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Review

The novelty P3: an event-related brain potential (ERP) sign of the brain's evaluation of novelty

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Abstract

A review of the literature that examines event-related brain potentials (ERPs) and novelty processing reveals that the orienting response engendered by deviant or unexpected events consists of a characteristic ERP pattern, comprised sequentially of the mismatch negativity (MMN) and the novelty P3 or P3a. A wide variety of evidence suggests that the MMN reflects the detection of deviant events, whereas the P3a is associated more with the evaluation of those events for subsequent behavioral action. On the scalp, the novelty P3a is comprised of at least two aspects, one frontal the other posterior, each with different cognitive (and presumably neurologic) correlates. Intracranial ERP investigations and studies of patients with localized brain lesions (and, to some extent, fMRI data) converge with the scalp-recorded data in suggesting a widespread neural network, the different aspects of which respond differentially to stimulus and task characteristics.

Keywords: Cognitive brain potentials; Orienting response; Novelty P3; P3a; P3b

Contents

1. Introduction

Distinguishing between what is novel and what has already been experienced, or between degrees of novelty encompasses fundamental processes that enable one to appropriately react to stimuli in the environment. What is considered novel and/or salient depends also upon the context in which the eliciting event is encountered. For example, car honks while being a pedestrian are not as salient as those same environmental sounds when driving your car to work during rush hour. During the latter, it is a

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common experience for the driver to proceed from point A to point B without conscious awareness of how that stretch of highway was negotiated. The 'noise' outside as well as inside the automobile recedes into the background while focal attention is drawn to inner thoughts, or to the information conveyed by the radio. Yet, even while deep in thought, a biologically significant change in the background 'noise', such as a car horn or tire screech will cause a shift in attention i.e., an orienting response.

The orienting response [59,87] is an involuntary shift of attention that appears to be a fundamental biological mechanism necessary for survival. Orienting is a rapid response to new (never experienced before), unexpected (out of context) or unpredictable stimuli, which essentially functions as a 'what-is-it' detector. Given the examples of the car horn and tire screech described above, the detection of the event precedes orienting and, if it is sufficiently deviant, engenders the involuntary capture of attention, enabling the event to enter consciousness, thus permitting an evaluation of the significance of the stimulus. This could lead, if the event is deemed significant, to behavioral action. The importance of this ubiquitous response can be seen from studies showing that human infants as young as 3 months old exhibit an orienting response to novel stimuli. For example, Kagan [46] demonstrated that infants oriented to the sudden onset of a female voice, while Fagan [22] showed that infants maintained their gaze for a longer time at novel stimuli when presented within a pair of novel and already viewed (i.e., familiar) stimuli.

Sokolov [87] demonstrated the plasticity of the orienting response by showing that stimuli which initially evoked the response no longer did so with repeated presentation. Habituation of the response is proposed to indicate that some type of memory for these prior events has been formed which modifies the response to the repeated incidences. It has been further proposed [88] that novel stimuli elicit processes that enable the construction of neural representations for these new events. As stimulus exposure continues and the neural representation is formed, the constructed representation is then continuously compared to incoming information. Habituation occurs when the representation matches sufficiently the external stimulus. Finally, future encounters with this, no longer novel, item will be facilitated.

2. Scope of this review

Orienting, habituation and memory processes for novel events have been measured physiologically and are the topics of the present review. The primary purpose of this review is to acquaint the reader with the state of knowledge concerning the temporal characteristics and neural substrates of the detection and evaluation of novel or unexpected events. As most of the physiological research regarding brain responses to novel events has been performed within the auditory modality, this review will focus on that modality. The first section of this paper will present a brief review of event-related brain potential (ERP) methodology, because much of the recent research concerning the brain's response to novelty has been accomplished using the ERP technique. This will be followed by a description of the ERP signs of deviance detection and evaluation and the putative brain regions that are involved. Next, the results of a series of investigations on the cognitive underpinnings of the brain's ERP response to novelty will be discussed. The next section will attempt to integrate the ERP findings with those obtained from intracranial ERP recordings, ERP studies of patients with localized brain lesions, and fMRI investigations. We will close with a discussion of the functional significance of the ERP responses that comprise the brain's evaluation of novelty.

3. The scalp-recorded event-related brain potentials (ERPs)

ERPs are voltage fluctuations in the electroencephalogram (EEG) induced within the brain that are time locked to sensory, motor, or cognitive events. They provide a direct, non-invasive measure of the temporal course of the voltage changes that are extremely sensitive to manipulations of the cognitive context within which the eliciting stimuli are embedded. By contrast, the spatial resolution for identification of the neural sources generating these signals has been poor relative to the newer brain imaging techniques. However, recent developments in high-density recording arrays in conjunction with more sophisticated analyses of the data has enabled improved recovery of spatial information. As a consequence, there has been a renewed interest in ERPs as a brain imaging technique.

The ERP consists of a sequence of positive and negative voltage fluctuations labeled components. These components reflect various sensory, cognitive (e.g., stimulus evaluation) and motor processes that are classified on the basis of their scalp distribution and response to experimental variables. Moreover, ERP components are useful as measures of covert information processing, as differences between conditions can be obtained in the absence of behavioral responding (e.g., the detection of unexpected, novel events).

ERPs are quite small (1–30 millionths of a volt) relative to the background electroencephalographic (EEG) activity and, therefore, require the use of signal-averaging techniques for their elucidation. Successful delineation of a component is a function of the signal-to-noise ratio, and is determined by the amplitude of a component relative to the background EEG amplitude, the number of experimental trials comprising an averaged waveform, and the degree of artifact in the original data. Fortunately, many cognitive ERP components are large and overlap little with the frequencies of the waking EEG so that averages with good signal-to-noise ratios can be generated on the basis of relatively few trials (e.g., 15–30).

An ERP waveform can be quantitatively characterized

across three dimensions, amplitude, latency and scalp distribution [43]. Amplitude provides an index of the extent of neural activity (and how the component responds functionally to experimental variables), and latency (i.e., the time point at which peak amplitude occurs) reveals the timing of this activation. Scalp distribution provides the pattern of a component's voltage gradient over the scalp at any point in time, and is indicative of the underlying neuroanatomical activity.

Although there are difficulties in determining the brain sites from which specific ERP components emanate, the scalp distribution of an ERP component can provide very useful and complementary information to that derived from amplitude and latency. Comparison of the scalp distributions of ERPs elicited by different stimuli, either within or across conditions, allows one to infer whether the two stimuli engender different patterns of neural activity and, hence, reflect different functional processes [44]. Therefore, by combining the temporal and spatial information available in the ERP waveform recorded over a large number of different areas of the scalp, it is possible to determine the temporal characteristics (both onset and duration) of stimulus- and condition-specific patterns of brain activity.

With the recent advent of large-array recording techniques, the easiest and clearest way to represent the data is with topographic maps. Two types of maps can be generated, raw voltage (or surface potential, SP) and current source density (CSD). Although both types of maps are derived directly from the original amplitude data, each provides a very different view of brain activity (see ref. [78] for a complete description). The scalp-recorded ERP voltage activity reflects the summation of both cortical and subcortical neural activity during any given temporal window. By contrast, CSD maps reflect primarily cortical surface activity, because the amplitudes are spatially filtered with an algorithm that removes the volume conducted activity from subcortical areas as well as cortical areas distal to the recording electrode(s). This results in a spatially-sharpened, reference-free display of positive and negative current densities that emphasize local (i.e., cortical) differences [72,78]. Because local generators are represented by this technique, CSD maps are useful for forming hypotheses about neural sources in superficial cortex [77].

4. Limitations of techniques for assessing the brain's novelty response

All of the techniques used to understand the brain's novelty response have their limitations, and these will be delimited here. However, the strengths of the different techniques can counterbalance the weaknesses when multiple techniques are used convergently to record brain activity in response to novel events. For example, the recovery of spatial information from the ERP waveform can be difficult, because for some ERP components there is no direct relation between the surface activity and the underlying intracranial generators. Some methods for extraction of spatial information are more viable than others [29,54,69,99]. One such procedure is source modeling. This technique uses a mathematical solution to describe the location, orientation, and strength of an hypothesized dipolar source(s) to explain the measured scalp distribution of an ERP component. However, as with all modeling solutions, problems exist. One is that there is no single, unique solution. A second is that the solution is sensitive to the initial number and location of sources proposed to account for the measured distribution. This information is rarely known a priori. One way to deal with this is to constrain the number and location of possible dipole sources based on imaging data from PET and fMRI neuroimaging, as these techniques have better spatial resolution than the ERP method (see Section 7.3). That is, one 'seeds' the coordinates of activated brain regions generated in comparable PET or fMRI studies, and determines whether the measured scalp distribution of an ERP component can be explained by sources in those locations [38,67,74,75]. Complementary approaches are to infer the generators of ERP components from studies of patients with localized brain injuries [48] or from electrodes implanted intracranially [6].

Although hemodynamic techniques afford better spatial localization, they have much poorer temporal resolution, and at least three methodological issues should be considered when interpreting the results of blood flow studies. First, one major problem in relating ERPs to hemodynamic phenomena is the markedly different temporal scales of each. Second, the activated areas based on hemodynamic techniques do not necessarily correspond to the neural activity identified by ERP techniques. Third, early fMRI investigations employed blocked designs. This type of design confounds differences related to stimulus categories (e.g., target vs standard; target vs novel) with changes in subjects' strategies due to differences in the density of the different stimulus types across blocks of trials.

Studies of patients with lesions involve previous damage to the brain and, therefore, do not necessarily allow an unequivocal view of normal brain function. In addition, lesions are typically not confined to one, discrete, region of the cortex, but often encroach upon several Brodmann areas. Therefore, functions ascribed to, for example, 'dorsolateral' prefrontal cortex, might also be subserved by other prefrontal regions within the vicinity of the lesioned area. Similarly, intracranial ERP investigations are limited to certain recording sites dictated by clinical concerns and interests that may not coincide with experimental requirements. Hence, all relevant brain regions may not be sampled, rendering this technique silent to some of the contributing structures.

5. Definition of ERP terms

Low frequency, deviant, events presented within a train of homogeneous stimuli elicit an orienting response. ERPs

elicited by these same stimuli are comprised sequentially of the mismatch negativity (MMN) and the novelty P3, both of which will be described in detail in this review. Throughout the remainder of this paper we will use the term 'novelty P3' to refer to the P3 component elicited by events about which the subject has not been instructed prior to the experiment (e.g., environmental sounds). These events are, by definition, unexpected. The term 'target P3' will refer to the P3 component elicited by events about which the subject has been instructed and to which the subject is required to generate some kind of response (e.g., speeded reaction time). The terms 'P3a' and 'P3b' refer to ERP components that can be elicited by a variety of stimuli, including those that are defined as targets as well as novels, and can also co-occur within the same ERP waveform. The P3a is frontally-oriented, whereas the P3b is localized to posterior scalp. However, this is not meant to imply that the posterior foci observed for the Novelty P3 are always incidents of P3b. Although this is likely to be the case, there are currently no experiments that have explored this issue. Therefore, a definitive conclusion on this point cannot yet be drawn.

6. ERP paradigms for studying 'novelty'

Several methods have been devised to study the physiological antecedents and consequences of the orienting response within a laboratory setting. Perhaps the most often used paradigm is one that has been termed the *Regular oddball task*. By far, the vast majority of investigators have used the auditory modality, and much is known about the ERP correlates of orienting to deviant auditory events (see Refs. [70,71] for detailed discussions). In a typical oddball experiment, two classes of stimuli are presented, a frequently occurring or 'standard', and an infrequently occurring deviant or oddball. In the 'active' oddball, participants are required to detect the occurrence of the oddball events (deemed 'targets') either by silently counting these events or by reaction time responses. In the 'passive' oddball, the subject's attention is directed away from the auditory stream by engaging them in a primary task, such as watching a silent movie, or reading a book. Thus, participants ignore the auditory stimuli.

Another type of oddball task, labeled the *Novelty oddball*, has also been employed to study the brain's orienting response. In this paradigm, three classes of stimuli are delivered, a standard, high-probability event, a low-probability target deviant, and an equally improbable series of unique, unexpected 'novel' events. Because these initially novel events are unexpected, this laboratory procedure mimics more closely the real-world involuntary attentional capture by novel or unexpected events.

7. Physiological indices of the orienting response

The underlying physiology and neuroanatomical substrates of the brain's response to novel events has been assessed with a number of different methods, including (but not limited to) galvanic skin conductance [65], pupillary dilation [23], scalp-recorded ERPs [9], intracranially-recorded ERPs [6], and functional magnetic resonance imaging (fMRI) [74], and for various subject populations such as older adults [20], children [13], and patients with localized brain lesions [48].

7.1. The detection of auditory deviant and novel events

The early, obligatory, sensory ERP components prior to 100 ms or so after stimulation reflect the arrival of acoustic information in subcortical relay nuclei and cortical sensory areas. The earliest ERP activity that indicates that the brain has detected a change in an otherwise invariant background of homogeneous events is labeled the mismatch negativity or MMN [66]. Based on a variety of evidence, including scalp-recorded ERPs [30,82,84], magnetoencephalographic recordings [3], indwelling electrodes in cats and monkeys [10,41,42], infrared optical techniques [81], and fMRI [75], the MMN is thought to be generated in and around primary auditory cortex. Furthermore, a generator in auditory association cortex has also been implicated [56], based on evidence from intracranial recordings in pre-surgical epilepsy patients. The MMN appears to reflect the operation of a comparator mechanism, i.e., a response to the difference between successive stimuli, as it cannot be elicited by stimuli at the beginning of a sequence, or by infrequently presented stimuli without intervening standards. The amplitude of the MMN is directly proportional and its latency inversely related to the degree of difference between standard and deviant stimuli. The MMN is most clearly seen by subtraction of the ERP elicited by the standard stimulus from that elicited by the deviant stimulus during a passive oddball paradigm when both of those stimuli are unattended or 'ignored.' Because the MMN is evoked by stimuli that fall outside the focus of attention, it is considered to be a relatively automatic, pre-attentive response to stimulus deviance. Fig. 1 depicts the ERP waveforms elicited by standard and deviant events in a situation in which the deviant differs only slightly from the standard. The depicted data were obtained while subjects were watching a silent movie and ignored the auditory events. Note that the brain discriminates the deviants from the standards quite rapidly at approximately 120 ms following the deviant event (as evidenced by the divergence of the standard and deviant waveforms on the left and the onset of the MMN on the right).

In addition to the generator(s) presumably located in primary auditory cortex, a secondary, frontal source has also been proposed based on the observation of a focus on the scalp overlying the frontal lobes in surface mapping studies [16,30,56]. This notion of a frontal generator gains some support from the finding that patients with prefrontal cortical lesions show reduced MMNs [2,4]. One hypothesis is that the frontal aspect of the MMN reflects input to the frontal lobes from the sensory-specific MMN generator

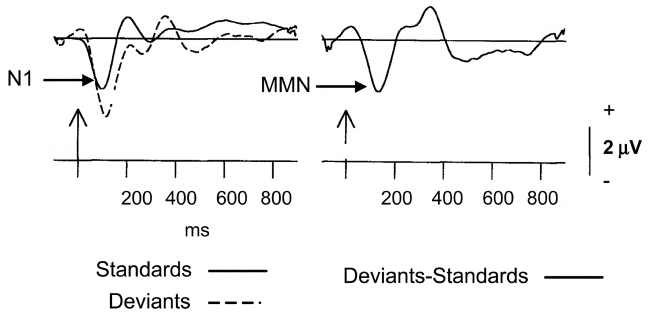

Fig. 1. *Left*. Grand mean ERPs elicited by standards and deviants during a simple auditory oddball procedure in which subjects were instructed to ignore the stimuli while watching a silent movie. *Right*. Grand mean difference waveform obtained by subtracting the standard ERPs from the deviant ERPs depicted on the left. Arrows mark stimulus onset with timelines every 200 ms.

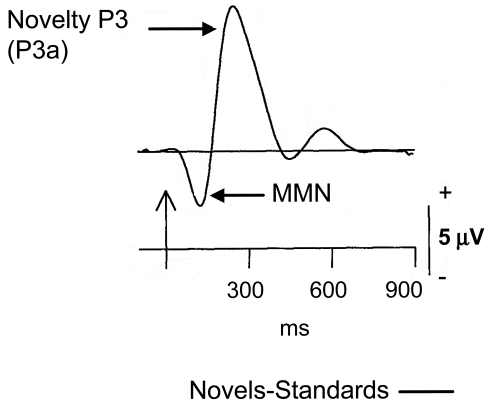

Fig. 2. Grand mean difference waveform obtained by subtracting the standard ERPs from the novel ERPs in the same situation as described for Fig. 1.

mechanism, signaling a potentially significant biological event. The frontal aspect of the MMN could thus reflect a 'call' to involuntarily orient to a potentially significant biological background event.

In certain circumstances, the information from the MMN system is transmitted to a frontal lobe mechanism that presumably serves to make the event available to consciousness and behavioral control. As we will argue throughout this review, that neural event is the frontal aspect of the novelty P3, i.e., the P3a. For example, if the event is sufficiently deviant, the MMN is followed by the P3a. The data depicted in Fig. 2 were also obtained while participants viewed a silent movie. The eliciting events in this case, however, were highly deviant environmental sounds, such as dog barks, machine noises, musical sounds etcetera. Note, by contrast with the ERPs depicted in Fig. 1, that these deviant sounds elicit a large-amplitude, positivity, the P3a, which indicates that the novel event has involuntarily captured attention and, at that point in time, is most likely within the focus of attention. This occurs as early as 280 ms post-stimulus.

Evidence that this sequence of neural events plays a role

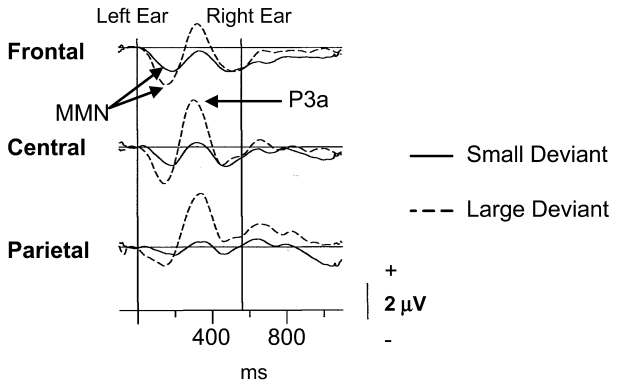

Fig. 3. Grand mean difference waveforms (deviant-standard) when the task-relevant, S2 stimuli were preceded by small (solid lines) and large (dashed lines) deviants. The waveforms include ERPs to the preceding S1 stimuli (unattended) and the following S2 stimuli (task relevant). Waveforms are for correct Go responses to the S2 stimuli classified according to the type of preceding S1 stimulus (i.e., small or large deviant). Vertical lines mark the onset of the left ear and right ear stimuli.

in involuntary attentional capture has been provided by the results of experiments in which the processing of task-relevant stimuli delivered in one channel is disrupted by task-irrelevant stimuli delivered in a second channel [19,28,85]. In the study by Gaeta and colleagues [28], task-relevant auditory stimuli were delivered to the right ear. These consisted of two, equiprobable, 1000 Hz tones of different intensities, of which the lower intensity stimulus was designated the target. Preceding the right-ear stimuli by a few hundred ms, standard ($P = 0.90$; 700 Hz) small- ($P = 0.05$; 650 Hz) and large-deviant ($P = 0.05$; 500 Hz) task-irrelevant auditory stimuli were delivered to the left ear. Fig. 3 presents the grand mean difference waveforms. These waveforms were constructed by subtracting the ERPs elicited when standard tones preceded target tones from the ERPs elicited when either small or large deviants preceded target tones. The stimulus onset asynchrony between left ear and right ear stimuli in this condition was 560 ms. The first and second vertical lines indicate the onset of the left and right ear tones, respectively. The difference waveforms reflect primarily the brain's response to the first (task-irrelevant) stimulus, as the subtraction eliminates components that are common to the second (task-relevant) stimulus. As can be seen, as the degree of deviance increases MMN amplitude increases. However, although a significant MMN is elicited by both small and large deviants, a significant P3a is elicited only by the large deviant, suggesting a dissociation between the MMN and the P3a. In other words, the MMN does not appear to reflect the involuntary capture of attention or orienting, the P3a does.

The most ubiquitous physiological indicators of the orienting response have been the galvanic skin conductance response and heart rate deceleration; both of these measures have been extremely well researched [73]. Stimuli which engender an orienting response are typically accompanied by a phasic change in skin conductance as well as heart rate,

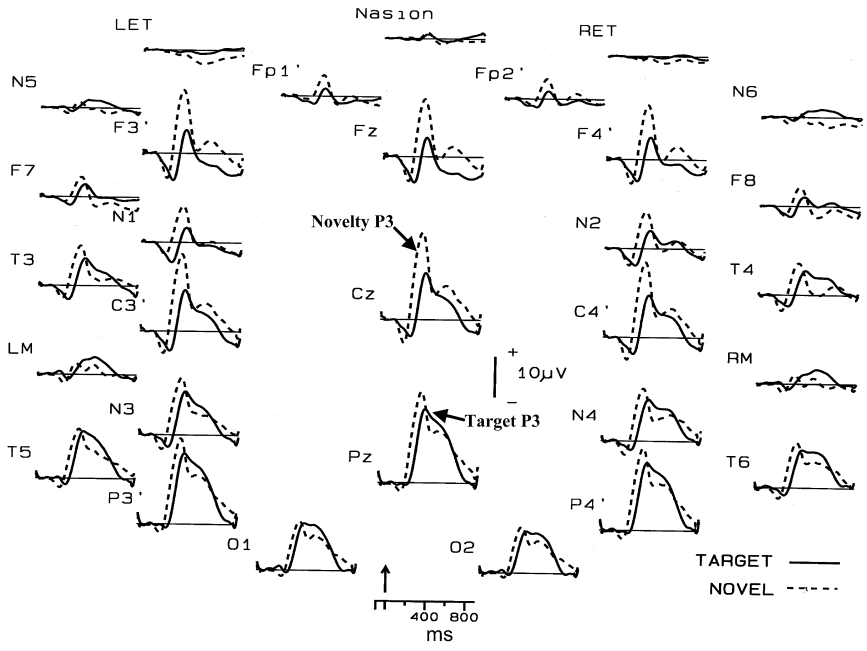

Fig. 4. Grand mean ERPs elicited by infrequently occurring targets and equally infrequent novel, environmental sounds during an actively attended novelty oddball task. The data are depicted at all 30 scalp sites.

i.e., deceleration. Evidence that the MMN does not reflect orienting per se comes from studies in which ERPs and galvanic skin conductance as well as heart rate measures have been recorded in response to unexpected or novel events. For example, Lyytinen and colleagues [61] reported that MMN amplitude did not differ between trials in which a skin conductance response or heart rate deceleration was elicited by deviant events. On the other hand, the P3 component elicited by deviant events was larger when associated with a phasic skin conductance response compared to when no skin conductance response was present. Similarly, Knight [49] showed that, in normal controls, the P3 elicited by novel auditory events was accompanied by a phasic skin conductance response, whereas in patients with posterior hippocampal lesions the skin conductance response as well as the P3 elicited by novel environmental sounds was dramatically reduced. Taken together, these data suggest that the MMN is not a surrogate for the orienting response. By contrast, the P3a appears to reflect an aspect of the orienting response, a conclusion given added weight by the data of Schröger [85] and Gaeta and colleagues [28] described above.

By contrast with the P3a, another aspect of the ERP waveform, labeled the P3b [94], is also elicited by infrequently occurring events, but these events must typically be task-relevant, or involve a decision, to evoke this component. A great deal is known about the cognitive correlates of the P3b, although a consensus as to its functional significance has not been achieved. By contrast with the P3a, the scalp distribution of the P3b is usually, though not always, focused over posterior parietal scalp (Figs. 4 and 5). Recent evidence from this laboratory (reviewed below), however, suggests that the P3b is often elicited in tandem with the P3a, and that these two components reflect the output of a widely distributed (primarily cortical) neural network. Further, these data indicate that the various aspects of this network respond differentially to stimulus and task characteristics, thus accounting for the fact, clearly evident in the literature [44], that the scalp topography of the P3b has been observed to vary under different experimental conditions.

In most situations, the P3 (elicited by targets) recorded at frontal electrode sites peaks earlier than its posterior counterpart. This has led some investigators to consider the frontal and posterior aspects manifestations, respectively, of the P3a and the P3b. On the other hand, there are also situations in which the two aspects appear to occur with similar latency (Fig. 4), so that this criterion might not always be definitive.

7.2. The evaluation of novelty—the P3a

In the 10 years that elapsed from the discovery of the P3b by Sutton and coworkers in 1965 [94], it was thought that the P3 was a monolithic component, always occurring with the identical scalp distribution under the same task (relevant) circumstances, with the same functional significance in all situations. This view currently has its proponents [17,90]. However, in two seminal experiments, Courchesne and colleagues [9] and Squires et al. [92] showed that highly deviant, task-irrelevant stimulus events engendered a P3 component that was significantly different compared to that induced by events designated as targets. In Courchesne's experiment, the novels were infrequently and unexpectedly occurring complex visual patterns that were difficult to

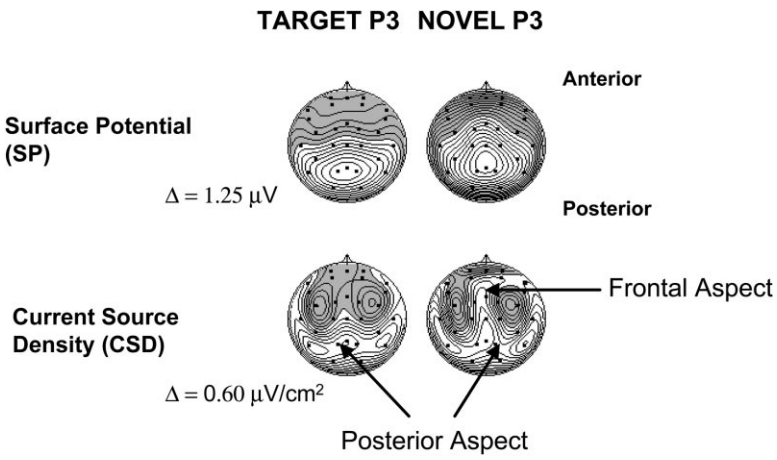

Fig. 5. *Top Row*. Surface potential (SP) maps of, respectively, target and novel P3 activity. *Bottom Row*. Current source density (CSD) maps of target and novel P3 activity. Dots indicate electrode positions on the scalp.

label, whereas the equally infrequent targets and frequent standards were highly familiar single digits (or letters). Courchesne et al. [9] observed that the P3 elicited by novels (peaking at about 300 ms) was more frontally oriented compared to the P3 elicited by targets, which showed a parietal scalp focus typical of the P3b. This finding was interpreted to mean that unexpected, task irrelevant novel events were processed differently, at least initially, compared to the pre-categorized targets. As these events were unexpected and highly deviant, they most likely induced orienting, a function known to depend upon the frontal lobes [59], presumably resulting in the frontally-focused scalp topography.

A similar conclusion was reached by Squires and colleagues [92] in the auditory modality, although they did not employ novel stimuli. Rather, they demonstrated that when highly improbable (i.e., $P = 0.10$), deviant events were delivered intermixed with frequently occurring standards ($P = 0.90$), another P3 component (labeled the P3a) with a fronto-central scalp distribution and a latency to peak of about 280 ms was elicited. Although the novelty P3 and the P3a were elicited by distinctly different stimuli during quite different task circumstances, it is generally believed that they reflect the output of a similar configuration of neural sources.

The hypothesis that the P3a component reflects the engagement of the frontal lobe aspect of the neural network that responds to deviant events [86] is supported by studies showing that it is dramatically reduced in patients with dorsolateral prefrontal lesions when compared to normal controls [15,48], or patients with lesions elsewhere within the brain [53]. Other evidence for a prefrontal cortical contribution to this electrical activity comes from intracranial ERP investigations [6], and current source density mapping studies of surface recorded ERP activity [20,86]. The P3a component is thought to reflect the activation of an attentional switching mechanism. Although the prefrontal cortex is a critical aspect of the system that gives rise to the P3a or the novelty P3, there is good evidence for a distributed network of cortical regions, including the auditory cortex [3,74], posterior hippocampus [49], temporo-parietal junction [18,53], medial frontal gyrus [62], and anterior cingulate gyrus [67]. As will become evident in later sections of this review, the P3a is thought to reflect an evaluative, conscious, aspect of the orienting response [11,69], as opposed to the detection of deviant events per se, which appears to be accomplished at a pre-attentive level and is reflected by the MMN.

To assess these kinds of phenomena with more electrode sites than had been used previously, Fabiani and Friedman [20] designed a 3-stimulus novelty oddball paradigm. Fig. 4 depicts the ERPs recorded during this paradigm from 30 scalp sites. The ERPs were elicited by both pre-instructed auditory 'target' (to which the subject responded via button-press) and unexpected, task-irrelevant, 'novel' events. Two aspects of these ERP data deserve mention. First, the amplitudes of the ERPs elicited by the novel, environmental sounds are larger than their target counterparts. Second, the amplitude difference appears to be much more marked over the frontal scalp, and is less obvious across the posterior scalp. This anterior/posterior, target-novel amplitude differential suggests a difference in scalp distribution between the P3 components elicited by these two stimuli. This can be observed in Fig. 5, in which surface potential (SP; i.e., the raw voltage) and current source density (CSD) maps are depicted. Both types of maps lead to a similar conclusion—the target P3 shows a clear posterior scalp focus, whereas the P3 elicited by the novel sounds shows not only a posterior scalp focus of positive activity but also an anterior area of positive activity. However, there are areas of difference between the SP and CSD maps: while the SP maps tend to show widespread areas of positive activity, the CSD maps decompose this into bilateral areas of posterior positive current densities abutting smaller, bilateral frontal areas of negative current densities. While the CSD maps emphasize cortical sources, the SP maps reflect

activity emanating from cortical as well as deeper regions, such as the medial temporal lobe, consistent with contributions from the hippocampus for both the P3b [37] and the P3a components [49].

On the basis of the data depicted in Fig. 4, we [25] concluded that the brain's response to novelty (as recorded from the scalp) is comprised of at least two activities, frontal and posterior. The next sections detail the results of experiments that confirm this view with more compelling evidence based on the fact that the frontal and posterior aspects respond differentially to a variety of experimental variables, including habituation, familiarity and attention. In all of the experiments described below, subjects were not informed about the presence of the environmental sounds, and were required to respond only to the tonal targets via speeded reaction time (RT).

7.3. Reduction of the P3a with 'experience'

One of the functions of the orienting response is to prepare the organism to deal with the novel stimulus. However, with repetition of the same or similar stimuli, a neuronal model is formed and those stimuli no longer evoke the same magnitude reaction [89]. Hence, one of the hallmarks of the orienting response is its rapid habituation [60]. From the earliest studies of novelty processing with the ERP [9], it had been shown that the P3a component habituated rapidly, i.e., within a single recording session, or within the first few trials. Furthermore, although the data were recorded from only a few electrode sites along the scalp midline, the amplitude reduction was more dramatic at the frontal compared to the parietal scalp location. This same phenomenon was observed by Knight [48] in control subjects, but not in patients with unilateral lesions in dorsolateral prefrontal cortex, again implicating the prefrontal cortex as a critical element in the brain's response to novelty [100].

The data reported by Courchesne et al. [9] and Knight [48] implied a change in scalp distribution of the P3 elicited by the novels (and, hence, a difference in the configuration of neuronal generators) from frontally-oriented early in the stimulus sequence when subjects had little experience with the complex visual patterns (or environmental sounds), to posteriorly-focused as more experience was obtained. This selective diminution of the frontal aspect of the novelty P3 has been replicated with a greater number of electrode sites [26], permitting statistical confirmation of the distributional change [63,83]. Consistent with Fabiani and Friedman's [20] conclusion mentioned earlier, the fact that the posterior aspect did not change as rapidly as the frontal aspect suggests that these two components of the brain's response to novelty reflect different cognitive functions.

Friedman and Simpson [26] assessed habituation of the novelty P3 within a block of trials in a novelty oddball task in which 48 unique environmental sounds (none of which repeated; $P = 0.12$), equally infrequent target tones ($P = 0.12$) and highly probable ($P = 0.76$) standard tones were randomly intermixed. There were six novel sounds presented during each of eight blocks of stimuli. To measure the extent of habituation from the first through the sixth novel event within a block of trials, ERP averages were comprised of the eight novels across the eight blocks of trials categorized according to their numerical order within the block (i.e., 1–6). The results indicated that the reduction in novelty P3 amplitude from the first to the sixth event was more marked for the frontal than the posterior electrode sites, leading to a statistically reliable change in scalp distribution; i.e., the topography to the first novel was frontally oriented, whereas that associated with the sixth novel showed a posterior distribution.

Repetition of verbal and pictorial concepts [96] induces a facilitation in processing the repeated stimulus labeled 'priming', and is demonstrated by faster reaction time to the second relative to the first presentation. Blood flow studies of repetition priming [91] have shown that the facilitation in processing the repeated stimulus is associated with a reduction in brain activity in modality specific cortical regions. In a follow-up of the Friedman and Simpson experiment [26], Kazmerski and Friedman [47], (see also Ref. [13]) built repetition of the environmental sounds into their design and hence were able to determine the nature of the changes induced by repetition of the identical environmental sound. The midline ERPs, surface potential and current source density maps from that study are depicted in Fig. 6. As was observed by Friedman and Simpson [26] for the recurrence of *unique* novel events, repetition of the *identical* novel sound induces a reduction in the amplitude of the P3 component that is greater at frontal compared to posterior scalp sites, again leading to a statistically reliable change in scalp distribution (right side of Fig. 6). These data are consistent with the results of PET and fMRI studies [39] and suggest that the frontal aspect of the novelty P3 (P3a) reflects a reduction in brain activity engendered by the repeated environmental sound.

One other critical aspect of repetition priming by pictorial and verbal materials is that behavioral facilitation will typically occur only if the particular stimulus has a pre-existing representation in semantic memory [96]. Although the research data based on non-linguistic (environmental) sounds is less extensive than those for their verbal counterparts, there is some evidence suggesting similarities in the ways in which sounds and words are processed. For example, sounds that are encountered often in the environment (i.e., those that are more familiar) are easier to identify than those that are less common [5]. In analagous fashion to word repetition priming effects, Stuart and Jones [93] demonstrated that identification of environmental sounds was facilitated by prior exposure to the same sound. Furthermore, Van Petten and Rheinfelder [97], who used meaningful environmental sounds and related words, demonstrated semantic priming of both words and sounds regardless of whether the nonspeech sound or the related word served as prime or target.

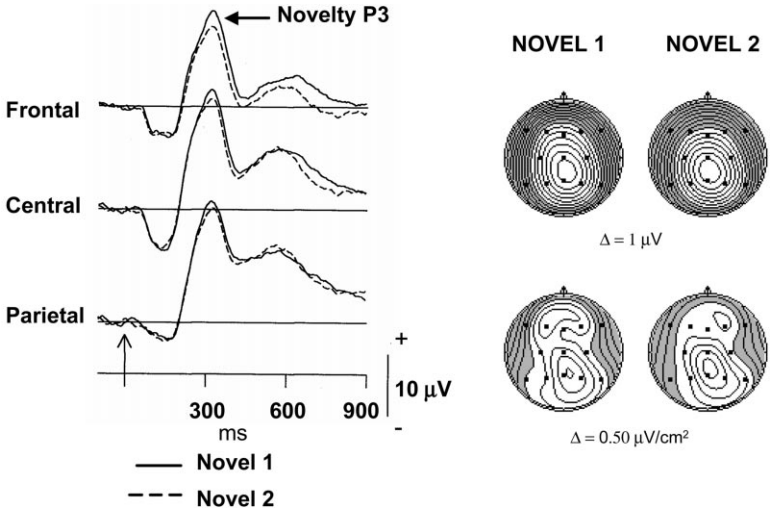

Fig. 6. *Left*. Grand mean ERPs elicited by first (novel 1) and second (novel 2) presentations of the identical environmental sounds during a novelty oddball task in which repetition was built into the design. *Right*. Surface potential (SP) and current source density (CSD) maps of the P3 activity elicited by first and second presentations of the novel sounds based on the ERP data depicted on the left. Dots indicate electrode positions on the scalp.

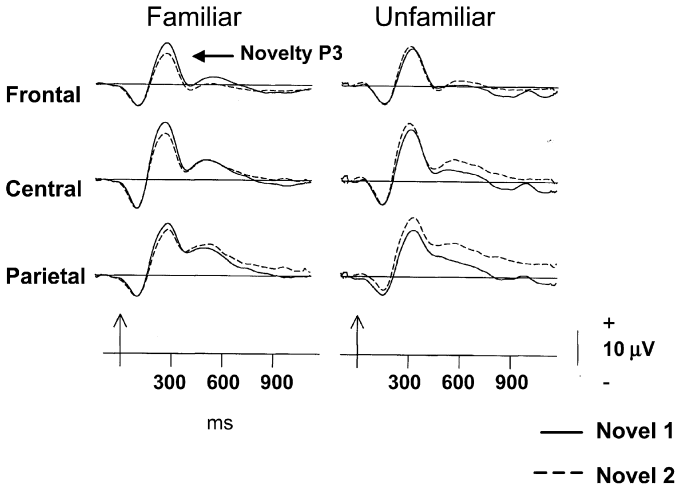

Fig. 7. Grand mean ERPs elicited by first (novel 1) and second (novel 2) presentations of the identical environmental sounds categorized according to whether they were (familiar) or were not (unfamiliar) correctly assigned to the appropriate semantic category.

The sounds presented by Kazmerski and Friedman [47] had not been categorized according to their familiarity. To determine if the novelty P3 would be affected by the familiarity of the stimuli, Cycowicz and Friedman [11] collected ERPs during a version of the novelty oddball task similar to that designed by Kazmerski and Friedman [47]. Then, following the ERP recording session, the 16 volunteers attempted to identify the environmental sounds that had been presented during the oddball series. Correct identifications were based on naming norms for 96 unique environmental sounds [21]. This enabled Cycowicz and Friedman [11] to average the ERPs based on the subject's ability to identify each sound. This process resulted in four averages per subject, first and second presentations of the environmental sounds categorized according to whether or not they were conceptually identified correctly (i.e., assigned to the appropriate semantic category during naming performance). These categories were labeled, respectively, familiar and unfamiliar.

The resulting ERP data are depicted in Fig. 7. Note that there is a double dissociation between the familiarity dimension and the frontal and posterior aspects of the P3 elicited by the sounds. For familiar sounds repetition induces a reduction in the frontal aspect of the novelty P3, but no significant difference for the posterior aspect. For unfamiliar sounds, there is no real change with repetition for the frontal aspect, but the posterior aspect is enhanced. These data provide compelling evidence in support of the view that the scalp-recorded novelty P3 is comprised of at least two aspects, each with its own unique functional significance.

Because novelty P3 amplitude appears to be modulated by the familiarity of the sound, this was interpreted to mean that it must reflect a fairly late stage of information processing, perhaps one that is close to the extraction of the

sound's semantic attributes. One way of interpreting these findings is to employ the explanations used in behavioral studies of priming phenomena, by postulating that a familiar environmental sound contacts a previously stored representation, whereas an unfamiliar one does not. On this basis, the reduction in the frontal aspect of the novelty P3 with repetition for familiar sounds implies that *less* processing was necessary when the familiar sound was repeated, an explanation highly similar to those proposed to account for word repetition effects [96]. On the other hand, the posterior aspect, which is assumed to reflect the categorization of the sound [9,51], is enhanced indicating greater processing due to the relative unfamiliarity of the eliciting sounds. Perhaps this enhancement reflects the formation of a new representation in semantic memory.

The outcomes of the Cycowicz and Friedman [11] investigation are similar to those of a recently published event-related fMRI study by Henson et al. [39]. Henson et al. assessed the effect on blood flow activation of repeating familiar and unfamiliar faces as well as familiar and unfamiliar symbols. They found that repetition of familiar symbols and faces engendered a reduction in blood flow in the fusiform gyrus, whereas repetition of unfamiliar faces led to an enhancement of blood flow in this same region. These authors offered a similar explanation of their results to those of Cycowicz and Friedman [11] to account for the differences in repetition-related modulation of the blood flow response: with a familiar stimulus, a repeated item contacts a previously stored representation of that concept within the brain's primary processing region (i.e., visual cortex). This leads to a reduction in brain activity. On the other hand, with an unfamiliar stimulus, and hence no pre-existing representation, repetition leads to processes that solidify the formation of a new representation, also within modality-specific cortical regions. Cycowicz and Friedman [11] recorded from only 16 scalp locations. Current studies in our laboratory with 62 scalp channels and current source density analyses should enable the observation of modality-specific current densities if such are produced in response to the environmental sounds [3].

The ERP data reported by Cycowicz and Friedman [11] are joined by the data published by Mecklinger and colleagues [66]. These investigators also employed identifiable and non-identifiable environmental sounds categorized in similar fashion to the sounds used by Cycowicz and Friedman [11], although repetition was not built into their oddball paradigm. Mecklinger et al. [66] found that non-identifiable sounds elicited a larger P3a than identifiable sounds. In addition, they suggested that the identifiable novels also elicited a right-sided parietal N400 component, a negativity that followed their P3a component. As N400 is thought to reflect semantic processing [57], only sounds that have a pre-existing representation should have evoked this component. This effect was replicated in independent groups of subjects by Opitz et al. [74] (see discussion of their fMRI data below). Although the Mecklinger et al. [66] and Opitz et al. [74] data are not identical to the Cycowicz and Friedman [11] results, they are sufficiently similar to add to the evidence that the P3a reflects a late, evaluative, stage of information processing, and that these brief environmental sounds are most likely processed by the brain in similar fashion to words and pictures.

Fabiani and Friedman [20] reasoned that it was unlikely that the sequence of brain events engendered by novel stimuli was due solely to the unusualness or 'weirdness' of the environmental sounds used in their studies. Rather, this novelty response should occur to other kinds of stimuli, even those with which the subject might be familiar, i.e., it is the context within which the event is embedded that determines whether it will or will not be considered 'novel'. To determine if this would be the case, Fabiani and Friedman [20] presented sequentially a series of three oddball tasks. The first was a regular oddball consisting of standards and targets, and served as the practice block of trials. The second was also a regular oddball task identical to the practice series. The final series comprised the novelty oddball as previously implemented. In other words, although the participants were undoubtedly familiar with tonal target stimuli, the context in which these were presented, in a laboratory embedded within an unfamiliar oddball task, would serve to make even these tonal stimuli 'novel', in the first regular oddball practice block. The ERP data that resulted (A) along with the maps of P3 activity (B), and the location of the dipoles that were 'seeded' (C) are depicted in Fig. 8. The ERPs elicited by the target tones that were recorded over the three time periods (panel A) demonstrate that the P3 amplitude difference between frontal and parietal scalp sites becomes larger from Time 1 (practice) to Time 3 (novelty oddball), again suggesting a change in the scalp distribution of the P3, from frontally- to parietally-oriented with time on task. In addition, inspection of the maps of target P3 activity (panel B) reveals this change even more dramatically, showing a diminution in the frontal aspect of the distribution with no apparent change in the posterior aspect. Furthermore, comparison of the scalp maps of P3 activity elicited by the novels (at Time 3) with those elicited by the targets at Time 1 reveals a remarkable degree of similarity. In other words, the targets elicit a 'novelty-like' scalp distribution, even though these were stimuli about which the subject was instructed prior to the task.

We built on previous work [74,75] to model the habituation effects [20] on the frontal and parietal sources associated with the P3 component. The location of putative intracranial generators (C in Fig. 8) were estimated using areas of cerebral activation obtained from hemodynamic studies [18,62,74,75] with paradigms constructed in similar fashion to the regular and novelty oddball tasks used by Fabiani and Friedman [20]. These areas of hemodynamic activation were then input as dipolar sources into the brain using the reported x, y, and z coordinates [95]. Two sets of dipoles (bilateral medial frontal gyri; bilateral temporo-parietal junctions) resulted in the smallest amount of resi-

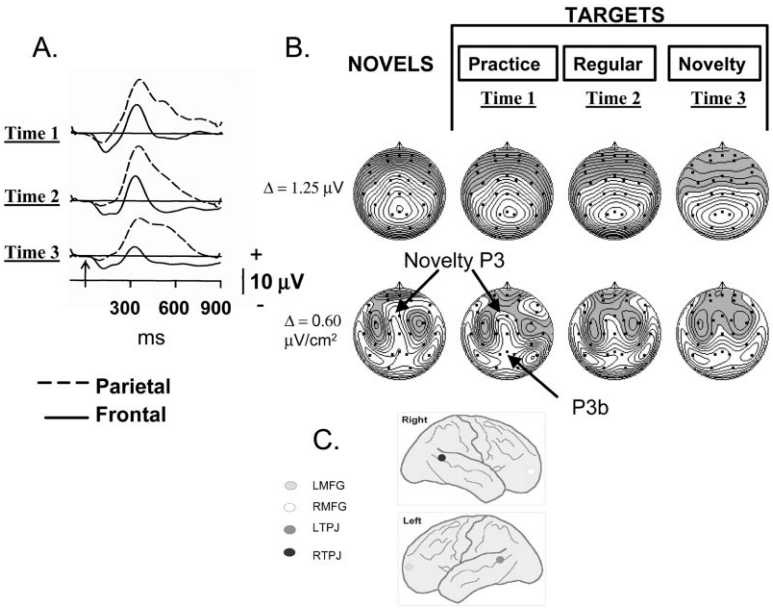

Fig. 8. (A). Grand mean ERPs elicited at midline frontal and parietal scalp locations during three, sequentially administered oddball tasks (Time1, Time 2, Time 3). (B) SP (top row) and CSD (bottom row) maps of P3 activity elicited, respectively, by novels at Time 3 and targets at Times 1 through 3. Dots indicate electrode positions on the scalp. (C). Approximate locations of the four 'seeded' dipoles: L/RMFG = left/right medial frontal gyrus; L/RTPJ = left/right temporo-parietal junction. Note that the brain views are 'transparent', with all dipoles depicted in each view.

dual variance, i.e., the variance in the observed scalp distributions unexplained by the scalp distributions predicted by the dipole model. The most important finding from this investigation (Friedman and Fabiani, unpublished observations) is that only the frontal dipoles showed a reduction with time on task, by contrast with the temporo-parietal dipoles, which showed no consistent relation to time on task. The Friedman and Fabiani data extend the initial reports of a selective frontal decline in P3a amplitude as a function of experience with rare stimulus events [9,48] by placing neuroanatomical coordinates on the putative sources of this electrical activity. These source modeling data also add to the evidence that the scalp-recorded P3 component can be functionally dissociated into at least two subcomponents, a frontal aspect that shows reduction with time on task, and a posterior aspect that does not change in a consistent manner as subjects gain experience with a variety of auditory events. It should be noted, however, that this is simply a model that accounts reasonably for the observed P3 scalp distribution. At the current state of knowledge, it is clear that many brain regions, not just one or two bilateral sets of dipoles, contribute to scalp-recorded P3 activity [36].

Gaeta and colleagues (unpublished observations) also demonstrated that the brain's response to novelty depends upon the context within which the eliciting event is embedded. In Gaeta's experiment, two environmental sounds, a dog bark and a bird call were presented in the context of a regular oddball task, with the stimulus serving as target counterbalanced across subjects. Subjects were pre-instructed as to which stimulus would serve as the target and made RT responses to each target event. When presented in this fashion, neither stimulus produced a frontal scalp distribution; rather, the scalp distribution associated with these pre-instructed 'novel' environmental sounds was typical of that of the P3b to target events, posteriorly-oriented with a maximum around parietal scalp.

7.4. Effects of attention

The brain's response to novelty has been well studied under conditions in which participants must pay attention in order to detect targets embedded within a series of frequent standards and infrequent novel, environmental sounds. With few exceptions [3,40], however, very little work has been performed in a situation in which subjects are instructed to ignore the stimulus series. This is an important aspect of orienting behavior and neurophysiology because it is typically while attention is focused elsewhere that the detection and evaluation of biologically salient events is most critical. In this vein, Friedman and colleagues [25] compared the ERPs elicited by environmental sounds during attend and ignore conditions. Separate groups of 16 young adult subjects were assigned to either the attend condition (respond to oddball targets, with no instruction concerning environmental sounds) or the ignore condition (no instruction about any stimuli; simply ignore the stimulus series while reading self-selected text). The data presented in Fig. 9 were recorded during these two kinds of novelty oddball tasks. Friedman et al. [25] averaged across the novel events elicited during every two blocks of trials, resulting in five averaged waveforms per subject. It is clear from Fig. 9 that, during the active oddball task, only the P3s at the frontal electrode site show a reduction as a function of block number

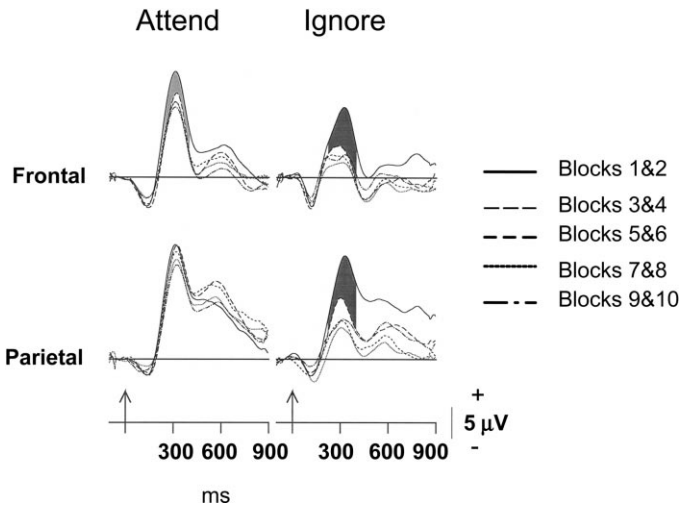

Fig. 9. Grand mean ERPs elicited by novel, environmental sounds during an attended (left) and ignored (right) oddball series. The data are depicted as a function of block number. Light gray shading indicates the difference between the novelty P3s elicited during blocks 1 and 2 and blocks 3 and 4 from the attend series; dark shading indicates the difference between the novelty P3s elicited during blocks 1 and 2 and blocks 3 and 4 from the ignore series.

(the light gray shading indicates the reduction in amplitude from blocks 1 and 2 to blocks 3 and 4 during the attend series). By contrast, during the task in which subjects ignored the stimuli, the P3s at both frontal and parietal sites show a reduction in magnitude (the dark shading indicates the reduction in amplitude from blocks 1 and 2 to blocks 3 and 4 during the ignore series). Furthermore, the rate of reduction during the ignore session is much greater than that of its active counterpart. The fact that the rate of reduction was greater during the ignore condition, suggests that the amplitude diminution reflects a change in a relatively *automatic biological* response (i.e., orienting) that involuntarily captures attention.

To summarize, the frontal and posterior aspects of the brain's response to novel events respond differently to the effects of attention, to the familiarity of the environmental sounds, and to time on task. Hence, these data strongly reinforce the hypothesis that the frontal and posterior aspects of the novelty P3 reflect different cognitive functions and the activity of different, but perhaps overlapping, neural generators. The posterior aspect of the Novelty P3 shows features in common with the P3b elicited by target stimuli. This suggests that novel stimuli elicit both a frontally-oriented P3a and a posteriorly-oriented P3b. However, it is not possible to determine definitively whether the posterior aspect of the Novelty P3 and the P3b are synonymous until this issue is tested experimentally.

The next sections are concerned with where in the brain the generator sources of these aspects of the novelty P3 might be located, based on surface-recorded ERPs in patients with lesions, intracranial ERP and fMRI data.

7.5. Neural basis of the novelty response: lesion studies and intracranial ERP recordings

Based on lesion studies, Knight [48] reported a neuroanatomical locus for the generation of the P3a. Knight recorded from patients with unilateral lesions of the dorsolateral prefrontal cortex, a region believed to play a major role in orienting [14,31,59,100]. Knight's experimental paradigm was an auditory analog of Courchesne et al.'s [9] visual novelty task. The major finding was that, relative to the controls, the P3a components of the patients were markedly reduced at frontal scalp sites, whereas the same was not true of the P3 to pre-instructed target stimuli. These data suggested that the dorsolateral prefrontal cortex makes a major contribution to the scalp-recorded P3a. Subsequent experiments performed in patients with prefrontal lesions since Knight's initial investigation [48] have confirmed this observation [15,50].

Other lesion studies, using similar paradigms, have demonstrated additional neuroanatomical structures that also contribute to the scalp-recorded ERP response to novel stimuli. One such region is bilateral temporo-parietal junction [53]. Knight et al. [53] assessed the brain's response to a variety of novel events in an auditory novelty oddball paradigm and in a dichotic listening, selective attention paradigm in patients who either had unilateral: (1) lesions to the temporo-parietal junction, including the posterior superior temporal plane and inferior parietal cortex or (2) the lateral parietal lobe, including the inferior parietal lobe and portions of the superior parietal lobe. Under both paradigms, lesions of parietal cortex had very little effect on the distribution of either the target or novelty P3. By contrast, lesions in the vicinity of the temporo-parietal junction reduced or eliminated the target P3 and the novelty P3 at central and posterior scalp sites during both the novelty oddball and dichotic listening procedures.

In a follow-up investigation, Yamaguchi and Knight [101] assessed the effect of temporo-parietal, lateral parietal, and dorsolateral prefrontal cortex lesions on the ERPs elicited by somatosensory target and novel events.

Consistent with the findings of Knight et al. [53], parietal lesions had little effect on the distribution of either the target or novelty P3. Frontal lesions only reduced the frontal aspect of the novelty P3 and had little effect on the posterior aspect of either the novelty or target P3. By contrast, temporo-parietal lesions reduced the P3 activity elicited by both targets and novels at all scalp locations.

Knight [49], used auditory and somatosensory versions of the novelty oddball task, and reported that the posterior hippocampus is an essential substrate for the brain's ERP response to novelty. This was based on his finding that patients with posterior hippocampal lesions showed a dramatic reduction of the frontal aspect of both the novelty P3 and the target P3 (both considered instances of the P3a), but little evidence of reductions in the P3s recorded at central-posterior scalp locations. As described earlier, the controls but not the patients, produced phasic skin conductance responses to the novel events, providing converging evidence for the role of the P3a in orienting.

In general, the brain loci reported to make a significant contribution to the P3a on the basis of lesion studies, have also been corroborated by intracranial ERP studies in presurgical epilepsy patients. For example, in an extensive series of studies, Halgren and his colleagues [6,34,35], (see also Ref. [1]) recorded from a large number of intracranial sites during regular and novelty oddball blocks. Compelling evidence for *local* generation of intracranial ERPs (as opposed to volume conduction from distant sites) is polarity reversal or steep current gradients across short distances within neural tissue. This indicates that the source of the electrical activity is located somewhere between the recording electrodes showing the opposite polarities. Baudena et al. [6] used this methodology to provide evidence for a P3a-like component. They reported polarity reversals or steep current gradients within the orbito-frontal, dorsolateral prefrontal (Brodmann Area BA 46), anterior cingulate cortices, and the gyrus rectus, which they attributed to the P3a. Other sites showing consistent polarity reversals or steep current gradients, also attributed to the P3a, included the supramarginal gyrus, the posterior cingulate gyrus [34], the temporal pole, posterior parahippocampal gyrus, fusiform gyrus, and various regions within the middle temporal gyrus [35]. In addition, Kropotov and colleagues [55] recorded P3a-like components from contacts in BA 42 (auditory cortex). These investigators also recorded P3a-like potentials in frontal cortex and areas within the temporo-parietal junction. However, no evidence of polarity reversals were described in this report, rendering localization of the neuroanatomical source of this activity problematic. Magnetoencephalographic activity (MEG) is particularly sensitive to dipolar activity located in auditory cortex. Alho et al. [3] reported the presence of the MEG counterpart of the P3a in auditory cortex, consistent with the intracranial data of Kropotov et al. [55]. The observation of P3a-like components in frontal and temporo-parietal cortex by Kropotov et al. is also consistent with results of the other intracranial recording and lesion studies discussed above.

To summarize, the lesion and intracranial data add to the evidence that the novelty P3 is generated by a widespread network of brain regions, consistent with the differing functional correlates of its frontal and posterior aspects discussed earlier. Further, the fact that lesions to these regions affect the auditory and somatosensory ERPs similarly suggest that the evaluative aspect of the orienting response, as reflected by the P3a, is modality non-specific. Moreover, based on the lesion as well as the intracranial data, a consistent finding is that activity from the temporo-parietal junction and posterior hippocampal formation appear to be essential for the generation of the scalp-recorded target as well as novelty P3. This is concordant with the interpretation, based on the topography of scalp-recorded P3 activity, that the brain's response to novelty is comprised of a mix of these electrical activities. In addition, the brain regions that putatively account for the P3a are highly similar to areas hypothesized to comprise a network devoted to the orienting of attention [68] and for orienting to novel events [79], again consistent with the presumed functional role of the P3a.

8. Neural basis of the novelty response: functional MRI data

Some of the same neuroanatomical regions shown to contribute to the generation of the P3a by ERP methods have also been observed to show increased blood flow in hemodynamic studies conducted under similar experimental conditions. Unfortunately, to our knowledge, there is only one study that used complex, environmental stimuli (i.e., novels) [74]similar to those presented in the novelty oddball studies described earlier in this review. However, based on intracranial and lesion studies, common neural substrates have been shown to contribute to the ERPs elicited by target and novel stimuli. Therefore, this section will review hemodynamic studies of the regular as well as novelty oddball tasks. To our knowledge, Menon and colleagues [67] and McCarthy et al. [62] were the first to use fMRI in a regular oddball paradigm to determine the brain regions activated when target as opposed to frequent events are detected. Menon et al. used an auditory task with event-related fMRI and reported significantly greater activations for target compared to standard events in bilateral supramarginal gyri, bilateral thalamus and the anterior cingulate. In the identical oddball task with the same subjects on a second experimental visit, Menon et al. [67] recorded ERP activity. These investigators seeded the supramarginal locations (based on their fMRI data) into a source modeling algorithm, and determined that the supramarginal dipoles explained well the scalp distribution of target P3 activity, providing a degree of converging evidence between ERP and fMRI methods. In a more recent experiment, Opitz

and coworkers [75] also recorded ERPs and fMRI signals during an auditory version of the regular oddball task under both attend and ignore conditions. Unlike Menon et al. [67], however, these investigators used a blocked design (standard blocks = 24 standards; deviant blocks = 16 standards and eight deviants). Areas activated by deviant stimuli during attend and ignore sequences included left and right transverse gyri (primary auditory cortex) and left and right superior temporal gyri. Using the seeding technique mentioned earlier, only the dipole model based on bilateral superior temporal gyri produced the best fit with the observed target P3 component scalp distribution (i.e., showed the smallest amount of residual variance).

In a visual oddball task with event-related fMRI, McCarthy et al. [62] reported target activations in bilateral middle frontal gyri, bilateral inferior parietal lobe (supramarginal gyrus), and the posterior cingulate gyrus. These investigators did not report the Talairach coordinates [95] for these activations, so they have been estimated in Fig. 10. Both Menon et al. [67] and McCarthy, but not Opitz et al. [75], reported supramarginal activations, but the differences in areas activated may be due to differences in presentation modality (Menon et al. and McCarthy et al. used visual stimuli, while Opitz et al. used auditory stimuli).

Fig. 10 is compiled from our review of eight fMRI studies by placing markers (colored circles) at the *x*, *y*, and *z* Talairach coordinates [95] of blood flow activation in response to visual and auditory deviants. Medial sites of hemodynamic activity are not depicted. The lateral brain regions that were most consistently activated by targets and novels from the eight fMRI investigations are depicted. The ellipses encompass areas that were found to be critical for target and/or novelty P3 generation from studies of patients with brain injuries, and their extent has been estimated, when available, from the figures and description of Brodmann areas published in those investigations. It should be noted that these are only rough approximations. Nevertheless, there is a good degree of overlap between the fMRI areas of activation and the regions found to be critical via studies of brain injured patients.

Three fMRI studies have compared directly hemodynamic areas of activation between visual and auditory oddball tasks. Linden et al. [58] recorded event-related fMRI with two target detection conditions, silent counting and button-press. They reported highly similar results for both auditory and visual presentations. For both modalities and response conditions, areas of activation were observed at bilateral supramarginal gyri, the frontal operculum and the insula. With the exception of the auditory button-press oddball, activation was also observed in supplementary motor area, and anterior cingulate cortex. Areas that were activated only for visual or auditory stimuli included primary and secondary visual areas for the visual tasks, and right middle temporal gyrus, posterior cingulate and right middle frontal gyrus during auditory tasks. Yoshiura et al. [102] also compared event-related hemodynamic

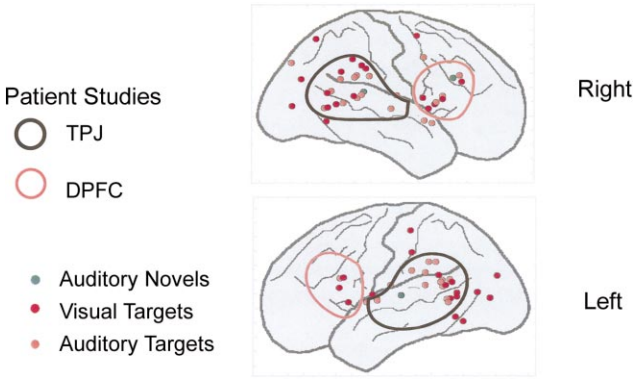

Fig. 10. Approximate locations (in Talairach space) of areas of fMRI hemodynamic activation (red, green, and pink filled circles) as viewed on left and right lateral surface renderings of the brain. Medial activations are not depicted. The areas depicted were obtained from the *x*, *y*, and *z* coordinates listed in the following investigations: Linden et al. [58]; Opitz et al. [74,75]; Downar et al. [18] (the tactile activations are not depicted); Menon et al. [67]; Yoshiura et al. [102]; McCarthy et al. [61] (*x*, *y*, and *z* coordinates were not listed and have been estimated), and Clark et al. [8]. If a study reported multimodal regions of activation engendered by both auditory and visual deviants, these regions have been depicted for both types of stimulus events. Also depicted roughly (in elliptical outlines) are the regions that proved critical for either novelty P3 (TPJ = temporo-parietal junction; DPFC = dorsolateral prefrontal cortex) and/or target P3 (TPJ) generation based on studies of patients with localized lesions from Daffner et al. [15]; Knight [48,50]; Knight et al. [53], and Yamaguchi and Knight [101].

responses in visual and auditory oddball tasks when the behavioral task involved silent counting of targets, and found that infrequent auditory targets activated the primary auditory area (transverse temporal gyri) and the superior temporal gyrus, whereas visual targets activated primary visual areas bilaterally and the occipitotemporal region bilaterally. Both types of targets also activated several modality non-specific regions, including the supramarginal gyrus, the anterior cingulate gyrus, the middle frontal gyrus, and the insula, consistent with previously reported areas of activation. In addition, hippocampal formation activation was noted for targets in both auditory and visual oddball tasks.

In an interesting experiment that bears some resemblance to the oddball paradigm, Downar et al. [18] recorded event-related fMRI to a continuous stream of visual, auditory and tactile events. Deviant events consisted of infrequent pseudo-random changes from the presentation of stimuli in one modality to stimuli in another. fMRI areas of activation to visual changes included bilateral fusiform gyri and bilateral middle occipital gyri; for auditory changes the left and right superior temporal gyri were activated; for tactile stimuli bilateral postcentral gyri were activated. Common activations to all types of stimulus changes were observed in some of the same areas that have been mentioned above for both visual and auditory regular oddball tasks, including bilateral temporo-parietal junctions, right middle temporal gyrus, right inferior frontal gyrus and right anterior and posterior insula. Of these multimodal activations, the cortex

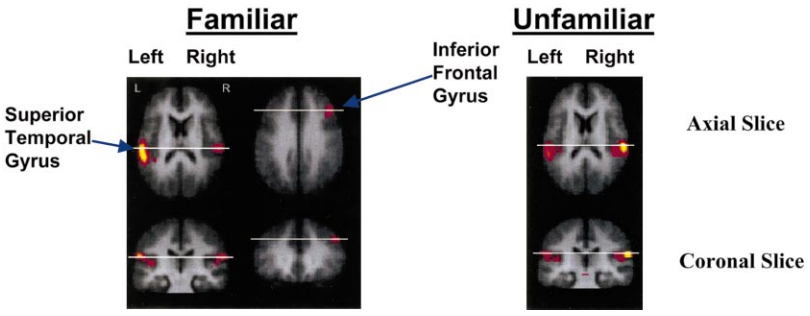

Fig. 11. Areas of blood flow activation observed by Opitz et al. [74] in response to familiar and unfamiliar novel auditory oddball stimuli. Reprinted by permission of Oxford University Press from Opitz et al. [74]

in the vicinity of the temporo-parietal junction showed the greatest magnitude responses.

There have been two fMRI investigations of the novelty oddball, one auditory [74] and one visual [8]. Results from these studies show that some neuroanatomical regions activated by deviant targets are also activated by novels. The investigation by Opitz et al. [74] employed similar stimuli to those used by Cycowicz and Friedman [11], familiar and unfamiliar environmental sounds, but without repetition of the environmental sounds. In addition, a blocked design was used which creates problems for comparisons between the ERP and fMRI data. The averaged fMRI data from a group of subjects who showed larger amplitude N400s to familiar compared to unfamiliar environmental sounds are depicted in Fig. 11. From Fig. 11 it can be seen that blood flow changes occur in the superior temporal gyrus for both familiar and unfamiliar sounds, most likely reflecting the activation of auditory cortex. An area of activation is also observed in the right prefrontal cortex, but only for the familiar sounds. The finding of unilateral activation differs from the results of most other ERP studies of the novelty oddball, which typically report bilateral activity. Because of the poor temporal resolution of the blood flow response relative to the time course of cognitive processes, it is difficult to interpret the cognitive significance of this right prefrontal activation. It may reflect a control or strategic function, such as attentional control and/or retrieval of the semantic aspects of the sound into working memory, as right prefrontal activations have been reported in working memory as well as episodic memory retrieval paradigms (see Ref. [24] for a review). The frontal activation is consistent with a variety of ERP and neuropsychological data implicating frontal cortex as playing a central role in the evaluation of novel events.

Clark and colleagues [8] employed a somewhat different novelty oddball task. Instead of having many unique novel events, they used only a single ‘distractor’ or uninstructed ‘novel’ stimulus (the letter ‘C’, to which the subject did not respond), while targets were the letter ‘X’ and standards, the letter ‘T’. Infrequent targets engendered activation patterns consistent with those reported previously for both visual and auditory deviant stimuli. Regions of activation included the right fusiform gyrus, right middle frontal gyrus, left inferior frontal gyrus, and right inferior parietal lobule (which included the superior temporal gyrus, the postcentral gyrus and the supramarginal gyrus). The event-related fMRI response to distractors was weak relative to previously reported levels of activation for distractor stimuli. It is not clear why this should be so, but may be due to the letter C’s not being especially salient within the context in which it was presented. However, there was no habituation of the blood flow response as a function of repetition of the identical stimulus [26,48]. Instead, an enhancement in the percentage of MR signal change was reported. Clark et al. [8] suggest that this could be due to different neural mechanisms reflected by fMRI and ERP, and/or by neural activity that can be observed with the fMRI technique, but that is invisible to the ERP technique (e.g., closed electrical fields). On the other hand, the use of a single distractor is not optimal for inducing novelty, and fMRI experiments need to be performed with many unique novel events embedded in the stimulus sequence.

Although, based on ERP intracranial and patient studies, medial temporal lobe generators appear likely for the target [37,64] as well as novelty P3 [49], only one fMRI study has reported robust hippocampal activation in response to targets [102]. Nevertheless, despite such discrepancies, there is a degree of overlap (as can be observed in Fig. 10) among the brain areas activated by deviant target as well as novel events in fMRI studies of the oddball paradigm. More important, these areas correspond to brain regions found to be critical in the generation of the target and novelty P3 component from intracranial, source modeling, and patient lesion studies.

To summarize, the most consistently observed areas of hemodynamic activation during the regular oddball task appear to be regions surrounding the temporo-parietal junction, dorsolateral prefrontal cortex and, in the case of auditory stimuli, the superior temporal gyrus. Visual stimuli appear to show hemodynamic activity in visual areas of the brain. Some of these same areas also show blood flow increases during the presentation of novel auditory events, although the data on which this conclusion is based are extremely limited.

8.1. Functional significance of the novelty P3

It seems clear, based on a variety of converging evidence, that the novelty P3 reflects the activity of a widespread cortical network whose aspects respond differentially to stimulus and task characteristics. As revealed by intracranial as well as scalp-recorded ERP studies, the sequence of neural events resulting from the detection of deviant events occurs quite rapidly, within 300 ms following the stimulus. This kind of rapid response is obviously of great biological significance, having evolved undoubtedly in response to the necessity to interpret quickly environmental events that might signal danger. It has been argued previously [12,25,52] that the frontal aspect of the novelty P3 reflects processes related to orienting. These processes do not reflect the detection of the deviant event per se, but rather processes that are active after the deviant event has been detected by the brain, such as bringing the event to consciousness for subsequent evaluation and appropriate action. The reduction of the frontal portion of the novelty P3 with experience (i.e., as more novels are presented) is consistent with this hypothesis, as processes subsumed under orienting should no longer be necessary or would be called upon to a lesser extent once the novel events have been categorized as infrequent nontarget events. When stimuli are 'novel', in addition to more posterior generators, the anterior aspect of this system is activated. When they are no longer novel, the activity of the frontal aspect of this network is diminished, although the posterior activity remains. A neural system consistent with this interpretation and involving these brain regions has been advanced by Goldman-Rakic and her colleagues as a mechanism to account for the maintenance of working memory templates [32,33].

However, even when participants did not attend to the stimuli [25], the amplitude of the P3a decreased with time on task. As previously discussed, from a biological point of view such a relatively automatic system would be important because, as more novels occurred and no special action was necessary, there would be no need for the organism to pay attention to stimuli that were not, in some fashion, meaningful or salient. In showing selective reduction of the frontal aspect of the P3 distribution as more events are experienced, these data are similar to the results of regional cerebral blood flow [98], PET [7,45,80] and ERP [76] investigations that have shown reductions in prefrontal brain activity with time on task.

Based on the findings that: (1) the posterior portion of the novelty P3 did not change as markedly as the frontal portion as more and more novel events were experienced [9,12,25,26,48] and (2) there was a change from a frontally oriented to a more posterior scalp distribution with novel event recurrence, it was suggested that the posterior aspect of the novelty P3 reflects a categorization process. On this view, one could infer that, as more novel events are delivered, they induce the formation of a representation in which their characteristics are stored, consistent with a working memory template [20]. This template (perhaps maintained by the prefrontal cortex and reflected in the P3a) enables these initially uncategorized events to be classified into a discrete group of items (e.g., 'novel sounds'). Under the assumption that the posterior aspect of the novelty P3 reflects a classification process [12], it would have to be active whenever one pays attention to the acoustic stream, thus accounting for the lack of habituation at posterior electrode sites while subjects paid attention [25]. On the other hand, when participants are engaged in a primary task (e.g., watching a silent movie) and are instructed to ignore the auditory stream, there is no active processing of the sounds aside from the initial 'automatic' orienting (reflected by the frontal portion of the novelty P3). In other words, a classification of the sound is not necessary, as an overt discrimination between 'target' and 'novel' deviants is unnecessary. This would account for the fact that, during ignored sequences, the posterior aspect of the novelty P3 shows the same degree of habituation seen at the anterior sites, even though attention was 'captured' by the deviant novel sounds.

Even though the information contained in the environmental sounds that we and other have employed is brief, these kinds of sounds are most likely represented in semantic memory networks similar to those observed for words and pictures. Further support for this contention could be provided by experiments in which the sounds are embedded within semantic priming and repetition priming tasks [93]. If they engender behavioral and ERP semantic and repetition priming effects, we will be on more solid ground in drawing this conclusion.

Finally, whether the frontal and posterior aspects of the novelty P3 are direct reflections of, respectively, prefrontal and posterior cortical activity requires additional corroborative evidence. From the review of the fMRI literature on the oddball paradigm it is fairly clear that there are frontal and posterior areas of activation when novel as well as target stimuli are presented [62,67,74] (Fig. 10). Whether these observed areas of blood flow activation correspond to the identical regions based upon ERP recordings has yet to be determined definitively, and much more work will be required before this relation can be known precisely. In addition, more fMRI studies of the novelty oddball are necessary as, to date, only one such investigation, with a highly similar design to those reported in the ERP literature, exists [74]. These studies should be performed, whenever possible, with event-related procedures as it is only then that comparisons with ERP data can be made more decisively.

9. Conclusions

This review makes it clear that multiple techniques will be required to understand more completely the temporo-spatial processing of novelty information by the brain. The fine-grained temporal information provided by scalp-recorded

and intracranial ERP data converge in suggesting that the P3a component reflects a late stage of novelty processing, most likely related to the evaluative aspects of the orienting response. The excellent spatial resolution of fMRI combined with surface-recorded ERP data in patients with localized lesions implicate, as noted by others [50], an anterior/posterior neuronal network that is critical in the brain's response to novelty. This kind of circuit is consistent with the known neuroanatomical connections among the brain regions activated by novel events and identified in this review [27]. Preinstructed target, as well as uninstructed 'novel', events engender brain activity in overlapping regions. However, as demonstrated by the scalp-recorded ERP data, the magnitude of activity of the various generators depends upon stimulus and task characteristics, and/or the context within which the 'novel' event is embedded. This, in turn, suggests that the electrical events recorded at the scalp reflect the activity of a distributed system that gives rise, in toto, to the P3 waveform.

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