Neural Origins of the P300

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Abstract

A review of the literature investigating the neural origins of detection behavior in humans reveals two event-related potential components, P3a and P3b, each with a distinct neural organization and cognitive function. The P3a is involved in automatic novelty detection and characterized by a more anterior cortical distribution, whereas the P3b is concerned with volitional target detection and has a more posterior cortical distribution. Intracranial investigation, studies with patients with focal brain lesions, and functional neuroimaging (fMRI) studies converge with the scalp-recorded ERP data in suggesting that a widespread cortical network gives rise to both automatic and controlled detection behavior. The main regions consistently attributed to generating detection related brain activation include the temporal-parietal junction, medial temporal complex, and the lateral prefrontal cortex. The extant human and animal literature addressing the neural networks, neuropharmacological underpinnings, and behavioral significance of “the P300” potential will be reviewed.

Keywords: novelty detection; orienting response; detection behavior; event-related potentials; P300; P3-like; P3a; P3b; P3a-like; P3b-like

Neural Origins of the P300

Introduction:

The ability to discriminate and categorize new and old events is a highly evolved human characteristic that develops in early infancy. Fagan, for instance, measured the gaze time of infants to novel stimuli when they were presented with new and previously viewed targets. He found that infants as young as 3 months of age were capable of distinguishing between new and old targets that had been presented up to hours, days, or weeks prior. Furthermore, novelty detection is not only limited to the ability to make discriminations, but it can also have a powerful affect on memory for everyday events outside the laboratory setting. For example, infrequent personal events such as the birth of a child or a death are deeply encoded. Similarly, rare but engaging external events such as assassinations are better remembered. Several factors influence this effect: (1) the repetition of the news of Kennedy’s assassination in part drives deep encoding of that event, and (2) many individuals also distinctly remember the first moments in which they became informed of Kennedy’s death. Note the latter instance has been referred to as flash-bulb memory in the literature and serves as an example of how a discrete isolated event can have a profound influence on subsequent memory encoding. Novelty also influences other human behaviors. For instance, creative behavior is commonly defined in direct relation to the degree of novelty. This relationship extends to all fields of endeavor with typical examples including distinguished performance in art and science. After all, great art is by definition defined by originality.

In everyday life humans continually detect and respond to discrete environmental events. People may allocate attention to an event either voluntarily or automatically. Examples of voluntary attention include simple tasks such as looking for a pencil on your desk or more complicated tasks such as finding one key scientific reference in a large pile of papers. Both tasks involve the ability to maintain a template of what you are looking for and when that template is matched to mount an appropriate behavioral response. Involuntary or automatic attention, however, involves orienting towards an unexpected or unanticipated event. For example, hearing a tire screech when crossing an otherwise quiet street may initiate a shift in attention (or orienting response) towards the vehicle. Due to its ubiquitous contribution to virtually all aspects of behavior, the neural systems underlying detection capacity have become a key topic of interest for cognitive neuroscience.
Scalp recorded event-related potentials (ERPs) have been integral to understanding the cortical basis of discrimination processes. Through the application of this technique, scientists have discovered that both voluntary and automatic attention yield distinct scalp recorded ERPs, referred to as the P3b and the P3a respectively. The P300 (or P3) thus refers to a family of positive potentials generated from 300-600 msec subsequent to voluntary and involuntary stimulus detection. P300 responses are generated in all sensory modalities and have been recorded in multiple mammalian species. Since the initial discovery of the P300, scientists have concerned themselves with attempting to elucidate the neural origins and cognitive basis of the P300 phenomenon. In doing so, they have employed both human and animal models.

The following review will focus on delineating the behavioral significance, the neuropharmacological underpinnings, and the neural networks of detection behavior (or the “the P300” potential), and it is divided into five main sections. The first section will begin with an overview of detection behavior, both voluntary (target detection or P3b) and involuntary (novelty detection or P3a) detection will be discussed. The second section will provide information regarding the human models developed to explain detection behavior. Close attention will be paid to those studies examining pharmacology, intracranial recordings, and brain lesions. The third section will discuss information obtained from human neuroimaging studies. The fourth section will provide a review of the animal literature examining detection behavior. Again the review will focus on pharmacological manipulations, intracranial recordings, and lesion studies. The fifth and final section, the conclusion, will turn to the goal of this review which is to coalesce the information obtained from both the human and animal studies in an effort to determine whether the information obtained to date will address the question: How do the brain regions involved in detection functionally connect to give rise to detection or orienting behavior? Note there is a vast literature examining P300 abnormalities in psychiatric and neurological disorders. This literature will not be discussed, and the reader is referred to several excellent reviews (see ref# 104).

Review of ERPs. Readers who are familiar with ERPs may want to skip this section. Beginning in the 1960’s, researchers started employing scalp recorded ERPs to study a wide range of sensory and cognitive processes including attention, motor performance, memory, and language. ERPs are voltage fluctuations in an electroencephalogram (EEG) that are time-locked to a series of cognitive, motor, or sensory events. In most cases these potentials are significantly smaller than the background EEG; thereby the ERP (or signal) is extracted from the EEG (or background noise) by signal averaging techniques.

Generally, ERPs consist of a series of positive and negative voltage fluctuations called components, and the components are typically associated with various sensory, motor, or cognitive events. As a rule of thumb, the earlier components are most commonly associated with sensory events and the later with more cognitive events. Furthermore, ERPs can be characterized across three dimensions: (1) amplitude, (2) latency, and (3) scalp distribution. The amplitude generally provides information regarding the extent of the neural activation, the latency the onset of the activation, and the scalp distribution the underlying activity or the pattern of brain activation.31

ERPs provide a direct and non-invasive measure of the temporal course of various cognitive processes, but they do lack in spatial resolution. That is, relative to the latest brain imaging techniques, ERPs do not provide adequate information regarding the neural generators of a particular brain potential. Nonetheless, high-density recording arrays in conjunction with sophisticated data analysis techniques have enabled researchers to extract some information regarding the location of various neural generators. For instance, dipole source localization techniques have been employed wherein researchers seed dipoles, located in regions thought to be involved in the generation of a particular ERP component, into a source modeling algorithm. The algorithm, in turn, provides information regarding the scalp distribution of the seeded dipoles. If the distribution significantly resembles (or explains) that of the component in question then it can be concluded that the chosen region is a potential generator of that ERP component. This is also known as the forward solution. Note, however, there is also an inverse problem, which states that scalp distributions can not be used to localize (or determine) neural generators, because
there are an infinite number of solutions (or dipole positions) that can potentially sum to give rise to each scalp recorded distribution.

Finally, ERPs can be displayed as either waveforms or topographic maps. The waveforms depict the component(s) of interest and provide information about amplitude and latency. Topographic maps, on the other hand, are derived from the amplitude data and can take two forms: (1) raw voltage or (2) current source density (CSD). The raw voltage maps reflect the summation of both cortical and subcortical neural activity that occurs in a set time window. Whereas, the CSD maps represent only the cortical surface activity. Specifically, CSD maps are filtered with an algorithm that removes the volume conducted subcortical activity, thereby yielding a display of positive and negative current densities that depict local cortical differences.

Detection Behavior:

**Voluntary Detection and the Target P3B.** As previously mentioned, during voluntary attentive search distinct scalp recorded ERPs are generated to correctly detected stimuli. Researchers generally employ the ‘oddball task’ to operationalize detection behavior. The paradigm requires either passive (e.g., silently count the number of task relevant stimuli that appear) or active (e.g., button press) detection of infrequent and low probability ‘target’ stimuli that are embedded in a sequence of high probability repetitive ‘standard’ or background stimuli. In 1965, two separate laboratories described a large positive parietal maximal scalp potential (P300) peaking in amplitude from 300-500 milliseconds after stimulus delivery and generated by the voluntary detection of a task relevant event. This ERP is referred to as a P3b response to distinguish it from scalp positive potentials (P3a) generated by task-irrelevant novel stimuli.

Hence, voluntary detection of an infrequent and task-relevant stimulus generates a large amplitude (5-15 μV) P300 response maximal over parietal scalp sites (target P3b). This effect is observed in the auditory, visual, somatosensory, and olfactory sensory systems. The modality-specific nature of the P3b has been extensively studied. Topographic EEG studies in normal subjects, patients with temporal lobectomy, and patients with callosotomy, in addition to magnetoencephalographic studies in normal subjects, demonstrate that there are modality-specific contributions to the P3b. The modality specific components are likely generated in secondary association cortices. Note that scalp topography and intracranial recordings indicate that the longer latency (~600 ms) scalp positivity generated during recognition memory tasks which predicts subsequent memory for the eliciting stimulus - appears to be distinct from the P3b.

Both P3b amplitude and latency are responsive to stimulus probability, subjective probability, stimulus meaning, and task relevance. Not surprisingly the P3b is linked behaviorally to a range of cognitive processes. One theory proposes that the P3b represents closure of an epoch of voluntary stimulus processing in association cortex. According to this theory, the P3b is generated during completion of a discrete epoch of stimulus processing and measures inhibition of regional activity involved in processing of expected stimuli. Another major theory supported by extensive cognitive psychophysiolologic research is that the P3b indexes updating of activity in corticolimbic circuits during attention and working memory. Working memory refers to the online ability to manipulate information generated by either external sensory events or internal mental activity. The concept of working memory encompasses a range of cognitive processes. A trivial example is rehearsal of a new phone number while waiting to dial. A more complex example is the cognitive processes involved in comparing the experience of a new event with a past situation or in the prediction of a future outcome. Other proposals such as those linking P3b and template matching may be subsumed under the concept of context updating in working memory.

**Involuntary Detection and the Novelty P3a.** The ability to detect and respond to novel events as well as produce novel behaviors is critical to both survival and creative behavior. In 1933, Von Restorff showed that novel stimuli are better remembered, but subsequently, little effort had been directed towards elucidating
the neural circuits responsible for this powerful behavioral effect. Nonetheless, in the mid-1970s, the situation changed with the publication of two papers reporting the generation of scalp potentials to novel or deviant stimuli. The researchers employed the ‘novelty oddball’ paradigm, which like the ‘oddball’ paradigm consists of both ‘target’ and ‘standard’ stimuli, but differs in that it is also composed of low probability ‘novel’ stimuli (i.e., dog barks, visual fractals, etc.) embedded in the train of ‘target’ and ‘standard’ stimuli. They demonstrated that involuntary orientation to an unexpected and novel stimulus generates a P300 response (P3a) similar in some regards to that generated by a voluntarily detected stimulus. The novel response, however, differs in three important aspects: (1) the P3a has a more fronto-central scalp distribution, (2) it peaks 60-80 msec earlier in all sensory modalities, and (3) it undergoes rapid habituation over frontal recording sites within the first 5-10 stimulus presentations.

The P3a is proposed to be a central marker of the orienting response, the rapid and involuntary attentional shift towards a new or unexpected stimulus. To begin, as described by Friedman, Cycowicz, and Gaeta, Sokolov examined the orienting response and in so doing demonstrated that it disappeared (or habituated) with repeated presentation of the same stimulus. Hence, Sokolov concluded that the habituation of a response indicates that some sort of memory engram for the event has been created, and for this reason the event no longer generates a response when repeated. Sokolov further postulated that novel events contribute towards the development of neural representations for the new events. Consequently, each time a novel event is experienced it is compared to the previously created neural representation, and if it is sufficiently deviant the process begins again, but if it is not (i.e., it is the same) then habituation (or a lack of response) occurs. Regarding the P3a, the rapid amplitude reduction of the potential with exposure to repeated trials of novel stimuli supports the notion that the P3a is the electrophysiological manifestation of the orienting response.

**Human Models:**

**Pharmacology.** Currently, it is widely accepted that ERPs reflect the electrical activity (or extracellular dipole) generated by neurons. Hence, ERPs are, in effect, induced by either excitatory or inhibitory postsynaptic potentials (EPSP and IPSP), which in turn are generated by neurotransmitter release. For this reason, in understanding the neural generators of the P300 in humans, it is also necessary to examine the pharmacology that influences the component.

The human literature, like the animal literature, contains divergent information regarding the various pharmacological manipulations, specifically with regard to those involving the monoamines. Research investigating the effects of amphetamines on the P300 yields incongruent results. For instance, studies administering the stimulant drugs methylphenidate and amphetamine, both of which increase catecholamines by blocking their re-uptake, have reported that stimulants speed up reaction times, but do not affect P300 latency. The researchers concluded that amphetamines are involved in response selection, and not response evaluation. Yet, Herning, Jones, Hooker, and Tulunay, employing an auditory oddball paradigm, reported that cocaine reduces P300 amplitude. In a subsequent study, however, Herning, Hooker, and Jones reported that cocaine does not alter the amplitude and latency of the P300.

Halliday et al. reported that if the P300 is measured from single trials, as opposed to group averages, then a small but significant decrease in its latency is obtained after the administration of D-amphetamine. That is, they found that D-amphetamine speeds up P300 latency on a trial-by-trial basis. In the same study, the authors also demonstrated that yohimbine, a drug that increases norepinephrine activity, causes a decrease in the latency of the visually evoked P300, whereas clonidine which decreases norepinephrine activity, increases P300 latency. Studies, employing auditory discrimination tasks, have further demonstrated that clonidine results in the reduction of P300 amplitude. Hence, the data regarding the pharmacological manipulations of norepinephrine are consistent with the animal literature; that is, they both suggest that the P300 may, in part, be controlled by the locus coeruleus norepinephrine system.
More recently, d’Ardhuy et al.\textsuperscript{18} compared the effects of fluoxetine, tianeptine, and clomipramine, all anti-depressant drugs affecting serotonin levels. They found that fluoxetine, tianeptine, and clomipramine reduced P300 amplitude. However, fluoxetine and tianeptine continued to reduce P300 amplitude up to eight days after treatment, whereas clomipramine demonstrated no additional diminution after eight days of treatment with respect to day one. The researchers concluded that serotonin selective drugs have a slower onset of P300 amplitude decrease than clomipramine, a drug that has additional affects on the monoaminergic and cholinergic systems. Meador et al.\textsuperscript{82} compared the effects of scopolamine, a cholinergic antagonist, to those of methysergide, a serotonergic antagonist, and found that both drugs affected recent memory, but only scopolamine affected the auditory P300. The authors concluded that the serotonergic system did not seem to be essential for P300 generation. Luttringer et al.\textsuperscript{78} demonstrated that apomorphine, a dopamine agonist, did not significantly alter the P300, although they did report a tendency towards an increase in P300 latency.

Again, consistent with the animal literature, the data reporting pharmacological manipulations of the cholinergic as well as the benzodiazepine systems are more congruent. For instance, scopolamine has repeatedly been shown to increase P300 latency and reduce P300 amplitude in both the visual and auditory modalities.\textsuperscript{10,81,82} Hammond, Meador, Aung-Din, and Wilder\textsuperscript{45} further reported that scopolamine not only reduces auditory P300 amplitude and increases P300 latency, but it also impairs recent memory, and that the administration of physostigmine, an anticholinesterase, partially reverses its deleterious effects. The human data like the animal data support the hypothesis that the cholinergic system plays a significant role in the production of the P300 potential. Recently, Hayakawa et al.\textsuperscript{50} demonstrated that the administration of triazolam, a benzodiazepine hypnotic and GABA receptor agonist, results in a decrease in the amplitude of the auditory evoked P300. For a summary of the effects of the various pharmacological manipulations on the P300 see table 1.

| Table 1: The Effects of Pharmacological Manipulations on the P300 potential in humans. |
|-----------------|-----------------|-----------------|-----------------|
| **Drug** | **Action** | **Modality** | **Effect on P300** | **Reference** |
| **Monoamines:** | | | | |
| MP | Increases CA activity | Visual | No effect on latency | Naylor et al. (1985) |
| Amph | Increases CA activity | Visual | No effect on latency | Halliday et al. (1987) |
| Cocaine | Increases CA activity | Auditory | Decreased amplitude & No effect | Herning et al. (1985); Herning et al. (1987) |
| Yohimbine | Increases NE activity | Visual | Decreased latency | Halliday et al. (1994) |
| Clonidine | Decreases NE activity | Visual | Increased latency & Decreased amplitude | Halliday et al. (1994) |
| **Antidepressants:** | | | | |
| Fluoxetine | Affects 5-HT | Auditory | Decreased amplitude & Decreased amplitude | d’Ardhuy et al. (1999) |
| Tianeptine | Affects 5-HT | Auditory | Decreased amplitude | d’Ardhuy et al. (1999) |
| Clomipramine | Affects 5 HT, other monoamines, ACh systems | Auditory | Decreased amplitude, but showed no additional diminution after 8 days. | |
| **Cholinergic:** | | | | |
| Scopolamine | ACh antagonist | Auditory | Increased latency & Decreased amplitude | Meador et al. (1987; 1989) |
| | | Visual | Increased Amplitude | Callaway et al. (1985) |
| **Benzodiazepine:** | | | | |
| Triazolam | BDZ hypnotic, GABA agonist | Auditory | Decreased amplitude | Hayakawa et al. (1999) |

Abbreviations: MP, methylphenidate; Amph, amphetamine; DA, dopamine; NE, norepinephrine; 5-HT, serotonin; LC, CA, catecholamine; BDZ, benzodiazepine; GABA, gamma-aminobutyric acid; ACh, acetylcholine.

In conclusion, in reviewing the pharmacology literature, Frodl-Bauch, Bottlender, and Hegerl\textsuperscript{33} developed a model explaining the neurochemical processes underlying the P300 potential; for a schematic of the model see figure 1.

Specifically, Frodl-Bauch et al.\textsuperscript{33} have proposed that the transmission of glutamate directly causes EPSPs, which in turn initiates P300 activity. In support of this notion, Oranje et al.\textsuperscript{98} demonstrated that the administration of Ketamine, a non-competitive NMDA antagonist, reduces the amplitude of the P300. The glutamate induced EPSPs (and consequentially the P300) are in turn indirectly influenced by other transmitter substances; specifically, acetylcholine, which enhances P300 amplitude and decreases its latency, and GABA, which reduces P300 amplitude and increases its latency. Finally, the other transmitter systems, the dopaminergic and serotonergic systems, have a modu-
Intracranial Recordings.

Intracranial recordings from patients who are either being evaluated for or undergoing surgery have also contributed towards the identification of the neural generators of the scalp-recorded P300 potential. Specifically, P3-like activity has been recorded from multiple cortical and subcortical regions, such as the frontal lobe, the parieto-occipital junction, the inferior parietal lobe, the thalamus, and the hippocampus among other medial temporal lobe structures.

In a series of three comprehensive studies, Halgren, et al., Halgren, et al., and Baudena, Halgren, Heit, and Clarke recorded ERPs from depth electrodes implanted in epileptic patients being evaluated for surgical treatment. All three studies employed the standard auditory oddball paradigm wherein participants discriminated between standard, target, and non-target rare stimuli. The first study employed 41 patients and involved recording ERPs from 537 superior temporal plane and parietal lobe sites. Halgren, et al. concluded that the P3a-like potential engaged a distribution of generators in association cortex, specifically in the inferior parietal, cingulate, and dorsolateral prefrontal cortices. The P3b-like potential, however, engaged multimodal association cortex, including possibly the superior parietal lobule and the limbic medial temporal lobe. The second study which involved recording ERPs in 39 patients, from 1221 sites in the medial, lateral, and posterior aspects of the temporal lobe, demonstrated that in addition to recruiting the aforementioned generators, the P3a-like potential also engaged posteromedial temporo-frontal cortices. The third study included recordings from 991 sites located in the frontal and peri-rolandic regions in 36 patients. Baudena, Halgren, Heit, and Clarke recorded polarity reversing responses, which they attributed to the P3a-like potential, in the dorsolateral, orbitofrontal, and anterior cingulate cortices, as well as the gyrus rectus. Refer to figure 2 for a summary of the findings.

In sum, Halgren, et al. have concluded that the scalp recorded P300 engages multiple brain structures, and thereby allows behavioral accuracy and consequences to be monitored, incidental learning to occur, and stimulus information to achieve widespread integration with context and memory. In support of their notion Clarke, Halgren, and Chauvel have conducted a set of studies examining the effects of stimulus lateralization on depth recorded ERPs in occipital and peri-Rolandic, as well as in temporal, parietal, and frontal recording sites. The researchers employed an oddball paradigm involving a lateralized visual discrimination task, which could be fully processed by a single cerebral hemisphere. Despite the lateralized presentation, the studies revealed that, with the exception of the initial input and output stages of information processing, both hemispheres were equally

Figure 1. Findings about neurochemical substrates of the P300 suggest this hypothetical model of P300 generation. The glutamatergic neurotransmission directly causes the EPSPs, which are responsible for the P300 activity. These EPSPs and as a consequence the P300 are modulated both indirectly by influences of acetylcholine, enhancing P300 amplitude and decreasing P300 latency, and by influences of GABA, reducing P300 amplitude and prolonging P300 latency. The adrenergic system and with minor importance, the dopaminergic, and serotonergic systems have a modulatory influence on the indirect effects of the acetylcholinergic and GABAergic systems. (compliments of Frodl-Bauch et al., 1999: S. Karger AG).

Intracranial Recordings. Intracranial recordings from patients who are either being evaluated for or undergoing surgery have also contributed towards the identification of the neural generators of the scalp-recorded P300 potential. Specifically, P3-like activity has been recorded from multiple cortical and subcortical regions, such as the frontal lobe, the parieto-occipital junction, the inferior parietal lobe, the thalamus, and the hippocampus among other medial temporal lobe structures.
engaged. Specifically, Clarke, Halgren, and Chauvel recorded a bilaterally-symmetric (or equal in amplitude) P3-like component, for both ipsilateral and contralateral stimulus conditions. In essence, both studies suggest that interhemispheric coupling rather than hemispheric independence predominates information processing.

Lesion Studies. Lesion studies allow scientists to make strong inferences between brain regions and their functions, and have proved quite useful in elucidating the cerebral origins of the P300. By converging ERPs with a lesioned brain researchers can directly evaluate whether the observed region is necessary to perform the task at hand. That is, if the lesion is in a critical brain region then the P300 waveform should be either non-existent or altered (e.g., decreased amplitude, increased latency, etc.), but if it is not then no change(s) should be observed. See figure 3 for a pictorial representation of the major brain regions involved in the generation of the P3b and the P3a as shown by lesion studies.

Lesion Studies P3b. Large field potentials are recorded in the hippocampal region during tasks that generate scalp P3b responses.\(^{42}\) However, scalp P3bs peak 30-50 ms before intracranial hippocampal field potentials and are intact in patients with mesial temporal damage due to hypoxia,\(^{108}\) anterior temporal lobectomy,\(^{55,80,151}\) herpes simplex encephalitis,\(^{95,98}\) tumor,\(^{122}\) and hippocampal infarction.\(^{70}\) These results indicate that the brunt of the scalp recorded P3b is not due to volume conducted field potentials from hippocampal regions. Anterior temporal lobectomies,\(^{80}\) bilateral mesial temporal lesions due to herpes simplex encephalitis,\(^{95}\) and unilateral posterior hippocampal infarctions\(^{70}\) result in significant P3b reductions at far lateral temporal and frontal sites, which suggests that mesial temporal structures may either generate field potentials that propagate to the surface at these lateral scalp sites or are providing modulatory input necessary for P300 generation in these regions.

Discrete damage in the temporoparietal junction including posterior temporal plane and superior temporal sulcus results in severe reduction of P3b activity at posterior scalp sites in both the auditory\(^{75}\) and somatosensory modalities\(^{159,160}\) and in partial reductions in the visual modality\(^{72}\) (Fig. 4).

Verleger, Heidi, Butt, and Kompf\(^{149}\) independently confirmed that the auditory P3b was dispropor-
tionately reduced in comparison to the visual P3b after temporoparietal damage. These data combined with magnetoencephalographic (MEG) studies in normal subjects suggest that modality-specific regions contribute to the P3b. Intracranial recordings, showed P3b potentials in posterior cortical sites, including the superior temporal sulcus, are in further accord with the results of the lesion studies.

Subregions of the human temporoparietal junction may correlate anatomically to multimodal area caudal superior temporal sulcus polysensory region (cSTP) and auditory association area Tpt in monkeys. These multimodal regions located in the posterior STS of monkeys have bidirectional connections to area TH in the parahippocampal gyrus and have been implicated in learning and memory in animals and humans. The P3b reductions in patients with temporoparietal lesions are accompanied by attention and memory deficits. Temporoparietal lesions in monkeys also result in auditory memory deficits. The convergence of results from these human and monkey studies suggests that the posterior scalp P3b component marks activity in posterior association cortex generated during engagement of early attention and memory processes. This posterior neocortical system may interact with hippocampal regions during encoding of sensory inputs and updating of working memory.

**Figure 4.** Summary of the target P3b and novelty P3a effects in controls and three patient groups with focal cortical damage. The center of the lesion overlap in each group is shown (left). The waveform from selected electrodes with maximal response amplitude [parietal zone (Pz) for target and frontal zone (Fz) for novel stimuli] 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, somatosenory, or visual modalities. This implies that substantial regions of dorsolateral prefrontal and parietal association cortex are not critical for the parietal maximal P3b generated in simple tasks. 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. Left: 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 (adapted from Knight and Scabini, 1998).

Hippocampal field potentials are generated ~50 ms after the posterior scalp P3b, supporting the notion that the scalp P3b may index readout of cortical information to limbic regions for memory updating.

**Lesion Studies P3a.** Prefrontal damage results in differential effects on scalp P3a and P3b responses. The parietal maximal P3b generated to task relevant, correctly detected stimuli in sensory discrimination tasks is largely unaffected by prefrontal damage. However, parietal P3b reductions after prefrontal damage are observed in more complex tasks. Conversely, prefrontal lesions markedly reduce P3a responses to both simple and complex unexpected novel stimuli. Comparable P3a decrements have been observed in the auditory, visual, and somatosensory modalities in human subjects with damage to the prefrontal cortex. In addition to P3a reductions over prefrontal scalp sites subsequent to focal prefrontal damage, the P3a is also reduced through-
out the lesioned hemisphere (Figs. 5 and 6).

The P300 data, in conjunction with additional contingent negative variation (CNV)\textsuperscript{116} and visual attention results,\textsuperscript{141} provide strong evidence that dorsolateral prefrontal regions modulate neural activity in posterior association cortex. For instance, Barceló, Suwazono, and Knight\textsuperscript{6} have shown that patients with dorsolateral prefrontal cortex lesions have reduced neuronal activity in the extrastriate cortex of the lesioned hemisphere. The human ERP results in conjunction with neuropsychological observations,\textsuperscript{84} and monkey single-unit and metabolic data\textsuperscript{32} support an interaction between prefrontal and posterior regions during both voluntary and involuntary attention and working memory. Furthermore, in a recent study, Rule, Shimamura, and Knight\textsuperscript{117} presented emotion-

Figure 5. Scalp event-related potentials (ERPs) to rare unexpected novel auditory stimuli not requiring a behavioral response (p = 0.10). The data represent a grand average from 10 patients with a focal prefrontal lesion (3 right, 7 left). Scalp sites are indicated as ipsilateral (i) or contralateral (c) to the side of the lesioned hemisphere. Frontal lesions reduced the amplitude of the P3a component throughout the lesioned hemisphere, with reductions most prominent over frontal sites (Fi, shows data from frontal electrodes over lesioned cortex; i.e., F3 for left lesions and F4 for right lesions, vs Fe, shows data from electrodes over intact prefrontal cortex) (adapted from Knight and Scabini, 1998).

Figure 6. Scalp voltage topographies for target and novel stimuli in controls. The increase in prefrontal activity in controls to the novel stimuli in all sensory modalities was marked. \textbf{Left}: Effects of prefrontal or hippocampal lesions on the brain novelty response. Unilateral prefrontal damage results in multimodal decrease in the novelty response maximal over lesioned cortex (all lesions are projected onto the left side). 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 perturbances in the environment (adapted from Knight and Scabini, 1998).

ally laden tactile and auditory stimuli (i.e., mild shocks and unusual sounds) to patients with ventromedial- or dorsolateral- prefrontal cortex lesions, as well as control subjects. They found that patients with ventromedial prefrontal cortex lesions elicited a larger P300 as compared to both the control subjects and the patients with dorsolateral prefrontal cortex lesions who showed reduced P3a responses.

The ERP findings indicate a lateral prefrontal source for the frontal scalp component of the novelty P3a and, with the intracranial data, clinical observations, and animal experimentation, support a critical role of prefrontal structures in the detection of novel stimuli.\textsuperscript{65} As noted, temporoparietal damage including inferior parietal lobe,
posterior superior temporal plane, and superior temporal sulcus reduces the amplitude of both P3a and P3b potentials over lesioned cortex, suggesting that posterior cortex is engaged by phasic attention to all deviant stimuli independent of the degree of stimulus novelty. The lesion results, however, cannot rule out differential contributions of subregions of the temporal-parietal cortices to P300 generation.

Unilateral damage centered in the posterior hippocampal region has no significant effect on parietal P3b activity generated to auditory, visual, and somatosensory stimuli, but markedly reduces frontocentral P300 activity to both target and novel stimuli in all modalities. Reductions are most prominent over frontal regions and for novel stimuli in.

These reductions are comparable to and in some instances greater in amplitude than those observed after focal prefrontal damage is sustained. However, unilateral hippocampal damage reduces P300 potentials over both prefrontal cortices, whereas prefrontal damage results in predominantly unilateral reductions over the lesioned hemisphere. These observations support involvement of a prefrontal-hippocampal system in the detection of deviances in the ongoing sensory stream and show that the hippocampal formation has bilateral facilitatory input to prefrontal cortex. Reciprocal intra- and inter-hemispheric pathways crossing through retrosplenial cortex or the cingulate may provide the anatomic substrates for prefrontal-hippocampal interactions during novelty detection and memory processing.

The amplitude and habituation characteristics of peripheral autonomic sympathetic skin responses (SSRs; also termed galvanic skin response or GSR) to random wrist shocks are also altered by hippocampal damage. The SSR is a well-studied peripheral marker of the orienting response. SSR amplitude is reduced and patients with hippocampal lesions exhibit a flat habituation curve. Such patients show reductions in SSR amplitude to orienting stimuli presented ipsilaterally and contralaterally to the lesion. These results of ERP and SSR studies
indicate that both peripheral and central orienting responses are impaired by mesial temporal damage. In a previous study of normal subjects, correlations between the amplitudes of the P3a and the SSR, were reported, indicating that these potentials measure combined central and peripheral orienting responses to novel or sufficiently deviant stimuli.\textsuperscript{40} The SSR to auditory orienting stimuli is also reduced by prefrontal and posterior association cortex damage,\textsuperscript{145} providing evidence that distributed cortical and limbic regions are engaged in novelty processing. Recently described hippocampal-hypothalamic pathways may subserve the peripheral autonomic orienting response.\textsuperscript{111}

Single-unit,\textsuperscript{87} PET\textsuperscript{146} and neural modeling studies\textsuperscript{86} have also implicated prefrontal and mesial temporal regions in novelty detection. These observations, along with the ERP results, provide strong evidence of prefrontal-hippocampal involvement in the detection of deviances in the ongoing sensory stream. Prefrontal-hippocampal interactions during orientation to novel stimuli may underlie the classic von Restorff memory effect wherein novel or out of context stimuli are better remembered.\textsuperscript{61,86,150} Recent observations show that the amplitude of the novelty P3a at encoding predicts subsequent recall of items,\textsuperscript{134} which provides an additional link between the novelty P3a and the von Restorff effect. Neural circuits dependent on the hippocampal region appear to maintain a template of the recent past for comparison with incoming sensory stimuli. Deviation from this template activates a distributed behavioral response to and memory storage of discrete novel events.

The ERP data provide evidence that the P3a, like the P3b component, is not a unitary phenomenon but instead represents distributed neural activity in corticlimbic regions engaged during involuntary response to discrete environmental events. Although this view is more complicated than initial proposals of a unitary nature for P300 activity, it strengthens the potential utility of scalp ERP recording, because it provides a method for the measurement of neural activity in distributed brain regions in the time domain of cognitive processing. P3a-like potentials have been reported in many mammalian species, also suggesting that this hippocampal-neocortical network may provide a core substrate for orientation to novelty.

**Neuroimaging:**

In general, the human lesion and intracranial studies have predominately demonstrated temporoparietal, frontal, limbic, and paralimbic P300 generators. Although, these two approaches provide the most direct access to the generators, they do maintain a few shortcomings. For instance, lesion studies are beneficial in correlating cognitive functions with brain structures, but are limited by the difficulties in obtaining patients with the lesion of interest, localizing the exact focus of the lesion, and there is a risk of confounds resulting from the “reorganization” of brain functions to different brain regions. Furthermore, human intracranial recordings, like lesion studies, also involve specific groups of participants, namely those who are undergoing a neurosurgical procedure. In addition, intracranial investigations are limited to recording from restricted brain regions. In sum, both techniques: (1) do not employ healthy normal working brains, and (2) provide information relating to a limited number of brain regions that have not necessarily been identified through experimental requirements; consequently, they cannot provide a complete picture of the P300 and its generators.\textsuperscript{77} Fortunately, imaging techniques, such as functional magnetic resonance imaging (fMRI), provide excellent spatial resolution of the intact brain, even though they do not necessarily provide adequate temporal resolution to determine the sequence of the neural events that occur during a task. As such, neuroimaging techniques can complement the lesion and intracranial findings, by allowing non-invasive investigations of the entire healthy human brain.

Functional neuroimaging studies employing the oddball paradigm, to date, have served to validate the brain regions that have been implicated in the generation of the P300 by both lesion and intracranial techniques. To begin, Stern and colleagues\textsuperscript{133} conducted one of the first fMRI investigations examining novelty encoding. They reported statistically significant bilateral increases in the blood oxygen level-dependent (BOLD) signal during the encoding of novel pictures in the posterior hippocampal formation and parahippocampal gyrus as well as in the lingual and fusiform gyri. McCarthy, Luby, Gore, and Goldman-Rakic\textsuperscript{79} demonstrated that the detection
of visual target stimuli, in a standard visual oddball paradigm, evoked transient event-related activation, beginning 1.5 sec after target onset and peaking between 4.5 and 6 sec after onset, bilaterally in middle frontal gyrus, the inferior parietal lobe, and the inferior aspect of the posterior cingulate gyrus. In an effort to examine both the spatial and temporal characteristics of the P3b, Menon, Ford, Lim, Glover, and Pfefferbaum conducted a set of auditory oddball studies, the first employed event-related fMRI and the second ERPs. fMRI revealed three significant clusters of brain activation, when target rather than standard stimuli were detected, in the bilateral supramarginal gyrus, the bilateral thalamus (primarily the anterior nucleus), and the anterior cingulate. The fMRI data was then used to model the scalp recorded ERP distribution. Specifically, Menon et al. seeded dipoles in those regions with maximal event-related brain activation as determined by fMRI (i.e., the supramarginal gyrus) into a source modeling algorithm. These investigators reported that: (1) the supramarginal gyrus is the main generator of the scalp recorded P3b, and (2) the generators are activated in the interval of 285-610 ms following target detection.

Opitz and colleagues also conducted a series of combined fMRI and ERP studies; however, they employed blocked fMRI designs, which makes it more difficult to make direct comparisons between their fMRI and ERP findings. The first study aimed at determining the spatiotemporal characteristics of the target P3b; hence, an auditory oddball paradigm was utilized. As revealed by fMRI, target detection resulted in bilateral activation of the superior temporal gyrus and the neostriatum; these regions served as constraints for the localization of the event-related current dipoles. Inverse source analysis demonstrated that the scalp recorded P3b could be modeled by two dipoles located in the posterior aspect of the superior temporal gyrus. The second study examined the spatiotemporal characteristics of the novelty P3a; therefore, a novelty auditory oddball paradigm was employed. fMRI analysis revealed that novel stimuli evoke bilateral activations of the middle portion of the superior temporal gyrus. Again these regions served to constrain the dipole source localizations, and in turn demonstrated that the middle part of the superior temporal gyrus contributes significantly to the generation of the P3a. Opitz and coworkers concluded that the sources of the P3a are located more anterior in the superior temporal gyrus than the sources of the P3b.

The studies discussed thus far have either employed the visual or the auditory oddball paradigm. Studies, however, have been conducted which directly compare the hemodynamic responses evoked by visual and auditory oddball paradigms. Linden et al. conducted an event-related fMRI study, unlike the studies discussed thus far that required participants to make two types of responses, button-press and silent counting. The two response conditions served as a control to determine the extent to which the changes in the BOLD signal could be attributed to the type of response required. They found significantly greater bilateral activation of the supramarginal gyrus, the frontal operculum, and the insular cortex when participants detected target versus non-target stimuli. For all of the conditions, with the exception of the auditory button-press condition, additional activations were obtained in the supplementary motor area (SMA) and the anterior cingulate gyrus. Finally, additional modality specific clusters of activation occurred in the primary and secondary visual cortices for the visual tasks and the right middle temporal gyrus, the left Rolandic cortex, the precuneus, the posterior cingulate gyrus, and the right middle frontal gyrus for the auditory tasks. Yoshiura et al. also compared the event-related hemodynamic response for both auditory and visual target detection, but unlike Linden et al. they used silent counting as their response method. Yoshiura et al. obtained auditory specific activations in the transverse temporal gyrus (primary auditory area) bilaterally and posterior superior temporal planes, and visual specific activations bilaterally in the occipital lobes (primary visual areas) and the occipitotemporal region. They also observed several modality non-specific activations, which include the parietal and temporal association areas, prefrontal cortex, premotor areas, supplementary motor areas, anterior cingulate gyrus, thalamus, and the hippocampal formation.

An interesting event-related fMRI study examined the detection of deviant visual, auditory, and tactile events. Downar and colleagues, however, did not employ the standard oddball paradigm. That is, they presented participants with a stream of continuous visual, auditory, and tactile stimuli, and defined deviance as the transition of stimuli from one stimulus state to another (e.g., the change of the sound of running water to a croaking frog).
Visual specific areas of activation included bilateral fusiform gyrus and bilateral middle occipital gyrus; auditory specific areas included the left and right superior temporal gyri; and tactile specific areas included bilateral secondary somatosensory cortex. Areas that were activated by changes in all three sensory modalities included bilateral temporal-parietal junction, right middle temporal gyrus, bilateral inferior frontal gyrus, anterior and posterior regions of the right insula, and the left anterior cingulate. Even though a modified oddball paradigm was employed, the results are consistent with the previously presented visual and auditory oddball studies.

Currently, there are four fMRI studies that have employed event-related fMRI to investigate novelty detection. Kirino and colleagues\textsuperscript{66} conducted a visual novelty oddball study that involved recording both event-related fMRI and ERPs. The ERPs revealed a large P3b wave to target events, a smaller P3b wave to novel events and no P300 wave to standard events. Interestingly, the novel events did not elicit a P3a. fMRI revealed that only targets evoked transient bilateral activation of the prefrontal cortex, primarily within the right middle frontal gyrus. These results are incompatible with lesion studies, \textsuperscript{68} which have shown that the prefrontal cortex is involved in the orienting response or novelty detection. The authors have proposed that the lack of novelty-related activation could be a direct result of the stimuli used - that is, the novel stimuli employed were everyday objects with very minimal, if any, affective content (e.g., bicycle), whereas previous investigations have employed stimuli with some degree of affective attributes (e.g., dog barks); or the novel events may have activated the middle frontal gyrus, but like with ERPs, the activity rapidly habituated over the first few trials, hence the activation may not have been evident in the across-run fMRI averages given the signal-to-noise ratio.

Clark and colleagues\textsuperscript{13} used a slightly different visual novelty oddball task. The novelty oddball paradigm typically inserts unique novel events (e.g., a picture of a dog) among the targets (e.g., squares) and the standards (e.g., circles), whereas Clark and colleagues employed letters as the standards (T), targets (X), and novels (C). The study supports previous ERP lesion studies that have demonstrated prefrontal involvement in novelty detection, \textsuperscript{68} and further indicates that the following regions may also be involved: bilateral inferior parietal lobule, lateral and medial cerebellum, and the left occipital-temporal cortex. Target detection evoked activations in multiple brain regions including the thalamus, the bilateral inferior parietal lobule, cingulate, and middle frontal gyrus. Furthermore, contrary to the ERP findings, \textsuperscript{68} Clark et al. did not observe a decrease in the amplitude of the hemodynamic response over stimulus repetition – that is, habituation. They argue that the discrepancy between the ERP and fMRI findings may be a result of the different neural mechanisms generating the signals in the two techniques.

Finally, Kiehl and colleagues\textsuperscript{63,64} also used event-related fMRI as a means to investigate detection behavior in both the visual and auditory systems. In their first study, Kiehl et al.\textsuperscript{63} employed a novelty auditory oddball task in an effort to elucidate the cerebral origins of both target and novelty detection. They found that auditory target processing elicited bilateral activations of primary auditory cortex, superior temporal gyrus, the inferior and middle frontal gyrus, temporal gyrus, inferior and superior parietal lobules, anterior and posterior cingulate, thalamus, caudate, as well as the amygdala and hippocampal complex. Novelty processing evoked bilateral activations of the inferior frontal gyrus, insula, inferior parietal lobule, in addition to the inferior, middle, and superior temporal gyri. These results are in accord with Kiehl et al.’s\textsuperscript{64} investigation of visual target and novelty processing, wherein they obtained activations in the anterior and posterior cingulate, inferior and middle frontal gyrus, bilateral parietal lobule, anterior superior temporal gyrus, amygdala, and thalamus for target detection, and the dorsolateral prefrontal cortex, inferior parietal lobule, as well as bilateral inferior and middle frontal gyri. Kiehl et al.\textsuperscript{64} compared the regions of activation between the two modalities for novelty processing and concluded that in general auditory stimuli result in significantly greater activations of the anterior cerebral regions, whereas the visual stimuli elicit greater activations in the posterior regions.

In sum, the neuroimaging data, in general, verify to a substantial degree both the lesion and intracranial findings regarding the P300. The studies described consistently demonstrate: (1) non-modality specific activations in the regions surrounding the temporal-parietal junction and the lateral prefrontal cortex, and (2) modality specific activations in the superior temporal gyrus (auditory tasks), and the occipital regions (visual tasks) (see
Animal Models:

Animal models are continuously employed as a tool to characterize and localize scalp recorded ERPs. The technique, however, does possess two very important limitations: (1) it is difficult to prove that the ERP component observed in one species is the same as that in another, and (2) some ERP components in humans cannot be described in animals, because they are not applicable; such as language specific responses. In order to circumvent these limitations, researchers must demonstrate that the ERP components found in animals resemble those found in humans in a range of task manipulations. Specifically, the animal and human components must have behavioral and anatomical correlates.

Characteristics for determining an animal homologue (i.e., P300- or P3-like potential) of the human P300 involve the component’s dependence on stimulus probability, its latency, and its scalp distribution. That is, the amplitude of the P300 is known to be inversely proportional to stimulus probability. In young adults, the P3b peaks near 350 msec after stimulus onset in the auditory modality and has a more parietal scalp distribution. The P3a peaks at about 280-300 msec after stimulus delivery and is characterized by a more fronto-central scalp distribution.

Furthermore, in order to avoid potential confounds it is imperative that the experimental paradigms employed in the animal studies resemble those utilized in the human. Animal studies typically employ the oddball task, in addition to one of the following three techniques, operant conditioning, classical conditioning, and passive viewing, as a method for training the animals to engage in the task. For example, Wilder, Farley, and Star{\textsuperscript{153}} identified a P3-like component in cats that resembled the human P300, but they employed a paradigm which involved aversive classical conditioning in artificially respirated paralyzed cats. Nonetheless, researchers have identified P3-like components that satisfy the aforementioned criteria. For instance, Pineda, Foote, and Neville{\textsuperscript{105}} identified a monkey P3-like component sensitive to stimulus probability that was largest over parietal electrode sites. Buchwald and Squires{\textsuperscript{9}} identified a similar component in cats.

In sum, P3-like waves have been identified in multiple mammalian species such as rats, cats, dolphins, rabbits, and monkeys. Since several studies have demonstrated a P3-like component in animals, which resembles the human component, researchers can now address its neural origin(s) through pharmacological manipulations, lesioning, and intracranial recordings.

**Figure 8.** Neuroimaging Studies: The white dots reflect increased blood flow during tasks generating a scalp P3b. The black dots reflect increased blood flow during tasks generating a scalp P3a. Data extracted from 12 fMRI experiments. See text for details.
Pharmacology. The pharmacology data aims at illuminating the neural circuitry involved in the generation of the P3-like potential, and it does so through the selective manipulation of specific transmitter systems. The results of the different drug manipulations diverge, most specifically when assessing the contributions of monoamines to the P300. For example, Glover, Ghilardi, Bodis-Woller, and Onofri demonstrated that 1-methyl-4-phenyl-1, 2-5, 6-tetrahydropyridine (MPTP), a drug that depletes dopamine and norepinephrine, abolished auditory P3-like potentials in macaque monkeys for about 30 to 40 days. Yet, Ehlers, et al. found that in rats, partial depletions of dopamine and serotonin did not affect the late positive potential recorded from the dorsal hippocampus and amygdala. Swick, et al. employed an auditory oddball task and demonstrated that the administration of clonidine, a drug known to suppress locus coeruleus activity, reduced the amplitude and increased the latency of the P3-like potential in squirrel monkeys. The drug, however, did not produce the same effect in the visual modality. Hence, they concluded that the locus coeruleus noradrenergic system makes a modality-specific contribution towards the generation of the P3-like potential. More recently, Takeuchi, et al. reported that the repeated administration of methamphetamine (MAP) caused a reduction in the amplitude (but no latency change) of the auditory P3-like potential in rats. They concluded that the change in catecholaminergic transmission induced by the repeated administration of MAP affects the mechanism eliciting the P300. In general, the monoamines seem to have a role in the generation of the P3-like potential, but their role seems to be indirect and possibly modality specific.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Species</th>
<th>Modality</th>
<th>Effect on P3-like</th>
<th>Reference</th>
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<tr>
<td>MPTP</td>
<td>Depletes DA</td>
<td>Macaque monkey</td>
<td>Auditory</td>
<td>Abolished potential for 30-40 days</td>
<td>Glover et al. (1988)</td>
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<td></td>
<td>Depletes NE</td>
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<td>6-OHDA</td>
<td>Depletes DA</td>
<td>Rat</td>
<td>Auditory</td>
<td>No effect</td>
<td>Ehlers et al. (1991)</td>
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<td>PCPA</td>
<td>Depletes 5-4HT</td>
<td>Rat</td>
<td>Auditory</td>
<td>No effect</td>
<td>Ehlers et al. (1991)</td>
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<td>Clonidine</td>
<td>Decreases LC</td>
<td>Squirrel monkey</td>
<td>Auditory</td>
<td>Decreased amplitude</td>
<td>Swick et al. (1994)</td>
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<td></td>
<td>activity</td>
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<td>Visual</td>
<td>No effect</td>
<td>Pineda &amp; Swick (1992)</td>
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<td>MAP</td>
<td>Increases CA activity</td>
<td>Rat</td>
<td>Auditory</td>
<td>Decreased amplitude</td>
<td>Takeuchi et al. (1991)</td>
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<td>Opioids:</td>
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<td>Naloxone</td>
<td>Opiate antagonist</td>
<td>Squirrel monkey</td>
<td>Auditory</td>
<td>Decreased latency</td>
<td>Ehlers et al. (1989)</td>
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<td>Ethanol</td>
<td>Effects opioids, BDZ/GABA</td>
<td>Squirrel monkey</td>
<td>Auditory</td>
<td>Decreased amplitude</td>
<td>Ehlers et al. (1988)</td>
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<td>Cholinergic:</td>
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<td>Scopolamine</td>
<td>ACh antagonist</td>
<td>Rhesus monkey</td>
<td>Auditory</td>
<td>Increased latency</td>
<td>Abe et al. (1999)</td>
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<td>AF102B</td>
<td>Muscarinic agonist</td>
<td>Macaque monkey</td>
<td>Auditory</td>
<td>Increased amplitude</td>
<td>O’Neill et al., (2000)</td>
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<td>Guanfacine</td>
<td>NE agonist</td>
<td>Macaque monkey</td>
<td>Auditory</td>
<td>Increased amplitude</td>
<td>O’Neill et al., (2000)</td>
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</tbody>
</table>

Abbreviations: MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; 6-OHDA, 6-hydroxydopamine; PCPA, parachlorophenylalanine; MAP, methamphetamine; DA, dopamine; NE, norepinephrine; 5-HT, serotonin; LC, locus coeruleus; CA, catecholamine; BDZ, benzodiazepine; GABA, gamma-aminobutyric acid; ACh, acetylcholine.
In sum, the data support the notion that the neural networks giving rise to the P3-like potential have a cholinergic and GABAergic component and may have an adrenergic component. A summary of the P3-like potential and its drug affects are presented in table 2.

**Intracranial Recordings.** Intracranial recordings allow direct access to the source of the ERP generator. In this method, focal polarity-inversions with the same timing and task correlate as the scalp-recorded waveform indicate that the probed neural region may be a local generator of the component in question. A second approach involves recording from single cells in the region(s) believed to be involved in the generation or modulation of the scalp-recorded potential. Studies employing both techniques are described below.

Intracranial recordings in cats yield polarity-inversions in the marginal gyri, suprasylvian gyri, hippocampus, entorhinal cortex, and amygdala, and they occur 200-500 msec subsequent to the presentation of rare stimuli. Furthermore, Katayama, Tsukiyama, and Tsubokawa employing multicontact electrode probes that passed through the cat thalamus, reported that the P3-like ERPs recorded at the cortical surface roughly correlated, in latency, with the negative ERPs that were recorded by the depth electrodes in the thalamus. Surface and depth recordings were also made in two macaque monkeys. The investigators demonstrated that the scalp recorded ERPs reached positive peaks at 260 to 300 msec after target onset, whereas the negative potentials recorded from the depth electrodes located in the medial temporal lobe occurred slightly later.

As previously described the locus coeruleus noradrenergic system is believed to contribute towards the generation of the P3-like potential. As such, Swick recorded locus coeruleus unit activity and scalp recorded ERPs concurrently in an effort to determine whether the activity of individual neurons in the locus coeruleus would be enhanced during the occurrence of P3-like potentials. Specifically, Swick exposed monkeys to a passive auditory oddball paradigm and found that some locus coeruleus cells showed a phasic activation subsequent to the rare tone. Swick argued that the generation of a P3-like potential was not always correlated with a phasic (related to the stimulus) locus coeruleus response to infrequent tones in the passive condition. For instance, in one trained monkey, locus coeruleus cells showed a tonic (related to the task) elevation in firing rate subsequent to target tone onset, and the activation increased when the monkey performed the task; hence, a phasic activation was related to the behavioral response rather than to the presentation of the stimulus.

**Lesion Studies.** Lesion studies can take two forms, those that involve the destruction of specific brain regions, and those that involve the ablation of the neurotransmitter systems. Both techniques have been employed in animal models; however, a definitive conclusion regarding the intracranial generators has not yet been drawn. Nonetheless, the following results have been reported. Paller, Zola-Morgan, Squire, and Hillyard compared the ERPs of intact macaque monkeys to those with bilateral ablations of the amygdala, hippocampus, and overlying cortical structures and found that these regions were not critical for the generation of normal P3-like responses recorded at the scalp. Studies in cats demonstrated that bilateral ablations of the primary auditory or polysensory association cortices did not significantly affect P3-like responses to rare clicks. However, it should be noted that these cat findings are not in accord with the extant human literature.

Research involving the ablation of the neurotransmitter systems has led to the following conclusions. Bilateral ablations of the medial septum and the vertical limb of the diagonal band of Broca, the major cholinergic input to the hippocampus, result in a temporary increase and then an eventual loss of the cat P3-like potential. Employing an auditory oddball paradigm, Pineda, Foote, and Neville examined the ERPs elicited by squirrel monkeys and demonstrated that conjoint lesions to the cell bodies of the noradrenergic nucleus locus coeruleus and the ascending axons from the nucleus, result in a significant amplitude reduction of the P3-like potential. Recently, using an auditory oddball task, Wang et al. demonstrated that lesions to the nucleus basalis of Meynert (nbM) in the basal forebrain, a major source of the cholinergic inervation for the entire cortex, result in a reduction of the P3-like amplitude in rabbits.
Conclusion:

The different methodological techniques currently employed to investigate the neural underpinnings of cognition have been useful in elucidating the neural origins of the P300, although not all issues pertaining to this brain potential have been resolved. Nonetheless, by complementing one another, the techniques allow for the development of a more complete picture of the neural basis of the orienting response and detection behavior. Through the use of the converging experimental methodologies scientists have been able to demonstrate that not only is the P300 composed of two functionally distinct potentials, the P3a and the P3b, but that multiple cortical generators give rise to each. See figure 9 for a composite figure summarizing P3a and P3b sources derived from human lesion studies, intracranial recordings, and fMRI investigations.

The physiological distinction between the P3a and the P3b is functionally consistent. Specifically, the P3a, which is involved in the detection of novel events and is characterized by its more anterior distribution habituates more rapidly than the more posterior P3b, which is concerned with voluntary target detection. This distinction is consistent; that is, at first when an event is novel a greater proportion of attentional resources need to be directed towards it in order to process and categorize the event. However, once this has been done it is no longer necessary to allocate as many resources, hence habituation occurs as initially proposed by Sokolov\textsuperscript{128,129,130}. In contrast, targets are constantly being sought out; thereby, a great deal of resources, are continuously allocated to them, and as such habituation does not necessarily occur.

Detection behavior is also critical to survival. For instance, detection enables people to orient towards a car upon hearing its horn while crossing a street, and as such the probability of getting hit by the car and sustaining injury or even death is decreased. As described in this review, research has demonstrated that detection behavior cannot be linked to a single neural generator but rather multiple cortical generators. Each of these generators perhaps serve a specific function or maybe subsets of different brain regions support a specific function and coordinated activity between the regions or subsystems contribute to the behavioral phenomenon.

Are multiple cortical generators involved in detection behavior as a method of compensation? That is, from an evolutionary perspective have we developed multiple generators so that when one brain region is lesioned another region can compensate, enabling organisms to continue orienting at some level? This seems unlikely since there is no reason to believe a system would have evolved simply to provide a substrate for re-organization after injury. Halgren and colleagues\textsuperscript{41} have proposed that the brain has developed a strategy in which it recruits all potentially useful regions in order to complete a task even though the probability that each region will contribute to the immediate task is low. This widespread activation of multiple parallel processing systems proves advantageous in the natural environment, as opposed to a laboratory setting, where it is necessary to rapidly identify and evaluate an event so that a response can be quickly initiated or withheld, and in turn increase the probability for survival and reproduction.
Although major progress has occurred regarding the neural basis of the P300, there are several issues that need to be addressed. For instance, the cellular infrastructure of the P300 phenomena needs to be delineated. A central issue in cognitive neuroscience is how do these multiple cortical generators or multiple processing systems functionally connect to give rise to the orienting response or detection behavior? Data recorded from humans with prefrontal, hippocampal, or temporal-parietal lesions, suggests that the novelty detection cascade is initiated by prefrontal cortex. In this view, prefrontal dependent cortical mechanisms initiate the novelty detection cascade, which in turn signals hippocampal regions that an event possibly deserving long-term storage has occurred.

In addition to defining the timing of interactions between cortical and limbic regions engaged in voluntary and automatic attention, a key question is how these brain regions communicate. Recent data suggests that coherent oscillatory theta, beta, and gamma activity may serve to bind together cortical regions. These rhythms, however, do not have enough band pass (i.e., do not have enough dynamic spectrum) to carry a neural code between regions. Hence, this information must reside in individual cell firing patterns, and unfortunately, no technique, to date, is capable of providing a complete analysis of information transfer between brain regions involved in cognitive processing. So a key question remains, how do these multiple brain regions functionally connect to give rise to the orienting response and/or detection behavior.

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