Attention and Sensory Interactions within the Occipital Cortex in the Early Blind: An fMRI Study

Kurt E. Weaver and Alexander A. Stevens

Abstract

■ Visual deprivation early in life results in occipital cortical responsiveness across a broad range of perceptual and cognitive tasks. In the reorganized occipital cortex of early blind (EB) individuals, the relative lack of specificity for particular sensory stimuli and tasks suggests that attention effects may play a prominent role in these areas. We wished to establish whether occipital cortical areas in the EB were responsive to stimuli across sensory modalities (auditory, tactile) and whether these areas maintained or altered their activity as a function of selective attention. Using a three-stimulus oddball paradigm and event-related functional magnetic resonance imaging, auditory and tactile tasks presented separately demonstrated that several occipital regions of interest (ROIs) in the EB, but not sighted controls (SCs), responded to targets and task-irrelevant distracter stimuli of both modalities. When auditory and tactile stimuli were presented simultaneously with subjects alternating attention between sensory streams, only the calcarine sulcus continued to respond to stimuli in both modalities. In all other ROIs, responses to auditory targets were as large or larger than those observed in the auditory-alone condition, but responses to tactile targets were attenuated or abolished by the presence of unattended auditory stimuli. Both auditory and somatosensory cortices responded consistently to auditory and tactile targets, respectively. These results reveal mechanisms of orienting and selective attention within the visual cortex of EB individuals and suggest that mechanisms of enhancement and suppression interact asymmetrically on auditory and tactile streams during bimodal sensory presentation. ■

INTRODUCTION

Sensory deprivation occurring during perinatal development results in the abnormal organization of the deprived sensory cortex (Knudsen, 2004; Berardi, Pizzorusso, & Maffei, 2000). Early-onset blindness (EB) leads to a reorganized occipital lobe, which responds to a variety of stimuli and cognitive tasks (Roder & Rosler, 2004; Bavelier & Neville, 2002). For instance, functional magnetic resonance imaging (fMRI) and positron emission tomography studies have demonstrated that different occipital areas in EB subjects respond during vibrotactile discrimination (Burton, Sinclair, & McLaren, 2004), sound-source localization (Gougoux, Zatorre, Lassonde, Voss, & Lepore, 2005; Weeks et al., 2000), auditory mental imagery tasks (De Volder et al., 2001), and detection of target sounds embedded in an auditory stream (Kujala et al., 2005). A variety of studies using Braille reading or auditory verbal stimuli consistently demonstrate occipital cortex involvement particularly within the calcarine sulcus (Amedi, Raz, Pianka, Malach, & Zohary, 2003; Burton, Diamond, & McDermott, 2003; Burton, Snyder, Diamond, & Raichle, 2002; Roder, Stock, Bien, Neville, & Rosler, 2002; Melzer et al., 2001; Buchel, Price, & Friston, 1998; Sadato et al., 1996, 1998).

Several researchers have hypothesized that EB results in the maintenance of synaptic connections from other brain areas that are normally pruned (Bavelier & Neville, 2002; Huttenlocker, 2002) or masked (Pascual-Leone & Hamilton, 2001) due to the lack of visual stimulation. This leads to reorganization by auditory and tactile afferents. Although studies in sighted animals have clearly established the presence of long-range cortico-cortical connections between early sensory cortices (Schroeder & Foxe, 2005; Clavagnier, Falchier, & Kennedy, 2004; Rockland & Ojima, 2003; Falchier, Clavagnier, Barone, & Kennedy, 2002), most evidence suggests that in cases of visual deprivation, the relative responsiveness of visual cortical areas to other sensory modalities is dramatically increased (Roder & Rosler, 2004; Rauschecker, 1995; Rauschecker & Korte, 1993; Hyvarinen, Carlson, & Hyvarinen, 1981). It is also likely that nonsensory afferents that project to the occipital cortex establish synaptic contacts on the local circuitry in their normal fashion, regardless of the sensory characteristics established in the cortical milieu (Huttenlocker, 2002; Pascual-Leone & Hamilton, 2001; Hyvarinen et al., 1981). This speculation is supported in part by a recent diffusion tensor imaging study showing limited changes in the occipitofrontal white matter tracts of EB subjects relative to sighted controls (SC) (Shimony et al., 2006). This leads to the hypothesis that occipital cortical areas in the

Oregon Health & Science University

EB that are engaged by auditory and/or tactile stimulation respond to these stimuli as a function of the focus of attention.

In support of this hypothesis, a number of electroencephalographic studies have suggested that occipital activation in the EB represents a posterior shift in the cortical networks that support top-down attentional behaviors (see Kujala, Alho, & Näätänen, 2000, for a review). In EB individuals, auditory or tactile target stimuli presented in a stream of similar nontarget "standards" elicited patterns of N2–P3 potentials at occipital leads but targets presented in unattended channels did not (Liotti, Ryder, & Woldorff, 1998; Kujala, Alho, Huotilainen, et al., 1997; Roder, Rosler, Hennighausen, & Nacker, 1996; Kujala, Alho, et al., 1995; Kujala, Huotilainen, et al., 1995; Alho, Kujala, Paavilainen, Summala, & Näätänen, 1993; Kujala, Alho, Paavilainen, Summala, & Näätänen, 1992). Recently, Hötting, Rosler, and Röder (2004) observed that EB and SC subjects showed complex differences in evoked potentials under conditions of auditory and tactile cross-modal spatial attention. Most notably, the SCs showed stronger influences of attended spatial location on both early and late event-related potentials (ERPs), whereas EBs showed a greater influence of modality cues on ERP responses (Hötting et al., 2004). The authors suggested that EB individuals tend to direct attention on the basis of modality, whereas SC individuals tend to rely on both modality and spatial cues. These alterations in brain responses under conditions of multimodal stimulation may reflect both alterations in attentional modulation of cross-modal interactions and functional changes in the reorganized occipital cortex in the EB. However, ERP studies lack the spatial resolution to determine the cerebral contributions to the evoked signals. Although fMRI provides the ability to better localize metabolic changes in altered brain organization, to date, no studies have examined the interaction of auditory and tactile domains under conditions of selective attention in the blind.

In the current experiment, we examined blood oxygen level dependent (BOLD) activity throughout occipital regions in EB and SC individuals to auditory and tactile change detection tasks in the form of an oddball paradigm (Polich, 2003). Behavioral and neuroimaging studies using a three-stimulus design have identified two distinct modality-independent attentional systems that gate deviant stimuli into awareness (Kiehl et al., 2005; Bledowski, Prvulovic, Goebel, Zanella, & Linden, 2004; Kiehl, Laurens, Duty, Forster, & Liddle, 2001; for a review, see Corbetta & Shulman, 2002; Halgren, Marinkovic, & Chauvel, 1998). One system reflects top-down control that directs and sustains attention to specific changes within a sensory domain and is operationalized by requiring detection of a specific target stimulus embedded within a stream of similar nontarget standards. The second system reorients attention via bottom-up mechanisms as a result of a significant change within a stimulus stream (Escera, Corral, & Yago, 2002; Knight, 1984). Experimentally, this is demonstrated by presenting highly salient but irrelevant stimuli.

To engage these attentional systems, standard stimuli were designed to be perceptually similar to the infrequent target stimuli (accomplished by adjusting for individual discrimination thresholds obtained prior to scanning) while the infrequent distracter stimuli were designed to be physically more distinct than either the target or the standard. Oddball tasks were presented throughout four fMRI scans. During the first two scans (unimodal conditions), subjects were either presented with monaural tones or vibrations to the left index finger. In the third and fourth scans (bimodal scans), the same tones and vibrations were presented simultaneously to subjects and were cued to alternately detect targets in one modality and then the other at regular intervals (never dividing attention).

Based on prior fMRI studies using a variety of auditory and tactile tasks (Gougoux et al., 2005; Burton et al., 2002, 2003, 2004; Sadato et al., 1998), as well as ERP observations (see Kujala et al., 2000; Roder et al., 1996), we predicted that striate and extrastriate occipital areas would respond to attended targets in both modalities but show little to no BOLD activity to the same stimuli when unattended. Occipital regions in the EB showing polymodal responses to target stimuli would reflect central processes critical to target detection, and polymodal regions responding to attended but not ignored targets would suggest a response related to top-down attention. In addition, occipital regions responding to distracters from different modalities would indicate a function linked to bottom-up attentional orienting (Comerchero & Polich, 1998).

METHODS

Subjects

Nine SC (6 women, mean number of years education, $SE = 18.11 \pm 0.84$) and 12 EB (5 women, mean number of years of education, $SE = 17.78 \pm 1.05$) individuals were recruited from the greater Portland area. Three EB individuals were excluded from the analysis due to mechanical failures during the scanning procedure. Exclusion criteria for the blind included age of blindness onset occurring after the first year of life, and light sensitivity defined as form, color, or motion perception. Of the nine EB subjects included in the analysis, all had peripheral retinal damage resulting from retrolental fibroplasia and seven had no light perception. Exclusion criteria for all subjects included self-reported hearing damage or loss, previously diagnosed comorbid psychiatric or neurological disease, and drug or alcohol abuse within the past 5 years. The mean age for the EB group was 50.78 years (range 36–59 years) and 49.63 years (range of 27 to 60 years) for the SC group. Subject's

handedness was assessed with a handedness survey (Oldfield, 1971). Of the nine SC subjects, two were left-handed and seven were right-handed. Of the nine EB individuals included within the analysis, three were rated as ambidextrous, one was left-handed, and five were right-handed. All subjects signed an informed consent prior to testing procedures and all experimental procedures were approved by the institutional review board of the Oregon Health & Science University.

Stimuli

All stimuli (tactile and acoustic) were 200 msec sinusoidal waveforms (with a rise/fall time of 10 msec for acoustic stimuli). Stimuli were created using Adobe Audition software (Adobe Systems, San Jose, CA) and generated by a SoundBlaster Audigy 2 ZS sound card (Creative, Singapore). All sound stimuli were monaurally presented at approximately 85 dB SPL (sound pressure level) in the left ear on Koss electrostatic headphones (Koss, Milwaukee, WI) fashioned into sound-attenuating ear defenders (Howard Leight, San Deigo, CA). Vibrotactile stimuli were produced by a nonmagnetic, ceramic piezo-electric bending element (i.e., benders; Q220-A4-303YB Quick Mount Bender, Piezo Systems, Cambridge, MA, www.piezo.com) placed directly under the index finger of the left hand. The benders were driven by sinusoidal waves presented at a high-amplitude value and produced a vibration that corresponded to that driving frequency. The amplitude (intensity) of the signal was amplified using a NAD T973 seven-channel Power Amplifier (NAD Electronics, London, UK). This allowed for a consistent peak-to-peak deflection of the benders across experiments of approximately 400 μm. Initial pilot testing suggested that at these amplitudes, subjects reported similar perceived intensities (equal salience) for all acoustic and tactile stimuli. The monaural and monotactile presentations were used to simplify the study design. The frequency of the standard, nontarget stimuli for both auditory and tactile modalities was determined prior to scanning for each subject on the basis of individual discrimination thresholds using a discrimination paradigm (see below). Additionally, for the auditory condition, the frequency of the target stimulus was 800 Hz and the distracter tone was 2000 Hz. The target tactile vibration was 50 Hz and the distracter vibration was 150 Hz. The target vibration was chosen based upon behavioral pilot data indicating a greater degree of discrimination ability at lower vibrotactile frequencies relative to a number of other frequencies tested. All experiments were controlled using Presentation software 9.1 (Neurobehavioral Systems, Davis, CA) running on a PC.

To accurately and consistently present vibrotactile stimulation to individuals, the left hand was securely fashioned into an antispasticity ball splint (Sammons Preston, Ontario, CA) on which the bender was mounted. This splint encases the upper third of the arm and the whole hand in

order to secure the position of the arm relative to the hand, and separates the digits to prevent changes in finger position and accidental stimulation of other fingers. The bender was adjusted and locked directly underneath the fingertip of the index finger of each individual subject. Foam pads with Velcro adjustments were wrapped around the arm while resting in the splint in order to prevent arm movements from affecting the position of the bender on the finger.

Discrimination Thresholds

Subjects' individual discrimination thresholds for frequency of stimulation were determined before the scanning session. Measurement of these discrimination thresholds controlled for perceptual discrimination differences that may exist between subjects, allowing us to roughly equate attentional demands across all oddball conditions.

Thresholds were determined with a two-alternative forced-choice task using a two-down one-up rule yielding estimates of thresholds for 70% accuracy (Levitt, 1970). On each trial, subjects heard or felt two stimuli, each 200 msec in length (with a 10-msec rise/fall time for acoustic stimuli) and separated by 2000 msec. The first stimulus on all discrimination trials was the target stimulus (i.e., 800 Hz tone for auditory thresholds or a 50-Hz vibration for tactile thresholds). On 50% of the trials, the same two tones or vibrations were presented again. On the other 50% of trials, the two stimuli were different. At the beginning of the experiment, the different stimulus was set at 900 Hz (for auditory thresholds) and 150 Hz (for tactile thresholds). This stimulus was then adjusted on the basis of the descending method of limits. After the just-noticeable-difference (JND) for the target stimulus was determined for each individual, it was used to produce auditory and tactile standard frequency values. The auditory standard was created by tripling the frequency difference (ΔF) between the target stimulus and the JND, and adding this value to the target stimulus frequency value (initial pilot testing in the scanner with 1 or 2× ΔF resulted in poor performance on the tasks). The tactile standard was created by doubling ΔF and adding it to the tactile target value. This led to comparable levels of performance on the auditory and tactile detection tasks.

Experimental Design and Imaging Paradigm

The oddball task was a three-stimulus design that presented a rare target, a rare nontarget (distracter), and a repeated nontarget (standard) stimuli in a serial fashion with a constant intertrial interval of 2250 msec. Target probability was set at 0.15 and distracter stimulus probability was set at 0.10. Subjects pressed a button on a scanner-safe button box in response to the target stimulus and a second button in response to either the standard or distracter stimuli.

Subjects underwent four functional, echo-planar imaging (EPI) scans: one each for the tactile- and auditory-alone conditions and two for the bimodal conditions. Each scan consisted of 180 trials. In Scans 1 and 2, tones (auditory alone) and vibrations (tactile alone) were presented alone. The order of the auditory-alone and tactile-alone scans was counterbalanced across subjects. Two scans consisted of the simultaneous presentation of auditory and tactile stimuli (bimodal scans). A verbal cue instructed subjects to ''switch'' attention between modalities every 30 acquisitions (creating six ''attend-to'' auditory blocks and six ''attend-to'' tactile blocks across the two scans) and respond to only stimuli within the attend-to modality. Targets within each modality were never presented simultaneously.

Magnetic resonance imaging was conducted on a 3.0-Tesla Siemens Trio magnet using a two-channel, radio-frequency transceiver head coil. The gradient-echo EPI scanning parameters consisted of: repetition time (TR) = 2250 msec, echo time (TE) = 35 msec, and a flip angle of 85°. The field of view (FOV) was set at 240 × 240 mm using a 64 × 64 matrix. Functional slices were acquired using a clustered volume technique (Edmister, Talavage, Ledden, & Weisskoff, 1999), in which all slices within a volume were collected in approximately the first 1/2 (or 1150 msec) of the TR. This technique allowed us to present stimuli during a period of silence in order to reduce interference from scanner noise. Each functional volume consisted of 20 axial slices (5 mm thick with 1 mm interslice gap) providing whole-brain coverage. A navigator echo was inserted within each functional scan to prospectively correct for motion artifacts. Stimulus presentation began after the second acquisition in order to insure homogenous saturation of the magnetic field.

Prior to the start of each functional scan, subjects were informed of which scan condition would be presented, followed by the presentation of five repetitions of the target and nontarget frequencies. Additionally, standards were purposefully presented on the first 10 trials within each scan to provide a steady-state stimulus baseline (i.e., pitch or vibration of the standard) prior to introducing a change within the stimulus array (i.e., a target of distracter frequency). Within the bimodal scans, a minimum of three standards were presented within the ''attend-to'' modality after each switch cue in order to avoid contamination related to attention switching. Throughout all functional scans, SC individuals were asked to keep their eyes closed.

Data Analysis

Functional Data Analysis

Functional data analyses, coregistration, and visualization were carried out using BrainVoyager QX Software (Brain Innovations, Maastricht, Netherlands). Prior to statistical analysis, slice-time differences within a volume were cor-

rected, linear trends were removed, and a high-pass filter of 3 cycles/scan was applied to reduce the effects of scanner drift. All scans were then interpolated into 1 × 1 × 1 mm³ isovoxels, and raw signal values were z-normalized and transformed into standardized Talairach stereotaxic space (Talairach & Tournoux, 1988). Time courses for each functional run were then analyzed and statistical parametric z-maps were created using a general linear model (GLM). For Scans 1 and 2 (unimodal scans), BOLD responses to target and distracter stimuli were modeled by assuming a value of one to each occurrence of a target or distracter and convolving this with a standard hemodynamic response function (Boynton, Engel, Glover, & Heeger, 1996). Stimulus predictors from Scans 3 and 4 (bimodal scans averaged together) included targets and distracters in the attended modality and targets in the unattended modality. Between-subjects z-maps were constructed by averaging across each group (EB and SC) using a random effects analysis allowing us to generalize back to the population level. Voxel by voxel comparisons were made for the different stimulus contrasts setting an α significance level of $p < .01$, uncorrected. In addition, a cluster filter correction was employed to reduce false positives, type I errors (Forman et al., 1995). This correction was used to adjust the p value to .05, ensuring the likelihood of 5% or less false positives within a minimum cluster size of 200 contiguous voxels.

Because patterns of activation throughout the occipital lobe were of interest, an anatomically restricted mask was created and applied to the group-averaged contrast maps (Figure 2) in order to limit the number of voxel-based analyses to ROIs and to reduce the number of statistical comparisons. Initial analyses used to identify the areas of significant activation were restricted to voxels posterior to the central sulcus.

Region-of-Interest Analysis

An ROI analysis within the occipital lobe was used to characterize the evoked BOLD responses by target and distracter stimuli. ROIs were created by identifying voxels that survived significance testing and a cluster filter correction in both auditory-alone and tactile-alone scans. Polymodal voxels were identified by overlaying the group-averaged auditory-alone and tactile-alone z-maps and by selecting all overlapping voxels between the two modalities {i.e., a voxel was included based on the contrast: [(aud(target + distracter) − (standard)) ∩ (tac(target + distracter) − (standard))]}. Four polymodal clusters were selected, including a site along the calcarine sulcus (Brodmann's area [BA] 17) corresponding anatomically to the primary visual cortex in the SC brain, a region within the cuneus (BA 18), the fusiform gyrus (BA 37), and a spot within the lingual sulcus (BA 19). Anatomical location of the occipital ROIs was confirmed through use of published human brain atlases (Damasio, 2005; Mai, Assheuer, & Paxinos, 1997) and through use of the

Talairach Demon (http://ric.uthscsa.edu/resources/body. html). We then extracted time courses from each ROI stemming from both unimodal and bimodal scans, and averaged the signal intensity change to each stimulus condition across subjects relative to a baseline of the three TRs preceding that event. ROIs in auditory and tactile control regions were localized based upon published Talairach coordinates (Stippich, Romanowski, Nennig, Kress, & Sartor, 2005; Wessinger et al., 2001; Hall et al., 2000) and human brain atlases (Damasio, 2005; Mai et al., 1997).
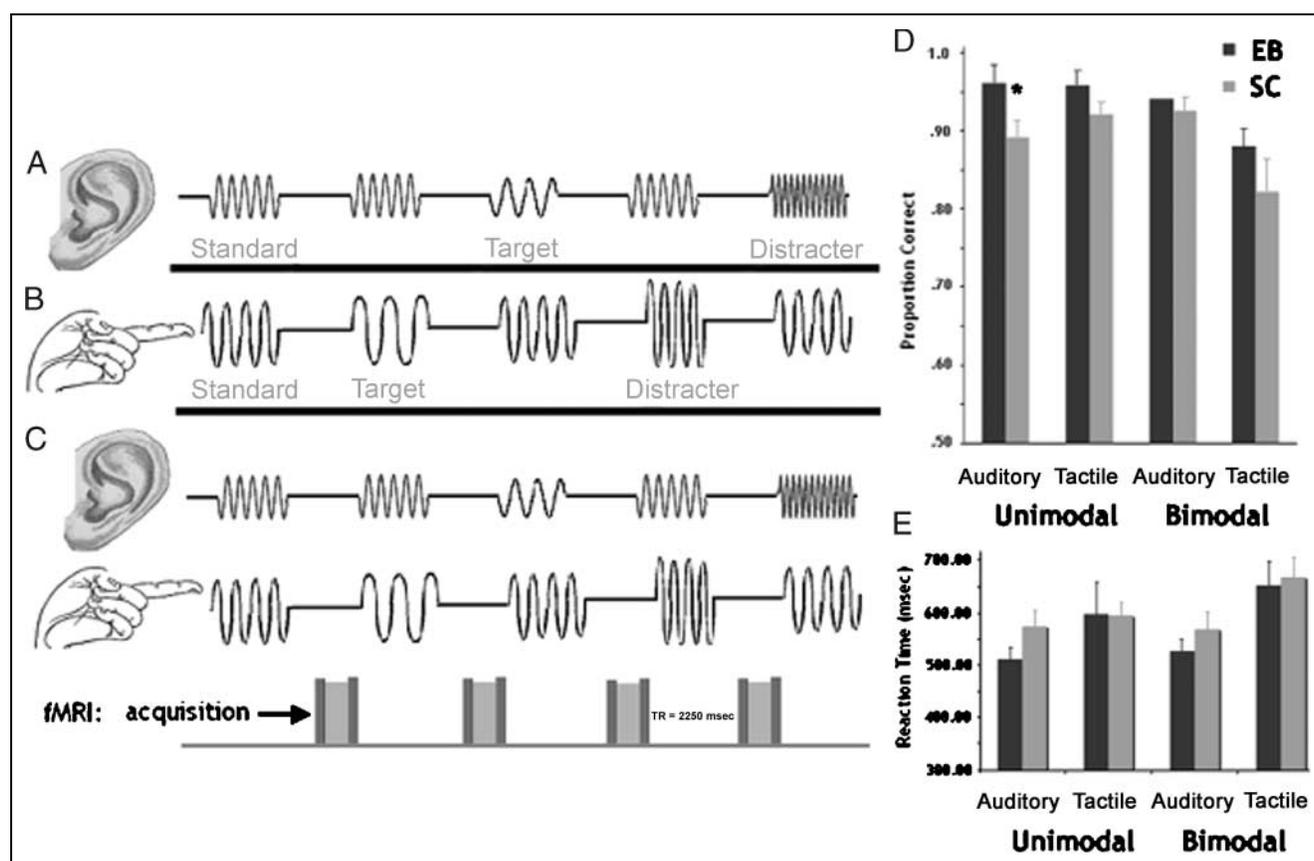
RESULTS

Auditory and Tactile Discrimination and Detection

For each subject, the frequency of the standard for each modality was established using discrimination thresholds prior to scanning. Mean discrimination threshold estimates were similar for EB and SC for auditory (808.11 ± 0.86 Hz vs. 808.11 ± 0.73 Hz, respectively; Student's t, $p = .98$) and tactile (73.44 ± 4.27 Hz vs. 78.56 ± 3.62 Hz, respectively; Student's t, $p = .37$) modalities.

Throughout all scanning conditions, target detection accuracy was high, with both groups detecting greater than 80% of all targets (Figure 1D). The EB were slightly more accurate than the SC in both modalities in the alone conditions (auditory alone: $SE = 0.96 ± 0.02$ vs. $SE = 0.89 ± 0.02$, respectively; tactile alone: $SE = 0.96 ± 0.02$ vs. $SE = 0.92 ± 0.01$, respectively) and for the bimodal presentations (auditory simultaneous: $SE = 0.94 ± 0.03$ vs. $SE = 0.93 ± 0.02$, respectively; tactile simultaneous: $SE = 0.88 ± 0.02$ vs. $SE = 0.82 ± 0.04$, respectively). A repeated measures analysis of variance (ANOVA) of modality (auditory, tactile), presentation

Figure 1. Task design and behavioral results. (A) Auditory-alone and (B) tactile-alone tasks presented pure tones or vibrations in separate scans to subjects during Scans 1 and 2 (counterbalanced across subjects) in a three-stimulus oddball format. Auditory stimuli consisted of an 800-Hz tone (target stimulus) presented on 15% of all trials, a 2000-Hz tone (distracter stimulus) presented on 10% of the trials, and a standard tone adjusted for each subject based upon individual pitch sensitivity. Vibrations during the tactile-alone scans were created using a novel piezoelectric bending element. The tactile target stimulus was a 50-Hz vibration, the distracter stimulus was a 150-Hz vibration, and the standard was adjusted based upon individual vibrotactile thresholds. All tones were presented monaurally to the left ear and vibrations were presented to the left index finger. (C) Scans 3 and 4 (auditory and tactile bimodal conditions) presented the same tones and vibrations simultaneously and cued subjects to switch attention between modalities every 30 trials. Subjects were required to respond to targets only in the attended modality. (D) Average target detection rates and (E) reaction times for auditory and tactile modalities for blind and sighted participants when stimuli were presented either alone or simultaneously. *Signifies a significantly higher detection of targets by EB than SC subjects ($p < .05$). Error bars denote standard error of the mean.

(unimodal, bimodal), and group (EB, SC) detected a significant main effect of group [$F(1,16) = 6.732$, $p = .02$] and modality [$F(1,16) = 5.028$, $p = .011$], and a trend toward significance for the main effect of presentation [$F(1,16) = 3.293$, $p = .088$]. There was also a significant interaction between modality and presentation [$F(1,16) = 10.753$, $p = .005$]. Post hoc Scheffé tests revealed that the EB group performed significantly better than the SC group ($p < .05$) in target detection in the auditory-alone condition. No other post hoc tests approached significance (all $ps > .20$).

Given the specific interest in the results of the EB, simple main effects of modality and presentation type were tested using a separate ANOVA to assess just EB performance across all scans as a within-subject factor. This analysis produced no main effect of modality [$F(1,8) = 2.075$, $p = .188$] or presentation type [$F(1,8) = 2.409$, $p = .159$].

Comparisons of response times to target stimuli (Figure 1E) between groups, modalities, and stimulus presentation produced no main effect of group [$F(1,16) = 0.455$, $p = .51$], but significant main effects of modality [$F(1,16) = 12.744$, $p = .003$] and stimulus presentation type [$F(1,16) = 8.723$, $p = .009$]. In addition, these main effects were modified by a significant Modality × Presentation interaction [$F(1,16) = 5.74$, $p = .03$].

Auditory-alone and Tactile-alone Scans

Active regions within the occipital lobe were identified by voxel-based contrasts of the target and distracter stimulus minus the baseline (standard) condition for the auditory- and tactile-alone scans using a random-effects GLM analysis. This approach uncovered stimulus-linked increases in BOLD signal in several regions of the occipital lobe of EB individuals, but no significant increases (or decreases) were detected in SC individuals (Figure 2). An overlay of the contrast maps for both modalities revealed several key points. First, a number of anatomically distinct regions in the occipital lobe of the EB responded to targets and/or distracters in either modality (Table 1). Second, in both scans, target and distracter stimuli presented to the left ear or the left index finger resulted in significantly greater levels of activation within the right hemisphere relative to the left (Figure 3A). Although this effect appears to be functionally similar to patterns of decussation that occur in normal, intact sensory systems, studies alternating stimulation sides in the blind are needed to test this hypothesis. Finally, there was a more robust response to the presentation of auditory stimuli when compared to tactile stimuli throughout the occipital cortex (Figure 3B). In fact, approximately 65% of tactile responsive voxels also responded to auditory stimuli, suggesting that these cortical fields contain polymodal response properties.
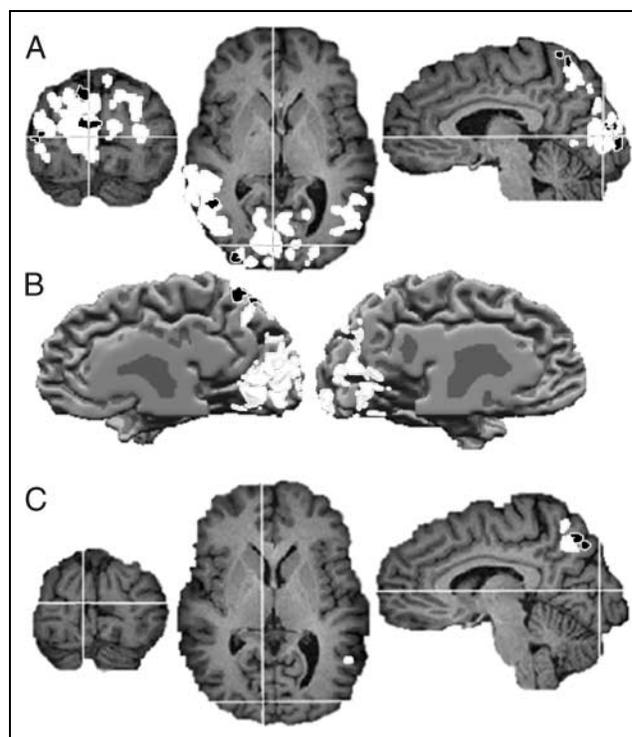
Figure 2. Auditory- and tactile-alone contrasts. Auditory and tactile contrast maps showing averaged target and distracter stimulus invoked activity using a contrast threshold value of $p < .01$, uncorrected. To protect against false positives, a cluster filter correction was implemented (see Methods). Auditory responsive regions are shown in white and tactile activity is shown in black. An anatomically restrictive map was applied to both groups in order to limit analyses to regions posterior of the central sulcus. Cross hairs show the location of the calcarine sulcus. (A) Coronal, axial, and sagittal views of averaged activity across EB subjects ($n = 9$). (B) Right and left medial views of responsive regions are shown on a three-dimensional morphed brain. (C) Tactile and auditory responsive regions in the SC ($n = 9$). All brains are shown in radiological convention.

Region-of-Interest Analysis

In order to differentiate BOLD responses between auditory and tactile targets and distracters, ROIs within the occipital lobe were identified that contained voxels active in both auditory-alone and tactile-alone scan conditions. Four ROIs within the right hemisphere were identified: clusters within the calcarine sulcus, the cuneus, the fusiform gyrus, and the lingual gyrus (Figure 4). In order to visualize auditory and tactile evoked responses, event-related time courses were extracted from the auditory- and tactile-alone scans. Paired t tests were run comparing the mean peak BOLD response from each stimulus time course to the average signal of the three TRs preceding that stimulus event (baseline).

When auditory stimuli were presented alone, peak BOLD responses for both the target and distracter stimuli were significantly greater ($p < .05$) than the corresponding baseline in the EB, but not in the SC, with the response for the distracter greater than the response

**Table 1.** Occipital Responsive Zones in the Early Blind

ROI	Hemisphere	Talairach Coordinates			Mean t Score	Mean p Value
		x	y	z		
Tactile Zones						
Cuneus	R	7	−92	1	2.58	.011
MOG	R	30	−94	−6	2.81	.013
POS	R	8	−84	31	2.85	.014
Inferior lingual sulcus	R	28	−69	−11	2.72	.015
Lingual gyrus	R	11	−60	1	2.75	.016
Fusiform gyrus	R	33	−54	−14	2.74	.016
Calcarine sulcus	R	1	−82	−13	2.67	.018
IOG	R	28	−89	−16	2.68	.019
MOG	L	−22	−99	−3	2.60	.019
MT	L	−52	−75	1	2.65	.019
Auditory Zones						
Calcarine sulcus	R	5	−84	6	6.02	.0001
POJ	R	12	−76	37	4.74	.0012
Lingual sulcus	R	27	−71	−13	4.35	.0015
Cuneus	R	8	−90	14	3.92	.0019
Lingual gyrus	R	13	−58	2	3.92	.002
SOG	R	12	−82	23	3.90	.0024
MT	R	42	−71	11	3.57	.0037
MOG	R	30	−90	6	3.46	.0046
Fusiform	R	32	−53	−13	3.10	.0071
IOG	L	−10	−94	−7	3.55	.004
Lingual sulcus	L	−15	−59	1	3.32	.005
MT	L	−41	−73	11	3.25	.006
SOG	L	−7	−87	22	3.12	.0071
Cuneus	L	−8	−90	11	3.11	.0074

POS = posterior occipital sulcus; IOG = inferior occipital gyrus; MOG = middle occipital gyrus; MT = middle temporal; POJ = parieto-occipital junction.

evoked by the target in all four ROIs. Vibrotactile stimuli produced similar effects in all occipital ROIs except the calcarine sulcus. Tactile distracters engendered significant peak responses within the calcarine sulcus, the cuneus, and lingual gyrus ROIs, but responses were smaller than target peak responses in all ROIs except the calcarine sulcus. Within the SC group, a nonsignificant increase in BOLD signal occurred in the cuneus to both auditory and tactile distracter stimuli. In summary, both auditory and tactile targets elicited responses in the cuneus, the calcarine sulcus, the lingual gyrus, and the fusiform gyrus in EB individuals suggesting that these

areas are responsive to attended stimuli in both modalities presented independently.

The latency for the time course signal to reach peak values for targets differed between modalities. Within the fusiform and lingual ROIs, auditory responses to the target stimuli peaked, on average, 4.5 sec after stimulus presentation, whereas tactile target responses peaked 6.75 sec after stimulus onset. In the calcarine sulcus and the cuneus, the latency to reach peak signal to auditory and tactile targets was similar, occurring approximately 6.75 sec after stimulus presentation. Responses to the auditory distracter stimuli reached peak values, on
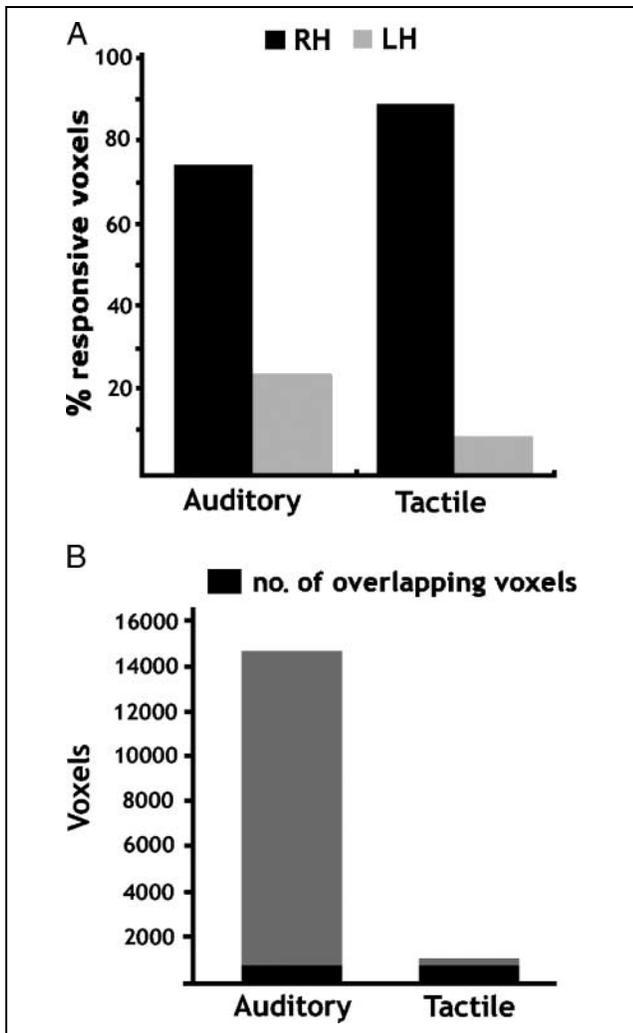
Figure 3. Characterizing occipital responsiveness in the EB. (A) shows the percentage of voxels at the group level within the right (RH) and left (LH) hemispheres that responded to either the target or distracter stimulus in the auditory and tactile modalities. (B) The total number of voxels that showed a significant response (at a contrast threshold of $p > .01$, uncorrected with a cluster filter correction) is shown for both modalities. The number of voxels that responded to both auditory and tactile stimulation is shown in dark gray.

average, 4.5 sec after stimulus presentation in all ROIs except for the calcarine sulcus, whereas tactile distracter responses peaked at 9 sec in all ROIs except within the lingual gyrus. Peak latency differences in the EB were compared between modalities and stimulus type (distracter and target) with a two-factor repeated-measures ANOVA for each occipital ROI. Significant main effects of modality were only observed in the lingual gyrus [$F(1,8) = 49.339$, $p < .001$], but a significant trend appeared within the fusiform gyrus [$F(1,8) = 4.571$, $p = .065$]. These results suggest a more rapid activation of occipital regions (specifically within the lingual gyrus) by auditory stimulation relative to tactile stimulation.

Bimodal Scans

Event-related Averages

When the same auditory and tactile stimuli were presented simultaneously and subjects attended to either auditory or tactile streams of stimuli, hemodynamic responses to targets were only detected in the modality to which subjects were attending (Figure 5). Within all four occipital ROIs, targets presented within the unattended channel did not evoke any detectable response. Furthermore, the observed negative peak response to the ignored auditory target within the calcarine sulcus (Figure 5A) was significantly less ($p = .02$) than the attended tactile standard at the corresponding time point. This suggests a suppressed response to the unattended target within this region. Within attended sensory streams, responses to the auditory events differed radically from the responses to the tactile events. Figure 5 shows the event-related averages from the bimodal scans extracted from the same four occipital ROIs shown in Figure 4. Paired t tests revealed statistically significant target or distracter effects, but only within the auditory domain. When attending to the auditory stimuli, significant target effects were observed within the lingual, cuneus, and fusiform ROIs, whereas significant distracter effects were observed in the calcarine sulcus and the cuneus. In contrast, when subjects attended to tactile stimuli during the bimodal scans, a significant event-related response appeared only in the calcarine sulcus. There was no significant response to tactile targets or distracters compared to baseline in any other occipital ROI. Finally, there were no significant target or distracter effects within the SC group in any occipital ROIs (Figure 6). However, in the SC group, the cuneus ROI was found to have a nonsignificant increase in BOLD signal to auditory and tactile distracter stimuli during the alone scans (Figure 4), but not during the bimodal scans (Figure 6). Analysis of individual subject event-related averages revealed that this effect was due to one SC individual.

Functional Control Regions

To determine whether the suppressed responses to the attended tactile stimuli observed in the bimodal scans were present in brain areas outside of the occipital cortex, we assessed event-related responses in auditory (superior temporal gyrus [STG]) and tactile (postcentral gyrus) responsive areas and the inferior frontal gyrus, which has commonly been associated with target detection (Kiehl et al., 2001; Stevens, Skudlarski, Gatenby, & Gore, 2000; Linden et al., 1999). Figure 7 illustrates that the hemodynamic responses in the somatosensory cortex (area S2) occurred only to attended tactile targets, whereas responses in the STG occurred only to attended auditory targets. Within the inferior frontal gyrus, responses occurred to both tactile and auditory attended targets. Unattended targets failed to evoke a significant
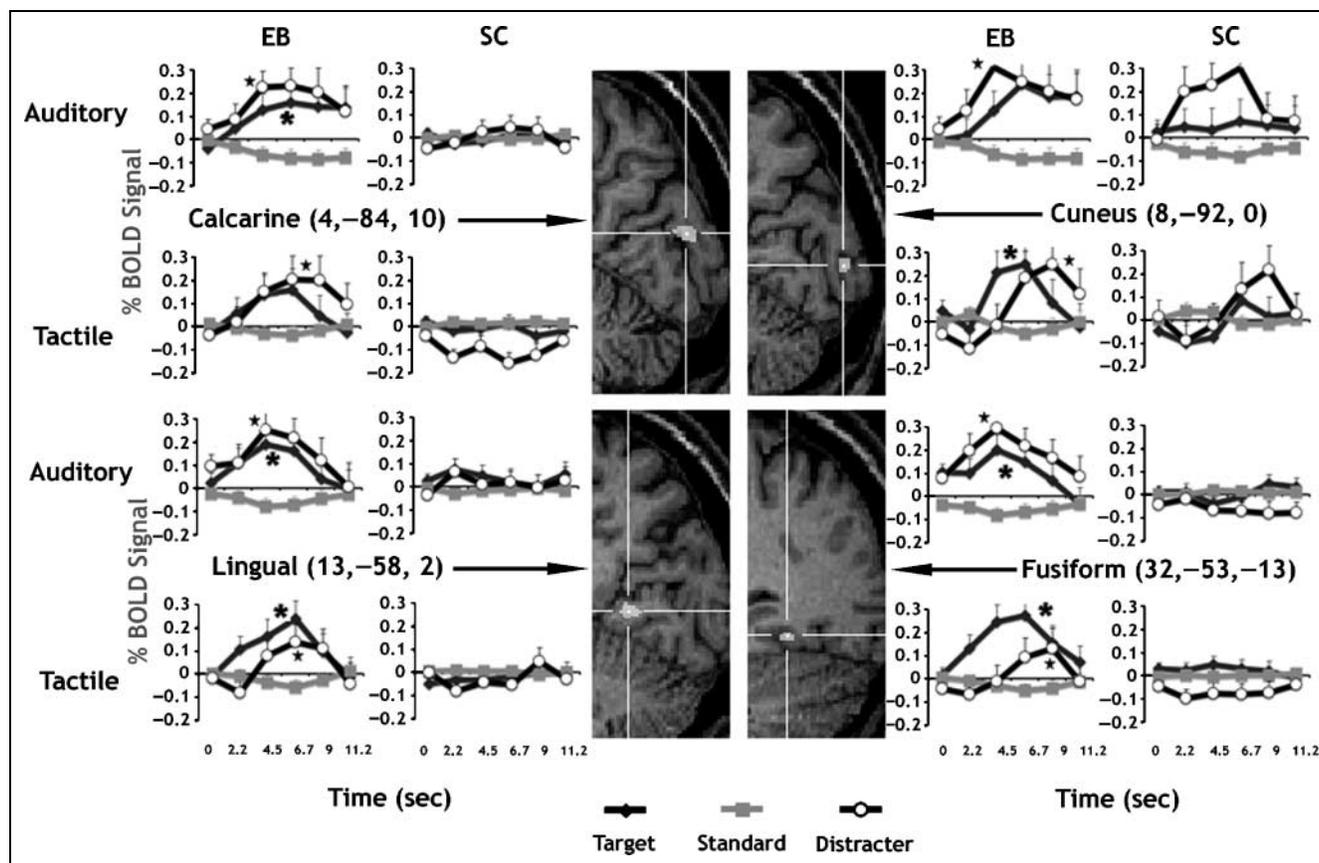
Figure 4. Alone scans (Scans 1 and 2) ROI analysis. Averaged event-related time courses were extracted from voxels showing active responses to both auditory and tactile stimuli. Four occipital ROIs are shown in the EB and SC. Target, distracter, and standard stimuli were presented at the baseline with each proceeding time point representing subsequent acquisitions (TR = 2.25 sec). Talairach coordinates for ROIs are listed in parentheses. *Denotes a significant *target* BOLD response ($p < .05$) compared to baseline. ★Denotes a significant *distracter* BOLD response ($p < .05$) compared to baseline. Error bars represent standard errors of the mean.

change in activity in any of these areas, indicating that the lack of a tactile target effect within the occipital lobe during the bimodal scans was not the result of a global failure to evoke responses or the result of MRI-based signal artifacts (e.g., poor signal to noise).

DISCUSSION

The current results uncovered evidence for attention-dependent modulations within several occipital cortical regions in EB individuals. Areas in the calcarine sulcus, lingual gyrus, fusiform gyrus, and cuneus produced comparable hemodynamic responses to targets or distracters in both the auditory-alone and tactile-alone conditions. Distracter responses within occipital ROIs observed from both auditory and tactile conditions reveal mechanisms of attentional reorienting related to stimulus salience. Previous ERP and fMRI studies have described irrelevant distracter responses as reflecting an involuntary neural mechanism that redirects attention to highly salient stimuli (Escera et al., 2002; Escera, Alho, Winkler, & Näätänen, 1998; Duncan & Humphreys, 1992; Knight,

1984). During the simultaneous auditory and tactile stimulus presentation, the functional response of these brain regions showed clear evidence of selective attention effects (i.e., signal changes occurred only to stimuli in the attended stream). The effect of selective attention was not equivalent in all ROIs, and several regions responded differently when the subject attended to the auditory and tactile streams when presented simultaneously. When EB subjects attended to the auditory stream and ignored tactile stimuli, auditory targets or distracters elicited BOLD responses comparable to or larger than those detected in the auditory-alone condition in the calcarine sulcus, lingual gyrus, and cuneus. When subjects attended to the tactile stimuli, the unattended auditory targets elicited no positive BOLD response in any of these regions. Thus, a response to auditory stimuli only appeared when they were attended. Surprisingly, when tactile stream was attended in the bimodal conditions tactile targets only elicited event-related responses in the calcarine sulcus. In the occipital ROIs outside of the calcarine sulcus, BOLD responses to tactile targets were partially or completely attenuated in the presence of unattended auditory stimuli.
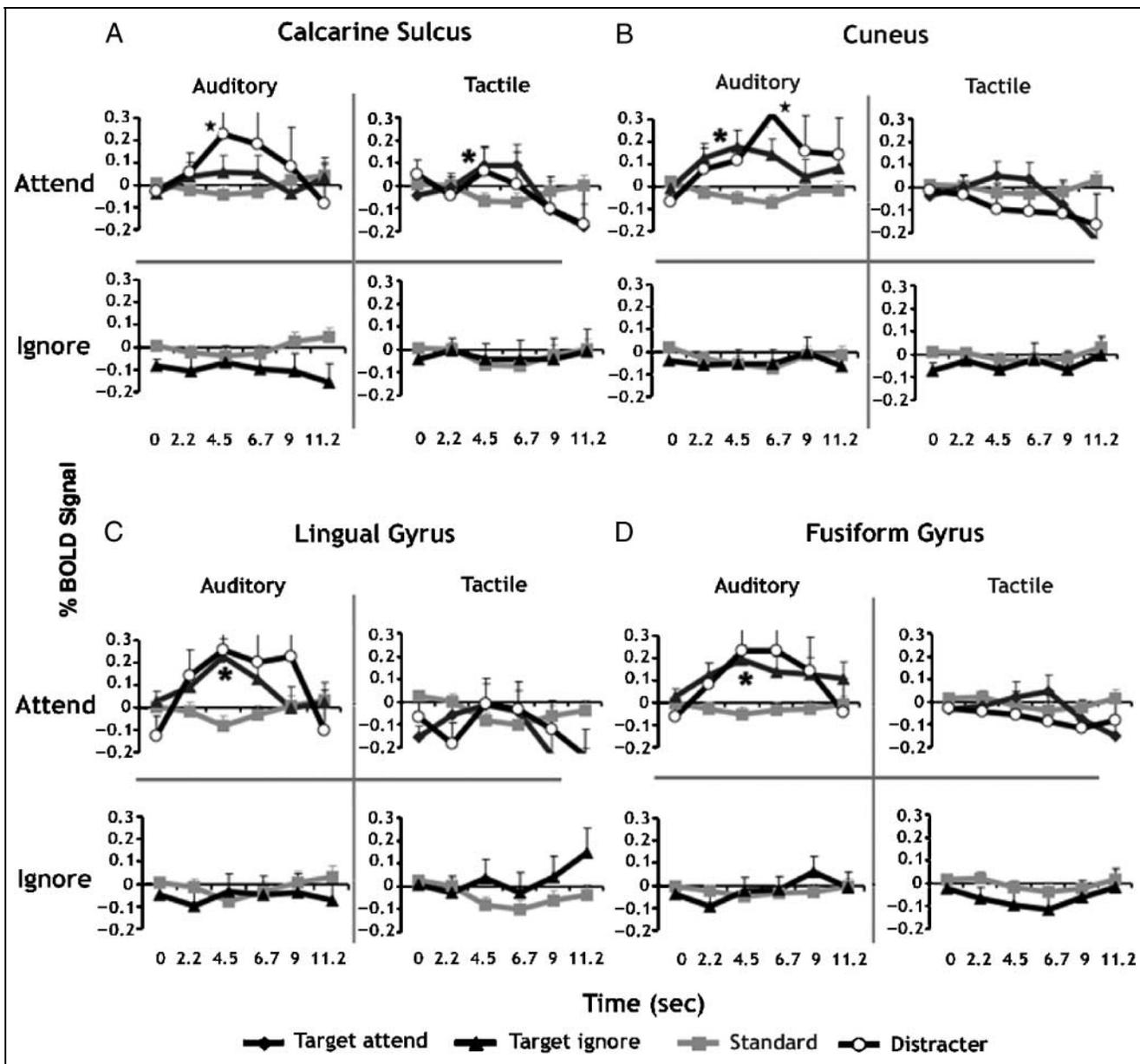
Figure 5. Bimodal scans (Scans 3 and 4) ROI analysis in the EB. Auditory and tactile event-related averages during different attentional conditions were extracted from the same occipital ROIs used in Figure 4. The resulting BOLD responses are shown for targets, distracters, and standard stimuli presented in the attended modality (target attend) and targets presented in the modality that was being ignored (target ignore). *Denotes a significant *target* BOLD response ($p < .05$) compared to baseline. ⋆Denotes a significant *distracter* BOLD response ($p < .05$) compared to baseline. Error bars represent standard errors of the mean.

The presence of a significant response to tactile targets in the calcarine sulcus within the occipital lobe as well as in control regions within the somatosensory cortex (area S2) and in the right inferior frontal gyrus demonstrated that this was not a global effect such as signal habituation. Nor was this sensory and attention interaction a result of changes in target detection accuracy, as EB subjects performed comparably on tactile target detection when tactile targets were presented alone and when presented simultaneously with auditory stimuli. Thus, with the exception of the calcarine sulcus,

temporally synchronous but unattended auditory stimuli appear to attenuate responses to attended tactile targets in extrastriate occipital areas and indicate complex interactions between auditory and tactile modalities and attention within the reorganized occipital cortex of EB individuals.

Calcarine Sulcus

The calcarine sulcus ROI showed effects reflecting a complex interaction of orienting responses, selective

Figure 6. Bimodal scans (Scans 3 and 4) ROI analysis in the SC. Mean event-related averages for auditory and tactile targets (ignored and attended) from the four occipital ROIs are shown for the SC group. Error bars represent standard errors of the mean.
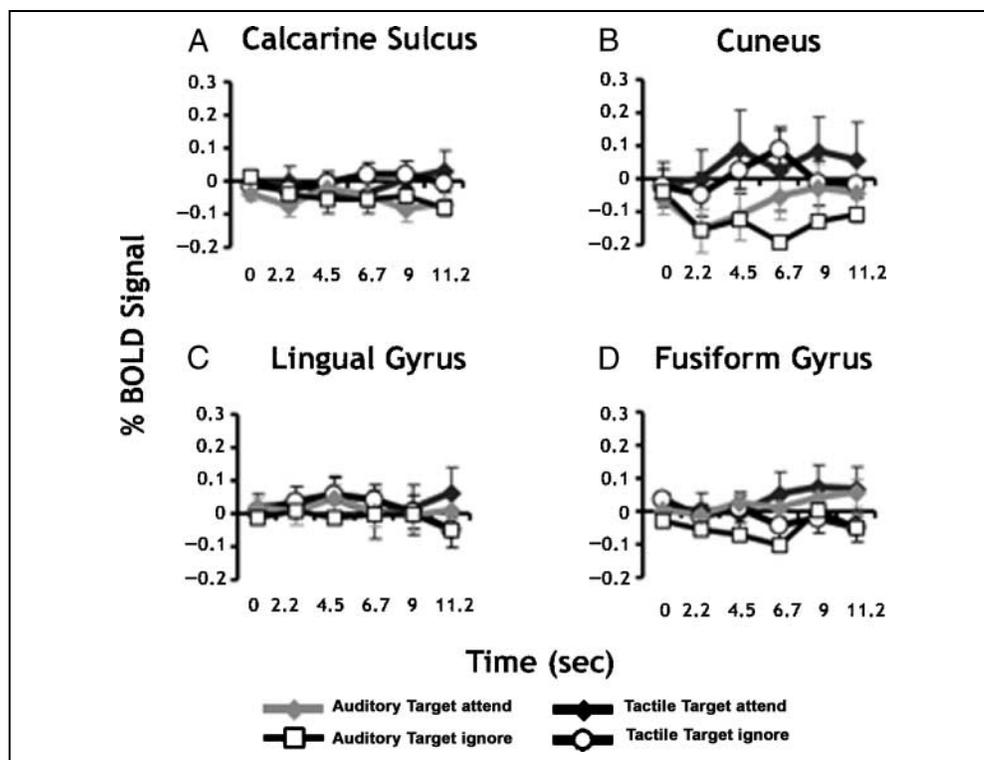
attention processes, and suppression of the auditory targets when attending to tactile stimuli. The greater event-related responses to the irrelevant but highly salient auditory distracters relative to the behaviorally relevant but less salient targets suggest that stimulus salience influences responses within this region, an effect likely related to attentional reorienting (Figure 4). In the bimodal scan, this orienting response persisted as indicated by a significant response to the auditory distracter (Figure 5A). The calcarine sulcus therefore may function within a larger network of regions (e.g., the ventral fronto-parietal network in the SC) involved in automatically orienting attention to novel or salient stimulus events (see Shulman, Astafiev, & Corbetta, 2004; Corbetta & Shulman, 2002). However, target effects were also observed within this region. A significant response to tactile targets was observed in the bimodal conditions and a trend for significance was observed in the alone conditions. Additionally, the auditory target evoked a significant response within the alone scans. These responses may reflect top-down functions involved in target selection. It is also conceivable that target responses within the calcarine sulcus reflect an orienting response to the (albeit less salient) deviant target stimulus.

In contrast to attended stimuli, unattended targets in both modalities failed to evoke detectable responses within the calcarine sulcus, indicating that selective attention modulates event-related responses within this region. In sighted individuals, decreases in signal in visual and auditory sensory cortices as a result of shifting attention away from stimuli in one modality have been widely documented using fMRI (Johnson & Zatorre, 2005; Petkov et al., 2004; Shomstein & Yantis, 2004; Woodruff et al., 1996). These studies suggest that under normal visual development, shifting attention between sensory modalities modulates responses within sensory cortical regions. When EB subjects were attending to the tactile stream, a sustained decrease in the BOLD response to unattended auditory targets appeared (Figure 5A). It is possible that the neural mechanisms that underlie normal suppressive functions found in the sighted visual cortex become functionally adapted to the reorganized afferents reaching the occipital cortex in the EB and are utilized under conditions of increased perceptual load (Pascual-Leone & Hamilton, 2001). For example, in sighted individuals, inhibitory effects have been reported using fMRI in the occipital cortex during a spatial-distracter suppression task (Serences, Yantis, Culberson, & Awh, 2004). These authors suggested that an inhibitory mechanism within the occipital cortex of sighted individuals aids in the regulation and suppression of distracting visual information. The suppressed response observed in the EB suggests that the calcarine sulcus may be actively inhibited when potentially interfering auditory information is ignored. A lack of a similar response to unattended tactile targets when attending to the auditory stream implies that this area modulates its response depending on whether auditory stimuli are present and whether they are attended or ignored. This speculation is consistent with the longer responses observed in tactile targets (Figure 1E), and suggests that
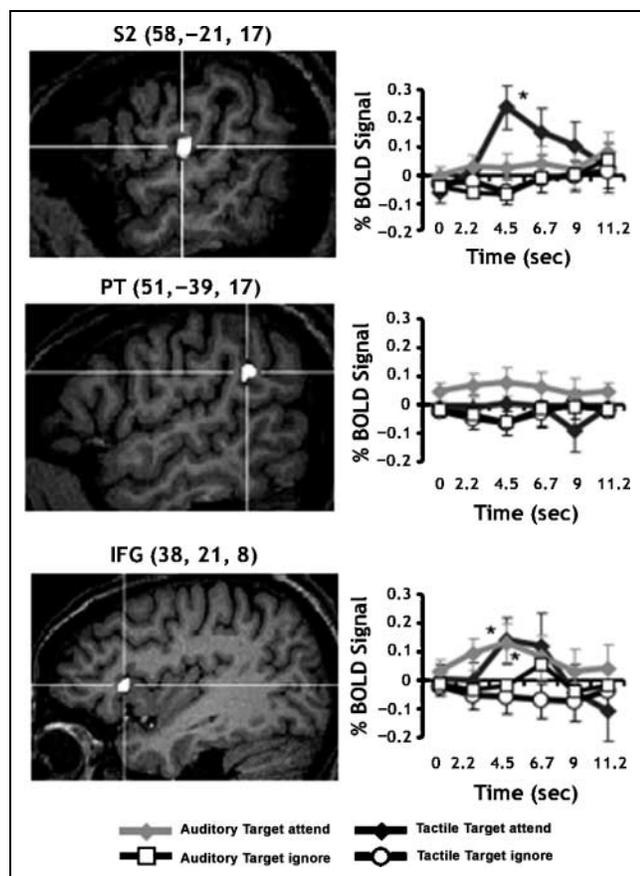
Figure 7. Event-related averages from functional control regions in the EB. Target-related BOLD signals were extracted from (A) a somatosensory association area (postcentral gyrus, S2), (B) an auditory association area (superior temporal gyrus), and (C) a frontal association cortex (inferior frontal gyrus, IFG) during the bimodal scans. Talairach coordinates for ROIs are listed in parentheses. *Denotes a significant difference at $p < .05$ between the peak BOLD response and the corresponding baseline. Error bars represent standard errors of the mean.

the calcarine sulcus in EB individuals may play a role in the specific gating of attention.

Supporting this claim, a recent auditory and tactile electrophysiological study in the EB demonstrating that stimuli in a task-irrelevant modality presented within an attended region of space did not show the normal space-based, attentional modulations commonly observed in SC individuals (Hötting et al., 2004). Rather, the blind showed a positively displaced ERP (as opposed to a negative response observed in the SCs) to the spatially congruent but modality-irrelevant stimuli within the late ERP windows. The authors speculated that this positivity in the blind is a reflection of an active suppression of stimuli presented within an irrelevant modality.

The calcarine sulcus has been the subject of the most extensive analysis in blind individuals and paralleling the current results has been shown to respond to stimuli in both auditory and tactile domains, as well

as to a host of language, memory, and discrimination tasks (Amedi, Floel, Knecht, Zohary, & Cohen, 2004; Burton et al., 2003, 2004; Amedi et al., 2003; Roder et al., 2002; Sadato, Okada, Honda, & Yonekura, 2002; Sadato et al., 1996). The breadth of tasks that engage the calcarine sulcus in EB individuals suggest that common mechanisms are likely to evoke responses from this normally primary sensory area. The pattern of responses detected in the present study suggests that selective attention and stimulus salience interact to engage this region. However, under conditions of stimulus competition, mechanisms associated with different aspects of attention may be revealed.

Extrastriate Regions

Similar to the calcarine sulcus ROI, the three ''extra-striate'' ROIs responded to the auditory and tactile deviants in the alone scan, however, with the tactile distracter evoking a smaller response relative to the tactile target within the lingual and fusiform ROIs. In contrast to the calcarine sulcus, significant auditory target responses in all extrastriate regions in both unimodal and bimodal presentations and significant tactile target effects greater than distracter responses in alone conditions suggest that these areas may be more sensitive to directing (i.e., selective) attention to detection of stimulus change than to orienting responses associated with the distracter stimulus. Although additional fMRI experiments are required to support this claim, it parallels a number of event-related studies that have reported late electroencephalogram potentials over occipital leads in response to detection of a change within an auditory or tactile stream (Liotti et al., 1998; Roder et al., 1996; Kujala, Alho, et al., 1995; Kujala, Huotilainen, et al., 1995). This hypothesis is supported by the current (and repeated) observation that attention focused away from target stimuli attenuates (or abolishes) posterior occipital responses (see Kujala et al., 2000, for a review). Therefore, we suggest that modality-independent mechanisms involved in selection of a target stimulus contribute to the signal changes within a number of extrastriate occipital regions.

There was, however, some response differences between ROIs. For example, the cuneus was the only extrastriate region to show equivalent responses (i.e., amplitude of response) to both tactile distracter and target stimuli during unimodal conditions and a significant response to the auditory distracter in the bimodal scans (although trends were evident within the lingual and fusiform ROIs). This raises the possibility that the posterior regions within the occipital lobe of EB individuals (i.e., calcarine sulcus and cuneus) may reflect more of an underlying attentional orienting response to stimulus salience stream, whereas the more anterior regions may be more sensitive to top-down mechanisms. This pattern of organization is similar to a postulate anterior–

posterior organization hypothesis proposed by Amedi et al. (2003, 2004). These researchers compared fMRI responses throughout the occipital lobe during a Braille reading task with no overt response to a verb generation task requiring subjects to silently generate a verb to an aurally presented noun. A differential pattern of activation between tasks led to the development of a ''reverse hierarchy,'' anterior–posterior hypothesis. It was proposed that anterior occipital regions (such as the lateral occipital complex) yield more perceptual-based functions, whereas posterior loci (such as the calcarine sulcus) are involved in higher order, cognitive functions (Amedi et al., 2003, 2004; Buchel, 2003). However, a few imaging studies have reported homogenous patterns of activation throughout occipital regions, more reflective of a uniform organization, with all occipital regions partaking in similar functional roles (Burton et al., 2004; Roder et al., 2002).

Whether the different patterns of event-related responses between the extrastriate and striate visual cortex in the current study reflects the existence of different functional systems throughout the occipital lobe is unclear. Despite regional differences, we observed some response uniformity across ROIs. For example, time course patterns and stimulus magnitude effects were similar for each modality throughout the four sampled ROIs when presented alone. This homogenous pattern is similar to a previous study of vibrotactile discrimination (Burton et al., 2004) and is contrary to the compartmentalization theory proposed by Amedi et al. (2003, 2004) and Buchel (2003). A true examination of an anterior–posterior hypothesis within the occipital cortex in the EB, however, requires a comparison of hemodynamic responses to tasks that parametrically manipulate perceptual and cognitive complexity and may require a greater specification of the underlying connectivity between and within regions.

Stimulus Modality and Attention

The attenuated event-related responses to attended tactile targets when presented simultaneously with unattended auditory stimuli (bimodal scans) suggest that areas within the occipital cortex may be biased towards the auditory domain. We observed that peak latencies from the alone scans occurred sooner to auditory targets relative to tactile targets within the cuneus and fusiform gyrus ROIs, an effect potentially attributed to auditory stimulation arriving at occipital loci prior to tactile stimulation. Paralleling peak latency differences, the blind also responded more rapidly to auditory relative to tactile targets, a finding previously reported to targets presented either alone (Kujala, Alho, et al., 1995) or simultaneously (Kujala, Huotilainen, et al., 1997). Faster conduction of auditory signals by innervating afferents, even when unattended, may have produced an inhibitory gating response within occipital areas that responded to both

modalities in the absence of competing sensory stimulation. This speculation is constrained, however, by a lack of a positively evoked BOLD signal by the unattended auditory target within any occipital ROIs.

An alternative suggestion accounting for the suppressed tactile occipital responses during bimodal conditions revolves around dedicating more attentional resources to the tactile modality during the bimodal conditions. The detection of tactile deviancy in the face of competing auditory stimulation may require directing more attentional resources (above what would be required during unimodal conditions) to nonoccipital circuits normally involved in somatosensory target detection. This hypothesis accounts for the observed tactile target responses within the somatosensory associated cortex and the inferior frontal cortex (Figure 7), two regions previously implicated in tactile target detection in SC individuals (Huang et al., 2005). A decrease in the amount of resources available during bimodal conditions could prevent the gating of somatosensory stimulation into occipital circuits.

Conclusions

Within the posterior occipital areas of our EB sample, event-related BOLD responses were identified as responding to both auditory and tactile target or distracter stimuli under unimodal conditions. These areas altered their responses under conditions of simultaneous presentation of auditory and tactile streams when subjects attended to one stream or the other, revealing complex interactions between attention and sensory modality. Therefore, the novel asymmetrical response observed within the bimodal conditions in the current study suggests that occipital areas in the EB may undergo active enhancement or suppression, depending on the attentional demands of the task.

We recognize that the current results do not provide clear evidence whether the regions identified in the occipital cortex are the *site* or the *source* of the observed attentional modulation. This distinction is fundamental to understanding how posterior occipital areas reorganize in early-onset blindness. Functionally, previous ERP oddball studies in EB have shown attentional enhancement effects to target stimuli in both auditory (Kujala, Alho, et al., 1997; Kujala, Huotilainen, et al., 1995; Kujala et al., 1992) and tactile (Kujala, Alho, et al., 1995) modalities. The variety of functional tasks that have been found to engage occipital regions in the EB (see Roder & Rosler, 2004; Theoret, Merabet, & Pascual-Leone, 2004; Burton, 2003; Bavelier & Neville, 2002, for reviews) suggests that the occipital cortex in the EB houses mechanisms common to a variety of information processing tasks; one such mechanism may be the control of selective attention.

The connectivity of the occipital lobe in the EB may provide some indication of the organization of attention

within the occipital cortex of the EB. A number of tracing studies in sighted animals and imaging studies in sighted humans have revealed the existence of auditory and tactile inputs into normal occipital cortex, indicating that complex interactions between sensory modalities occur in intact sensory cortices (Watkins, Shams, Tanaka, Haynes, & Rees, 2006; Schroeder & Foxe, 2005; Rockland & Ojima, 2003; Molholm et al., 2002; Giard & Peronet, 1999). Connections with the prefrontal and superior parietal cortex suggest that occipital regions in the EB might be the recipients of signal amplifications via selective attention mechanisms (Shimony et al., 2006; Kastner & Ungerlieder, 2001; Posner et al., 1990). It may be the case when, in the absence of vision during development, somatosensory and auditory afferents become the dominant source of sensory input, and nonsensory, fronto-parietal afferents feeding into the occipital cortex modulate their responses as a function of attention. Alternatively, projections from the superior colliculus and primary auditory cortices (Shimony et al., 2006; Tardif, Delacuisine, Probst, & Clarke, 2005; Falchier, Clavagnier, Barone, & Kennedy, 2002) may be retained facilitating a role in orienting or alerting effects. The presence of orienting responses, combined with the evoked auditory target responses, but only when attended, suggests that the added occipital activity in the EB may result in a greater sensitivity to attending and/or orienting to changes within the sensory environment (Kujala et al., 2005).

Acknowledgments

REFERENCES

Alho, K., Kujala, T., Paavilainen, P., Summala, H., & Näätänen, R. (1993). Auditory processing in visual brain areas of the early blind: Evidence from event-related potentials. *Electroencephalography and Clinical Neurophysiology, 86,* 418–427.

Amedi, A., Floel, A., Knecht, S., Zohary, E., & Cohen, L. G. (2004). Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. *Nature Neuroscience, 7,* 1266–1270.

Amedi, A., Jacobson, G., Hendler, T., Malach, R., & Zohary, E. (2002). Convergence of visual and tactile shape processing in the human lateral occipital complex. *Cerebral Cortex, 12,* 1202–1212.

Amedi, A., Raz, N., Pianka, P., Malach, R., & Zohary, E. (2003). Early ''visual'' cortex activation correlates with superior verbal memory performance in the blind. *Nature Neuroscience, 6,* 758–766.

Bavelier, D., & Neville, H. J. (2002). Cross-modal plasticity: Where and how? *Nature Reviews Neuroscience, 3,* 443–452.

Berardi, N., Pizzorusso, T., & Maffei, L. (2000). Critical periods during sensory development. *Current Opinion in Neurobiology, 10,* 138–145.

Bledowski, C., Prvulovic, D., Goebel, R., Zanella, F. E., & Linden, D. E. (2004). Attentional systems in target and distractor processing: A combined ERP and fMRI study. *Neuroimage, 22,* 530–540.

Boynton, G. M., Engel, S. A., Glover, G. H., & Heeger, D. J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. *Journal of Neuroscience, 16,* 4207–4221.

Buchel, C. (2003). Cortical hierarchy turned on its head. *Nature Neuroscience, 6,* 657–658.

Buchel, C., Price, C., & Friston, K. (1998). A multimodal language region in the ventral visual pathway. *Nature, 394,* 274–277.

Burton, H. (2003). Visual cortex activity in early and late blind people. *Journal of Neuroscience, 23,* 4005–4011.

Burton, H., Diamond, J. B., & McDermott, K. B. (2003). Dissociating cortical regions activated by semantic and phonological tasks: A fMRI study in blind and sighted people. *Journal of Neurophysiology, 90,* 1965–1982.

Burton, H., Sinclair, R. J., & McLaren, D. G. (2004). Cortical activity to vibrotactile stimulation: An fMRI study in blind and sighted individuals. *Human Brain Mapping, 23,* 210–228.

Burton, H., Snyder, A. Z., Diamond, J. B., & Raichle, M. E. (2002). Adaptive changes in early and late blind: A fMRI study of verb generation to heard nouns. *Journal of Neurophysiology, 88,* 3359–3371.

Clavagnier, S., Falchier, A., & Kennedy, H. (2004). Long-distance feedback projections to area V1: Implications for multisensory integration, spatial awareness, and visual consciousness. *Cognitive, Affective & Behavioral Neuroscience, 4,* 117–126.

Comerchero, M. D., & Polich, J. (1998). P3a, perceptual distinctiveness, and stimulus modality. *Brain Research, Cognitive Brain Research, 7,* 41–48.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3,* 201–215.

Damasio, H. (2005). *Human brain anatomy in computerized images.* New York: Oxford University Press.

De Volder, A. G., Toyama, H., Kimura, Y., Kiyosawa, M., Nakano, H., Vanlierde, A., et al. (2001). Auditory triggered mental imagery of shape involves visual association areas in early blind humans. *Neuroimage, 14,* 129–139.

Duncan, J., & Humphreys, G. (1992). Beyond the search surface: Visual search and attentional engagement. *Journal of Experimental Psychology: Human Perception and Performance, 18,* 578–588; discussion 589–593.

Edmister, W. B., Talavage, T. M., Ledden, P. J., & Weisskoff, R. M. (1999). Improved auditory cortex imaging using clustered volume acquisitions. *Human Brain Mapping, 7,* 89–97.

Escera, C., Alho, K., Winkler, I., & Näätänen, R. (1998). Neural mechanisms of involuntary attention to acoustic novelty and change. *Journal of Cognitive Neuroscience, 10,* 590–604.

Escera, C., Corral, M. J., & Yago, E. (2002). An electrophysiological and behavioral investigation of

involuntary attention towards auditory frequency, duration and intensity changes. *Brain Research, Cognitive Brain Research, 14,* 325–332.

Falchier, A., Clavagnier, S., Barone, P., & Kennedy, H. (2002). Anatomical evidence of multimodal integration in primate striate cortex. *Journal of Neuroscience, 22,* 5749–5759.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magnetic Resonance in Medicine, 33,* 636–647.

Giard, M. H., & Peronnet, F. (1999). Auditory–visual integration during multimodal object recognition in humans: A behavioral and electrophysiological study. *Journal of Cognitive Neuroscience, 11,* 473–490.

Gougoux, F., Zatorre, R. J., Lassonde, M., Voss, P., & Lepore, F. (2005). A functional neuroimaging study of sound localization: Visual cortex activity predicts performance in early-blind individuals. *PLoS Biology, 3,* e27.

Halgren, E., Marinkovic, K., & Chauvel, P. (1998). Generators of the late cognitive potentials in auditory and visual oddball tasks. *Electroencephalography and Clinical Neurophysiology, 106,* 156–164.

Hall, D. A., Haggard, M. P., Akeroyd, M. A., Summerfield, A. Q., Palmer, A. R., Elliott, M. R., et al. (2000). Modulation and task effects in auditory processing measured using fMRI. *Human Brain Mapping, 10,* 107–119.

Hötting, K., Rosler, F., & Röder, B. (2004). Altered auditory–tactile interactions in congenitally blind humans: An event-related potential study. *Experimental Brain Research, 159,* 370–381.

Huang, M. X., Lee, R. R., Miller, G. A., Thoma, R. J., Hanlon, F. M., Paulson, K. M., et al. (2005). A parietal–frontal network studied by somatosensory oddball MEG responses, and its cross-modal consistency. *Neuroimage, 28,* 99–114.

Huttonlocher, P. R. (2002). *Neural plasticity.* Cambridge: Harvard University Press.

Hyvarinen, J., Carlson, S., & Hyvarinen, L. (1981). Early visual deprivation alters modality of neuronal responses in area 19 of monkey cortex. *Neuroscience Letters, 26,* 239–243.

Johnson, J. A., & Zatorre, R. J. (2005). Attention to simultaneous unrelated auditory and visual events: Behavioral and neural correlates. *Cerebral Cortex, 15,* 1609–1620.

Kastner, S., & Ungerleider, L. G. (2001). The neural basis of biased competition in human visual cortex. *Neuropsychologia, 39,* 1263–1276.

Kiehl, K. A., Laurens, K. R., Duty, T. L., Forster, B. B., & Liddle, P. F. (2001). Neural sources involved in auditory target detection and novelty processing: An event-related fMRI study. *Psychophysiology, 38,* 133–142.

Kiehl, K. A., Stevens, M. C., Laurens, K. R., Pearlson, G., Calhoun, V. D., & Liddle, P. F. (2005). An adaptive reflexive processing model of neurocognitive function: Supporting evidence from a large scale ($N = 100$) fMRI study of an auditory oddball task. *Neuroimage, 25,* 899–915.

Knight, R. T. (1984). Decreased response to novel stimuli after prefrontal lesions in man. *Electroencephalography and Clinical Neurophysiology, 59,* 9–20.

Knudsen, E. I. (2004). Sensitive periods in the development of the brain and behavior. *Journal of Cognitive Neuroscience, 16,* 1412–1425.

Kujala, T., Alho, K., Huotilainen, M., Ilmoniemi, R. J., Lehtokoski, A., Leinonen, A., et al. (1997). Electrophysiological evidence for cross-modal plasticity in humans with early- and late-onset blindness. *Psychophysiology, 34,* 213–216.

Kujala, T., Alho, K., Kekoni, J., Hamalainen, H., Reinikainen, K., Salonen, O., et al. (1995). Auditory and somatosensory event-related brain potentials in early blind humans. *Experimental Brain Research, 104,* 519–526.

Kujala, T., Alho, K., & Näätänen, R. (2000). Cross-modal reorganization of human cortical functions. *Trends in Neurosciences, 23,* 115–120.

Kujala, T., Alho, K., Paavilainen, P., Summala, H., & Näätänen, R. (1992). Neural plasticity in processing of sound location by the early blind: An event-related potential study. *Electroencephalography and Clinical Neurophysiology, 84,* 469–472.

Kujala, T., Huotilainen, M., Sinkkonen, J., Ahonen, A. I., Alho, K., Hamalainen, M. S., et al. (1995). Visual cortex activation in blind humans during sound discrimination. *Neuroscience Letters, 183,* 143–146.

Kujala, T., Lehtokoski, A., Alho, K., Kekoni, J., & Näätänen, R. (1997). Faster reaction times in the blind than sighted during bimodal divided attention. *Acta Psychologica, 96,* 75–82.

Kujala, T., Palva, M. J., Salonen, O., Alku, P., Huotilainen, M., Jarvinen, A., et al. (2005). The role of blind humans' visual cortex in auditory change detection. *Neuroscience Letters, 379,* 127–131.

Levitt, H. (1970). Transformed up–down methods in psychoacoustics. *Journal of the Acoustical Society of America, 49,* 467–477.

Linden, D. E., Prvulovic, D., Formisano, E., Vollinger, M., Zanella, F. E., Goebel, R., et al. (1999). The functional neuroanatomy of target detection: An fMRI study of visual and auditory oddball tasks. *Cerebral Cortex, 9,* 815–823.

Liotti, M., Ryder, K., & Woldorff, M. G. (1998). Auditory attention in the congenitally blind: Where, when and what gets reorganized? *NeuroReport, 9,* 1007–1012.

Mai, J. K., Assheuer, J., & Paxinos, G. (1997). *Atlas of the human brain.* San Diego: Academic Press.

Melzer, P., Morgan, V. L., Pickens, D. R., Price, R. R., Wall, R. S., & Ebner, F. F. (2001). Cortical activation during Braille reading is influenced by early visual experience in subjects with severe visual disability: A correlational fMRI study. *Human Brain Mapping, 14,* 186–195.

Molholm, S., Ritter, W., Murray, M. M., Javitt, D. C., Schroeder, C. E., & Foxe, J. J. (2002). Multisensory auditory–visual interactions during early sensory processing in humans: A high-density electrical mapping study. *Brain Research, Cognitive Brain Research, 14,* 115–128.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9,* 97–113.

Pascual-Leone, A., & Hamilton, R. (2001). The metamodal organization of the brain. *Progress in Brain Research, 134,* 427–445.

Petkov, C. I., Kang, X., Alho, K., Bertrand, O., Yund, E. W., & Woods, D. L. (2004). Attentional modulation of human auditory cortex. *Nature Neuroscience, 7,* 658–663.

Polich, J. (2003). *Detection of change: Event-related potential and fMRI findings.* Boston: Kluwer Academic Publishing.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience, 13,* 25–42.

Rauschecker, J. P. (1995). Compensatory plasticity and sensory substitution in the cerebral cortex. *Trends in Neurosciences, 18,* 36–43.

Rauschecker, J. P., & Korte, M. (1993). Auditory compensation for early blindness in cat cerebral cortex. *Journal of Neuroscience, 13,* 4538–4548.

Rockland, K. S., & Ojima, H. (2003). Multisensory convergence in calcarine visual areas in macaque monkey. *International Journal of Psychophysiology, 50,* 19–26.

Roder, B., & Rosler, F. (2004). Compensatory plasticity as a consequence of sensory loss. In G. Calvert, C. Spence, & B. E. Stein (Eds.), *The handbook of multisensory processes.* Cambridge, MA: MIT Press.

Roder, B., Rosler, F., Hennighausen, E., & Nacker, F. (1996). Event-related potentials during auditory and somatosensory discrimination in sighted and blind human subjects. *Brain Research, Cognitive Brain Research, 4,* 77–93.

Roder, B., Stock, O., Bien, S., Neville, H., & Rosler, F. (2002). Speech processing activates visual cortex in congenitally blind humans. *European Journal of Neuroscience, 16,* 930–936.

Sadato, N., Okada, T., Honda, M., & Yonekura, Y. (2002). Critical period for cross-modal plasticity in blind humans: A functional MRI study. *Neuroimage, 16,* 389–400.

Sadato, N., Pascual-Leone, A., Grafman, J., Deiber, M. P., Ibanez, V., & Hallett, M. (1998). Neural networks for Braille reading by the blind. *Brain, 121,* 1213–1229.

Sadato, N., Pascual-Leone, A., Grafman, J., Ibanez, V., Deiber, M. P., Dold, G., et al. (1996). Activation of the primary visual cortex by Braille reading in blind subjects. *Nature, 380,* 526–528.

Schroeder, C. E., & Foxe, J. (2005). Multisensory contributions to low-level, ''unisensory'' processing. *Current Opinion in Neurobiology, 15,* 454–458.

Serences, J. T., Yantis, S., Culberson, A., & Awh, E. (2004). Preparatory activity in visual cortex indexes distractor suppression during covert spatial orienting. *Journal of Neurophysiology, 92,* 3538–3545.

Shimony, J. S., Burton, H., Epstein, A. A., McLaren, D. G., Sun, S. W., & Snyder, A. Z. (2005). Diffusion tensor imaging reveals white matter reorganization in early blind humans. *Cerebral Cortex, 16,* 1653–1661.

Shomstein, S., & Yantis, S. (2004). Control of attention shifts between vision and audition in human cortex. *Journal of Neuroscience, 24,* 10702–10706.

Shulman, G. L., Astafiev, S. V., & Corbetta, M. (2004). Two cortical systems for the selection of visual stimuli. In M. I. Posner (Ed.), *Cognitive neuroscience of attention* (pp. 114–126). New York: Guilford Press.

Stevens, A. A., Skudlarski, P., Gatenby, J. C., & Gore, J. C. (2000). Event-related fMRI of auditory and visual oddball tasks. *Magnetic Resonance Imaging, 18,* 495–502.

Stippich, C., Romanowski, A., Nennig, E., Kress, B., & Sartor, K. (2005). Time-efficient localization of the human secondary somatosensory cortex by functional magnetic resonance imaging. *Neuroscience Letters, 381,* 264–268.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain.* New York: Thieme Medical.

Tardif, E., Delacuisine, B., Probst, A., & Clarke, S. (2005). Intrinsic connectivity of the human superior colliculus. *Experimental Brain Research, 166,* 316–324.

Theoret, H., Merabet, L., & Pascual-Leone, A. (2004). Behavioral and neuroplastic changes in the blind: Evidence for functionally relevant cross-modal interactions. *Journal of Physiology (Paris), 98,* 221–233.

Watkins, S., Shams, L., Tanaka, S., Haynes, J. D., & Rees, G. (2006). Sound alters activity in human V1 in association with illusory visual perception. *Neuroimage, 31,* 1247–1256.

Weeks, R., Horwitz, B., Aziz-Sultan, A., Tian, B., Wessinger, C. M., Cohen, L. G., et al. (2000). A positron emission tomographic study of auditory localization in the congenitally blind. *Journal of Neuroscience, 20,* 2664–2672.

Wessinger, C. M., VanMeter, J., Tian, B., Van Lare, J., Pekar, J., & Rauschecker, J. P. (2001). Hierarchical organization of the human auditory cortex revealed by functional magnetic resonance imaging. *Journal of Cognitive Neuroscience, 13,* 1–7.

Woodruff, P. W., Benson, R. R., Bandettini, P. A., Kwong, K. K., Howard, R. J., Talavage, T., et al. (1996). Modulation of auditory and visual cortex by selective attention is modality-dependent. *NeuroReport, 7,* 1909–1913.