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The Hemodynamics of Oddball Processing During Single-Tone and Two-Tone Target Detection Tasks

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Abstract

Event-related potential (ERP) studies have shown that the neural systems engaged during performance of oddball tasks are sensitive to contextual manipulations, such as the number of stimulus classes. Some ERP components (i.e., N1) are modulated by the number of stimulus types, while others (i.e., P3) are not greatly affected. However, little is known about how these contextual manipulations affect the hemodynamics underlying oddball processing. The purpose of this study was to examine the hemodynamic correlates of target stimulus processing in singletone (targets alone) and two-tone (targets and standard tones) auditory oddball tasks. The primary hypothesis was that processing of salient stimuli in both contextual conditions would engage the same spatially distributed cortical and subcortical networks observed in previous oddball fMRI studies. Results were consistent with this hypothesis and suggest that the brain engages many potentially useful brain regions during salient stimulus processing despite the low probability that said regions are necessary for task performance, which likely reflects a form of “adaptive reflexive processing.” Results also were consistent with ERP data that shows the N1 is larger for single-tone tasks by showing greater amplitude of hemodynamic response for singletone targets, relative to two tone targets, in bilateral temporal cortex and bilateral inferior lateral frontal cortex. The results are discussed as they relate to the understanding of neurocognitive function pertaining to contextual manipulations in general, and orienting processes in particular.

Keywords

ORIENTING; MAGNETIC RESONANCE IMAGING; BRAIN; PSYCHOLOGY; COGNITION

The neural systems underlying processing of low probability target stimuli have been studied for over four decades. The impact of salient stimulus processing on brain electrical activity was first described by Sutton et al. (1965), who demonstrated that infrequently-presented task-relevant stimuli (“oddballs”) produce a sequence of time-locked electrical components, the

most prominent of which is a large positive potential that peaks approximately 300 milliseconds following the stimulus onset. This late event-related potential (ERP), termed the P300 or P3, is thought to reflect stimulus evaluation/categorization, and cognitive processes necessary to update mental models of context within working memory (Donchin & Coles, 1988). Since Sutton et al.'s seminal study, numerous reports have been published that detail how contextual manipulations in the oddball paradigm (e.g., manipulations of stimulus probability, inter-trial interval, sensory modality, etc.) modulate the latency, amplitude or topographic distribution of the P3 (Polich et al., 1996).

One contextual manipulation to the oddball task is to alter the number of stimulus classes presented within the task. Researchers most commonly use oddball tasks having either two-stimulus classes (low probability targets juxtaposed with frequent standards) or three-stimulus classes (low probability target and novel/distracter stimuli, and frequent standard stimuli). However, it has been shown that the P3 response also can be elicited using a single-stimulus task (Polich et al., 1994). In a single-stimulus task, the participant is simply required to detect the presence of a tone stimulus (which generally occur 3–15 seconds apart). In a two-stimulus task, the participants must discriminate the oddball (low probability targets) from standard stimuli. These latter stimuli usually differ in some context (such as frequency, size, duration, etc). In the three-stimulus task, the discrimination becomes slightly more difficult as novel/distracter stimuli typically are distracting and require more attentional resources to process. Comparisons of the ERP components elicited by oddball tasks with different numbers of stimulus classes suggest that some ERP components are modulated by task context while others are not. For example, one study (Katayama & Polich, 1996) compared P3 amplitude and latency in single-, two-, and three-tone auditory oddball tasks, keeping constant both the physical characteristics and the probability of occurrence of the target stimulus. They found no differences in P3 amplitude between task conditions at midline leads. However, the N1 amplitude was larger and N1 latency longer in the single tone condition than in the two-tone condition. Additionally, the P2 and N2 amplitudes were significantly more positive in a single-tone compared to two- or three-tone oddball conditions. These effects were interpreted as resulting from the longer 'effective' inter-stimulus interval in the single-tone condition compared to the two-tone and three-tone conditions. The inter-trial (or inter-target) interval is known to be positively correlated with the amplitude of the N1, but not the P3, in single-tone tasks (Polich & Starr, 1983), which is thought to be related at least in part to the direction of attention towards eliciting stimuli. There also was evidence for a shorter P3 latency in the single-tone condition compared with two-tone or three-tone tasks, which may reflect an absence of stimulus discrimination or the relative ease of the single-tone task relative to the other tasks. The results were interpreted as support for the idea that the target-elicited P3 is produced by similar neurocognitive mechanisms, with little modulation due to these contextual manipulations. This conclusion is supported by several other studies which did not observe any differences between conditions in the amplitude and latency of the P3 when comparing single- and two-stimulus oddballs (Polich et al., 1994; Polich & Heine, 1996). However, one study (Polich & Margala, 1997) noted that probability modulated P2 and N2 in the single-stimulus task. As target probability decreased, there were greater differences in P2 and N2 amplitude. In this study, the greatest P2/N2 difference between single- and two-tone tasks appeared in low target probability conditions (i.e., 10% of trials in the two-tone task and identical target tones in the single-tone task as opposed to target probabilities between 20 to 50%).

The neural generators of scalp-recorded ERPs elicited during target stimulus processing have been examined using depth-electrodes. In these studies, target stimuli produced activity in the ventral frontotemporal cortices, superior temporal sulcus, posterior parietal cortex, and the hippocampus, suggesting that these areas are neural generators associated with target-elicited P3 ERPs (Baudena et al., 1995; Halgren, 1980; Halgren et al., 1995a; Halgren et al., 1995b;

Halgren et al., 1998). Halgren and colleagues concluded that widespread brain activation involves integration of stimulus processing and context, which is necessary for the online monitoring of performance. ERP source localization studies suggest that the P3 is localized to the bilateral prefrontal cortex, parietal-occipital junction, and parietal lobe, while the N1 is localized predominantly to bilateral auditory cortex, with some evidence supporting additional sources in the prefrontal cortex (Anderer et al., 1998; Giard et al., 1994; Halgren et al., 1995a; Liegeois-Chauvel et al., 1994). Functional magnetic resonance imaging (fMRI) studies have confirmed and extended these findings (Braver et al., 2001; Casey et al., 2001; Clark et al., 2001; Clark et al., 2000; Kiehl et al., 2001a; Kiehl et al., 2001b; Kiehl & Liddle, 2003; Kiehl et al., 2005; Kirino et al., 2000; Linden et al., 1999; McCarthy et al., 1997; Menon et al., 1997; Opitz et al., 1999; Stevens et al., in press; Strange & Dolan, 2001). These studies report that target detection elicits widespread cortical and subcortical activation, including multiple foci in the prefrontal, temporal, parietal and occipital lobes, and subcortical sites. It is noteworthy that changes in stimulus probability or inter-stimulus interval in fMRI oddball tasks have effects on target-elicited hemodynamics that are analogous to the effects on the P3 component following similar manipulations (Casey et al., 2001; Clark et al., 2001; Horowitz et al., 2002). This suggests that much of the brain activity detected using fMRI corresponds to that associated with the P3 component. The consistency of fMRI target-related findings with ERP research suggests that Katayama & Polich's (1996) conclusion that similar neural generators produce target-related brain activity regardless of the number of stimulus classes included in the task also may apply to many aspects of the hemodynamic response data, insofar as fMRI captures the same neurocognitive processes that produce the ERPs in electrophysiology. Certainly, simultaneous recording of fMRI-measured hemodynamics and EEG shows a close relationship between the blood-oxygen-level-dependent (BOLD) signal and local field potentials reflecting synaptic activity to individual events (Logothetis et al., 2001).

The purpose of the current study was to use fMRI to examine whether contextual manipulation of the number of stimulus classes modulated the hemodynamic activity elicited during auditory oddball processing. Hemodynamic activity was examined in a group of participants who performed both a two-stimulus version of the oddball and a version containing only targets (single-stimulus) (Polich et al., 1994; Polich & Heine, 1996; Polich & Margala, 1997). The first aim of this study was to determine whether the brain areas previously activated by target detection during a three-stimulus oddball task (Kiehl et al., 2001a; Kiehl et al., 2001b; Kiehl & Liddle, 2003) also were activated by the different contextual task manipulations. It was hypothesized that target stimuli would elicit hemodynamic activity in the same diverse, spatially distributed neural network implicated in previous depth electrode and three-stimulus fMRI oddball studies. A second goal was to compare the magnitude of activation in single-tone and two-tone fMRI tasks. As reviewed above, ERP studies suggest that the N1, N2 and P2 amplitude differ between the two tasks. Thus, it was hypothesized that hemodynamic activity in brain regions known to be sources for the N1 will be modulated by the contextual manipulation. Specifically, it was predicted that auditory cortical areas in the temporal lobe and bilateral prefrontal cortex would show greater hemodynamic activity for the single-tone than the two-tone conditions. Specific hypotheses were not made linking single-tone and two-tone N2 and P2 to specific anatomical regions because the precise location of the sources of the N2 and P2 components remains controversial (Siedenberg et al 1996).

Methods

Participants

Participants were 20 healthy right-handed volunteers (10 men) with a mean age of 31.1 (SD 8.54). Participants were recruited via posted advertisements, presentations at local universities

and word-of-mouth at The University of British Columbia (UBC), Vancouver, BC. Participants provided written informed consent in protocols approved by the institution's governing Institutional Review Board responsible for participant protection and ethical conduct of research. All research procedures were conducted in adherence to ethical standards required for human subjects protection.

Procedure

Two versions of the auditory oddball task were used that differed in the overall number of stimulus classes presented to the participant. In each task version, participants were presented with two runs, each containing 24 target tones of 1500 Hz, yielding a total of 48 targets per each experimental condition. In the single-tone task, the target tones were accompanied by silence (i.e., no other stimuli). For the two-tone task, 220 1000 Hz tones were added as frequent, or 'standard' nontargets. Target stimuli occurred with a probability of approximately 11% in the two tone condition. Target stimulus characteristics and target-to-target onsets were the same in both conditions. Polich and colleagues have shown that .10 target probability is best for eliciting ERP differences between single tone and two tasks (Polich & Margala, 1997). The stimulus duration in each task was 200 msec, with a 2000 msec stimulus onset asynchrony (SOA) in the two-tone condition. The intervals between targets were allocated in a pseudo-random manner in the range 6–10 seconds so as to ensure that these stimuli had equal probability of occurring at 0, 1, and 2 seconds after the beginning of a three second image acquisition period. As a result, the hemodynamic response to each type of stimulus of interest was sampled uniformly at 1 second intervals. A custom visual and auditory presentation package (VAPP; <http://www.psychiatry.ubc.ca/sz/nilab/software/vapp>) was used to closely control the stimuli presentation timing. The two sessions were presented to the participant by a computer-controlled auditory sound system that delivered the auditory stimuli with insert earphones embedded within 30 dB sound attenuating MR compatible headphones. All participants reported that they could hear the stimuli and discriminate them from the background scanner noise.

In both conditions, participants were instructed to respond as quickly and as accurately as possible with their right index finger every time the target tone occurred (and not respond to the standard nontarget stimulus in the two-tone condition). Prior to beginning the task, each participant performed a 20 second practice trial to ensure understanding of the instructions. A commercially available MRI compatible fiber-optic response device (Lightwave Medical, Vancouver, BC) was used to acquire behavioral responses. Stimulus events and behavioral responses were recorded and monitored online using software run on a separate PC. Reaction times were computed on trials for which the participant responded correctly within 1500 ms post-stimulus. Omission errors included any missed target tones or any response with a latency of greater than 1500 ms following the onset of the target stimulus. The order of task administration was counter-balanced across participants.

Imaging parameters

Imaging was implemented on a GE 1.5T system fitted with an Horizon Echo-speed upgrade. The participant's head was firmly secured using a custom head holder. Conventional spin-echo T₁ weighted sagittal localizers were acquired for use in prescribing the functional image volumes. Functional image volumes were collected with a axial gradient-echo sequence (TR/TE 3000/40 ms, flip angle 90°, FOV 24 × 24 cm, 640 × 64 matrix, 62.5 kHz bandwidth, 3.75 by 3.75 mm in plane resolution, 5 mm slice thickness, 29 slices) effectively covering the entire brain (145 mm). The two stimulus runs each consisted of 167 time points, including a 12 second rest session at the beginning that was collected to allow for T₁ effects to stabilize. These initial images were not included in any subsequent analyses.

Image processing

Functional images were reconstructed offline and each session was realigned using INRIAlign (Freire & Mangin, 2001; Freire et al., 2002) as implemented in Statistical Parametric Mapping (SPM99). Translation and rotation corrections were less than 1.5 mm and 2.0 degrees for every participant. A mean functional image volume was constructed for each participant for each run from the realigned image volumes. This mean image volume was then used to determine parameters for spatial normalization into the modified Talairach space (i.e., Montreal Neurological Institute (MNI) space) employed in SPM99. The normalization parameters determined for the mean functional volume were then applied to the corresponding functional image volumes for each participant. The normalized functional images were then smoothed with a 12 mm full width at half-maximum Gaussian filter. In addition, the data underwent a fifth-order IIR Butterworth low-pass filter of 0.16 Hz to remove high frequency noise associated with alterations in the applied radio frequency pulses.

fMRI Statistics

Event-related responses to stimuli were modeled using a canonical hemodynamic response function (Josephs & Henson, 1999) and temporal derivative. The temporal derivative was employed to account for small variations in peak latency. The hemodynamic response elicited by target stimuli in each session was modeled by entering stimulus onset timings for only those events that each participant responded to correctly (e.g., targets with correct button-presses within 1500 msec, and correctly ignored standard/nontarget stimuli in the two-tone condition). Thus, every participant had an fMRI timeseries model specific to his or her behavioral response patterns. The number of error trials was small (less than 1 % of all trials); therefore, error events were not explicitly modeled.

Because each participant performed both task conditions, single-tone and two-tone data were entered into a single fixed-effects model and a single multiple regression model was calculated for each subject. Target amplitude and target temporal derivative were modeled for the single-stimulus session. Target amplitude and temporal derivative, standard stimulus amplitude and temporal derivative were modeled for the two-tone sessions. In the two-tone condition, standard nontarget stimuli were presented at the rate of once every 2 seconds with the object of maintaining a sustained hemodynamic response that did not vary substantially throughout the task. In this condition, the response to the standard stimuli was explicitly modeled for contrast to the target-elicited activity.¹ For the single-tone task, the baseline constituted the periods between stimuli. A high pass filter (cutoff period 32 seconds) was incorporated into the model to remove noise associated with low frequency confounds (e.g., respiratory artifact) for both single-tone and two-tone data.

Images containing the amplitude of the hemodynamic response and its temporal derivative for target stimuli in each condition were created. In order to reduce the impact of spatially varying hemodynamic delays and delays due to slice timing differences, the true amplitude of the hemodynamic response, which is a function of both the non-derivative and derivative terms, was calculated (Calhoun et al., 2004). These latter images were then entered into a random-effects analysis model. A region of interest (ROI) approach was used to determine whether the single- and two-tone tasks activated the same areas identified in previous work with a three tone oddball task (Kiehl et al., 2001b). Thirty-four spherical ROIs (clusters of 2.112 cm³; 8 mm radius) were defined and centered at the location reported in previous work (Kiehl et al.,

¹A supplemental analysis was performed in which the standard stimuli in the two-tone condition were not explicitly modeled (as was done in Kiehl et al., 2001a). In this latter model the standard stimuli were assumed to form a relatively constant baseline. Analyses with and without modeling the standard stimuli in the two-tone condition yielded comparable results. However, it is currently preferred to model all classes of stimuli in SPM analyses. Thus, we present in the manuscript the analyses with the standard stimuli modeled in the two-tone condition.

2001a; Kiehl et al., 2001b; Kiehl & Liddle, 2003; Kiehl et al., 2005). One-sample *t*-statistics for each ROI for single-tone and two-tone conditions are reported as the maximum *t*-score within *a priori* ROIs. Statistical significance of activity within the ROIs was maintained below an alpha of .05 using small volume correction (Worsley et al., 1996) and the false discovery rate (Nichols & Hayasaka, 2003).² Relatively small clusters were used to prevent overlap for those ROIs that were close together; one ROI from previous work (Kiehl et al., 2001b); located in the right temporal pole was excluded because of such overlap.

To address the question of whether there are differences in the amplitude of the hemodynamic response elicited in the single- and two-tone conditions, a supplementary analysis examining the entire brain was done. For these post hoc tests, a correction for multiple comparisons used the False Discovery Rate to control Type I error (Nichols & Hayasaka, 2003).

For ease of visualization, the *t*-score results of random effects analyses were converted to a color scale and superimposed on the T1-weighted image of the brain of a single adult included with SPM99.

Results

Behavioral Performance

A paired sample *t*-test showed that participants were on average 36 msec faster to respond for single-tone target stimuli (mean 336 msec, SD 84) than for two-tone target stimuli (mean 372 msec, SD 58); $t_{19} = -2.923, p < .01$). There were no differences in accuracy between conditions (percentage of correct hits for single-tone: 99.5%, SD 1.49%; two-tone: 99.9%, SD 0.47%); $t_{19} = -1.710, ns$).

Imaging Data

Consistent with predictions, target detection was associated with significant activation in all 34 ROIs for both the single-tone and two-tone conditions (see Figures 1 and 2, respectively; see also Table 1). Also consistent with predictions, single-tone target detection elicited greater hemodynamic activity than did two-tone stimuli in both the left ($x, y, z = -60, -24, -4$; $t_{19} = 3.31, q = .002$) and right ($x, y, z = 64, -24, -4$; $t_{19} = -4.00, q = .001$) middle temporal gyri ROIs, and the left ($x, y, z = -60, -36, 4$; $t_{19} = 3.29, q = .002$) superior temporal gyri ROIs. It also was predicted that single-tone targets would be associated with greater activity than would two-tone targets in the inferior prefrontal cortex. Single-tone activation had a significantly greater amplitude of the hemodynamic response in both the left ($x, y, z = -44, 32, -16$; $t_{19} = 3.28, q = .002$) and right ($x, y, z = 40, 36, -20$; $t_{19} = 3.76, q < .001$) inferior frontal gyri, and both the left ($x, y, z = -40, 32, 36$; $t_{19} = 4.75, q < .001$) and right ($x, y, z = 36, 36, 40$; $t_{19} = 3.40, q < .001$) middle frontal gyri (see Figure 3).

Post hoc analysis of the whole brain volume revealed that target stimuli in the single-tone condition elicited greater hemodynamic activity than target stimuli in the two-tone condition in bilateral medial frontal gyri BA 6 ($x, y, z = 0, 0, 60$; $t_{19} = 4.92, q < .001$), the left precentral gyrus ($x, y, z = -52, -4, 40$; $t_{19} = 4.13, q < .001$), posterior left superior temporal gyrus ($x, y, z = -48, -56, 8$; $t_{19} = 4.71, q < .001$), left inferior parietal lobule ($x, y, z = -56, -44, 44$; $t_{19} = 4.51, q < .001$), right parahippocampal gyrus ($x, y, z = 36, -20, -16$; $t_{19} = 4.40, q < .001$), right fusiform gyrus ($x, y, z = 44, -36, -28$; $t_{19} = 3.91, q < .001$), left precuneus ($x, y, z = -28, -76, 32$; $t_{19} = 3.68, q < .001$) right precuneus ($x, y, z = 20, -76, 36$; $t_{19} = 5.45, q < .001$), and the left ($x, y, z = -44, -88, 8$; $t_{19} = 3.95, q < .001$) and right ($x, y, z = 44, -80, 8$; $t_{19} = 3.76, q < .001$)

²For these data, this significance criterion surpasses a Bonferroni adjustment for multiple comparisons applied to a $p < .05$ voxelwise threshold (i.e., the correction for searching 34 regions (i.e., $p < .05/34$ ROIs = 0.0014).

middle occipital gyri. Other areas of greater single-tone activation included left ($x, y, z = -24, 12, 8; t_{19} = 5.34, q < .001$) and right putamen ($x, y, z = 24, -4, 0; t_{19} = 4.15, q < .001$), and left ($x, y, z = -24, -56, -20; t_{19} = 3.77, q < .001$) and right cerebellum ($x, y, z = 28, -56, -20; t_{19} = 4.53, q < .001$).

There were no areas of greater two-tone activation relative to single-tone.

Discussion

This study illustrates that a large ensemble of brain regions, known to be involved in target detection during three-tone auditory oddball tasks (Kiehl et al., 2001a; Kiehl et al., 2001b; Kiehl & Liddle, 2003), also are engaged by target detection in single- and two-tone auditory oddball paradigms. Target detection in both single-tone and two-tone fMRI auditory oddball tasks elicited significant hemodynamic activity in all 34 *a priori*-defined regions of interest (ROIs). These data confirm that target detection across task contexts elicits activity in a similar widespread, distributed neural network. Halgren and others (Halgren, 1980; Halgren et al., 1995a; Halgren et al., 1995b) have argued that this distributed, perhaps reflexive, response to salient stimuli may be 'adaptive' in an evolutionary sense. That is, it is likely that activating many potentially useful areas during salient stimulus processing, despite the low probability these regions are necessary for performance, may lead to superior incidental learning, memory and performance. This extensive network of brain regions associated with target detection may be similar to the attention network discussed by Mesulam (Mesulam, 1990; Mesulam, 2000). Others have suggested that processing salient stimuli is associated with an 'reflexive' or 'automatic' orienting process that is reliably activates an extensive neural network despite the low probability that all activated brain regions are required for successful task performance (Kiehl et al., 2001a; Kiehl et al., 2001b; Kiehl & Liddle, 2003; Kiehl et al., 2005).

Also consistent with study hypotheses, target detection was associated with greater hemodynamic activity during the single-tone condition compared to the two-tone condition in bilateral middle temporal gyrus, inferior frontal and middle prefrontal gyri. These findings are consistent with electrophysiological and magnetoencephalogram studies of single-, two- and three-tone oddball tasks. Previous EEG and MEG studies have shown that the amplitude and latency of the N1, N2 and P2 are differentially modulated by single-tone compared to two-tone target stimuli (Katayama & Polich, 1996; Polich & Margala, 1997). Some of the differences in hemodynamic activity between single- and two-tone tasks correspond to source localization studies of the N1 generators. These generators are believed to be located in bilateral middle and superior temporal gyrus, and bilateral inferior and middle frontal gyrus (Anderer et al., 1998; Tarkka et al., 1995; Yamazaki et al., 2000). A link between hemodynamic activity in these brain areas and the N1 ERP also are found in several recent studies that have tried to link hemodynamics (Horovitz et al., 2002; Liebenthal et al., 2003; Linden et al., 1999; Menon et al., 1997; Opitz et al., 1999) or event-related magnetic fields (Siedenberg et al., 1996) to the early ERP components observed in oddball paradigms. A simultaneous EEG/MEG study found that N1 waveforms during two-tone auditory oddball rare target detection was similar in both ERP and MEG, and were localized to temporal lobe regions (Siedenberg et al., 1996). It is important to note that the N1 ERP may consist of as many as three spatiotemporally-distinct components. In addition to previously well-described temporal and frontal sources (Giard et al., 1994), these include a non-specific cortical response most detectable in vertex EEG recordings (Naatanen & Picton, 1987). This component is thought to reflect an attentional triggering mechanism (Naatanen & Picton, 1987; Naatanen et al., 1992) and has been interpreted to represent the orienting response (Budd et al., 1998). Opitz et al. (1999) found that hemodynamic activity in bilateral temporal gyri was correlated with the amplitude of the N1 elicited during a mismatch negativity (MMN) paradigms for both attended and unattended deviant stimuli. Linden et al. (1999) interpreted hemodynamic activity in the temporal lobe as

relating to the process of updating memory of the auditory input sequence, and possibly related to ERP components that occur earlier than the P3.

Because several ERP studies have found no differences in the amplitude of the P3 in these conditions, it is unlikely that differences in the amplitude of the hemodynamic response between single- and two-tone oddball performance can be explained within the context of working memory and contextual updating cognitive processes commonly offered as the interpretation of oddball-task P3 results (Donchin & Coles, 1988). Therefore, the most parsimonious cognitive interpretation of the differences in the amplitude of the hemodynamic response between conditions in this study is that they likely are related to cognitive processes proposed to describe the early and middle-latency potentials N1, P2 and N2. Polich and colleagues interpret early ERP component modulations as relating to the variability in inter-stimulus intervals on these components (reviewed in Polich & Starr, 1983). Specifically, it has been argued that increases in inter-stimulus interval across the range of approximately 2 to 10 seconds also increases N1-P2 amplitudes (Polich & Starr, 1983). It is possible that the longer effective ITI in the one-tone task relative to the two-tone task leads to a greater capture or orienting of attention for long as opposed to short ITIs. Research has consistently shown that directing attention to a stimulus modulates the N1-P2 amplitude (Hillyard et al., 1973; Okita, 1979; Picton et al., 1971). Because of the absence of a standard stimulus in the single-tone task, it is possible that more 'effectively' rare stimuli elicit a larger attentional (i.e., orienting) response than is elicited by two tones. Recall that one putative spatiotemporally-distinct component is a non-specific cortical response most detectable in vertex EEG recordings (Naatanen & Picton, 1987) that is thought to reflect an attentional triggering mechanism (Naatanen & Picton, 1987; Naatanen et al., 1992) akin to an orienting response. Therefore, it is possible that the greater hemodynamic activity observed in the single-tone task represents the manifestation of greater automatic attentional modulation denoted by this particular N1 subcomponent.

Currently, there is little information available to link oddball task hemodynamics to the N2 and P2 ERPs. As noted above, studies attempting to localize brain function associated with the N2 and P2 have inconclusive results (Siedenberg et al., 1996), often because earlier ERP components are not examined, or because the experimental manipulations do not modulate N1, P2, or N2 (Horovitz et al., 2002). Thus, it is not currently possible to conclusively link N2 and P2 components to neural activity in specific brain areas, or to attribute cognitive properties reflected by N2 or P2 to neural activity within specific brain regions. Also, with the exception of a source localization study (Tarkka & Stokic, 1998) most previous studies of ERP components comparing single- and two-tone tasks typically recorded from midline sites only (i.e., Fz, Cz, and Pz), which limits the ability to spatially map potential differences in conditions. Visual inspection of the Tarkka & Stokic (1998) waveforms indicates that P2/N2 ERPs at lateral central sites appeared to be more positive in the single-tone than the two-tone task (Katayama & Polich, 1996). It is also noteworthy that P3 activity may be linked to medial temporal lobe generators (Halgren, 1980). Therefore, it is plausible that modulations in hemodynamic activity in the temporal lobe could be ascribed to any of the N1, P2, N2, and P3 ERPs. Moreover, Halgren has argued that the N2a/P3a/SW complex from intracranial recordings links diverse brain areas into a multilobar functional neural network, all of which are proposed to represent the function of an orienting response (Halgren & Marinkovic, 1996). Thus, at the present time, it is not possible to definitely state whether the hemodynamics are related to one or another ERP 'component.' While it is tempting to conclude that the differences in hemodynamics between single-tone and two-tone targets are related to early ERP components, this interpretation should be tempered by the fact that few studies have employed dense spatial arrays to completely map all relevant ERP responses in these tasks, either because a full topographic array was not employed and/or statistical results were not reported for all components in most previous single-tone and two-tone studies. It remains

possible that the P3 elicited by single-tone targets may differ from that elicited by two-tone targets at scalp locations not previously examined. In addition, it could be argued that N1, P2, and N2 ERPs are unlikely to contribute much to the overall fMRI response in many brain areas since they represent a small fraction of time of the overall fMRI response. However, in a brain region that is associated mainly with the early phases of cortical processing, it would be expected that the neural activity associated with the earlier ERP components would make a larger contribution than the neural activity associated with P3, which is a larger component with greater overall duration. Linking specific ERP components to profiles of hemodynamic change is complicated by the relatively slow temporal resolution of the hemodynamic response. Because the exact correspondence between fMRI and ERP signals remains unclear and is a matter of active research, the degree to which these ERPs contribute to localized hemodynamic change is not certain.

It might be considered surprising that regions in the basal ganglia, occipital lobe, and cerebellum were found to differ between single- and two-tone task conditions. It is not clear whether the hemodynamic activity in these areas reflects neuroelectric activity captured in specific N1, P2 or N2 ERP components (Polich & Margala, 1997). It is plausible that future source localization studies of ERP components may find these latter locations useful in deriving new dipole modules. With regard to the functional significance of these specific areas of greater amplitude of the hemodynamic response in the single-tone condition, previous research suggests possible relationships between target detection and these regions. Patients with radiologically identified right-sided basal ganglia lesions frequently (Ferro et al., 1987), though not reliably (Vallar & Perani, 1986), display left unilateral attentional neglect. This implicates the basal ganglia in attention, possibly the subcortical regulation of attention or attentional switching. The greater cerebellar activation in the single-tone condition might reflect higher cognitive and motor coordination demands associated with the significantly faster responding in the single-tone task. Lastly, previous ERP studies have localized a visual oddball-elicited N1 to areas of temporal-occipital cortex (Yamazaki et al., 2000), suggesting that modulation of occipital cortex activity by the single-tone task may reflect the functional interconnectedness of temporal-occipital areas during target-processing. Therefore, the occipital activation ultimately may be found to be an indication of the same attentional orienting processes in visual tasks reflected by the temporal lobe-N1 association in auditory task.

It also is possible that differences in hemodynamic activity between the single-tone and two-tone tasks might be the result of differences in the baselines used to measure BOLD signal change in each condition. In the current experiment, the two-tone task was designed so that the standard stimuli would form a stable baseline for comparison, whereas the single-tone condition did not include standard stimuli. One possible concern might be that frequent nontarget stimuli engage some brain regions that are not engaged during the single tone condition. For example, a recent large sample (n=100) fMRI study found that frequent nontarget stimuli engage bilateral middle and superior temporal gyrus, left middle frontal gyrus, and left cingulate gyrus. Of these regions, the current study found evidence for greater hemodynamic activity for single-tone target stimuli than two-tone target stimuli in bilateral superior and middle temporal gyri (see Figure 3). Thus, it is possible that differences between single-tone target and two-tone target stimuli in these latter areas reflect differences in baseline rather than differences in hemodynamic activity elicited by the target detection per se. Thus, these latter effects should be interpreted with caution.

In conclusion, target detection within oddball paradigms elicits hemodynamic activity in a distributed network of brain structures, regardless of whether participants are presented with one or two classes of stimuli. These findings are consistent with the argument (Halgren et al., 1998; Kiehl et al., 2005) that the ability to rapidly identify, evaluate, and coordinate neural activity in order to execute a salient behavioral response in different experimental contexts

engages multiple, spatially-distributed parallel processing systems. Thus, these data support the hypothesis that the mammalian brain has evolved to adopt a strategy of engaging many potentially useful brain regions despite the low probability that these brain regions are necessary for successful task performance. This has been termed ‘adaptive reflexive processing’ (Kiehl et al., 2005). Some brain areas showed evidence of comparatively greater amplitude of the hemodynamic response in the single-tone task. It remains unclear if these differences reflect differences in cognitive processes between the two tasks, or if they are the result of physiological mechanisms. However, existing evidence points most persuasively to greater attentional orienting, as reflected by electrophysiological experiments detailing the N1 ERP. The present study also demonstrates that fMRI contributes important information related to cognitive processes formerly only studied effectively with EEG. Although the relationship between ERP and fMRI signals is not completely understood and the use of combined EEG/fMRI techniques is as yet not widespread, many of the questions left unanswered by the current study might be effectively addressed by future studies combining fMRI and ERP technologies.

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References

- Anderer P, Pascual-Marqui RD, Semlitsch HV, Saletu B. Differential effects of normal aging on sources of standard N1, target N1 and target P300 auditory event-related brain potentials revealed by low resolution electromagnetic tomography (LORETA). *Electroencephalogr Clin Neurophysiol* 1998;108:160–174. [PubMed: 9566629]
- Baudena P, Halgren E, Heit G, Clarke JM. Intracerebral potentials to rare target and distractor auditory and visual stimuli. III. Frontal cortex. *Electroencephalogr Clin Neurophysiol* 1995;94:251–264. [PubMed: 7537197]
- Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A. Anterior cingulate cortex and response conflict: Effects of frequency, inhibition and errors. *Cereb Cortex* 2001;11:825–836. [PubMed: 11532888]
- Budd TW, Barry RJ, Gordon E, Rennie C, Michie PT. Decrement of the N1 auditory event-related potential with stimulus repetition: habituation vs. refractoriness. *Int J Psychophysiol* 1998;31:51–68. [PubMed: 9934621]
- Calhoun VD, Stevens MC, Pearlson GD, Kiehl KA. fMRI analysis with the general linear model: removal of latency-induced amplitude bias by incorporation of hemodynamic derivative terms. *Neuroimage* 2004;22:252–257. [PubMed: 15110015]
- Casey BJ, Forman SD, Franzen P, Berkowitz A, Braver TS, Nystrom LE, Thomas KM, Noll DC. Sensitivity of prefrontal cortex to changes in target probability: a functional MRI study. *Hum Brain Map* 2001;13:26–33.
- Clark VP, Fannon S, Lai S, Benson R. Paradigm-dependent modulation of event-related fMRI activity evoked by the oddball task. *Hum Brain Map* 2001;14:116–127.
- Clark VP, Fannon S, Lai S, Benson R, Bauer L. Responses to rare visual target and distractor stimuli using event-related fMRI. *J Neurophysiol* 2000;83:3133–3139. [PubMed: 10805707]
- Donchin E, Coles MGH. Is the P300 component a manifestation of context updating? *Beh Brain Sci* 1988;11:357–374.
- Ferro JM, Kertesz A, Black SE. Subcortical neglect: quantitation, anatomy, and recovery. *Neurol* 1987;37:1487–1492.
- Freire L, Mangin JF. Motion correction algorithms may create spurious brain activations in the absence of subject motion. *Neuroimage* 2001;14:709–722. [PubMed: 11506543]

- Freire L, Roche A, Mangin JF. What is the best similarity measure for motion correction in fMRI time series? *IEEE Trans Med Imag* 2002;21:470–484.
- Giard MH, Perrin F, Echallier JF, Thevenet M, Froment JC, Pernier J. Dissociation of temporal and frontal components in the human auditory N1 wave: a scalp current density and dipole model analysis. *Electroencephalogr Clin Neurophysiol* 1994;92:238–252. [PubMed: 7514993]
- Halgren E. Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. *Science* 1980;210:803–805. [PubMed: 7434000]
- Halgren E, Baudena P, Clarke JM, Heit G, Liégeois C, Chauvel P, Musolino A. Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. *Electroencephalogr Clin Neurophysiol* 1995a;94:191–220. [PubMed: 7536154]
- Halgren E, Baudena P, Clarke JM, Heit G, Marinkovic K, Devaux B, Vignal JP, Biraben A. Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. *Electroencephalogr Clin Neurophysiol* 1995b;94:229–250. [PubMed: 7537196]
- Halgren E, Marinkovic K. General principles for the physiology of cognition as suggested by intracranial ERPs. In: Ogura, C.; Koga, Y.; Shimokochi, M., editors. *Recent advances in event-related brain potential research*. Elsevier; Amsterdam ; New York: 1996. p. 1072–1084.
- Halgren E, Marinkovic K, Chauvel P. Generators of the late cognitive potentials in auditory and visual oddball tasks. *Electroencephalogr Clin Neurophysiol* 1998;106:156–164. [PubMed: 9741777]
- Hillyard SA, Hink RF, Schwent VL, Picton TW. Electrical signs of selective attention in the human brain. *Science* 1973;182:177–180. [PubMed: 4730062]
- Horowitz SG, Skudlarski P, Gore JC. Correlations and dissociations between BOLD signal and P300 amplitude in an auditory oddball task: a parametric approach to combining fMRI and ERP. *Magn Reson Imaging* 2002;20:319–325. [PubMed: 12165350]
- Josephs O, Henson RN. Event-related functional magnetic resonance imaging: modelling, inference and optimization. *Philos Trans R Soc Lond B Biol Sci* 1999;354:1215–1228. [PubMed: 10466147]
- Katayama J, Polich J. P300 from one-, two-, and three-stimulus auditory paradigms. *Int J Psychophysiol* 1996;23:33–40. [PubMed: 8880364]
- Kiehl KA, Laurens KR, Duty TL, Forster BB, Liddle PF. An event-related fMRI study of visual and auditory oddball tasks. *J Psychophysiol* 2001a;21:221–240.
- Kiehl KA, Laurens KR, Duty TL, Forster BB, Liddle PF. Neural sources involved in auditory target detection and novelty processing: An event-related fMRI study. *Psychophysiol* 2001b;38:133–142.
- Kiehl KA, Liddle PF. Reproducibility of the hemodynamic response to auditory oddball stimuli: A six-week test-retest study. *Hum Brain Map* 2003;18:42–52.
- Kiehl KA, Stevens MC, Laurens KR, Pearson G, Calhoun VD, Liddle PF. An adaptive reflexive processing model of neurocognitive function: supporting evidence from a large scale (n = 100) fMRI study of an auditory oddball task. *Neuroimage* 2005;25:899–915. [PubMed: 15808990]
- Kirino E, Belger A, Goldman-Rakic P, McCarthy G. Prefrontal activation evoked by infrequent target and novel stimuli in a visual target detection task: An event-related functional magnetic resonance imaging study. *J Neurosci* 2000;20:6612–6618. [PubMed: 10964966]
- Liebenthal E, Ellingson ML, Spanaki MV, Prieto TE, Ropella KM, Binder JR. Simultaneous ERP and fMRI of the auditory cortex in a passive oddball paradigm. *Neuroimage* 2003;19:1395–1404. [PubMed: 12948697]
- Liegeois-Chauvel C, Musolino A, Badier JM, Marquis P, Chauvel P. Evoked potentials recorded from the auditory cortex in man: evaluation and topography of the middle latency components. *Electroencephalogr Clin Neurophysiol* 1994;92:204–214. [PubMed: 7514990]
- Linden DE, Prvulovic D, Formisano E, Voellinger M, Zanella FE, Goebel R, Dierks T. The functional neuroanatomy of target detection: An fMRI study of visual and auditory oddball tasks. *Cereb Cortex* 1999;9:815–823. [PubMed: 10601000]
- Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal.[comment]. *Nature* 2001;412:150–157. [PubMed: 11449264]
- McCarthy G, Luby M, Gore J, Goldman-Rakic P. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *J Neurophysiol* 1997;77:1630–1634. [PubMed: 9084626]

- Menon V, Ford JM, Lim KO, Glover GH, Pfefferbaum A. Combined event-related fMRI and EEG evidence for temporal-parietal cortex activation during target detection. *Neuroreport* 1997;8:3029–3037. [PubMed: 9331910]
- Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol* 1990;28:597–613. [PubMed: 2260847]
- Mesulam, MM. Principles of behavioral and cognitive neurology. Vol. 2. Oxford University Press; New York: 2000.
- Naatanen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiol* 1987;24:375–425.
- Naatanen R, Teder W, Alho K, Lavikainen J. Auditory attention and selective input modulation: a topographical ERP study. *Neuroreport* 1992;3:493–496. [PubMed: 1391755]
- Nichols T, Hayasaka S. Controlling the Familywise Error Rate in Functional Neuroimaging: A Comparative Review. *Stat Methods Med Res* 2003;12:419–446. [PubMed: 14599004]
- Okita T. Event-related potentials and selective attention to auditory stimuli varying in pitch and localization. *Biol Psychol* 1979;9:271–284. [PubMed: 548127]
- Opitz B, Mecklinger A, Von Cramon DY, Kruggel F. Combining electrophysiological and hemodynamic measures of the auditory oddball. *Psychophysiology* 1999;36:142–147. [PubMed: 10098390]
- Picton TW, Hillyard SA, Galambos R, Schiff M. Human auditory attention: a central or peripheral process? *Science* 1971;173:351–353. [PubMed: 5559908]
- Polich J, Eischen SE, Collins GE. P300 from a single auditory stimulus. *Electroencephalogr Clin Neurophysiol* 1994;92:253–261. [PubMed: 7514994]
- Polich J, Ellerson PC, Cohen J. P300, stimulus intensity, modality, and probability. *Int J Psychophysiol* 1996;23:55–62. [PubMed: 8880366]
- Polich J, Heine MR. P300 topography and modality effects from a single-stimulus paradigm. *Psychophysiology* 1996;33:747–752. [PubMed: 8961797]
- Polich J, Margala C. P300 and probability: comparison of oddball and single-stimulus paradigms. *Int J Psychophysiol* 1997;25:169–176. [PubMed: 9101341]
- Polich, J.; Starr, A. Middle-, Late-, and long-latency auditory evoked potentials. In: Morre, EJ., editor. *Bases of Auditory Brain-Stem Evoked Responses*. Grune and Stratton; New York: 1983. p. 345–361.
- Siedenberg R, Goodin DS, Aminoff MJ, Rowley HA, Roberts TP. Comparison of late components in simultaneously recorded event-related electrical potentials and event-related magnetic fields. *Electroencephalogr Clin Neurophysiol* 1996;99:191–197. [PubMed: 8761055]
- Stevens MC, Calhoun VD, Kiehl KA. Hemispheric Differences in Hemodynamics Elicited by Auditory Oddball Stimuli. in press
- Strange BA, Dolan RJ. Adaptive anterior hippocampal responses to oddball stimuli. *Hippocampus* 2001;11:690–698. [PubMed: 11811663]
- Sutton S, Baren M, Zubin J, John ER. Evoked potential correlates of stimulus uncertainty. *Science* 1965;150:1187–1188. [PubMed: 5852977]
- Tarkka IM, Stokic DS. Source localization of P300 from oddball, single stimulus, and omitted-stimulus paradigms. 1998;11:141–151.
- Tarkka IM, Stokic DS, Basile LF, Papanicolaou AC. Electric source localization of the auditory P300 agrees with magnetic source localization. *Electroencephalogr Clin Neurophysiol* 1995;96:538–545. [PubMed: 7489675]
- Vallar G, Perani D. The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. *Neuropsychologia* 1986;24:609–622. [PubMed: 3785649]
- Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC. A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Map* 1996;4:58–73.
- Yamazaki T, Kamijo K, Kenmochi A, Fukuzumi S, Kiyuna T, Takaki Y, Kuroiwa Y. Multiple equivalent current dipole source localization of visual event-related potentials during oddball paradigm with motor response. *Brain Topogr* 2000;12:159–175. [PubMed: 10791680]

Figure 1. Illustration of the hemodynamic response elicited by target detection in the single-tone task. The results are thresholded at False Discovery Rate of $q < .0001$, corrected for multiple comparisons. The view is in neurological convention (i.e., left hemisphere is on the left).

Figure 2.

Illustration of the hemodynamic response elicited by target detection in the two-tone task. The results are thresholded at False Discovery Rate of $q < .0001$, corrected for multiple comparisons). The view is in neurological convention (i.e., left hemisphere is on the left).

Figure 3.

Illustration of the regions in which the amplitude of the hemodynamic response was larger for target detection in the single-tone task than in the two-tone task. The results are thresholded at a False Discovery rate of $q < .05$, corrected for multiple comparisons). The view is in neurological convention (i.e., left hemisphere is on the left).

Figure 4.

Fitted hemodynamic response estimates averaged across sessions and subjects for single- and two-tone target stimuli for selected regions in prefrontal cortex, parietal lobe, basal ganglia, and cerebellum regions. Single-tone (blue) reflects target hemodynamic response amplitude relative to the implicit baseline. Two-tone (red) reflects target hemodynamic response amplitude relative to frequent nontargets.

Table 1

Summary of the significant areas of activation for the comparison of target stimuli in single-tone versus implicit baseline and two-tone versus nontarget baseline in regions of interest defined by prior work (Kiehl, et al. 2001a)

		Kiehl, et al. 2001a Coordinates			Maximum ROI <i>t</i> -score ^a		
		x	y	z	1-Tone	2-Tone	
Frontal Lobes							
1	L Superior/Middle Frontal Gyrus	-28	48	28	10.44 ***	6.65 **	
2	R Superior/Middle Frontal Gyrus	24	52	28	7.93 ***	5.26 **	
3	L Inferior Frontal Gyrus	-60	8	24	9.59 ***	5.24 **	
4	R Inferior Frontal Gyrus	56	12	24	7.63 ***	6.97 ***	
5	Medial Frontal Gyrus	0	-8	56	11.77 ***	8.43 ***	
6	Anterior Cingulate Gyrus	0	16	40	9.56 ***	7.64 ***	
7	L Insula	-40	20	-12	10.60 ***	10.72 ***	
8	R Insula	44	24	-12	10.94 ***	9.17 ***	
9	L Precentral Gyrus	-36	-24	64	10.72 ***	9.24 ***	
10	R Precentral Gyrus	36	-4	60	8.35 ***	5.92 **	
Parietal Lobes							
11	L Postcentral Gyrus	-56	-20	20	11.72 ***	8.46 ***	
12	L Postcentral Gyrus	-24	-44	64	10.32 ***	7.96 ***	
13	R Postcentral Gyrus	64	-20	20	7.59 ***	7.76 ***	
14	L Superior Parietal Lobule	-36	-52	60	12.22 ***	7.58 ***	
15	R Superior Parietal Lobule	24	-60	56	7.24 ***	4.78 *	
16	L Inferior Parietal/Supramarginal Gyrus	-56	-40	32	13.22 ***	10.46 ***	
17	R Inferior Parietal/Supramarginal Gyrus	64	-36	24	10.25 ***	10.56 ***	
18	Posterior Cingulate Gyrus	0	-28	28	8.17 ***	7.75 ***	
19	Precuneus	0	-44	56	8.48 ***	6.01 **	
Temporal Lobes							
20	L Superior Temporal Gyrus	-56	12	-16	10.70 ***	10.71 ***	
21	L Middle Temporal Gyrus	-60	-56	4	13.14 ***	7.86 ***	
22	R Middle Temporal Gyrus	52	-20	-12	12.35 ***	8.93 ***	
23	L Inferior Temporal Gyrus	-52	-16	-16	8.44 ***	6.16 **	
24	R Inferior Temporal Gyrus	60	-64	5	7.87 ***	6.96 **	
25	L Parahippocampal Gyrus/Amygdala	-16	-4	-20	6.71 **	5.66 **	
26	R Parahippocampal Gyrus/Amygdala	20	-2	-20	7.54 ***	7.04 **	
Occipital Lobe							
27	L Lingual Gyrus/Cuneus	-12	-72	4	7.19 ***	6.59 **	
28	R Lingual Gyrus/Cuneus	20	-72	8	8.03 ***	5.83 **	
Deep Gray							
29	L Thalamus/Caudate	-8	-20	4	11.15 ***	9.06 ***	
30	R Thalamus/Caudate	12	-16	4	11.90 ***	7.72 ***	
31	L Putamen/Globus Pallidus	-36	0	-4	9.03 ***	8.22 **	
32	R Putamen/Globus Pallidus	24	0	0	9.46 ***	6.68 **	
Cerebellum							
33	L Cerebellum	-22	-64	-25	11.63 ***	10.55 ***	
34	R Cerebellum	19	-52	-30	16.04 ***	10.33 ***	

^a Small volume corrected significance levels using False Discovery Rate for each region of interest.

* $q < .05$,

100000000> d

100000000> d

100> d