Neural Networks of Top-Down and Bottom-up Attention in Early Onset Blindness

By

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CERTIFICATE OF APPROVAL

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TABLE OF CONTENTS

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Abstract

Recent functional neuroimaging studies have revealed that occipital or visual cortical areas in individuals blinded in or around birth are metabolically active during tactile, auditory and cognitive stimulation. These findings suggest that in the early blind (EB) the areas that are normally engaged by visual stimulation process non-visual information (a phenomenon referred to as cross-modal reorganization). However, the functional significance of occipital (Occ) activity in this population is not well understood. The aim of my dissertation was to determine whether different mechanisms of attention influence neural activity within Occ cortical regions in the EB. Identifying the functional domains that activate the Occ cortex in the EB will lead to a better understanding of the influences important for the establishment of cross-modal reorganization. In addition, EB results in superior performance on a number of auditory and tactile behavioral tasks relative to sighted counterparts (SC). A second goal was to determine whether EB relative to SC individuals show enhanced attentional abilities within auditory and tactile domains. This approach would allow me to determine whether an association exists between activity within the Occ cortex of the EB and alterations in attentional abilities.

Event-related functional magnetic resonance imaging (erfMRI) was combined with oddball, target detection tasks. Oddball tasks tap into various attentional mechanisms because they require the selection of a specific, infrequent target stimulus presented within a train of repeating and identical standard stimuli. Attention is generally considered a mechanism that resolves conflict between competing sensory signals such that stimuli relevant to ongoing behavior are gated into awareness. This gating is achieved through two processes. First is the purposeful selection of specific stimuli based on prior knowledge or expected goals and referred to as top-down selective control. The second, bottom-up process occurs through the unintentional capture of attention by highly salient stimuli.

Nine EB and nine SC individuals participated in a series of 3-stimulus oddball detection tasks. In addition to the infrequent target stimulus and the frequent, non-target standard, a third infrequent, non-target distracter stimulus was presented throughout the tasks. Although distracter stimuli are considered irrelevant, they are designed to capture attention through stimulus saliency (i.e. bottom-up) effects. Participants made a button press in response to target stimuli in one of three conditions: 1) within a stream of auditory tones, 2) within a stream of vibrotactile stimuli and 3) within a stream of simultaneously presented tones and vibrations (bimodal conditions) but requiring participants to select for either the auditory or tactile target.

In both groups, auditory and tactile target and the irrelevant distracter stimuli evoked activity in frontoparietal regions commonly implicated in a top-down and bottom-up attentional processes. However, significant auditory and to a smaller degree tactile evoked activity was observed in the occipital (Occ) cortex of EB individuals but not in SC individuals. Event-related, region-of-interest (ROI) analyses revealed distracter-related activity in Occ regions responding to both modalities. Because of the irrelevant nature of distracter stimuli, these results demonstrated bottom-up mechanisms of attention within the Occ cortex of EB individuals. During the bimodal scans when auditory and tactile stimuli were presented simultaneously, Occ regions of interest in the

EB responded to target stimuli in the auditory domain but only when subjects were selectively attending to the auditory modality. This modulation effect illuminates top-down selective attention mechanisms within the Occ lobe of EB individuals. This effect was not observed within the tactile domain, indicating a complex interaction of excitatory and inhibitory mechanisms under conditions of increased perceptual load. The close resemblance of Occ time courses with responses extracted from the supramarginal gyrus of SC individuals, a region consistently implicated in attentional gating mechanisms, further supports a role of attentional processing within the Occ.

Collectively, these findings reveal that in the absence of vision from an early age, bottom-up and top-down mechanisms of attention activate Occ regions. This suggests that attention likely provides a strong influence on the development of cross-modal reorganization in the EB. Furthermore, the EB were slightly more accurate than their sighted counterparts at detecting auditory targets. Therefore, Occ reorganization based on attention systems may be coupled to behavioral advantages that develop as a consequence of early blindness.

Chapter 1: General Introduction

Interaction with the environment results in a wealth of information continuously bombarding our senses. However, the human brain is limited in the amount of information that can be attended to at any given moment. Therefore, only a fraction of the total accumulation of sensory stimulation can be brought into awareness. Because of this limitation, many classic models of information processing and attention have proposed a two-stage process whereby sensory information is initially transduced and analyzed within a large-capacity system and subsequently selected for further analysis within a limited-capacity system (Broadbent, 1958; Triesman, 1960; Naatanen, 1988). It is generally thought that information entering the limited-capacity system is gated into consciousness and that attention is the mechanism that selects which information passes through to this system for further processing (Linsay & Norman, 1977).

A majority of sensory information enters into awareness through two attentional mechanisms (Egeth & Yantis, 1997; Shiffrin, 2002). One mechanism is the result of purposeful selection of information that has entered into the large-capacity system. To this extent, selection can occur to any modality and can be divided either between or even within modalities (Allport & Reynolds, 1972; Parasuraman & Davies, 1984). Attention is often biased to select information related to specific goals. The ability to purposefully select streams of sensory input based upon current or future goals is commonly referred to as top-down attentional bias (Posner et al., 1980; Corbetta & Shulman, 2002). However, due to capacity limitations within the top-down system, a second attentional mechanism ushers information into awareness as a function of sensory salience. This bottom-up process is triggered by the appearance of a potentially important stimulus event occurring outside of the attentional focus such as a twig snapping in a silent forest. These novel stimulus events can automatically draw attention away from a current focus and redistribute attentional resources to the new event (Knight, 1984; Knight & Nakada, 1998; Escera et al., 1998). The novel stimulus appears as a 'deviant' relative to the input a moment prior within that sensory channel (Polich, 2003). The detection of deviants can also occur as a function of top-down selection. That is, attention can be intentionally allocated to one modality in order to detect an anticipated deviant event. For example, we can selectively focus our attention to the acoustic environment in anticipation of a beeping oven timer in order to prevent food from burning.

Distinct neocortical regions that support bottom-up and top-down attention mechanisms have been identified through various neursopsychological, electrophysiological and neuroimaging studies. These techniques have revealed extensive interconnected and distributed networks throughout the frontal and parietal lobes that in part determine which environmental stimuli are gated into awareness and which information is disregarded as background noise (for reviews see Egeth & Yantis, 1997; Mesulam, 1998, 1999; Mausell & Cook, 2002; Corbetta & Shulman, 2002; Swick & Knight, 2000).

The aim of this dissertation project was to characterize the neural architecture and behavioral parameters of bottom-up and top-down attentional systems in individuals blinded early in life (i.e. prior to the second year of life). A number of functional imaging studies have revealed that occipital (Occ) cortical regions in early blind (EB) individuals are active during a number of auditory and tactile-based cognitive tasks (see Kujala et al., 2000; Burton, 2003; Theoret et al., 2004). These experiments suggest that Occ regions in the EB are reorganized to perform other, non-visual functions, a phenomenon referred to as cross-modal reorganization. However, the precise function of Occ activity remains controversial and the developmental factors that are important for the establishment of Occ reorganization have not been identified. In addition, numerous behavioral studies have demonstrated that EB results in heightened non-visual behaviors (Bavelier & Neville, 2002; Roder & Rosler, 2004). A second question not well understood is the extent to which behavioral advantages observed in the EB are a consequence of Occ reorganization.

Therefore, I sought to assess the effects of EB on the neural and behavioral processes underlying deviance detection in auditory and tactile modalities as a means to identify the functional operations tied to Occ cortex. The experiments presented here were designed to address several issues related to the effects of EB. The first was to determine whether Occ regions participate in top-down and/or bottom-up (or both) mechanisms of attention. The second goal was to determine whether EB relative to SC individuals develop a greater sensitivity to detect sensory deviance within auditory and tactile domains. Finally, if Occ activity is reflective of attention-based mechanisms, whether Occ activity is associated with a greater sensitivity to the detection sensory deviance in the EB. Identifying the sensory or cognitive factors that activate Occ cortical regions in the EB will provide insight to the functions that drive the establishment of cross-modal reorganization. Furthermore, a reorganization of the neural architecture that supports attention in the EB may serve as a mechanism for a broad range of compensatory behavioral advantages that develop as a result of early visual loss.

Behavioral Adaptations as a result of Early Blindness

Blind individuals must become more reliant on auditory and tactile modalities in order to detect novel stimuli. Anecdotally, it is commonly held that the blind develop enhanced perceptual abilities within spared modalities, an effect likely due to the over-reliance on non-visual modalities (Diederot, 1798 cited in Morgan, 1999; Pascual-leone & Hamiliton, 2001). However, only just recently has empirical support addressing this question begun to gain significant momentum. A variety of behavioral studies have suggested that blindness alone does not result in heightened sensitivity to either auditory or tactile stimulation (although this hypothesis is controversial, see Roder et al., 2003). Rather, compensatory adaptations typically appear when visual loss occurs prior to the closure of critical developmental windows for visual maturity (Rice et al., 1969; Gougouex et al., 2004; Bavelier & Neville, 2002). Moreover, behavioral advantages in the EB rarely develop at lower-tiers of sensory processing such as frequency or intensity discrimination (Weaver & Stevens, 2006; Collingnon et al., 2006; Niemeyer & Starlinger, 1981; Yates et al., 1972; but see Goldreich et al., 2003 & Pasual-loene & Hamilton, 2001) but come to surface on tasks requiring complex discriminations or higher-level cognitive manipulation such as tests of language, memory or attention (Collingnon et al., 2006; Stevens & Weaver, 2005; Hugdahl et al., 2004; Amedi et al., 2003; Roder et al., 2003). For example, Yates et al., (1972) adjusted the volume of pure tones presented to EB and SC listeners in order to compare amplitude (i.e. hearing) thresholds between groups. The authors found no statistical differences between the groups, suggesting that the intensity required to perceive a pure tone was not augmented as a result of early blindness. In contrast, on a task requiring subjects to store and hold a pure tone in working memory to complete a same-difference judgment, the EB were significantly more accurate at long inter-stimulus intervals (5000 msecs.) than sighted counterparts (Stevens, AA, unpublished observations). Together these two studies suggest that the loss of sight early in development does not alter auditory perception per se, but rather improves the ability to manipulate or perform mental operations with auditory stimuli (Theoret et al., 2004). A substantial number of studies have been published that support this speculation. EB individuals, relative to SC peers, remember significantly more naturalistic-based sounds after a sizeable retention interval of several minutes (Roder et al., 2003) and are able to recognize significantly more words after a very long delay of six months (Amedi et al., 2003; Raz et al., 2005). The EB are also more accurate than SC individuals when judging the order of two stimuli presented nearly simultaneously (temporal order judgment tasks) suggesting enhanced temporal processing mechanisms (Stevens & Weaver, 2005; Gougouex et al., 2004; Roder & Rosler, 2004) and are more precise at locating sounds using only monaural cues (Lessard et al., 1998). Behavioral differences between EB and SC subjects on tests of cognition have been reported within the tactile domain as well. On a series of *n-back* working memory tasks where subjects had to remember and compare a raised, embossed letter with a letter that was presented either 3, 2, 1 or 0 letters back, EB subjects significantly outperformed (i.e. smaller number of incorrect responses) SC individuals at all intervals except for the 0 back condition (Bliss et al., 2004). Because the 0 back condition is a test of letter recognition, these group differences suggest working memory abilities are enhanced in the EB rather than a discrepancy in the encoding or recognition of embossed letters.

Recent research has also demonstrated that EB individuals are more efficient when dividing attentional resources between simultaneously presented auditory and tactile streams. Collignon et al., (2006) presented SC and EB subjects with combinations of a pure tone to either the left or right ear and a square wave tactile pulse to either the left or right middle finger. One of four pairs of stimuli (left ear-left finger, left ear-right finger, etc.) were presented on any given trial. Subjects made a verbal response when a tone was presented to the right ear and the vibratory pulse was presented to the left hand, while remaining silent to all other combinations. The EB group proved to be significantly more accurate and responded faster to target combinations than their age matched sighted counterparts. These performance differences cannot be explained by a heightened sensitivity to acoustic or vibrotactile stimulation in the EB because individual intensity discrimination differences were adjusted for both auditory and tactile stimuli. Therefore, the authors proposed that these discrepancies are a result of an enhanced "role of attention" when subjects elicit a response on the basis of modality and spatial information. Superior detection abilities during a dichotic recognition study presenting verbal constants (Hugdahl et al., 2004) supports this hypothesis and raises the possibility that behavioral advantages reported in the EB may be the result of greater than normal attentional mechanisms aiding in a number of cognitive and perceptual realms. For instance, the EB are better than the SC at suppressing distracting or unwanted information (Hotting et al., 2004; Roder et al., 2004). Distracter suppression advantages could result in reduced proactive interference effects on information stored within working memory yielding greater recall accuracy (Keppel & Underwood, 1962; Conway & Engle, 1994; Cowan et al., 2005).

Provided the EB develop compensatory behavioral advantages relative to SC subjects, what are the neural mechanisms supporting these adaptations? One line of research suggests that the occipital (Occ) or visual cortex is recruited for non-visual operations providing additional processing of auditory and tactile information (Amedi et al., 2003; Theoret al., 2005).

Functional Reorganization in the EB

The Occ cortex in adult EB individuals retains high levels of metabolic activity despite a lack of visual stimulation (Wanet-Delfaque et al., 1988). This activity is likely not a result of some epiphenomenon or non-neuronal activity but rather a consequence of non-visual, neural-derived electrophysiological activity (see Pascual-leone & Hamilton, 2001 for a review). Evidence for this claim stems from the observations that neurological lesions and transient deactivations induced by repetitive transcranial magnetic stimulation (rTMS) within the Occ lobe results in a variety of behavioral changes including deficits in Braille reading (Hamilton et al., 2000; Cohen et al., 1997) and the generation of verbs (Amedi et al., 2004).

Consequently, a variety of functional neuroimaging techniques including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have been used to identify sensory, cognitive and/or behavioral functions subserved by 'traditional' visual regions in the EB. Sadato and colleagues (1996, 1998) demonstrated that regions throughout the Occ cortex including striate cortex (corresponding to primary visual cortex, V1 in the SC brain) and a variety of extrastriate regions had significantly greater hemodynamic activity during Braille reading relative to control tasks. Braille evoked responses have also been observed within an inferior Occ region (Broadman's area 37) corresponding to the fusiform gyrus (Buchel et al., 1998). Similar patterns of Occ activations in the EB were reported during a Braille verb generation task (Burton et al., 2002). When EB subjects were required to covertly generate a verb in response to reading a noun during fMRI scanning, significant increases in neural activity occurred within V1, lingual and fusiform gyri and within the cuneus, activity that was not observed in the SC. Because activity within these regions was not observed during the passive feeling of nonlexical Braille strings, the authors concluded that the Occ cortex in EB individuals works to transform tactile stimuli into a neural code that can be utilized by traditional linguistic networks (Burton et al., 2002). Subsequent studies demonstrated significant Occ activity in the EB but not SC during a variety of auditory language tasks, including aural verb generation. These combined results led to a modified hypothesis that Occ circuits support linguistic operations independent of modality (Roder et al., 2002; Burton et al., 2002, 2003; Burton, 2003). However, contrary to this hypothesis numerous other studies have linked Occ activity to nonverbal auditory behaviors such as sound source localization (Weeks et al., 2000; Gougouex et al., 2005), mental imagery (DeVolder et al., 2002), auditory motion discrimination (Poirier et al., 2006) and tactile functions such as discriminating between vibrotactile stimuli (Burton et al., 2004). Furthermore, the passive perception of nonvisual stimuli does not engage Occ regions. For example, no Occ activity in the EB was observed during passive electromagnetic stimulation of the median nerve (Gizweski et al., 2003) or when EB subjects passively swept their fingers over raised dots (Sadato et al., 1998). Collectively, this evidence demonstrates a clear distinction for Occ involvement in tasks that require the active manipulation of information from tasks that simply tap into sensory and/or perceptual functions (Roder & Rosler, 2004). This hypothesis does not however clarify whether a distinct function(s) is localized to a given region (striate or extrastriate) within the Occ cortex of the EB.

Characterization of the patterns of connectivity between Occ cortex and other brain regions in the EB may help elucidate the issue of functional specificity (Bavelier & Neville, 2002). Specifically, identifying regions that project to the Occ cortex in the EB would establish the origins of information flow into the Occ cortex. For instance, neurons within primary visual cortex (calcarine sulcus) in the SC brain function predominantly within the visual sensory pathway because they receive cortically-naïve light information directly from the lateral geniculate nucleus of the thalamus (Van Essen et al., 1992; Zeki, 1993). In EB individuals, only one study to date has directly investigated patterns of Occ connectivity (Shimony et al., 2006). These authors, studying the EB, utilized a relatively new MRI based technique, diffusion tensor imaging (DTI) and a statistical analysis tool, diffusion tensor tractography (DTT) to examine the integrity and connectivity of white matter tracts known to innervate Occ regions in SC populations. The combination of these techniques revealed abnormal (degraded) thalamocortical white matter tracts in the EB relative to matched SC participants. Corticocortical white matter tracts between Occ and temporal and Occ and frontal regions were similar between the groups, suggesting relative sparring of these fibers. It was reasoned that thalamocortical tracts degrade from a lack of activity-dependent support (i.e. see Katz & Shatz, 1996; Fox, 1992; Grossman et al., 2002), and hypothesized that corticocortical, axons originating from non-Occ cortical loci (i.e feedback projections in the SC brain) provide the primary source of afferent activation into Occ regions (Shimony et al., 2006; Wittenberg et al., 2004).

Because DTI does not delineate between afferent and efferent fibers (Ramnani et al., 2004), the cortical regions that project to Occ regions in the EB have not been specifically identified in either blind humans or animals. In SC individuals however, extensive afferent projections develop between regions throughout the brain and the Occ lobe (Ungerleider et al., 1994). For example, corticocortical innervations into Occ cortex have been found to originate from non-visual sensory cortical regions such as primary auditory cortex (Falchier et al., 2002), auditory association areas (Rockland & Ojima, 2003), and multimodal association cortex (Jones & Powell, 1970). Additionally, anterograde tract-tracing studies in non-human primates have revealed a large number of connections from frontal and parietal regions involved in top-down attention into striate and extrastriate regions of the Occ lobe (Cavada & Goldman-Rakic, 1989; Anderson et al., 1990; Rockland & Ojima, 2003; Kastner & Ungerlieder, 2000). Electrophysiological evidence and functional neuroimaging evidence has demonstrated that these feedback connections into Occ cortex serve to potentiate signals stimulated by attended objects (for a review see Kastner & Ungerlieder, 2001; Moran & Desimone, 1985). It is likely that these connections are maintained in the EB brain because activation is not a sole function of visual stimulation (Zangaladze et al., 1999; Molholm et al., 2001; Amedi et al., 2001; Watkins et al., 2006; Hofinger et al., 2000), (Pascual-leone & Hamilton, 2001). Activation of the Occ lobe in the EB may thus be a result of one of three possible alternatives (assuming thalamocortical connections are non-functional; Bavelier & Neville, 2002). First, signals from innervating corticocortical projections from sensory or association cortex may drive activity within Occ regions. Second, metabolic responses are a result of feedfoward activity originating from Occ neurons. Third, activity originates in other regions that feed into Occ cortex (i.e. the pulvinar nucleus of the thalamus).

The hypothesis that neural signals originate within Occ regions raises the possibility that activity within these regions reflects modality-independent, top-down control over attention. Such a hypothesis could account for the diversity of tasks and stimuli that engage Occ regions in the EB (Roder et al., 1996; Roder & Rosler, 2004) because attention is a critical component to tasks that examine information processing (Spitzer et al., 1988; Posner, 2005). However, no experiment to date has specifically manipulated attention during functional neuroimaging in the EB. To test this hypothesis, functional imaging techniques would have to be combined with a task that requires discrimination of stimuli of different modalities while manipulating selective attention. One such task is the oddball, target detection task (See Polich, 2003).

The Oddball Detection Task

The detection of infrequent or rare sensory events was first used experimentally by Sutton and colleagues in 1965 (latter to be referred to as the oddball or target detection task). Oddball tasks have now become one of the most widely utilized experimental paradigms within the study of cognition and the neural processes supporting cognition (For example, see Polich, 2003; Dochin et al., 1986). Two versions of the oddball tasks are commonly employed. Both versions involve a basic design that presents a train of stimuli separated by a specific inter-stimulus interval (ISI). The majority (typically >

80%) of stimuli are identical and referred to as standard stimuli. In the 2-stimulus version, the other trials consist of presenting a second, target stimulus that deviates along some physical parameter from the standard (e.g. pitch or color). Because targets are presented less frequently than standards, they appear as a deviant stimulus within the stimulus train. Often, participants are asked to respond to the target stimulus (therefore are behaviorally-relevant). In this case, subjects are made aware of the identity of the target stimulus and its relationship to the standard prior to the start of the task. Detection of a target then becomes a function of top-down, goal-directed processing relying on contributions from selective attention systems, working memory stores and template matching (Stevens et al., 2000; Polich, 2003). The second version of the oddball design is the 3-stimulus paradigm (Courchesne et al., 1975). This design presents an infrequent ‘distracter’ deviant in addition to standard and target stimuli. Distracters are typically more salient than target stimuli. The subject’s goal however is to detect target stimuli. Thus, when a distracter is presented it tends to capture subject’s attention, temporarily redirecting it away from the primary task of selecting for the target stimuli (Knight, 1984; Escera et al., 2002, 2003). The 3-stimulus design therefore provides a distinct advantage over the 2-stimulus alternative as it allows researchers to examine top-down and bottom-up attentional mechanisms within the same task.

The Neural Basis of Deviant Detection

Initial oddball studies used scalp EEG to identify a number of event-related potentials (ERPs) that are evoked by the presentation of deviant events but not to the presentation of standard stimuli. Researchers typically match the sequence of perceptual and cognitive processes linked to target detection (top-down) or distracter (bottom-up) processing with their evoked time-locked deflections. However, an inherent obstacle in EEG research is a relatively poor spatial resolution. This drawback arises when the source of a given signal is blurred by additional and simultaneous activity occurring above or below the desired signal.

The ability to locate the origins of neural signals throughout the human brain has dramatically improved with the advent of high-resolution neuroimaging techniques such as fMRI or PET. Functional MRI is particularly well suited to this endeavor as it allows a non-invasive examination of whole brain activity and provides high-resolution, detailed anatomical pictures onto which functional activity can be mapped. fMRI indirectly measures neural signals (i.e. local field potentials) through sensitivity to magnetic field fluctuations that arise from the decoupling of oxygen molecules and iron particles located within hemoglobin. These fluctuations are modulated by a hemodynamic response that is linked to neural activity (Logothetis et al., 2001; Logothetis, 2003; Tanako et al., 2006). Neurally-coupled vasculature and hemodynamic changes have been termed the blood oxygen level dependency (BOLD) signal (see Logothetis, 2002).

INSERT CHAPTER 1, FIGURE 1 ABOUT HERE

A number of researchers have identified the sources or neural generators of various deviant-evoked ERPs using fMRI and other imaging techniques. These efforts have led to the identification of two distinct but distributed neural systems that gate stimuli into awareness (Conner et al., 2004; Corbetta & Shulman, 2002; Shulman et al., 2004). These networks, which have been dissociated using top-down and bottom-up behavioral tasks (see chapter 1, fig. 1), are composed of a variety of regions throughout the neocortex. Investigators typically attempt to match specific functions associated with deviance detection to regions showing a response to a deviant. However, this is not to argue that brain regions active during target and distracter processing are functionally isolated, independent of the rest of the brain. Rather we interpret a response within a region as reflecting activity as part of a network of regions acting in near concert to accomplish a desired goal. As information flows through these neural networks, different regions contribute some facet of sensory, perceptual and cognitive function. It is the coordination between these regions that allows the completion of a task (Posner et al., 1988; Meslum, 2002).

Initial fMRI studies using 2-stimulus auditory or visual oddball tasks localized BOLD signals throughout the inferior parietal lobule (IPL) including the supramarginal gyrus (SMG) and temporal parietal junction (TPJ) and a small number of activations within the frontal lobe including the middle frontal gyrus (MFG) and the anterior cingulate (ACC) (Menon et al., 1997; McCarthy et al., 1997). These studies were limited by a lack of whole brain coverage. Subsequent studies sampling from the whole brain have identified a larger network of regions activated by auditory or visual target stimuli but not by the repeated standard stimuli. These include the superior parietal lobule (SPL) and the precuneus within the parietal lobe and the superior frontal gyrus (SFG), inferior frontal gyrus and insular within the frontal lobe (Linden et al., 1999; Stevens et al., 2000; Kiehl et al., 2001). Based on attentional cueing studies, it has been reasoned that activity within the superior parietal lobule and superior frontal gyrus reflects top-down control signals (Hopfinger et al., 2000; Corbetta et al 2000; Miller & D'Esposito, 2005). Evoked activity within the middle frontal gyrus including areas falling within the dorsal lateral prefrontal cortex have been implicated in working memory operations in a number of visual paradigms (Braver et al., 1997, Awh et al., 1996; D'esposito et al., 2000) and has consequently been hypothesized to reflect the working memory component necessary for target detection (Stevens et al., 2000). Dorsally localized frontoparietal BOLD activity is assumed to reflect operations underlying central processes essential to target detection because these responses are not affected by modality of stimulation or response demands (Downar et al., 2000, 2001, 2002; Stevens et al., 2000; Yoshiura et al., 1999; Linden et al., 1999). In addition a number of subcortical regions play a role in detection of target stimuli including the thalamus, medial temporal lobe structures such as the hippocampus and striatal loci such as the caudate (Opitz, 2003).

The presentation of distracter stimuli also activate regions throughout the frontoparietal attentional network. However, this activity is typically observed within more inferior or ventral regions and is generally restricted to the right hemisphere (Kiehl et al., 2001, Bledlowski et al., 2004; Stevens et al., 2005). In nearly all fMRI studies using a 3-stimulus design, BOLD responses were linked to the presentation of either auditory or visual distracter stimuli in the SMG/TPJ and the IFG regions despite the absence of any explicit response (Kiehl et al., 2001, 2005; Clark et al., 2000; Bledlowski et al., 2004). These findings suggest that ventral IPL regions such as the SMG/IPL and the IFG do not exclusively support top-down functions. Some researchers have reasoned that the SMG/TPJ areas function in bottom-up stimulus detection and explain target-related activity as simply activation of the same bottom-up cortical mechanisms to any stimulus that deviates from a repetitive stimulus (Menon et al., 1997; Downar et al., 2000). Ventral frontal regions including the IFG have been shown to be involved in a variety of cognitive functions including semantic processing and response inhibition (Konishi et al., 1998, 1999; Aron et al., 2004). The bottom-up activation of these regions is generally considered to reflect the evaluation of stimulus deviance and the reallocation of attention to the distracter (Corbetta & Shulman, 2002).

The combined, systems level model of deviance detection suggests a regional dissociation of networks supporting bottom-up and top-down mechanisms of attention in the normal brain (see *chapter 1, fig. 1*; Corbetta & Shulman, 2002; Shulman et al., 2004; Serences et al., 2006). During target detection tasks, sensory stimuli are first routed through modality-specific sensory cortex (e.g. auditory signals within temporal cortex, tactile signals through somatosensory parietal cortex, etc). When a deviant is encountered, an electrophysiological signal is evoked that is different than the signal engendered by the repeated standard. This difference in signal results in an exogenous mismatch of neural activity (referred to as the mismatch negativity, MMN) that develops within sensory association cortices (Naatanen, 1990, 1992; Jaaskelainen et al, 2004). If attention is focused on a given stimulus train expected to contain a deviant, top-down projections from superior frontal and parietal regions feeding into these sensory cortical regions amplify signals within that modality (Peossa et al., 2005). This amplification process facilitates additional processing of the stimuli (for example, related to working memory processes) necessary for accurate target detection (Woldorff et al., 1991; Sussman et al., 2003). When an unattended deviant is encountered, the MMN response activates ventrally located frontal and parietal regions. This ventral network then acts as a circuit-breaker, interrupting activity within the dorsal network and redirecting the focus of attention to the unattended deviant (Corbetta Shulman, 2002).

Change Detection in the Early Blind

Electrophysiological Studies

A number of ERP studies have used oddball tasks to examine the effects of early blindness on the neural basis of target detection (see Kujala et al., 2000 for a review). Auditory deviance detection studies have reported that the sensory-based N1 potential and MMN do not show any spatially distributed reorganization in the EB (Kujala et al., 1995b; Liotti et al., 1998). This suggests that the auditory sensory/perceptual functions underlying target processing do not show reorganization into new cortical territory (at least under the spatial resolution provided by EEG). In contrast, the most commonly reported observation in the EB is a more posteriorly distributed P300 (typically located over Occ leads) in response to a target relative to SC individuals. The P300 potential reflects a number of mental operations related to deviance processing including the on-line maintenance of stimuli, focused attention, working memory mechanisms and context updating (Kok, 2003; Polich, 2003). This ERP redistribution in the EB has been reported in response to a wide variety of targets including spatially disparate sounds (Kujala et al., 1992;), deviant frequencies (Alho et al., 1993; Kujala et al., 1995b,1997a) and spatially segregated vibrations (Kujala et al., 1995a). Insensitivity to the physical properties of targets is a trademark of the P300 in SC populations and suggests that the functions represented by the reorganized P300 in the EB are likely analogous to those reflected in P300 of sighted subjects. Rather, P300 topography differences imply a reorganization or expansion of the various top-down functions that evoke the P300.

In addition, a few ERP studies in the EB have tested the effects of selective attention using a dichotic target detection task. For example, after controlling for intensity discrimination differences, Liotti et al., (1998) had EB and SC subjects selectively attend to dichotically presented deviants in one ear or the other. Posteriorly distributed P300 in the EB developed to targets presented within attended ears but not to targets presented in the unattended ear. These results in addition to similar findings during attentional shifts between auditory and tactile modalities have led to hypothesis that the selective attention to a sensory stream is a prerequisite for the activation of the Occ circuits (Kujala et al., 1995a,b; Roder et al., 1996; Liotti et al., 1998).

The summed results from ERP studies in the EB using oddball tasks indicate that the neural basis of auditory and tactile target detection is altered in the EB. However, an accurate characterization of the neural circuits in the EB supporting the detection of target stimuli requires the spatial resolution afforded by hemodynamic-based techniques.

Hemodynamic-Based Studies

Only one study to date has combined fMRI and target detection tasks (Kujala et al., 2005). In this study, five EB and five SC individuals detected target vowel or tone stimuli in a block design format. Blocks of standard stimuli containing one target stimulus were compared to blocks of only standard stimuli. The block containing the target activated a variety of Occ regions relative to blocks of standards. The authors also report that the block of standards containing a target tone elicited a greater BOLD response within a number of Occ regions in four out the five subjects than the block of standards containing a target vowel. The authors interpreted these results as an expanded network in the EB used to "process sound changes within an attended stimulus stream"

(Kujala et al., 2005). Interpretations of these data are restricted however by the low number of subjects used and limited statistical power inherent to block designs (Rosen et al., 1998).

In this dissertation, the neural networks supporting top-down and bottom-up attention were examined in a group of nine EB and nine matched SC individuals. Event-related functional MRI was combined with 3-stimulus auditory and tactile oddball tasks. Prior to scanning, auditory and tactile discrimination thresholds were determined. Thresholds were then used to adjust oddball stimuli in order to prevent differences in sensory sensitivity between groups from confounding the attentional demands of the task. Four scans were run for each subject. In the first two scans, patterns of BOLD responses were measured throughout the brain in response to target and distracter stimuli presented in either auditory or tactile domains alone (i.e. unimodal conditions). In the third and forth scans, subjects were presented with the same oddball task but both modalities were presented simultaneously (bimodal conditions). Participants were asked to attend to only one modality at a time and cued to switch attention between modalities every thirty trials. This design allowed for the examination of BOLD responses to target stimuli that were selectively attended and ignored.

Robust responses within the Occ lobe were detected but only in EB participants. In chapter 2, I detail the patterns of activity limited to the Occ cortex in the group of EB and SC individuals in response to auditory and tactile target detection and distracter processing. I also describe target detection performance that was observed within each group. In chapter 3, I report the cortical regions responding to auditory and tactile targets and distracters throughout the brain in the SC. Finally, in the discussion, the functional neuroanatomical similarities and differences between the groups are examined. In addition, I discuss compensatory changes in target detection behaviors and plastic neural alterations (and their possible relationship) that develop as a consequence of early visual deprivation.

Chapter 2: Attention and Sensory Interactions Within The Occipital Cortex in the Early Blind: an fMRI Study

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Abstract

Visual deprivation early in life results in occipital cortical responsiveness across a broad range of perceptual and cognitive tasks. In the reorganized occipital areas of EB subjects, 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 if occipital cortical areas in EB were responsive to stimuli across sensory modalities (auditory, tactile) and if these areas maintained or altered their activity as a function of selective attention. Using a 3-stimulus oddball paradigm and event-related fMRI, auditory and tactile tasks presented separately demonstrated that several occipital regions of interest in the EB, but not sighted controls (SC) responded to targets and task-irrelevant distracter stimuli of both modalities. When auditory and tactile stimuli were presented simultaneously with subjects alternating attention to the auditory and tactile 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 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 visual cortex in 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 et al., 2000). Early onset blindness (EB) leads to a reorganized occipital lobe which responds to a variety of stimuli and cognitive tasks (Röder & Rosler, 2004; Bavelier & Neville, 2002). For instance, functional MRI and PET studies have demonstrated that different occipital areas in EB subjects respond during vibrotactile discrimination (Burton et al., 2004), sound source localization (Weeks et al., 2000; Gougoux et al., 2005), auditory mental imagery tasks (DeVolder 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 Occ involvement particularly within the calcarine sulcus (Sadato et al., 1996, 1998; Buchel et al., 1998; Melzer et al., 2001; Röder et al., 2002; Burton et al., 2002; 2003; Amedi et al., 2003). Under normal conditions of visual development, projections from auditory and tactile areas are either substantially reduced or silenced through competition with visual afferents. Several researchers have hypothesized that the EB, these synaptic connections are sustained (Huttenlocker, 2002; Bavelier & Neville, 2002) or unmasked (Pascual-Leone and Hamilton, 2001) due to the lack of visual stimulation and lead to reorganization by auditory and tactile afferents. While studies in sighted animals have clearly established the presence of long range cortico-cortical connections between early sensory cortices (Flaicher et al., 2002; Clavagnier et al., 2004; Rockland & Ojima, 2003; Schroeder and Foxe, 2005), most evidence suggests that in cases of visual deprivation the relative responsiveness of visual cortical areas to other sensory modalities is dramatically increased (Hyvarinen et al. 1981; Rauschecker, 1995; Rauschecker & Korte, 1993).

Furthermore, it is likely that non-sensory 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 (Hyvarinen et al., 1981; Huttenlocker, 2002; Pascual-Leone and Hamilton, 2001). This is suggested in part by recent studies showing limited changes in the white matter tracts originating in primary visual cortex of EB subjects relative to sighted controls (SC) using diffusion tensor imaging (Shimony et al., 2005) as well as the heterogeneity of tasks and stimuli that engage occipital areas in EB. It is probable that the visual cortical areas in the 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 Occ activation in the EB represents a posterior shift in the cortical networks that support top-down attentional behaviors (See Kujala et al., 2000, for a review). In EB individuals, auditory or tactile target stimuli presented in a stream of similar non-target "standards" elicited patterns of N2-P3 potentials at Occ leads but targets presented in unattended channels did not (Alho et al., 1993; Kujala et al., 1992, 1995a,b, 1997a; Röder et al., 1996; Liotti et al., 1998). Recently, Hötting and colleagues (2004) observed that EB and sighted control (SC) subjects showed complex differences in evoked potentials under conditions of auditory and tactile cross-modal spatial attention. Most notably, the SC showed stronger influences of attended spatial location on both early and late ERPs, while 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 based on modality while SC 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. While 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 BOLD activity throughout Occ regions in EB and SC individuals to auditory and tactile stimuli in an oddball design, with standard stimuli intermixed with rare targets and a third, irrelevant distracter stimulus (Polich, 2003). Behavioral and neuroimaging studies using a 3-stimulus oddball design have identified two distinct modality-independent attentional systems that gate deviant stimuli into awareness (Kiehl et al., 2001, 2005; Bledlowski et al., 2004, for a review see Halgren et al., 1998; Corbetta & Shulman, 2002). One, the selection of a specific target stimulus embedded within a stream of similar non-target standards reflects a top-down system that functions to direct and sustain attention to a specific change within a sensory domain. And two, a second system that works to reorient attention via bottom-up mechanisms to deviant stimuli that are highly salient (Knight, 1984; Escera et a., 2002).

To engage these attentional systems, standard stimuli were designed to be perceptually similar to the infrequent target stimuli (accomplished by adjusting the frequency of the standard based on 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 a counterbalanced design and asked to press a button to the presentation of the target stimulus and a different button in response to the standards and distracters. In the 3rd and 4th 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).

This design allowed us to address two outstanding issues with regard to the reorganization of Occ cortex in the EB. We first wanted to address whether Occ activity in the EB associated with the top-down functions critical to target detection, or rather reflects the bottom-up orienting of attention triggered by distracter stimuli. It has been reasoned that regions responding to targets of different modalities reflect operations tied to top-down attentional functions associated with target detection rather than distinct perceptual functions (Downar et al., 2000, 2002; Stevens et al., 2001). Alternatively, Occ regions activated by distracter stimuli from different modalities indicates a function linked to bottom-up attentional orienting (Comerchero & Polich, 1998). Second, we wanted to investigate the influence of selective attention on the responses to auditory and tactile stimuli in the occipital areas of EB. Based on prior ERP observations (See Kujala et al., 2000 for a review), we predicted that various Occ ROIs would respond to attended targets but show little to no BOLD activity to the same stimuli that were ignored.

- INSERT FIGURE 1 ABOUT HERE –

Materials and Methods

Subjects

Nine sighted control (6 female, mean number of years education, 18.11 ± .84 s.e.) and twelve early blind (5 female, mean number of years of education, 17.78 ± 1.05 s.e.) 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, 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 (RLF) 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 five years. The mean age for the EB group was 50.78 (range 36 to 59) and 49.63 (range of 27 to 60) years for the SC group. Subjects 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, 1 left handed and 5 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 Oregon Health & Science University.

Stimuli

All stimuli (tactile and acoustic) were 200 ms sinusoidal waveforms (with a rise/fall time of 10 ms for acoustic stimuli). Stimuli were created using Adobe Audition software (Adobe Systems Incorporated, 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 Inc., Milwaukie, WI) fashioned into sound-attenuating ear defenders (Howard Leight Inc., San Deigo, CA). Vibrotactile stimuli were produced by a non-magnetic, ceramic piezoelectric bending element (i.e. benders; Q220-A4-303YB Quick Mount Bender, Piezo Systems, Inc., Cambridge, MA - http://www.piezo.com) placed directly under the index finger of the left hand. The monaural and monotactile presentations were used to simplify the study design. 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's. Initial pilot testing suggested that at these amplitudes, subjects reported similar perceived intensities (equal salience) for all acoustic and tactile stimuli. The frequency of the standard, non-target stimuli for both auditory and tactile modalities was determined prior to scanning for each subject based on 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 Inc, 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 2 down 1 up rule yielding estimates of thresholds for 70% accuracy (Levitt, 1970). On each trial, subjects heard or felt two stimuli, each 200 ms in length (with a 10 ms rise/fall time for acoustic stimuli) and separated by 2000 ms. 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 based on 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 (using 1 or 2X ΔF resulted in poor performance on the tasks in the scanner during pilot testing). The tactile standard was created by doubling ΔF and adding it to the tactile target value.

Experimental Design and Imaging Paradigm

The oddball task was a three-stimulus design that presented a rare target, a rare non-target (distracter) and repeated non-target (standard) stimuli in a serial fashion with a constant inter-trial interval (ITI) of 2250 ms. 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 planer imaging (EPI) scans: one each for the tactile and auditory alone conditions and 2 for the simultaneous conditions. Each scan consisted of 180 trials. In scans 1 & 2, tones (aud alone) and vibrations (tac alone) were presented alone. The order of the aud alone and tac alone scans were counter-balanced across subjects. Two scans consisted of the simultaneous presentation of auditory and tactile stimuli (simultaneous scans). A verbal cue instructed subjects to "switch" attention between modalities every 30 acquisitions (creating 6 "attend-to" auditory blocks and 6 "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.

MR imaging was conducted on a 3.0 Tesla Siemens Trio magnet using a 2 channel, RF transceiver head coil. The gradient-echo EPI scanning parameters consisted of: TR = 2250, TE = 35 and a flip angle of 85°. The field of view (FOV) was set at 240 x 240 mm using a 64 x 64 matrix. Functional slices were acquired using a clustered volume technique (Edmister et al., 1999) in which all slices within a volume were collected in approximately the first 1/2 (or 1150 ms) of the TR. This technique allowed us to present stimuli during a period of silence to reduce interference from scanner noise. Each functional volume consisted of 20 axial slices (5 mm thick with 1 mm inter-slice gap) providing whole brain coverage. A navigator echo was inserted within each functional scan in order to prospectively correct for motion artifacts. Stimulus presentation began after the 2nd 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 non-target frequencies. Additionally, standards were purposefully presented on the first ten 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 simultaneous 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 the functional scans, SC individuals were asked to keep 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 corrected, linear-trends removed and a high-pass filter of 3 cycles/scan was applied reduce the effects of scanner drift. All scans were then interpolated into 1x1x1 mm^3 isovoxels, and raw signal values were z-normalized and transformed into standardized Talairach stereotaxic space (Talairach & Tourneaux, 1988). Time courses for each functional run were then analyzed and statistical parametric z-maps were created using a general linear model. For scans 1 and 2 (alone 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 et al., 1996). Stimulus predictors from scans 3 and 4 (simultaneous scans averaged together) included targets and distracters in the attend 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 $p < 0.01$, uncorrected. In addition, a cluster filter correction was employed to reduce false positives, type I error (Forman et al., 1995). This correction was used to adjust the *P* value to 0.05, insuring the likelihood of 5% or less false positives within a minimum cluster size of 200 contiguous voxels.

Because patterns of activation throughout the Occ lobe were of interest, an anatomically restricted mask was created and applied to the group averaged contrast maps shown in figure 2 in order to limit the number of voxel-by-voxel multiple comparisons. The map included all functional voxels posterior to the central sulcus.

Region of interest analysis

Regions of interest (ROI) within the Occ lobe were identified by selecting voxels that responded to both auditory and tactile alone scan conditions and surviving a cluster filter threshold. Voxel selection was guided by overlaying the normalized group-averaged auditory and tactile alone z-maps and choosing only those that overlapped between modalities. All polymodal regions were identified and selected. Here we report four targeted regions based on *a priori* selection criteria (i.e. consistently showing acoustic or tactile modulation, see Röder et al., 2002; Burton et al., 2003, 2004; Weeks et al., 2000; Buchel et al., 1998). The four selected regions included a site along the calcarine sulcus (Brodmann's Area, BA17) corresponding anatomically to primary visual cortex in the SC brain, a region within the cunues (BA18), the fusiform gyrus (BA37) and a spot within the lingual sulcus (BA19). Anatomical location of the Occ ROIs was confirmed through use of published human brain atlases (Mai et al., 1997; Damasio, 2005) 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 3 TRs preceding that event. ROIs in auditory and tactile control regions were localized based upon published Talairach coordinates (Hall et al., 2000; Wessinger et al., 2001; Stippich et al., 2005) and human brain atlases (Mai et al., 1997; Damasio, 2005).

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 ± .86 Hz. vs. 808.11 ± .73 Hz., respectively; student's t, $p = 0.98$) and tactile (73.44 ± 4.27 Hz. vs. 78.56 ± 3.62 Hz., respectively; student's t, $p = 0.37$) modalities.

Throughout all scanning conditions target detection accuracy was high, with both groups detecting greater than 80% of all targets (fig 1d). The EB were slightly more accurate than the SC in both modalities in the alone conditions (*aud alone*: 0.96 ± 0.02 s.e. vs 0.89 ± 0.02 s.e., respectively; *tac alone*: 0.96 ± 0.02 s.e. vs. 0.92 ± 0.01 s.e., respectively) and for the simultaneous presentations (*aud simult*: 0.94 ± 0.03 s.e. vs 0.93 ± 0.02 s.e., respectively; *tac simult*: 0.88 ± 0.02 s.e. vs. 0.82 ± 0.04 s.e., respectively). A repeated measures ANOVA of modality (aud, tac), presentation (alone, simultaneous) and group (EB, SC) detected a significant main effect of group [$F(1,16) = 6.732$, $p = 0.02$] and modality [$F(1, 16) = 5.028$, $p = 0.011$], and a trend in 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 using pairwise comparisons corrected for multiple comparisons ($p < 0.05$) revealed a significant difference in target detection between the groups only in the aud alone condition. No other interaction approached significance (all p's > 0.20).

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 = 0.159].

Comparisons of response times to target stimuli (fig. 1e) between groups, modalities and stimulus presentation produced no main effect of group [F(1,16) = .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 by presentation interaction [F(1,16) = 5.74, p = .03].

- INSERT FIGURE 2 ABOUT HERE -

Auditory and Tactile Alone Scans

Active regions within the Occ 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 general linear model (GLM) analysis. This approach uncovered stimulus-linked increases in BOLD signal in several regions of the Occ lobe of EB but no significant increases (or decreases) were detected in SC individuals (fig. 2). An overlay of the contrast maps for both modalities revealed several key points. First, a number of anatomically distinct regions in the Occ 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 left index finger resulted in significantly greater level of activation within the right hemisphere relative to the left (fig. 3a). While 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 Occ cortex (fig. 3b). In fact, approximately 65% of tactile responsive voxels also responded to auditory stimuli, suggesting that these cortical fields contain polymodal response properties.

- INSERT TABLE 1 ABOUT HERE -

Region of Interest (ROI) Analysis

In order to differentiate BOLD responses between auditory and tactile targets and distracters, regions of interest (ROI) within the Occ were identified that contained voxels active in both auditory alone and tactile alone scan conditions. Four ROIs within the right hemisphere were identified: a region within the calcarine sulcus, the cuneus, the fusiform gyrus and lingual gyrus (fig. 4). In order to analyze 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).

- INSERT FIGURE 3 ABOUT HERE –

When auditory stimuli were presented alone, peak BOLD responses for both the target and distracter stimulus were significantly greater ($p < 0.05$) than the corresponding baseline in the EB but not in the SC, with the response for the distracter greater than the response evoked by the target in all four ROIs. Vibrotactile stimuli produced similar effects in all Occ 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 non-significant 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 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 fusifrom and lingual ROIs, auditory responses to the target stimuli peaked on average 4.5 seconds after stimulus presentation, while tactile target responses peaked 6.75 seconds after stimulus onset. In the calcarine sulcus and cuneus, the latency to reach peak signal to auditory and tactile targets were similar occurring approximately 6.75 secs after stimulus presentation. Responses to the auditory distracter stimuli reached peak values on average 4.5 seconds after stimulus presentation in all ROIs except for the calcarine sulcus, while tactile distracter responses peaked at 9 seconds 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 2-

factor repeated-measures ANOVA for each Occ 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 Occ regions (specifically within the lingual gyrus) by auditory stimulation relative to tactile stimulation.

- INSERT FIGURE 4 ABOUT HERE -

Simultaneous Scans

Event Related Averages

When the same auditory and tactile stimuli were than presented simultaneously and subjects attended to either auditory or tactile streams of stimuli, hemodynamic responses were only detected in the modality to which subjects were attending (fig 5). Within all four sampled Occ ROIs, targets presented within the unattended channel did not evoke a response greater than their zero point. Furthermore, the observed negative peak response to the ignored auditory target within the calcarine sulcus (fig 5a) was significantly less (p = 0.02) 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 simultaneous scans extracted from the same four Occ 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. Significant distracter effects were observed in the calcarine sulcus and cuneus. In contrast, when subjects attended to tactile stimuli during the simultaneous auditory-tactile 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 Occ ROI. Finally, there were no significant target or distracter effects within the SC group in any Occ ROIs (fig. 6). However, in SC group the cuneus ROI was found to have a non-significant increase in BOLD signal to auditory and tactile distracter stimuli during the alone scans (fig. 4) but not during the simultaneous scans (fig 6). Analysis of individual subject event related averages revealed this effect was due to one SC individual.

Functional Control Regions

To determine whether the suppressed response to the attended tactile stimuli observed in the simultaneous scans reflected a global effect, we assessed event-related responses in auditory (superior temporal gyrus, STG), and tactile (post-central gyrus) sensory areas and the inferior frontal gyrus (IFG) which has commonly been associated with target detection (Stevens et al., 2000; Kiehl et al., 2001; Linden et al., 1999). Figure 7 illustrates the hemodynamic responses in S2 occurred only to attended tactile targets while responses in 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 change in activity. These results substantiate that the lack of a tactile target effect within the Occ during the simultaneous scan 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).

- INSERT FIGURE 5 AND 6 ABOUT HERE -

Discussion

The current study demonstrates auditory and tactile responses within several visual cortical regions of 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. However, when EB subjects attended to either the sensory streams when presented simultaneously, these areas revealed clear evidence of attentional modulations. However, the effect of attention was not equivalent in all ROIs, and the response depended on which modality was attended. When EB subjects attended to the auditory stream and ignored simultaneously presented 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. Conversely, ignored auditory targets elicited no positive BOLD response in any of these regions. Thus, a response to auditory stimuli only appeared when they were attended. Attended tactile targets presented simultaneously with auditory stimuli elicited a similar event-related response only in the calcarine sulcus. In the other ROIs, BOLD responses to tactile targets were suppressed in the presence of unattended auditory stimuli. 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. This sensory-by-scan interaction was not directly related to behavioral measures of target detection, as EB subjects performed comparably on tactile target detection during the simultaneous presentation and detection accuracy of tactile targets presented alone. Thus, with the exception of the calcarine sulcus, temporally synchronous but unattended auditory stimuli appear to attenuate responses to attended tactile targets in extrastriate Occ areas.

- INSERT FIGURE 7 ABOUT HERE -

Calcarine Sulcus

The calcarine sulcus ROI showed effects reflecting a complex interaction of orienting responses, selective 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 suggests that stimulus salience influences responses within this region (fig. 4). These salience effects in both alone and simultaneous scans likely reflect orienting responses, which have been ascribed to involuntary neural mechanisms that allow for the capture of attention by highly salient stimuli (Knight, 1984; Escera et al., 1998, 2002; Duncan & Humphreys, 1992). In the simultaneous scan, this orienting response persisted as indicated by a significant response to the auditory distracter (fig 5a). The calcarine sulcus therefore may function within a larger network of regions (for example the ventral frontoparietal network in the SC) involved in automatically orienting attention to novel or salient stimulus events (see Corbetta & Shulman, 2002; Shulman et al., 2004). However, target effects were also observed within this region. A significant response to the tactile target was observed in the simultaneous 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 this ROI also 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, suggesting that selective attention mechanisms modulate auditory 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 (Woodruff et al., 1996; Petkov et al., 2004; Shomstein & Yantis, 2004; Johnson & Zatorre, 2005). 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 (fig 5a). It is possible that the neural mechanisms that underlie normal suppressive functions found in sighted visual cortex become functionally adapted to the reorganized afferents reaching the Occ 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 Occ cortex during a spatial-distracter suppression task (Serences et al., 2004). These authors suggested that an inhibitory mechanism within 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 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 to tactile targets (Fig 1e), and suggests that 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 refection of an active suppression of stimuli presented within an irrelevant modality.

The calcarine sulcus has been the subject to 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 (Sadato et al., 1996, 2002; Amedi et al., 2003, 2004; Röder et al., 2002; Burton et al., 2003, 2004). The breadth of tasks that engage the calcarine sulcus in EB individuals suggests 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 'extrastriate' 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 alone and simultaneous presentations and significant tactile target effects greater than distracter responses in alone conditions suggests that these areas maybe 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 EEG potentials over Occ leads in response to detection of a change within an auditory or tactile stream (Kujala et al., 1995a,b; Röder et al., 1996; Liotti et al., 1998). This hypothesis is supported by the current (and repeated) observation that attention focused away from target stimuli attenuates (or abolishes) posterior Occ 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 extrastriate occipital cortex.

General Organization of Occ cortex in the EB

There were 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 simultaneous scans (although trends were evident within the lingual and fusiform ROIs). This raises the possibility that the posterior regions within the Occ lobe of EB individuals (i.e. calcarine sulcus & cuneus) may reflect more of an underlying orienting response (attentional salience) whereas the responses stemming from the anterior regions maybe indicative of top-down mechanisms. This pattern of organization is similar to a postulate anterior-posterior organization hypothesis proposed by Amedi and colleagues (Amedi et al., 2003, 2004). These researchers compared fMRI responses throughout the Occ 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 postulated that anterior Occ regions (such as the lateral occipital complex) yield more perceptual based functions while 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 Occ regions reflective of more of a uniform organization, with all Occ regions partaking in similar functional roles (Röder et al., 2002; Burton et al., 2004).

Whether the different patterns of event-related responses between 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 and colleagues (Amedi et al., 2003, 2004; Buchel, 2003). A true examination of an anterior-posterior hypothesis within the

Occ 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.

Mechanisms of Tactile Attenuation

The attenuated tactile responses observed during the simultaneous scans maybe attributed to auditory stimulation arriving at Occ loci prior to tactile stimulation. 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. Paralleling peak latency differences, the blind also responded more rapidly to auditory targets relative to tactile targets, a finding previously reported to targets presented either alone (Kujala et al., 1995a) or simultaneously (Kujala et al.,1997b). Faster conduction of auditory signals by innervating afferents, even when unattended, may have produced inhibitory gating within occipital areas that responded to both modalities in the absence of competing sensory stimulation. This may lead to the activation of inhibitory mechanisms within Occ areas possibly preventing the activation of these circuits from attended tactile stimuli.

Alternatively, Occ responses may aid in suppressing ignored auditory information, a finding observed during unattended auditory target presentation in the simultaneous condition within the calcarine sulcus. This would potentially cause a baseline shift to tactile-evoked responses accounting for attenuated responses.

Summary and Conclusions

Within posterior occipital areas of our EB sample, event-related BOLD responses were observed to in response to auditory and tactile target and distracter stimuli but only when attended. Within the unimodal scans, significant auditory or tactile distracter responses were detected in the calcarine sulcus, cuneus, fusiform and lingual gyri, suggestive of an attentional orienting response. Significant target effects observed within the lingual, and fusiform ROIs in both modalities and trends for significance observed within the calcarine and cuneus ROIs imply complex interactions between bottom-up and top-down functions. Under conditions of simultaneous stimulation, attended auditory stimuli continued to evoke responses in these regions, while responses to tactile deviants observed when presented alone were abolished. This study thus provides a bridge between attention and modality effects in Occ regions in the EB. Previous target detection and ERP studies in the EB have shown attentional enhancement effects to target stimuli without competing streams of sensory information in both auditory (Kujala et al., 1992, 1995b, 1997a) and tactile (Kujala et al., 1995a) modalities. Therefore, the asymmetrical response observed within the bimodal conditions suggests that these areas may undergo active enhancement or suppression, depending on the attentional demands of the task.

Attention-based enhancements to the auditory target suggest that Occ regions in the EB either aid in the control of selective attentional mechanisms or are the recipient of top-down signals from frontal and parietal regions (Posner et al., 1990; Kastner & Ungerlieder, 2001) and therefore function within auditory and tactile processing pathways. The variety of functional tasks that have been found to engage Occ regions in the EB (See Bavelier & Neville, 2002; Burton, 2003; Theoret et al., 2004; Roder & Rosler, 2004 for reviews) suggests that the Occ cortex in the EB houses a mechanism common to different tasks of information processing; one such mechanism maybe the control of selective attention. Alternatively, support for the latter speculation stems from a number of tracing studies in sighted animals and functional imaging studies in SC humans revealing the existence of auditory and tactile inputs into normal Occ cortex. (Amedi et al., 2002; Giard & Peronet, 1999; Molhom et al., 2002; Watkins et al., 2006; Rockland & Ojima, 2003; Schroeder & Foxe, 2005). It may be the case that in the absence of vision during development, these somatosensory and auditory afferents become the dominant source of sensory input, while non-sensory, fronto-parietal afferents feeding into Occ cortex modulate their responses as a function of attention (see Rockland & Ojima, 2003 for a description of non-Occ innervation into V1 in sighted monkeys).

The presence of orienting responses combined with the evoked auditory target responses but only when attended suggest that Occ regions in the EB likely function within larger networks of brain regions responsible for attending or orienting to changes within the sensory environment (see for example Kiehl et al., 2001; Bledowski et al., 2004; Kujala et al., 2005). Because the EB were more accurate then their sighted counterparts at detecting changes in the acoustic stream, one possibility is that Occ reassignment leads to behavioral adaptation in the EB by providing additional processing of changes within a steady-state sensory background.

Acknowledgements

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Chapter 2 Figure Captions

Fig 1. Task design and behavioral results. *a) Aud Alone* and *b) Tac 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 individual subject based upon individual pitch sensitivity. Vibrations during the tac alone scans were created using a novel piezo-electric 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 (*Aud and Tac Simult conditions*) presented the same tones and vibrations simultaneously and cued subjects to switch attention between modalities every thirty 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 ($P < 0.05$). Error bars denote standard error of the mean.

Fig. 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 $p < 0.01$, uncorreted. To protect against false positives, a cluster filter correction was implemented (see methods). Auditory responsive regions are shown in orange and yellow and tactile activity is shown in green. 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.

Fig. 3. Characterizing Occ responsiveness in the EB. *a)* shows the percent 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 $p > 0.01$, 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 grey.

Fig. 4. Alone scans (scans 1 & 2) region of interest analysis. Averaged event-related time courses were extracted from voxels showing active responses to both auditory and tactile stimuli. Four Occ regions of interest (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 secs). Talairach coordinates for ROIs are listed in parentheses. *Denotes a significant **Target** BOLD response ($P < 0.05$) compared to baseline. ^{M}Denotes a significant **Distracter** BOLD response ($P < 0.05$) compared to baseline. Error bars represent standard errors of the mean.

Fig. 5. Simultaneous scans (scans 3 & 4) region of interest analysis in the EB. Auditory and tactile event-related averages during different attentional conditions were extracted from the same Occ ROIs used in Fig. 4. The resulting BOLD responses are shown for targets, distracter 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 ($P < 0.05$) compared to baseline. ^{M}Denotes a significant **Distracter** BOLD response ($P < 0.05$) compared to baseline. Error bars represent standard errors of the mean.

Fig. 6. Simultaneous scans (scans 3 & 4) region of interest analysis in the SC. Mean event-related averages for auditory and tactile targets (ignored and attended) from the four Occ ROIs are shown for the SC group. Error bars represent standard errors of the mean.

Fig. 7. Event-related averages from functional control regions in the EB. Target related BOLD signals were extracted from a) a somatosensory association area (post-central gyrus, S2), b) an auditory association area (superior temporal gyrus) and c) a frontal association cortex (inferior frontal gyrus, IFG) during the simultaneous scans. Talairach coordinates for ROIs are listed in parentheses. * Denotes a significant difference at $P < 0.05$ between the peak BOLD response and the corresponding baseline. Error bars represent standard errors of the mean.

Table 1. Occipital Responsive Zones in the EB

ROI	Hemisphere	Talairach Coordinates			Mean T Score	Mean P value
		X	Y	Z		
Tactile zones						
Cuneus	R	7	-92	1	2.58	0.011
MOG	R	30	-94	-6	2.81	0.013
POS	R	8	-84	31	2.85	0.014
Inferior Lingual Sulcus	R	28	-69	-11	2.72	0.015
Lingual Gyrus	R	11	-60	1	2.75	0.016
Fusiform Gyrus	R	33	-54	-14	2.74	0.016
Calcarine sulcus	R	1	-82	13	2.67	0.018
IOG	R	28	-89	-16	2.68	0.019
MOG	L	-22	-99	-3	2.60	0.019
MT	L	-52	-75	1	2.65	0.019
Auditory zones						
Calcarine Sulcus	R	5	-84	6	6.02	0.0001
POJ	R	12	-76	37	4.74	0.0012
Lingual sulcus	R	27	-71	-13	4.35	0.0015
Cuneus	R	8	-90	14	3.92	0.0019
Lingual gyrus	R	13	-58	2	3.92	0.002
SOG	R	12	-82	23	3.90	0.0024
MT	R	42	-71	11	3.57	0.0037
MOG	R	30	-90	6	3.46	0.0046
Fusiform	R	32	-53	-13	3.10	0.0071
IOG	L	-10	-94	-7	3.55	0.004
lingual sulcus	L	-15	-59	1	3.32	0.005
MT	L	-41	-73	11	3.25	0.006
SOG	L	-7	-87	22	3.12	0.0071
Cuneus	L	-8	-90	11	3.11	0.0074

POS - posterior occipital sulcus; IOG - inferior Occipital Gyrus; MOG - middle occipital gyrus; MT - middle temporal;
POJ - parietoccipital junction

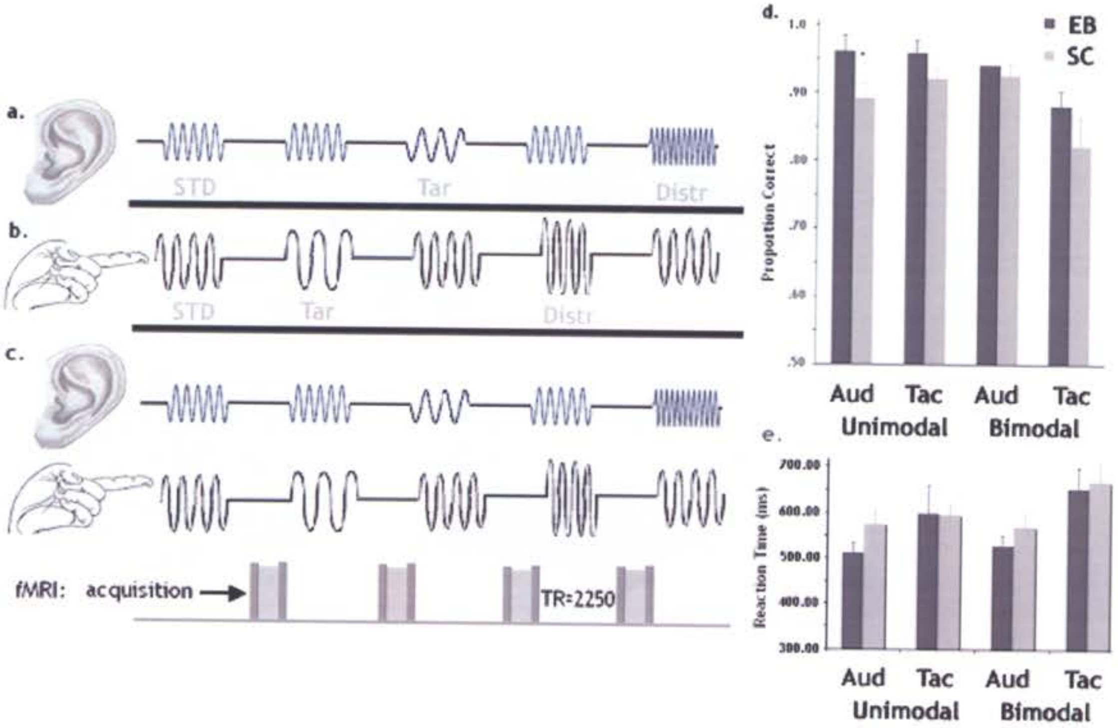

a.
STD
Tar
Distr
b.
STD
Tar
Distr
c.
fMRI: acquisition
TR=2250
d.
EB
SC
Proportion Correct
1.0
.90
.80
.70
.60
.50
Aud
Tac
Aud
Tac
Unimodal
Bimodal
e.
Reaction Time (ms)
700.00
600.00
500.00
400.00
300.00
Aud
Tac
Aud
Tac
Unimodal
Bimodal

Figure 1.

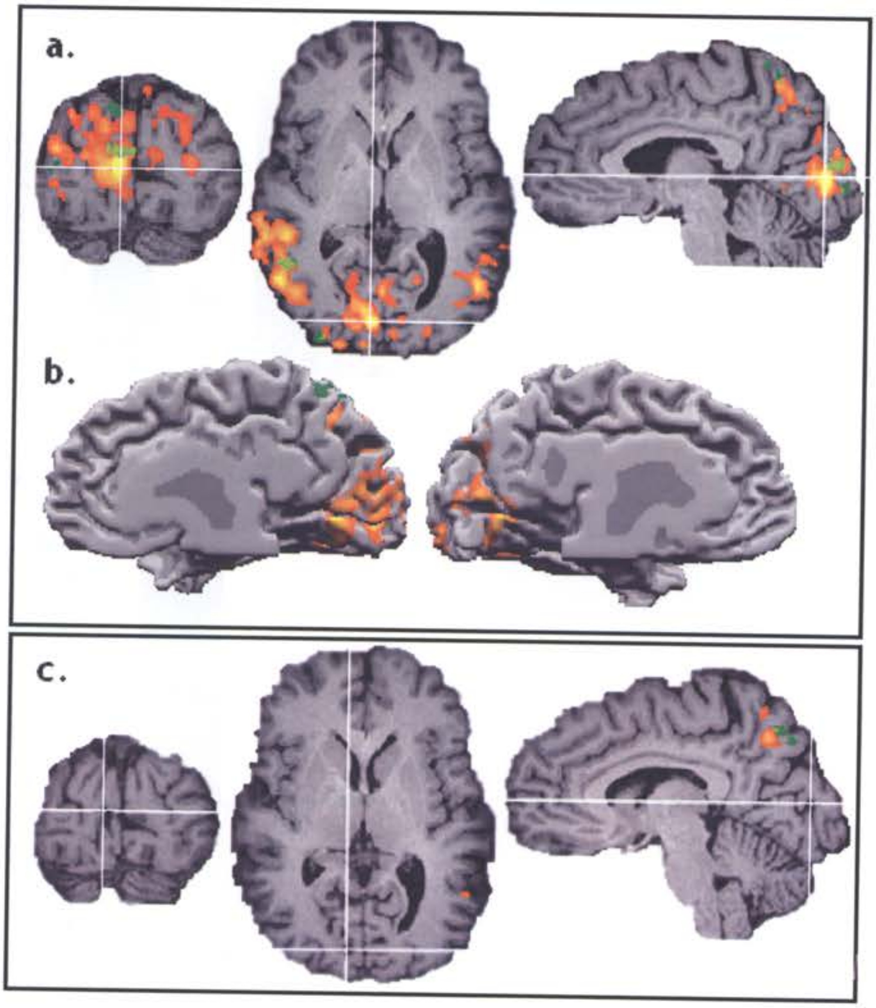
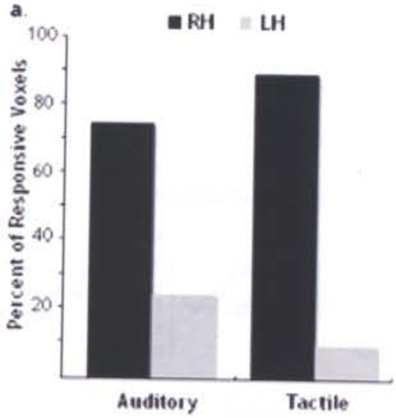
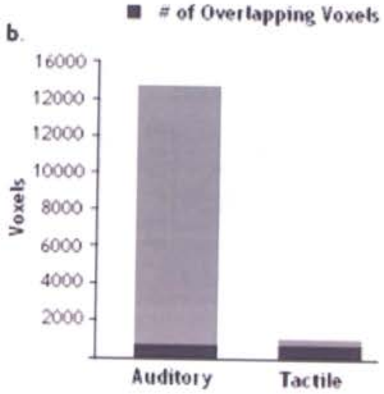


Figure 2.

a.


RH
LH
100
80
60
40
20
Percent of Responsive Voxels
Auditory
Tactile

b.


# of Overlapping Voxels
16000
12000
12000
10000
8000
6000
4000
2000
Voxels
Auditory
Tactile

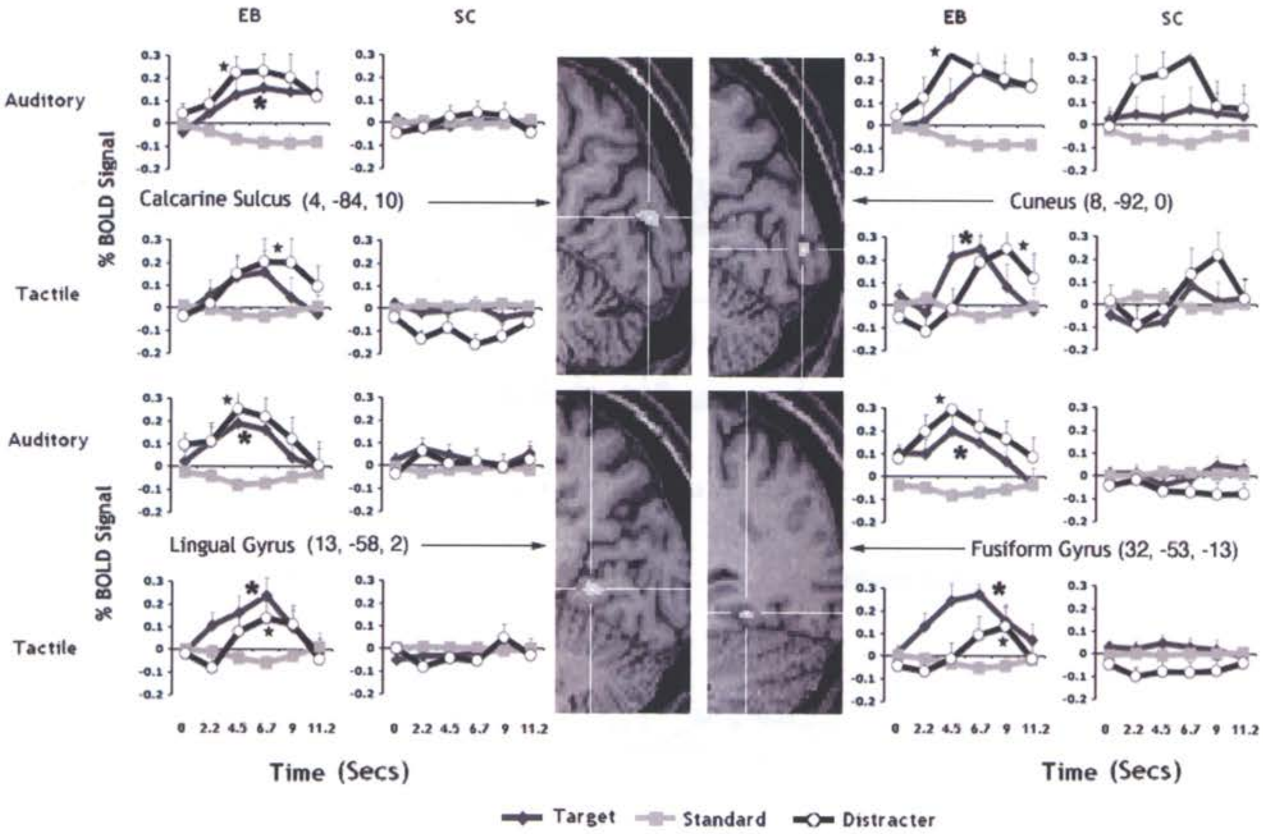

EB
SC
EB
SC
Auditory
Tactile
Auditory
Tactile
% BOLD Signal
% BOLD Signal
Calcarine Sulcus (4, -84, 10)
Cuneus (8, -92, 0)
Lingual Gyrus (13, -58, 2)
Fusiform Gyrus (32, -53, -13)
0.3
0.2
0.1
0
-0.1
-0.2
0 2.2 4.5 6.7 9 11.2
Time (Secs)
Time (Secs)
Target
Standard
Distracter

Figure 4.

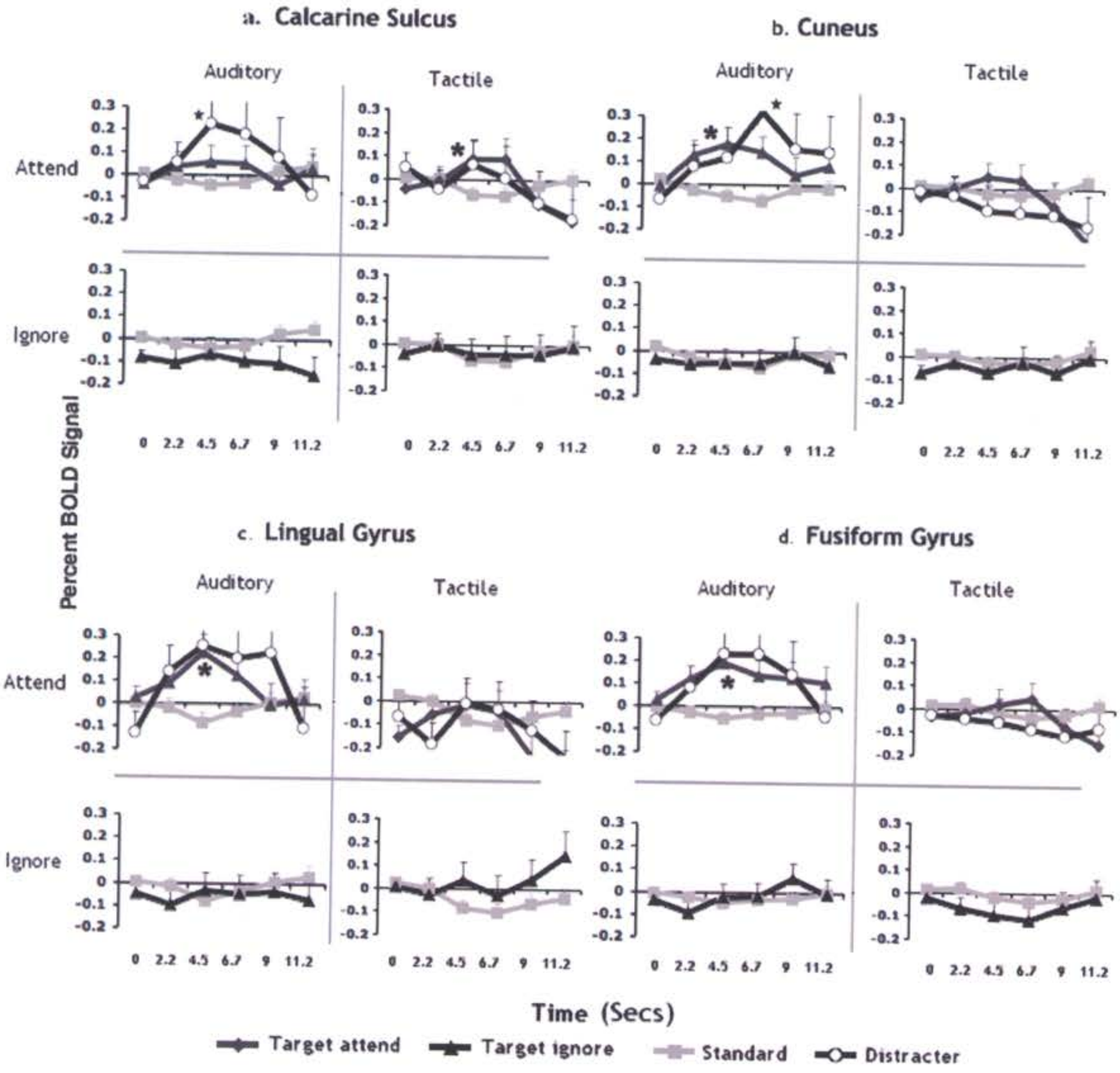

a. Calcarine Sulcus
b. Cuneus
c. Lingual Gyrus
d. Fusiform Gyrus
Auditory
Tactile
Attend
Ignore
Percent BOLD Signal
0.3
0.2
0.1
0
-0.1
-0.2
0
2.2
4.5
6.7
9
11.2
*
Time (Secs)
Target attend
Target ignore
Standard
Distracter

Figure 5.

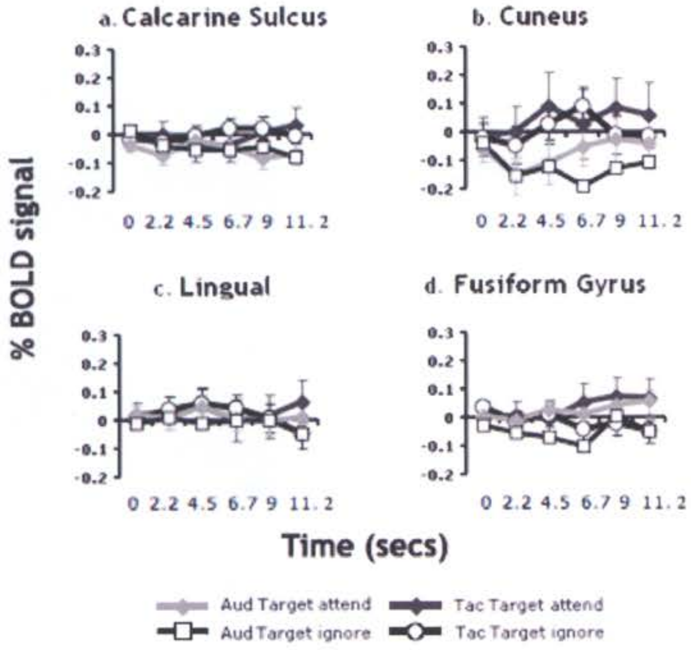

a. Calcarine Sulcus
b. Cuneus
c. Lingual
d. Fusiform Gyrus
% BOLD signal
0.3
0.2
0.1
0
-0.1
-0.2
0 2.2 4.5 6.7 9 11.2
Time (secs)
Aud Target attend
Aud Target ignore
Tac Target attend
Tac Target ignore

Figure 6.

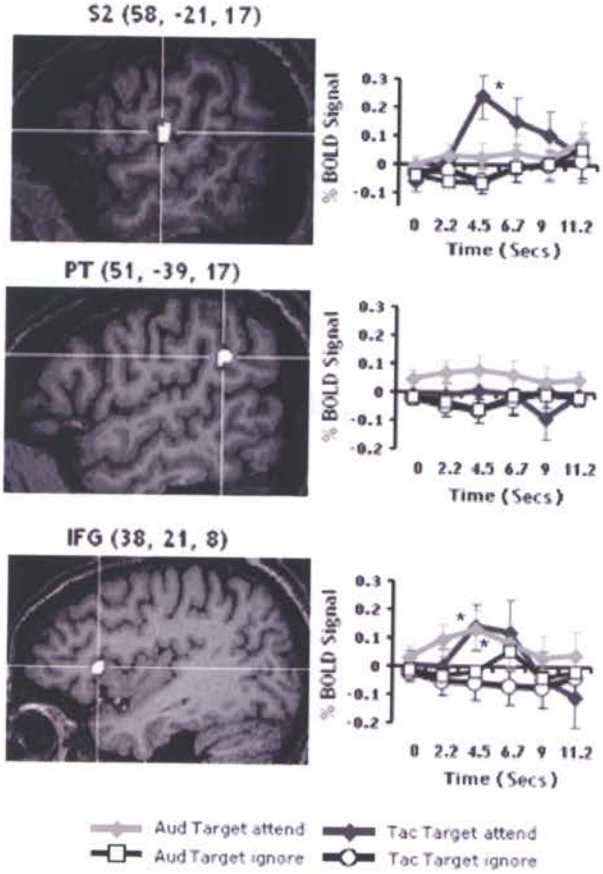

S2 (58, -21, 17)
PT (51, -39, 17)
IFG (38, 21, 8)
% BOLD Signal
0.3
0.2
0.1
0
-0.1
-0.2
*
0 2.2 4.5 6.7 9 11.2
Time (Secs)
Aud Target attend
Aud Target ignore
Tac Target attend
Tac Target ignore

Figure 7.

Chapter 3: Multimodal target detection and distraction: An fMRI review and analysis

Kurt E. Weaver and Alexander A. Stevens

This chapter has not yet been submitted for publication, but will be submitted to NeuroImage.

Abstract

Awareness of deviant stimuli that appear within a background of noise can facilitate rapid behavioral responses to potentially meaningful or harmful situations. An abundance of behavioral and functional imaging studies incorporating the classic 'oddball' paradigm have identified two attentional systems that function to gate deviant stimuli into awareness. Top-down systems allow deviant stimuli to be purposefully selected from within a stream of sensory stimulation while bottom-up mechanisms alert the organism to salient changes in the environment. An extensive review of the functional neuroimaging literature indicates that oddball tasks consistently activate a variety of parietal and frontal regions including the supramarginal gyrus, inferior and middle frontal gyri. In the current study, we examined these areas during auditory and tactile processing using a three-stimulus oddball design. Consistent with the relevant literature, detection of behaviorally-relevant auditory targets engaged regions throughout the frontoparietal attention networks. Behaviorally-relevant tactile targets also engaged similar frontoparietal regions suggesting the multimodal nature of theses circuits. Distracter stimuli in both modalities on the other hand, activated parietal regions but failed to produce any significant responses within the right IFG, a region commonly implicated in bottom-up orienting. In contrast with previous 3-stimulus oddball tasks, participants were required to initiate a motor-response to distracters, albeit the same response to the standard. These results suggest that rather than orienting to salience, the right IFG plays a role in planning or inhibiting behavioral responses to deviant stimuli. We conclude by proposing a mechanism through which top-down and bottom-up networks may interact in order to accurately detect deviant stimuli and initiate appropriate behavior.

Introduction

The awareness of deviating sensory signals from meaningless background noise allows for the preparation of appropriate responses to novel stimuli. Deviating stimuli are gated into awareness through specific attentional mechanisms (Corbetta & Shulman, 2002; Herrmann & Knight, 2001). In an experimental setting, attentional systems have been characterized using the target detection or oddball paradigm. In the two-stimulus oddball design, individuals must respond to rare, target stimuli that are inter-mixed within a stream of repetitive, standard stimuli. In this setting, the perceptual differences between standards and targets are near discrimination thresholds. As a consequence, the detection of 'task-relevant' targets relies on top-down, voluntary attention directed to that deviation. In the alternate version of the oddball paradigm (the three stimulus design), bottom-up mechanisms orient attention to rare and irrelevant, yet highly deviant or distracting stimuli.

A vast electrophysiological literature has consistently shown that the presentations of deviants elicit a variety of time-locked brain responses (event-related potentials, ERPs); events that do not develop after repeated presentations of the standard (Naatanen, 1992). With the advent of event-related functional magnetic resonance imaging (fMRI) techniques (Dale and Buckner, 1997) numerous studies have attempted to localize the neural generators of different ERP components related to deviance detection. Auditory and visual oddball studies using fMRI have demonstrated that detection of target stimuli or distracter processing activates a large distributed cortical network throughout frontal, temporal and parietal lobes (i.e. Mulert et al., 2004; Downar et al., 2001). It has been proposed that identification of common cortical regions engaged by targets of different modalities reflects a top-down network involved in directing attention to stimulus deviance (Downar et al., 2000, 2002; Stevens et al., 2000). Cortical regions commonly engaged by target selection include the supramarginal gyrus (SMG), the superior parietal lobule (SPL), the anterior cingulate gyrus (ACC) and the middle frontal gyrus (MFG). Regions responding to task-irrelevant distracter stimuli of different modalities reflect a network specialized for automatically reorienting attention to salient sensory events (Halgren et al., 1998; Escera et al., 1998). Cortical loci often associated with distracter processing include the supramarginal gyrus (SMG), tempropariateal junction (TPJ), middle temporal gyrus (MTG) and the inferior frontal gyrus (IFG).

Review of event-related Responses under oddball conditions

In the present study, we provide for the first time a comprehensive review of fMRI studies that have employed the oddball design. We reviewed all published fMRI reports that employed either a two-stimulus or a three-stimulus oddball design in only neurologically normal individuals using Pubmed {articles published prior to 2006 - see table 1}. Reports were excluded from the review if whole brain activations were not reported (e.g. if only region of interests analyses were reported testing specific hypotheses). Over 20 such fMRI studies have been published. Table 1 summarizes the brain regions that have been reported during target detection and distraction tasks. Although methodological approaches vary from study to study (i.e. two vs. three stimulus design, task-relevant or "attend to" vs. task-irrelevant or "ignore", response made, modalities tested and analysis software) there is a high level of consistency of active regions throughout temporal, parietal and frontal cortices. The size and exact location within a sulcus or gyrus of a reported activation varies and greatly depends upon the parameters of a given study. However, a common generality that appears across the literature reveals that regions engaged by targets overlap to a large degree with regions supporting distracter orienting. Moreover, targets relative to distracters almost always appear to engage regions to a greater capacity (i.e response magnitude, number of voxels showing a significant response; see Kiehl et al., 2005). Conversely, differences observed across studies are not only due to diverse experimental parameters but potentially the assorted statistical analyses and various thresholds used from study to study.

Figure 1 reports all cortical regions that have been associated with either target detection or distracter processing and quantifies the number of reviewed studies reporting activity within each region. The most overwhelmingly observed activation across all studies independent of modality, deviant type or response category occurred within inferior parietal regions along the posterior portions of perisylvan fissure (most often corresponding to Broadman's Area, BA 40) which includes the supramarginal gyrus (SMG) / tempropariteal junction (TPJ – see figure 1). The one exception, Mitchell et al., 2005, reported results not including parietal loci. BOLD changes within the IPL/SMG/TPJ region appear to be insensitive to modality of presentation and deviance type (target, distracter). Deviants engage the SMG/TPJ in a task-relevant and behaviorally neutral (i.e. requiring no response) scenario but not when subjects are engaged in an unrelated task (see Opitz et al., 1999; Downar et al., 2000; 2002; Sabri et al., 2004; Kincade et al., 2005). Collectively, these characteristics suggest that activation of the TPJ/SMG region is highly correlated with processes related to the gating of behaviorally relevant highly and/or significant deviant stimuli into awareness (Downar et al., 2001; Serences et al., 2005).

Activation of the middle temporal gyrus (MTG; BA 21) during deviance detection has been reported in 8 published auditory and 4 visual studies, suggesting MTG also contains some degree of multimodal convergence. Activation of the MTG across these studies was independent of task relevancy in both auditory and visual studies (Yoshiura et al., 1999; Downar et al., 2000) and response type in the auditory domain (Brazdil et al., 2005; Kiehl et al., 2001). The MTG has been implicated in a wide variety of functions including a variety of acoustic (Spect & Reul, 2003) and linguistic operations (see Price, 2000; Price & Binder, 2001; Indefrey & Levelt, 2004).

- INSERT TABLE AND FIGURE 1 ABOUT HERE -

Within the frontal lobes, multimodal activations have been reported in nearly all studies within the inferior frontal gyrus (IFG; BA 45/47) and the middle frontal gyrus (MFG; BA 9/46). Generally, targets and distracters engage IFG regions independent of modality or behavioral context. Recruitment of the IFG during task-irrelevant deviance processing (particularly within the visual domain) has lead to the hypothesis that this region functions in the automatic orienting of attention to salient sensory events (Corbetta & Shulman, 2002; Kincade et al., 2005). However, other theories propose the IFG underlies functions related to inhibiting pre-potent motor responses to distracter stimuli (Konishi et al., 1998, 1999) or involved in retrieving and maintaining task-specific response rules (Casey et al., 2001; Downar et al., 2002; Bunge, 2004). The MFG, which incorporates parts of the dorsal lateral prefrontal cortex (DLPFC), has been reported to respond to both targets and distracters in both visual and auditory domains. Relative to more ventral regions within the frontal cortex, the MFG is significantly more sensitive to task relevancy and behavioral context. Of the 5 studies not requiring an active response to stimulus deviance in table 1, only one study (Horn et al., 2003) reported activation within MFG regions. Interestingly, in that study subjects were not required to make an overt response but were told to attend to the target stimulus (a 1000 Hz tone) while ignoring the non-target tone (a 4000 Hz tone); suggesting that this region may modulate stimulus driven sensory activity (see Horn et al., 2003; Barcelo et al., 2000). Functionally, the MFG and specifically the DLPFC have been most commonly associated with maintenance of working memory (e.g. Braver et al., 1997; Barch et al., 1997; D'Esposito et al., 2000), indicating that these regions may aid in maintaining the representation of the perceptual difference between target and standard stimuli (or the specific target if a category of stimuli are used such as shapes) across time (McCarthy et al., 1997). It has also been suggested, based upon ERP and human lesion studies, that lateral prefrontal regions initiate the processing cascade underlying attentional orienting to salient, novel events (Alain et al., 1998; Knight et al., 1999).

If hemodynamic activity within frontal, temporal and parietal regions during oddball paradigms is truly reflective of attentional systems supporting deviance detection, then these systems should respond to targets or distracters within any modality. Despite the logic to this hypothesis, the true polymodal nature of these networks has not been tested. Specifically, to the best of our knowledge no fMRI or PET study has examined the cortical systems underlying task-relevant target and distracter detection in the tactile domain (although somatosensory ERPs have been well characterized, see Yamaguchi et al., 1991; Kekoni et al., 1996; Mauguiere et al., 1997; Huang et al., 2005), We therefore aimed to examine tactile and auditory response profiles from the regions most commonly associated with target detection and distraction. Results from whole brain functional MR imaging of acoustic and somatosensory 3-stimulus oddball tasks are presented during which subjects were required to generate a button press to all target stimuli and press a different button to distracter and standard stimuli. We conducted four EPI BOLD scans. In scans 1 & 2, auditory and tactile stimuli alone (unimodal conditions) were presented in a counterbalanced fashion. In scans 3 & 4 the same auditory and tactile stimuli were presented simultaneously (bimodal conditions) during which subjects were cued to attend and respond to one modality at a time. We examined time courses from the four regions of interest chosen from the results detailed in figure 1 that were most commonly reported in pervious auditory and/or visual studies. These ROIs included the supramarginal gyrus/temporoparietal junction, the middle temporal gyrus, the middle frontal sulcus and the inferior frontal gyrus. As a secondary aim, we assessed response profiles from these ROIs when the same auditory and tactile targets were deemed task-irrelevant (Downar et al., 2001). Although previous fMRI studies have mapped cortical activity during task-irrelevant somatosensory target processing (Downar et al., 2001; 2002), this condition was included to further delineate top-down responses within our ROIs during tactile processing. We conclude by integrating the current findings with the extent literature and discuss of the cortical networks involved in top-down and bottom-up attentional systems and their relation to the detection of deviancy across all sensory systems.

Materials and Methods

Subjects

Nine neurologically normal individuals (6 female, mean age 49.63, range of 27 to 60) were recruited from the greater Portland area. Subjects were excluded if they had previously diagnosed hearing damage or loss, comorbid psychiatric disease, had played a string guitar for more then 20 hours/week and drug or alcohol abuse within the past five years. The mean number of years of education was 18.11 ± .84 s.e. Two subjects were left handed as assessed by the Oldfield handedness survey (Oldfield, 1971). All subjects signed an informed consent prior to testing procedures and all experimental procedures were approved by the institutional review board of Oregon Health & Science University.

Stimuli

A detailed description of the oddball design and stimuli and have been reported elsewhere (Weaver & Stevens, 2006). Briefly acoustic and tactile stimuli were 200 ms sinusoidal waveforms (with a rise/fall time of 10 ms for acoustic stimuli). Sound stimuli were monaurally presented at approximately 85 dB SPL (sound pressure level) in the left ear. Vibrotactile stimuli were produced by a non-magnetic, ceramic piezoelectric bending element (i.e. bender, Q220-A4-303YB Quick Mount Bender, Piezo Systems, Inc., Cambridge, MA - http://www.piezo.com) placed directly under the index finger of the left hand. The amplitude (peak to peak deflection) of the vibrations was set at approximately 400 µm's. Prior to scanning, each subject's 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 to prevent changes in finger position or 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. During scanning, subjects rested their left arm comfortably upon their left leg to prevent ipsilateral spatial-referent effects during attend-to tactile conditions (Driver & Grossenbacher, 1996; Driver & Spence, 1998).

The frequency of the standard stimuli for both modalities was determined prior to scanning for each subject based on individual discrimination thresholds using a discrimination paradigm (see below). For the auditory stimuli, 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. Additional pilot testing suggested that at these frequencies and amplitudes subjects reported similar perceived intensities (equal salience) for all acoustic and tactile stimuli when presented simultaneously. All experiments were controlled using Presentation software 9.1 (Neurobehavioral Systems Inc, Davis, CA) running on a PC.

Discrimination Thresholds

Subjects' individual discrimination thresholds for frequency of stimulation were determined before the scanning session. Matching for discrimination thresholds controlled for absolute sensitivity differences between subjects. Thresholds were determined with a two-alternative forced choice task using a 2-down 1-up rule yielding estimates of thresholds for 70% accuracy (Levitt, 1970). On each trial, subjects heard or felt two stimuli, each 200 ms in length separated by 2000 ms. The first stimulus on all discrimination trials was the target stimulus. 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 second stimulus was set at 900 Hz for auditory thresholds and 150 Hz for tactile thresholds. This stimulus was then adjusted based on the descending method of limits. After the just-noticeable-difference (JND) for the target stimulus was determined for each individual, it was tripled (for the auditory conditions) or doubled (for the tactile conditions) and added to the target frequency to create the frequency value for the standard. Use of 1 or 2X DF resulted in poor performance on the oddball tasks in the scanner during pilot testing.

Experimental Design and Imaging Paradigm

The oddball task was a standard three-stimulus design that presented a rare target and distracter and repeated non-target (standard) stimuli in a serial fashion with a constant inter-stimulus interval (ISI) of 2250 ms. Each oddball task consisted of 180 trials with target probability set at .15 and distracter stimulus probability set at .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 planer imaging (EPI) scans: one each for the tactile and auditory alone conditions (unimodal scans) and 2 for the simultaneous conditions (bimodal scans). In scans 1 and 2, tones (aud alone) and vibrations (tac alone) were presented alone. The order of the alone scans was counter-balanced across subjects. Scans 3 and 4 consisted of the simultaneous presentation of auditory and tactile stimuli (simultaneous scans). A verbal cue instructed subjects to "switch" attention between modalities every 30 acquisitions (creating 6 "attend-to" auditory blocks and 6 "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. It should be noted that a bimodal cued paradigm results in two different fMRI designs: an event-related design where subjects focus attention on individual events within the a given sensory stream and a block design where subjects must sustain attention to one modality or the other across time. Given the interest in event-related modulations (i.e. from task-relevant and irrelevant targets and distracter stimuli) on specific ROIs underlying top-down and bottom-up attention we choose to focus our analyses on the individual deviant events rather than averaged 'blocked' responses extracted from an 'attend-to' stimulus blocks.

MR imaging was conducted on a 3.0 Tesla Siemens Trio magnet using a standard 2 channel, RF transceiver head coil. The gradient-echo EPI scanning parameters consisted of: TR = 2250, TE = 35 and a flip angle of 85°. The field of view (FOV) was set at 240 x 240 mm using a 64 x 64 matrix. Functional slices were acquired using a clustered volume technique (Edmister et al., 1999) in which all slices within a volume were collected in approximately the first 1/2 (or 1150 ms) of the TR. This technique allowed us to present stimuli during a period of silence to reduce interference from scanner noise. Each functional volume consisted of 20 axial slices (5 mm thick with 1 mm inter-slice gap) providing whole brain coverage. A navigator echo was inserted within each functional scan in order to prospectively correct for motion artifacts. Stimulus presentation began after the 2nd 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 non-target frequencies. Additionally, standards were purposefully presented on the first ten trials within each scan to provide a steady state stimulus baseline prior to introducing a target or distracter. Within the simultaneous scans, a minimum of three standards were presented within the "attend to" modality after each switch cue. Throughout all functional scans, subjects were instructed to keep their eyes closed.

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 corrected, linear-trends were removed and a high-pass filter of 3 cycles/scan was applied. All scans were then interpolated into 1x1x1 mm^3 isovoxels, and raw signal values were z-normalized and transformed into standardized Talairach stereotaxic space (Talairach & Tourneaux, 1988). Time courses for each functional run were then analyzed and statistical parametric z-maps were created using a general linear model. For scans 1 and 2 (alone 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 et al., 1996). Stimulus predictors from scans 3 and 4 (simultaneous scans averaged together) included "attend to" targets and distracter stimuli in both modalities and auditory and tactile "ignore" targets. Contrast based z-maps were constructed by averaging across the group using a random effects analysis allowing us to generalize back to the population level. For all contrasts, voxel-wise comparisons for the different stimulus conditions were made using standard linear t-tests. An alpha significance threshold at $p < 0.005$. In addition, a cluster filter correction was employed to reduce false positives, type I error (Forman et al., 1995). This correction adjusted the *P* value to 0.05, insuring the likelihood of 5% or less false positives within a minimum cluster size of 300 contiguous voxels.

Conjunction and contrast analyses

In order to confirm voxel clusters showing significant polymodal target responses, a conjunction analysis (Price & Friston, 1997) was conducted between auditory and tactile modalities averaging across responses from only the target stimulus conditions. A confirmatory, contrast analysis was used to examine regions uniquely contributing to target or distracter processing. This contrast analysis averaged target evoked activity between modalities within each voxel and contrasted it directly with averaged distracter responses, resulting in voxels showing a [(Aud_targ + Tac_targ) > (Aud_dist + Tac_dist)] contrast. To protect against type 1 errors (false positives), the alpha significance level was set to 0.001 and corrected for multiple comparisons with a false discovery rate. In addition, a cluster filter of 100 contiguous voxels was employed.

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Region of interest analysis (ROI)

Time courses were selected from *a priori* regions of interest (ROIs) based upon the four most commonly reported regions in previous target and distracter fMRI studies (see figure 1). The supramarginal gyrus, middle frontal sulcus and inferior frontal gyrus regions of interest were constructed by choosing all active voxels within that region based on the auditory and tactile target conjunction z-maps. The middle temporal gyrus, pre and post central gyri ROI was generated using the auditory and tactile contrast map. Event-related time courses were extracted and averaged from each voxel within an ROI and the mean percent signal change for each condition was calculated based upon a baseline estimate of the 3 TRs prior to the presentation of that event.

Results

- INSERT FIGURE 2 ABOUT HERE -

Whole brain fMRI of tactile and auditory deviance processing

Behavioral Performance

Target detection accuracy was high across conditions, suggesting that subjects were actively attending to the stimuli. Mean proportion detection rates for the alone scans were 0.89 and 0.92 for auditory and tactile modalities, respectively and 0.92 and 0.82 for auditory and tactile targets presented simultaneously. A one-way repeated measures ANOVA using a Greenhouse-Geiser correction for violations of sphericity revealed no main effect of condition [F = (1.847, 14.775) = 3.044, p = .081].

Target contrast maps

Using a general-linear model approach, target evoked BOLD responses were determined by a voxel-wise contrast between target stimuli and the standard condition within each modality extracted from the unimodal, alones scans (fig. 2). Both auditory and tactile task-relevant targets produced activations within a variety of frontal and parietal loci (fig 1, and summarized at the bottom of table 1; see online supplemental material, table 1 for a comprehensive description). No activation was observed within the occipital lobe for either modality. Overall, auditory stimuli were more effective at evoking significant BOLD responses than tactile stimuli (particularly for distracters) and right hemisphere responses were generally larger than left (with the exception of a number of left localized activations in the frontal lobe to tactile targets). Task-relevant targets in both modalities produced right locallized activations in classic perisylvian temporparietal regions including the SMG and throughout the IPL, demonstrating the polymodal nature of this region within a behaviorally relevant context. Polymodal clusters were also observed in the frontal lobe within the SFG bilaterally, the IFG, MFG, MFS, insula and the OFG within the right hemisphere and the ACC. Auditory but not tactile targets were associated with activity in the STS in two spots and the commonly reported bleeding from the IPL into the STG in the right hemisphere. Auditory targets also engaged the SMG and IPL in both hemispheres and the right IFS in the frontal lobe. Tactile but not auditory targets engaged MFG, MFS and the insula within the left hemisphere and the left precuneus.

Motor responsive regions

In agreement with a right hand button response, left hemisphere activations within the PreSMA and PreCentral gyrus were observed in both auditory and tactile target conditions while the SMA showed a significant response to only the tactile target.

Distracter contrast maps

Presentation of distracters from the unimodal scans in both modalities engaged brain regions including small foci within IPL bilaterally in both modalities (but to a greater extent in the auditory domain; see fig., 2). Within the frontal lobes, the ACC within the right hemisphere responded to both tactile auditory and distracters but these clusters did not overlap. Auditory only activations were observed within the angular gyrus in the right hemisphere and the IPL within the left hemisphere and within the left ACC. A robust auditory distracter response was observed along the STS and STG within the right hemisphere. Tactile distracters did not evoke any significant BOLD responses within the temporal lobes but were linked with a small hot spot of activity in the right SFS.

Conjunction Analysis

To confirm target-evoked responses throughout frontoparietal regions, we performed a conjunction analysis between the target-based activations across auditory and tactile modalities (fig. 3a). The results from this analysis demonstrate the bimodal nature of a variety of frontoparietal loci including the SMG/TPJ, IFG, MFG, SFG and the insula

- INSERT FIGURE 3 ABOUT HERE -

Modality independent target and distracter contrasts

A contrast analysis was carried out to display activity uniquely related to task-relevant target detection and distracter processing independent of modality (Fig., 3b). Targets engaged the SMG/TPJ region to a greater extent than distracters. This analysis uncovered target but not distracters evoked responses within the IFG, orbital frontal, MFG and SFG regions and the precentral gyrus.

Event-related time courses

Fig. 4 presents event-related time courses extracted from the unimodal scan conditions from the 4 *a priori* selected ROIs (Fig. 1). Auditory and tactile targets evoked significant mean event-related BOLD changes within three of the four ROIs (the right SMG/TPJ, IFG and MFG). Auditory but not tactile targets evoked a strong, positive response within the right STG (fig. 4). In addition, we observed distracter evoked responses in both modalities within the SMG/TPJ ROI but not within the right IFG ROI.

- INSERT FIGURE 4 ABOUT HERE -

We next obtained time courses from the bimodal scans in order to investigate the effect of directed attention on target stimuli within the 4 preselected ROIs (fig 6). By instructing subjects to attend and respond to only one modality at a time, we were able to compare BOLD effects to target stimuli when attended and ignored. Clear attentional modulations were observed to both tactile and auditory targets within the right TPJ/SMG and MFG ROIs. Within the IFG ROI, the presentation of both attended and ignored auditory targets evoked responses however with slightly different time course profiles: ignored auditory targets evoked a response that showed an initial increase followed by rapid decline. Tactile targets did not appear to evoke responses different than those from tactile standards.

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Discussion

In general agreement with the extent fMRI literature, auditory and tactile targets engaged frontoparietal regions including perisylvian regions throughout the IPL and within the SMG/TPJ complex, bilaterally, the right IFG, insular regions, the MFG and the ACC (fig 2a,b). Tactile activity in a behaviorally relevant context in these regions combined with previous studies demonstrating auditory and visual activity (see table 1) reveals the polymodal response properties of these regions. Modality independent activations strongly supports the hypothesis that frontoparietal regions participate in the cognitive rather than sensory/perceptual operations tied to detecting deviant stimuli. In addition, distracter stimuli in both modalities activated the SMG/TPJ and ACC regions within the right hemisphere. However, distracters in either modality failed to produce a measurable response in the right IFG. This finding conflicts with a number of other published fMRI studies using 3-stimulus oddball designs as well as established models of novelty processing (Kiehl et al., 2005; Halgren et al., 1998, 1995; Corbetta & Shulman, 2002), and suggests that the processing within the right IFG may not specifically serve to orient attention to salient stimuli.

- INSERT FIGURE 6 ABOUT HERE -

Despite a multitude of studies demonstrating the involvement of frontoparietal regions to the detection of sensory deviance, the precise role performed by a region during detection of deviance remains contentious. Corbetta & Shulman (2002) described a network-based model of the cortical regions involved in goal-directed and stimulus-driven attention (see also Driver & Frackowiak, 2001; Shulman et al., 2005; Serences & Yantis, 2006). Their model proposes the existence of a dorsal frontoparietal stream that mediates top-down control over which stimuli receive attentional resources and a ventral stream which functions to reorient attention away from the current focus to stimuli that are particularly salient. The dorsal stream is primarily composed of posterior parietal loci including the SPL, precuneus and the intraparietal sulcus (IPS) and superior frontal regions, including the frontal eye fields (FEF) and superior frontal sulcus (SFS). The ventral stream, which functions as an attentional "circuit breaker" of the dorsal stream when a salient or distracting stimulus is transduced, is composed of the SMG/TPJ complex and ventral frontal cortical regions (VFC) including IFG region within the right hemisphere. The development of this model was based on a wealth of visuospatial cueing and spatial reorienting studies (Hopfinger et al., 2000; Corbetta et al 2000; Serences et al., 2005; Kincade et al., 2005). One area that has received little attention within the literature is the degree to which the proposed functions originating from the dorsal and ventral frontoparietal networks apply to non-visual modalities.

Multimodal cortical regions of bottom-up processing of novelty

The SMG/TPJ region plays a key role in deviance detection. This region has been found to be active in nearly all studies of deviance detection, regardless of modality or stimulus type, increases with task relevance (See table 1) and is insensitive to differential response strategies (Astafiev et al., 2006). It is unlikely that this region modulates cortical sensory regions in a top-down manner. This speculation is based on attentional cueing studies that fail to show sustained responses during pre-stimulus cueing periods (i.e. forced attention) in either the visual (Hopfinger et al., 2000; Corbetta et al., 2000) or the auditory domain (Stevens et al., unpublished data). Moreover, polymodal responses within the right SMG/TPJ suggest a post-perceptual level of processing. In the current study, the right SMG/TPJ showed a robust response to target and distracter stimuli in both somatosensory and auditory modalities, but not to targets that were deemed behaviorally-irrelevant (ignored targets – see fig 6). A recent study by Todd and colleagues demonstrated that manipulating attentional demands in a primary task modulated SMG/TPJ responses to unexpected, salient stimuli presented in an unattended channel (Todd et al., 2005). Based on their results, the authors suggested that suppression of SMG/TPJ activity during heavy attentional loads diminishes the ability of salient stimuli to capture attention. Collectively, fMRI evidence leads to the conclusion that the right SMG/TPJ region resolves whether a stimulus that deviates from the background sensory environment, regardless of the modality or current focus of attention, is relevant for the allocation of attentional resources (Serences et al., 2005; Kiehl et al., 2005; Bledlowski et al., 2004; Downar et al., 2000, 2001). This resolution is likely based on the interplay between the amount of deviation from background noise (i.e. novelty) and top-down modulations from regions involved in goal-directed behaviors (Sussman et al., 2003; Serences et al., 2005).

In general agreement with ventral frontoparital involvement in stimulus reorienting, ventral PFC regions also showed a robust response to auditory and tactile targets. We observed significant involvement within the inferior extent of the IFG in response to tactile and auditory target detection. Most network models of bottom-up attention hypothesize similar roles for ventral PFC as proposed for IPL regions. It has been suggested that the right IFG functions in the evaluation of stimulus novelty and that reallocation of attention during bottom-up capture critically depends upon VFC resources (Corbetta & Shulman, 2002). Investigators studying task-irrelevant auditory deviance detection have argued that activity within the IFG reflects a signal to trigger a shift of attention to the unattended auditory stream (Rinne et al., 2000, Opitz et al., 2002). This line of reasoning is supported by the current observation that ignored (task-irrelevant) auditory targets evoked a significant event-related BOLD response in the right IFG region (fig., 4).

A reorienting hypothesis within the right IFG does not however resolve the lack of significant distracter-related responses in either modality. All other fMRI studies utilizing a 3-stimulus design report activation throughout the IFG in response to target and distracter stimuli. To confirm this observation, we employed three analyses: 1, distracter responses were directly contrasted with standards in each modality separately (fig., 1), 2, distracter related activity was averaged between modalities (thereby increasing the overall power to detect any significant response) which was contrasted with averaged target related responses (fig., 2b) and 3, mean time-course responses were extracted from ROI's centered around the right IFG. One possibility for a lack of activation seen here stems from the suggestion that distracter related activity within the right IFG is reflective of response inhibition to distracting stimuli. A host of functional imaging studies have consistently reported an association between ventral PFC activation (typically within the IFG) and *suppression of responding* in go/no go tasks (Kawashima et al., 1996; Konishi et al., 1998, 1999; see Aron et al., 2004 for a review). The null effect observed here within right IFG maybe illuminating the addition of a response to distracters, albeit the same response made to standards. Inferior frontal regions would not have to intervene in this scenario as a result of subjects not having to inhibit a response to the stimulus deviation. This speculation corresponds well with 'distracter related IFG activity' observed in previous studies, as no other fMRI study of distracter processing to date has required a response to the distracter stimulus. A second explanation of the null effect within the IFG comes from studies of motor planning. Casey et al., (2001) reported that ventral PFC regions were more sensitive to conditions where responding to targets was more frequent relative to a lower rate of responding when targets were less frequent. These authors reasoned that ventral PFC regions help maintain task-specific response commands (i.e. integrating perception to action), a hypothesis that had been previously suggested (Cohen &, Servan-Schreber, 1992) and supported on the basis of fMRI data (Downar et al., 2002; see also Bunge, 2004). The event-related similarity between standards and distracters in the current experiment combined with the fact that a motor output was initiated to each stimulus raises the possibility of a habituated response within the IFG. That is, if the IFG serves to maintain task specific response commands, then the repeated initiation of the motor response to the standard and distracter resulted in a complete habituation of the BOLD signal. In support of a role in motor processes, the event-related response pattern within the motor cortex (left precentral gyrus) is similar to the pattern of activity within the right IFG, despite an elicited response on each trial.

Given their involvement in a large number of higher cognitive processes, it is likely that IFG and SMG/TPJ cortical regions provide more complex roles in deviance processing then described here (e.g. see Fiez, 1997; Poldrack et al., 1999; Aron et al., 2004; Price, 2000; Sakai et al., 2001). However, based upon the current and previous studies, we propose that the processing of any novel stimulus regardless of modality through the SMG/TPJ region aids in determining whether a stimulus is significant enough for the (re)allocation of attentional support and the right IFG evaluates and resolves whether a motor response (including suppression of a response) should be elicited to that given sensory event based upon prior knowledge (Downar et al., 2001).

Multimodal cortical regions of top-down deviance detection

Detection of behaviorally-relevant target stimuli within a sensory stream is dependent on focused and directed attention to that stimulus modality. It is well established that the posterior parietal cortex specifically the SPL is crucial for control of selective attention (Hopfinger et al., 2000; Pessoa et al., 2003; Liu et al., 2003; Berhmann et al., 2004). Little is known regarding the role of the PPC in selective attention to non-visual modalities despite its involvement in a few auditory oddball tasks (Kiehl et al., 2001, 2005). However, a recent fMRI study reported that the SPL was modulated by shifts of attention between male and female voices, independent of spatial location (i.e. speakers presented dichotically or diotically; Shomstien & Yantis, 2006). It was suggested that the SPL aids in "reconfiguring" the focus of attention in a domain-specific modality-independent manner (e.g. from male to female in the auditory domain, or shape to color in the visual domain; see also Yantis et al., 2003). Here, rather than requiring a shift of the attention between different domains within or between modalities, subjects simply had to This speculation may account for the lack of a statistically observable responses from either the auditory or tactile target within superior parietal regions. It is known that target detection requires the recognition of a mismatch of signals that automatically develops within sensory association cortex after the presentation a deviant that was preceded by several standards (Naatanen, 1992; Woldorff et al., 1998; Jaasakalinen et al., 2004).

Within the frontal lobe, the observed activity within the SFG to target selection corresponds well with the top-down control over stimulus or modality selection. Based on a number of models of selective attention, superior frontal regions contribute to the source of top-down or directed attention, particularly when attending to different locations of space (Posner & Driver, 1992; Driver & Fraickowiak, 2001; Corbetta & Shulman, 2002). Again, visual spatial cueing experiments during fMRI have demonstrated that SFG regions are active during cue directed orienting but not during detection of target stimuli (Hopfinger et al., 2000; Corbetta et al., 2000; Serences et al., 2004; Kincade et al., 2005). However, target detection in these studies involved visual search through a series of an array of distracters within a single trial. Thus, SFG activity during target detection, oddball tasks may reflect directed attention to and in turn amplify the response mismatch that is evoked by a target that was preceded by repeated standards.

A number of other cognitive processes are involved in the recognition of stimulus deviance including working memory and template matching (Stevens et al., 2000).

Activity within the MFG and DLPFC are typically discussed within the realm of working memory processes (Braver et al., 1997; Awh et al., 1996). Here, task-relevant target but not distracter or task-irrelevant target stimuli evoked responses within this region (fig. 3 & 4) and is consistent with a role in goal-directed working memory/template matching (McCarthy et al., 1997; Stevens et al., 2000). Although we replicate target responsivity within this region, all other 3-stimulus oddball studies have reported MFG activity in response to distracter stimuli. This discrepancy may be explained by the type of distracter encountered. Whereas other studies have used more complex stimuli (e.g. environmental sounds, Kiehl et al., 2001, 2005; visual shapes, Bledolwski et al., 2004), the distracters in this study were simple pure tones and vibrations. Distracter evoked MFG activity may therefore be a reflection of more complex yet automatic processing of these stimuli, potentially relating to linguistic properties.

ACC activity in the current study resulting from the presentation of targets and distracters in both modalities may be indicative of any one of a number proposed functions involved with cognitive control. For example, in accordance with a generalized pattern of activation to all deviant stimuli, the ACC may dictate the mapping of specific responses to a given stimulus (Kiehl et al., 2000). However, this possibility is unlikely given that distracter responses were directly contrasted with standard to which the same response was elicited. Alternatively, ACC activity may reflect behavioral adjustments in conflict (Kerns et al., 2004). As subjects transition from target unfamiliarity at the beginning of the scan to target certainty, the ACC may monitor and update mental and behavioral representations of the target and required responses (Botvinick et al., 2001).

Conclusions: Neural Networks of Deviance Detection

Given the popularity of the oddball design to the study of the neural correlates of cognition, the importance of the current study provides a missing link within the fMRI literature. We show for the first time that deviant tactile stimuli when regarded as behaviorally-relevant engage frontoparietal loops associated with attentional behaviors. We conclude that these networks in part work to detect and focus attention on afferent inputs from a variety of sensory systems whose activity deviates in some manner from previous, background stimulation.

The activation of ventral frontoparietal regions by task-relevant targets and lack of distracter related activity in both modalities supports the notion that rather than aiding in the reorienting of attention specifically to salient stimuli this network is engaged by some common mechanism inherent to the processing of rare stimulus events (Bledlowski et al., 2004). Based on an extensive review of the literature, we suggest that ventral IPL regions within the right hemisphere help delineate whether a deviant stimulus, independent of modality, receives attentional resources and enter into awareness. This process is triggered by the development of an exogenous mismatch of activity within sensory cortical regions when a stimulus deviates from a repetitive background (see Naatanen, 1992; Woldorff et al., 1998; Jaaskelainen et al, 2004). A number of electrophysiological experiments have demonstrated that the amplitude of this response is a positively coupled to the amount of physical deviation from the standard (Naatanen & Alho, 1997; Kujala & Naatanen, 2003). These experiments suggests that the more physically distinct a deviant is from the standard the larger the mismatch response. Within an unattended sensory stream, the greater the mismatch response to a deviant, the more success it will have activating the right SMG/TPJ and reorienting attention. Alternatively, when an insignificant mismatch develops to an unattended deviant, it fails to engage the right SMG/TPJ region and fails to interrupt the current focus of attention. However, when a deviant is selectively attended, top-down connections from superior frontal regions amplify the evoked mismatch response (Sussman et al., 2003; Szymanski et al., 1999). This amplification allows a predetermined yet perceptually discriminable stimulus deviating from some background sensory stream to engage the right SMG/TPJ region and enter into awareness. This interplay between bottom-up and top-down processes results in competition between attended and unattended stimuli fighting for attentional resources. We suggest that this interplay is resolved within the right SMG/TPJ region (Serences et al., 2005; Todd et al., 2005).

After a deviant stimulus is routed through attentional buffers, the right IFG aids in determining an appropriate course of action. Moreover, we propose that dorsal frontoparietal regions such as loci located within the ACC, SFG and MFG not only contribute to directing attention to a specific sensory modality (i.e. enhancement of activity in associative sensory cortices) but may also modulate activity within the right ventral IPL regions to help meet current and goal directed expectations. For example, if a goal is to ignore distracters and focus attentional resources to a primary task, dorsal frontoparietal regions may selectively inhibit ventral IPL mechanisms to prevent any significantly novel stimuli from entering into awareness (for example see Todd et al., 2005). Efficient processing through these networks would thus allow an individual to be able to attend to only stimuli that maybe relevant to behavior and rapidly plot a course of action.

Abbreviations

ACC	Anterior Cingulate Gyrus
ANOVA	Analysis of Variance
BA	Broadmans Area
db SPL	Decibels Sound Pressure Level
DLPFC	Dorsolateral Prefrontal Cortex
EPI	Echo-Planar Imaging
BOLD	Blood Oxygen Level Dependency
ERP	Event-related Potentials
FEF	Frontal Eye Fields
fMRI	functional Magnetic Resonance Imaging
IFG	Inferior Temporal Gyrus
IFS	Inferior Frontal Sulcus
IPL	Inferior Parietal Lobule
IPS	Intraparietal sulcus
ISI	Inter-stimulus Interval
ITG	Inferior Temporal Sulcus
JND	Just noticeable Difference
MEG	Magnetoencephalography
MFG	Middle Frontal Gyrus
MNN	Mismatched Negativity
PCG	Postcentral Gyrus
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PPC	Posterior Parietal Cortex
Pre SMA	PreSupplementary Motor Area
ROI	Region of Interest
SFG	Superior Frontal Gyrus
SFS	Superior Frontal Sulcus
SMA	Supplementary Motor Area
SMG	Supramarginal Gyrus
SPL	Superior Parietal Lobule
STG	Superior Temporal Gyrus
STS	Superior Temporal Sulcus
TPJ	Temporoparietal Junction
TR	Time of Repetition
VFC	Ventral Frontal Cortex

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Chapter 3 Figure Captions

Fig., 1. Condition-based contrast maps showing target (orange) and distracter (green) related activations for the auditory (a) and tactile (b) modalities averaged across nine subjects. All active voxels are statistically significant at an alpha of 0.005 (uncorrected). To limit false positives (type 1 error), a cluster filter correction was implemented (see methods). All brains are shown in radiological convention (right on left).

Fig. 2. Conjunction analysis and target/distracter contrast maps are shown under a statistical threshold of $p > 0.001$, and corrected for multiple comparisons using a false discovery rate (FDR) technique. The conjunction (a) was performed between auditory and tactile modalities for the target related conditions. The target/distracter contrast map (b) shows 1) highly significant activity that was exclusively evoked by all target stimuli and 2) a lack of statistically significant activity for the distracter conditions greater then target conditions averaged across both modalities. All brains are shown in radiological convention (right on left).

Fig 3. An event-related ROI analysis is shown from four regions plotting target, distracter and standard time course information from both auditory and tactile modalities. Time courses were extracted from unimodal conditions where auditory and tactile modalities were presented alone. Active voxels within each ROI was determined from the conjunction analysis. Talairach coordinates of the center voxel within each region is provided.

Fig 3. Averaged event-related responses for attended and ignored targets and distracter stimuli is presented from four ROIs extracted from the bimodal scans. Subjects were cued to switch attention between simultaneously presented stimulus streams every thirty trials and respond to only stimuli presented within the attend modality.

	modality(s) tested	distracter included	response made; task relevancy	# of slices	conditions	Parietal						
						SMG/TPJ/IPL	SPL	angular	precuneus	IPS	Post Cing	PCG
	Auditoy											
et al., 1997	auditory	no	button press	6	target	x						
t al., 1999	auditory	no	count	7	target	x						
et al 1999	auditory	no	Neutral / passive listening	10	deviant	x						
t al., 2001	auditory	yes (complex acoustic tones)	button	29	target distracter	x o	x		x		x	
t al., 2002	auditory	no / 3 complex tones with small, medium large deviations	task irrelevant / watched silent movie	8	small deviation medium deviation larget deviation							
t al., 2003	auditory	no	No response / active listening	15	deviant	x						
nn et al., 2004	auditory	yes (2-letter cyllables - dichotically presented)	button press	8	target in left ear target in right ear * distracter activations not provided			 x	x x	 x	x	
et al., 2004	auditory	no	button press	10	target	x			x			
s et al., 2005	auditory	yes (complex acoustic tones)	button	29	target distracter	x o	x o		x			
t al., 2005	auditory	yes (complex acoustic tones)	button	29	target distracter	x o	x o		x		x	
et al., 2005	auditory	no	count	16	target	x						
l et al., 2005	auditory	no	button press on attend conditions	16	attend ignroe (perform visual discrim task)							

	modality(s) tested	distracter included	response made/ task irrelevant	# of slices	conditions	Parietal						
						SMG/TPJ	SPL	angular	precuneus	IPS	Post Cing	PCG
	Visual											
hy et al., 1997	visual	no	count	4	target	x					x	
t al., 2000	visual	yes (the letter x)	button press	20	target distracter	x o	x					
ni et al., 2002	visual	no	count	15	target	x	x				x	
ski et al., 2004	visual	yes (distracter varied witt shape and viewing angle)	button press	16	target distracter	x o	x o			 o		
	Polymodal											
et al., 1999	auditory, visual	no	button press & count	12	Aud press Aud count Vis press Vis count	x x x x			x x		x x	
a et al., 1999	auditory, visual	no	count	10	auditory visual	x x		x x		x x		
et al., 2000	auditory, visual	no	count	8	auditory visual	x x					x	
et al., 2000	auditory, visual, tactile	no	Neutral / passive attention	25	auditory visual tactile	x x x	 x					 x
et al., 2001	auditory, visual presented simultaneously	no	Finger raise	25	aud relevant aud irrelevant vis relevant vis irrelevant	x x x x			x x		x x x x	
et al., 2002	auditory, visual, tactile	no	Neutral / passive attention	25	auditory visual tactile	x x x						
& Stevens	auditory, tactile	yes	button press	20	Aud Target Aud Distracter Tac Target Tac Distracter	x o x o		 o	 x			

Table 1a. Study parameters and reported activations within the frontal lobe of fMRI tasks employing oddball tasks. x: denotes target related activity, o: represents activity to distracters

	conditions	Temporal					Frontal											
		STS	STG	MTG	MTS	ITG	IFG	IFS	insula	frontal oper	orbital	MFG	MFS	SFG	Cing Gyr	ACC	SMA	Pre SMA
n et al., 1997	target															x		
et al., 1999	target		x															
et al 1999	deviant		x				x											
et al., 2001	target		x	x		x	x		x			x		x		x		
	distracter		o	o		o	o		o			o				o		
et al., 2002	small deviation		x															
	medium deviation		x				x			x								
	larget deviation		x				x			x								
et al., 2003	deviant		x						x			x				x	x	
ann et al., 2004	target in left ear		x				x											
	target in right ear		x						x									
	* distracter activations not provided																	
et al., 2004	target		x						x			x			x		x	
ns et al., 2005	target			x		x	x					x		x				
	distracter			o		o	o					o						
et al., 2005	target		x	x		x	x		x			x		x		x		
	distracter		o	o		o	o		o			o				o		
l et al., 2005	target			x			x					x				x		
ll et al., 2005	attend		x				x					x				x		
	ignroe (perform visual discrim task)		x															

	conditions	Temporal					Frontal											
		STS	STG	MTG	MTS	ITG	IFG	IFS	insula	frontal oper	orbital	MFG	MFS	SFG	Cing Gyr	ACC	SMA	Pre SMA
thy et al., 1997	target											x						
et al., 2000	target		x				x		x			x						
	distracter		o				o					o		o				
ni et al., 2002	target								x			x				x		x
wski et al., 2004	target	x		x			x		x			x			x			
	distracter						o	o	o			o						
	Polymodal																	
et al., 1999	Aud press								x	x								
	Aud count			x					x	x		x				x	x	
	Vis press								x	x						x	x	
	Vis count								x	x						x	x	
ra et al., 1999	auditory	x	x	x					x			x				x	x	
	visual	x		x					x			x				x	x	
s et al., 2000	auditory	x	x	x			x					x			x			
	visual			x			x					x			x	x		
r et al., 2000	auditory		x	x			x		x								x	
	visual			x			x		x								x	
	tactile			x			x		x								x	
r et al., 2001	aud relevant		x			x	x		x			x				x	x	
	aud irrelevant		x			x	x		x			x				x	x	
	vis relevant		x			x	x		x			x				x	x	
	vis irrelevant		x			x	x		x			x				x	x	
r et al., 2002	auditory		x			x	x		x							x		
	visual		x			x	x		x							x		
	tactile		x			x	x		x							x		
& Stevens	Aud Target	x	x				x	x	x		x		x	x		x		x
	Aud Distracter	o	o													o		
	Tac Target						x	x	x		x	x	x	x		x	x	
	Tac Distracter													o		o		

Table 1b. Activations within the parietal and temporal lobes of fMRI studies employing oddball tasks. x: denotes target related activity, o: represents activity to distracters

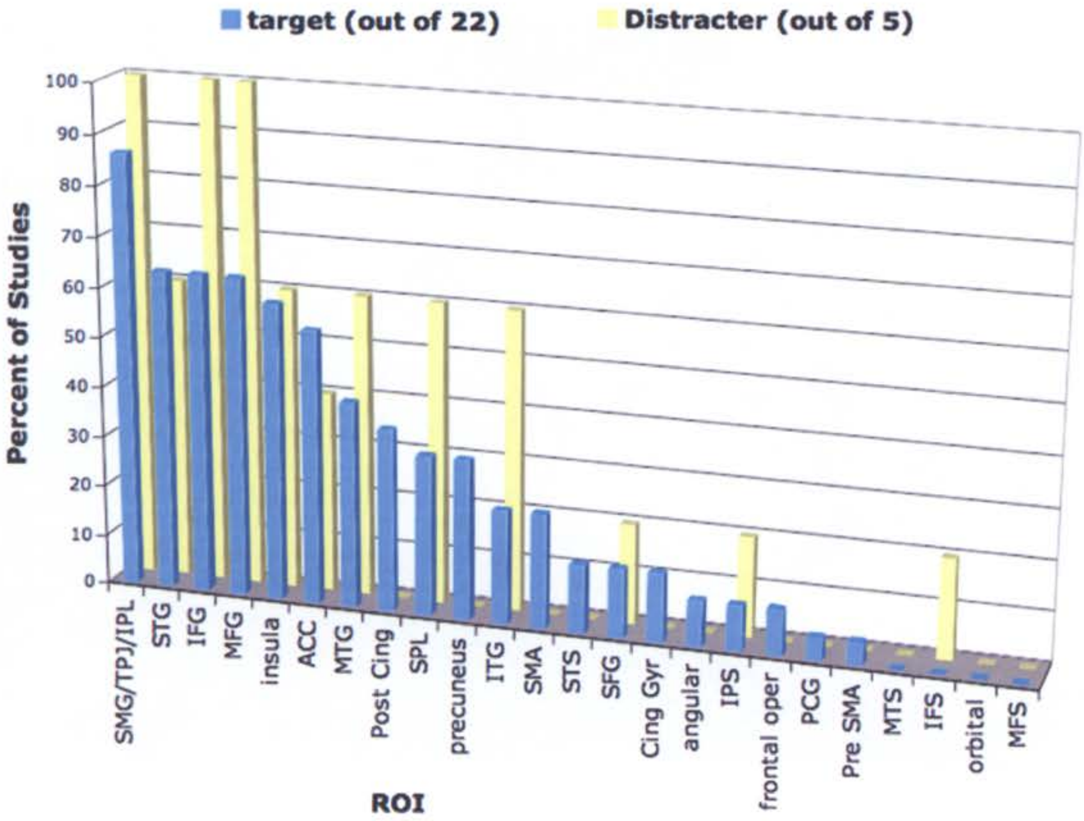
target (out of 22)
Distracter (out of 5)
Percent of Studies
100
90
80
70
60
50
40
30
20
10
0
SMG/TPJ/IPL
STG
IFG
MFG
insula
ACC
MTG
Post Cing
SPL
precuneus
ITG
SMA
STS
SFG
Cing Gyr
angular
IPS
frontal oper
PCG
Pre SMA
MTS
IFS
orbital
MFS
ROI

Figure 1.

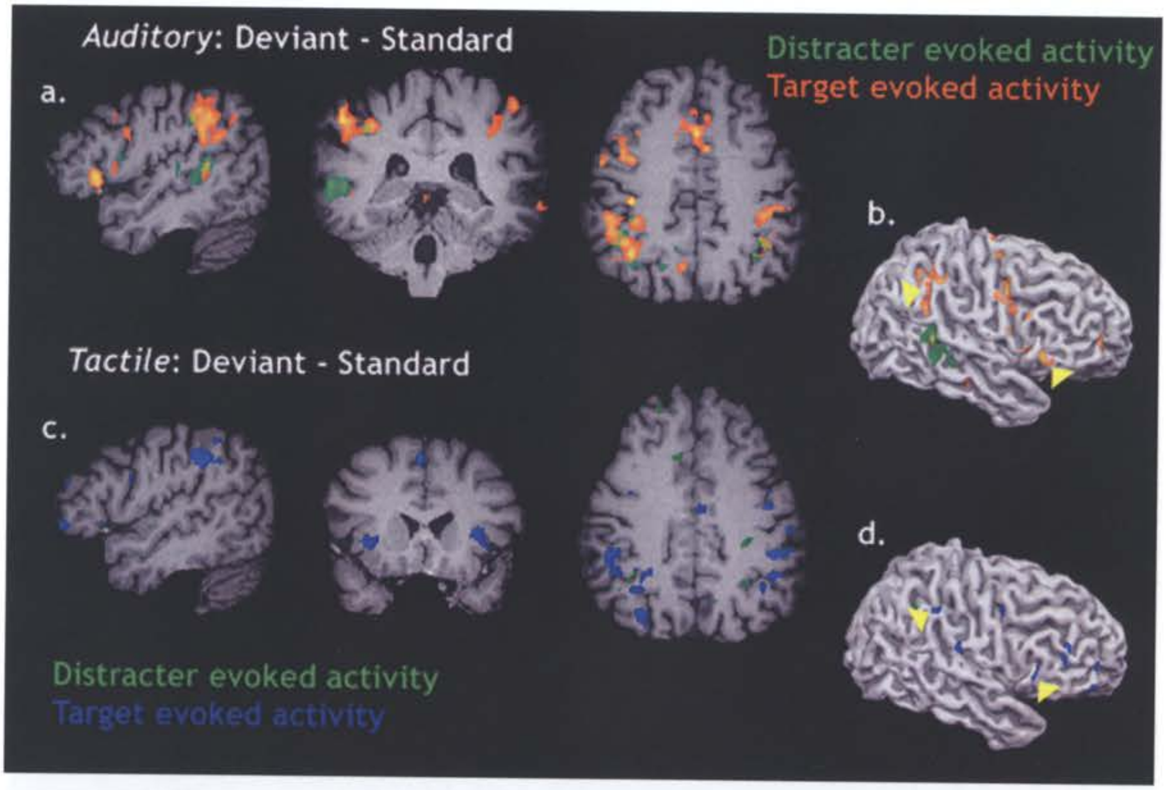
Auditory: Deviant - Standard
a.
Distracter evoked activity
Target evoked activity
b.
Tactile: Deviant - Standard
c.
d.
Distracter evoked activity
Target evoked activity

Figure 2.

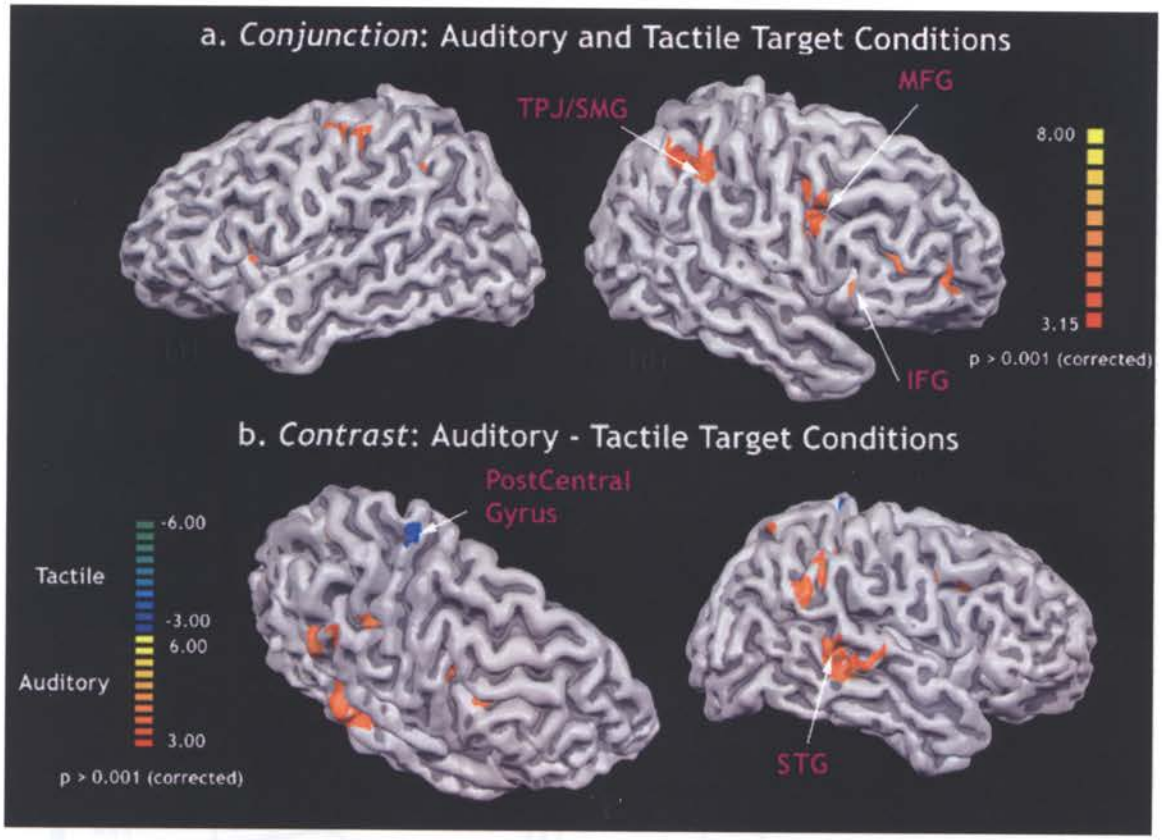
a. *Conjunction*: Auditory and Tactile Target Conditions
TPJ/SMG
MFG
8.00
3.15
p > 0.001 (corrected)
IFG
b. *Contrast*: Auditory - Tactile Target Conditions
PostCentral
Gyrus
-6.00
Tactile
-3.00
6.00
Auditory
3.00
p > 0.001 (corrected)
STG

Figure 3.

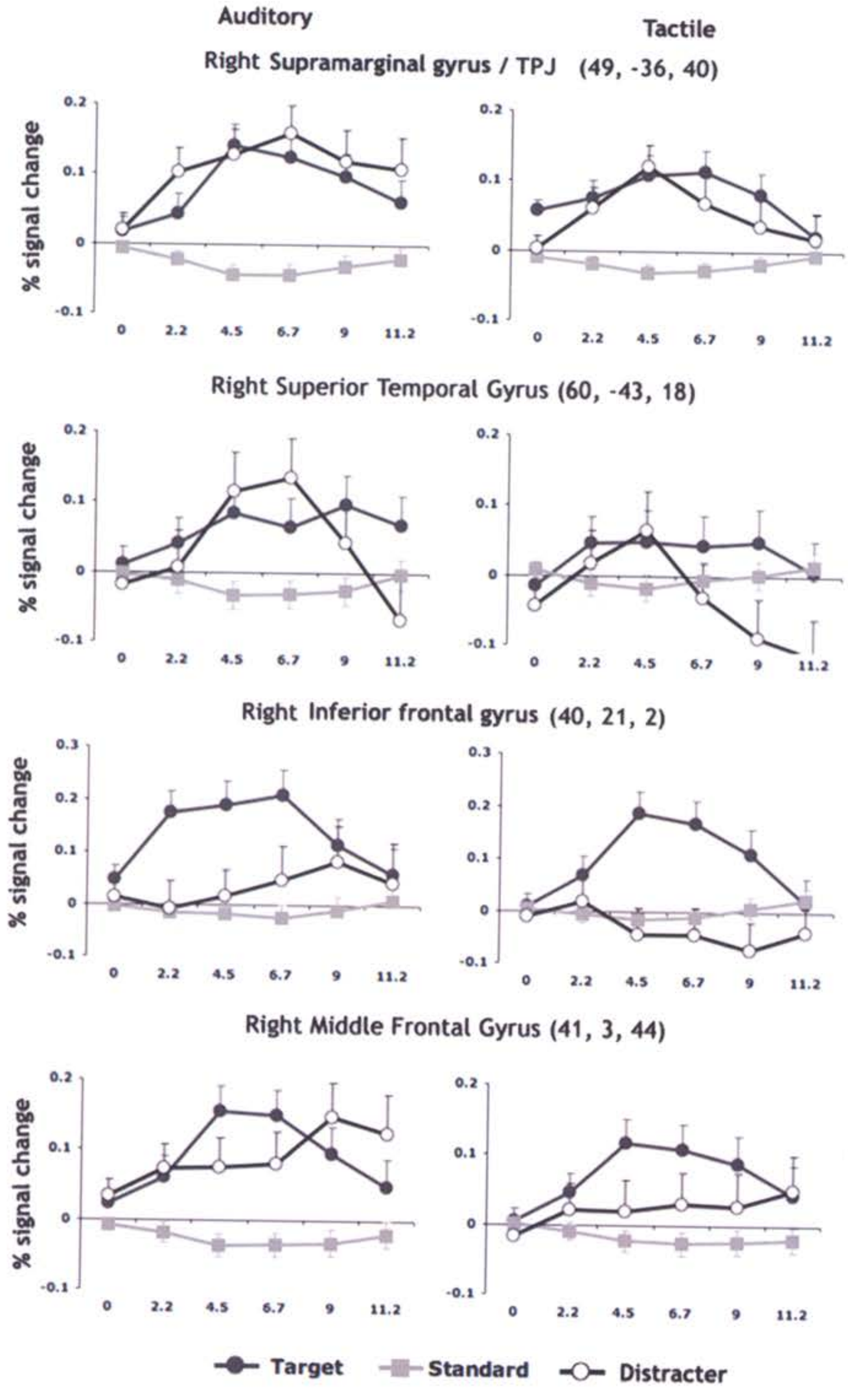
Auditory
Tactile
Right Supramarginal gyrus / TPJ (49, -36, 40)
Right Superior Temporal Gyrus (60, -43, 18)
Right Inferior frontal gyrus (40, 21, 2)
Right Middle Frontal Gyrus (41, 3, 44)
% signal change
0.3
0.2
0.1
0
-0.1
0
2.2
4.5
6.7
9
11.2
Target
Standard
Distracter

Figure 4.

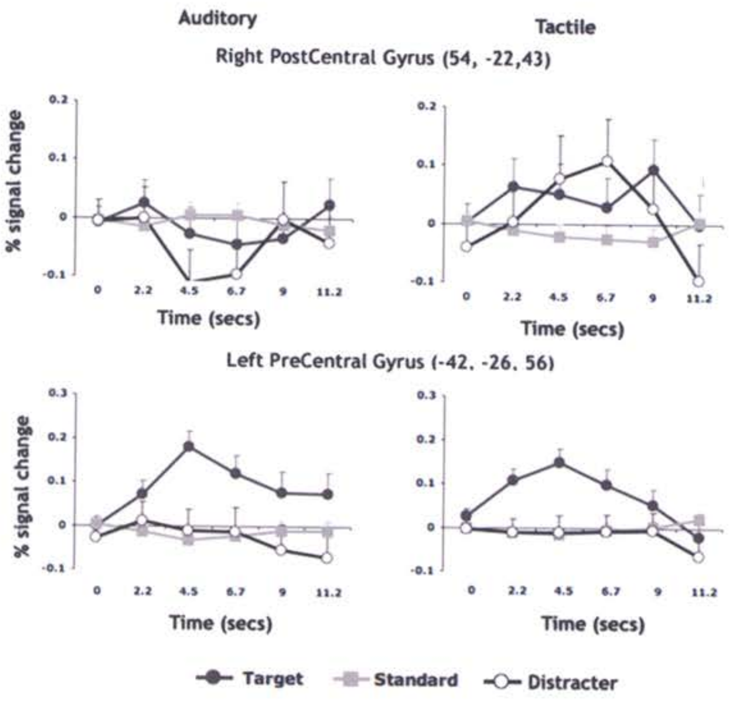
Auditory
Tactile
Right PostCentral Gyrus (54, -22,43)
% signal change
0.2
0.1
0
-0.1
0
2.2
4.5
6.7
9
11.2
Time (secs)
Left PreCentral Gyrus (-42, -26, 56)
0.3
Target
Standard
Distracter

Figure 5.

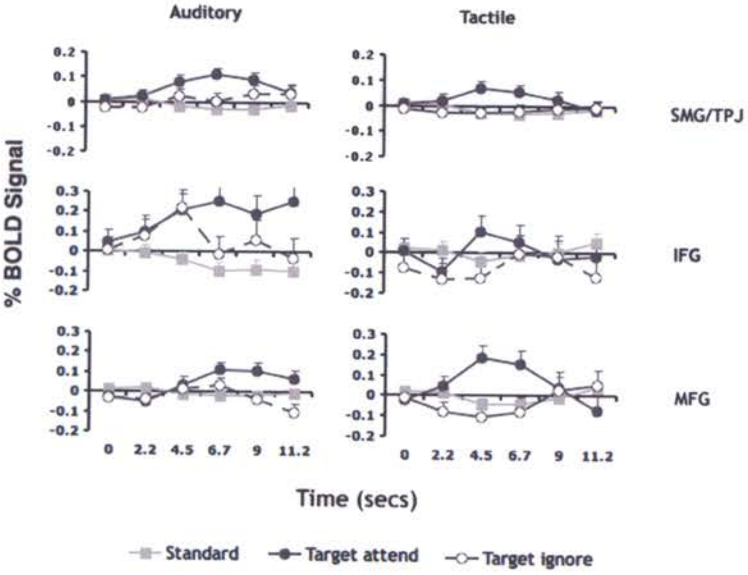
Auditory
Tactile
% BOLD Signal
0.2
0.1
0
-0.1
-0.2
0.3
SMG/TPJ
IFG
MFG
0
2.2
4.5
6.7
9
11.2
Time (secs)
Standard
Target attend
Target ignore

Figure 6.

Chapter 3, Supplementary information:

Tables 1a and 1b are to be posted online to accompany hard copy material

The following table outlines tactile (table 1a) and auditory (table 1b) evoked activity in response to targets and distracter stimuli. Active voxels were a result of target or distracter conditions contrasted with standard stimuli at a significance threshold of $p > 0.005$ extracted from the unimodal scans. False positives were restricted through use of a cluster filter threshold.

Supplematry Table 1a. Tactile Responsive Zones

ROI		Hemisphere	Talairach Coordinates X	Y	Z	Mean T Score	Cluster size
Tactile Target							
Frontal							
	IFG	R	38	22	4	3.756	765
	IFS	R	43	38	7	3.798	114
	Insula	R	30	17	5	3.658	403
	MFS	R	37	33	18	3.539	386
	Oribital Frontal	R	35	56	11	3.584	490
	SFG	R	21	-14	61	3.771	422
	ACC	L	-3	-8	40	3.620	160
	Insula	L	-29	16	9	3.539	568
	MFG	L	-43	30	24	4.171	358
	Precentral Sulcus	L	-28	-16	56	3.687	541
	SFG	L	3	17	51	3.805	376
	SFG	L	0	7	46	3.593	364
	SMA	L	-3	-5	44	3.806	343
Parietal							
	IPL	R	32	-55	41	3.677	400
	Precuneus	R	23	-69	38	3.804	519
	SMG/TPJ	R	48	-37	41	3.776	1013
	IPL	L	-55	-27	31	4.012	496
Subcortical							
	Caudate	R	11	4	8	3.617	354
	Putamen	R	23	14	6	3.690	187
Tactile Distracter							
Frontal							
	ACC	R	10	21	38	3.647	130
	SFS	R	21	39	47	3.612	117
Parietal							
	IPL/SMG	R	35	-46	38	3.534	80

Supplematry Table 1b. Auditory Responsive Zones

ROI	Hemisphere	Talairach Coordinates X	Y	Z	Mean T Score	Cluster size
Auditory Target						
Frontal						
ACC	R	9	17	36	3.763	693
IFG	R	49	22	2	3.965	1504
IFS	R	49	4	27	3.773	474
Insula	R	32	20	5	3.769	754
MFS	R	40	1	44	3.98	1394
Orbital	R	32	52	6	3.633	947
SFS	R	22	-10	56	4.064	1282
SFG		1	12	42	3.77	1398
PreSMA		-1	-9	62	3.749	1266
PreCentral	L	-32	-16	56	3.942	1340
Parietal						
IPL	R	34	-59	32	3.771	345
IPL	R	39	-48	44	3.991	2002
SMG	R	49	-39	42	4.072	1745
IPL	L	-38	-52	35	3.683	770
SMG	L	-40	-46	46	3.086	825
Temporal						
STG	R	61	-20	5	3.769	289
STG	R	49	-44	28	3.93	897
STS	R	46	-41	8	3.625	375
STS	R	58	-28	1	3.672	275
Subcortical						
Caudate	R	13	6	11	4.113	2257
Putamen	R	23	8	5	3.832	446
Caudate	L	-18	15	10	3.941	297
Putamen	L	-14	1	10	3.751	565
Thalamus	L	-16	-15	15	3.848	430
Auditory Distracter						
Frontal						
ACC	R	3	-4	36	3.709	161
ACC	L	-6	-4	36	3.874	138
Parietal						
IPL	R	36	-60	42	3.609	115
SMG/TPJ	R	42	-44	42	3.517	372
Angular	R	35	-63	30	3.821	245
IPL/SMG	L	-36	-51	39	3.567	751
Temporal						
STS	R	52	-38	8	3.839	2344
STG	R	63	-21	11	3.852	330
Subcortical						
Putamen	R	23	6	7	3.681	691

Chapter 4: General Discussion

Summary of Findings

The general finding from the oddball experiments reveal that auditory and tactile target and distracter but not standard stimuli evoked event-related BOLD responses within occipital regions in EB individuals. There was no evoked Occ activity from any stimulus condition in the matched SC participants. These response discrepancies within Occ regions of the EB suggest that differences in the underlying processing between infrequent deviant events and repeated standard events activate Occ regions in the EB but not the SC. The distracter stimuli were designed to be salient from the standard stimuli but were regarded as irrelevant (i.e. behaviorally equivalent to the standard). Therefore, significant distracter responses detected in both modalities reveals the presence of bottom-up orienting mechanisms within these regions. In addition, clear attentional modulations of target stimuli were revealed during the bimodal conditions. The effect of attention was not equivalent in all ROIs and the response depended on which modality was attended. When EB subjects attended to the auditory stream and ignored simultaneously presented tactile stimuli, auditory targets elicited BOLD responses comparable to or larger than those detected in the auditory alone condition in the calcarine sulcus, lingual gyrus and cuneus. Conversely, ignored auditory targets elicited no positive BOLD response in any of these regions. Thus, a response to auditory stimuli only appeared when they were attended. This amplification effect of attention demonstrates similar mechanisms of attention observed within the SC brain (Posner & Driver, 1992; Driver & Frackowiak, 2001; Kastner & Ungerlieder, 2001) and suggests that Occ regions in the EB are either the recipient (site) or reflects the control (source) of such modulations.

These results uncover mechanisms of both bottom-up and top-down attentional mechanisms within Occ regions of the EB. Although the precise function of these regions within attentional systems is unclear, top-down and bottom mechanisms likely play a key role in driving Occ cross-modal reorganization during development without vision. An expanded cortical network dedicated to the detection of deviant stimuli may account for the enhanced target detection abilities observed within the auditory conditions.

Neural Networks of Attention in the Sighted Control

Target detection and distracter processing in the SC detailed in chapter 3 activated regions linked to top-down and bottom-up processes reported throughout the literature. A number of temporal lobe regions, including the STS and MTG responded to auditory deviants but not to tactile stimuli, corresponding well with a role in auditory perceptual functions. Deviants of both modalities evoked responses within the SMG/TPJ (BA 40) region within the right hemisphere. This result supports the hypothesis that ventral IPL regions resolve whether a stimulus of any modality that deviates from background noise is relevant to engage attentional resourses (Downar et al., 2001; Serences et al., 2005). The results from the unimodal scans in the SC in addition to previous studies (see Aron et al., 2004) suggest that the right IFG determines an appropriate motor plan in response to various deviant stimuli. When attention is focused on a given stimulus train expected to contain a deviant, top-down afferents from superior frontal regions amplify the electrophysiological responses evoked by the deviant within sensory cortex.

INSERT CHAPTER4, FIGURE 1 ABOUT HERE

Neural Networks of Attention in the Early Blind

Non-Occipital Activity

Targets and distracters in both modalities evoked similar patterns of responses within frontoparietal regions in EB participants. An overlay of whole brain target contrast maps from both SC and EB groups reveals overlapping activity to auditory targets within the SMG/TPJ and IPL, bilaterally and the right insula (see chapter 4, fig. 1). As in the SC group, there was no significant BOLD response observed within superior parietal regions. A number of frontal regions were active in both groups as well, including the ACC and right SFG (see Chapter 4, Table 1 for a description of overlapping regions). Auditory targets also engaged a region with the STG in both groups. Responsive regions to auditory distracters did not result in nearly the same extent of group overlap as the target conditions, with the exception of a large overlapping cluster within the right STS. There were however a number of non-overlapping active clusters within regions. For example, the right IPL was active in both groups but the cluster was located more ventrally within the EB. Within the frontal lobe, the left ACC showed small degree of overlap response in both groups.

Detection of tactile targets engaged overlapping regions between groups within the IPL and SMG, bilaterally and right IFG and left insula within the frontal lobe. Tactile distracters did not engage any overlapping voxels.

INSERT CHAPTER 4, TABLE 1 ABOUT HERE

A few previous fMRI reports have also examined whole brain similarities between EB and SC groups. Burton et al., (2003) reported greater left IFG activity during a semantic relative to a phonological task in both SC and EB individuals. The same authors also observed comparable activations within classic language regions such as Wernicke's area during a verb generation task (Burton et al., 2002). Taken together, this evidence suggests that non-occipital regions in people with early visual loss do not develop the same degree of functional reorganization observed within the Occ cortex. Because of the functional similarities (i.e. similar regions in both groups responding to the same task conditions) in this and other studies, it is possible that regions outside of the Occ lobe provide analogous functional roles in each group (for example, see Burton et al., 2004b; Garg et al., 2006).

INSERT CHAPTER 4, TABLE 2 ABOUT HERE

However, there were notable whole brain group differences (see Chapter 4, Table 2 for a list of non-Occ regions in the EB). Auditory targets activated a large area within the posterior cingulate but only in the EB group. In addition, auditory targets also activated a larger number of right localized frontal regions in the SC, including spots within the MFG and IFG. Conversely, the left IFG showed a significant BOLD response to auditory targets in only the EB. Auditory distracters were more effective at activating frontal regions within the EB, including the right IFG, a region implicated in many studies examining auditory distraction in SC people (Halgren et al., 1998; Kiehl et al 2001, 2005; Stevens et al., 2005). Interestingly, tactile targets in the EB engaged a number of spots within the SPL, bilaterally. This condition was the only stimulus event that was effective in engaging superior parietal regions consistently implicated in top-down control (Pessoa et al., 2003; Corbetta & Shulman, 2002). It is unclear what the significance of differentially active regions in the EB relative to the SC within in any condition. The blind may have used different strategies to accomplish the same task and thus resulted in different patterns of brain activity. For example, the left IFG has been implicated in a number of verbal tasks including semantic processing (Poldrack et al., 1999). Thus, auditory-evoked BOLD responses within the left IFG in the EB may be a reflection of semantic labeling. Alternatively, regions throughout the brain such as the posterior cingulate may develop new functional roles as a result of early visual loss. Further research is needed to examine these possibilities given the few number of studies that have conducted whole brain comparisons between EB and SC individuals.

INSERT CHAPTER 4, FIGURE 2 ABOUT HERE

One striking effect that appeared between groups was large decrease in the summed number of active voxels across the brain in response to auditory and tactile target conditions (excluding Occ voxels in the EB – see chapter 4, fig. 2). This effect was not washed out even when Occ voxels in the EB were included (data not shown). The significance of an overall weaker response in the EB is uncertain, but maybe an indication of greater processing efficiency. EB individuals may not need to devote the same level of neural and/or metabolic resources as SC individuals to achieve similar (and even better than) performance levels.

A Functional Role for Occipital Cortex in the Early Blind

The most substantial group differences were observed within the Occ lobe of EB individuals. In the SC, Occ regions respond to visual but not auditory or tactile deviants, implicating these regions in visual perceptual roles (Clark et al., 2000; Ardekani et al., 2002; Bledlowski et al., 2004). To delineate the functional role of Occ ROIs in the EB, time course profiles were extracted from various regions throughout the cortex and compared to Occ ROIs (Chapter 4, Figure 3). Event-related averages extracted from an auditory association region, the right MTG revealed a response to auditory targets and distracters but not to tactile stimuli. Likewise, event-related responses from somatosensory cortex showed a response to tactile but not auditory deviants (Chapter 4, Figure 3a,b). This implies that the MTG and postcentral gyrus are involved in auditory and tactile perceptual operations, respectively. Modality-specific results also imply that activity within sensory association cortex does not reflect a polymodal, cognitive-based mechanism. The bimodal responses to targets and distracters within Occ regions of the EB highlights the functional differences between Occ regions and auditory and somatosensory cortex, substantiating that Occ ROIs are not an extension of sensory cortex. An ROI analysis from the precentral gyrus (i.e. primary motor cortex) revealed a response to target but not distracter stimuli in both modalities (Chapter 4, Figure 3c). This suggests that Occ activity to targets and distracters is in addition also not reflective of a motor response, a hypothesis that has previously been put forth on the basis of fMRI (Gizewski et al., 2003) and TMS evidence (Amedi et al., 2004).

INSERT CHAPTER 4, FIGURE 3 ABOUT HERE

The functional role provided by Occ regions maybe similar to the right SMG/IPL region. The SMG/TPJ region showed similar response time courses and signal amplitudes across modalities and stimulus types for both SC (detailed in Chapter 3) and EB (Chapter 4, Figure 3d) groups, suggesting activity in this region in the EB reflects polymodal attentional functions. The nearly identical response profiles for all deviant stimuli between Occ ROIs and the SMG/TPJ region therefore supports the hypothesis that Occ cortex provides a more generalized, uniform role within information processing pathways in the EB (Roder et al., 1996; Roder & Rosler, 2004).

An overwhelming majority of neurophysiological, hemodynamic and TMS evidence suggests that the Occ cortex in the EB supports a late role within various information processing pathways (Liotti et al., 2003; Amedi et al., 2004; Pascual-Leone et al., 2001; Neville & Roder, 2002). A number of ERP studies have observed a posterior shift in the late ERP deflections, specifically the P2b and P3 complex in response to target stimuli (Kujala et al., 1992, 1997; Alho et al., 1993). Functional neuroimaging studies have linked Occ cortical regions in EB individuals to a variety of higher-level, cognitive based functions including memory encoding and retrieval (Amedi et al., 2003, 2004), auditory mental imagery (DeVolder et al., 2001) and semantic analysis during sentence processing (Roder et al., 2002) but not to the passive perception of sensory stimuli (Gizewski et al., 2003; Sadato et al., 1998). Very recently, investigators used TMS to show that a transient disruption of a region located within the cuneus did not interfere with lower level acoustic processing tasks (i.e. acoustic frequency and intensity discrimination) but rather impaired discrimination on a complex pattern recognition task

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(Collingnon et al., 2006). The wide range of discriminations and cognitive tasks reported to engage Occ cortex combined with evidence suggesting Occ regions are not engaged during passive sensory stimulation opens the possibility that Occ neurons in the EB are engaged by a shared cognitive mechanism common to all tasks of information processing. One potential mechanism is attention.

Bottom-up Attentional Orienting

The current observations outlined in chapter 2 suggest that a number of Occ regions in the EB facilitate the reorienting of attention to salient sensory stimuli. All Occ ROIs in the blind showed a significant response to auditory and tactile distracter stimuli during unimodal conditions and significant auditory distracter effects within the calcarine sulcus and cuneus in the bimodal conditions. This effect was unanticipated in view of the irrelevant nature of the distracter stimulus (i.e. subjects were told to ignore distracters and make the same response as the standard). For instance, Gizewski et al., (2003) reported no Occ BOLD activity in response to passive electrical stimulation of the right median nerve (leading to a perception of vibratory stimulation) of EB and SC subjects. However, in the aforementioned study, the applied electrical stimulation was identical across the scan. Thus, distracter activation within the Occ lobe in the EB reflects processes related to the deviance of the distracter. Similar to the SMG/TPJ region, significant responses to both auditory and tactile distracters within Occ ROIs suggests that this activity reveals mechanisms of attentional reorienting.

Distracters in a 3-stimulus paradigm are designed to capture attention away from the primary task of target detection (Courchesne et al., 1975; Knight, 1984; Escera et al., 2002; Combs & Polich, 2006). For example, previous behavioral studies have shown that unattended distracters relative to unattended standards disrupt discrimination performance on a primary task. Furthermore, the magnitude of deviation between the distracter and the standard is positively correlated with the amount of performance disruption on the primary task (Escera et al., 2002; Yago et al 2001). These results suggest that the unanticipated presentation of infrequent distracters captures attention and redirects it away from the primary focus (Knight, 1984; Escera et al., 2002; Serences et al., 2005).

In the blind, a greater sensitivity to redirecting attention to salient, unexpected stimuli would be a highly advantageous behavior. It is possible that Occ regions in the blind are an expansion of the network responsible for reorienting attention to salient auditory and tactile stimuli (i.e. ventral frontoparietal regions, see Corbetta & Shulman, 2002). A larger network designated to reorient attention to salient deviant events would potentially allow for a greater precision in, or a more rapid detection of potentially meaningful stimuli (Kujala et al., 1997; 2005). Furthermore, expansion of bottom-up mechanisms to the Occ cortex may account for sound source location advantages previously described in EB individuals. Lessard et al., 1998 demonstrated that some EB individuals are significantly more accurate than SC listeners at detecting the location of a sound source along the azimuth under monaural listening conditions. A PET study by the same group found that Occ regions including the calcarine sulcus were active during monaural localization but in only the EB individuals that showed an initial advantage (Gougoux et al., 2005). Occ processing of unexpected stimuli that occur outside of the current attentional focus (in this case occurring at unattended locations) may allow individuals to pick up on subtle acoustic cues resulting in distinct behavioral advantages.

It should be noted however, in a separate study EB individuals actually performed more poorly when sounds were presented along the vertical plane (Zwiers et al., 2002). The authors speculated that the poorer performance in the EB is the result of an underdeveloped visual-spatial calibration system. Although the blind maybe more sensitive to non-visual stimuli presented outside of the attentional focus, this evidence clearly points the influence of visual information on 3-dimensional detection abilities.

Top-down Attentional Control

Attention-based modulations observed in response to auditory target stimuli contribute to the hypothesis established by ERP studies that Occ regions in the EB respond as a function of selective attention (Kujala et al., 2000). Target amplifications were observed to the auditory target but not in response to the auditory standard. This suggests that attentional mechanisms boosted the neural response evoked by the behaviorally-relevant target stimulus but not to the background standard. It is now well established that selective attention mechanisms function to potentiate or 'amplify' stimulus-specific neural signals. A wealth of neuroscience-based research including monkey single and multiple unit recordings, human ERP and fMRI studies supports this view (Motter, 1993; McAdams & Maunsell, 1999: Somers et al., 1999; Manusell & Cook, 2002; Egner & Hirsch, 2005). These studies demonstrated that neural activity to a selectively attended stimulus within sensory cortical regions is significantly higher then the neural response to the same stimulus when ignored. Attention-based amplification within the Occ cortex of EB individuals raises two possibilities: one, that Occ regions are either themselves modulated by attentional mechanisms (i.e. the recipient of signal enhancement, commonly observed in extrastriate cortex of intact sensory systems) or two, these regions aid in control over signal enhancement mechanisms and thus reflect control over the operations of attention (see Posner & Driver, 1992; Kastner & Ungerlieder, 2001 for a discussion of cortical regions involved in these processes in the SC).

A second mechanism that aids in the selective attention process is the suppression of neural activity evoked by distracting or irrelevant stimuli (Reynolds et al., 1999; Awh & Pashler, 2000; Serences et al., 2004). During the bimodal scans, subjects were told to ignore the simultaneously presented tones when attending to the vibrations. This condition resulted in a negative event related response extracted from the calcarine sulcus ROI. This negative response suggests that the calcarine sulcus may actively inhibit or suppress irrelevant auditory stimuli (see Shmuel et al., 2002, 2006 for a discussion on the negative BOLD). Support for the existence of suppressive mechanisms in Occ regions of the EB comes from a study that simultaneously presented auditory and tactile stimuli during ERP recordings (Hotting et al., 2004). When subjects were asked to simultaneously attend to a specific location and a specific modality, a persistent positivity was observed in the EB to stimuli of the ignored modality when presented at the attended location. Because the SC showed an enhanced negativity (relative to unattended stimuli presented at the unattended location), the authors speculated that the EB actively inhibit ignored modalities even when presented at attended locations.

The current fMRI results also uncovered mechanisms of suppression within the Occ lobe to attended tactile responses. This response suppression, which was observed during the bimodal scans, occurred despite focused attention to the tactile stream. The asymmetrical response observed between unimodal and bimodal scans (i.e. positive event-related responses to tactile targets presented alone) indicates that the addition of simultaneously presented pure tones resulted in an inhibited tactile response. This effect may account for the slower response times observed to tactile targets. One possible mechanism underlying the suppression of tactile responses during the bimodal scans is the arrival of auditory stimulation to the Occ cortex prior to the tactile stimulation. It is conceivable that the engagement of Occ circuits by unattended auditory information prior to the arrival of tactile stimulation may have prevented tactile responses. However, this possibility is unlikely, as ignored auditory targets did not induce a positive BOLD response within Occ ROIs. A second alternative may be an increased inhibitory tone from frontoparietal connections feeding into the Occ lobe in an attempt to ignore the irrelevant auditory stimuli.

Occipital lobe in the EB: organization and attention

The event-related results from the current study clearly demonstrate a complex interaction of both top-down and bottom-up mechanisms within Occ regions in the EB. As detailed in chapter 2, there is some evidence to suggest a differential expression of this interaction throughout the Occ lobe. For example, posterior Occ ROIs (calcaine *sulcus and cuneus) showed larger or equivalent responses to the auditory and tactile* distracters in both the unimodal and auditory distracters in the bimodal conditions relative to target responses. Conversely, larger or equivalent responses to tactile targets relative to distracters were observed from the unimodal scans within the anterior Occ ROIs (the lingual and fusiform gyri). Anterior regions did not respond significantly to auditory distracters but showed significant responses to the auditory targets from the bimodal scans. This pattern of event-related responses supports the hypothesis that the Occ lobe in the EB is parcelled into distinct functional domains (Amedi et a., 2003, 2004; Buchel, 2003; Raz et al., 2005). Tentatively, these results suggest that anterior Occ regions operate more during target detection and posterior regions respond more to stimulus saliency. Future fMRI studies that manipulate the saliency and behavioral-relevance of distracter and target stimuli are required to support this speculation.

The function of a given region within the Occ lobe however, may revolve around the pattern of efferent and afferent connectivity to and from that region. In the SC, extrastriate and striate Occ cortical regions received top-down signals through feedback connections originating from a variety of frontoparietal regions (Miller & D'Eposito, 2005; Hopfinger et al., 2000; Somers et al., 1999; Corbetta et al., 2000; Sack et al., 2002; Kastner & Pinsk, 2004). In addition, tract-tracing studies in sighted animals have established the presence of long range corticocortical connections between auditory and tactile sensory cortices and the Occ lobe (Flaicher et al., 2002; Clavagnier et al., 2004; Rockland & Ojima, 2003; Schroeder and Foxe, 2005). In the absence of vision during development, these corticocortical connections remain intact (Shimoney et al., 2006; Wittenberg et al., 2004; Hyvarinen et al., 1981). Bottom-up orienting to distracters within Occ regions of the EB could only occur if these regions had access to stimulus-driven sensory signals. Therefore, distracter responses within the Occ lobe support the notion that afferent auditory and tactile information is routed to the Occ lobe via corticocortical connections. The attention-based amplifications observed to auditory target stimuli suggest one of two distinct anatomical possibilities. First, auditory information is feeding into Occ cortex from auditory or multimodal cortical regions and attentional control signals from frontoparietal regions are modulating these responses (see Bavelier &

Neville, 2002). Second, Occ regions are sending out top-down signals, implying control of attention.

The current evidence does not allow for a distinction between Occ activity as reflecting top-down control signals and whether auditory or tactile signals feed in from corticocortical connections. If Occ signals in the EB code for the control of selective attention, then lesions within these regions should result in abnormalities of attention allocation. TMS studies that transiently disrupt activity within Occ regions in the EB have not directly tested this speculation. However, TMS over Occ sites has been shown to interfere with linguistic processing (Amedi et al., 2005), Braille reading (Cohen et al., 1997) and auditory pattern recognition (Collingnon et al., 2006). A case study of an EB woman who developed bilateral damage to the calcarine sulcus and surrounding extrastriate regions following an ischemic stroke did not show impairments of attentional allocation (e.g. no cognitive dysfunction after the stroke). This woman did developed complete Braille alexia, or the inability to read (Hamilton et al., 2000). However, this evidence does not completely rule out an Occ top-down control hypothesis. The otherwise normal cognition she displayed after the stroke is a likely result of intact normal circuitry supporting bottom-up and top-down attention (i.e. frontal and parietal lobes). Therefore, to investigate the interactions between these regions TMS studies manipulating the locus of TMS stimulation (such as over the Occ lobe and then stimulating superior frontal lobe regions) during both top-down and bottom-up deviant processing are suggested.

Behavioral Adaptation: a Consequence of Cortical Reorganization?

If Occ activity in the EB is linked to different attentional mechanisms, does processing within the Occ cortex result in enhanced attentional behaviors? In the current experiment, the EB detected significantly more auditory targets than SC peers. Although both groups of subjects detected a high number of targets during the unimodal scans (mean detection score > 85%), detection accuracy was statistically higher in the group of blind individuals. However, there were no correlations within any Occ ROI between peak BOLD signal and the percentage of auditory target detected or the response time to target stimuli. (data not shown). This null effect is the result of a ceiling performance across EB subjects and thus does not exclude the possibility that said brain-behavior relationships develop. For instance, Amedi et al., (2003) observed a significant positive correlation in the EB but not SC individuals between the number of words that could be recalled from long-term memory stores (6 months after encoding) and the amount of signal change observed within area V1 during recall. Because the mean number of words recognized by the EB group was significantly greater than the SC group, the authors suggested that this correlation reflects a cortical adaptation aiding in greater mnemonic abilities (Amedi et al., 2003). Supporting an association between Occ activation and behavior, sound localization accuracy using only monaural cues (with one ear plugged) significantly correlated with percent signal change within V1 and dorsal and ventral extrastriate regions (Gougouex et al., 2005) but in only EB individuals.

Several other possible mechanisms outside of Occ cortical reorganization could account for the superior auditory target detection in the EB. For example, an enlarged tonotopic map within auditory cortical regions in the EB may alter the normal processing of acoustic stimuli (Elbert et al., 2002). Plastic changes within auditory cortex could alter the normal MMN produced by a deviant stimulus presented within a train of standards. In turn, this effect could have enhanced target detection abilities. However, previous ERP studies in the EB reported that the mismatched negativity, MMN response to a deviant showed normal amplitude and topography compared to the SC individuals (see Kujala et al., 2000). Additionally, the current behavioral results demonstrated that EB and SC subjects were not different on an acoustic sensitivity task (i.e. Δ Hz. needed to discriminate the difference between two frequencies – sensory threshold task, see Chapter 4, Figure 4a). This suggests that plastic changes within auditory cortex do not specifically relate to advantages in behaviors supported by these circuits (see Phillips, 1995; Masterton, 1997; Rasuchecker, 1998 for reviews) and are unlikely to underlie target detection abilities observed in the EB (Roder & Rosler, 2004).

INSERT CHAPTER 4, FIGURE 4 ABOUT HERE

Second, target detection advantages in the EB may be the result of an enhanced working memory capacity. The detection of a target stimulus presented within a sequence of repeated standards requires a number of sensory and cognitive-based processes (Donchin & Coles, 1988; Polich, 2003). For example, participants must selectively attend to a predetermined stimulus stream (i.e. the one containing the target). After a stimulus is encoded and perceived, a memory trace must be maintained within working memory across the inter-stimulus interval in order to assess whether the succeeding stimulus is different. A growing body of evidence has revealed that EB individuals consistently outperform SC peers on tasks that tax various memory systems. Roder and others reported that the EB were more accurate at recognizing previously encoding words (2001) or complex environmental sounds (2003) after a delay of several minutes. This advantage has also been shown to extend to simple pure tone stimuli within a working memory setting. Previous work in our lab presented EB and SC listeners with a 2-alternative force task requiring subjects determine whether two pure tones separated by a variable delay were the same or different. The EB proved to be statistically more accurate (show less forgetting) across the longest delay of 5000 ms (See Chapter 4, Figure 4b). There were however, no significant group differences at any of the shorter retention intervals (including 1000 and 3000 ms). This evidence suggests that the blind outperform sighted counterparts on a variety of memory related tasks but only when the retention interval is sufficiently long. However, based on this previous experiment, the ISI in the current oddball task (set at a fixed value of 2250 ms) argues against the notion that the superior auditory detection in the EB is a function of working memory advantages.

A third alternative accounting for greater detection accuracy in the EB stems from improved attentional abilities. A few behavioral studies have provided some evidence to support this hypothesis. For instance, EB individuals outperform the SC when having to divide their attention between auditory and tactile modalities (Kujala et al., 1997) or between modality and space (Collingnon et al., 2006). These experiments suggest that the EB can attend to a larger capacity of information at any given moment. EB individuals were also less distracted by irrelevant syllables presented in an unattended ear during a dichotic listening task (Hugdahl et a., 2004). Enhanced attentional abilities could account for a greater capacity to discriminate between auditory targets and standard stimuli. The blind may be more sensitive to the MMN evoked by targets after the presentation of a repeated standard within auditory pathways. That is, the consequences of blindness may result in greater sensitivity to the MMN response arising from auditory association cortex, independent of the magnitude or intensity of that response. Based on a number of previous ERP studies in the SC, the amplitude of this response in the current study was relatively small (at least the response produced by SC listeners) because target stimuli were physically similar to the standards (see Kujala & Naatanen, 2003 for a review). SC listeners may have missed significantly more targets due to less efficient detection of the weak MMN response feeding up through auditory cortex.

Despite a lack of comprehensive neural evidence in the EB, the Occ top-down attentional control hypothesis is very appealing. In the current study, Occ regions may have played a role for enhanced target detection abilities in the EB. If Occ regions generate top-down attention control signals, this may have amplified the MMN response evoked by target stimuli to a greater degree than in SC subjects.

Occ reorganization in the EB may also expand the amount of cortical neurons available to amplify sensory signals as a function of the attentional focus. In the current study, the EB and SC had relatively similar patterns of responding within frontoparietal networks. Therefore, a larger attentional network may result in the ability to amplify more signals at any given moment. Such an expansion may resulted in a decrease in the number of missed potentials evoked by auditory targets. This speculation could also account for the results reported by Collignon et al., 2006. In this study, subjects had to dived attentional resources between modality and space to accurate report the presentation of a target. An increase in the amount of cortex dedicated to selective attention could allow for a greater amount of resources dedicated to each sensory stream when dividing attention. This, in consequence, would cause EB subjects to be less susceptible to missing target stimuli. Alternatively, it could be the case that Occ regions function to resolve whether infrequent, deviant stimulus events are behaviorally-relevant (analogous to the hypothesized role the SMG/TPJ provides in the SC). A larger cortical space dedicated examining the behavioral-relevance of signals evoked by deviants could result in a greater probability that deviants would enter awareness.

Summary and Conclusions

In my dissertation, top-down and bottom-up attentional functions were examined in individuals lacking vision from birth. EB and SC participants performed 3-stimulus oddball tasks while undergoing event-related fMRI scanning. It was observed that frontoparietal networks commonly engaged during auditory and tactile target detection or distracter processing showed similarities between groups. However, Occ regions in the EB but not SC responded to both auditory and tactile targets and distracters when stimuli were presented alone. In addition to the attentional amplification effects observed from the bimodal scans, these results imply complex interactions between bottom-up and top-down attentional mechanisms within Occ regions. Asymmetric responses between modalities within intact sensory cortical regions suggest that Occ ROIs are not an extension of auditory or tactile sensory cortex. The time course and amplitude similarities between responses extracted from the SMG/TPJ region of both EB and SC subjects and the Occ cortex suggest that Occ cortical regions in the EB are linked with attentional operations. Significant responses to the irrelevant distracter within the Occ lobe suggest bottom-up orienting of attention. Target modulations during the bimodal scans combined with a number of ERP studies (see Kujala et al., 2000 for a review) suggest that Occ regions in the EB are modulated as a function of selective attention. In addition, the EB were significantly more accurate at detecting auditory targets under unimodal conditions.

Taken as a whole, the current evidence, previous functional neuroimaging and various behavioral studies converge on the hypothesis that Occ regions in the EB support attention-related processes and that this added processing may lend itself to advantages in non-visual behaviors (Roder et al., 1996; Bavelier & Neville, 2002; Theoret et al., 2004; Roder & Rosler, 2004; Collignon et al., 2006; Hugdahl et al., 2004; Kujala et al., 2000). Early evidence suggests that cotricocortical connections between the Occ lobe and temporal, parietal and frontal regions are the anatomical substrate that facilitates Occ reorganization (Shimoney et al., 2006; Wittenberg et al., 2004). Although the precise function of Occ regions within attentional systems is unclear, top-down and bottom mechanisms of attention likely play a key role in driving the establishment of functional activity within the Occ cortex during development of individuals blinded at birth.

These results have broader implications regarding occipital cortex in individuals suffering from complete visual loss. For example, with the development of visual prostheses it will soon be possible to reintroduce vision back into the brain of blind individuals. Success of these prosthetics in early blind people will likely hinder on the ability reutilize the Occ cortex for visual function (Merabert et al., 2005). A through understanding of how Occ regions function in the EB will be critical to this endeavor (Fernandez et al., 2005). Additionally, individuals with late-onset blindness (i.e. LB, or individuals who lost their vision after full visual maturity) generally do not show the same degree of Occ activity as EB individuals (although this finding is controversial: Sadato et al., 2002; Buchel et al., 1998; Burton et al., 2001; 2002). If a relationship exists between Occ cortical activity and non-visual behavioral advantages in the EB, it maybe possible to bring 'on-line' Occ regions in the LB through training on an attention related tasks. If Occ recruitment were to develop and was long lasting, such training may allow LB people greater adaptability to a life dependent on non-visual information. Clearly, much work is needed to thoroughly understand what happens to the visual cortex in people without vision.

Abbreviations

ACC	Anterior Cingulate Gyrus
DLPFC	Dorsolateral Prefrontal Cortex
EPI	Echo-Planar Imaging
BOLD	Blood Oxygen Level Dependency
ERP	Event-related Potentials
FEF	Frontal Eye Fields
fMRI	functional Magnetic Resonance Imaging
IFG	Inferior Temporal Gyrus
IFS	Inferior Frontal Sulcus
IPL	Inferior Parietal Lobule
IPS	Intraparietal sulcus
ISI	Inter-stimulus Interval
ITG	Inferior Temporal Sulcus
MFG	Middle Frontal Gyrus
MMN	Mismatch Negativity
PCG	Postcentral Gyrus
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PPC	Posterior Parietal Cortex
Pre SMA	PreSupplementary Motor Area
ROI	Region of Interest
SFG	Superior Frontal Gyrus
SFS	Superior Frontal Sulcus
SMA	Supplementary Motor Area
SMG	Supramarginal Gyrus
SPL	Superior Parietal Lobule
STG	Superior Temporal Gyrus
STS	Superior Temporal Sulcus
TPJ	Temporoparietal Junction
VFC	Ventral Frontal Cortex

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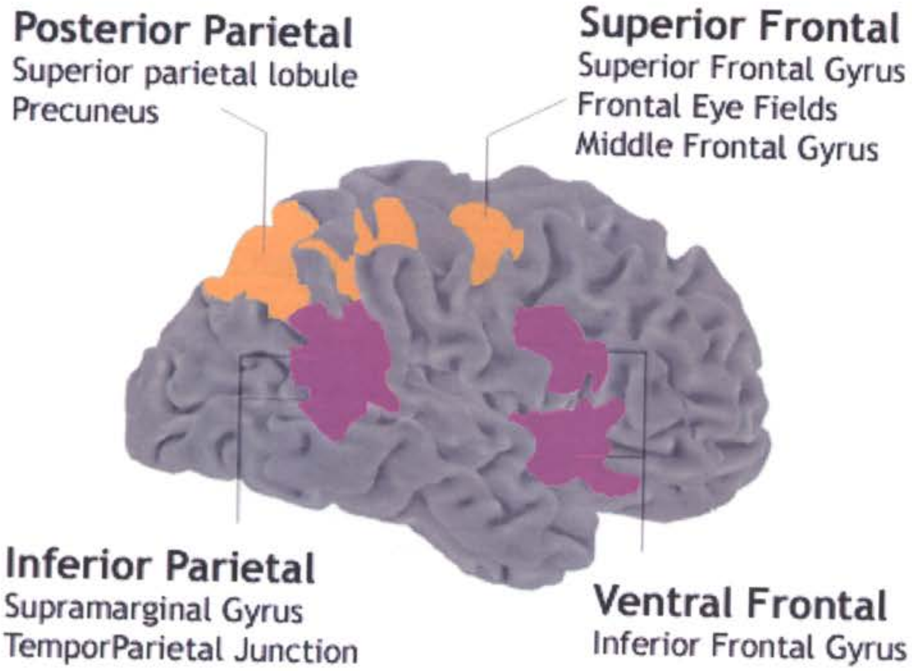
Chapter 1 – Figure 1



(Adapted from Corbetta & Shulman, 2002)

Chapter 1, Figure 1. Dorsal and ventral frontoparietal regions associated with attention in the sighted brain. Dorsal regions (orange) reflect control over top-down selection of sensory information. Ventral regions (purple) direct attention to salient stimuli through bottom-up mechanisms.

Chapter 4 – Tables and Figures

***Chapter 4, Table 1.* Group Overlap of Tactile Responsive Zones**

ROI	Hemisphere	Talairach Coordinates			# of Overlapping Voxels
		X	Y	Z	
Tactile Target					
Frontal					
IFG	R	42	22	3	206
Insula	L	-30	17	11	340
Insula	R	36	21	3	384
Precentral Sulcus	L	-44	-23	56	510
PreSMA	R	6	10	52	184
Parietal					
SMG/TPJ	R	52	-34	48	318
IPL	R	44	-53	48	267

Group Overlap of Auditory Responsive Zones

ROI	Hemisphere	Talairach Coordinates			# of Overlapping Voxels
		X	Y	Z	
Auditory Target					
Frontal					
ACC		1	1	42	396
MFG	R	33	-6	37	114
SFS	R	24	-9	57	369
PreSMA		0	-8	58	518
PreCentral	L	-38	-17	58	869
Parietal					
IPL	R	33	-53	43	112
IPL	R	43	-39	42	505
SMG	R	45	-43	34	227
IPL	L	-42	-37	44	466
Temporal					
STG	R	54	-45	31	425
Auditory Distracter					
Frontal					
Insula	L	-35	7	7	144
ACC	L	-7	-3	35	130
Parietal					
IPL	R	28	-65	40	453
SMG/TPJ	R	39	-40	39	112
Temporal					
MTG	R	61	-22	2	208
STS	R	50	-38	11	861

Chapter 4, Table 1. Overlapping active regions between EB and SC groups in response to tactile and auditory targets and distracter stimuli minus standards during the unimodal scans. Voxels were included if they were found to be active with a significance criteria of $p > 0.01$ and surviving a cluster filter threshold in both groups. The cluster filter limited cluster sizes to at least of at least 300 contiguous voxels. No significant overlapping activity was observed from the tactile distracter stimulus.

Chapter4, Table 2a. Tactile Responsive Zones in the EB - Non-Occipital

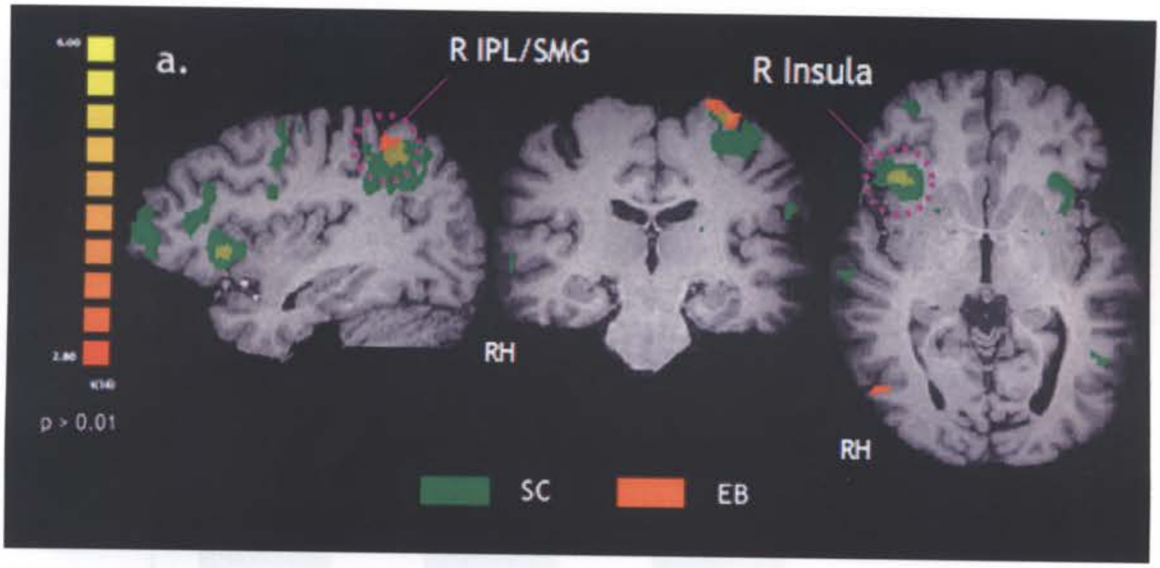
ROI	**Hemisphere**	**Talairach Coordinates**			**Mean T Score**	**Cluster size**
		X	**Y**	**Z**		
Tactile Target						
Frontal						
IFG	R	43	22	0	3.323	281
Insula	R	36	20	2	3.509	679
Insula	R	43	-5	16	3.332	452
SFG	R	7	9	55	3.508	485
IFG	L	-44	22	2	3.465	398
Insula	L	-36	12	6	3.247	1350
PreCentral	L	-30	-21	66	3.182	459
Parietal						
IPL	R	43	-49	52	3.296	1157
IPS	R	13	-62	58	3.186	263
PostCentral Gyrus	R	37	-34	64	3.397	289
SMG	R	51	-35	50	3.555	648
SMG	R	37	-46	56	3.424	785
SPL	R	25	-59	58	3.517	739
IPL	L	-43	-35	57	3.396	1159
IPS	L	-27	-58	56	3.311	1117
Temporal						
ITG	R	59	-47	-8	3.311	215
Tactile Distracter						
Frontal						
SFG	R	35	-5	56	3.406	177
MFG	L	-20	39	29	3.106	143
Parietal						
IPL	R	21	-39	52	3.670	119

Chapter 4, Table 2a. Active regions (outside of the Occ cortex) in response to tactile targets and distracter stimuli minus standards during the unimodal scans in the EB. Clusters were considered active if they met a significance criteria of $p > 0.01$ and survived a cluster filter threshold limiting cluster sizes to at least of at least 300 contiguous voxels.

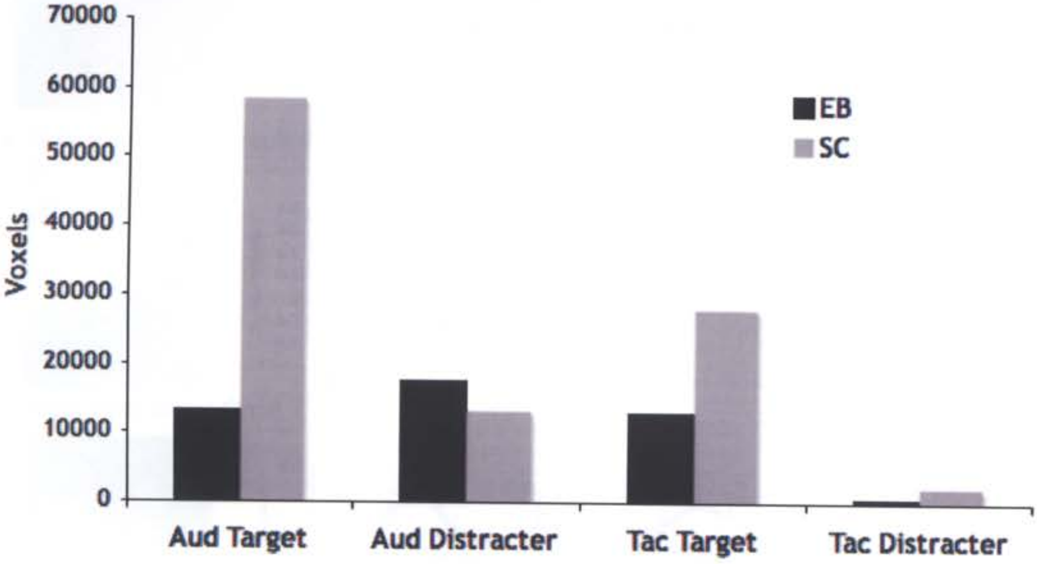
Chapter4, Table 2b. Auditory Responsive Zones in the EB - Non-Occipital

		Talairach Coordinates				
ROI	**Hemisphere**	**X**	**Y**	**Z**	**Mean T Score**	**Cluster size**
Auditory Target						
Frontal						
ACC		-1	0	44	3.816	465
MFG	R	32	-7	42	3.285	219
SFG	R	28	-7	58	3.746	366
SFS	R	29	-6	47	3.206	182
IFG	L	-45	16	2	3.314	749
MFG	L	-49	-9	44	3.472	933
PreCentral Gyrus	L	-26	-21	66	3.124	167
SFG	L	-10	-3	70	3.785	528
SFG	L	-23	-11	53	3.296	540
PreSMA		1	-58	70	3.569	1008
Parietal						
Posterior Cingulate	R	3	-27	29	3.468	638
IPL	R	33	-53	38	3.232	296
SMG	R	43	-40	40	3.411	521
IPL	L	-49	-39	43	3.160	557
SMG	L	-28	-55	43	3.451	1081
Temporal						
STG	R	56	-43	33	3.270	529
Auditory Distracter						
Frontal						
IFG	R	37	21	9	3.197	685
MFG	R	31	35	23	3.396	548
SFG	R	23	-8	62	3.329	813
ACC	L	-9	0	37	3.302	141
IFS	L	-49	5	12	3.135	384
Insula	L	-38	6	7	3.288	557
MFG	L	-34	26	37	3.416	1001
MFS	L	-37	22	19	3.267	723
PreSMA		0	4	46	3.661	2692
Parietal						
IPL	R	31	-66	26	3.295	643
PreCuneus	R	29	-65	40	3.531	790
SPL	R	18	-68	52	3.237	304
PreCuneus	L	-8	-65	44	3.353	599
Temporal						
STG	R	67	-37	16	3.409	843
STS	R	55	-37	7	3.640	2391
PT	L	-46	-40	23	3.428	342
STG	L	-58	-17	11	3.440	599
SubCortical						
Thalamus	L	11	-16	8	3.458	396

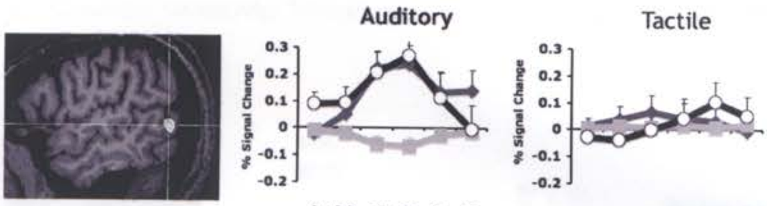
Chapter 4, Table 2b. Active regions (outside of the Occ cortex) in response to auditory targets and distracter stimuli minus standards during the unimodal scans in the EB. Clusters were considered active if they met a significance criteria of $p > 0.01$ and survived a cluster filter threshold limiting cluster sizes to at least of at least 300 contiguous voxels.



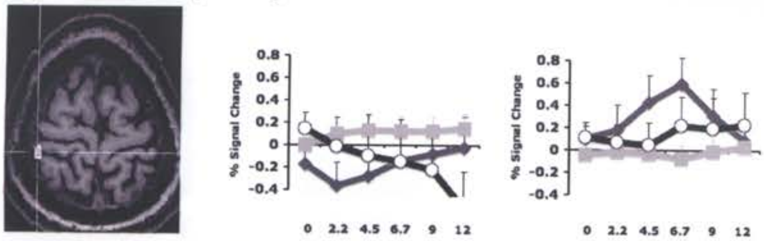
Chapter 4, Figure 1. Whole brain target conjunction analysis between EB and SC groups. a) A conjunction analysis was performed on the averaged auditory and tactile target conditions from the unimodal scans. EB (orange) and SC (green) subjects are overlaid to show overlapping regions responsive to targets irrespective of modality. Data was analyzed by the same method as outlined in chapter 2. Voxels were considered active if they met a statistical threshold of $p > 0.01$. A cluster filter correction was employed to reduce false positives, limiting cluster sizes to at least of 300 contiguous voxels.



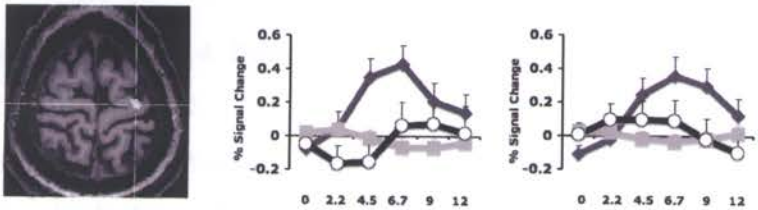
Chapter 4, Figure 2. Active voxel counts summed across the whole brain (excluding Occ located voxels) from group average contrast maps. Total counts were made from auditory and tactile target and distracter contrast maps derived from the unimodal scans. Contrast maps were created by the same method detailed in chapter 2. A voxel was counted if it met a statistical threshold of $p > 0.01$ and survived a cluster filter correction.



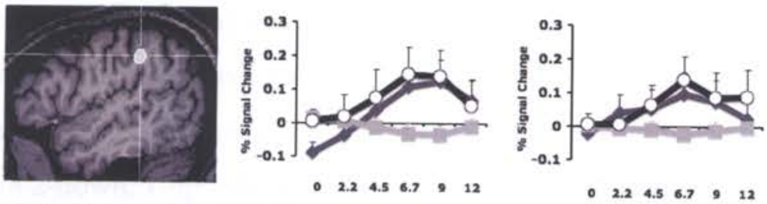
a. Right Middle Temporal Gyrus



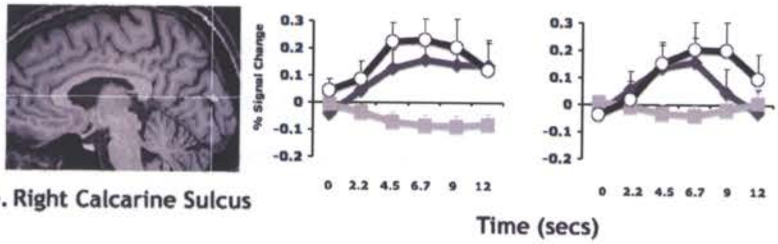
b. Right PostCentral Gyrus



c. Left PreCentral Gyrus

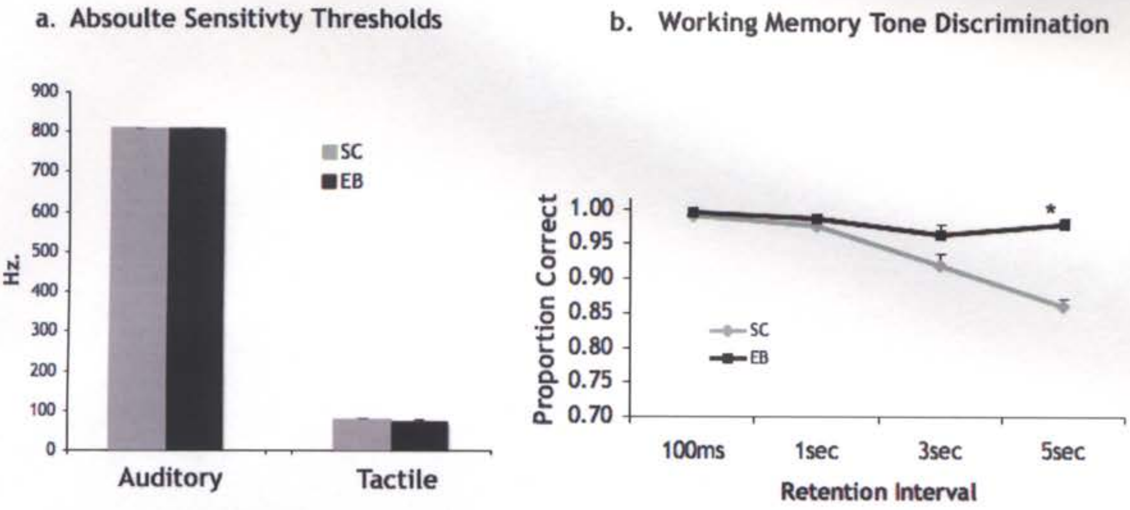


d. Right Supramarginal Gyrus



e. Right Calcarine Sulcus

Chapter 4, Figure 3. EB group averaged event-related responses extracted from sensory (a, middle temporal gyrus, and b, postentral gyrus), motor (d, precentral gyrus) and higher-order association (e, supramarginal gyrus) cortical ROIs. Active voxels were selected from an overlay of auditory and tactile unimodal scan conditions. Target, distracter and standard stimuli were presented at the baseline with each proceeding time point representing subsequent acquisitions (TR = 2.25 secs). Error bars represent standard errors of the mean.


a. Absoulte Sensitivty Thresholds

b. Working Memory Tone Discrimination

Chapter 4, Figure 4. Behavioral results between EB and SC individuals on a) an auditory and tactile threshold discrimination task and b) an auditory working memory paradigm. a) Subjects (n = 9 for each group) were presented with 2 tones (or vibrations) on each trial and asked to make a same or different judgment. The inter stimulus interval (held constant on all trials) was set at 2250 ms. The first tone or vibration on each trial was always the target used in the oddball tasks (800 Hz. tone and a 50 Hz vibration). Thresholds or the just-noticeable-difference was determined using a staircase method with 2-down, 1-up rule (see chapter 1 methods for details). Bars represent the mean threshold value (frequency) for each group. No significant threshold differences were observed between groups. b) EB (n = 11) and SC (n = 13) listeners were presented with pairs of tones separated by variable retention intervals and asked to make a same or different judgment. Tones were randomly drawn from a frequency range of 200 – 6000 Hz and a 128 trials were presented (data collected by Alexander A. Stevens). EB and SC performance was statistically similar at all retention intervals except the longest interval of 5 secs. Data were analyzed using a repeated measure ANOVA with a Greenhouse Geiser correction for violations of sphericity. * denotes a significant difference at 0.05 significance level as revealed by Scheffé's post hoc tests.