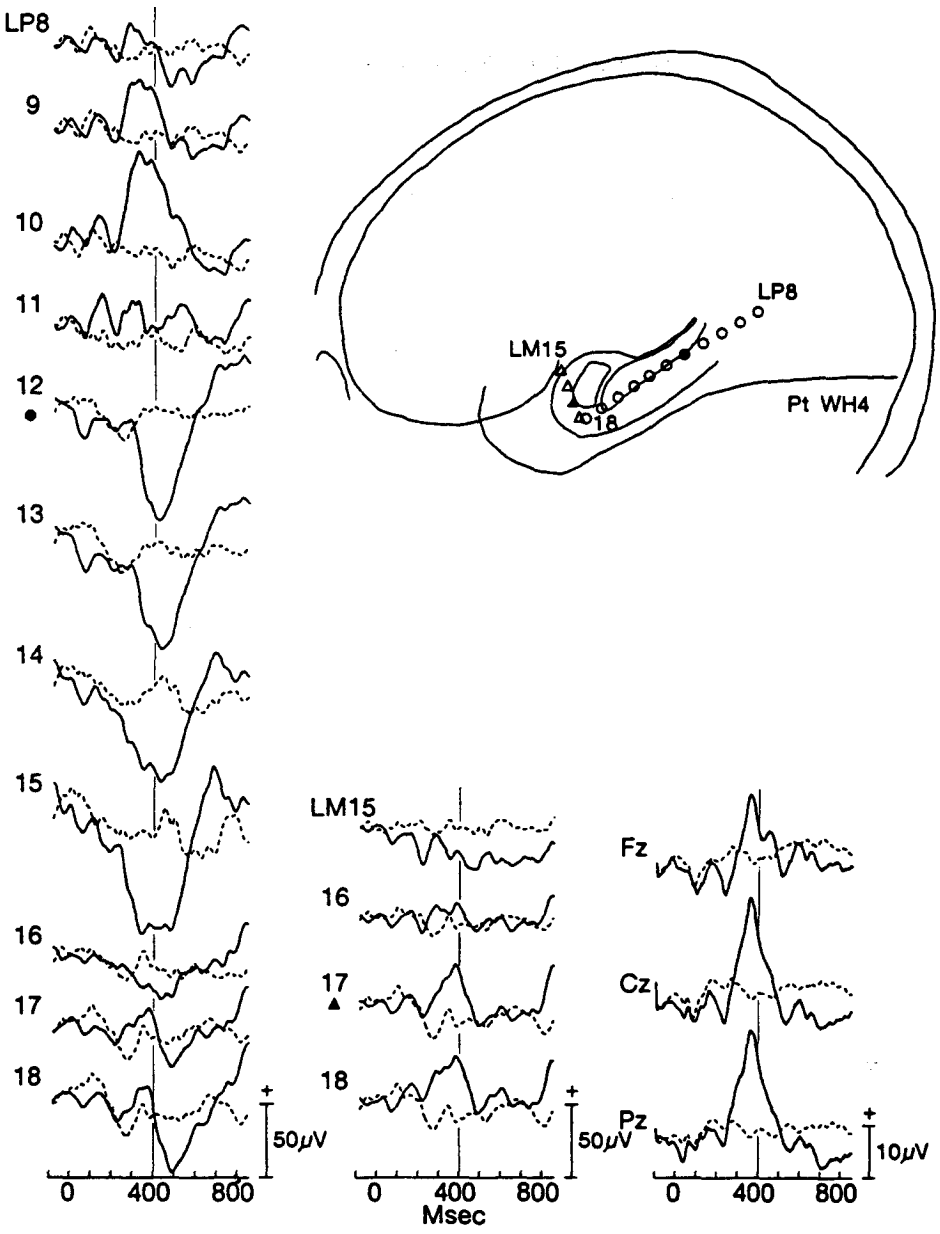


**Figure 7** ERPs elicited by auditory count (solid) and ignore (dashed) targets for LP (circle) and LM (triangle) contacts in patient WH4. LP 12 and LM17 are depicted as filled symbols. Scalp-recorded ERPs elicited by auditory count targets (solid) and standards (dashed) prior to implant surgery are shown in the right-most column for comparison. Reproduced with permission from McCarthy, Wood, Williamson, & Spencer (1989).

named the region of the medial geniculate as a possible generator, since the "P300" component had the largest amplitude and shortest latency there. Kropotov and Ponomarev (1991) recorded ERPs and multiple unit activity from the globus pallidus and ventro-lateral thalamus of Parkinson's patients performing an oddball task. These investigators reported a P300-like component in these structures in response to task-relevant, rare visual stimuli. No phase reversals were observed, but the authors speculated that the generators might be found in adjacent regions. Approximately 20% of all multi-unit populations showed robust, long-latency firing only after the rare, relevant stimuli. Another 22% had short-latency responses to both targets and standards but showed enhanced activity in response to targets that started at 200-400 msec.

Although P300-like activity has been recorded from a number of intracranial sites in humans, the findings of Smith and colleagues (1990), combined with lesion data implicating temporal-parietal junction (Knight et al., 1989; Yamaguchi & Knight, 1991), suggest that a major generator of the scalp component may be in the inferior parietal lobe (IPL) and the posterior superior temporal plane. Smith et al. (1990) claimed that the diencephalon makes a minimal contribution to scalp P300; the small potentials recorded there may be volume conducted from other sources. In the frontal lobe, polarity inversions were found in the premotor area but not dorsolateral prefrontal cortex, anterior cingulate gyrus, or supplementary motor area. The frontal potentials may be too small in amplitude to make a substantial contribution to scalp P300. Conversely, very large positive potentials were observed in the IPL. No polarity reversals were seen, but steep voltage gradients were observed at sites anterior, posterior, superior, inferior, and medial to the IPL contacts.

The studies reviewed here illustrate the utility of examining ERPs in patients with brain lesions and intracranial electrodes. Contributions from particular neural sources can be inferred indirectly through detailed analysis of magnetic resonance images and computed tomographs in lesioned patients and more directly by localizing polarity inversions and voltage gradients with depth recordings. In turn, locating the neural generators with greater anatomical precision allows inferences to be made regarding the brain areas that are critical to the aspects of attention, memory, language processing, and so on reflected by the ERP in question.

## IV. ELECTRICAL AND MAGNETIC RECORDINGS

The combined use of electrical and magnetic recordings has proven to be a valuable approach in the study of the neural generators of ERPs. Both

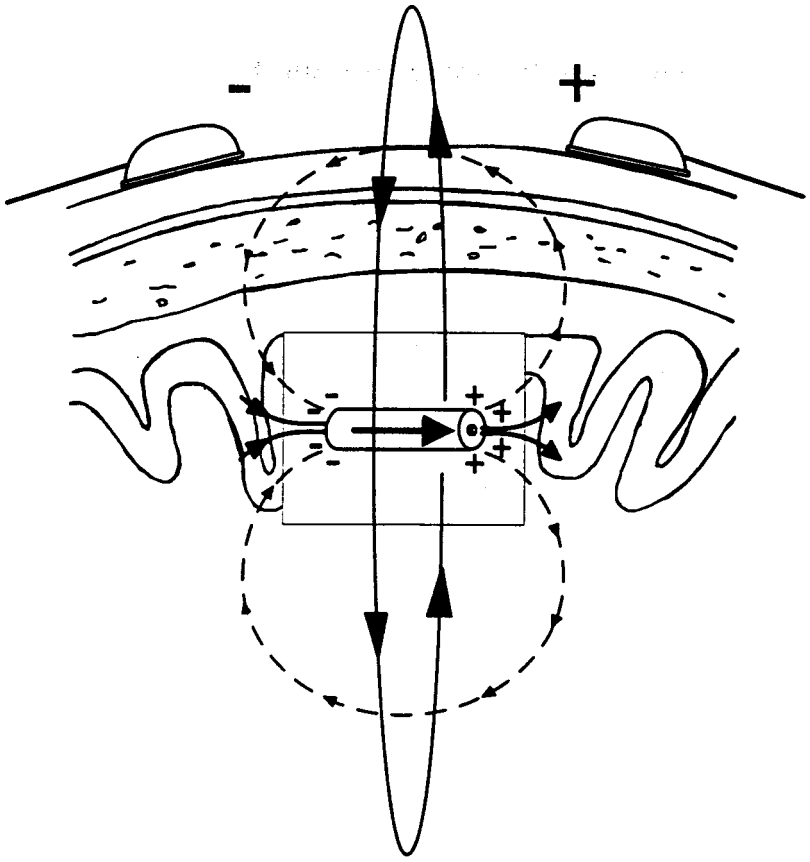


**Figure 8** Theoretical distribution of electrical and magnetic fields produced by a current dipole within the cerebral cortex, schematically localized beneath the scalp and skull. Dotted lines represent the electrical volume currents that constitute the EEG. The solid line represents the magnetic field produced by the current dipole. Adapted from Fig. 1 of Kaufman, Okada, Brenner, & Williamson, (1981). On the relation between somatic evoked potentials and fields. *International Journal of Neuroscience, 15,* 223-239.

magnetoencephalography (MEG) and magnetic resonance imaging (MRI) have improved the accuracy of localizing current dipoles in the brain. MEG measures the neuromagnetic field that results from intracellular current flux in populations of activated neurons (Fig. 8; for reviews of MEG, see Beatty, 1990; Pizzella & Romani, 1990; Williamson & Kaufman, 1991). The skull and scalp are essentially transparent to these magnetic fields, a major advantage over EEG recordings which must contend with attenuation and smearing. A major disadvantage of MEG is its insensitivity to radially oriented fields.

A great deal of controversy surrounds discussions of the relative utility of MEG versus EEG in the localization of electrical sources in the brain (see Crease, 1991). Some researchers claim that MEG can achieve more

accurate localization than ERPs, but the two methodologies can be seen as complementary. MEG is reflective of sulcal sources tangential to the brain surface, whereas EEG is composed of both radial and tangential sources. A typical figure cited for MEG accuracy is within approximately 3 mm, based on measurements of magnetic fields from current dipoles placed in a saline-filled lucite sphere and a plastic skull (Yamamoto, Williamson, Kaufman, Nicholson, & Llinas, 1988). An experiment performed by Cohen and colleagues (1990), however, did not support this contention. Weak current pulses were passed through depth electrodes of known locations implanted in epilepsy patients for clinical purposes. MEG and EEG were recorded separately, and the inverse solutions were calculated. The average error of localization was 8 mm for MEG and 10 mm for EEG. The methods of Cohen and colleagues have been criticized by other groups as inadequate and not up to current standards (Hari, Hamalainen, Ilmoniemi, & Lounasmaa, 1991; Williamson, 1991). For example, only one sensor was used to make sequential measurements, rather than using a 7- or 37-channel magnetometer. Since the position of the single sensor may not have been specified properly, a possible source of error was introduced. Despite these differences of opinion, the general conclusion is that, when combined, MEG and EEG can provide a wealth of information.

For instance, both magnetic fields and electrical potentials were recorded after stimulation of the median nerve in human subjects (Wood, Cohen, Cuffin, Yarita, & Allison, 1985). The SEP recorded from the scalp and cortical surface included the parietal N20-P30, largest over the hand area of somatosensory cortex, and the frontal P20-N30, maximal over the hand area of motor cortex (Allison, Goff, Williamson, & Vanglider, 1980). Three alternative sources for N20 and P20 have been proposed: thalamus and thalamocortical afferents, two radial sources in somatosensory and motor cortices, and one tangential source in somatosensory cortex; Wood and colleagues (1985) examined these possibilities. The resultant magnetic and potential distributions were dipolar, centered over sensorimotor cortex, and diverged in orientation by about 90°. The thalamus and thalamocortical afferents were too deep to account for the observed magnetic and potential extrema, nor could the combined data accommodate two radially oriented dipoles. One equivalent dipole with tangential current flow in somatosensory area 3b best explained the data. The magnetic and potential waveforms were similar but not identical, however, implying a smaller contribution from radial source(s) in somatosensory and/or motor cortices. Lesion and intracranial results from monkeys and humans have further indicated that these early SEPs are generated entirely within primary somatosensory cortex (reviewed by Allison, McCarthy, Wood, & Jones, 1991).

Magnetic and electrical recordings were also obtained from subjects performing a visual oddball task to determine the source locations of the magnetic equivalents of N200 and P300 (Okada, Kaufman, & Williamson, 1983). Isofield contour maps were plotted from magnetic field measurements for the two components, the sources of which were assumed to be a single equivalent dipole in each hemisphere (see subsequent discussion for descriptions of contour maps and equivalent dipoles). Calculations using the locations of the field extrema and a spherical head model estimated the sources of both components to be in or near the hippocampal formation. The spherical head model, however, may be an oversimplification that could lead to errors of 5-10 mm, particularly for deep brain structures (Barth, Sutherling, Broffman, & Beatty, 1986). Additionally, simultaneously active generators, hence contributions from other areas, must be considered as well.

Using a 7-channel magnetometer, another group recorded magnetic fields over the right hemisphere of subject counting auditory targets presented to the left ear in an oddball task (Rogers et al., 1991). Sources were estimated for successive 5-msec intervals using a single equivalent dipole model and projections onto MRIs. The P3m sources (300-450 msec) moved from medial (thalamus) to lateral (near superior temporal lobe) in some subjects, although a great deal of variability was noted. The mean locus of activity was near auditory cortex. Again, the single dipole assumption may discount multiple generators overlapping in time.

Neuromagnetic recordings, dipole localization methods, and reference to individual subject MRIs were combined to localize the source of the M100, the magnetic counterpart to the N1 component of the auditory evoked potential, within the transverse temporal (Heschl's) gyrus (Pantev et al., 1990). Primary auditory cortex is located on Heschl's gyrus and is thought to be the generator of M100 (see also Yamamoto et al., 1988). Woldorff and colleagues (1993) simultaneously recorded 37 channels of magnetic fields and 3 channels of ERPs over the left hemisphere of subjects performing a dichotic listening task. Stimuli were presented rapidly to maximize the selective focusing of attention to tones in one ear while ignoring tones of a different pitch in the other ear. Preliminary results from this experiment suggested that, as in previous ERP studies, tones in the attended ear elicited an early enhanced positivity between 20 and 50 msec (the P20-50 described by Woldorff & Hillyard, 1991), followed by an attention-related negativity, partially composed of an enhancement of the N1 component between 50 and 150 msec (early Nd or N1 attention effect; Hansen & Hillyard, 1980; Giard, Perrin, Pernier, & Peronnet, 1988; Hillyard et al., 1973; Woldorff & Hillyard, 1991; Woods, Alho, & Algazi, 1993). Magnetic counterparts to these electrical components showed highly di-

polar field distributions, inverting in polarity from anterior to posterior sites. Dipole source localization techniques and comparisons with MRIs placed the generators of the M50, the M1, and the M1 attention effect within Heschl's gyrus.

In an attempt to dissociate the magnetic N1 (N1m) and Nd (Ndm) components, Arthur and co-workers used constant 800-msec interstimulus interval (ISIs) in subjects performing an auditory selective attention task (Arthur, Lewis, Medvick, & Flynn, 1991). Sources were modeled as single equivalent current dipoles in a conducting sphere (since the field distributions were dipolar), and their coordinates were related to MRI sections. Based on field distributions and dipole models, the generator of Ndm was near but anterior to that of N1m; both were located in auditory cortex in the region of the posterior superior temporal plane (Fig. 9). These findings and those of Woldorff et al. (1993) address the hotly debated question of whether the Nd reflects an "early selection/ sensory gating" theory of attention, in which irrelevant stimuli are filtered out before full analysis, or a "late selection/ attentional trace" model, which predicts complete analysis of stimuli before matching to a representation maintained in sensory memory (see Hansen & Woldorff, 1991; Naatanen, 1988, 1990; Woods, 1990). For instance, if Ndm represents modulation of the exogenous Nlm component, the sources of both would likely be in the same location. This example illustrates how localization of an ERP component can illuminate theories in cognitive psychology and how MEG can assist in this endeavor.

## V. CURRENT SOURCE DENSITY ANALYSES

Important information on the generators of the brain processes that give rise to ERPs has come from the topographic analysis of scalp-recorded electrical activity. Topographic displays of scalp potentials permit informative visual analyses useful in generating hypotheses about the localization of ERP generators. However, further analysis is required to specify ERP generators more accurately. A simple and direct way to improve the spatial resolution of scalp potential topography is to apply the current source density (CSD) technique, that is, to calculate one of several surface Laplacians (see Nunez, 1990, for a comparison of the different Laplacians). Currently most widely applied, the spline Laplacian provides estimates of local radial current density through the skull into the scalp. Since the Laplacian method estimates the second spatial derivative of the surface potential distribution, it eliminates the effects of tangential current flow. Thus, this method acts as a spatial filter that amplifies the contribution of local sources and diminishes the contribution of distant sources. An

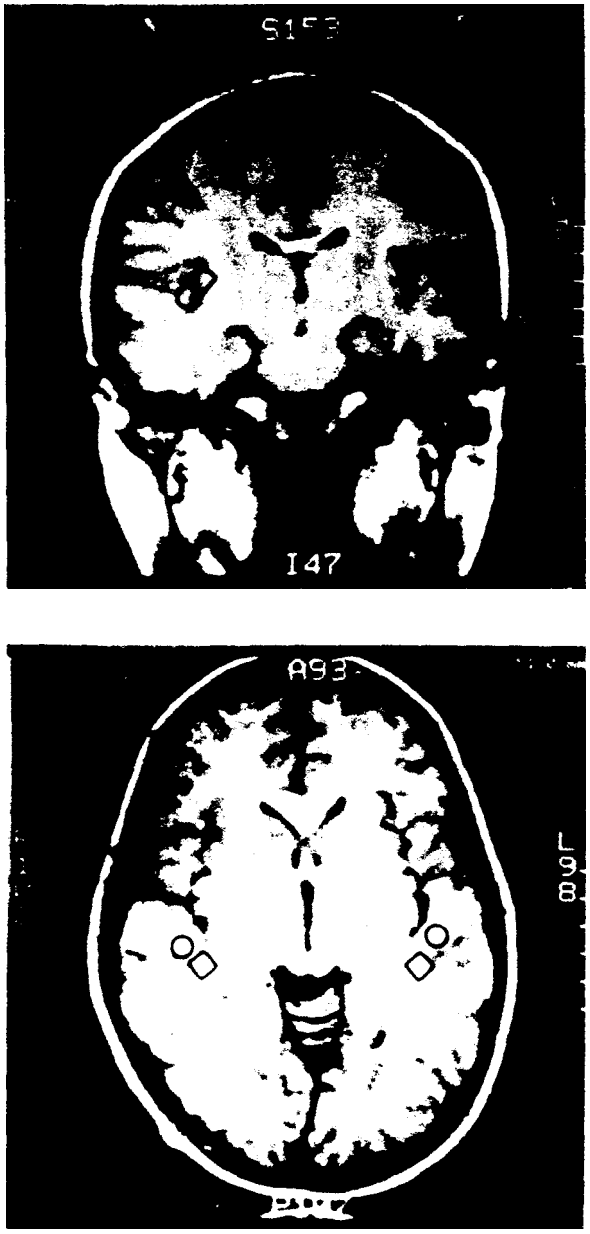


**Figure 9** Coronal (Y Z) (*top*) and horizontal (X-Y) (*bottom*) MRI sections from subject DA with N1m (diamond) and Ndm (circle) centroid locations superimposed. Reproduced with permission from Arthur, Lewis, Medvick, & Flynn (1991).

additional advantage provided by this approach is that the density of current flow is independent of the recording reference, thus mitigating concerns about estimates of the relative degree of activation of reference sites. Most published CSD data have been based on a three-concentric-

sphere model of the head. In the future, extending the spline Laplacian approach to realistic ("finite element") head models including estimates of local skull resistance (which is highly variable over the surface), and the use of very high density electrode placements, will markedly improve the accuracy of this approach. Nonetheless, even as currently employed, a comparison of potential maps and surface Laplacians of modeled cortical dipoles, of epileptic spikes, and of ERPs clearly indicates the greater power of the Laplacian in localizing dipole sources (Giard et al., 1988; Mangun, Hillyard, & Luck, 1993; Nunez, 1990; see Fig. 10). According to the modeled results in Fig. 10, the spatial resolution of the CSD is on the order of a few centimeters.

Analysis of the CSD has been employed to explore the question of whether visual-spatial attention acts by modulating the flow of sensory information or by the activation of cortical areas additional to those along the afferent sensory pathway. Several studies have demonstrated that, during visual-spatial selective attention, ERP components P1 (at 75-100 msec) and N1 (at 100-200 msec) are significantly enhanced over visual cortical areas (Eason, Harter, & White, 1969; Mangun & Hillyard, 1987; Van Voorhis & Hillyard, 1977). Moreover, the amplitude increases of these

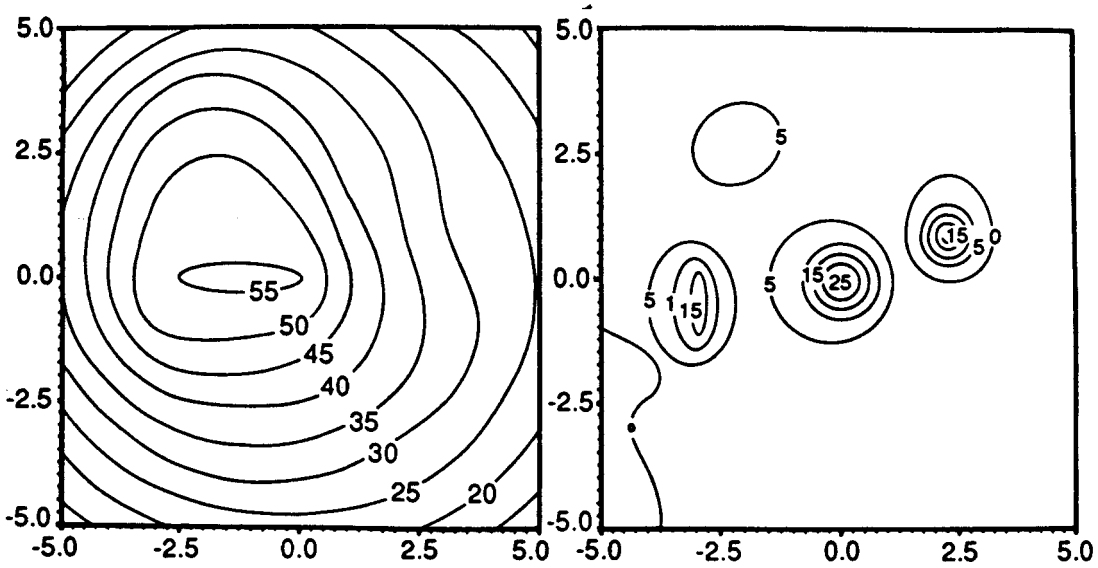


**Figure 10** Theoretical potential (*left*) and surface Laplacian (*right*) for five dipoles in the three-concentric-spheres model. Four dipoles with various orientations are located within 2 cm of the outer spherical surface, and one stronger dipole is located near the center of the spheres. Potential distribution is maximum along the axis of the deep dipole and shows no evidence of four superficial dipoles. In contrast, surface Laplacian indicates the presence of all four superficial dipoles. Reproduced with permission from Nunez (1990).

ERP components occur without attendant changes in morphology or distribution. These results are consistent with the hypothesis that early sensory gating may play an important role in attentional processes. To localize the source of the attention effects and to determine further whether these generators are identical for attended and unattended stimuli, Hillyard, Mangun, and colleagues have related CSD distributions of these effects to the underlying cortical anatomy as revealed by MRI scans of the same subjects' brains (Hillyard, Mangun, Luck, & Heinze, 1990; Mangun et al., 1993). The CSD maps revealed that the earliest attention effect (on P1) displayed a current source identical in location to that of the sensory evoked response (see Fig. 11). This similarity of location supported the hypothesis that visual-spatial attention acts by modulating the

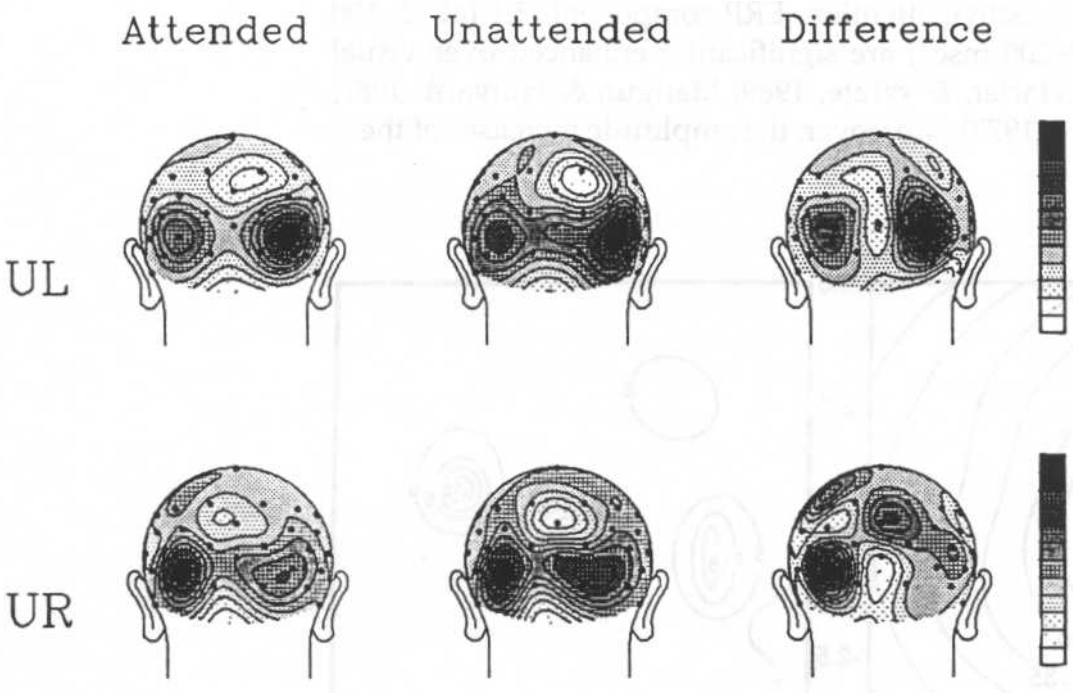


**Figure 11** Scalp topography of grand average current source densities (CSD) calculated for the P1 component (at 108 msec) in response to upper left (UL) and upper right (UR) stimuli. Separate CSD maps are shown for the P1 component elicited by those flashes when attended and when unattended (averaged over the 3 other attention conditions). (*Far right*) The CSD distribution of the attention-related P1 difference formed by subtracting the ERPs in the unattended condition form those in the attended. The darkest zones represent current sources (current flowing out of the head), whereas the lightest zones represent current sinks. Each map is scaled individually to indicate 10 levels of CSD between the minimum and maximum values observed for that map. Reproduced with permission from Mangun, Hillyard, & Luck (1993).

amplitude of sensory activity along the afferent pathway but does not, at this latency, activate additional neural generators.

Additional analyses determined that the P1 attention effect was not generated in striate cortex. The CSD maps were similar in polarity and location in response to upper and lower visual field stimuli (see Fig. 11). A striate generator would have produced different CSD distributions because of the opposed orientation of cortical neurons for upper and lower field stimuli. In fact the CSD maps, when brought into register with the MRIs, indicated that the likely generator of P1 and the effect of attention on it (i.e., the locus of maximum current density) occurs over ventrolateral prestriate cortex, on the border of areas 18 and 19. This result is consistent with studies of monkeys that report no effects of attention on single neurons in striate cortex but significant effects in prestriate areas (Moran & Desimone, 1985; Wurtz, Goldberg, & Robinson, 1980).

Another study also utilized CSD analyses to explore the idea that nonidentical brain systems mediate different aspects of language (Neville, Mills, & Lawson, 1992). Words that convey primarily grammatical or semantic information were associated with different distributions of current at specific times. Additionally, a comparison of CSD maps from normal hearing subjects and congenitally deaf adults who learned English late and imperfectly raised the hypothesis that some of the brain systems important in grammatical processing are more dependent on early exposure to language for their normal development than are systems important in semantic processing. The results raise several hypotheses about the role of early experience in the development of different brain systems within and between the two hemispheres.

Clearly, the CSD approach will continue to be useful in generating and exploring hypotheses about the location of brain systems important to specific sensory and cognitive functions. In addition to being useful on their own, CSD analyses will be powerful in generating hypotheses that can be tested using dipole modeling approaches.

## VI. DIPOLE MODELING TECHNIQUES

Another approach used by researchers to assist in the identification and localization of neural sources underlying ERP components is dipole modeling. The flow of ionic currents inside a volume conductor generates electrical potentials that can be recorded on.the scalp. Electrical field theory can be employed to calculate the sources within the volume conductor from the potential field distribution measured at the surface, a query known as the inverse problem (Balish & Muratore, 1990; van Oosteram,

1991; Wood, 1982). Additional constraints and a basis in physiological reality are essential to accurately solve the "mathematically ill-posed" inverse problem, since myriad source configurations can yield the same potential distribution due to the principle of superposition. This principle states that the fields generated by any number of sources will sum linearly, rendering inverse solutions meaningless without some prior knowledge about source locations. Wood (1982) provides an excellent overview of dipole localization methods (DLMs), particularly those of Darcy, Ary, and Fender (1980) and Sidman, Giambalvo, Allison, and Bergy (1978), and their application to identifying the sources of ERPs.

A number of assumptions about the sources and the volume conductor are made in these models. Neuronal sources are modeled as dipolar to more easily approximate the generators of a resultant potential field, although the sources are not actually thought to be physical dipoles. The potential field generated by an "equivalent" dipole can be used as a "best estimate" of the fields generated by several neighboring sources, for example. With these assumptions in place, the inverse problem can be addressed by least squares parameter estimation. Each generator, or dipole, can be described by six parameters: three of these specify location on the *x*, *y*, and *z* axes and three specify dipole moment (strength) and orientation (for details, see Snyder, 1991; van Oosteram, 1991; Wood, 1982). DLM uses numerical minimization algorithms to estimate the best-fitting dipole for a particular scalp potential field. A single equivalent dipole (ED) is anatomically fictitious in most cases, however (Vaughan, 1987). More authentic are source models incorporating constructs such as dipole layers (de Munck, 1988) and distributed sources (Balish & Muratore, 1990).

Additional assumptions must be made in models of the volume conductor. Differences in conductivity between brain, cerebrospinal fluid (CSF), skull, and scalp necessitate that the simplest model consist of 3 or 4 concentric spheres (for EEG). A major advantage of MEG, of course, is that magnetic fields are not affected by skull and scalp, so a single sphere model can be used. A sphere may be a fair approximation for superficial sources, but more realistic head models are needed for deeper sources (van Oosteram, 1991). These newer, more complicated models based on MRIs from individual subjects may allow localization accuracy of a few millimeters (Dale & Sereno, 1993; Meijs & Peters, 1987; Stok, Meijs, & Peters, 1987). Other mathematical methods simulate the potentials that would be recorded directly from the brain surface. The cortical imaging technique of Sidman and colleagues (summarized by Sidman, 1991) and the finite element model deblurring technique of Gevins and associates (Gevins, Brickett, Costales, Le, & Reutter, 1990; Gevins, Le, Brickett,

Reutter, & Desmond, 1991) aim to reduce the skull's smearing and attenuating effects on scalp potential fields.

Snyder (1991) has pointed out that inverse DLMs work best for early sensory evoked responses, which can be modeled by one or two EDs. The number of recording electrodes must exceed the number of parameters to be estimated; these parameters or constraints increase with each additional generator. The technique has rarely been applied to later "cognitive" components such as P300 because of possible intrinsic limitations (however, see Sidman, Ford, Ramsey, & Schlichting, 1990; Turetsky, Raz, & Fein, 1990). For instance, the ability to distinguish correct from incorrect models drastically deteriorates as the number of generator loci increases to the theoretical limit allowed by the number of electrodes.

Furthermore, assumptions about multiple generators should be biologically plausible. Wood (1982) reminds us that, for components generated not by a single focal source that is stable over time but by many asynchronous sources, "it is particularly important not to confuse the numerical adequacy of DLM solutions with their physiological validity" (p. 148). This cautionary note holds even for scalp fields generated by a single focal source. For example, the DLM solution for the human SEP N20-P20, although mathematically reasonable, placed the equivalent dipole outside of the head (Wood, 1982). Vaughan (1987), however, is more optimistic about solving the inverse problem. Although an infinite number of source configurations exists in theory, this number is much smaller-in reality, restricted by the brain's actual anatomy and physiology.

The benefits and drawbacks of models utilizing a single moving dipole versus multiple fixed dipoles are discussed by Lopes da Silva and Spekreijse (1991). These investigators applied these two strategies to visual evoked potential (VEP) data elicited by the appearance of a checkerboard pattern. For the single dipole model, a moving ED was calculated for consecutive 5-msec intervals starting at 35 msec and ending at 160 msec after pattern onset. Two clusters of EDs were obtained at 80-120 and 125-150 msec. Principle component analysis (PCA), which decomposes scalp-recorded ERPs into factors representing independent sources of variance (for discussion of PCA, see Turetsky et al., 1990), was used to describe two major components in the multiple fixed dipole model (see also Maier, Dagnelie, Spekreijse, & van Dijk, 1987). Both models obtained similar solutions: the earlier VEP component CI was accounted for predominantly by a radially oriented ED located in area 18/19; the second component CII was accounted for by a tangentially oriented ED located in area 17. Other models, however, have obtained different solutions. For example, the iterative minimization technique used by Butler et al. (1987) placed the ED corresponding to the CI generator in area 17. The sources of

CI and CII have been disputed since the initial studies of Jeffries and Axford (1972a,b) proposed them to be in areas 17 and 18, respectively.

Scherg and co-workers have developed a method, called brain electric source analysis (BESA), for decomposing scalp-recorded ERPs into their constituent or source waveforms (reviewed in Scherg & Picton, 1991). In their spatio-temporal dipole model, sources must have fixed positions and orientations. This multiple stationary dipole assumption allows more sources to be active at once. The number of sources (m) must merely be less than the number of recording sites (n), instead of less than the number of parameters (6) times n, as in other methods of calculating the inverse solution. For example, Scherg and Von Cramen (1986) decomposed middle- and long-latency AEPs into "dipole source potentials." To restrict the number of possible solutions, two dipoles in each hemisphere were assumed to represent the AEP sources. These dipoles were allowed to vary in strength over time. After solving the requisite equations, bilateral tangential and radial dipoles in auditory cortex accounted for the empirical AEP data recorded from normal subjects.

BESA is most effective when used to test hypotheses about the neural generators of specific ERPs, given that the sources are tentatively identified through other means (e.g., imaging, lesion, and depth data). Posing initial constraints on the possible solutions can overcome the difficulty of an arbitrary starting point. For instance, BESA and comparison with individual subject MRIs were used to localize component sources of the VEP to circular checkerboard stimuli (Clark, Fan, & Hillyard, 1991). The effects of different stimulus positions on scalp topography and component amplitude were also examined. The C1 (i.e., CI) showed a polarity inversion about 20-40° below the horizontal meridian instead of at the horizontal meridian as previously believed. The C1 component source was placed just lateral to the medial surface of the contralateral occipital lobe near the calcarine fissure, implicating striate cortex as the most likely generator. The tentative locations of N150 and P220 sources were found to be in several extrastriate regions.

Dale and Sereno (1993) criticize the nonlinear optimization technique used by Scherg and co-workers as computationally difficult. These researchers also question the a priori determination of the number of equivalent dipoles and the lack of confidence measures with which to evaluate the solutions. Their alternative approach, based on work in progress (Dale & Sereno, 1993), takes MRI data from individual subjects and shrinks a deformable template onto the images to determine the shape of the cortical sheet. The position and orientation of possible current sources is established from these transformed MRIs, with the assumption that current flow is perpendicular to the cortical sheet. Linear techniques then can be

used to solve the inverse problem, which becomes well posed and constrained with the addition of regularization terms based on empirical EEG, MEG, and positron emission tomography (PET) data.

Other critiques of BESA include those of Turetsky et al. (1990) and Achim, Richer, and Saint-Hilaire (1991). Although the refined nonparametric model (Scherg & Von Cramen, 1986) avoids the arbitrary constraints of the earlier parametric model, it is more likely to be affected by noise (Turetsky et al., 1990). Overmodeling is a chronic problem; the model assumes a very high signal-to-noise ratio and fails to adequately account for the signal in the presence of physiological noise (Achim et al., 1991). Furthermore, there are no summary measures of dipole activity and therefore no clear procedures for analyzing results, as others have recognized. Turetsky and colleagues (1990) offered an alternative dipole component model, which they applied to auditory P300. A major advantage of their model is the incorporation of latency variations across subjects and conditions, although one problem is that the head was modeled as a homogeneous sphere instead of three concentric spheres. Fitting the model to the data proved to be a very computationally intensive procedure, perhaps prohibiting these additional constraints.

## VII. SUMMARY

This chapter has reviewed several different approaches currently being implemented to improve the spatial resolution of (i.e., localize the neural generators of) ERPs. To the extent that specific ERP components index particular sensory and cognitive processes (an issue not addressed here but reviewed by Brunia, Gaillard, & Kok, 1990; Hillyard & Picton, 1987; Kutas & Van Petten, 1990; Regan, 1989), knowledge about their neural origins will contribute to several different issues in neuropsychology and cognitive neuroscience. Of course knowledge about the neural structure(s) that supports different aspects of perception and cognition is of intrinsic interest and will lay the groundwork for determining the inputs and outputs of these systems. Additionally, this information will provide information about the biological validity of different conceptions of the organization of specific sensory and cognitive systems. To the extent that different putative subsystems within a domain rely on nonidentical neural structures, this information may be considered evidence for their isolability and independence. The techniques for localizing these cognitive systems have improved considerably over the past 10 years. The next 10 years are likely to see improvements an order of magnitude greater than the last.

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