

The Brain's Orienting Response: An Event-Related Functional Magnetic Resonance Imaging Investigation

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Abstract: An important function of the brain's orienting response is to enable the evaluation of novel, environmental events in order to prepare for potential behavioral action. Here, we assessed the event-related hemodynamic (erfMRI) correlates of this phenomenon using unexpected (i.e., novel) environmental sounds presented within the context of an auditory novelty oddball paradigm. In ERP investigations of the novelty oddball, repetition of the identical novel sound leads to habituation of the novelty P3, an ERP sign of the orienting response. Repetition also leads to an enhancement of a subsequent positivity that appears to reflect semantic analysis of the environmental sounds. In this adaptation for erfMRI recording, frequent tones were intermixed randomly with infrequent target tones and equally infrequent novel, environmental sounds. Subjects responded via speeded button press to targets. To assess habituation, some of the environmental sounds were repeated two blocks after their initial presentation. As expected, novel sounds and target tones led to activation of widespread, but somewhat different, neural networks. Contrary to expectation, however, there were no significant areas in which activation was reduced in response to second compared to first presentations of the novel sounds. Conversely, novel sounds relative to target tones engendered activity in the inferior frontal gyrus (BA 45) consistent with semantic analysis of these events. We conclude that a key concomitant of the orienting response is the extraction of meaning, thereby enabling one to determine the significance of the environmental perturbation and take appropriate goal-directed action. *Hum Brain Mapp* 30:1144–1154, 2009. © 2008 Wiley-Liss, Inc.

Key words: attention; habituation; functional MRI; acoustic stimulation

INTRODUCTION

The orienting response is an involuntary shift of attention that appears to be a fundamental biological mechanism necessary for survival [Friedman et al., 2001; Ranganath and Rainer, 2003; Sokolov, 1990]. 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. A stimulus that is sufficiently deviant engenders the involuntary capture of attention, enabling the event to enter consciousness. This permits an evaluation of its meaning and significance and, if deemed necessary, appropriate behavioral action.

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The brain's orienting response has been most often studied using the event-related potential technique (ERP) and the auditory novelty "oddball" paradigm. In this task, participants hear three stimulus events, a frequently occurring tone, an infrequently occurring tone (referred to as the target) to which the subject responds via button press, and equally infrequent, but task irrelevant and unexpected, novel sounds. The latter do not require a response and are typically comprised of a wide variety of animal, human, musical, and mechanical environmental sounds [Fabiani et al., 1996].

In a substantial number of investigations (reviewed in Friedman et al., 2001 and Ranganath and Rainer, 2003), it has been shown that the P3 component elicited by the infrequent target (labeled P3b) displays an amplitude distribution that is focused over the parietal scalp midline with a latency to peak that depends upon the difficulty of the target judgment (between ~300 and 800 ms). On the other hand, the P3 elicited by the infrequent novels (labeled novelty P3 or P3a) shows a topography that is centered over fronto-central scalp and has a relatively early latency to peak of ~300 ms. This difference in scalp topography has been interpreted by many investigators to indicate that the two components reflect the operation of at least partially nonoverlapping neural generators and cognitive functions. The P3a is thought to reflect an aspect of the orienting response indicating that the novel event is within the focus of attention and under evaluation. Consistent with this interpretation, the P3a shows reductions in amplitude or habituation with time on task and/or repetition [Friedman et al., 2001], in highly similar fashion to other ubiquitous markers of the orienting response [Sokolov, 1963]. Moreover, on the basis of intracranial ERP recordings (iERP; Halgren et al., 1998a), the generators of the P3a have been shown to comprise a widespread brain system that includes dorsolateral prefrontal cortex, supramarginal gyrus, and areas of the cingulate gyrus. By contrast, the P3b is thought to reflect decision and/or categorization processes because it is typically elicited by task relevant events that require a decision. Its principal intracranial generators are somewhat different than those of the P3a and include medial temporal regions, posterior superior parietal cortex, and ventrolateral prefrontal cortex [Halgren et al., 1998a].

Although the scalp-recorded ERP provides excellent temporal resolution and can, thereby, indicate the sequencing of events in the information processing chain, the intracranial generators of scalp-recorded potentials are more difficult to infer from scalp-recorded data alone. Furthermore, although, in principle, it should be possible to obtain more precise estimates of localized generators using iERP, this technique is limited by the clinical interests of the patients, so that not all of the potential neuronal generators of ERP activity can be sampled. By contrast, the fMRI technique is not limited by this latter concern and has excellent spatial resolution, although its temporal precision is relatively poor. It is not surprising, therefore, that

the likely generators of the scalp-recorded P3a and P3b components have been sought using fMRI techniques alone [Gur et al., 2007; Kiehl et al., 2001a,b, 2005] complemented by separate [Menon et al., 1997; Opitz et al., 1999] or simultaneous [Liebenthal et al., 2003] ERP recording. However, to our knowledge, only four studies of the auditory novelty oddball exist and, of those that do, only three employed event-related designs [Kiehl et al., 2001a,b, 2005], while one used a blocked design [Opitz et al., 1999]. In the current investigation, we used event-related fMRI (erfMRI) and well-characterized, unique novel, environmental sounds [Fabiani et al., 1996] that have been demonstrated to elicit the novelty P3 and engender its habituation with repetition in previous ERP protocols [Friedman et al., 1998].

The results of the extant fMRI studies of the auditory novelty oddball, in similar fashion to the iERP investigations and hemodynamic investigations of the novelty oddball paradigm with visual stimuli [McCarthy et al., 1997; Yamaguchi et al., 2004], have implicated a widespread network of brain regions in the computations associated with the detection of target and novel events. For example, Kiehl et al. [Kiehl et al., 2001b] presented infrequent target (1,500-Hz tone), and nonrepeating, random, digital signals (e.g., tone sweeps, whistles) as novel events embedded within a series of frequent standards (1,000-Hz tone). Participants responded via button press only to the infrequent targets. The areas of activation in response to target and novel events were generally consistent with those obtained from human intracranial ERP recordings. For targets, these regions comprised the inferior frontal gyrus bilaterally, regions in and around auditory cortex including the anterior superior temporal gyrus, the anterior cingulate gyrus, the parietal lobes, parahippocampal gyrus/amygdala, putamen and globus pallidus, and thalamus. For novel sounds, similar regions of auditory cortex were activated bilaterally in addition to the middle and inferior frontal gyrus. Additional regions of activation not seen with intracranial recordings were also observed [see also Kiehl et al., 2005]. Despite the overlap in regional activation between iERP and fMRI, it is evident that the commonality is only partial [Brazdil et al., 2005], and only some of the regions that contribute to the scalp-recorded novelty P3 and target P3b may be observable with the fMRI technique. Similarly, brain regions that do not have the appropriate orientation with respect to the scalp may show hemodynamic activity, but will not be observable on the scalp surface.

In addition to the novelty P3, task-irrelevant, unexpected environmental sounds also elicit a longer-latency positivity, originally labeled the P3₂ by Friedman and Simpson [Friedman and Simpson, 1994]. This activity had a latency to peak of ~670 ms, about 370 ms later than the novelty P3. Because the majority of environmental sounds, though brief, represented meaningful concepts [Fabiani et al., 1996]. Friedman and Simpson [1994] suggested that the longer-latency P3₂ could have reflected a form of secondary categorization. Friedman and Simpson [1994] posited

that the P3₂ could have reflected an attempt to retrieve the semantic information associated with the environmental sound concept, a critical aspect of the orienting response [Lynn, 1966]. Subsequent investigations in which the environmental sounds were categorized into meaningful and nonmeaningful concepts indicated that this could very well have been the case [Cycowicz et al., 1996; see also Mecklinger et al., 1997]. The interpretation that this second positivity could have reflected some type of semantic retrieval was lent some support via its left-sided topography [Friedman et al., 1993]. This hypothesis has been strengthened by recent hemodynamic investigations of environmental sound analysis [Lewis et al., 2004].

In the current study we introduced a manipulation that, to the best of our knowledge, has not been employed before with oddball designs using erfMRI. As mentioned, the novelty P3 shows habituation in response to repeated occurrences of the identical novel event [Friedman et al., 1998; Kazmierski and Friedman, 1995] or recurrence of unique novel sounds within- or across-blocks of trials [Friedman and Simpson, 1994]. Habituation is typically fairly rapid, occurring within the first few presentations of novel events [Friedman and Simpson, 1994; Knight, 1984]. Nonetheless, it is also observed over longer periods of time, such as when minutes rather than seconds intervene between first and second presentations of the identical novel, environmental sound [Kazmierski and Friedman, 1995]. On the basis of studies of patients with lesions of the frontal lobes [Knight, 1984; Woods and Knight, 1986], it has been suggested that the habituation of the novelty P3 is governed, at least in part, by regions of the prefrontal cortex. Hence, to determine if prefrontal cortex plays a role in habituation to repeated novel events, environmental sound stimuli were repeated during the course of the oddball task, which also included frequent standard and infrequent target tones to which the subject responded via button press. It was expected that the regions recruited by the processing of target and novel events would be highly similar to those reported previously (e.g., cingulate cortex, auditory cortical regions, inferior frontal cortex). If novelty P3 reduction has a hemodynamic counterpart, then we expected a reduction in the BOLD signal with repetition of the identical novel events in prefrontal regions. If semantic analysis is reflected in the hemodynamic concomitants of the orienting response, then we expected left-sided activations (for example, left inferior frontal gyrus) to the novel sounds consistent with the retrieval of or search for the semantic information inherent in the environmental sound concept [Lebrun et al., 1998; Lewis et al., 2004].

SUBJECTS AND METHODS

Subjects

Fifteen young adult males (mean age = 25, range = 18–28) recruited by means of local newspaper advertisements and notices posted within the Columbia Presbyterian Medical

Center participated. All were initially screened via telephone and were accepted into the study only if they reported themselves to be in good health without a history of psychiatric or neurological disorders. All reported normal auditory acuity. All volunteers signed informed consent and received payment for their participation. The study was approved by the New York State Psychiatric Institute's Institutional Review Board.

Auditory Stimuli and Experimental Procedure

Stimuli

The stimuli were pure tones and environmental sounds. The pure tones were 500 and 350 Hz, with durations of 336 ms. The environmental sounds were 48 unique sounds that have been described in detail by Fabiani et al. [Fabiani et al., 1996]. They were chosen from six categories: animal, bird, human, musical instrument, environmental, and electronic. The environmental sounds varied in duration from 159 to 399 ms (mean = 336 ms ± 61 ms). In all of our ERP investigations, the sounds are matched for peak equivalent SPL to the pure tones using a dB meter. Thus, to maintain, to the greatest extent possible, methodological similarity between the ERP studies and the current fMRI investigation, the same procedure was followed here.

Procedures

The experiment consisted of three phases. The first was a short practice block for the standard auditory oddball task, the second was comprised of two blocks of the standard oddball task, and the third consisted of ten blocks of a novelty oddball task. For all blocks, pure tones and environmental sounds were presented with an interstimulus interval of 2,000 ms, along with randomly intermixed 2,000 ms "null" events. Sounds and pure tones were presented binaurally using a MRI-compatible auditory system (Psychology Software Tools) at ~84 dB peak SPL measured at the headphones. All volunteers indicated that they could easily hear the sounds and discriminate them from the background scanner noise (see behavioral data below). Stimuli were randomized separately for each subject, with the restrictions that a target or a novel could not occur as the first or the last stimulus, and that two targets or novels could not be presented sequentially. Subjects were instructed to press a button (emphasizing speed and accuracy equally) with the thumb of the right hand as soon as they heard the target tone. A LUMItouch, hand-held MRI-compatible fiber-optic response system (Photon Control Company) was used to register reaction times (RT). The tone that served as target was counterbalanced across subjects. RTs between 200 and 2,000 ms poststimulus were accepted as correct responses.

Practice oddball task. To ensure that participants understood the instructions and were responding appropriately, they were presented with high and low pure tones in ran-

dom order during a short practice block. One tone was presented 44 times and was designated the standard and the other tone was presented 6 times and designated the target. There were 12 null events.

Standard oddball task. Subjects were presented with high and low pure tones in random order. One tone was presented 88 times and was designated the standard and the other tone was presented 12 times and was designated the target. There were 25 null events. There were two blocks each with 125 trials.

Novelty oddball task. Following the standard oddball task, subjects were presented with 10 blocks, each comprised of 84 standard tones, 8 target tones, 8 novel, environmental sounds, and 25 null events. To maintain novelty, at least initially, subjects were not informed of the occurrence of the novel stimuli. Of the 48 unique environmental sounds, 32 were repeated (see below). In the first two blocks, all of the novel events were new, while in the rest of the blocks only half were new. The 16 sounds that did not repeat (labeled "unique") comprised half of the novel items in the first two and the last two blocks (four in each block). Repetition of the novel stimuli occurred two blocks after their initial presentation, such that, for example, the environmental sounds initially presented in the first block were repeated in the third block.

Imaging methods

All imaging was performed on a Philips Intera 1.5T scanner. Following a localizer scan, 13 functional image scans were acquired (FEEPI, 17 axial slices; $3.125 \times 3.125 \times 8$ mm voxels; TR/TE 3000/50 ms, 64×64 matrix). The first functional scan, comprising 42 volumes, was acquired for the practice standard oddball block. The next functional scans, each consisting of 84 volumes, were performed for the two blocks of the standard oddball task. The last 10 functional scans each consisted of 84 volumes acquired during the 10 novelty oddball blocks. Following the 13 functional scans, two anatomical reference scans were obtained (TSE, 17 axial 8 mm slices, TR/TE 2000/100 ms, 256×256 matrix, 200 FOV; SPGR, 99 axial, 1.5 mm slices, TR/TE 25/3 ms, 256×256 matrix, 230 FOV).

erfMRI analyses

Image analysis was performed using FSL (<http://www.fmrib.ox.ac.uk/fsl/>). Functional images were analyzed with FEAT (FMRI Expert Analysis Tool) version 5.43. Images were motion corrected, brain extracted, spatially smoothed with a Gaussian kernel of 8 mm FWHM, intensity normalized, and temporally high-pass filtered (100s) to remove low frequency drift. Time series statistical analysis was carried out using local autocorrelation correction. A first level (run) fixed effects analysis was performed for the 10 novelty oddball blocks, modeling tar-

gets, standards, first novels (novel 1), and repeated novels (novel 2), convolved with a double-gamma hemodynamic response function. Statistical maps were generated for each event type vs. the implicit baseline and, in addition, contrast maps were calculated for targets vs. standards, novels (collapsed across novel 1 and novel 2) vs. the implicit baseline, and novels vs. targets. Statistical images were then aligned to the Montreal Neurological Institute (MNI) 152 standard brain space by registering the EPI to the subject's SPGR with a 6 parameter linear fit. These higher resolution images were then registered to the common template with a 12 parameter warp. A second level (within-subject) fixed effects and third level (across-subject) mixed effects analysis was then performed for all contrasts. For the novel 1 versus novel 2 comparison, a paired *t*-test was performed (e.g., block 1, novel 1 versus block 3, novel 2, etc.). For all contrasts, the resulting data were thresholded at $P < 0.001$, uncorrected. Areas of activation depicted in Figures 2 and 3 are in MNI Z space superimposed on axial slices of a brain representation that was averaged across the high-resolution images of all 15 participants.

RESULTS

Only the behavioral and erfMRI data from the 10 novelty oddball blocks are the subject of this report

Behavioral Data. During the novelty oddball task, subjects were very accurate in detecting the target (99.9% SD \pm 0.09) with mean RT of 568 ms (SD \pm 125 ms) and very occasionally had false alarms to standard tones (0.08%) and the novel, environmental sounds (0.6%).

erfMRI Data. With the exception of the repetition of novel sounds, the current paradigm is most similar to an investigation by Kiehl et al. published in 2001 [Kiehl et al., 2001b] and a more recent, 2005 study [Kiehl et al., 2005]. However, the current investigation was begun before the study by [Kiehl et al., 2005], who reported erfMRI data based on 100 volunteers. Their contrasts, therefore, were associated with a great deal of power. Hence, with the exception of the novel 1 versus novel 2 contrast, we computed the same contrasts employed by Kiehl et al. This was based on the assumption that any similarity in findings between the current study and the Kiehl et al. investigation could be held with a reasonable degree of confidence. The major difference between the studies by Kiehl et al. [Kiehl et al., 2001b, 2005] and the current investigation is the baseline used for the target and novel contrasts. Kiehl et al. [2005] reported their results relative to the frequent standards, whereas we report activations versus the implicit baseline. Although we replicated the results of [Kiehl et al., 2005] in our data when we used the frequent standards as the baseline, we noted that some of the "activation" was due to greater negative correlation between the event time course and the BOLD signal in the standards than in the stimulus of interest (see Fig. 1). This issue is certainly present in any contrast measure. However, it masks the underlying source of the activation and thus

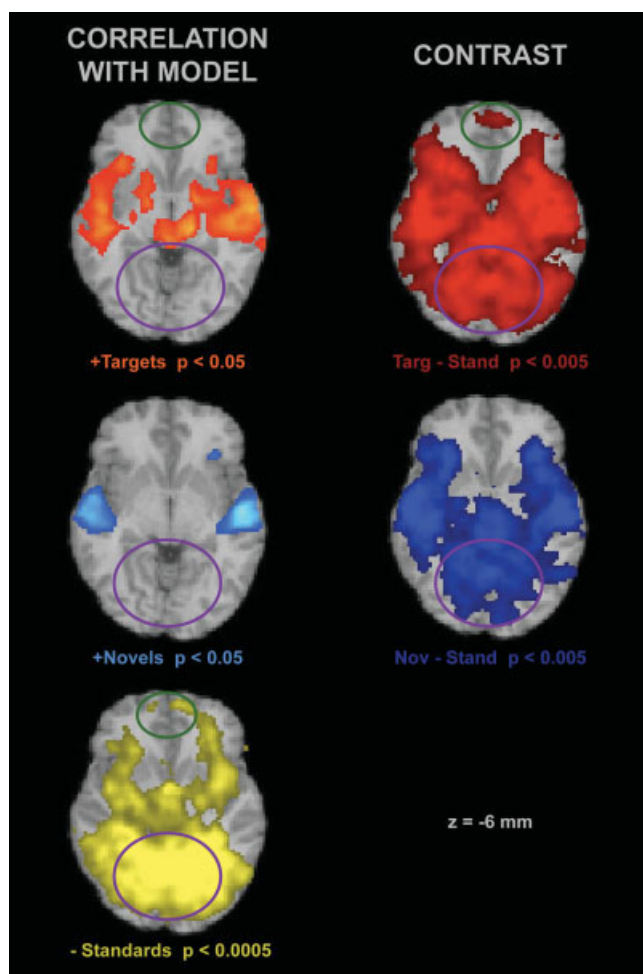


Figure 1.

Data showing strong contribution of $-B$ in an $A-B$ contrast. The left column shows BOLD signal correlation with the model for Targets (positive, $P < 0.05$, red), Novels (positive, $P < 0.05$, blue), and Standards (negative, $P < 0.0005$, yellow) in the same axial MNI slice ($z = -6$). Significance level was purposely set low for the positive correlations and high for the negative correlations to illustrate the point. Areas circled in green (frontal) and purple (occipital) show significant findings ($P < 0.005$) in Targets vs. Standards (dark red) and Novels vs. Standards (dark blue) contrasts (right column). However, this is due, at least in part, to the strong negative correlation between the BOLD signal and the Standards' time course (yellow). Targ = Targets; Nov = Novels; Stand = Standards.

complicates interpretation of the BOLD correlation. In other words, for a contrast $A-B$, areas of both $(+A)$ and $(-B)$ appear positive. Negative correlation of the BOLD signal to standard tones may indicate areas of habituation or active suppression, and should not necessarily be interpreted as generators of the target response. For the current oddball task, the BOLD signal is strongly negatively correlated with presentation of the target tones in large areas of

cortex similar to those shown to be negatively correlated with the alpha rhythm [Fig. 1; Goldman et al., 2002; Laufs et al., 2003; Moosmann et al., 2003] and may, therefore, reflect a disengaged or resting state. Hence, all results shown here are vs. the implicit (null) baseline. For comparison with the papers by Kiehl et al., we have depicted the regions of activation in MNI space at similar slices in Figures 2 and 3 as those depicted in their 2005 study [Kiehl et al., 2005].

As noted earlier, three predictions were made: (1) BOLD activations elicited by target and novel stimuli will occur in brain regions similar to those demonstrated in previous studies of the novelty oddball [Kiehl et al., 2001b, 2005]: cingulate cortex, auditory cortical regions, inferior frontal cortex; (2) Prefrontal regions will show a reduction in BOLD response to repeated novel events; and (3) Environmental sounds will recruit left inferior frontal gyrus, indicative of access to semantic information. We present, each in turn, the results of analyses to determine whether these expectations were or were not met in the sections below.

Similarity in Recruitment of Brain Regions to Previous Studies

Targets versus baseline

Figure 2 depicts the regions that showed significant activation in the Target versus baseline comparison (red to yellow). Clearly, as in previous investigations of the novelty oddball, the detection of target events recruits a widespread neural network. Table I presents the MNI coordinates, corresponding Brodmann areas (BA) of these regions, along with the maximum Z - and corresponding P -values. The majority of activated areas depicted in Figure 2 and listed in Table I have been reported by Kiehl et al. [Kiehl et al., 2001b, 2005]. A number of sublobar regions are activated including the brainstem, thalamus, basal ganglia and insula. Other areas include primary and secondary auditory cortical regions, medial parietal cortex, as well as several prefrontal cortical regions including the anterior cingulate gyrus and left precentral gyrus. The latter area of activation is consistent with the right-hand button press with which subjects responded to target tones.

Novel, environmental sounds versus baseline

To determine the regions activated by novel sounds, all first and second novel events were considered in a novel versus baseline contrast. First and second presentations of the environmental sounds were combined to enable the novel versus implicit baseline contrast to be based on a similar number of trials as that of the target versus baseline contrast. Figure 2 depicts, superimposed upon the areas activated in response to targets, the regions activated by the environmental sounds (blue to light blue). A direct, statistical conjunction analysis (common areas activated by targets and novels) was not performed. Nonetheless, to

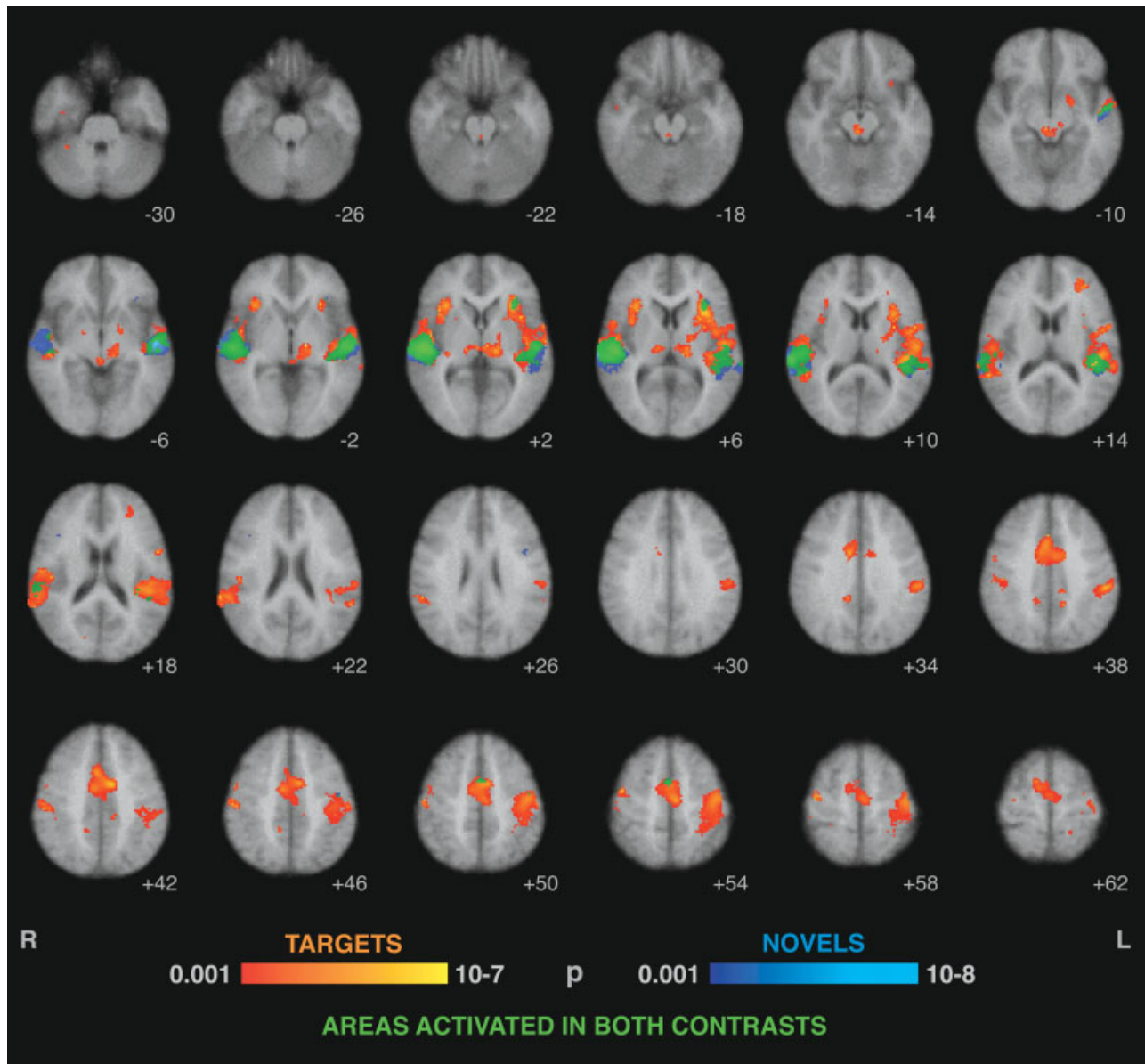


Figure 2.

Depiction of the regions activated by target tones and environmental sounds in relation to the implicit baseline. Target activations are illustrated in red to yellow, environmental sound activations in blue to light blue. For purposes of illustration, areas of

overlap between target and novel activations are illustrated in green. The numbers below and to the right of each axial slice represent the height, in MNI z-space at which the brain was imaged. The images are depicted in radiological convention.

show visually the similarity in the regions recruited, areas of overlap between target and novel activations are indicated in green in Figure 2. Table II presents the MNI coordinates, associated regional names, BAs, maximum Z- and corresponding *P*-values. In similar fashion to previous investigations, the environmental sounds activate bilaterally regions in proximity to auditory cortex. In addition to these regions, novel sounds also engender activity in the right superior frontal gyrus and the left insula (see Table

II). With two exceptions, the areas of activation reported here are in accord with those described by Kiehl et al. [Kiehl and Liddle, 2001; Kiehl et al., 2005] in their novel versus standard baseline contrasts. Although Kiehl et al. [2001b, 2005] demonstrated activations in left anterior cingulate gyrus and bilateral inferior frontal gyrus, these regions do not show reliable activations at the threshold used here. This discrepancy may also be due to the different baseline used in our study.

TABLE I. Areas of activation in MNI space for the target versus baseline contrast including Brodmann areas (BA), maximum Z- and P-values

| Target vs. baseline | Region/Brodmann area | x | y | z | Z | P |
|-------------------------------------|------------------------------------|-----------------------------------|-----|-----|------|------|
| Frontal | Left inferior frontal gyrus BA 44 | -54 | 4 | 18 | 5.06 | **** |
| | Right inferior frontal gyrus BA 47 | 32 | 24 | -4 | 4.50 | *** |
| | Right inferior frontal gyrus BA 45 | 34 | 26 | 8 | 4.57 | *** |
| | Right superior frontal gyrus BA 6 | 6 | -6 | 64 | 4.51 | *** |
| | Left middle frontal gyrus BA 10 | -28 | 45 | 13 | 3.68 | ** |
| | Right medial frontal gyrus BA 6 | 4 | -10 | 66 | 4.93 | **** |
| | Left precentral gyrus BA 6 | -52 | 2 | 10 | 5.07 | **** |
| | Left precentral gyrus BA 4 | -44 | -11 | 48 | 4.32 | *** |
| | Right precentral gyrus BA 6 | 50 | -10 | 8 | 4.65 | *** |
| | Right precentral gyrus BA 4 | 40 | -11 | 54 | 3.83 | ** |
| | Left cingulate gyrus BA 24 | -10 | -2 | 42 | 4.74 | **** |
| | Right cingulate gyrus BA 24 | 10 | 4 | 36 | 4.68 | **** |
| | Right cingulate gyrus BA 32 | 2 | 20 | 38 | 4.66 | *** |
| | Left middle temporal gyrus BA 21 | -55 | -6 | -6 | 3.82 | ** |
| | Temporal | Right middle temporal gyrus BA 21 | 54 | -26 | -4 | 4.99 |
| Left superior temporal gyrus BA 22 | | -48 | -12 | -8 | 5.50 | **** |
| Right superior temporal gyrus BA 22 | | 58 | -44 | 12 | 4.67 | *** |
| Right superior temporal gyrus BA 22 | | 68 | -40 | 20 | 5.45 | **** |
| Right superior temporal gyrus BA 41 | | 52 | -22 | 4 | 5.30 | **** |
| Right postcentral gyrus BA 1 | | 53 | -17 | 47 | 4.05 | ** |
| Right postcentral gyrus BA 3 | | 53 | -19 | 38 | 3.39 | * |
| Parietal | Left postcentral gyrus BA 2 | -55 | -19 | 45 | 4.22 | *** |
| | Left postcentral gyrus BA 2 | -51 | -27 | 36 | 4.60 | *** |
| | Right posterior cingulate BA 31 | 12 | -39 | 35 | 3.28 | * |
| | Left posterior cingulate BA 31 | -12 | -31 | 36 | 3.04 | * |
| | Precuneus BA 31 | -12 | -43 | 37 | 3.27 | * |
| | Left inferior parietal lobule BA 2 | -40 | -34 | 49 | 3.50 | * |
| | Brainstem, midbrain | 2 | -29 | -7 | 3.25 | * |
| Sublobar | Left globus pallidus | -20 | -2 | -7 | 3.35 | * |
| | Left thalamus | -14 | -16 | -2 | 5.22 | **** |
| | Right thalamus | 14 | -19 | 5 | 3.57 | * |
| | Left claustrum (basal ganglia) | -32 | 2 | 10 | 5.18 | **** |
| | Left insula BA 13 | -38 | 12 | 2 | 4.97 | **** |
| | Right insula BA 13 | 48 | -20 | 18 | 4.61 | *** |
| | Right insula BA 13 | 32 | 18 | 6 | 4.58 | *** |

* $P < 0.001$.

** $P < 0.0001$.

*** $P < 0.00001$.

**** $P < 0.000001$.

Repetition-Induced Reduction in BOLD Response to Novels in Prefrontal Regions

Contrary to expectation, when first-presentation novels were contrasted with their second-presentation counterparts, no reliable differences were revealed. In addition, analyses which modeled linear and exponential trends across the 10 novelty oddball blocks failed to reveal any regions in which there was a reliable trend for amplitude reduction in response to the recurrence of novel sounds across blocks.

Left Inferior Frontal Gyrus Activation by Novel Sounds

Novels versus targets

The third expectation was assessed by contrasting novel sounds with targets. Figure 3 depicts, in blue to light blue,

the regions in which activation was greater for novels compared to targets. This contrast reveals greater hemodynamic activity in the right middle temporal gyrus, BA 21 (55, -18, -3; $Z = 3.74$, $P < 0.0001$), a region in which reliable hemodynamic activity was not observed in the novel versus baseline contrast. Moreover, while the target versus baseline comparison reveals activation of the left inferior frontal gyrus in BA 44 (Table I), the environmental sound versus target contrast shows activation of BA 45 (-49, 26, 8; $Z = 3.33$, $P < 0.0005$) within the left inferior frontal gyrus, a region anterior to that observed in the target vs. baseline comparison.

Targets versus novels

Figure 3 also depicts the regions in which hemodynamic activity was greater in response to targets relative to novels (red to yellow). These regions are highly similar to

TABLE II. Areas of activation in MNI space for the Novels versus baseline contrast including Brodmann areas (BA), maximum Z- and P-values

| Novel vs. Baseline | Region/Brodmann area | x | y | z | Z | P |
|--------------------|-------------------------------------|-----|-----|----|------|------|
| Frontal | Right superior frontal gyrus BA 6 | 2 | 4 | 48 | 3.36 | * |
| | Right superior temporal gyrus BA 42 | 65 | -27 | 10 | 5.55 | **** |
| Temporal | Right superior temporal gyrus BA 22 | 53 | -17 | 3 | 5.07 | **** |
| | Right superior temporal gyrus BA 21 | 63 | -12 | -3 | 4.32 | *** |
| | Right superior temporal gyrus BA 22 | 63 | -38 | 11 | 3.94 | ** |
| | Left superior temporal gyrus BA 22 | -55 | -18 | -1 | 5.32 | **** |
| | Left superior temporal gyrus BA 41 | -48 | -34 | 13 | 3.76 | ** |
| | Left insula BA 13 | -42 | -25 | 14 | 3.48 | * |
| | Left superior temporal gyrus BA 22 | -63 | -35 | 9 | 3.35 | * |
| Sublobar | Left insula BA 13 | -32 | 23 | 3 | 3.43 | * |

* $P < 0.001$.

** $P < 0.0001$.

*** $P < 0.00001$.

**** $P < 0.000001$.

those observed in the target versus baseline contrast, with highly similar maximum Z-values (>4.0). Hence, for the sake of brevity, the x , y , and z values are not tabled. In addition, this contrast reveals greater hemodynamic activity in the inferior parietal lobule (BA 40), a region not identified in the target versus baseline comparison. There are also reliable activations in the left ($-57, -30, 27$; $Z = 4.24$, $P < 0.00001$) and right ($42, -29, 38$; $Z = 4.31$, $P < 0.00001$; $50, -26, 23$; $Z = 3.62$, $P < 0.0001$) inferior parietal lobules.

DISCUSSION

Similarity in Recruitment of Brain Regions to Previous Studies

Consistent with the first of our predictions, there was a great deal of overlap between the regions of hemodynamic activation reported here and those described in previous investigations of the auditory oddball paradigm [Kiehl et al., 2001a,b, 2005; Menon et al., 1997; Opitz et al., 1999]. For targets, these included bilateral inferior frontal gyrus, bilateral anterior cingulate gyrus, regions in close proximity to auditory cortex comprising bilateral middle and superior temporal gyrus, and subcortical areas including the thalamus.

For the environmental sounds, areas activated were not as widespread as those observed for target tones. Nonetheless, the majority of the regions recruited in the current investigation, which included left and right superior temporal gyrus, were highly similar to those reported previously in the novel versus frequent, standard baseline contrasts by Kiehl et al., [2001a, 2005]. By contrast, some of the activated regions that Kiehl et al., [2001b] had observed in response to the environmental sounds were not seen here, i.e., left anterior cingulate gyrus and bilateral inferior frontal gyrus. The reasons for these discrepancies are not immediately clear. Procedural differences (use of the

implicit baseline here versus the standard baseline in the Kiehl et al. studies) and divergence in the construction of the environmental sounds (digital noises in Kiehl et al. versus common, everyday sounds in the current study) may have played a role.

Repetition-Induced Reduction in BOLD Response to Novels in Prefrontal Regions

Contrary to expectation, there was no evidence for a reduction in hemodynamic activity in any region when first and second presentations of novel sounds were contrasted. Although a null result requires interpretive caution, it may be instructive, nonetheless, to consider briefly why habituation may not have been observed. In the ERP laboratory, the reduction in novelty P3 amplitude that is typically seen can be quite small, on the order of 0.5–1 μV [Friedman et al., 1998; Kazmerski and Friedman, 1995; Knight, 1984]. Moreover, the ERP amplitude diminution can occur quite rapidly, i.e., within the first few presentations [Friedman and Simpson, 1994; Knight, 1984]. Additionally, given the small magnitude of the habituation effect and relatively poor hemodynamic signal-to-noise ratios, it is possible that fMRI at 1.5 T might be insensitive to such a small change (by contrast, see Yamaguchi et al., 2004, for a habituation effect recorded at 4 T to novel visual events). It is also arguable that the high-intensity noise produced by the scanner might serve to make all novel sounds less surprising. Finally, in order to accommodate the parameters of fMRI recording, the 1-s inter-stimulus-interval (ISI) used most often in our previous ERP experiments was changed to 2 s and null events (also with 2-s durations) were added. Compared to the intervals we have employed in the ERP novelty oddball paradigm with repetition, these parameters more than doubled the time between first and second presentations (~ 4 –5 min in the current protocol). Therefore, the presumed memory trace for a very brief environmental sound may have decayed

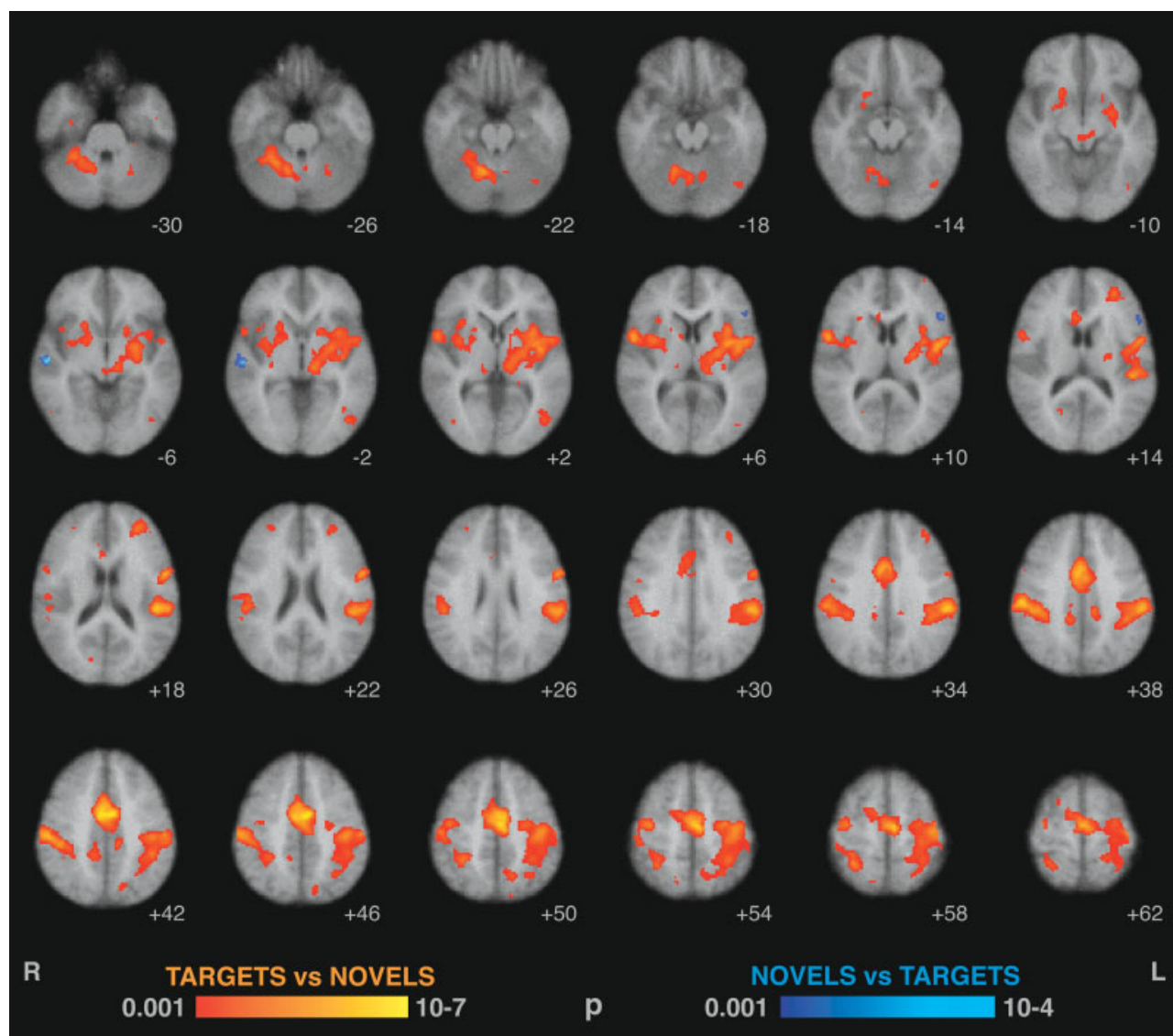


Figure 3.

Depiction of the regions in which novel sounds elicited greater hemodynamic activity than target tones (blue to light blue) and target tones elicited greater activity than novel sounds (red to yellow). The numbers below and to the right of each axial slice represent the height, in MNI z-space at which the brain was imaged. The images are depicted in radiological convention.

prior to its second presentation, precluding a reduction in hemodynamic activity to the second occurrence.

Left Inferior Frontal Gyrus Activation by Novel Sounds

Consistent with the third prediction, relative to target tones, the environmental sounds elicited greater activation in the left inferior frontal gyrus (BA 45), a region that has been implicated in the semantic analysis of a wide variety of stimuli during several different task paradigms [Otten

et al., 2001; Thompson-Schill et al., 1997; Wagner et al., 2001] including the recovery of meaning from and identification of environmental sounds [Lewis et al., 2004].

One particularly important concomitant of the orienting response is the evaluation of the potential significance of the environmental event [Lynn, 1966]. In the current context, this most likely would involve the extraction of meaning from the environmental sound. Consistent with this view, when the hemodynamic response of the novel sounds was contrasted with that associated with target tones, left-hemisphere activations in the inferior frontal

gyrus were revealed. Highly similar regional activations were obtained by Lewis et al. [Lewis et al., 2004], albeit in a very different experimental context. These investigators asked their subjects to respond on the basis of whether or not they could identify a wide selection of environmental sounds which varied in duration between 1 and 2 s. The identical sounds played in reverse served as controls. In addition to hemodynamic activations within the left supra-marginal gyrus and the posterior middle temporal gyrus bilaterally, correctly identified compared to unidentified sounds elicited activation in a large swath of the left inferior frontal cortex, which included BA 45. Although the sounds presented in the current study were quite brief (mean = 336 ms), the conceptual sources of many of them have been shown to be identifiable [Fabiani et al., 1996], concordant with the left-hemisphere activations observed here. Two caveats temper the strength of this interpretation. First, although the left-hemisphere activation was expected, an explicit identification of the environmental sound was not called for as in the study by Lewis et al. [2004]. Second, the statistical significance of the activations observed in this region occurred at a lower level than the majority of those that resulted from the Target versus baseline, Novel versus baseline or Target versus Novel contrasts. Nonetheless, the left inferior frontal activations found here are broadly consistent with the interpretation that extraction of meaning from environmental sounds is putatively reflected by the left inferior frontal activation. In addition, these data suggest that environmental sounds are most likely stored in semantic networks in similar fashion to words and pictures. The P3₂ component has also been interpreted to reflect the extraction of (and/or search for) meaning in ERP studies of the novelty oddball [Cycowicz and Friedman, 1998]. However, whether it receives contributions from any of the left-hemisphere regions shown to be activated here is difficult to determine without further investigation.

The current and previous fMRI data implicate widespread, but somewhat different, cortical networks in the detection of task-relevant target and task-irrelevant novel events (as is also suggested by the iERP data summarized by Halgren et al., 1998b). As noted earlier, while ERP data allow very precise temporal estimates of cognitive processing, it is more difficult to infer spatial information from scalp-recorded data. On the other hand, fMRI data allow very precise spatial estimates of the regional activations engendered by specific cognitive tasks, while the temporal information provided is quite poor relative to the speed of the cognitive operations under scrutiny. Hence, although methods are under development for relating ERP and fMRI data (e.g., [Dale et al., 2000; Logothetis et al., 2001; Phillips et al., 2002]), the extant auditory oddball ERP and fMRI data suggest that the two sets of signals may reflect different phenomena. For example, as previously observed by Kiehl et al., [2005], targets in the current study elicited greater hemodynamic activity than environmental sounds in many more brain regions than where the converse was

the case (see Fig. 2). On the other hand, in ERP studies of the auditory novelty oddball the typical finding is that the task-irrelevant, environmental sounds elicit significantly greater ERP activity over more regions of the scalp compared to targets than where the opposite relation holds [Fabiani and Friedman, 1995; Friedman et al., 2001; Gaeta et al., 2003; Opitz et al., 1999]. Thus, interpretive caution is required when attempting to relate the data from the two techniques.

Nonetheless, it is noteworthy that the results of this investigation with 15 participants are entirely consistent with the data, based on 100 volunteers, provided by Kiehl et al., (2005). Although relative to the Kiehl et al. study, the power associated with our contrasts is undoubtedly lower, the similarity in findings suggests that these phenomena are quite robust and, therefore, can be supported with confidence.

In conclusion, the current data join previous investigations of the auditory novelty oddball in implicating a widespread cortical network in the detection of task-relevant target events. The brain's orienting response, here reflected in the regional activations engendered by novel, task-irrelevant events, also involves a widespread network with overlapping but also somewhat different brain regions compared to targets. The left inferior frontal gyrus activation (BA 45) observed here most likely reflects the extraction of meaning from the environmental sound, an important aspect of the orienting response. This enables one to determine the significance of the environmental perturbation and to take appropriate goal-directed action.

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