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Cross-modal plasticity for tactile and auditory stimuli within the visual cortex of early blind human subjects

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Cross-modal Plasticity for Tactile and Auditory Stimuli Within the Visual Cortex of Early Blind Human Subjects

A Dissertation submitted in partial satisfaction of the Requirements for the degree Doctor of Philosophy

in

Psychology

by

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2009

The Dissertation of Lindsay Burke Lewis is approved, and it is acceptable in quality and form for publication on microfilm:

Chair

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LIST OF ABBREVIATIONS

2-AFC = two-alternative forced choice

2D = two-dimensional

3D = three-dimensional

AF = *auditory frequency*

AM = *auditory motion*

AT = *auditory trigrams*

BOLD = blood oxygenation-level dependent

DTI = diffusion tensor imaging

EPI = echo planar imaging

ERP = event-related potential

FDR = false discovery rate

FFA = fusiform face area

FM = frequency-modulated

FMRI = functional magnetic resonance imaging

GLM = general linear model

ILD = interaural level difference

IP = intraparietal

ITD = interaural time difference

ITS = inferior temporal sulcus

LatS = lateral sulcus

LH = left hemisphere

LGN = lateral geniculate nucleus

LOS = lateral occipital sulcus

LOtv = lateral occipital tactile-visual area

MEG = magnetoencephalography

MGN = medial geniculate nucleus

MPRAGE = magnetization-prepared rapid gradient echo

MRI = magnetic resonance imaging

MT+ = medial temporal complex

MTG = middle temporal gyrus

PET = positron emission tomography

RH = right hemisphere

ROI = region of interest

STS = superior temporal sulcus

TA = *tactile animals*

TMS = transcranial magnetic stimulation

TO = *tactile orientation*

TR = repetition time

TT = *tactile trigrams*

VA = *visual animals*

VM = *visual motion*

VO = *visual orientation*

VP = ventral posterior

VT = visual trigrams

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Saenz, M., Lewis, L.B., Huth, A.G., Fine, I., & Koch, C. (2008) Visual motion area MT+/V5 responds to auditory motion in human sight-recovery subjects. *Journal of Neuroscience*, 28(20), 5141-5148.

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PRESENTATIONS

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ABSTRACT OF THE DISSERTATION

Cross-modal Plasticity for Tactile and Auditory Stimuli Within the Visual Cortex of Early Blind Human Subjects

by

Lindsay Burke Lewis

Doctor of Philosophy in Psychology

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Professor Karen Dobkins, Chair

A number of studies have demonstrated cross-modal responses within visual cortex as a result of blindness. However, little is known about the organizational principles that drive cross-modal plasticity. One possibility is that cross-modal plasticity in visual cortex is *pluripotent* – cross-modal responses in visual cortex may not show strong selectivity for either modality or task. Alternatively, if cross-modal plasticity is driven by *functional specificity*, similar activations might be expected for a given task, regardless of modality; whereas if cross-modal plasticity is driven by *anatomical connectivity* between visual cortex and other sensory cortical areas, similar activations might be expected for a given modality, regardless of task.

Here we present work from two studies. In the first study, fMRI responses to a variety of tasks in auditory and tactile modalities were measured in early blind and sighted subjects. We found cross-modal plasticity (greater fMRI responses in blind than sighted subjects) in visual cortex for all tasks, with many areas showing cross-modal plasticity for all the tasks that we tested – across much of cortex the degree of specialization underlying cross-modal plasticity seems to be relatively weak (*pluripotency*). However, in dorsal-occipital and ventral regions of visual cortex, we did find evidence for selectivity based on modality (greater response to tactile than auditory tasks), and in occipital-temporal regions of cortex we found modulation of cross-modal response by task.

In our second study we specifically tested the *functional specificity* hypothesis in visual motion area MT+. To more accurately define MT+, we used two rare sight-recovery subjects. In these subjects MT+ responded to auditory motion, while in visually normal subjects MT+ did not show similar auditory responses. These auditory responses in MT+ were specific to motion compared with other complex auditory stimuli, suggesting that cross-modal plasticity can be influenced by the normal functional specialization of a cortical region. Our results further demonstrate that in the case of sight recovery, cross-modal responses can coexist with regained visual responses within the visual cortex.

INTRODUCTION

The primary sensory areas of cortex have classically been defined according to the type of sense that each normally subserves: visual/occipital cortex subserves vision, auditory cortex subserves audition, and somatosensory cortex subserves touch. In the strict version of this view, there exists a parallel hierarchy in which each sense is at first separately processed in its respective area during early stages of processing, and then ultimately integrated within multimodal association areas at later stages of processing. This framework allows for cross-modal influences on primary sensory areas via top-down feedback, but assumes that these influences merely modulate responses to the dominant sensory input. However there is now substantial evidence suggesting that sensory cortices can play an active role in cross-modal processing, and hence these divisions of sensory cortices may not be nearly as rigid as previously thought. Recent findings indicate that, in addition to top-down influences from multimodal association areas, sensory cortical areas can indeed receive some direct input from other modalities, predominantly via cortical cross-modal interconnections.

It is perhaps the effects of sensory deprivation that provide the most striking evidence for the existence of cross-modal connectivity, particularly when deprivation occurs early in life. While each sensory cortical area probably possesses both genetic and computational predispositions towards subserving a particular modality, abnormal sensory experience can greatly modify normal patterns of selectivity, allowing other senses to “colonize” deprived region of cortex. Cortical areas normally devoted to the missing sense begin to process aspects of the remaining senses; for example, in blind subjects visual cortex responds to tactile and auditory stimulation, and in deaf subjects auditory cortex responds to visual stimulation. It is thought that this reorganization may be important in allowing remaining senses to be enhanced or modified in compensation for the missing sense.

Interestingly, even short-term sensory deprivation and training can have significant effects on cortical organization. The rapid nature of these changes strongly suggests that connections between different sensory areas may be pre-existing, and are simply latent until “unmasked” as a result of specific experiences. These effects are also consistent with the existence of modifiable interconnections between sensory cortices within adult humans. While interesting in its own right, understanding cross-modal plasticity as a result of short-term experience can also shed light on the processes that mediate and limit cross-modal responses under less extreme circumstances.

Despite the growing literature in blind subjects demonstrating auditory and tactile responses in visual cortex, the organizational principles that underlie this cross-modal plasticity in humans are still not understood. In normally sighted subjects, visual cortex is known to consist of sub-regions specialized for different aspects of visual processing (e.g. motion processing in MT+; regions selective for objects and faces in fusiform and lingual gyri); whether this organization carries over in some form for cross-modal processing is unclear. One possibility is that cross-modal plasticity in visual cortex is *pluripotent* – cross-modal responses in visual cortex may not show strong selectivity for either modality or task. Alternatively, if cross-modal plasticity is driven by *functional specificity*, similar activations might be expected for a given task (possibly mapped onto normal specializations of visual cortex), regardless of modality; whereas if cross-modal plasticity is driven by *anatomical connectivity* between visual cortex and other sensory cortical areas, similar activations might be expected for a given modality, regardless of task.

To date, neuroimaging studies of cross-modal plasticity in visual cortical areas of blind human subjects have focused on a very small number of tasks and a single modality. As a result, little is known about how the patterns of cross-modal plasticity compare across tasks or modalities.

The goal of our first study (*Study 1*) was to conduct in early blind subjects a comprehensive fMRI (functional magnetic resonance imaging) investigation of cross-modal responses in visual cortex across a variety of tasks and across modalities (auditory and tactile), so to better elucidate the organizational principles underlying cross-modal plasticity in visual cortex. We found cross-modal plasticity (greater fMRI responses in blind than sighted subjects) in visual cortex for all tasks, with many areas showing cross-modal plasticity for all the tasks that we tested – across much of cortex the degree of specialization underlying cross-modal plasticity seems to be relatively weak. However, in dorsal-occipital and ventral regions of visual cortex, we did find evidence for selectivity based on modality (greater response to tactile than auditory tasks), and in occipital-temporal regions of cortex we found modulation of cross-modal response by task.

In our second study (*Study 2*) we specifically examined the "strong" version of the *functional specificity* hypothesis – that modulation of cross-modal response by task is related to the usual function of the region - in visual motion area MT+/V5. Because MT+ (as well as other visual cortical sub-regions) cannot be reliably defined based on anatomy, these areas are typically identified in normally sighted subjects based on functional visual responses – which is obviously not possible in blind subjects. Accordingly, it is likely that our first study (*Study 1*), as well as previous studies of cross-modal plasticity in blind subjects, did not accurately localize MT+ across subjects. In our second study we had rare access to two early-blind subjects with partial sight recovery in adulthood (“sight-recovery subjects”). Sight-recovery subjects afforded a unique and critically important opportunity to localize MT+ based on functional responses to visual motion, and observe cross-modal responses within that area, all within the same individual’s visual cortex.

An understanding of the interaction of cross-modal plasticity and restored vision in visual cortex, and the nature of its dependence on specific task and cortical area, should prove increasingly important as new sight restoration procedures (such as retinal implants, epithelial stem cell replacements, gene therapies and retinal transplants) become available.

CHAPTER 1: Cross-Modal Connectivity of the Visual System in Normal Development and Adulthood

The literature discussed here is largely focused on cross-modal plasticity of visual cortex in early blindness. A variety of papers provide comprehensive reviews of cross-modal plasticity within auditory cortex and compensatory hypertrophy of visual cortex (changes in visual processing) as a result of auditory deprivation (Bavelier & Neville, 2002; Dow, Scott, Stevens & Neville, 2006; Fine, Finney, Boynton & Dobkins, 2005; Neville & Lawson, 1987a; Neville & Lawson, 1987b; Neville & Lawson, 1987c).

(1.1) Normal Developmental Connectivity

The connectivity of the immature sensory brain, although now understood to be relatively more established than previously thought (for a review see Ruthazer, 2005), is known to be shaped by experience over the course of development. While much of initial sensory cortical architecture and thalamocortical/corticocortical connectivity is determined by intrinsic, genetically-controlled factors (such as molecular cues), this basic structure is often relatively imprecise, and further refinement, maintenance, and efficiency of this connectivity is highly dependent on early patterns of sensory input during a sensitive or “critical” period (e.g. Catalano & Shatz, 1998; Crair, Gillespie & Stryker, 1998; Crowley & Katz, 1999; Crowley & Katz, 2000; Kahn & Krubitzer, 2002; Sur, Angelucci & Sharma, 1999). In particular, early exposure to patterns of information across multiple sensory modalities (i.e. visual, auditory, and somatosensory) may be especially essential for sensory integration, in order for accurate mapping between senses to be established (Ruthazer, 2005).

The exact nature of these modifications during sensory development continues to be investigated. There is evidence that experience-dependent effects are mediated by (a) adjustments in the weighting/gain of pre-existing connectivity (Ruthazer, 2005), (b) the guidance of new projections to target areas (Catalano & Shatz, 1998; Ghosh & Shatz, 1992), and/or (c) the stabilization vs. destruction (“pruning”) of transient exuberant projections to these areas (Rodman & Consuelos, 1994). These processes are not necessarily mutually exclusive, and in fact, it seems likely that a combination of these mechanisms probably contribute to sensory plasticity. Nonetheless, a common underlying theme is that competition, based on experience, mediates connectivity; more active projections are strengthened at the expense of less active projections (Pascual-Leone, Amedi, Fregni & Merabet, 2005; Pascual-Leone & Hamilton, 2001; Rauschecker, 1995).

In infant animals, there is substantial physiological evidence for exuberant connectivity within the layers of visual cortex itself (primates: Callaway, 1998; kittens: Price & Blakemore, 1985a; Price & Blakemore, 1985b; Price, Ferrer, Blakemore & Kato, 1994) as well as between visual cortex and other cortical areas (primates: Rodman & Consuelos, 1994; cats: Innocenti, 1995). In kittens, there have been reports of projections from auditory/temporal areas to visual cortex (Clarke & Innocenti, 1986; Dehay, Bullier & Kennedy, 1984; Dehay, Kennedy & Bullier, 1988; Innocenti, Berbel & Clarke, 1988; Innocenti & Clarke, 1984), from somatosensory/fronto-parietal cortex to visual cortex (Clarke & Innocenti, 1986), as well as from subcortical visual thalamus (lateral geniculate nucleus, LGN) to auditory cortex (Catalano & Shatz, 1998; Ghosh & Shatz, 1992). These findings suggest that during early development the substrate for multisensory integration exists even at the level of primary sensory cortices (Ghazanfar & Schroeder, 2006). However, it appears that a large proportion of these connections are pruned off (or re-allocated) during the course of maturation, which strongly suggests that initial exuberant cross-connectivity plays some kind of transient role in the plasticity or fine-tuning of sensory cortex specialization during development (Innocenti & Clarke, 1984; Neville & Bavelier, 2002; Rodman & Consuelos, 1994).

Consistent with animal data, a human infant study also suggests that cross-modal connectivity may be more pronounced in infancy than in adulthood. Whereas auditory ERP (event-related potential) responses are usually small or completely absent in occipital regions (visual areas) of the adult brain, large auditory ERP responses have been shown in occipital regions of six-month old infants (Neville & Bavelier, 2002). Furthermore, the amplitude of auditory ERP responses over occipital areas in infants appears to gradually decrease as a function of age. In contrast, auditory ERP responses over temporal/auditory areas remain relatively constant in magnitude from infancy to adulthood. These findings imply that the extent of projection of auditory information to visual cortex may gradually decrease during the course of development (Neville & Bavelier, 2002).

Thus, both animal and human literature suggest that in normal visual development a large proportion of cross-modal connections are “pruned” (or re-allocated) during the course of maturation (Innocenti & Clarke, 1984; Neville & Bavelier, 2002; Rodman & Consuelos, 1994). However, in the case of abnormal experience such as lack of visual input, this normal pruning process may fail to occur, and an “infantile” pattern of anatomical connectivity may be retained (Collignon, Voss, Lassonde & Lepore, 2008; Neville & Bavelier, 2002).

(1.2) Normal Adulthood Connectivity

While there is evidence demonstrating that sensorily normal "unimodal" cortices can exhibit responses to input from other modalities it is often unclear the extent to which cross-modal responses in sensory cortices are mediated by direct input from other sensory areas, or are due to top-down influence from multimodal association areas.

Until recently, it has generally been assumed that in adult animals and humans with normal sensory experience the majority of connectivity between modalities occurs at levels of processing beyond unimodal sensory cortices, in multimodal association areas, i.e. intraparietal (IP) and superior temporal sulcus (STS) areas of cortex, insular cortex, and perhaps even frontal and prefrontal cortex (Amedi, von Kriegstein, van Atteveldt, Beauchamp & Naumer, 2005b; Bushara, Hanakawa, Immisch, Toma, Kansaku & Hallett, 2003; Calvert, 2001; Felleman & Van Essen, 1991; Ghazanfar & Schroeder, 2006; Lewis, Beauchamp & DeYoe, 2000; Sadato, 2005; Saito, Okada, Morita, Yonekura & Sadato, 2003)[1]. Feedback from cross-modal processing in multimodal association areas is thought to modulate processing in unimodal sensory areas, and may in fact lead to suppression of processing in unimodal sensory areas (Bushara et al., 2003).

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[1] Although the superior colliculus is also known to be involved in multisensory integration (Stein, 1998), it depends on information from cortical levels of processing, and likely plays a role in motor orienting as opposed to perceptual processing (Jiang, Wallace, Jiang, Vaughan & Stein, 2001).

However, there is now some anatomical evidence in primates for sustained cross-modal projections between sensory cortices in adulthood. It has recently been shown in adult primates that there are projections from auditory to visual cortex (Clavagnier, Falchier & Kennedy, 2004; Falchier, Clavagnier, Barone & Kennedy, 2002; Poremba, Saunders, Crane, Cook, Sokoloff & Mishkin, 2003; Rockland & Ojima, 2003), from visual to auditory cortex (Schroeder & Foxe, 2002; Schroeder, Smiley, Fu, McGinnis, O'Connell & Hackett, 2003), and from visual to somatosensory cortex (Cappe & Barone, 2005). It therefore seems likely that there is direct communication between sensory cortices.

In the animal literature, many early studies demonstrated that, in addition to visual input, some neurons in primary visual cortex of normal cats also respond to auditory and somatosensory input (e.g. Bental, Dafny & Feldman, 1968; Fishman & Michael, 1973; Horn, 1965; Morrell, 1972; Murata, Cramer & Bach-y-Rita, 1965; for reviews see also Bavelier & Neville, 2002; Sathian, 2005). However, it is not clear if by today’s standards some of these neurons would still be regarded as belonging to primary visual cortex; they may in fact lie in extrastriate visual cortex (Sathian, 2005). More recently, it was shown in monkeys that visual area V4 responds to tactile orientation, but only when it was task relevant (Haenny, Maunsell & Schiller, 1988). Furthermore, in adult rats it has been shown that border regions between sensory-specific areas tend to contain clusters of neurons that are multisensory and integrative in nature (Ghazanfar & Schroeder, 2006; Wallace, Ramachandran & Stein, 2004).

In the human literature, there is also a handful of studies in sensorily normal adult humans that have shown cross-modal responses in sensory cortices. Some subjects exhibit activation of primary auditory cortex by visual stimulation (Bavelier & Neville, 2002). While primary visual cortex has thus far not been shown to exhibit cross-modal responses, many other areas of visual cortex do show cross-modal responses. For example, motion-selective visual area MT+ has been shown to respond to tactile motion (Blake, Sobel & James, 2004; Hagen, Franzen, McGlone, Essick, Dancer & Pardo, 2002) and to auditory motion (Poirier, Collignon, Devolder, Renier, Vanlierde, Tranduy & Scheiber, 2005), and object-related region lateral occipital complex (LOC)/inferior temporal (IT) gyrus has been shown to respond to tactile object recognition (Amedi, Jacobson, Hendler, Malach & Zohary, 2002; Amedi, Malach, Hendler, Peled & Zohary, 2001; James, Humphrey, Gati, Servos, Menon & Goodale, 2002; Pietrini, Furey, Ricciardi, Gobbini, Wu, Cohen, Guazzelli & Haxby, 2004). Using positron emission tomography (PET), it has been shown that dorsal-occipital extrastriate visual areas are activated during tactile orientation discrimination, and furthermore, that transcranial magnetic stimulation (TMS) applied over these areas interferes with performance of this task (Sathian & Zangaladze, 2002; Zangaladze, Epstein, Grafton & Sathian, 1999) as well as with performance of a tactile distance task (Merabet, Thut, Murray, Andrews, Hsiao & Pascual-Leone, 2004)[2]. These findings suggest that not only are extrastriate visual areas active during these tactile tasks, but that they are functionally involved in tactile processing. However, the extent of the role of extrastriate visual cortex in tactile processing may be limited to certain tasks; no visual cortical activation is seen for either a tactile spatial frequency task (Sathian & Zangaladze, 2002), or for tactile letter

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[2] It would be interesting to conduct further occipital TMS investigations in sighted subjects with a range of auditory tasks.

recognition (Cohen, Celnik, Pascual-Leone, Corwell, Falz, Dambrosia, Honda, Sadato, Gerloff, Catala & Hallett, 1997).

Although primary visual cortex in visually normal human adults has not been shown to exhibit cross-modal responses to purely auditory or tactile stimuli, responses in primary visual cortex to visual input can be modulated by information from other senses (Shams, Iwaki, Chawla & Bhattacharya, 2005; Watkins, Shams, Tanaka, Haynes & Rees, 2006); Shams, Kamitani, Thompson & Shimojo, 2001). Furthermore, there are instances in the human literature in which normal responses in sensory cortices are enhanced in magnitude by additional congruent information from another modality. Functional magnetic resonance imaging (fMRI) responses in visual cortex have been found to be higher to conjunctions of visual and auditory input, or visual and tactile input, than to visual input alone, when the input from the other modality is congruent with the visual input (Calvert, Brammer, Bullmore, Campbell, Iversen & David, 1999; Macaluso, Frith & Driver, 2000).

Interestingly, it has also recently been proposed that cases of synesthesia in adults may be a remnant of exuberant connectivity in development, whereby cross-modal projections in infants that are usually transient in nature are instead maintained or reinforced into adulthood (Maurer & Mondloch, 2004; Mondloch & Maurer, 2004). Consistent with this hypothesis, activation of visual areas to non-visual input has been reported in synesthetes (but not control subjects) in a variety of studies (Aleman, Rutten, Sitskoorn, Dautzenberg & Ramsey, 2001; Nunn, Gregory, Brammer, Williams, Parslow, Morgan, Morris, Bullmore, Baron-Cohen & Gray, 2002; Steven, Hansen & Blakemore, 2006). Furthermore, diffusion tensor imaging (DTI) tractography has recently been used to demonstrate increased structural connectivity in the case of grapheme-color synesthetes within inferior temporal, superior parietal and frontal cortex (Rouw & Scholte, 2007), supporting the notion that synesthesia in adults may be related to reduced pruning in development (Maurer & Mondloch, 2004; Mondloch & Maurer, 2004).

(1.3) Summary of Normal Cross-modal Connectivity

In sum, both animal and human evidence suggest that in infancy there is substantial cross-modal circuitry between visual and other sensory cortices. In adulthood only a small proportion of cross-modal circuitry remains. However in some cases the effects of this remaining circuitry may nonetheless be significant, particularly in extrastriate visual cortex.

The fact that many findings of cross-modal responses in sensory cortices of sensorily normal adult animals and humans seem to be either only observed in some individuals, or for some specific areas, or for some stimuli, indicates that cross-modal connectivity in adults is somewhat weak in most cases. Nonetheless, there does seem to be an inherent ability of adult sensory cortex to exhibit at least some cross-modal plasticity that can be significantly enhanced under certain conditions, such as visual deprivation.

CHAPTER 2: Cross-modal Processing in the Visual System as a Result of Long-term Visual Deprivation

(2.1) Animal Evidence

(2.1.1) Visual Deprivation. The most dramatic evidence of the critical role that sensory experience plays in the connectivity of visual cortex, particularly during the course of development, comes from cases in which sensory experience is abnormal. In animals, such studies include manipulations of visual experience or visual deprivation (blindness). Although a variety of research since the early 1960s has used deprivation as a tool to examine the role of experience in early wiring within visual cortex (e.g. cats: Wiesel & Hubel, 1963; Wiesel & Hubel, 1965; monkeys: Hubel, Wiesel & LeVay, 1977), more recently it has become increasingly evident that the extent of effects of abnormal visual experience on sensory wiring reaches beyond within-modal connectivity.

Visual deprivation leads to cross-modal connectivity between subcortical thalamic nuclei and visual cortex, as well as from other sensory cortical areas to visual cortex. In adult opossums that have undergone early bilateral eye enucleation, while some normal thalamocortical projections from visual thalamus (lateral geniculate nucleus, LGN) to visual cortex remain, the procedure additionally results in abnormal thalamocortical projections from auditory (medial geniculate nucleus, MGN) and somatosensory (ventral posterior nucleus, VP) thalamus to visual cortex (Kahn &

Krubitzer, 2002; Karlen, Kahn & Krubitzer, 2006). Furthermore, in addition to the normal connectivity within visual cortex, there are abnormal corticocortical projections from auditory and somatosensory cortex to visual cortex (Kahn & Krubitzer, 2002; Karlen et al., 2006). Similarly, in early bilaterally deprived cats, portions of the anterior ectosylvian area that are typically driven purely by visual input are almost completely taken over by auditory and somatosensory inputs (Rauschecker, 1995; Rauschecker & Korte, 1993), and in early bilaterally deprived monkeys, some primary and extrastriate visual cortical areas are found to be recruited by tactile input (Hyvarinen, Carlson & Hyvarinen, 1981; Toldi, Rojik & Feher, 1994).

Interestingly, in the congenitally blind mole rat, non-degenerated visual cortex is found to respond to auditory (and sometimes somatosensory) stimulation. The inferior colliculus, in addition to its usual projections to the MGN, is found to additionally project to the LGN, which in turn projects to visual cortex (Doron & Wollberg, 1994; Heil, Bronchti, Wollberg & Scheich, 1991; Kudo, Moriya & Mizuno, 1997). Likewise, in several strains of mice that are congenitally deaf, retinal projections to the MGN have been reported (Hunt, King, Kahn, Yamoah, Shull & Krubitzer, 2005), as well as responses in auditory cortex to both visual and somatosensory input (Hunt, Yamoah & Krubitzer, 2006).

(2.1.2) Experimental Manipulation of Projections (“Rewiring”). Although there is a lack of animal evidence examining rewiring of visual cortex for the processing of other sensory modalities, rewiring studies in auditory and tactile cortex have lent support for the capacity of sensory cortical areas to be recruited for visual processing (and hence are relevant to the current topic in a more general sense). In newborn hamsters, there are retinal projections to somatosensory thalamus (VP), which normally gradually disappear during the first few days of life (Frost, 1984). However, when the usual targets of the retinal projections, the superior colliculus and the LGN, are experimentally destroyed, and the usual somatosensory projections to VP are also experimentally destroyed (leaving more space to be colonized by visual projections), these retinogeniculate projections can be artificially stabilized. The resulting visual input is carried by VP to somatosensory cortex. Somatosensory cortex is then found to reliably respond to visual input in a partially organized/retinotopic manner; in fact, cells in somatosensory cortex are found to exhibit visually selective principles such as orientation and directional selectivity (Frost, 1981; Frost & Metin, 1985; Metin & Frost, 1989). Similarly, in hamsters as well as ferrets, when retinal projections are induced to auditory thalamus (MGN), the resulting visual input is then carried by MGN to auditory cortex. Neurons in auditory cortex are again found to respond to visual stimulation with some evidence of retinotopic mapping, and also exhibit oriented receptive fields and directional selectivity (Ptito, Giguere, Boire, Frost & Casanova, 2001; Roe, Pallas, Hahm & Sur, 1990; Roe, Pallas, Kwon & Sur, 1992; Sharma, Angelucci & Sur, 2000; Sur, Garraghty & Roe, 1988; Sur, Pallas & Roe, 1990; for reviews see Horng & Sur, 2006; Sur et al., 1999; Theoret, Merabet & Pascual-Leone, 2004)[3]. This selective tuning is not evident in MGN cells (Roe,

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[3] However, although these cells in auditory cortex possess many response features typical of cells in

Garraghty, Esguerra & Sur, 1993) and there is no fundamental change in the structure of the projections from MGN to auditory cortex, suggesting that this retinotopic mapping must therefore be driven by an activity-dependent process in auditory cortex itself (Sur et al., 1999). There is also evidence that this rewired cortex in fact mediates visual behavior. Rewired ferrets respond appropriately to visual stimulation presented in a receptive field represented only in the rewired auditory cortex, and not in visual cortex (von Melchner, Pallas & Sur, 2000), and rewired hamsters (unlike normal hamsters) respond appropriately to visual stimulation even after ablation of visual cortex (Frost, Boire, Gingras & Ptito, 2000).

In addition to cross-modal responses invoked by abnormal retinogeniculate connectivity, it has also been demonstrated that cross-modal responses can be invoked by abnormal thalamocortical connectivity. When thalamocortical projections from lateral pulvinar (LP) thalamus, which normally project to visual cortex, are instead rerouted to auditory cortex, visual topography is evident in the cortical map created within auditory cortex (Pallas, Roe & Sur, 1990).

(2.1.3) Implications of Visual Deprivation and Rewiring Studies. The anatomical studies described above suggest that sensory areas may start out as multimodal (receiving input from multiple modalities) early in development. The results of rewiring studies show that sensory cortices do have the capacity to represent

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visual cortex, the orientation preference arrangement of these selective cells is significantly more disorganized – a reminder that although auditory cortex can to some extent be recruited for visual processing, it is not a perfect substitution.

non-classical sensory input in an organized manner. Thus, to some extent at least, sensory cortices seem to have the ability to receive and represent information from other modalities.

The broad effects of deprivation and various rewiring manipulations on cross-modal responses in animals, therefore, serve to confirm the existence of commonalities in processing circuitry across different sensory cortices, and provide direct evidence that sensory cortices can indeed be recruited for other senses based on experience. In fact, perhaps sensory areas start out as multimodal and only become unimodal as a consequence of experience. Each sensory cortical area may possess genetically or computationally predefined superiority for subserving a particular given modality, e.g. the structure of occipital cortex may be optimal for spatial processes, and hence more likely to acquire high-acuity visual input than input from less spatially precise modalities (Theoret et al., 2004). However, whether or not the area acquires that modality may depend on a competitive interaction between groups of neural networks competing for specific sensory processes, which is highly susceptible to effects of deprivation. Of course processing of non-classical modalities is likely not entirely identical to normal processing, in either organization or function.

It is perhaps not surprising that sensory cortices come to subserve processing of other modalities in the event of early sensory deprivation. In cortical neurons of the deprived modality, there is no statistically meaningful activation to the usual modality, yet, as described above, there are anatomical interconnections between these neurons and neurons representing other modalities (whether via subcortical pathways, directly from other sensory cortices, or by way of multimodal association areas). Simple Hebbian plasticity would thus predict cross-modal plasticity in cases of sensory deprivation (Holmes, unpublished; Maurer, Lewis & Mondloch, 2005).

However, while there is an extensive literature examining the anatomical consequences of visual deprivation using both primate and non-primate animal models, it is not clear to what extent this literature can be generalized to humans. Humans rely more heavily on vision than almost all other animals, and primates seem to have a far larger number, and more richly interconnected, visual areas than other animals (Van Essen, 2005).

(2.2) Human Visual Deprivation Evidence

In humans blinded early in life, many studies have demonstrated that primary and extrastriate visual cortical areas maintain their general macroanatomy and exhibit levels of glucose metabolism and regional cerebral blood flow (rCBF) equal or greater than that of sighted subjects (Arno, De Volder, Vanlierde, Wanet-Defalque, Streel, Robert, Sanabria-Bohorquez & Veraart, 2001; De Volder, Bol, Blin, Robert, Arno, Grandin, Michel & Veraart, 1997; Phelps, Mazziotta, Kuhl, Nuwer, Packwood, Metter & Engel, 1981; Uhl, Franzen, Podreka, Steiner & Deecke, 1993; Veraart, De Volder, Wanet-Defalque, Bol, Michel & Goffinet, 1990; Wanet-Defalque, Veraart, De Volder, Metz, Michel, Dooms & Goffinet, 1988; for reviews see Kujala, Alho & Naatanen, 2000; Sadato, 2005). Moreover, early blind subjects exhibit similar oxygen-to-glucose metabolic ratios as sighted subjects, implying normal metabolism and neural activity

(De Volder et al., 1997). These findings suggest some functioning of deprived visual cortex. However, it has required further examination to determine whether the presence of activity in deprived visual cortex directly relates to the processing of other modalities.

In fact, despite some mixed findings regarding the extent of differences in sensory sensitivity between blind and sighted subjects, significant cross-modal effects of blindness on responses in visual cortex have been shown in many different paradigms. Neuroimaging (functional magnetic resonance imaging, fMRI and positron emission tomography, PET), event-related potential (ERP), and transcranial magnetic stimulation (TMS) studies in humans have demonstrated that the visual cortex of early blind individuals responds to a variety of non-visual input, including both tactile and auditory tasks.

(2.2.1) Braille Tactile Processing in Visual Cortex. Numerous studies have examined cross-modal responses in visual cortex of blind subjects to Braille reading. In an early ERP study, early blind subjects were reported to show a more posterior/occipital distribution of response than sighted subjects during Braille reading (sighted subjects tactilely read embossed Roman letters) (Uhl, Franzen, Lindinger, Lang & Deecke, 1991). In several following neuroimaging studies, early blind subjects have consistently shown greater responses to Braille words than to non-words (or other appropriate control stimuli) in primary as well as extrastriate visual cortex, whereas late blind subjects have shown greater responses in extrastriate (but usually not primary) visual cortex (Cohen, Weeks, Sadato, Celnik, Ishii & Hallett, 1999; Gizewski, Gasser, de Greiff, Boehm & Forsting, 2003; Sadato, Pascual-Leone, Grafman, Ibanez, Deiber, Dold & Hallett, 1996; Sadato, Pascual-Leone, Grafman, Deiber, Ibanez & Hallett, 1998; for reviews see Sadato, 2005; Theoret et al., 2004)[4]. It has also been shown in early blind subjects that the magnitude of responses to Braille in primary visual cortex is highly correlated on an individual basis with verbal memory ability, suggesting a relationship between extent of cross-modal responses and Braille abilities (Amedi, Raz, Pianka, Malach & Zohary, 2003). However, in another study, although extrastriate visual cortex was again activated to Braille reading in both early and late blind subjects, cross-modal responses to Braille reading in primary visual cortex were found only in late blind subjects (and not early blind subjects – in contrast to the aforementioned studies) (Buchel, Price, Frackowiak & Friston, 1998). Hence, in this study, activation of primary visual cortex to Braille is attributed to visual imagery, which presumably late blind subjects have, and early blind subjects do not. It should be noted, though, that the design of this particular study was not very well-controlled; rather than a comparison of Braille words vs. non-words, the Braille word task was compared to an auditory word task. As is discussed in more detail below (*2.2.3*), there is significant evidence that in early blind subjects, visual cortex also responds to auditory input. Therefore, it seems quite possible that the negative result regarding primary visual cortex activation for early blind subjects

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[4] However, one research group has additionally reported in late blind subjects responses to Braille reading in primary visual areas (Burton, Snyder, Conturo, Akbudak, Ollinger & Raichle, 2002a; Burton, 2003).

in this study is simply a consequence of the methodology (Holmes, unpublished) – significant Braille activation in primary visual cortex was likely cancelled out by the subtraction of significant auditory activation.

Several TMS studies provide clear evidence for the functional role of visual cortex in Braille reading. TMS delivered to visual cortex while reading Braille induces significantly more errors in Braille performance than during sham stimulation in early blind (but not late blind) subjects (Cohen et al., 1997; Cohen et al., 1999; for reviews see Kujala et al., 2000; Sadato, 2005; Theoret et al., 2004). This disruption of Braille performance suggests that the visual cortex does play a functional role in Braille reading at least in early blind subjects. Additionally, there is a case study of an early blind woman who, following an occipital stroke, lost the ability to *read* Braille without loss of her ability to detect Braille letters or loss of her other somatosensory abilities (Hamilton, Keenan, Catala & Pascual-Leone, 2000). Similarly, while TMS delivered to the visual cortex of early blind subjects does not seem to interfere with the detection of Braille tactile stimulation, it does interfere with the processing of Braille (Hamilton & Pascual-Leone, 1998; Theoret et al., 2004; Pascual-Leone et al., 2005). These studies provide strong evidence that responses found to Braille reading in visual cortex are not epiphenomena, and in fact are functionally necessary for the comprehension (but not detection) of Braille. Furthermore, it seems that these responses in visual cortex are a late part of an extended network of areas subserving Braille processing. TMS applied to occipital cortex interferes with Braille processing only after a delay of 50-80 ms, as compared to lesser time periods of 20-40 ms when applied to somatosensory cortex (Hamilton & Pascual-Leone, 1998; for reviews see Amedi, Merabet, Bermpohl & Pascual-Leone, 2005a; Burton, 2003; Pascual-Leone et al., 2005).

Overall, in early blind subjects it does seem clear that extrastriate and probably primary areas of visual cortex are recruited for Braille reading, and that cross-modal responses in visual cortex are functionally relevant. In late blind subjects, it is probable that extrastriate (but not primary) visual cortex is activated during Braille processing; however, it seems that activation in visual cortex during Braille reading in late blind subjects likely does not have a functional role.

(2.2.2) Non-Braille Tactile Processing in Visual Cortex. It is often suggested that blind subjects have enhanced tactile abilities. Obviously, a comparison of Braille performance between blind and sighted subjects is not a valid assessment of effects of blindness, since blind subjects tend to have much more extensive experience with Braille than even well-trained sighted subjects. Accordingly, non-Braille tactile tasks are typically considered a better measure of the direct effects of blindness on tactile abilities. Interestingly, it is not entirely clear whether blind subjects exhibit enhanced acuity for non-Braille tactile discrimination tasks. In one study, no significant differences in sensory, touch, or two-point discrimination thresholds were found between early blind and sighted subjects (Pascual-Leone & Torres, 1993). In several more recent studies, tactile acuity has been found to be significantly higher in early blind subjects than sighted subjects for embossed Roman letters (Cohen et al., 1997) and grating orientation discrimination (Goldreich & Kanics, 2003; Van Boven, Hamilton, Kauffman, Keenan & Pascual-Leone, 2000). Taken together these data suggest that visual deprivation and/or tactile experience in early blind subjects may perhaps provide selective advantages for some, but not all, tactile tasks (Theoret et al., 2004).

There is some evidence that benefits in tactile discrimination abilities in blind vs. sighted subjects may be largely due to effects of experience. In several studies, although blind subjects initially exhibit superior performance compared to sighted subjects on a range of tactile tasks, when practice is accounted for between blind and sighted subjects, there are no longer differences in performance (Grant, Thiagarajah & Sathian, 2000; Pascual-Leone & Torres, 1993). These data suggest that tactile superiority in the blind is driven at least in part by tactile experience, since training sighted subjects can reduce performance differences. However, in another study it has also been shown that sighted subjects perform better at Braille letter discrimination when they are blindfolded during a preceding five-day period than when they are allowed normal vision, irrespective of whether or not they have been trained. In fact, blindfolded subjects who have not been trained at all in the task even perform better than nonblindfolded subjects who are trained in the task over the five-day period (Kauffman, Theoret & Pascual-Leone, 2002). These findings suggest there is some significant role of visual deprivation in enhanced tactile abilities of blind subjects, independently of (and perhaps in addition to) tactile experience (Theoret et al., 2004). Furthermore, the fact that sighted Braille teachers read Braille visually (from the shadows of the letters) rather than by touch, suggests that loss of visual input is important for tactile fluency (Pascual-Leone, personal communication). Most likely, visual deprivation and tactile experience both play significant roles in subserving the tactile performance benefits observed in blind subjects.

Regardless of the extent to which better performance is due to visual deprivation or to tactile experience, cross-modal responses in visual cortex of early as well as late blind subjects have been shown for a variety of non-Braille reading tactile discrimination tasks. In one study, early blind subjects showed a more posterior/occipital distribution of response than sighted subjects during even a simple passive tactile task (subjects passed their finger over a random-dot pattern) (Uhl et al., 1991). Furthermore, when performing same/different judgments of grooves or embossed letters, early blind subjects show an increase in visual cortex activation, whereas sighted subjects show a decrease in visual cortex activation; however, neither blind nor sighted subjects show changes in visual cortex activation to these tasks when no response is required, suggesting that attention to the tactile stimulation may be necessary – in contrast to the results of Uhl et al. 1991 (Sadato et al., 1996). Accordingly, it is not totally clear whether or not attention is necessary to yield non-Braille reading tactile responses in visual cortex (although most studies, including the ones discussed below, involve attention to the tactile stimulus).

As is the case for Braille reading, although it seems fairly certain that both primary and extrastriate visual areas respond to non-Braille tactile discrimination in early blind subjects, and that extrastriate visual areas respond to non-Braille tactile discrimination in late blind subjects, it seems that primary visual cortex does not respond to non-Braille tactile discrimination in late blind subjects. Early blind (but not late blind) subjects show fMRI responses in primary visual cortex to a same/different Braille letter tactile discrimination task[5], whereas both early and late blind subjects show fMRI response in extrastriate visual cortex, suggesting that recruitment of primary visual cortex for non-reading tactile discrimination, like Braille reading, may only be present in early blind subjects and hence be subject to a critical period (Sadato, Okada, Honda & Yonekura, 2002). Interestingly, recently late blind subjects who are naïve to Braille also show fMRI responses to tactile discrimination in extrastriate visual cortex, suggesting that cross-modal response to tactile input in extrastriate cortex may not be dependent on experience with Braille (Sadato, 2005; Sadato, Okada, Kubota & Yonekura, 2004). However, responses in visual cortex to tactile stimulation can be evoked in sighted as well as early and late blind subjects; in another study, sighted as well as both early and late blind subjects showed responses to embossed Roman letter identification in visual cortex (Burton, McLaren & Sinclair, 2006). This finding suggests that extrastriate visual cortical activation in late blind subjects for tactile tasks may be due to visual imagery (because it is also exhibited by sighted subjects).

As is found for Braille reading, the tactile recruitment of visual cortex in early blind subjects seems to have a functional role. TMS delivered to visual cortex (vs. sham stimulation) of early blind subjects while performing an embossed letter

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[5] Note that although Braille letter discrimination involves Braille, it is not a reading task, and so in this paper is included in this section about non-Braille tactile discrimination.

discrimination task induces significantly more errors, suggesting a functional role of visual cortex even in non-Braille tactile tasks (Cohen et al., 1997). However, the functional role of visual cortex in tactile discrimination may be selective for only certain qualities of tactile processing; in early blind subjects, TMS delivered to occipital areas interferes with performance during spatial distance judgments, but not roughness judgments for raised dot stimuli (Merabet et al., 2004).

There is additionally evidence for cross-modal responses in visual cortex of blind subjects to complex tactile processing. During tactile imagery, early blind subjects (none of whom ever had vision) exhibit ERP responses in extrastriate visual cortex (Uhl, Kretschmer, Lindinger, Goldenberg, Lang, Oder & Deecke, 1994). In early and late blind subjects, ERP responses over occipital cortex are also shown during encoding of tactile stimuli, and mental rotation of those stimuli (Rosler, Roder, Heil & Hennighausen, 1993). Moreover, early blind subjects show category-related patterns of response for tactile manmade objects in IT and fusiform/ventral areas of visual cortex (Pietrini et al., 2004). Conversely, in late, but not early blind subjects, tactile motion and tactile face perception evoke responses in area MT+ and fusiform face area (FFA), respectively – a finding, again, thought likely to be due to visual imagery (Goyal, Hansen & Blakemore, 2006).

Interestingly, some evidence supports the notion that the primary source of tactile cross-modal plasticity in visual cortex of blind subjects is corticocortical (as opposed to thalamocortical). Stimulation of primary somatosensory cortex in early blind subjects by TMS yields PET activation in primary visual cortex (Wittenberg, Werhahn, Wassermann, Herscovitch & Cohen, 2004). Furthermore, tactile stimulation of one hand of blind subjects leads to bilateral activation of visual cortex (Sadato et al., 1996; Sadato et al., 1998; Sadato et al., 2002; for a review see Sadato, 2005). Because only the contralateral side of the body is represented at the thalamic level, the bilateral nature of these responses implies that tactile information must be delivered to visual cortex by cortical mechanisms beyond the thalamus.

In sum, evidence from tactile studies strongly suggests that in early blind subjects, primary and extrastriate visual cortex respond to Braille reading as well as a range of non-Braille tactile tasks, and that these responses are functionally relevant. Although in late blind subjects extrastriate visual areas have been found to respond to Braille and non-Braille reading tactile tasks, it seems unlikely in late blind subjects that visual cortex plays a functional role in tactile processing.

(2.2.3) Auditory Processing in Visual Cortex. Although a majority of cross-modal research in blind subjects has examined effects of somatosensory stimulation, a small number of studies have investigated cross-modal responses in visual cortex to auditory stimulation. Some studies have found little evidence for overall improved auditory sensitivity in blind subjects (e.g. Starlinger & Niemeyer, 1981). However, it still seems that there are some selective benefits of blindness on auditory perception, and that visual cortex is in fact recruited for some aspects of auditory processing.

In an early study, ERPs evoked by a dichotic listening task to auditory tones were reported to have shown a more posterior scalp distribution in early blind than in sighted subjects, for auditory input from the attended as well as the unattended ear (Alho, Kujala, Paavilainen, Summala & Naatanen, 1993). This suggests that visual areas may subserve auditory processing regardless of attention. However, more recently, auditory responses in visual cortex for auditory frequency discrimination have been shown in early blind (as well as late blind) subjects, but only when attention is directed to the auditory stimulus (MEG: Kujala, Huotilainen, Sinkkonen, Ahonen, Alho, Hamalainen, Ilmoniemi, Kajola, Knuutila, Lavikainen & et al., 1995; ERP: Kujala, Alho, Huotilainen, Ilmoniemi, Lehtokoski, Leinonen, Rinne, Salonen, Sinkkonen, Standertskjold-Nordenstam & Naatanen, 1997; fMRI: Kujala, Palva, Salonen, Alku, Huotilainen, Jarvinen & Naatanen, 2005; for a review see Kujala et al., 2000). In another attentional auditory ERP study, early blind subjects have been reported to exhibit larger and more posteriorly distributed N2 responses than sighted subjects (as well as faster auditory target detection times) (Roder, Rosler & Neville, 1999).

There is also evidence for selective auditory responses to sound localization in visual cortex of early blind subjects, as well as some behavioral evidence for generally superior localization abilities (Lessard, Pare, Lepore & Lassonde, 1998; Muchnik, Efrati, Nemeth, Malin & Hildesheimer, 1991), particularly to peripheral space (Roder, Teder-Salejarvi, Sterr, Rosler, Hillyard & Neville, 1999; Zwiers, Van Opstal & Cruysberg, 2001). Auditory responses in primary and extrastriate visual cortex have been shown in early blind subjects to sound localization (Kujala, Alho, Paavilainen, Summala & Naatanen, 1992), but these responses may be driven by those early blind subjects who also behaviorally demonstrate superior sound localization accuracy; the extent of activation in early blind subjects is in fact correlated on an individual basis with sound-source localization accuracy (PET: Gougoux, Zatorre, Lassonde, Voss & Lepore, 2005; ERP: Leclerc, Saint-Amour, Lavoie, Lassonde & Lepore, 2000) (for a recent review see Collignon et al., 2008). This finding suggests that cross-modal responses to sound localization in visual cortex may have functional importance. These visual responses may be lateralized; in another PET study, auditory responses in extrastriate visual cortex in early blind subjects to sound localization is reported in the right, but not the left, visual cortex (Weeks, Horwitz, Aziz-Sultan, Tian, Wessinger, Cohen, Hallett & Rauschecker, 2000). Responses to sound-source localization have been additionally been shown with PET in extrastriate visual cortex of late blind subjects, again with a seemingly right hemisphere dominance (Voss, Gougoux, Lassonde, Zatorre & Lepore, 2006). This right hemisphere bias for sound location in early and late blind subjects is consistent with laterality effects shown in auditory cortex of sighted subjects for sound localization (Kaiser, Lutzenberger, Preissl, Ackermann & Birbaumer, 2000) as well as in visual cortex of sighted subjects for spatial processing (Heilman, Bowers, Valenstein & Watson, 1986; see also Collignon, Lassonde, Lepore, Bastien & Veraart, 2007; for a review see Collignon et al., 2008).

Related to sound localization, there are also several studies that have investigated the effect of the use of sensory substitution devices for sound localization in visual cortex of blind subjects. In one study, early blind and blindfolded sighted subjects used an echolocation device which transduces ultrasonic echoes into auditory signals (De Volder, Catalan-Ahumada, Robert, Bol, Labar, Coppens, Michel & Veraart, 1999; Holmes, unpublished). Replicating previous findings, during a sound localization task (not using the device), higher PET activation was evident in extrastriate (and probably primary) visual cortex of early blind than of blindfolded sighted subjects. However, it was additionally found that while there was no difference in visual cortex activation for blindfolded sighted subjects during sound localization using the device vs. not using it, for early blind subjects there was a clear (but non-significant) trend toward higher extrastriate (and probably primary) visual cortex activation during sound localization when the device was used. In another study, early blind and blindfolded sighted subjects were trained to use a visual-to-auditory sensory substitution device for spatial pattern recognition, and again during use of this device higher PET activation was found in extrastriate visual cortex of early blind than blindfolded sighted subjects (Arno et al., 2001). It seems highly unlikely that short-term training with these devices could result in the creation of new connections between auditory and visual cortices, and so most likely these effects are a consequence of pre-existing organization in visual cortex of early blind subjects that is operational for non-visual spatial processing. Therefore, the results of these studies suggest that in early blind subjects visual cortex remains recruitable even into adulthood for novel functions, in this case, the processing of new spatial information provided via auditory input.

Several studies have shown that both primary and extrastriate visual cortex in early blind subjects (but not sighted subjects) are recruited for processing auditory language, with greater extent of activation for semantic tasks compared to phonological processing tasks or passive indecipherable sounds (Burton, Diamond & McDermott, 2003; Burton, Snyder, Diamond & Raichle, 2002b; Roder, Stock, Roesler, Bien & Neville, 2001; for a review see Burton, 2003). There is also some evidence for left hemisphere dominance of cross-modal plasticity for language tasks (Burton et al., 2002b). Similarly, in late blind subjects (who are naïve to Braille), responses in primary and extrastriate visual cortex have been shown for auditory language processing (Burton et al., 2003; Burton & McLaren, 2006). This finding in late blind subjects suggests that cross-modal responses to auditory verbal content in primary and extrastriate visual cortex may not be heavily dependent on blindness onset occurring early in life[6].

Recently, it has been suggested that in early blind subjects visual extrastriate area MT+ responds to auditory motion (Poirier, Collignon, Scheiber, Renier, Vanlierde, Tranduy, Veraart & De Volder, 2006; however this study was unable to functionally define MT+, and also finds responses to auditory motion in sighted subjects; see *Study 2*).

Additionally, it has been shown in early blind subjects that auditory-triggered mental imagery of shape yields PET activation in extrastriate visual cortex, suggesting that these areas can be used for perceptual representation even in absence of vision

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[6] It is possible, though, that in blind subjects familiar with Braille cross-modal responses seen to auditory words may be due to an associative link made between heard words and Braille (Burton, 2003).

(De Volder, Toyama, Kimura, Kiyosawa, Nakano, Vanlierde, Wanet-Defalque, Mishina, Oda, Ishiwata & Senda, 2001).

There have been very few TMS studies reported that have directly investigated the functionality of cross-modal auditory responses in visual cortex. TMS delivered to visual cortex of early blind subjects during verb generation in response to auditorily-presented nouns results in semantic errors, particularly when the left hemisphere is stimulated (Amedi, Floel, Knecht, Zohary & Cohen, 2004), consistent with left hemisphere lateralization for language processing. This finding suggests that visual cortex is involved in high-level verbal processing. However, the late timing of the TMS pulses (660 ms after word presentation onset), as well as subject reports indicating clear auditory perception of the stimulus, make it highly unlikely that the TMS affected the auditory processing of the stimulus per se, as compared to the processing of verbal content. Nonetheless, TMS may directly affect some aspects of auditory processing. Recently, it has been shown in early blind subjects that TMS delivered to right occipital areas interferes with an auditory localization task, but does not significantly interfere with an auditory pitch or intensity discrimination task (Collignon et al., 2007). This finding suggests that in early blind subjects right visual cortex plays a functional role in auditory localization, and is perhaps specifically involved in the analysis of spatial components necessary for such tasks[7].

In sum, it thus far seems that early blind as well as late blind subjects show responses in extrastriate and sometimes primary areas of visual cortex to a range of

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[7] However, in this study TMS was not delivered to the left hemisphere, and so conclusions regarding functional role of a right hemisphere dominance are somewhat speculative.

auditory discrimination, localization, and language tasks. Furthermore, responses in visual cortex to sound-source localization may be lateralized to the right hemisphere, whereas responses in visual cortex to oral language processing may be lateralized to the left hemisphere. There is some TMS evidence in early blind subjects that cross-modal responses to sound localization in the right visual cortex are functionally relevant. Importantly, though, it also should be noted that this area of research seems to be lacking TMS studies that determine the functionality of auditory responses in visual cortex for a wider range of auditory tasks, and for both hemispheres.

(2.3) Summary of Cross-modal Processing in Long-term Deprivation

Cross-modal interconnections seem to play a substantial role in cases of visual deprivation, particularly when deprivation occurs early in life. The accumulation of evidence from both tactile and auditory studies of cross-modal processing in visual cortex of early blind subjects suggests that primary as well as extrastriate visual areas are extensively recruited for processing of other senses. There is some evidence for functional significance of these cross-modal responses (e.g. Braille in visual cortex); however, more TMS research is needed, particular regarding the functional significance of auditory responses in visual cortex.

On the other hand, in late blind subjects, there is overall only strong evidence for activation of extrastriate visual areas – and even though activated, these areas may not necessarily be functionally necessary for tasks to which they respond (e.g. TMS to occipital cortex does not interfere with Braille reading in late blind subjects, Cohen et al., 1999).

The generally stronger evidence for functionally relevant cross-modal processing in visual cortex of early blind as opposed to late blind subjects perhaps lends particular support to the aforementioned notion that in early blindness, the "pruning" process that normally takes place during development may fail to occur, and cross-modal responses in early blind subjects are mediated through the retention of an "infantile" pattern of anatomical connectivity (Collignon et al., 2008; Neville & Bavelier, 2002).

It is also worth noting that measurements of cross-modal responses within early and late blind subjects have either focused on "primary stimuli", such as simple tactile discrimination or auditory frequency tasks, or on tasks which are presumably more relevant or meaningful in blindness, such as Braille reading, auditory localization or auditory language. While cross-modal plasticity seems to be stronger for more meaningful tasks, it should be noted that these tasks/stimuli also tend to be more complex.

Cross-modal plasticity is likely to interact with the normal developmental time course for different visual processes and the age at which the blind person was deprived of sight. For example, the dorsal pathway (including area MT+/V5), which subserves motion processing, is known to mature earlier in development than the ventral pathway, which subserves other visual functions, such as the ability to see form (Fine, Wade, Brewer, May, Goodman, Boynton, Wandell & MacLeod, 2003;

Ellemberg, Lewis, Maurer, Brar & Brent, 2002; T.L. Lewis et al., 2002). In fact, we (Dobkins, Lewis & Fine, 2006) have found that infants as young as two months of age are capable not only of processing simple motion, but also of integrating one- and two-dimensional motion signals into a coherent global motion percept, as evidenced by susceptibility to the barber-pole illusion. It therefore seems possible that, given such early development, perhaps motion processing areas are less modifiable by effects of experience or deprivation (especially when occurring later in life) than other visual areas. In fact, MT+ has been shown to be remarkably robust to deprivation. It has been shown in an early-deprived blind subject who has regained some visual abilities following a corneal transplant (sight recovery patient MM, who also takes part in *Study 2*), that after compensation for reduced acuity, motion processing is essentially normal. In contrast, the ability to recognize 3D form is severely impaired (Fine et al., 2003).

For a given cortical area to be successfully colonized by cross-modal input there must be some sort of direct or indirect anatomical pathway, and the underlying neuronal connectivity of the cortical area to be colonized must be capable of suitably representing the information contained within the cross-modal sensory input. In early deprived animals or human subjects it is likely that there is both a greater proliferation of viable anatomical routes, and greater flexibility in the neuronal connectivity of the deprived cortical area. In later deprived and sighted subjects both anatomical routes and neuronal connectivity are likely to be more constrained. Extrastriate visual areas may show more potential for cross-modal responses not simply because these areas have suitable anatomical connections, but also because they have the representational flexibility to deal with novel sensory input.

CHAPTER 3: Cross-modal Processing in the Visual System as a Result of Short-term Experience

(3.1) Short-term Visual Deprivation

Even short-term sensory deprivation can have striking effects on cortical organization. It has been shown that sighted subjects blindfolded for just forty-five minutes exhibit lowered thresholds for TMS-induced phosphene elicitation and higher fMRI visual cortical activation levels (Boroojerdi, Bushara, Corwell, Immisch, Battaglia, Muellbacher & Cohen, 2000). A series of acute deprivation experiments conducted by Pascual-Leone and colleagues, as well as further studies by other investigators, have shown cross-modal behavioral and neurophysiological effects in visual cortex of normal subjects who have been blindfolded for just a period of several days.

In a group of these experiments (discussed in Pascual-Leone & Hamilton, 2001; for reviews see Pascual-Leone et al., 2005; Theoret et al., 2004), sighted subjects were visually deprived via blindfolding for a period of five days, and visual cortex was assessed with fMRI while they performed auditory and tactile tasks. In the auditory task, subjects listened to a series of tones and performed a same/different task on each tone compared to the previous tone. In the tactile task, subjects performed a same/different task on pairs of Braille symbols. On the first day of blindfolding, there was no response in visual cortex to either the auditory or tactile tasks. However, by the second day of blindfolding (and especially by the fifth day of blindfolding), there was increasing activation of primary and extrastriate visual cortex during both the auditory and tactile tasks. In fact, in parallel to findings of effects of TMS on Braille letter discrimination abilities in early blind subjects (e.g. Cohen et al., 1997; Cohen et al., 1999), TMS applied to occipital cortex in blindfolded sighted subjects (but not sighted control subjects) on the fifth day significantly interfered with performance on the tactile Braille discrimination. This finding suggests that responses in visual cortex during this task are functionally relevant[8]. Furthermore, on the sixth day (just twenty-four hours after removal of the blindfold, although with the blindfold used again just during scanning), the activation of visual cortex in response to tactile or auditory stimulation was no longer apparent, and TMS applied to occipital cortex no longer interfered with the tactile Braille task. These latter findings indicate that exposure to vision for just a day is sufficient to eliminate the visual cortical activation induced during the blindfolding period.

Additional evidence for effects of short-term visual deprivation on cross-modal responses in visual cortex has been provided by another research group. In this study, sighted subjects were blindfolded for two hours, and then cortical activations were assessed with fMRI as they performed several tactile discrimination tasks. A comparison of blindfolded subjects vs. control subjects revealed a task-specific increase in activation in area LOC for a global form task (but not a gap detection task), as well as an unexpected decrease in activation in intermediate visual areas for both tactile tasks (Weisser, Stilla, Peltier, Hu & Sathian, 2005).

These data imply that activation of visual cortex during processing of other senses is not necessarily an exclusive feature of blindness; the mechanisms for cross-modal plasticity are present even in normally sighted individuals (Theoret et al., 2004). The

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[8] It would be interesting to investigate in the context of this paradigm the effects of occipital TMS on the auditory task, as well as Braille *reading* and other non-Braille tactile tasks.

rapid nature of these changes further suggests that connections between different sensory areas may be pre-existing, and simply latent until “unmasked” or strengthened as a result of specific experiences such as temporary or longer-term deprivation (Amedi et al., 2005a; Pascual-Leone & Hamilton, 2001). In other words, when a sensory cortical area is deprived of its normal input, existent cross-modal connections allow this area to respond to input from other modalities.

However, it remains possible that mechanisms uncovered by blindfolding paradigms do not necessarily represent the same mechanisms that mediate cross-modal plasticity in blind subjects. This possibility perhaps seems particularly likely given that evidence for functional significance of cross-modal activations in late blind subjects is not very strong – it is curious that TMS studies show functional significance of cross-modal activation in blindfolded sighted subjects, but not in late blind subjects. In blindfolded sighted subjects a finding of responses in visual cortex to input from other modalities could be a consequence of “unmasking” or release from inhibition (a fast, and easily reversed, effect), whereas in early blind subjects the same finding could be a consequence of the establishment of new connectivity – a slow effect not possible in blindfolded sighted subjects (Amedi et al., 2005a). In fact, it seems possible that in the case of actual vision loss, the initial reinforcement of pre-existing connections (similar to what has been demonstrated in the short-term in blindfolded sighted subjects) may in the long-term lead to permanent structural modifications in pathways between visual cortex and other sensory areas (Pascual-Leone et al., 2005). Indeed, differences in extent or pattern of cross-modal plasticity in early vs. late blind subjects might also be attributed to such a difference (or relationship) between mechanisms (Pascual-Leone et al., 2005). It seems possible that long-term new connectivity might fundamentally differ between early and late blind subjects – perhaps accounting for weaker cross-modal findings in late blind subjects. For example, if new connectivity in late blind subjects is fairly limited, and if perhaps short-term cross-modal effects seen in blindfolded sighted subjects do not persist (or change in some way) after a few days or weeks, then weaker findings in late blind subjects might be expected.

(3.2) Cross-modal Training

In addition to short-term deprivation, there is some evidence in normally sighted subjects of effects of induced sensory experiences on visual cortical cross-modal responses.

In several recent studies, it has been shown that after a learning period where an auditory stimulus is consistently paired with a visual stimulus, presentation of the auditory stimulus alone is sufficient to evoke activation in extrastriate visual cortex (PET: McIntosh, Cabeza & Lobaugh, 1998; fMRI: Tanabe, Honda & Sadato, 2005).

In another study, sighted subjects trained extensively on Mah-Jong have been reported to show fMRI activation of primary visual cortex during both a Mah-Jong tactile discrimination as well as an unfamiliar Braille character matching task, whereas untrained subjects did not show activation of primary visual cortex to either of these tasks (Saito, Okada, Honda, Yonekura & Sadato, 2006).

Interestingly, recently one research group has trained blindfolded sighted subjects to use a camera prosthesis that translates visual information into auditory input while making two-dimensional (2D) pattern recognition and three-dimensional (3D) spatial distance judgments, and have found PET activation during this task in extrastriate visual cortex (Renier, Collignon, Poirier, Tranduy, Vanlierde, Bol, Veraart & De Volder, 2005).

These findings demonstrate that unimodal sensory cortices may play a role in the acquisition of novel cross-modal associations (Calvert, 2001), and further suggest that visual deprivation may not be the only route to “unmasking” of cross-modal connectivity. As discussed earlier in the case of blindness, it seems most likely that both visual deprivation and sensory training play significant roles in the evolution of cross-modal responses in visual cortex.

(3.3) Summary of Short-term Effects on Cross-modal Processing

The fact that short-term visual deprivation and training in sighted subjects can result in similar cross-modal effects as are found in blind subjects strongly suggests that connections between different sensory areas are pre-existing, and modifiable, even within adults. However it remains possible that mechanisms uncovered by these paradigms do not necessarily represent the same mechanisms (or perhaps only represent partially similar mechanisms) that mediate cross-modal plasticity in blind subjects. It seems likely that in early blindness, cross-modal plasticity is primarily mediated by the maintenance of connectivity between visual cortex and other sensory areas that is normally pruned off, whereas in late blindness or studies of temporary deprivation, cross-modal plasticity is primarily mediated by the strengthening of pre-existing cortical interconnections that are present (although active to a lesser extent) even in sighted subjects.

CHAPTER 4: Study 1: Cross-modal Plasticity for Tactile and Auditory Stimuli Within the Visual Cortex of Early Blind Human Subjects

(4.1) Introduction

Despite the growing literature in blind subjects demonstrating auditory and tactile responses in visual cortex, the organizational principles that underlie this cross-modal plasticity in humans are still not well understood. In normally sighted subjects, visual cortex is known to consist of subregions specialized for different aspects of visual processing; but whether this organization carries over in some form for cross-modal processing is unclear. One possibility is that cross-modal plasticity in visual cortex is *pluripotent* – cross-modal responses in visual cortex may fail to show strong selectivity for either modality or task. Alternatively, if cross-modal plasticity is driven by *functional specificity*, similar activations might be expected for a given task (possibly mapped onto normal specializations of visual cortex), regardless of modality; whereas if cross-modal plasticity is driven by *anatomical connectivity* between visual cortex and other sensory cortical areas, similar activations might be expected for a given modality, regardless of task.

To date, neuroimaging studies of cross-modal plasticity in blind human subjects have tended to focus on a single task or a single modality, preventing a general understanding of how cross-modal plasticity may differ across tasks or modalities. Partly as a consequence of this, there is a remarkable disconnect between previous studies of cross-modal plasticity in animals versus studies of cross-modal plasticity in humans. Animal studies have exclusively focused on examining anatomical connectivity between visual cortex and other sensory areas; however, these studies have not investigated whether these connections play a task-specific role. On the other hand, the vast majority of human studies have examined differences in cross-modal processing of various tasks (within a modality), but have not compared effects between modalities. While attempts have been made to relate patterns of cross-modal plasticity to the "normal" functional role of sensory cortices, a direct mapping of cross-modal processing to functional areas of visual cortex has not yet been established.

There is some reason to suspect that cross-modal responses within reorganized visual cortex might map in some systematic way onto "normal" cortical organization. One previous study showed left hemispheric verbal responses in the visual cortex of blind subjects, consistent with left hemisphere cortical dominance for language; however, this effect is presumably driven by top-down feedback from language areas rather than the natural specializations of visual cortex (Amedi et al., 2003). Finney et al. (Finney, Fine & Dobkins, 2001; Finney, Clementz, Hickok & Dobkins, 2003) found right hemisphere dominance for visual motion processing within the auditory cortex of deaf subjects, consistent with right hemisphere dominance found for auditory motion found within hearing subjects (Baumgart, Gaschler-Markefski, Woldorff, Heinze & Scheich, 1999). However, this study only examined visual motion processing, so there was no way of determining whether or not the right hemisphere dominance for cross-modal visual processing in auditory cortex was motion-specific. One reason that it has been difficult to map cross-modal responses onto the normal specializations of visual cortex is that it impossible to functionally define visual areas in blind subjects (e.g. retinotopic mapping). As a result, distinctions between primary and extrastriate visual areas are only rough estimations, and any claims to have identified individual visual areas, such as MT+ or primary visual cortex must be treated with caution.

Our goal in our first study was to conduct in early blind subjects a comprehensive fMRI (functional magnetic resonance imaging) investigation of cross-modal responses in visual cortex across a variety of tasks, and across modalities (auditory and tactile).

We used fMRI to compare neural responses to a range of auditory and tactile tasks in early blind and sighted subjects. Sighted subjects also performed visual analogues of these tasks. Tasks included simple orientation or frequency discrimination, motion processing, letter identification, and object recognition. These tasks were chosen to tap into primary and secondary visual areas within both dorsal and ventral pathways.

We were able to investigate the organization of cross-modal responses by examining this range of tasks *in the same group of blind subjects.* Specifically, across visual cortex we examined the extent to which cross-modal plasticity is driven by task as compared to modality. If cross-modal plasticity is non-specific then we should see similar distributions of neuronal responses, regardless of task or modality. If cross modal plasticity is driven by anatomical connections from cortical or subcortical auditory and somatosensory areas then we would expect different tasks in the same modality to produce a similar distribution of neuronal responses. Finally, if cross-modal plasticity is driven by functional task we would expect similar distributions of neuronal responses for similar tasks across different modalities.

(4.2) METHODS

Subjects

Seven early blind subjects (ages 32-56, mean = 47.0 years, s.e. = 3.3 years; 4 men; 5 right-handed) and six normally sighted control subjects (ages 26-55, mean = 36.3 years, s.e. = 4.3 years; 3 men; 5 right-handed) participated. Details of blind subjects can be found in Table 1. All sighted subjects had normal or corrected-to-normal vision. All subjects reported no neurological or psychiatric problems, and no current use of any psychoactive medications. All subjects gave written, informed consent. Data from one additional sighted control subject was excluded from analysis due to significant head motion artifacts. Experimental procedures were approved by the California Institute of Technology Committee for the Protection of Human Subjects and the University of California, San Diego Human Research Protections Program.

Table 1: Study 1: Blind Subjects**.**

Subject	Gender	Age	Age of Blindness	Handedness	Reason for Blindness	Full-term or Pre-mature	Light On/Off?	Light Blocked?	Count Fingers?
NG	M	32	birth	right	Leber's disease, congenital	full-term	yes	yes	high contrast
KW	F	38	birth	right	Retinopathy of prematurity, congenital	pre-mature, 2 months	yes	probably not	no
GB	F	48	birth	left	Anophthalmia (right), microphthalmia (left), congenital	full-term	no	no	no
BS	M	54	birth	left	Retinopathy of prematurity, congenital	pre-mature, 1.75 months	maybe when younger	probably not	no
AE	M	50	0-18 months	right	Retinoblastoma, enucleation at 12-18 months	full-term	no	no	no
JA	M	56	6 months	right	Fever, 6 months	full-term	no	no	no
TA	F	51	birth	right	Retinopathy of prematurity, congenital	pre-mature, 2.5 months	probably not	probably not	no

MRI scanning

Blood oxygenation-level dependent (BOLD) functional imaging was performed with a 3 Tesla Siemens (Erlangen, Germany) TRIO scanner at California Institute of Technology (3x3x4 mm voxels; repetition time (TR), 12 s; echo time, 30; flip angle, 90º; field of view, 192; matrix size, 64x64; 30 slices; slice acquisition order, sequential). Slices were obliquely oriented for optimal coverage of visual, auditory, and somatosensory cortices. The first volume of every scan was discarded. Three-dimensional (3D) anatomical images were acquired using a 1x1x1 T1-weighted MPRAGE (magnetization-prepared rapid gradient echo) sequence.

A sparse EPI (echo planar imaging) pulse sequence was used in all experiments to allow the presentation of stimuli uninterrupted by MRI scanner noise (Hall, Haggard, Akeroyd, Palmer, Summerfield, Elliott, Gurney & Bowtell, 1999). Each 2 s volume acquisition was preceded by a 10 s quiet delay (TR = 12 s) during which visual, auditory, or tactile stimuli were presented. Due to the hemodynamic delay (approximately 5 seconds to peak response (Boynton, Engel, Glover & Heeger, 1996)), each volume acquisition therefore measured the BOLD response to stimulation during the middle of the stimulus period, with relatively little contribution from the auditory noise of the previous acquisition.

Tasks and Stimuli

As described above, each block consisted of a 10 s stimulation period followed by a 2s data acquisition period. All trials in a given 10 s stimulation period always consisted of the same task.

For blind subjects, tasks presented during the stimulation period included a control task (*no stimulus/key-press*), 3 auditory tasks (*auditory trigrams* (AT), *auditory motion* (AM), and *auditory frequency* (AF)), and 3 tactile tasks (*tactile trigrams* (TT), *tactile animals* (TA), and *tactile orientation* (TO); see Figure 1 and below for further details about each task. For sighted subjects, task conditions consisted of the same control task (*no stimulus/key-press*) and 6 auditory and tactile tasks as blind subjects, as well as an additional 4 visual tasks (*visual trigrams* (VT), *visual animals* (VA), *visual orientation* (VO), and *visual motion* (VM)[9]); see Figure 1. All tasks consisted of a two-alternative forced choice (2-AFC) judgment. For most tasks we used a structure containing 2 stimulus presentation intervals, followed by a response period. For all auditory tasks (*auditory trigrams*, *auditory motion*, and *auditory frequency*) and all trigram tasks (*auditory trigrams*, *tactile trigrams*, and *visual trigrams*), each of the 2 intervals was 1 s in length and the response period was 0.5 s, for a total of 4 trials per 10 s stimulation period. For *tactile orientation*, as well as its visual equivalent *visual orientation*, we found we had to allow more time per trial: thus orientation tasks contained a single 2 s interval and a 0.5 s response period, also resulting in a total of 4 trials per 10 s stimulation period. The timing of the control

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[9] The *visual motion* task was not included for one of the seven sighted control subjects, since it was added as a task after collecting data on that subject.

task (*no stimulus/key-press*) and *visual motion*, both of which subjects responded to with alternating key-presses, matched that of the aforementioned tasks, with 4 trials/key-presses per 10 s stimulation period. For *tactile animal*s, as well as its visual equivalent *visual animals*, we found we had to allow more time per trial: thus animal tasks contained two 4.75 s intervals and a 0.5 s response interval, resulting in a single trial in a 10 s stimulation period.

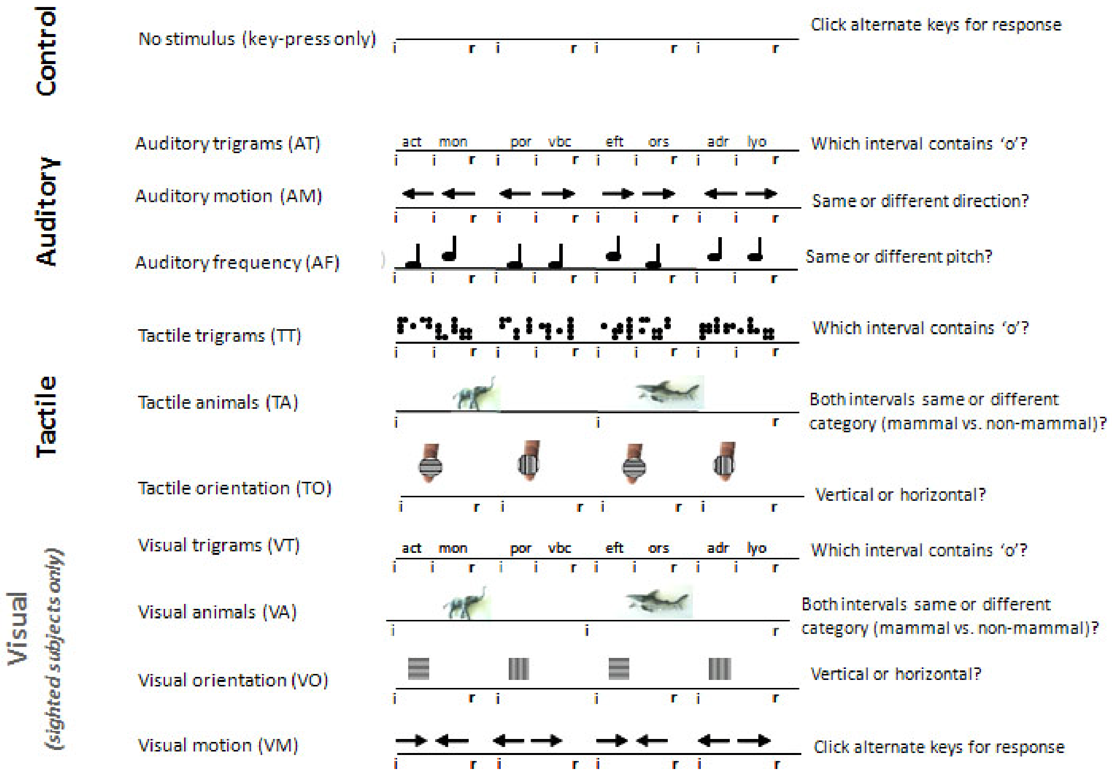

Figure 1: Study 1: The arrangement of trials in a 10 s stimulation period for each task. i = interval, r = response.

Because it was technically impossible (and would be confusing to the subject) to present all tasks within a single scan, we presented a pseudo-random subset of three tasks per scan, plus the *no stimulus/key-press* control task, for a total of four tasks per scan. For blind subjects, these three tasks per scan could consist of any combination of auditory and tactile tasks. For sighted subjects, these three tasks per scan could consist of any combination of auditory, tactile, and visual tasks.

During each scan, each sequence of four tasks was repeated eight times (each scan therefore contained 32 blocks in total, for a scan duration of 6 minutes and 24 seconds).

Each task was included within six scans for each subject. For each task we therefore collected data from 48 block repetitions in total. Scan order was randomized across subjects. Subjects were typically able to complete 6-7 scans per one hour session. Blind subjects carried out 12 scans in total across two one-hour sessions, whereas sighted subjects carried out 18-21 scans in total across three one-hour sessions (sighted subjects were required to carry out more scans because of the extra visual conditions). Because the *no stimulus/key-press* task was included in every scan, in blind subjects we collected 96 block repetitions in total for that task, and in sighted subjects we collected 144-168 block repetitions in total for that task.

Stimuli. Visual and auditory stimuli were generated using MATLAB and Psychophysics Toolbox (www.psychtoolbox.org) (Brainard, 1997; Pelli, 1997), and were delivered to the subject via MRI-compatible stereo headphones (MRCONFON).

A separate computer also used MATLAB to deliver auditory cues to an *experimenter's* headphones; these auditory cues signalled information to this experimenter about tactile stimuli (i.e. when to present vs. withdraw each tactile stimulus for the subject).

For every task, at the beginning of each response interval, there was a brief "click" sound which was presented as a reminder to the subject that it was time to press a key.

Tasks were informally controlled for task difficulty based on pilot data, but the nature of the tasks and the complexity of the experimental design made it impossible to run individual staircases for each subject/task. As a result, it is possible that attentional demands varied across tasks.

No Stimulus/Key-Press Task. The *no stimulus/key-press* task was included as a baseline to which other tasks could be compared. This stimulus contained no task or stimulus besides key-pressing timed to match most of the other tasks in the study. After 2 s of no auditory or tactile stimulation, the standard "click" sound was presented, and subjects had a 0.5 s response period during which to press a key. Subjects were asked to alternate between pressing each of the two possible response keys across the four trials within each 10 s block.

Auditory Tasks. There were 3 types of auditory task: "auditory trigrams" (AT), "auditory motion" (AM), and "auditory frequency" (AF).

The *auditory trigrams* stimulus consisted of two sets of three letters, produced via a computer-generated voice that orally pronounced sets of letters. Each set of letters (a trigram) was randomly generated from the alphabet (excluding the letter “O”), with the exception of one letter in either the first or second trigram, which was randomly selected and replaced with the target letter “O”. In each *auditory trigrams* trial, each trigram was presented for a duration of 1 s, and both trigrams were followed by a 0.5 s response period (for a total of 2.5 s per trial, with 4 trials per 10 s stimulus block). The subject’s task was to indicate via key-press whether the letter “O” was contained in the first or second trigram.

The *auditory motion* stimulus was created by linearly ramping (between 0 and max-intensity) the volume of a 600 Hz tone in opposite directions between the left and right speakers, creating the vivid percept of a sound source moving horizontally from one side of the head to the other. Maximum auditory intensity was approximately 50 dB and was adjusted to a comfortable level for individual subjects. In each *auditory motion* trial, this stimulus was presented twice, for a duration of 1 s per presentation, and both presentations were followed by a 0.5 s response period (for a total of 2.5 s per trial, with 4 trials per 10 s stimulus block). For a given presentation, the direction of auditory motion was equally likely to be from left-to-right, or from right-to-left. Subjects performed a “same-different” task, indicating via key-press whether the auditory motion was in the same direction during both presentations, or in different directions.

The *auditory frequency* stimulus was a 580 Hz, 600 Hz, or 620 Hz tone with equal intensity (0.5 of max intensity) in the two speakers, creating the percept of a centrally located stationary sound source. In each *auditory frequency* trial, this stimulus was presented twice, for a duration of 0.9 s per presentation, with an inter-stimulus interval (ISI) of 0.2 s (to slightly increase task difficulty), and both presentations were followed by a 0.5 s response period (for a total of 2.5 s per trial, with 4 trials per 10 s stimulus block). For a given set of presentations, the frequency of the auditory tone was equally likely to be 600 Hz in both presentations, or 580 Hz in one presentation, and 620 Hz in the other presentation (accordingly, the frequency was always centered around 600 Hz). Subjects performed a "same-different" task, indicating via key-press whether the auditory tones were the same or different frequencies.

Tactile Tasks. There were 3 types of tactile tasks: "tactile trigrams" (TT), "tactile animals" (TA), and "tactile orientation" (TO). All tactile stimuli were applied to the subject's hand manually by the experimenter, who stood as still as possible just outside the scanner, near where the subject's hand rested on a firm piece of cardboard placed on his or her lap.

For blind subjects, the *tactile trigrams* stimulus consisted of two trigrams. Each trigram contained three Braille letters, produced via a Braille labeler, embossed onto tape, and placed in a row (with a space between each pair of trigrams) on an index card. Each distractor letter was randomly generated from the alphabet (excluding the letter “O”), with the exception of one letter in either the first or second trigram, which was randomly selected and replaced with the target letter “O”. The subject had 1 s to read both trigrams, followed by a 0.5 s response period (for a total of 2.5 s per trial, with 4 trials per 10 s stimulus block). The subject’s task was to indicate whether the letter “O” was contained in the first or second trigram. To reduce motion in the scanner, we arranged each index card with four rows of trials, so that each card contained all the trials for a given stimulus block. Accordingly, unlike the other tasks in this study, the *tactile trigrams* task was necessarily self-paced by the subject.

For sighted subjects (since they did not read Braille), we created a modified *tactile trigrams* stimulus. The stimulus and procedure were as described above, except that instead of embossed Braille letters, we used the embossed Roman letter “I” for every distractor and the Roman letter "O" as the target. This task was surprisingly difficult for our sighted subjects (see Behavioral Performance in the Results).

The *tactile animals* stimulus consisted of a collection of toy plastic animals, with equal numbers of mammals (pig, goat, bear, gorilla, giraffe, elephant), and non-mammals (snake, insect, lizard, turtle, crab, shark). During each of two (4.75 s) intervals, a plastic animal was placed into the subject’s hand by the experimenter, and the subject was encouraged to feel them actively with the hand (while minimizing movement of the arm). Mammals and non-mammals were presented with equal frequency, and the probability of their belonging to the same category was 50%. This was followed by a 0.5 s response period, for a total of 10 s per trial, and one trial per 10 s stimulus block. Subjects performed a “same-different” task, indicating via key-press whether or not both animals belonged to the same mammal/non-mammal category.

For the *tactile orientation* task, the experimenter applied a JVP dome (2.0 mm, Stoelting Co., IL, see Figure 2) tactile grating to the index finger of the subject by slowly “swiping it” along the fingertip. Similar methods using JVP domes have been used by others (e.g. Sathian & Zangaladze, 2002; Zhang, Mariola, Stilla, Stoesz, Mao, Hu & Sathian, 2005). Each “swipe” was oriented such that the indentations of the JVP dome ran parallel to the length of the finger (“vertical”), or such that the indentations ran across the width of the finger (“horizontal”). Each swipe was presented over a duration of approximately 2 s, and was followed by a 0.5 second response period (for a total of 2.5 s per trial, with 4 trials per 10 s stimulus block). The subject’s task was to indicate via key-press whether the orientation of the grating had been vertical, or horizontal.

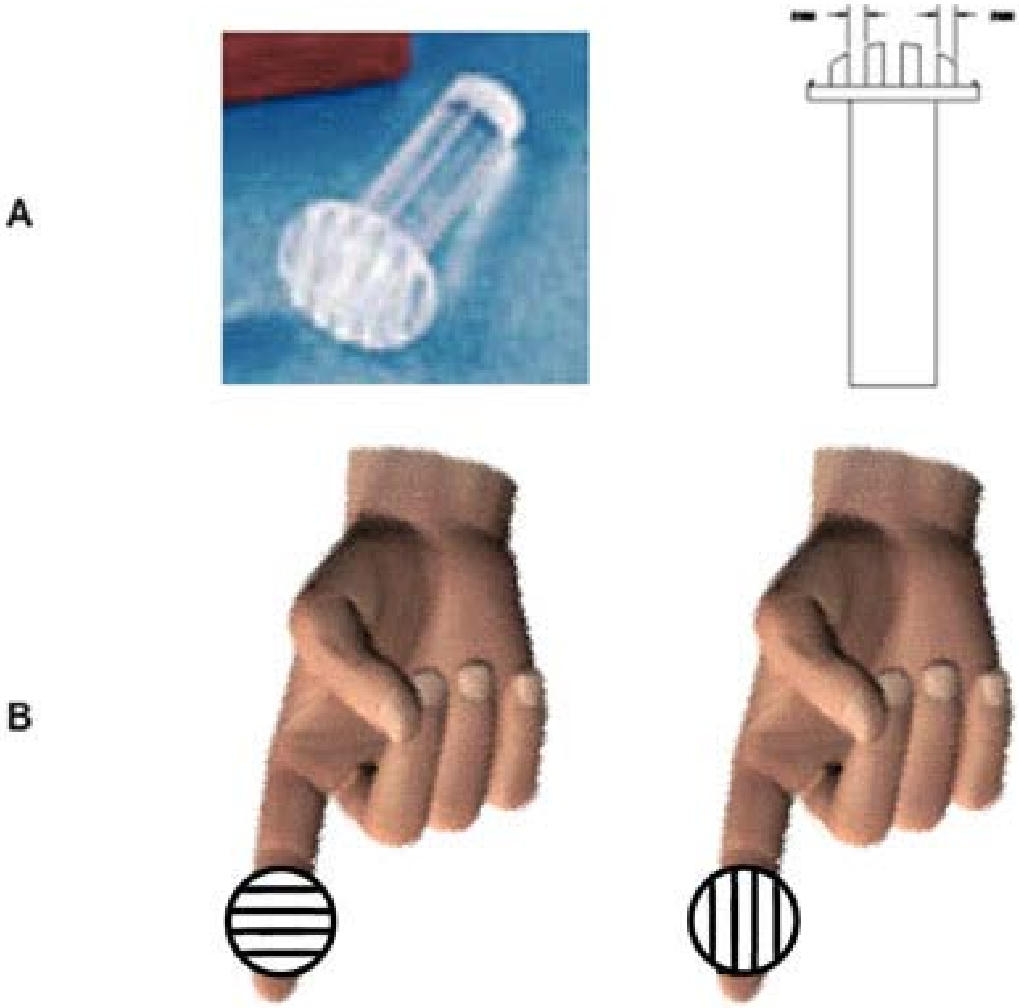

Figure 2: Study 1: **(A)** Photo and illustration of a 2.0 mm JVP dome, used in the *tactile orientation* stimulus. **(B)** Illustration of the tactile pattern produced on the fingertip by application of the JVP dome in the “horizontal” and “vertical” orientations, respectively.

Visual Tasks (carried out in sighted subjects only). Four types of visual tasks were presented to the sighted subjects: “visual trigrams” (VT), “visual animals” (VA), “visual orientation” (VO), and “visual motion” (VM). Visual stimuli were projected onto a rear-projection screen visible from within the MRI scanner via an angled mirror. All visual stimuli were presented against a gray background (except for *visual* *motion*, which was presented against a black background), and contained a central fixation point, subtending 0.27º x 0.27º visual angle. The fixation point was white at all times, except during visual tasks, in which it was gray and placed over the stimuli. This gray background and white fixation point also remained present during all auditory and tactile tasks, as well as the *no stimulus/key-press* task. Subjects were encouraged to always maintain fixation.

The *visual trigram*s stimulus consisted of a visual presentation of two trigrams of three letters, which were white, centered at fixation, and displayed within a black rectangular background subtending 6.37º x 16.00º visual angle. Each letter was roughly 3.20º x 3.20º visual angle, and centered 3.20º from center of fixation. Each distractor letter was randomly generated from the alphabet (excluding the letter “O”), with the exception of one letter in either the first or second trigram, which was randomly selected and replaced with the target letter “O”. Each trigram was presented for 1 s, and both trigrams were followed by a 0.5 s response period (for a total of 2.5 s per trial, with 4 trials per 10 s stimulus block). The subject’s task was to indicate via key-press whether the letter “O” was contained in the first or second trigram.

The *visual animals* stimulus consisted of a set of grayscale photos of the plastic animals, which were equally likely to be a mammal (pig, goat, bear, gorilla, giraffe, elephant), or a non-mammal (snake, insect, lizard, turtle, crab, shark). The stimulus was centered at fixation and subtended 6.37º x 8.58º visual angle. Mammals and non-mammals were presented with equal frequency, and the probability of their belonging to the same category was 50%. To match the timing of the equivalent *tactile animals* task, each presentation had a duration of 4.75 seconds. This was followed by a 0.5 s response period, for a total of 10 s per trial, and one trial per 10 s stimulus block. Subjects performed a "same-different" task, indicating via key-press whether or not both animals belonged to the same mammal/non-mammal category.

The *visual orientation* stimulus was a vertically or horizontally oriented pattern stimulus comprised of square wave gratings of mixed spatial frequencies, with the same mean luminance as the gray background. It was centered at fixation, and subtended 11.05º x 11.05º visual angle. It was presented for a duration of 2 s, and was followed by a 0.5 s response period (for a total of 2.5 s per trial, with 4 trials per 10 s stimulus block). The subject's task was to indicate via key-press whether the orientation of the grating was horizontal, or vertical; see Figure 3.

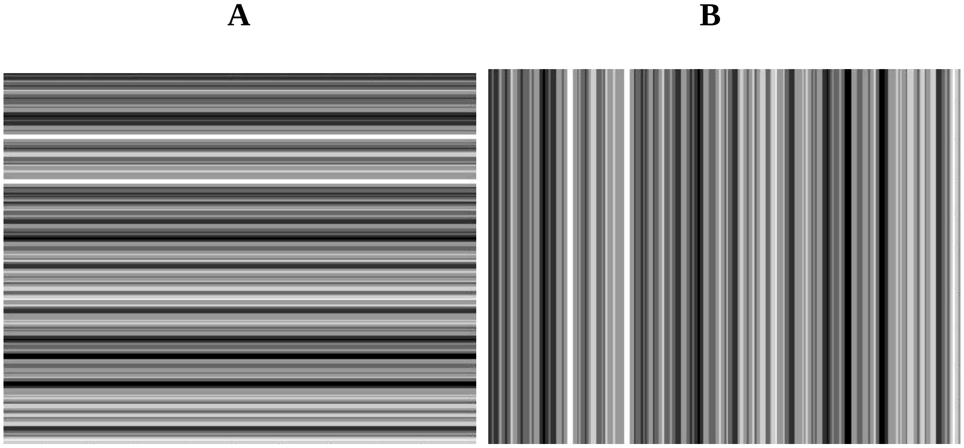

Figure 3: Study 1: Illustration of the *visual orientation* stimulus in a "horizontal" orientation **(A)**, and a "vertical" orientation **(B)**.

The *visual motion* stimulus consisted of a field of random white dots on a black background, centered at fixation, subtending 13.66º x 13.66º, moving 7.65º/s radially inward and outward, and alternating direction every 1 s. Individual dots

(100/field) subtended 0.70º x 0.70º. Subjects did not perform a motion task, but passively viewed the stimulus and performed key-pressing timed to match most of the other tasks in the study. For a given trial, after 2 s the standard “click” sound was presented, and subjects had a 0.5 s response period during which to press a key (for a total of 2.5 s per trial, with 4 trials per 10 s stimulus block). Subjects were asked to alternate between pressing each of the two possible response keys across the four trials within each 10 s block.

Data Analysis

Brain Voyager QX (Brain Innovation, Maastricht, The Netherlands) and MATLAB (Mathworks) were used for data analysis. fMRI data pre-processing included linear trend removal, temporal high-pass filtering, and motion correction.

GLM Analyses (Brain Voyager). For general linear model (GLM) analyses, individual 3D anatomical images were transformed into Talairach space and segmented at the gray/white matter boundary. This allowed for cortical surface reconstruction of each individual subject’s brain hemispheres. Cortex-based alignment was applied to further improve inter-subject alignment beyond Talairach correspondence. The reconstructed cortical surfaces were each transformed into a spherical representation that was subjected to non-rigid alignment to a selected target brain sphere based on the gyral/sulcal folding pattern (Fischl, Sereno, Tootell & Dale, 1999). fMRI data were aligned to same-session anatomical volumes and transformed into the cortex-based aligned coordinate space. Fixed-effects[10] GLM analyses were corrected for multiple comparisons using the false discovery rate (FDR) method (Genovese, Lazar & Nichols, 2002).

Table 2 contains a list and brief description of all GLMs used in this study. Because blind subjects did not perform the visual task conditions our design was unbalanced. We therefore created two "split" GLMs. The first contained only data from the auditory, tactile, and the *no stimulus/key-press* tasks for blind and sighted subjects, with all visual conditions manually removed ("Aud/Tact GLM"). The second contained only data from the visual and *no stimulus/key-press* tasks for sighted subjects, with all auditory and tactile tasks manually removed ("Vis GLM"). Data for the *no stimulus/key-press* task were included in both GLMs.

We also created a variety of alternate versions of our GLMs for additional analyses. See Table 2 and the Results section for details. For each version listed, there was additionally an alternate version containing right-handed subjects only[11].

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[10] We did not have a sufficient number of subjects to conduct random-effects GLM analyses. Nonetheless, data from each subject was separately defined in the GLM in order to allow us to specify subject groups (blind and sighted).

[11] Five of seven blind subjects and four of six sighted subjects were right-handed.

Table 2: Study 1: List of General Linear Models (GLMs)

	Auditory	Tactile	Visual	Subjects	Tasks Collapsed?
"Aud/Tact GLM"	yes	yes	no	all	no
"Vis GLM"	no	no	yes	sighted	no
"Aud/Tact GLM (blind)"	yes	yes	no	blind	no
"Aud/Tact GLM (sighted)"	yes	yes	no	sighted	no
"Aud/Tact/Vis GLM (sighted)"	yes	yes	yes	sighted	no
"Aud/Tact GLM (blind, by modality)"	yes	yes	no	blind	across modality (auditory vs. tactile. vs. no task)
"Aud/Tact GLM (sighted, by modality)"	yes	yes	no	sighted	across modality (auditory vs. tactile. vs. no task)
"Aud/Tact/Vis GLM (sighted, by modality)"	yes	yes	yes	sighted	across modality (auditory vs. tactile. vs. visual vs. no task)
"Aud/Tact GLM (blind, task vs. no task)"	yes	yes	no	blind	across all tasks (task vs. no task)
"Aud/Tact GLM (sighted, task vs. no task)"	yes	yes	no	sighted	across all tasks (task vs. no task)
"Aud/Tact/Vis GLM (sighted, task vs. no task)"	yes	yes	yes	sighted	across all tasks (task vs. no task)

GLM data were used within Brain Voyager for subtraction analyses, to define regions of interest (ROIs) based on subtraction analyses, and for ROI ANOVAs (to calculate variability accounted for by each GLM type within each ROI).

ROI Analyses (Brain Voyager + MATLAB). GLM data were also exported from Brain Voyager to custom software in MATLAB in order to carry out region-of-interest (ROI) analyses, described in more detail in the Results section.

ROI analyses are more sensitive than whole-brain analyses, and typically have the benefit of being based on individual subject data. However, because we defined our ROIs using differences across subject groups (blind - sighted), we were unable to define ROIs on an individual subject basis. Therefore, we chose to conduct our ROI analyses using group analyses aligned in 2D cortex-based alignment space as opposed to 3D Talairach space.

(4.3) RESULTS

Behavioral Performance

Behavioral data, shown in Figure 4, were analyzed using MATLAB.

Due to technical problems at the scanner, behavioral data for several scans were lost. For two blind subjects, behavioral data were missing for 2 scans each. For three sighted subjects, behavioral data were missing for 1 scan each, and for one sighted subject, behavioral data were missing for 4 scans. For one sighted subject, this technical problem resulted in missing data for all scans in the *auditory trigrams* condition. Subjects were unaware of the technical problems, and so presumably performed the tasks as usual while in the scanner.

Additionally, due to a technical glitch in the MRI-compatible button box, some responses were not recorded. Unfortunately, these responses are not distinguishable from subjects failing to respond within the allotted response interval. A two-way mixed ANOVA (subject group x task) on percentage of lost/late responses indicated that although there was no effect of subject group [$F(1,11)=1.58$, $p=0.23$] and no interaction effect [$F(5,55)=0.68$, $p=0.63$]; data corrected for lack of sphericity), there was a main effect of task [$F(5,55)=10.03$, $p<0.001$]; data corrected for lack of sphericity). Individual *t*-tests confirmed that the percentage of lost/late responses did not significantly differ between blind and sighted subjects for any task (mean across all tasks: 21.8% vs. 25.7%, respectively, $p=0.32$; *auditory trigrams*: 10.3% vs. 25.5%, respectively, $p=0.08$; *auditory motion*: 7.0% vs. 21.0%, respectively, $p=0.13$; *auditory* *frequency*: 8.6% vs. 15.4%, respectively, p=0.44; *tactile trigrams*: 51.1% vs. 52.0%, respectively, p=0.92; *tactile animals*: 50.9% vs. 57.6%, respectively, p=0.73; *tactile orientation*: 33.5% vs. 21.8%, respectively, p=0.40). The main effect of task is explained by t-tests across subject groups; the percentage of lost/late responses for both *tactile trigrams* and *tactile animals* was significantly greater than percentage of lost/late responses for all other auditory and tactile tasks ($p<0.02$ for all comparisons), and the percentage of lost/late responses for *tactile orientation* was significantly greater than the percentage of lost/late responses for *auditory frequency* ($p<0.05$). These findings perhaps suggest that it was generally more difficult for subjects to respond within the allotted time period to tactile tasks than to auditory tasks. Behavioral data were analyzed with and without lost responses; results were qualitatively similar across both analyses.

When lost/late responses were included as incorrect responses, a two-way mixed ANOVA (subject group x task) indicated that although there was no effect of subject group [$F(1,11)=2.63$, p=0.13] and no interaction effect [$F(5,55)=0.78$, p=0.57; data corrected for lack of sphericity], there was a main effect of task [$F(5,55)=13.90$, $p<0.0001$; data corrected for lack of sphericity]. Individual t-tests confirmed that task performance was not significantly different between blind vs. sighted subjects for any task (mean across all tasks: 73.8% vs. 70.2% correct, respectively, p=0.36; *auditory trigrams*: 86.7% vs. 72.2% correct, respectively, p=0.09; *auditory motion*: 83.6% vs. 75.7% correct, respectively, p=0.42; *auditory frequency*: 91.1% vs. 81.4% correct, respectively, p=0.34; *tactile trigrams*: 43.1% vs. 32.1% correct, respectively, p=0.18;

tactile animals: 45.5% vs. 36.0% correct, respectively, p=0.57; tactile orientation: 62.7% vs. 76.0% correct, respectively, p=0.36). However the main effect of task is explained by t-tests across subject groups; performance for both *tactile trigrams* and *tactile animals* was significantly worse than performance for all three auditory tasks (p<0.01 for all comparisons), and performance for *tactile orientation* was significantly worse than performance for *auditory frequency* (p<0.05), while significantly better than performance for *tactile trigrams* and *tactile animals* (p<0.01 for both comparisons). Also, performance for *auditory frequency* was significantly better than performance for *auditory motion* (p<0.02). It can be seen from informal inspection of Figure 4 that, when lost/late responses were included as incorrect responses, that performance on tactile tasks was indeed generally lower than performance on auditory tasks.

When late/lost responses were excluded, a two-way mixed ANOVA (subject group x task) indicated that although there was no effect of subject group [F(1,11)=1.72, p=0.22], there was again a main effect of task [F(5,55)=11.29, p<0.0001; data corrected for lack of sphericity] and an interaction effect [F(5,55)=5.29, p<0.01; data corrected for lack of sphericity]. Individual t-tests confirmed that task performance was not significantly different between blind vs. sighted subjects, with the exception of tactile trigrams (mean across all tasks: 94.3% vs. 94.6% correct, respectively, p=0.86; *auditory trigrams*: 96.5% vs. 96.8% correct, respectively, p=0.84; *auditory motion*: 90.0% vs. 94.8% correct, respectively, p=0.19; *auditory frequency*: 99.7% vs. 94.9% correct, respectively, p=0.13; *tactile trigrams*:

89.1% vs. 67.5% correct, respectively, p=0.01; *tactile animals*: 91.7% vs. 92.9% correct, respectively, p=0.84; *tactile orientation*: 94.0% vs. 95.8% correct, respectively, p=0.72). It is perhaps not surprising that sighted subjects performed more poorly on *tactile trigrams* than blind subjects, since not only were they unable to read Braille, but they were also not used to reading Roman letters tactilely (i.e. in our non-Braille version of *tactile trigrams*). The main effect of task is explained by t-tests across subject groups; performance for *tactile trigrams* was significantly worse than performance for all other auditory and tactile tasks (p<0.02 for all comparisons), performance for *tactile animals* was significantly worse than performance for *auditory frequency* (p<0.03), and performance for *auditory trigrams* and *auditory frequency* were significantly better than performance for *auditory motion* (p<0.03 for both comparisons). The interaction effect is explained by t-tests comparing each task within each subject group: in sighted subjects performance for *tactile trigrams* was significantly worse than performance for all other auditory and tactile tasks (p<0.01 for all comparisons); in blind subjects performance for *auditory trigrams* was significantly better than performance for *auditory motion* and *tactile trigrams* (p<0.05 for both comparisons), performance for *auditory frequency* was significantly better than performance for *auditory trigrams*, *auditory motion*, and *tactile trigrams* (p<0.02 for all comparisons), and performance for *tactile trigrams* was significantly worse than performance for *tactile orientation* (p<0.05). It can be seen from informal inspection of Figure 4 that, when lost/late responses were excluded, that in sighted subjects performance on *tactile trigrams* was generally lower than performance on all other tasks.

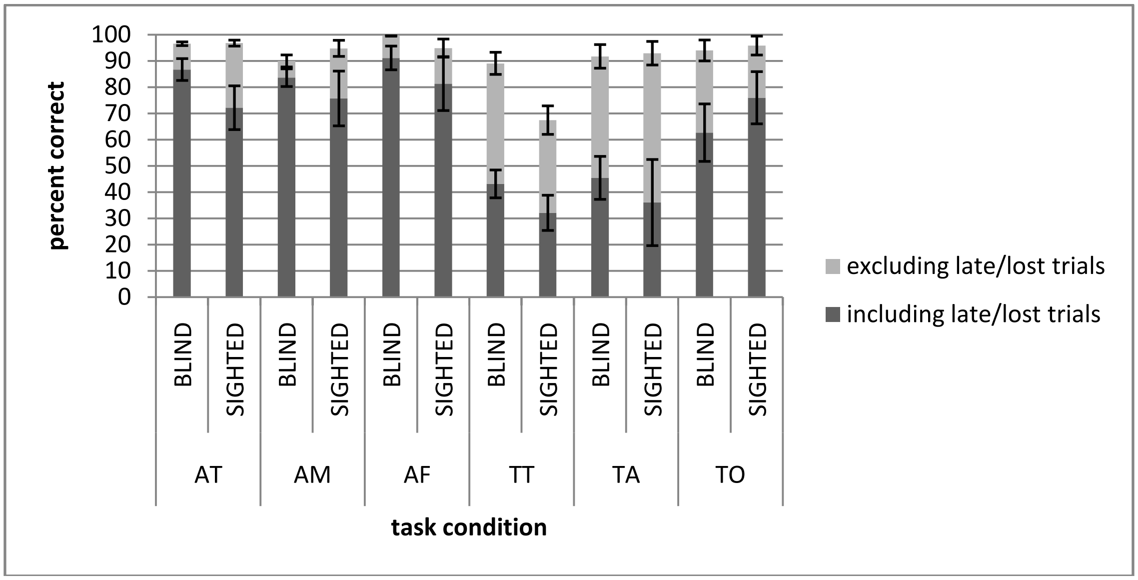

Figure 4: Study 1: Behavioral performance for blind and sighted subjects including and excluding late/lost trials. AT = *auditory trigrams*, AM = *auditory motion*, AF = *auditory frequency*, TT = *tactile trigrams*, TA = *tactile animals*, TO = *tactile orientation*. Error bars represent SEM.

Surface Maps of Activation and ROI Selection

Surface activation maps below show responses to individual tasks vs. *no stimulus/key-press* task across all subjects in the case of auditory tasks, and across in all right-handed subjects in the case of tactile tasks (using the "Aud/Tact GLM", see Table 2). Warm colors represent greater BOLD responses to the specific task than to the *no stimulus/key-press* task.

For all ROIs, we used very conservative thresholds of q(FDR)<0.003 or lower. In some cases the threshold was made even more conservative and/or some restriction of the ROI was done by hand in order to restrict the ROI to the desired anatomical location. The stereotaxic locations and volumes for each ROI are reported in Table 3.

Table 3: Study 1: ROI Talairach coordinates.

	Left Hemisphere (lower bound; center; upper bound)									Right Hemisphere (lower bound; center; upper bound)								
	x		y				z			x			y			z		
	Lower Bound	Center	Upper Bound	Lower Bound	Center	Upper Bound	Lower Bound	Center	Upper Bound	Lower Bound	Center	Upper Bound	Lower Bound	Center	Upper Bound	Lower Bound	Center	Upper Bound
Auditory	-66	-51	-35	-42	-24	-3	-6	5	16	38	54	66	-38	-17	8	-7	7	20
Somatosensory	-63	-43	-19	-68	-43	-21	12	41	64	18	45	66	-62	-39	-14	14	36	60
AUD$_{OccTemp}$	-62	-48	-34	-79	-65	-54	-11	2	15	35	47	60	-82	-67	-52	-14	0	12
AUD$_{DorsOcc}$	-34	-19	0	-93	-78	-65	5	31	58	11	26	36	-86	-75	-65	4	27	50
AUD$_{Vent}$	-53	-36	-17	-75	-56	-30	-26	-16	-4	16	38	60	-77	-52	-22	-24	-14	-2
TAC$_{OccTemp}$	-55	-44	-33	-82	-70	-57	-12	0	13	22	43	58	-91	-73	-56	-11	0	12
TAC$_{DorsOcc}$	-50	-22	0	-96	-77	-56	8	33	53	0	20	38	-96	-81	-65	-1	24	52
TAC$_{Vent}$	-55	-38	-20	-84	-66	-43	-26	-14	-5	16	39	62	-82	-55	-18	-26	-13	4

Sensory Activation and ROIs. Figure 5A shows responses to the *auditory frequency* versus *no stimulus/key-press* task averaged across all blind and sighted subjects, collapsed (using the “Aud/Tact GLM”, q(FDR)<0.001 - see Table 2)[12]. Figure 5C shows responses to *tactile orientation* versus *no stimulus/key-press* task in all right-handed subjects. Warm colors represent greater BOLD responses to the *auditory frequency* or *tactile orientation* task than to the *no stimulus/key-press* task. As expected, we see activation within auditory and somatosensory cortex respectively. In the case of the tactile task, activation is also seen in motor cortex. We then defined bilateral sensory ROIs for auditory cortex (Figure 5B) and somatosensory cortex (Figure 5D). These ROIs were defined based on a combination of anatomy and functional responses.

Auditory ROI. As shown in Table 3 and Figure 5, we defined the auditory cortex ROI as the region in all subjects (blind and sighted subjects, collapsed) that showed larger responses to *auditory frequency* (the “simplest” auditory task) than the *no stimulus/key-press* task, at q(FDR)<0.001 [center of activation Talairach coordinates: left hemisphere (LH): -51, -24, 5; right hemisphere (RH): 54, -17, 7; Brodmann area 22, possibly extending into Brodmann areas 41/42], shown as black overlay in Figure 5B.

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[12] Separate activation maps for blind and sighted subjects are shown in Appendix A.

Somatosensory ROI. We defined the somatosensory cortex ROI as the region in somatosensory cortex of right-handed[13] blind and sighted subjects, collapsed, that showed larger BOLD responses to *tactile orientation* (the "simplest" tactile task) than the *no stimulus/key-press* task at q(FDR)<0.001 [center of activation Talairach coordinates: left hemisphere (LH): -43, -43, 41; right hemisphere (RH): 45, -39, 36; Brodmann areas 1/2/3/5], shown as olive green overlay in Figure 5D. In the left hemisphere, the somatosensory cortex ROI was hand-drawn in order to isolate it from nearby motor cortex activation.

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[13] We conducted the same analyses using a somatosensory cortex ROI that was defined using all subjects, and the results were qualitatively similar. However we felt it was more appropriate to show results for analyses restricted to only right-handed subjects.

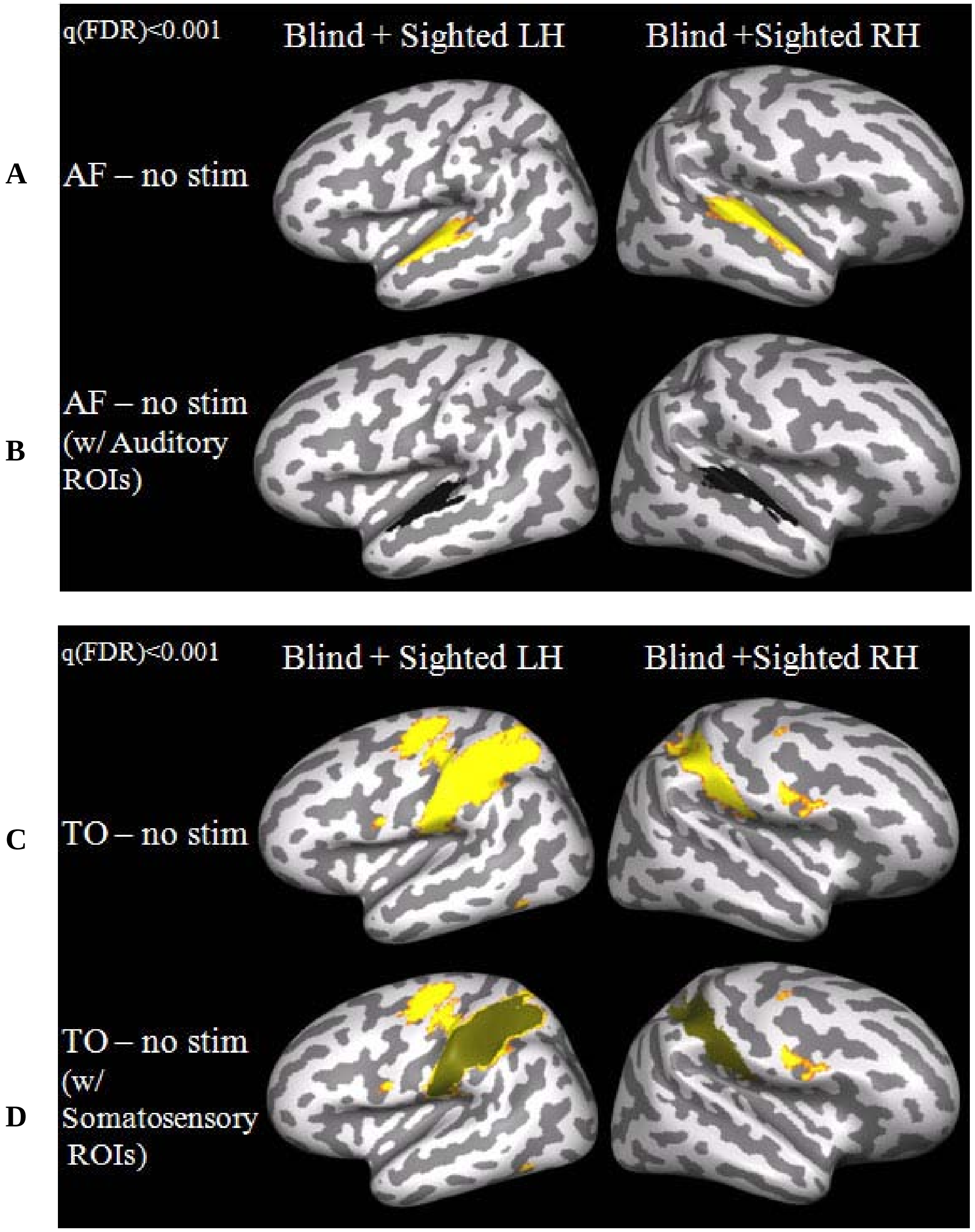

Figure 5: Study 1: Sensory ROIs (auditory and somatosensory), overlaid over the comparisons by which they were defined. All images are from a lateral view. **(A)** *Auditory frequency* vs. *no stimulus/key-press* task in all subjects (blind and sighted subjects, collapsed), and **(B)** with auditory ROI (black). **(C)** *Tactile orientation* vs. *no stimulus/key-press* task in all right-handed subjects, and with **(D)** somatosensory ROI (olive green). Warm colors represent greater BOLD responses to the *auditory frequency* or *tactile orientation* task than to the *no stimulus/key-press* task. AF = *auditory frequency*, TO = *tactile orientation*, no stim = *no stimulus/key-press*; auditory ROI = black, somatosensory ROI = olive green; LH = left hemisphere, RH = right hemisphere. Data are conservatively thresholded at q(FDR)<0.001.

Cross-modal Activation and ROIs Defined by Auditory Tasks. Figure 6A, C and D show responses to the auditory tasks versus *no stimulus/key-press* task based on group averages of blind – sighted responses to each auditory task vs. the *no stimulus/key-press* task, [using the "Aud/Tact GLM," q(FDR)<0.003, see Table 2][14]. Warm colors represent greater BOLD responses to the auditory task than to the *no stimulus/key-press* task in blind than in sighted subjects. Significant cross-modal plasticity within visual cortex can be observed, with the pattern of activity showing strong similarities across all auditory tasks and both hemispheres. It is worth noting that a significant portion of visual cortex seems to demonstrate cross-modal plasticity, more than has generally been observed in previous studies using similar stimuli (see Chapter 1). Although we had relatively few subjects (though comparable to most other studies of blindness) we carried out a large number of repetitions/task (48 repetitions/task) given our block design. In addition, the very large number of repetitions (96 repetitions in blind subjects, 144-168 repetitions in sighted subjects) for the *no stimulus/key-press* task, the sparse pulse sequence, and the high quality of our scanner gave our analysis additional power. Compared to many previous studies, our current study had very high signal-to-noise ratio. This allowed us to use extremely conservative thresholds in determining regions of activation.

We then defined three bilateral cross-modal ROIs based on these auditory tasks. Shown in Figure 6B and E are cross-modal ROIs (i.e. greater BOLD responses

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[14] Separate auditory activation maps for blind and sighted subjects are shown in Appendix A.

in blind than sighted subjects) defined bilaterally, based on group averages of blind – sighted responses to a single auditory task vs. the *no stimulus/key-press* task.

Three main regions of cross-modal activation were noted for auditory vs. *no stimulus/key-press* tasks: occipito-temporal ($AUD_{OccTemp}$), dorsal-occipital ($AUD_{DorsOcc}$) and ventral (AUD_{Vent}). For each of these regions we selected an ROI for further processing, shown as colored overlays in Figure 6B and E and in Table 3.

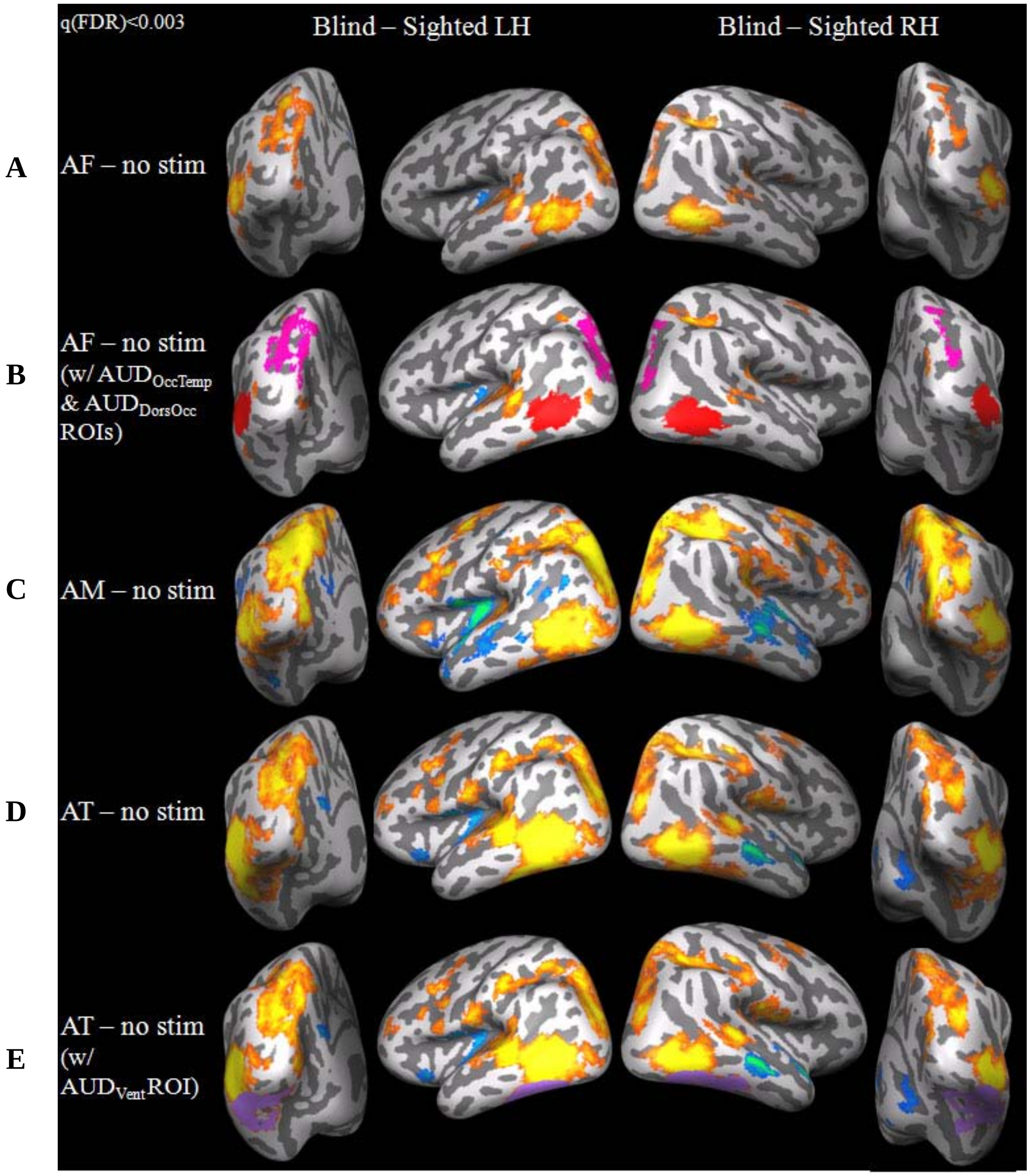

Figure 6: Study 1: Cross-modal BOLD response for auditory tasks vs. the *no stimulus/key-press* task, with cross-modal auditory ROIs (AUD$_{\text{OccTemp}}$, AUD$_{\text{DorsOcc}}$, and AUD$_{\text{Vent}}$) overlaid over the comparisons by which they were defined. Lateral views are presented in the center, whereas views from behind occipital pole are presented on the sides. Warm colors represent greater BOLD response in blind than sighted subjects (cross-modal plasticity), cool colors represent greater BOLD response in sighted than blind subjects. **(A)** *Auditory frequency* (AF) vs. *no stimulus/key-press* (no stim) task, **(B)** with cross-modal ROIs defined by this comparison (AUD$_{\text{OccTemp}}$, light red; and AUD$_{\text{DorsOcc}}$, light pink). **(C)** *Auditory motion* (AM) vs. *no stimulus/key-press* (no stim) task. **(D)** *Auditory trigrams* (AT) vs. *no stimulus/key-press* (no stim) task, **(E)** with the cross-modal ROI defined by this comparison (AUD$_{\text{Vent}}$, light purple). LH = left hemisphere, RH = right hemisphere. Data are conservatively thresholded at q(FDR)<0.003.

$AUD_{OccTemp}$. Occipito-temporal cross-modal BOLD responses were noted for all three auditory tasks vs. the *no stimulus/key-press* task, [q(FDR)<0.003]. The area that showed cross-modal plasticity in the *auditory frequency* vs. the *no stimulus/key-press* task was selected as an ROI for further analysis [center of activation Talairach coordinates: left hemisphere (LH): -48, -65, 2; right hemisphere (RH): 47, -67, 0; intersection of Brodmann areas 19/37/39], shown as light red overlay in Figure 6B.

$AUD_{DorsOcc}$. Bilateral dorsal-occipital cross-modal BOLD responses were also noted for all three auditory tasks vs. the *no stimulus/key-press* task, [q(FDR)<0.003]. The area that showed cross-modal plasticity in the *auditory frequency* vs. the *no stimulus/key-press* task was again selected as an ROI for further analysis [center of activation Talairach coordinates: left hemisphere (LH): -19, -78, 31; right hemisphere (RH): 26, -75, 27; Brodmann areas 18/19, possibly extending anteriorly into a small portion of Brodmann area 7], shown as light pink overlay in Figure 6B.

AUD_{Vent}. Bilateral cross-modal BOLD responses in ventral cortical regions were above threshold for the *auditory trigrams* and *auditory motion* (but not *auditory frequency*) tasks vs. the *no stimulus/key-press* task, [q(FDR)<0.003]. The area that showed cross-modal plasticity for the *auditory trigram* task was selected as an ROI for further analysis (note that this ROI was hand-selected so as to be restricted to the ventral region) [center of activation Talairach coordinates: left hemisphere (LH): -36, -56, -16; right hemisphere (RH): 38, -52, -14; Brodmann areas 19/37, possibly extending anteriorly into a small portion of Brodmann area 20], shown as light purple overlay in Figure 6E.

Cross-modal Activation and ROIs Defined by Tactile Tasks. Figure 7A, C and D show responses to the tactile tasks versus *no stimulus/key-press* task based on group averages of blind – sighted responses (right-handed subjects only) to each tactile task vs. the *no stimulus/key-press* task [using the “Aud/Tact GLM”, q(FDR)<0.003, see Table 2][15]. Warm colors represent greater BOLD responses to the tactile task than to the *no stimulus/key-press* task in blind than in sighted subjects. Significant cross-modal plasticity within visual cortex can again be observed, with a wide pattern of cross-modal activity that once again shows strong similarities across all tactile tasks and hemispheres.

An analogous ROI selection procedure was carried out for tactile tasks as was carried out for auditory tasks. Shown in Figure 7B and E are cross-modal ROIs (i.e. greater BOLD responses in blind than sighted subjects) defined bilaterally, based on group averages of blind – sighted responses (in right-handed subjects only) to each single tactile task vs. the *no stimulus/key-press* task.

The same main regions of cross-modal activation were noted for tactile vs. *no stimulus/key-press* tasks: occipito-temporal ($TAC_{OccTemp}$), dorsal-occipital ($TAC_{DorsOcc}$) and ventral (TAC_{Vent}). For each of these regions we selected an ROI for further processing, shown as colored overlays in Figure 7B and E and in Table 3.

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[15] Separate tactile activation maps for blind and sighted subjects are shown in Appendix A.

In addition to these ROIs, for all tactile tasks we also found larger cross-modal BOLD responses within sighted than blind subjects (as shown by cool colors) bilaterally within auditory cortex, the inferior frontal gyrus, and the supramarginal gyrus at the posterior end of the lateral fissure (Brodmann area 40). Because the focus of this thesis is on cross-modal plasticity in occipital areas, these data are discussed in Appendix A.

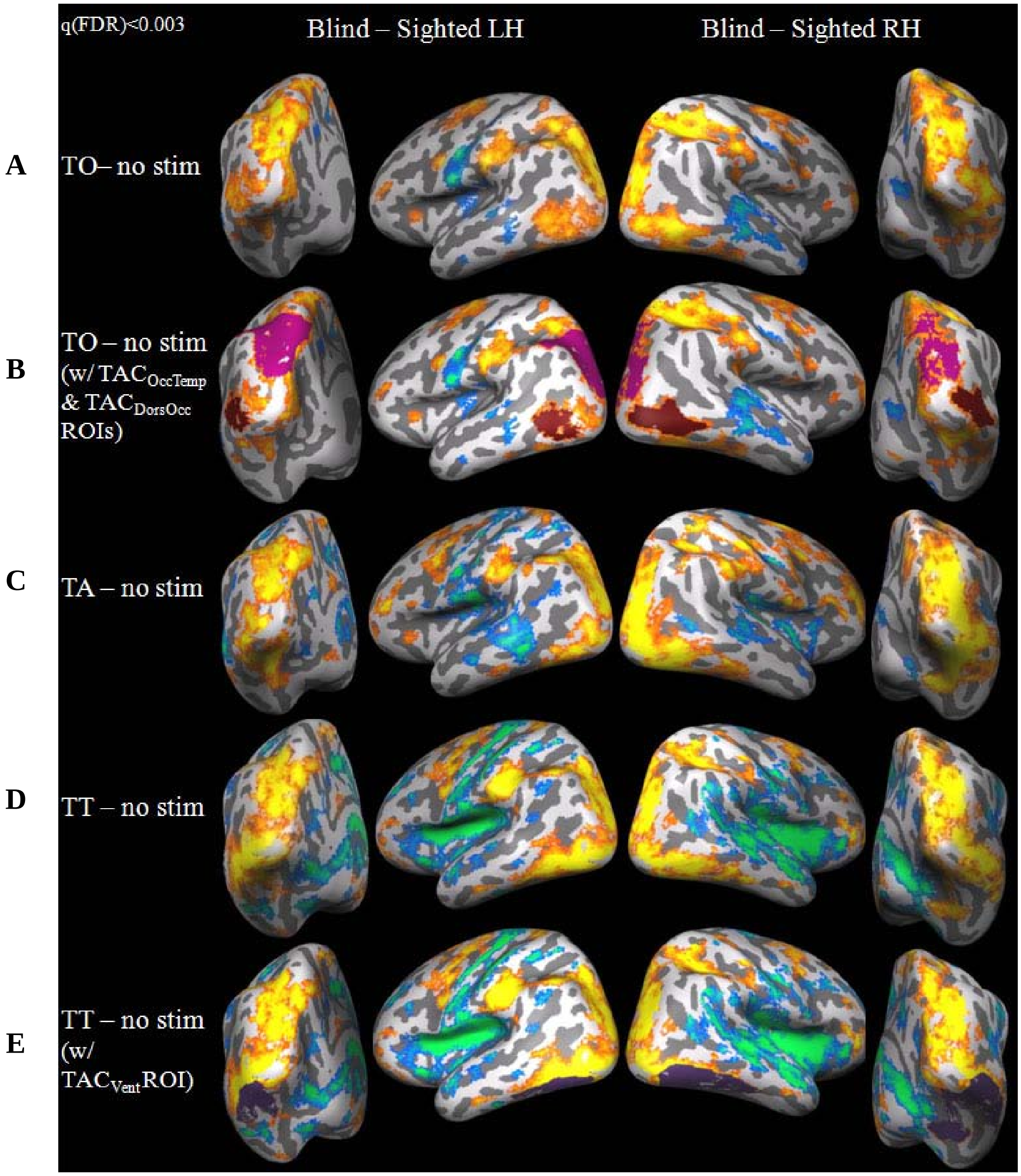

Figure 7: Study 1: Cross-modal BOLD response for tactile tasks vs. the *no stimulus/key-press* task, with cross-modal tactile ROIs ($\text{TAC}_{\text{OccTemp}}$, $\text{TAC}_{\text{DorsOcc}}$, and TAC_{Vent}) overlaid over the comparisons by which they were defined. Lateral views are presented in the center, whereas views from behind occipital pole are presented on the sides. Warm colors represent greater BOLD response in blind than sighted subjects (cross-modal plasticity), cool colors represent greater BOLD response in sighted than blind subjects. **(A)** *Tactile orientation* (TO) vs. *no stimulus/key-press* (no stim) task, **(B)** with cross-modal ROIs defined by this comparison ($\text{TAC}_{\text{OccTemp}}$, dark red; and $\text{TAC}_{\text{DorsOcc}}$, dark pink). **(C)** *Tactile animals* (TA) vs. *no stimulus/key-press* (no stim) task. **(D)** *Tactile trigrams* (TT) vs. *no stimulus/key-press* (no stim) task, **(E)** with the cross-modal ROI defined by this comparison (TAC_{Vent}, dark purple). LH = left hemisphere, RH = right hemisphere. Data are conservatively thresholded at q(FDR)<0.003.

$TAC_{OccTemp}$. Bilateral occipito-temporal cross-modal BOLD responses were noted for all three tactile tasks vs. the *no stimulus/key-press* task, [q(FDR)<0.003]. For all three tactile tasks the region showing cross-modal plasticity tended to be slightly smaller than that found for auditory tasks, and tended to be in a location that was slightly ventral and posterior to the regions of cross-modal activity found for auditory tasks (compare Figure 7 to Figure 6, or see Figure 8). The area that showed cross-modal plasticity in the *tactile orientation* vs. the *no stimulus/key-press* task was selected as an ROI for further analysis (note that this ROI was hand-selected so as to be restricted to the occipito-temporal region) [center of activation Talairach coordinates: left hemisphere (LH): -44, -70, 0; right hemisphere (RH): 43, -73, 0; intersection of Brodmann areas 19/37/39], shown as dark red overlay in Figure 7B.

$TAC_{DorsOcc}$. Bilateral dorsal occipital cross-modal BOLD responses were noted for all tactile tasks vs. the *no stimulus/key-press* task, [q(FDR)<0.003]. These responses showed significant overlap with auditory cross-modal activation, as shown in Figure 9. The area that showed cross-modal plasticity in the *tactile orientation* vs. the *no stimulus/key-press* task was selected as an ROI for further analysis (note that this ROI was hand-selected so as to be restricted to the dorsal-occipital region) [center of activation Talairach coordinates: left hemisphere (LH): -22, -77, 33; right hemisphere (RH): 20, -81, 24; Brodmann areas 18/19, possibly extending anteriorly into a small portion of Brodmann areas 5/7/31], shown as dark pink overlay in Figure 7B.

TAC_{Vent}. Bilateral ventral cross-modal BOLD responses were found for all three tactile tasks vs. the *no stimulus/key-press* task, [q(FDR)<0.003]. As will be described below using the ROI analysis, sighted subjects did show some tactile response within ventral cortex, however responses in blind subjects were larger and extended more medially. The area that showed cross-modal plasticity in the *tactile trigrams* vs. *no stimulus/key-press* task was selected as an ROI for further analysis (note that this ROI was hand-selected so as to be restricted to the ventral region) [center of activation Talairach coordinates: left hemisphere (LH): -38, -66, -14; right hemisphere (RH): 39, -55, -13; Brodmann areas 19/37, possibly extending anteriorly into a small portion of Brodmann area 20], shown as dark purple overlay in Figure 7B.

Overview of ROI Locations. Cross-modal ROIs in occipito-temporal regions are shown in Figure 8, in dorsal-occipital regions are shown in Figure 9, and in ventral regions are shown in Figure 10. Within a given anatomical location cross-modal ROIs defined using auditory and tactile stimuli showed significant overlap.

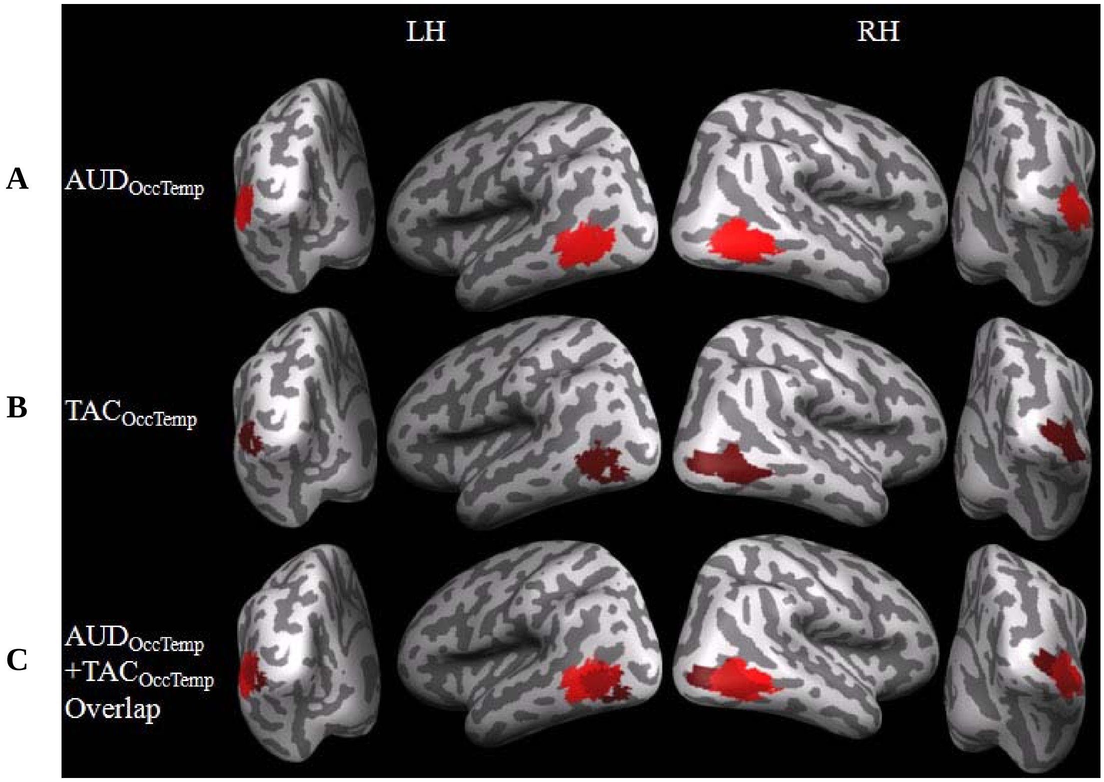

Figure 8: Study 1: Cross-modal occipito-temporal ROIs (AUD$_{\text{OccTemp}}$ and TAC$_{\text{OccTemp}}$). Lateral views are presented in the center, whereas views from behind occipital pole are presented on the sides. **(A)** AUD$_{\text{OccTemp}}$ = light red. **(B)** TAC$_{\text{OccTemp}}$ = dark red. **(C)** Overlap between AUD$_{\text{OccTemp}}$ and TAC$_{\text{OccTemp}}$ = medium red. LH = left hemisphere, RH = right hemisphere.

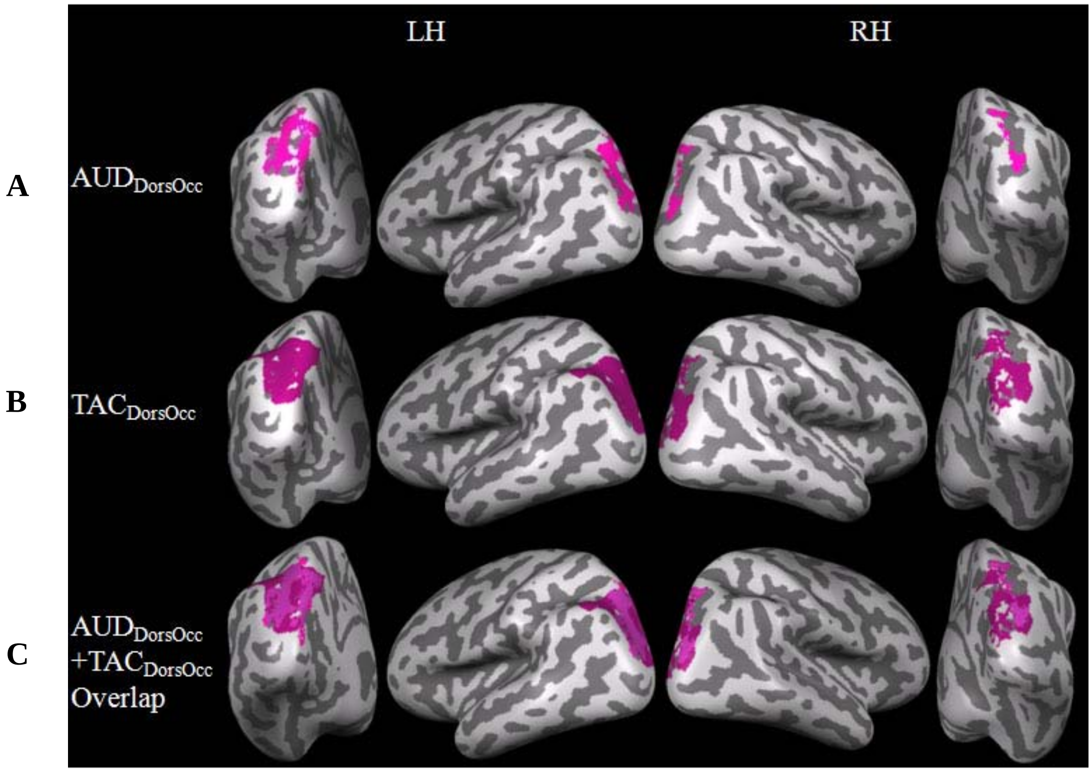

Figure 9: Study 1: Cross-modal dorsal-occipital ROIs (AUD$_{\text{DorsOcc}}$ and TAC$_{\text{DorsOcc}}$). Lateral views are presented in the center, whereas views from behind occipital pole are presented on the sides. **(A)** AUD$_{\text{DorsOcc}}$ = light pink. **(B)** TAC$_{\text{DorsOcc}}$ = dark pink. **(C)** Overlap between AUD$_{\text{DorsOcc}}$ and TAC$_{\text{DorsOcc}}$ = medium pink. LH = left hemisphere, RH = right hemisphere.

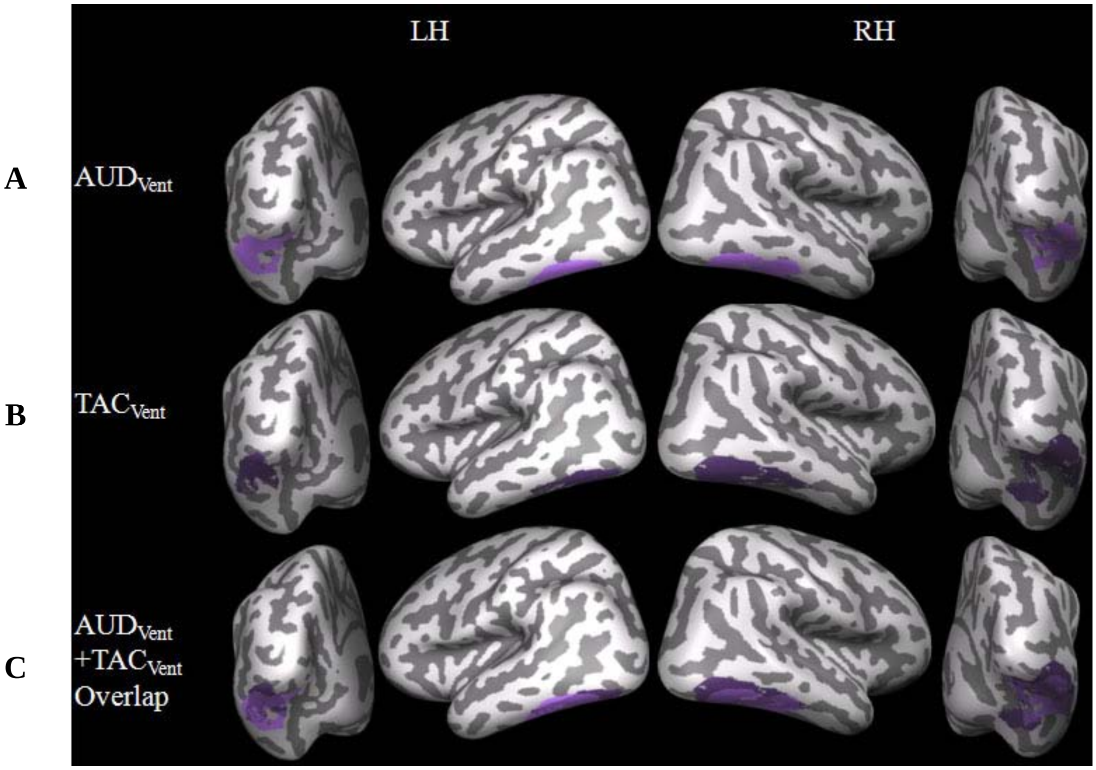

Figure 10: Study 1: Cross-modal ventral ROIs (AUD$_{\text{Vent}}$ and TAC$_{\text{Vent}}$). Lateral views are presented in the center, whereas views from behind occipital pole are presented on the sides. **(A)** AUD$_{\text{Vent}}$ = light purple. **(B)** TAC$_{\text{Vent}}$ = dark purple. **(C)** Overlap between AUD$_{\text{Vent}}$ and TAC$_{\text{Vent}}$ = medium purple. LH = left hemisphere, RH = right hemisphere.

We calculated percentage overlap between auditorily and tactilely-defined ROIs using two measurements: the percentage of the auditory ROI that was also contained within the tactile ROI (PC$_{\text{Aud}\in\text{Tac}}$ = 100 x the number of vertices[16] within both the auditory and tactile ROIs, divided by the number of vertices within the auditory ROI), and the percentage of the tactile ROI that was also contained within the auditory ROI (PC$_{\text{Tac}\in\text{Aud}}$ = 100 x the number of vertices within both the auditory and tactile ROIs, divided by the number of vertices within the tactile ROI). If, for example

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[16] A "vertex" in cortex-based alignment space is the analogue of a "voxel" in Talairach space; during transformation from Talairach space to cortex-based alignment space, multiple voxels are condensed into a single vertex, such that a single vertex represents data from multiple voxels.

the auditory ROI entirely contained the tactile ROI, then $PC_{Aud \in Tac}$ =70% (for example) while $PC_{Tac \in Aud}$ =100%.

Overlap values are shown in Table 4, with the larger percentage overlap across each pair of comparisons in bold. Across all ROIs there was significant overlap. Within the occipito-temporal ROIs in left and right hemispheres over 70% of the tactilely-defined ROI was also contained within the auditorily-defined ROI. Overlap was greatest within the dorsal-occipital ROIs, where over 80% of the auditory ROI was also contained within the tactile ROI. Within the ventral ROIs, 65% of the tactilely-defined ROI was also contained within the auditorily-defined ROI in the LH, and 65% of the auditorily-defined ROI was also contained within the tactilely-defined ROI in the RH.

Table 4: Study 1: Overlap Between Cross-modal Auditory and Tactile ROIs. See text above for details.

ROI	**Hemisphere**	**$PC_{Aud \in Tac}$**	**$PC_{Tac \in Aud}$**
Occipito-Temporal	LH	42%	**70.1%**
Occipito-Temporal	RH	65.3%	**73.6%**
Dorsal-Occipital	LH	**87.9%**	52.1%
Dorsal-Occipital	RH	**81.4%**	22.5%
Ventral	LH	48.8%	**65.8%**
Ventral	RH	**67.7%**	46.4%

In contrast to some previous studies (see Chapter 2) we did not find strong evidence of cross-modal plasticity in the foveal confluence (occipital pole). This is likely to be at least partially due to alignment issues consequent upon translating data to Talairach space and averaging across subjects. The location of occipital pole in Talairach space varies widely across individuals and is thus responses in that region are highly susceptible to being “washed out” by averaging. We do see some evidence of cross-modal plasticity in occipital pole of individual subjects (data not shown), particularly for tactile tasks; however once transformed to Talairach space and averaged across subjects these responses are “cut off” (this sharp drop-off of activation is visible in Figure A1 of Appendix A). Furthermore, anatomical definition of the foveal confluence is better accomplished in other software besides Brain Voyager. We plan to carry out a ROI-based analysis of these data in the near future in which we will define individual foveal confluences anatomically (Dougherty, Koch, Brewer, Fischer, Modersitzki & Wandell, 2003) and measure responses within individual subjects within these ROIs.

Differences Between Auditory and Tactile Tasks

Differences between auditory tasks were computed for all blind – sighted subjects [using the “Aud/Tact GLM”, q(FDR)<0.003, see Table 2] and are shown in Figure 11A, C, and E. ROIs based on auditory tasks are included for comparison in Figure 11B, D, and F. Differences between tactile tasks were also computed for right-handed blind – sighted subjects [using the “Aud/Tact GLM”, q(FDR)<0.003, see Table 2] and are shown in Figure 12A, C and E. ROIs based on tactile tasks are included are included for comparison in Figure 12B, D, and F.

Warm colors represent larger cross-modal BOLD responses for blind than sighted subjects on a given task comparison; i.e. task A – task B for blind subjects > task A – task B for sighted subjects.

Differences between blind and sighted subjects in these task comparisons might come about in a variety of ways: blind subjects might show a larger response than sighted subjects in task A, with no difference between blind and sighted subjects in task B. Alternatively blind and sighted subjects might show no difference in response for task A, but sighted subjects show larger responses than blind subjects in task B. Another possibility is that blind subjects might show weaker inhibition than sighted subjects on task A (similarly, blind subjects might show stronger inhibition than sighted subjects on task B). Cool colors in Figure 11 and 12 represent regions where differences in the magnitude of response between blind and sighted subjects are larger for task B than for task A, where the inverse logic applies. To a certain degree, it is possible to qualitatively determine how our patterns of differential responses are obtained, by comparing each differential response pattern with the basic task vs. baseline comparison (the *no stimulus/key-press* task) - i.e. Figure 6 and 7, or by looking at responses to each task vs. the *no stimulus/key-press* task separately in blind and sighted individuals (see Appendix A). We chose to use an ROI analysis based on the areas outlined in the section above to more fully characterize these differential responses, as described below.

Differences Between Auditory Tasks. It is noticeable that differences in cross-modal plasticity across different auditory tasks were relatively small, as compared to the large regions of cortex that showed cross-modal plasticity for any auditory task compared to the *no stimulus/key-press* task. This is consistent with the observation that, on the whole, patterns of cross-modal plasticity were similar across the three auditory tasks.

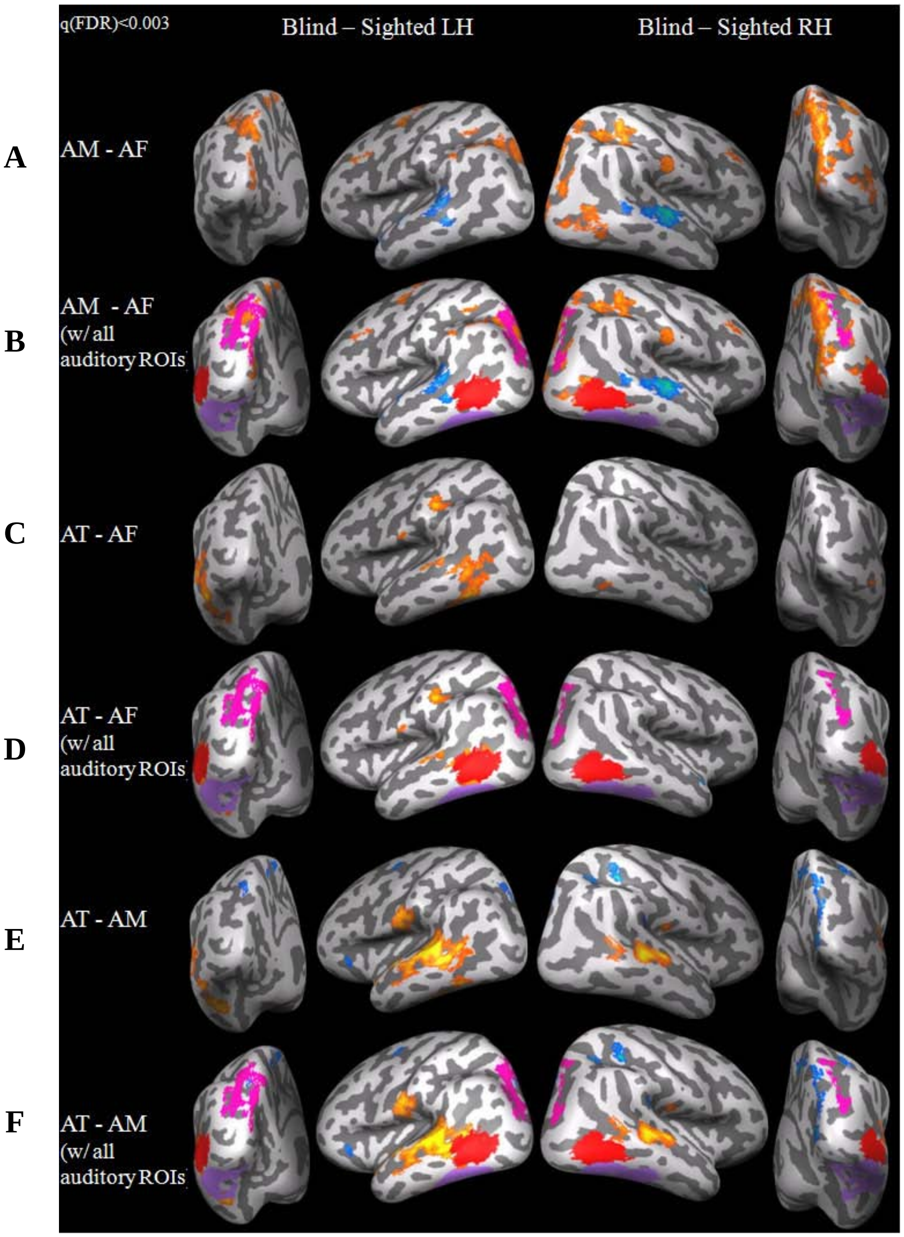

Figure 11: Study 1: Differences in cross-modal BOLD response between auditory tasks, with cross-modal auditory ROIs ($\text{AUD}_{\text{OccTemp}}$, $\text{AUD}_{\text{DorsOcc}}$, and AUD_{Vent}) overlaid. Lateral views are presented in the center, whereas views from behind occipital pole are presented on the sides. See text for explanation of warm versus cool colors. **(A)** *Auditory motion* (AM) vs. *auditory frequency* (AF) task, **(B)** with cross-modal auditory ROIs overlaid. **(C)** *Auditory trigrams* (AT) vs. *auditory frequency* (AF) task, **(D)** with cross-modal auditory ROIs overlaid. **(E)** *Auditory trigrams* (AT) vs. *auditory motion* (AM) task, **(F)** with cross-modal auditory ROIs overlaid. $\text{AUD}_{\text{OccTemp}}$ = light red, $\text{AUD}_{\text{DorsOcc}}$ = light pink, AUD_{Vent} = light purple; LH = left hemisphere, RH = right hemisphere. Data are conservatively thresholded at q(FDR)<0.003.

Auditory Motion vs. Auditory Frequency. In both the left and right hemisphere there were larger cross-modal BOLD responses to the *auditory motion* task than to the *auditory frequency* task in dorsal-occipital cortex, [q(FDR)<0.003]. In the right hemisphere there were also larger cross-modal BOLD responses to *auditory motion* than *auditory frequency* in occipito-temporal cortex, [q(FDR)<0.003]. Based on Figure 7 this differential cross-modal plasticity across tasks seems to be due to the fact that while both tasks showed cross-modal plasticity (greater responses in blind than sighted subjects) in bilateral dorsal-occipital and right occipito-temporal cortex, cross-modal responses in these areas were larger for *auditory motion* than for *auditory frequency*. Responses in both these areas appear to be larger in the right hemisphere than the left hemisphere; this is perhaps consistent with previous evidence for right hemisphere dominance of motion-processing (e.g. auditory motion processing in auditory cortex of sighted subjects: Baumgart et al., 1999; visual motion processing in auditory cortex of deaf subjects: Finney, Fine & Dobkins, 2001; Finney, Clementz, Hickok & Dobkins, 2003). Potential differences between *auditory motion* and other auditory tasks will be more closely examined in the ROI analyses below, and also specifically in area MT+/V5 in *Study 2* (which was not able to be definitively located in occipito-temporal areas here; see *Study 2*).

Auditory Trigrams vs. Auditory Frequency. There were greater cross-modal BOLD responses for the *auditory trigrams* task than *auditory frequency* task within left, though not right, occipito-temporal and ventral cortex, [q(FDR)<0.003]. Again, examination of Figure 7 shows that both tasks elicited positive cross-modal BOLD responses in both areas, but these responses were slightly stronger in the left hemisphere for *auditory trigrams* than for *auditory frequency*. This is perhaps consistent with previous evidence for left hemisphere dominance of cross-modal plasticity for language tasks (Amedi et al., 2004; Burton et al., 2002b). Potential differences between *auditory trigrams* and both auditory tasks will be more closely examined in the ROI analyses below.

Auditory Trigrams vs. Auditory Motion. There were greater cross-modal BOLD responses for the *auditory trigrams* task than *auditory motion* task within auditory cortex and Brodmann area 40 in both hemispheres, [q(FDR)<0.003]. Examination of Figure 6 shows that only the *auditory trigrams* task elicited activation in these auditory areas – responses to *auditory motion* were, if anything, slightly negative in these areas. We also saw a differential cross-modal response across the two tasks within left ventral cortex, [q(FDR)<0.003]. Examination of Figure 6 shows that both tasks elicited positive cross-modal BOLD responses in both areas, but these responses were slightly stronger for the *auditory trigrams* task than the *auditory motion* task. Again this is perhaps consistent with previous evidence for left hemisphere dominance of cross-modal plasticity for language tasks (Amedi et al., 2004; Burton et al., 2002b), and will be more closely examined in the ROI analyses below. There were additionally small regions in right dorsal-occipital cortex that showed higher BOLD response for *auditory motion* than *auditory trigrams*;

examination of Figure 6 shows that both tasks elicited positive cross-modal BOLD responses in this area, but these responses were slightly stronger for the *auditory motion* task than the *auditory trigrams* task; this is perhaps again consistent with previous evidence for right hemisphere dominance of motion-processing (e.g. auditory motion processing in auditory cortex of sighted subjects: Baumgart et al., 1999; visual motion processing in auditory cortex of deaf subjects: Finney, Fine & Dobkins, 2001; Finney, Clementz, Hickok & Dobkins, 2003).

Differences Between Tactile Tasks. On the whole, differences in cross-modal plasticity across different tactile tasks were once again relatively small, as compared to the large regions of cortex that showed cross-modal plasticity for any tactile task compared to the *no stimulus/key-press* task. This suggests that, on the whole, patterns of cross-modal plasticity were similar across the three tactile tasks.

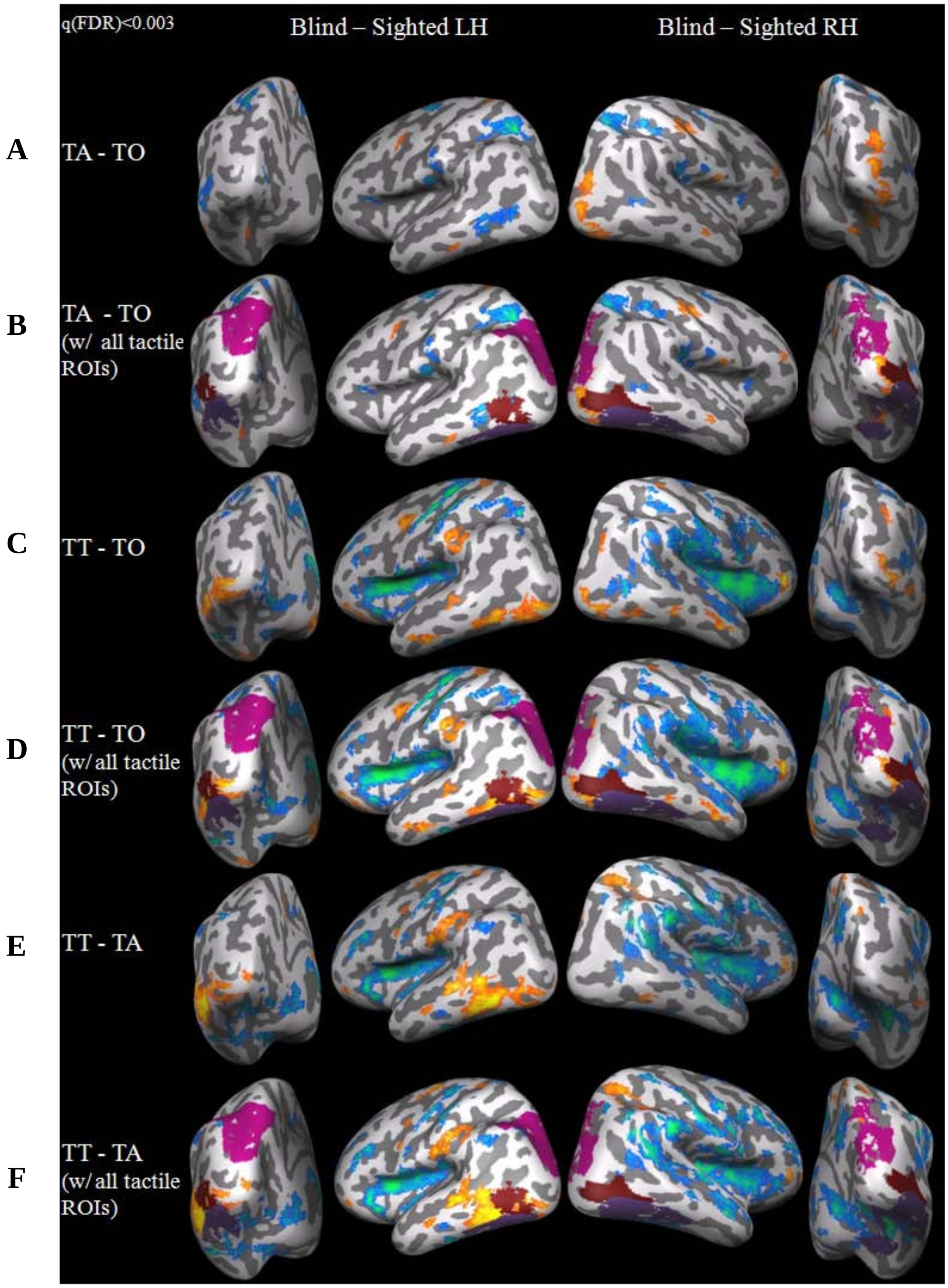

Figure 12: Study 1: Differences in cross-modal BOLD response between tactile tasks, with cross-modal tactile ROIs ($\text{TAC}_{\text{OccTemp}}$, $\text{TAC}_{\text{DorsOcc}}$, and TAC_{Vent}) overlaid. Lateral views are presented in the center, whereas views from behind occipital pole are presented on the sides. See text for explanation of warm versus cool colors. **(A)** *Tactile animals* (TA) vs. *tactile orientation* (TO) task, **(B)** with cross-modal tactile ROIs overlaid. **(C)** *Tactile trigrams* (TT) vs. *tactile orientation* (TO) task, **(D)** with cross-modal tactile ROIs overlaid. **(E)** *Tactile trigrams* (TT) vs. *tactile animals* (TA) task, **(F)** with cross-modal tactile ROIs overlaid. $\text{TAC}_{\text{OccTemp}}$ ROI = dark red, $\text{TAC}_{\text{DorsOcc}}$ ROI = dark pink, TAC_{Vent} ROI = dark purple; LH = left hemisphere, RH = right hemisphere. Data are conservatively thresholded at q(FDR)<0.003.

Tactile Animals vs. Tactile Orientation. There were greater cross-modal BOLD responses to the *tactile orientation* task than to the *tactile animals* task within left occipito-temporal cortex, [q(FDR)<0.003]. It seems from inspection of Figure 7 that this difference is due to stronger activation in blind than sighted subjects for *tactile orientation* than *tactile animals*. In right dorsal-occipital and ventral cortex, there were greater cross-modal BOLD responses to *tactile animals* than *tactile orientation*. It seems from inspection of Figure 7 that this difference is due to stronger activation in blind than sighted subjects for *tactile animals* than *tactile orientation*. These differences will be more closely examined using the ROI analysis below.

Tactile Trigrams vs. Tactile Orientation. When comparing *tactile trigrams* to *tactile orientation* we saw greater cross-modal BOLD responses in blind than sighted subjects to the *tactile orientation* task bilaterally within a region of the inferior frontal gyrus that seems to include Broca's area. It seems from inspection of Figure 7 that this difference is due to weaker activation in blind than sighted subjects for *tactile trigrams* than *tactile orientation*. There were also greater cross-modal BOLD responses to *tactile trigrams* than *tactile orientation* bilaterally in some small regions between occipito-temporal and ventral cortex. Inspection of Figure 7 reveals that this difference is due to stronger activation in blind than sighted subjects for *tactile trigrams* than *tactile orientation*. These differences will be more closely examined using the ROI analysis below.

Tactile Trigrams vs. Tactile Animals. There were greater cross-modal BOLD responses to the *tactile trigrams* task than to the *tactile animals* task within left occipito-temporal cortex. A very small region showed larger cross-modal responses to the *tactile trigrams* task within right occipito-temporal cortex. It seems from inspection of Figure 7 that both of these differences in bilateral occipito-temporal cortex are due to stronger activation in blind than sighted subjects for *tactile trigrams* than *tactile animals*. Larger cross-modal responses to the *tactile animals* condition were seen bilaterally within a region of the inferior frontal gyrus that seems to include Broca's area. It seems from inspection of Figure 7 that this difference is due to weaker activation in blind than sighted subjects for *tactile trigrams* than *tactile animals*. These differences will be more closely examined using the ROI analysis below.

The *tactile trigrams* task produced weaker BOLD responses than both the *tactile orientation* and the *tactile animal* tasks within Broca's area, suggesting that the *tactile trigrams* task suppressed responses within Broca's area more powerfully in blind than in sighted subjects. As described in Appendix A, one interesting possibility is that these weaker responses in blind subjects as compared to sighted subjects in Broca's area were due to a greater need for articulatory suppression in blind subjects.

Differences between auditory and tactile tasks are shown in Appendix A.

Response Amplitudes Within Each ROI

For our response amplitude analyses, we exported all blind and sighted timecourse data for each vertex[17] contained within each ROI from Brain Voyager to MATLAB where we calculated response amplitudes (percent BOLD signal change) for each task in each vertex by taking the ratio of activation for each task, normalized by the *no stimulus/key-press* task. Because each task did not occur in every scan, we calculated percent BOLD signal change for each task *per scan* (where that task did occur), and then calculated the mean of percent BOLD signal change for each task across scans. This ratio was calculated for each task *per scan* as follows:

$$(\overline{X}_{\text{task}} - \overline{X}_{\textit{no stimulus/key-press}}) \div \overline{X}_{\textit{no stimulus/key-press}}$$

where $\overline{X}_{\text{task}}$ is the mean activation for each task, and $\overline{X}_{\textit{no stimulus/key-press}}$ is the mean activation for the *no stimulus/key-press* task. Percent BOLD signal change for each task was then calculated as simply the mean of each of these ratios across all scans, and standard errors were calculated as the variance across scans.

Response amplitudes for sensory ROIs (auditory and somatosensory cortex) can be seen in Figure 13; for cross-modal occipito-temporal ROIs ($\text{AUD}_{\text{OccTemp}}$ and $\text{TAC}_{\text{OccTemp}}$) in Figure 15; for cross-modal dorsal-occipital ROIs ($\text{AUD}_{\text{DorsOcc}}$ and $\text{TAC}_{\text{DorsOcc}}$) in Figure 17; and for cross-modal ventral ROIs (AUD_{Vent} and TAC_{Vent}) in Figure 19.

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[17] A “vertex” in cortex-based alignment space is the analogue of a “voxel” in Talairach space; during transformation from Talairach space to cortex-based alignment space, multiple voxels are condensed into a single vertex, such that a single vertex represents data from multiple voxels.

All *p* values reported for response amplitude analyses were obtained via individual *t*-tests.

ANOVA Analyses Within Each ROI

The goal of the ANOVA analysis was to break down responses within blind and sighted subjects into task-specific, modality-specific and unspecific responses. To obtain proportion of variance values (R^2), we conducted ANOVAs in Brain Voyager across three GLM models. In the first model, "task-specified" [“Aud/Tact GLM (blind)”, “Aud/Tact GLM (sighted)” and “Aud/Tact/Vis GLM (sighted),” see Table 2], each task was specified by an individual predictor [6 predictors for “Aud/Tact GLMs” and 10 predictors for “Aud/Tact/Vis GLM (sighted)”]. In the second model, "modality" [“Aud/Tact GLM (blind, by modality)”, “Aud/Tact GLM (sighted, by modality)”, and “Aud/Tact/Vis GLM (sighted, by modality),” see Table 2], we collapsed tasks within modalities. Thus this GLM had 2-3 predictors [2 predictors for “Aud/Tact GLMs (by modality)” and 3 predictors for “Aud/Tact/Vis GLM (sighted, by modality)”], describing whether the task contained an auditory stimulus, a tactile stimulus, a visual stimulus, or was the *no stimulus/key-press* task [i.e. all auditory tasks were collapsed, all tactile tasks were collapsed, and all visual tasks were collapsed (if present in the GLM)]. In the third model, “task vs. no task” [“Aud/Tact GLM (blind, task vs. no task)”, “Aud/Tact GLM (sighted, task vs. no task)”, and “Aud/Tact/Vis GLM (sighted, task vs. no task),” see Table 2], we collapsed all tasks. Thus this GLM had a single predictor that simply described whether or not a given task was the *no stimulus/key-press* task [i.e. all auditory, tactile, and visual tasks (if present in the GLM) were collapsed]. We used adjusted R^2 values[18] to compensate for the different number of predictors across the three models.

The amount of variance explained by each of these GLM models for sensory ROIs (auditory and somatosensory cortex) can be seen in Figure 14; for cross-modal occipito-temporal ROIs in Figure 16; for cross-modal dorsal-occipital ROIs in Figure 18; and for cross-modal ventral ROIs in Figure 20.

Sensory ROI Analyses. Figure 13 shows response amplitudes (percent BOLD signal change) in right-handed blind and sighted subjects within auditory (Figure 13A) and somatosensory cortex (Figure 13B) ROIs. The task used to define each ROI is shown with a red asterisk; it should be noted that in those tasks (and only those tasks) there exists an issue of circularity, where we are measuring responses to the same task as was used to define the ROI.

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[18] Adjusted $R^2 = 1 – [SS_E/(n\text{-}p\text{-}1)/\ SS_T/(n\text{-}1)]$ where SS_E = sum of squared errors, SS_T =, total sum of squares, n = sample size, and p = number of predictors.

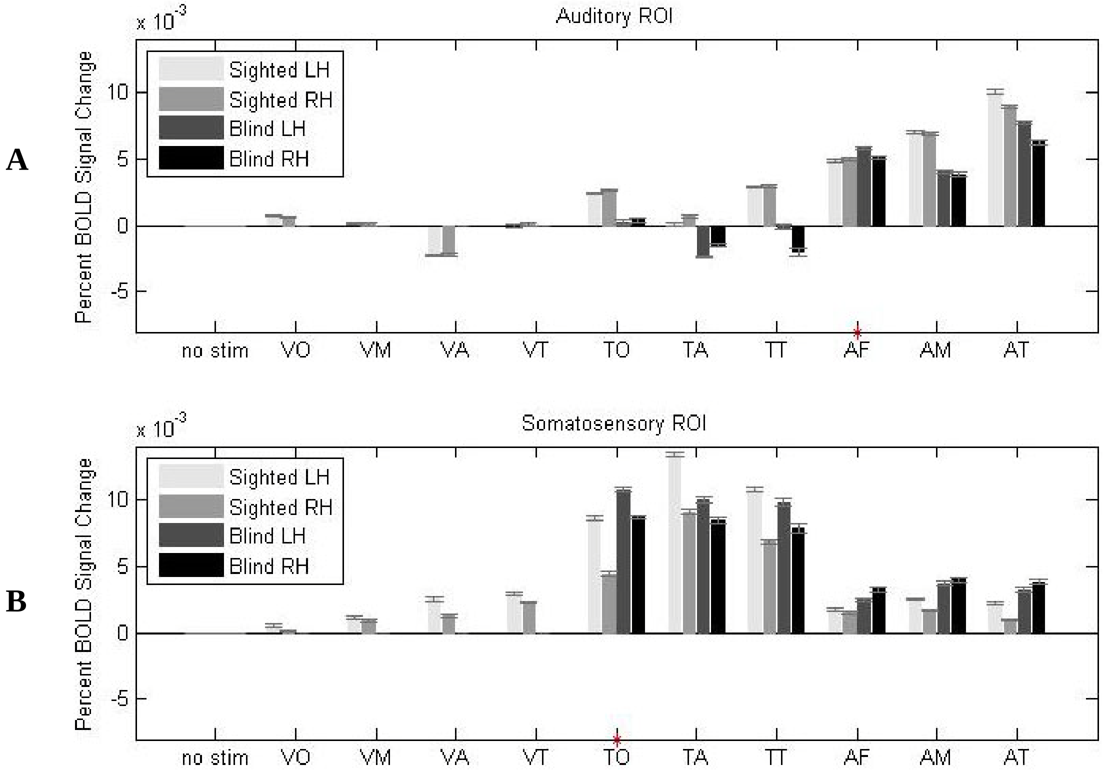

Figure 13: Study 1: Response amplitudes for sensory ROIs (auditory and somatosensory cortex), right-handed subjects only. **(A)** Auditory ROI: Percent signal change in the BOLD response for left and right hemispheres for blind and sighted subjects, across all tasks. **(B)** Somatosensory ROI: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. Single standard errors are shown. No stim = *no stimulus/key-press*, VO = *visual orientation*, VM = *visual motion*, VA = *visual animals*, VT = *visual* trigrams, TO = *tactile orientation*, TA = *tactile animals*, TT = *tactile trigrams*, AF = *auditory frequency*, AM = *auditory motion*, AT = *auditory trigrams*; LH = left hemisphere, RH = right hemisphere. The task used to define each ROI is shown with a red asterisk. Error bars represent SEM.

Auditory Cortex ROI Response Amplitudes. As described above, the auditory ROI was defined by responses to the *auditory frequency* vs. the *no stimulus/key-press* task across all subjects, using the “Aud/Tact GLM” (see Table 2). See Figure 13A for all response amplitudes in the auditory cortex ROI.

Within the auditory cortex ROI, as might be expected, in sighted subjects visual tasks generally resulted in either no change (p>0.11 for all visual tasks in both the LH and RH, with the exception of *visual animals*) or a reduction in response amplitude ($p<0.01$ for *visual animals* in both the LH and RH).

In the case of auditory tasks, as also might be expected, we saw large responses in both blind and sighted subjects ($p<0.01$ for all auditory tasks in both LH and RH). For auditory stimuli we saw a noticeable difference between blind and sighted subjects, with stronger responses within sighted than blind subjects to *auditory motion* and *auditory trigrams* ($p<0.01$ for *auditory motion* in both LH and RH; $p<0.02$ for *auditory trigrams* in LH). One possibility is that these tasks were slightly easier for the blind subjects, thereby reducing auditory responses.

However sighted subjects did show a bilateral elevation of the BOLD response for *tactile orientation* and *tactile trigrams* ($p<0.01$ for both tasks in both LH and RH). In blind subjects we saw slight suppression of the BOLD response for *tactile animals* ($p<0.05$ in LH and RH), but this effect was not large.

Somatosensory Cortex ROI Response Amplitudes. As described above, the somatosensory ROI was defined by responses to the *tactile orientation* task (right-handed subjects only[19]), using the “Aud/Tact GLM” (see Table 2). See Figure 13B for all response amplitudes in the somatosensory cortex ROI.

Within the somatosensory ROI, in sighted subjects we saw a consistent but relatively weak elevation of the BOLD response to visual tasks ($p<0.01$ for *visual*

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[19] We conducted the same response amplitude analyses using all subjects, and the results were qualitatively similar. However we felt it was more appropriate to show results for analyses restricted to only right-handed subjects. Response amplitude analyses containing all subjects (regardless of handedness) can be found in Appendix A.

trigrams in both LH and RH; $p<0.01$ for *visual animals* in the RH). It is a possibility that these effects may be due to visual imagery in sighted subjects.

In the case of tactile tasks, as expected, we saw large responses in both blind and sighted subjects ($p<0.01$ for all tactile tasks in both LH and RH). There were slightly stronger responses within sighted than blind subjects in the RH to *tactile animals* and *tactile trigrams* ($p<0.03$ for both tasks) and slightly stronger responses within blind than sighted subjects to *tactile orientation* ($p<0.01$ in both LH and RH). Again these results may have been due to slight differences in task difficulty for tactile tasks between blind and sighted subjects. Additionally, it should be noted that these mixed results may be due to a possibility that our somatosensory ROIs extended inferiorly into nearby regions. Inspection of Figure 7 reveals that there does seem to be a stronger response to tactile tasks in blind than sighted subjects in somatosensory areas; however, no such strong effect is evident in these ROI analyses. Thus, although there are subregions of these ROIs that respond more strongly to tactile tasks in blind than sighted subjects (compensatory hypertrophy[20]), this effect is not significant across the entire somatosensory ROIs.

We also saw slight elevation of the BOLD response for auditory tasks in both blind and sighted subjects ($p<0.02$ for all auditory tasks in both LH and RH, with the exception of *auditory frequency* in the LH of blind subjects, $p=0.17$); for the *auditory* motion task (as well as when all auditory tasks were collapsed) this activation was

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[20] While this evidence of compensatory hypertrophy (larger responses within somatosensory cortex to tactile stimuli for blind than sighted subjects) within subregions of somatosensory cortex is interesting, in this thesis, we have chosen to focus on cross-modal plasticity - i.e. differences between blind and sighted subjects within regions that are normally primarily visual.

slightly larger in the RH of blind than sighted subjects ($p<0.01$). An intriguing possibility is that increased feedback from multimodal areas due to visual deprivation might result in partial recruitment of right somatosensory cortex for auditory processing in blind subjects.

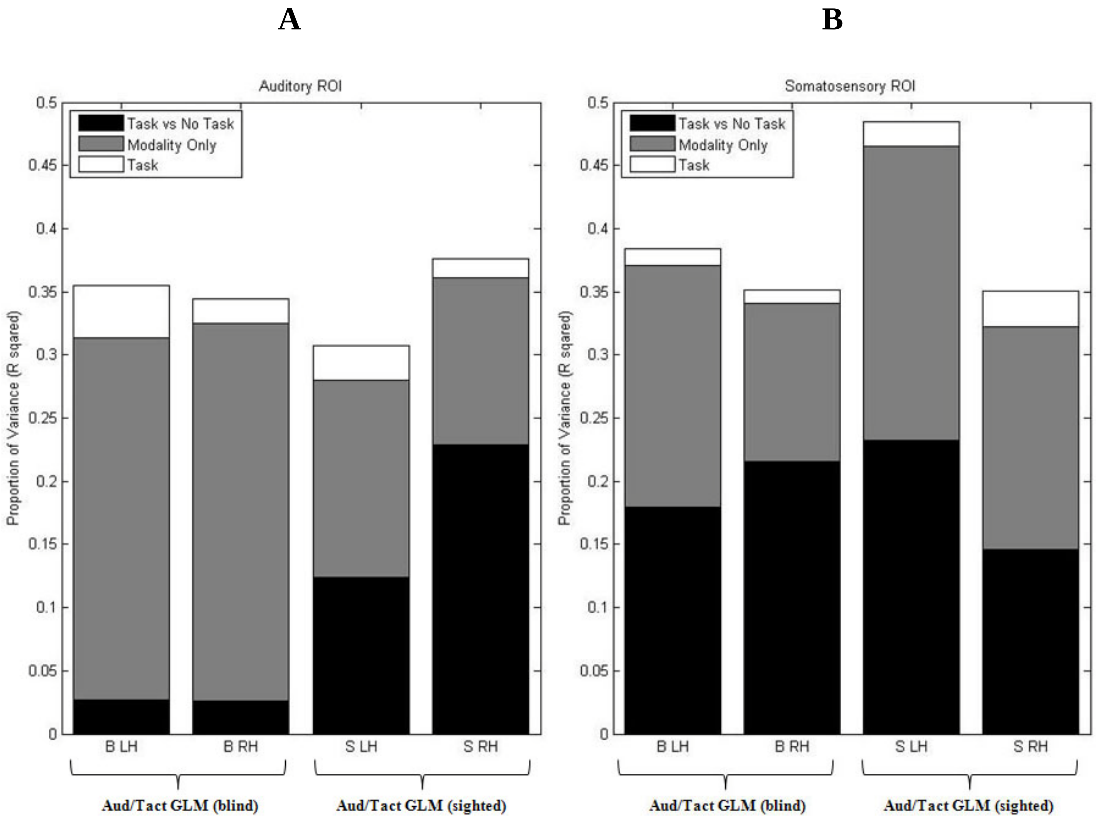

Figure 14: Study 1: ANOVA analyses [proportion of variance (R^2)] for sensory ROIs [**(A)** auditory and **(B)** somatosensory cortex ROIs)], for right-handed subjects only, explained across three different models, as described below. B LH = blind subjects, left hemisphere; B RH = blind subjects, right hemisphere; S LH = sighted subjects, left hemisphere; S RH = sighted subjects, right hemisphere. “Task vs No Task” = “task vs. no task” model, “Modality Only” = “modality” model, “Task” = “Task-Specified” model.

ANOVA Analyses Within Sensory ROIs. Figure 14 shows ANOVA analyses [proportion of variance values (R^2)] in right-handed[21] blind and sighted subjects within auditory cortex (Figure 14A) and somatosensory cortex (Figure 14B) ROIs.

To obtain proportion of variance values (R^2) for our ANOVA analyses in the sensory ROIs we used the following GLMs: “Aud/Tact GLM (blind)”, “Aud/Tact

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[21] We conducted the same ANOVA analyses using all subjects, and the results were qualitatively similar. However we felt it was more appropriate to show results for analyses restricted to only right-handed subjects. ANOVA analyses containing all subjects (regardless of handedness) can be found in Appendix A.

GLM (blind, by modality)", "Aud/Tact GLM (blind, task vs. no task)", "Aud/Tact GLM (sighted)", "Aud/Tact GLM (sighted, by modality)", and "Aud/Tact GLM (sighted, task vs. no task)". See Table 2 and above for explanations of these GLMs.

In the case of the auditory cortex ROI the vast majority of variance, as might be expected, was explained by the "modality" model. In sighted subjects the "task vs. no task" model explained more variance than in blind subjects, due to the weak tactile responses within auditory cortex found in sighted subjects. For both blind and sighted subjects very little variance was explained by the "task-specified" model (see Figure 14A).

In the case of the somatosensory cortex ROI the "task vs. no task" model explained a significant amount of the variance, but modality again played an important role as a regressor. Again for both blind and sighted subjects very little variance was explained by the "task-specified" model (see Figure 14B); in both sensory ROIs task-specific modulation was relatively weak.

Occipito-Temporal ROI Analyses. Figure 15 shows response amplitudes (percent BOLD signal change) in right-handed[22] blind and sighted subjects (using "Aud/Tact GLM", see Table 2) within $\mathrm{AUD}_{\mathrm{OccTemp}}$ (Figure 15A) and $\mathrm{TAC}_{\mathrm{OccTemp}}$ (Figure 15B) ROIs. The task used to define each ROI is shown with a red asterisk; it should be noted that in those tasks (and only those tasks) there exists an issue of

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[22] We conducted the same response amplitude analyses using all subjects, and the results were qualitatively similar. However we felt it was more appropriate to show results for analyses restricted to only right-handed subjects. Response amplitude analyses containing all subjects (regardless of handedness) can be found in Appendix A.

circularity, where we are measuring responses to the same task as was used to define the ROI.

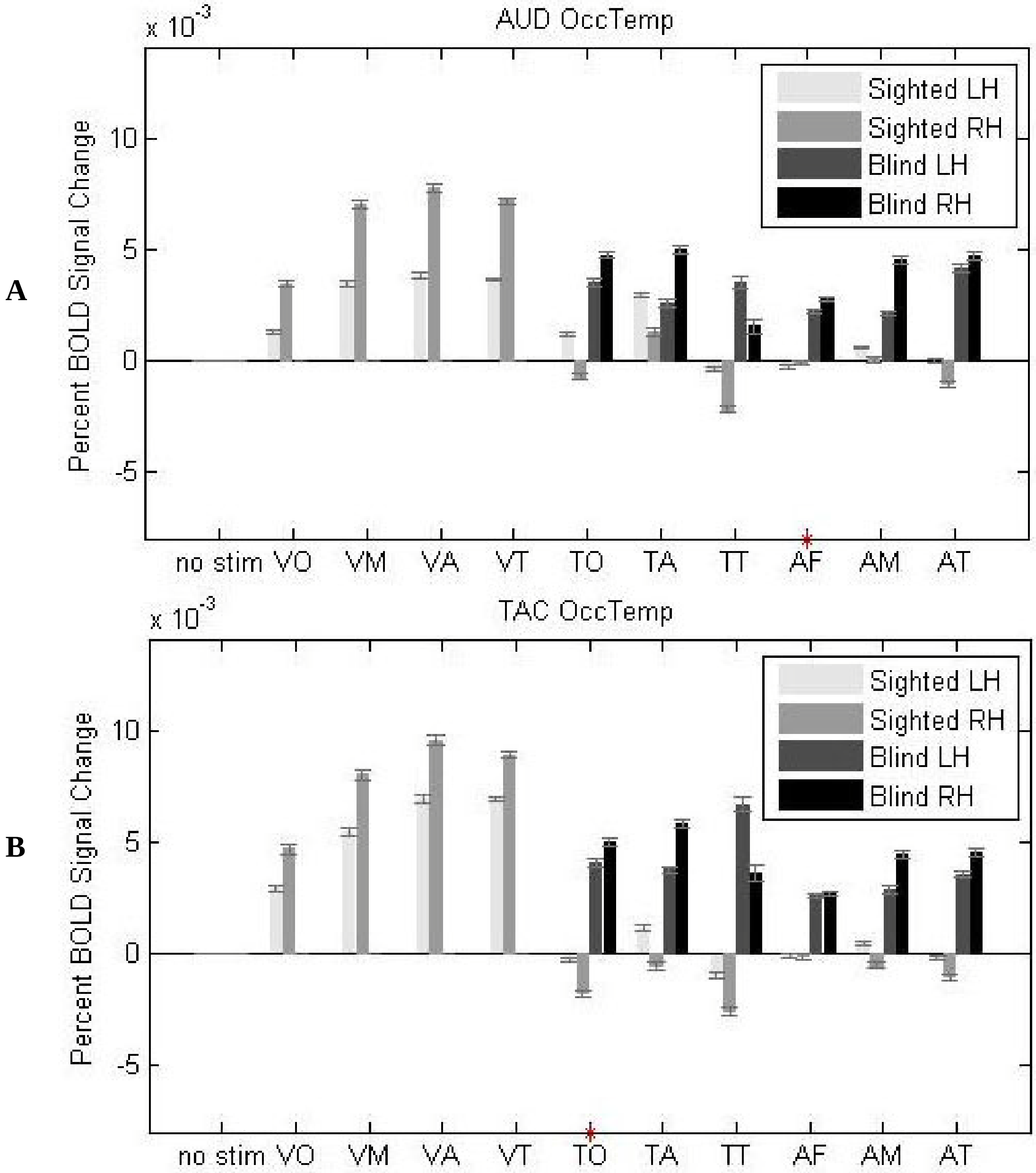

Figure 15: Study 1: Response amplitudes for cross-modal occipito-temporal ROIs ($\text{AUD}_{\text{OccTemp}}$ and $\text{TAC}_{\text{OccTemp}}$), for right-handed subjects only. **(A)** $\text{AUD}_{\text{OccTemp}}$: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. **(B)** $\text{TAC}_{\text{OccTemp}}$: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. Single standard errors are shown. No stim = *no stimulus/key-press*, VO = *visual orientation*, VM = *visual motion*, VA = *visual animals*, VT = *visual* trigrams, TO = *tactile orientation*, TA = *tactile animals*, TT = *tactile trigrams*, AF = *auditory frequency*, AM = *auditory motion*, AT = *auditory trigrams*; LH = left hemisphere, RH = right hemisphere. The task used to define each ROI is shown with a red asterisk.

***$AUD_{OccTemp}$* and *$TAC_{OccTemp}$* ROI Response Amplitudes.** The results of this analysis in the occipito-temporal ROIs can be seen in Figure 15.

In sighted subjects we see strong response amplitudes to all visual tasks, confirming that this region is normally a visual area ($p<0.01$ for all visual tasks for both LH and RH).

However in sighted subjects, although no significant change in the BOLD response was found in these areas to any of the auditory tasks, for tactile tasks there were some mixed results: for *tactile orientation* there was a slight elevation of the response amplitude in the LH for $\text{AUD}_{\text{OccTemp}}$ ($p<0.02$) versus a slight depression of response amplitude in the RH for $\text{TAC}_{\text{OccTemp}}$ ($p<0.03$); for *tactile animals* there was a slight elevation of response amplitude in the LH for $\text{AUD}_{\text{OccTemp}}$ ($p<0.01$); for *tactile trigrams* there was a depression of response amplitude in the RH for both $\text{AUD}_{\text{OccTemp}}$ and $\text{TAC}_{\text{OccTemp}}$ ($p<0.01$). In contrast, in blind subjects we see robust responses to all tactile and auditory tasks ($p<0.04$ for all tactile and auditory tasks for both LH and RH, with the exception of *tactile trigrams* in the right hemisphere in $\text{AUD}_{\text{OccTemp}}$, $p=0.28$), and these responses are only slightly weaker than those elicited by visual stimuli in sighted subjects.

In further support of cross-modal plasticity in this area, a direct comparison of blind vs. sighted subjects shows that across all auditory and tactile tasks there is generally a larger response amplitude in blind as compared to sighted subjects ($p<0.01$ for all tasks, when collapsed, for both LH and RH).

ANOVA Analyses Within Occipito-Temporal ROIs. Figure 16 shows ANOVA analyses [proportion of variance values (R^2)] in right-handed[23] blind and sighted subjects within $\text{AUD}_{\text{OccTemp}}$ (Figure 16A) and $\text{TAC}_{\text{OccTemp}}$ (Figure 16B) ROIs.

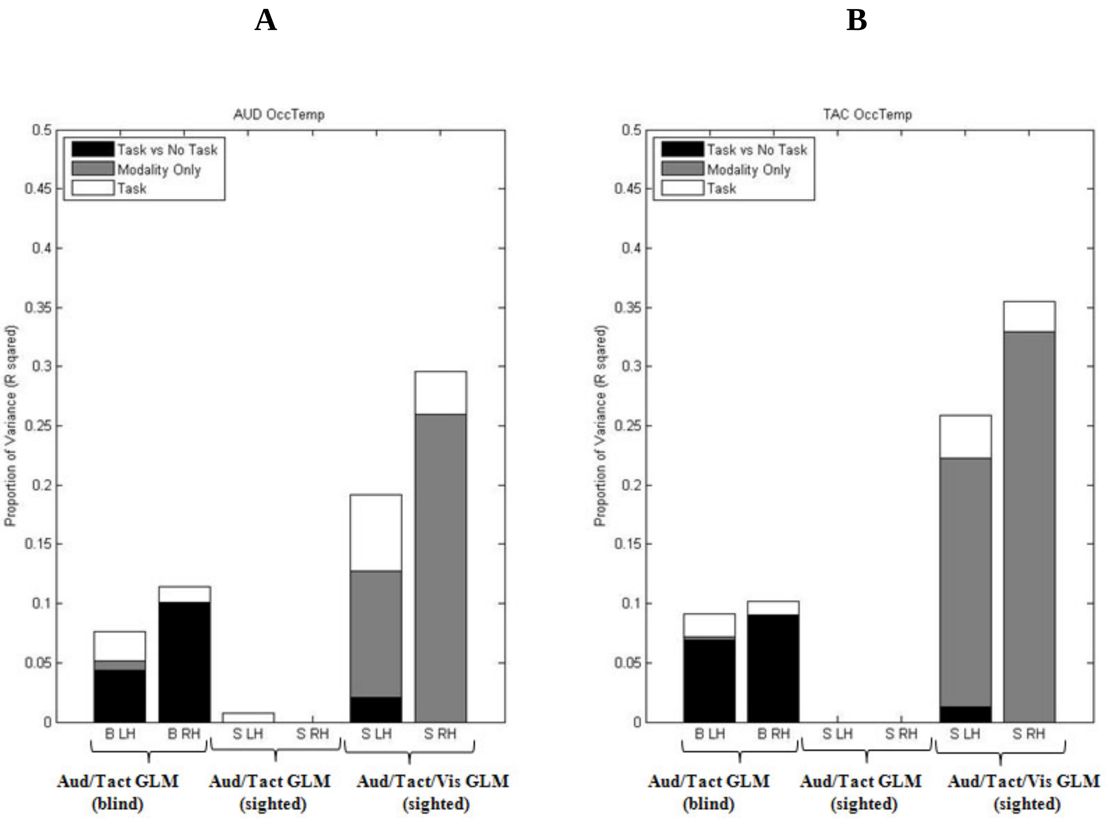

Figure 16: Study 1: ANOVA analyses [proportion of variance (R^2)] for occipito-temporal ROIs [**(A)** $\text{AUD}_{\text{OccTemp}}$ and **(B)** $\text{TAC}_{\text{OccTemp}}$], for right-handed subjects only, explained across three different models, as described below. B LH = blind subjects, left hemisphere; B RH = blind subjects, right hemisphere; S LH = sighted subjects, left hemisphere; S RH = sighted subjects, right hemisphere. “Task vs No Task” = “task vs. no task” model, “Modality Only” = “modality” model, “Task” = “Task-Specified” model.

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[23] We conducted the same ANOVA analyses using all subjects, and the results were qualitatively similar. However we felt it was more appropriate to show results for analyses restricted to only right-handed subjects. ANOVA analyses containing all subjects (regardless of handedness) can be found in Appendix A.

To obtain proportion of variance values (R^2) for our ANOVA analyses in the cross-modal occipito-temporal ROIs we used the following GLMs: “Aud/Tact GLM (blind)”, “Aud/Tact GLM (blind, by modality)”, “Aud/Tact GLM (blind, task vs. no task)”, “Aud/Tact GLM (sighted)”, “Aud/Tact GLM (sighted, by modality)”, “Aud/Tact GLM (sighted, task vs. no task)”, and “Aud/Tact/Vis GLM (sighted)”, “Aud/Tact/Vis GLM (sighted, by modality)”, “Aud/Tact/Vis GLM (sighted, task vs. no task)”. See Table 2 and above for explanations of these GLMs.

In sighted subjects, very little variance could be explained when visual tasks were excluded from the GLM [“Aud/Tact GLM (sighted)”, see Table 2], as might be expected by the relatively small responses to auditory and tactile tasks within this ROI (compared to responses to visual tasks). When visual tasks were included in the GLM [“Aud/Tact/Vis GLM (sighted)”, see Table 2], unsurprisingly, a large proportion of variance was explained by the “modality” mode, and some proportion of variance was also explained by the “task-specified” model. It should be noted that even in these visual areas in sighted subjects, most of the modulation is based on whether or not there is a visual stimulus, with only a small amount of modulation based on the specific visual task.

A very different pattern of results was observed in blind subjects. A significant proportion of variance was explained by the “task vs. no task” model. In fact the amount of variance explained by task was only slightly smaller than that seen in sighted subjects when visual conditions were included. The most striking result is that almost no variance was explained by knowing the modality of the stimulus.

In conclusion, we saw significant cross-modal responses across all tasks within occipito-temporal ROIs, but modulation of responses seemed to be entirely task-specific rather than modality-specific.

Dorsal-Occipital ROI Analyses. Figure 17 shows response amplitudes (percent BOLD signal change) in right-handed[24] blind and sighted subjects (using “Aud/Tact GLM”, see Table 2) within $\mathrm{AUD}_{\mathrm{DorsOcc}}$ (Figure 17A) and $\mathrm{TAC}_{\mathrm{DorsOcc}}$ (Figure 17B) ROIs. The task used to define each ROI is shown with a red asterisk; it should be noted that in those tasks (and only those tasks) there exists an issue of circularity, where we are measuring responses to the same task as was used to define the ROI.

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[24] We conducted the same response amplitude analyses using all subjects, and the results were qualitatively similar. However we felt it was more appropriate to show results for analyses restricted to only right-handed subjects. Response amplitude analyses containing all subjects (regardless of handedness) can be found in Appendix A.

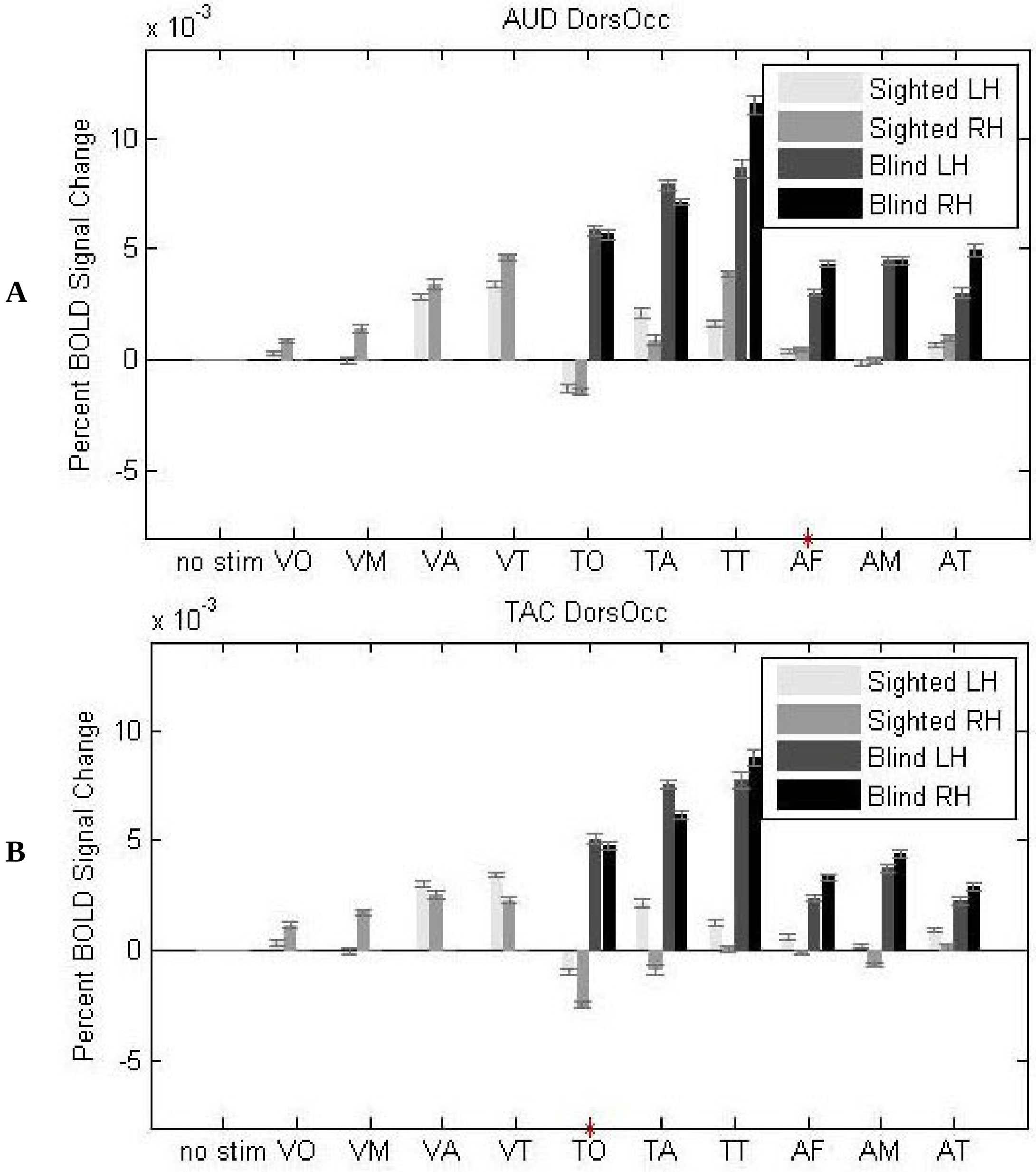

Figure 17: Study 1: Response amplitudes for cross-modal dorsal-occipital ROIs ($\text{AUD}_{\text{DorsOcc}}$ and $\text{TAC}_{\text{DorsOcc}}$), for right-handed subjects only. **(A)** $\text{AUD}_{\text{DorsOcc}}$: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. **(B)** $\text{TAC}_{\text{DorsOcc}}$: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. Single standard errors are shown. No stim = *no stimulus/key-press*, VO = *visual orientation*, VM = *visual motion*, VA = *visual animals*, VT = *visual* trigrams, TO = *tactile orientation*, TA = *tactile animals*, TT = *tactile trigrams*, AF = *auditory frequency*, AM = *auditory motion*, AT = *auditory trigrams*; LH = left hemisphere, RH = right hemisphere. The task used to define each ROI is shown with a red asterisk.

***AUD$_{DorsOcc}$* and *TAC$_{DorsOcc}$* ROI Response Amplitudes.** The results of this analysis in the dorsal-occipital ROIs can be seen in Figure 17.

In sighted subjects we again see positive response amplitudes to most visual tasks, confirming that this region is normally a visual area (p<0.01 for *visual animals* and *visual trigrams* for both LH and RH).

However in sighted subjects no BOLD response was found in these areas to all of the auditory tasks (p>0.16 in both LH and RH), though for tactile tasks there were some mixed results: there was some borderline significant elevation of response amplitude for the *tactile animal* task in the LH (p<0.07) and the *tactile trigram* task in the LH (p<0.06); a slight depression of response amplitude for *tactile orientation* in the RH (for AUD$_{\text{DorsOcc}}$, p<0.08; for TAC$_{\text{DorsOcc}}$, p<0.01); and an elevation in response amplitude to *tactile trigrams* in the RH for AUD$_{\text{DorsOcc}}$ (p<0.01). In contrast, in blind subjects we see robust responses to all tactile and auditory tasks (p<0.04 for all tactile and auditory tasks for both LH and RH).

In further support of cross-modal plasticity in this area, a direct comparison of blind vs. sighted subjects shows that across all auditory and tactile tasks there is generally a larger response amplitude in blind as compared to sighted subjects (p<0.01 for all tasks, when collapsed, for both LH and RH).

Furthermore, within blind subjects there is generally a larger response amplitude for tactile tasks as compared to auditory tasks (p<0.01, when collapsed across modality).

ANOVA Analyses Within Dorsal-Occipital ROIs. Figure 18 shows ANOVA analyses [proportion of variance values (*R^2*)] in right-handed[25] blind and sighted subjects within $\text{AUD}_{\text{DorsOcc}}$ (Figure 18A) and $\text{TAC}_{\text{DorsOcc}}$ (Figure 18B) ROIs.

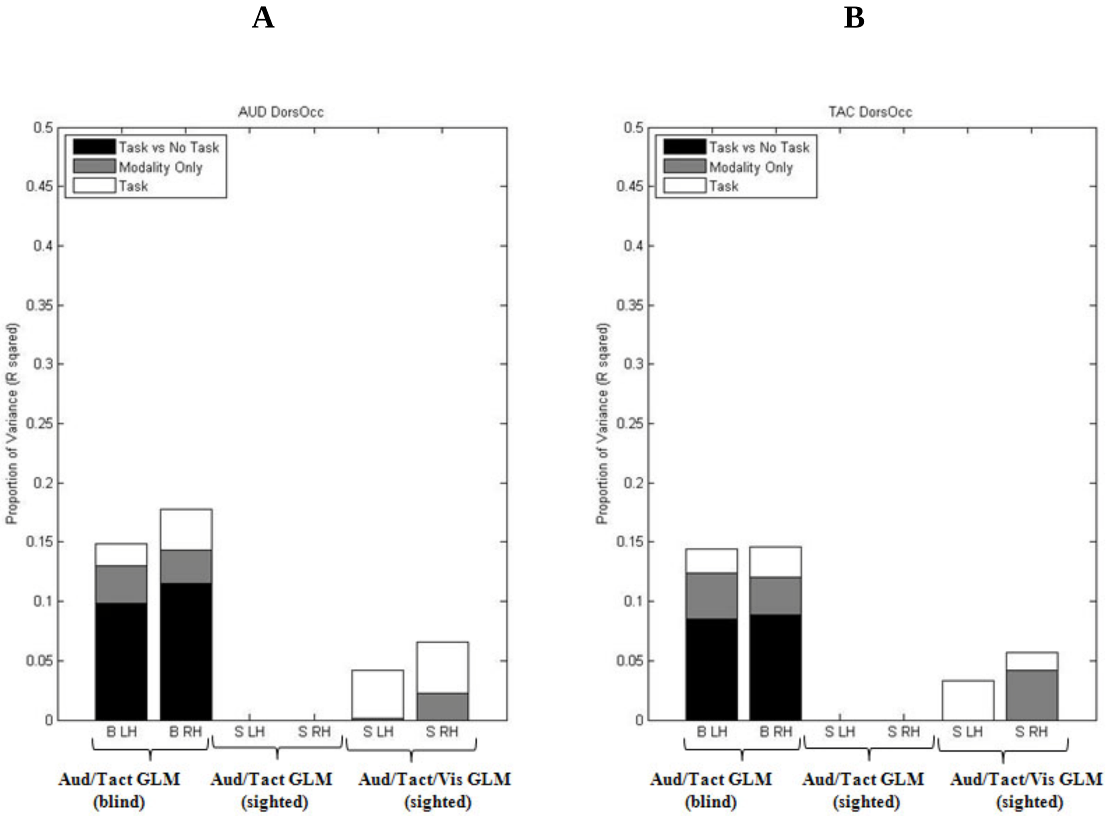

Figure 18: Study 1: ANOVA analyses [proportion of variance (*R^2*)] for dorsal-occipital ROIs [**(A)** $\text{AUD}_{\text{DorsOcc}}$ and **(B)** $\text{TAC}_{\text{DorsOcc}}$], for right-handed subjects only, explained across three different models, as described below. B LH = blind subjects, left hemisphere; B RH = blind subjects, right hemisphere; S LH = sighted subjects, left hemisphere; S RH = sighted subjects, right hemisphere. "Task vs No Task" = "task vs. no task" model, "Modality Only" = "modality" model, "Task" = "Task-Specified" model.

To obtain proportion of variance values (*R^2*) for our ANOVA analyses in the cross-modal dorsal-occipital ROIs we used the following GLMs: "Aud/Tact GLM

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[25] We conducted the same ANOVA analyses using all subjects, and the results were qualitatively similar. However we felt it was more appropriate to show results for analyses restricted to only right-handed subjects. ANOVA analyses containing all subjects (regardless of handedness) can be found in Appendix A.

(blind)”, “Aud/Tact GLM (blind, by modality)”, “Aud/Tact GLM (blind, task vs. no task)”, “Aud/Tact GLM (sighted)”, “Aud/Tact GLM (sighted, by modality)”, “Aud/Tact GLM (sighted, task vs. no task)”, and “Aud/Tact/Vis GLM (sighted)”, “Aud/Tact/Vis GLM (sighted, by modality)”, “Aud/Tact/Vis GLM (sighted, task vs. no task)”. See Table 2 and above for explanations of these GLMs.

In sighted subjects, no variance could be explained when visual tasks were excluded from the GLM [“Aud/Tact GLM (sighted)”, see Table 2], as might be expected by the relatively small responses to auditory and tactile tasks within this ROI (compared to responses to visual tasks). When visual tasks were included in the GLM [“Aud/Tact/Vis GLM (sighted)”, see Table 2], a significant amount of variance was explained by the “modality” model. A greater proportion of variance was explained by the “task-specified” model (as compared to the “modality” model) here, in the dorsal-occipital ROIs, than in the occipito-temporal ROIs (compare Figure 18 to Figure 16), possibly because this is a higher level visual area that responded relatively weakly to simple visual orientation and motion judgments.

Again, we see a strikingly different pattern of results in blind subjects with a significant proportion of variance explained by the “task vs. no task” model. The amount of variance explained by the “modality” and “task-specified” models remains roughly comparable to that of sighted subjects when visual tasks are included in the GLM. Like the occipito-temporal ROI this area showed cross-modal plasticity across all tasks, but unlike that area modulation of these cross-modal responses seemed to be based on modality as well as task. Responses were significantly stronger for tactile than for auditory stimuli. Given the proximity of this area to somatosensory cortices it is intriguing to speculate that responses in this area might be at least be partially mediated by somatosensory projections.

Ventral ROI Analyses. Figure 19 shows response amplitudes (percent BOLD signal change) in right-handed[26] blind and sighted subjects (using "Aud/Tact GLM", see Table 2) within AUD_{Vent} (Figure 19A) and TAC_{Vent} (Figure 19B) ROIs. The task used to define each ROI is shown with a red asterisk; it should be noted that in those tasks (and only those tasks) there exists an issue of circularity, where we are measuring responses to the same task as was used to define the ROI.

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[26] We conducted the same response amplitude analyses using all subjects, and the results were qualitatively similar. However we felt it was more appropriate to show results for analyses restricted to only right-handed subjects. Response amplitude analyses containing all subjects (regardless of handedness) can be found in Appendix A.

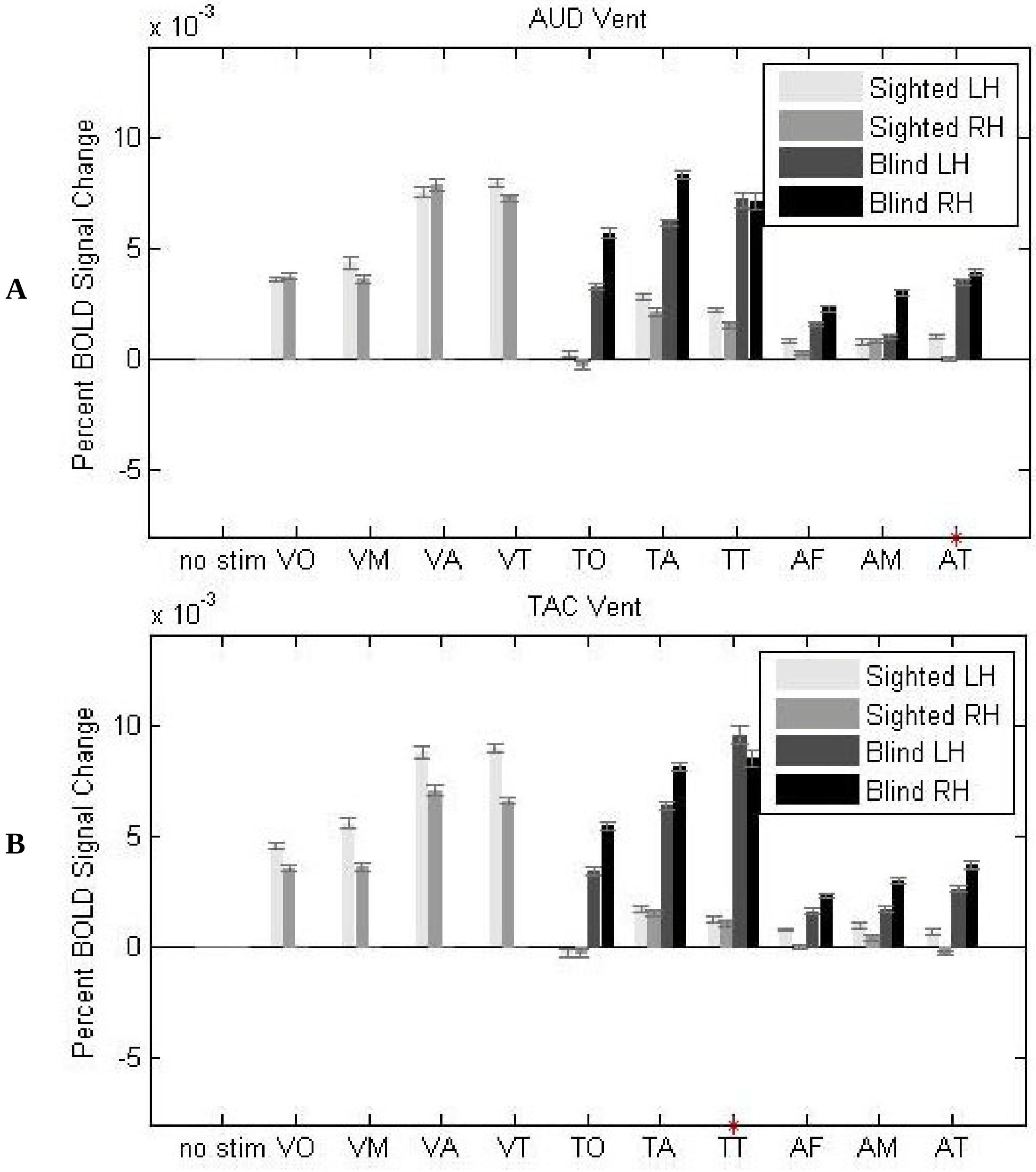

Figure 19: Study 1: Response amplitudes for cross-modal ventral ROIs (AUD_{Vent} and TAC_{Vent}), for right-handed subjects only. **(A)** AUD_{Vent}: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. **(B)** TAC_{Vent}: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. Single standard errors are shown. No stim = *no stimulus/key-press*, VO = *visual orientation*, VM = *visual motion*, VA = *visual animals*, VT = *visual* trigrams, TO = *tactile orientation*, TA = *tactile animals*, TT = *tactile trigrams*, AF = *auditory frequency*, AM = *auditory motion*, AT = *auditory trigrams*; LH = left hemisphere, RH = right hemisphere. The task used to define each ROI is shown with a red asterisk.

AUD_{Vent} and TAC_{Vent} ROI Response Amplitudes. The results of this analysis in the ventral ROIs can be seen in Figure 19.

In sighted subjects we see a strong positive response amplitude to all visual tasks, confirming that this region is normally a visual area ($p<0.01$ for all visual tasks for both LH and RH).

However in sighted subjects there was also an elevation of response amplitude to several auditory and tactile tasks: in the LH to *auditory frequency* and *auditory trigrams* for AUD_{Vent} ($p<0.05$), and for the *tactile animal* and *tactile trigrams* task ($p<0.05$ for both LH and RH, with the exception of *tactile trigrams* in the RH for TAC_{Vent}, $p=0.14$). In contrast, in blind subjects we see robust responses to most tactile and auditory tasks ($p<0.02$ for all tactile and auditory tasks for both LH and RH, with the exception of *auditory motion* in the LH for AUD_{Vent}, $p=0.10$).

In further support of cross-modal plasticity in this area, a direct comparison of blind vs. sighted subjects shows that across all auditory and tactile tasks there is generally a larger response amplitude in blind as compared to sighted subjects ($p<0.01$ for all tasks, when collapsed, for both LH and RH).

In blind subjects responses to tactile tasks were generally larger than the responses to auditory tasks ($p<0.01$, when collapsed across modality). In the case of tactile stimuli responses were similar in magnitude to the responses to visual stimulation in these areas in sighted subjects.

ANOVA Analyses Within Ventral ROIs. Figure 20 shows ANOVA analyses [proportion of variance values (R^2)] in right-handed[27] blind and sighted subjects within AUD_{Vent} (Figure 20A) and TAC_{Vent} (Figure 20B) ROIs.

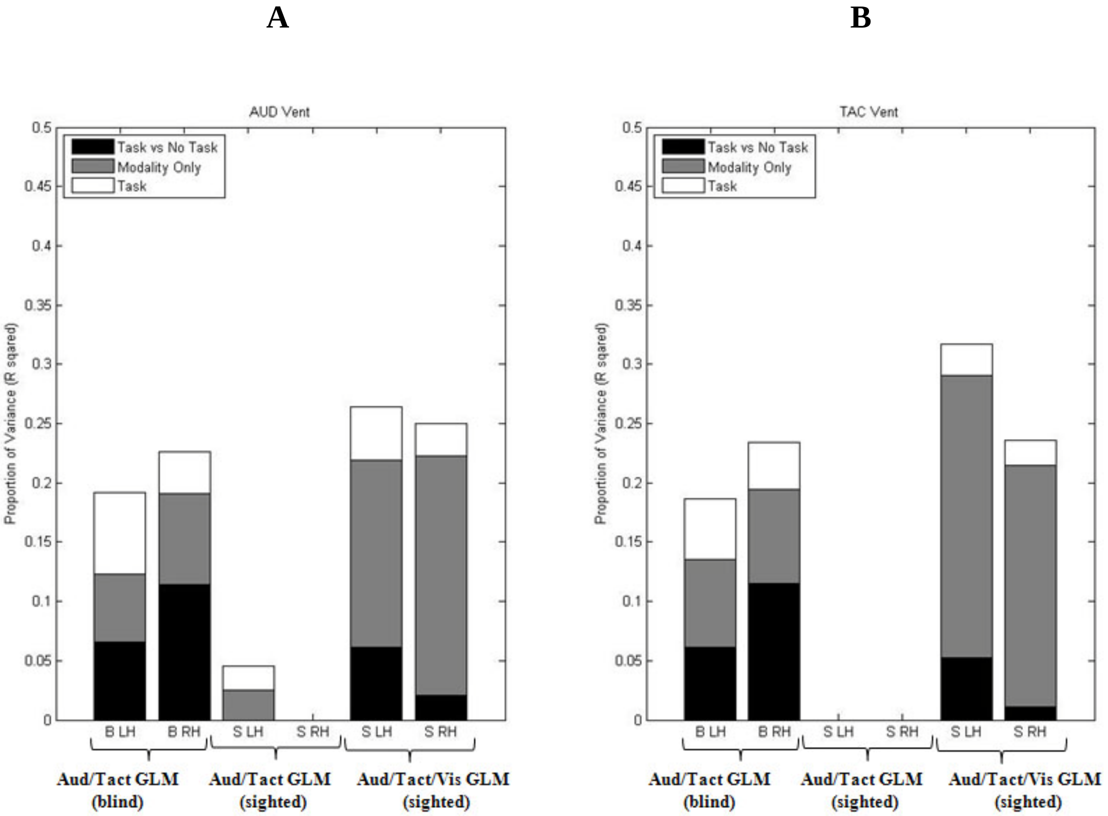

Figure 20: Study 1: ANOVA analyses [proportion of variance (R^2)] for ventral ROIs [**(A)** AUD_{Vent} and **(B)** TAC_{Vent}], for right-handed subjects only, explained across three different models, as described below. B LH = blind subjects, left hemisphere; B RH = blind subjects, right hemisphere; S LH = sighted subjects, left hemisphere; S RH = sighted subjects, right hemisphere. "Task vs No Task" = "task vs. no task" model, "Modality Only" = "modality" model, "Task" = "Task-Specified" model.

To obtain proportion of variance values (R^2) for our ANOVA analyses in the cross-modal dorsal-occipital ROIs we used the following GLMs: "Aud/Tact GLM

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[27] We conducted the same ANOVA analyses using all subjects, and the results were qualitatively similar. However we felt it was more appropriate to show results for analyses restricted to only right-handed subjects. ANOVA analyses containing all subjects (regardless of handedness) can be found in Appendix A.

(blind)", "Aud/Tact GLM (blind, by modality)", "Aud/Tact GLM (blind, task vs. no task)", "Aud/Tact GLM (sighted)", "Aud/Tact GLM (sighted, by modality)", "Aud/Tact GLM (sighted, task vs. no task)", and "Aud/Tact/Vis GLM (sighted)", "Aud/Tact/Vis GLM (sighted, by modality)", "Aud/Tact/Vis GLM (sighted, task vs. no task)". See Table 2 and above for explanations of these GLMs.

Once again, in sighted subjects little variance was explained when visual tasks were excluded from the GLM ["Aud/Tact GLM (sighted)", see Table 2] (though some variance was explained by the "task-specified" and "modality" models in the LH). When visual tasks were included ["Aud/Tact/Vis GLM (sighted)", see Table 2], a significant amount of variance was explained by the "modality" model, and a relatively small amount of variance was explained by either the "task vs. no task" model or the "task-specified" GLM.

Again, we see a strikingly different pattern of results in blind subjects. While the amount of variance that was explained by the "task-specified" model was comparable to that of sighted subjects when visual tasks were included in the GLM, less variance was explained by the "modality" model and more variance was explained by the "task vs. no task" model.

Therefore ventral ROIs, like the other cross-modal ROIs described above (occipito-temporal and dorsal-occipital), showed cross-modal plasticity across all tasks, but in this area, while there is once again modulation as a function of task, the modulation based on modality is even more powerful than in the dorsal-occipital ROIs. Responses were significantly stronger for tactile than for auditory stimuli.

Given the weak responses to tactile stimuli within sighted subjects (see also Burton et al., 2006), this suggests that modality-specific connections may drive responses within this ventral ROI [strong tactile cross-modal responses in ventral areas have also been shown previously (e.g Burton et al., 2006; Cohen et al., 1999; Sadato et al., 1998), although to some extent auditory cross-modal responses have also been shown in ventral areas (Burton et al., 2002b; Burton & McLaren, 2006)].

Response Amplitudes Across the Entire Cortex. In order to gain a more generalized view of cross-modal responses across visual cortex, we also calculated response amplitudes across the entire cortex.

In all sighted subjects, we separated the 10% of vertices that showed the highest percent BOLD signal change to visual tasks ("visual vertices") from the 90% of vertices that showed the least percent BOLD signal change to visual tasks ("nonvisual vertices"); this should be a conservative estimate since it is known that approximately one quarter of the brain responds to visual stimulation. Because blind and sighted subjects were aligned in cortex-based alignment space, we could then analyze data within these "visual vertices" versus "nonvisual vertices" for both subject types.

The results of this analysis for right-handed subjects only[28] can be seen in Figure 21. First, it can be seen that for blind subjects, across all tasks there is generally

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[28] We conducted the same response amplitude analyses using all subjects, and the results were qualitatively similar. However we felt it was more appropriate to show results for analyses restricted to

a larger percent BOLD signal change in “visual vertices” as compared to “nonvisual vertices” (as defined in sighted subjects) ($p<0.001$ for all tasks for both LH and RH), suggesting that cross-modal plasticity in blind subjects is not due to a general arousal effect (e.g. task difficulty differing between blind and sighted subjects). Furthermore, although sighted subjects do show some cross-modal plasticity in visual vertices, there is generally a larger percent BOLD signal change in visual vertices of blind subjects as compared to visual vertices of sighted subjects ($p<0.001$ for all tasks for both LH and RH).

Second, in visual vertices of blind subjects there is generally a larger response amplitude in tactile tasks than in auditory tasks ($p<0.001$ for both LH and RH).

Third, there is a right hemisphere lateralization for all auditory tasks; the response for all auditory tasks is larger in the right hemisphere than the left hemisphere ($p<0.001$).

Fourth, it can be seen in visual vertices of blind subjects that there is a very strong left hemisphere lateralization for *tactile trigrams*; there is a larger response for *tactile trigrams* in the left hemisphere than in the right hemisphere ($p<0.001$); in fact the response for *tactile trigrams* in the left hemisphere is larger than all other responses for all tasks in both hemispheres ($p<0.001$).

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only right-handed subjects. Response amplitude analyses containing all subjects (regardless of handedness) can be found in Appendix A.

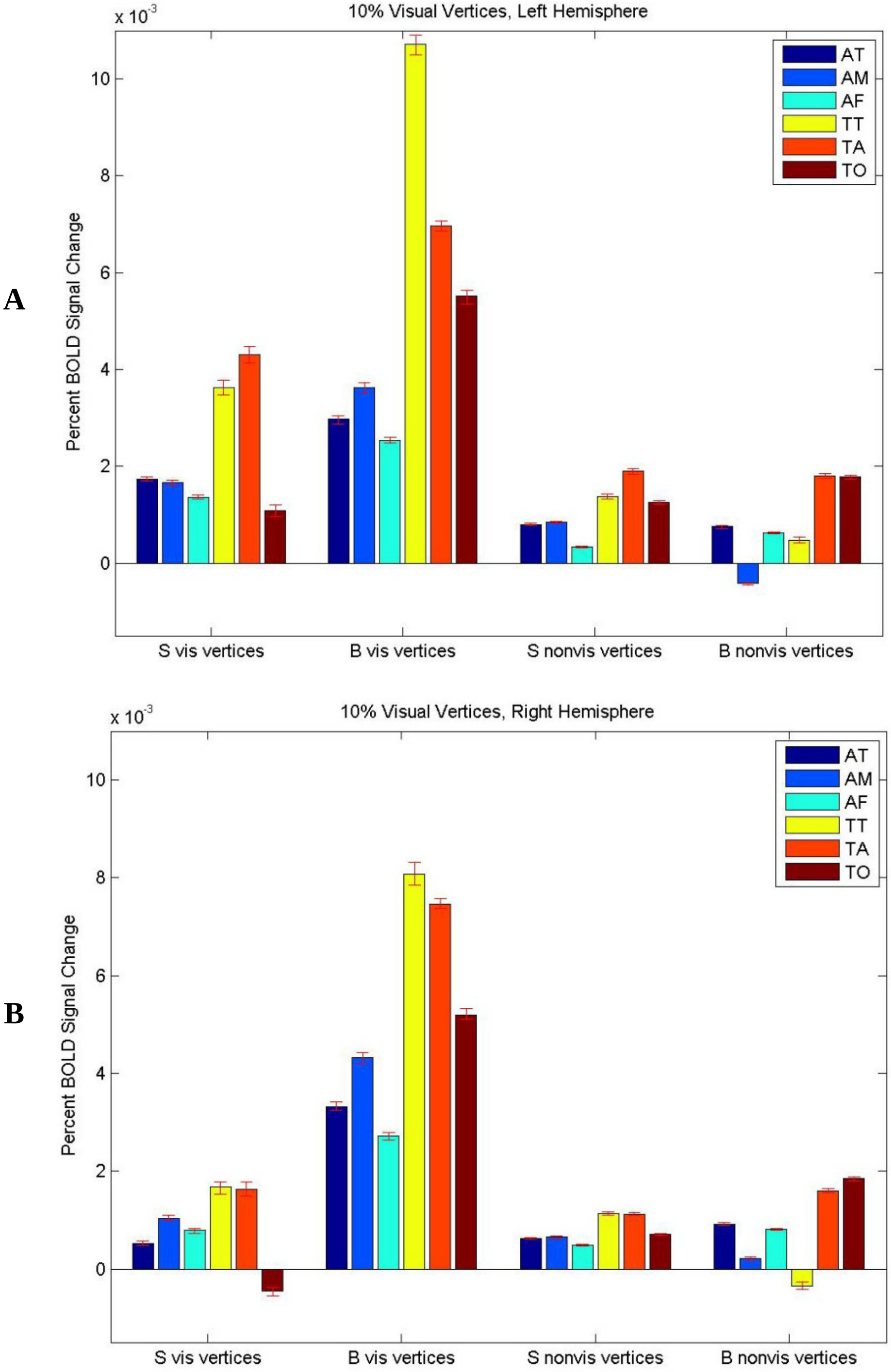


Figure 21: Study 1: Response amplitudes across the entire cortex of right-handed subjects for 10% visual vertices in **(A)** the left hemisphere and **(B)** the right hemisphere (RH). "S" = sighted, "B" = Blind, "vis vertices" = visual vertices; "nonvis vertices" = non-visual vertices; AT = *auditory trigrams*, AM = *auditory motion*, AF = *auditory frequency*, TT = *tactile trigrams*, TA = *tactile animals*, TO = *tactile orientation*. Single standard errors are shown.

(4.4) CONCLUSIONS

fMRI responses to a variety of tasks were measured in early blind and normally sighted subjects. Auditory tasks included frequency, motion, and letter trigram discrimination. Tactile tasks included orientation, letter trigram, and plastic animal discrimination. In sighted subjects, visual tasks included orientation, letter trigram, and animal picture discrimination, as well as a motion stimulus. Data were collected with a GLM design using a sparse pulse sequence.

We found cross-modal plasticity in blind subjects across all tasks, with many visual cortical areas showing cross-modal responses across all the tasks that we tested. Comparison of cross-modal responses to a wide range of tactile and auditory tasks within specific brain regions revealed further insight into the organization of cross-modal plasticity.

We found large scale cross-modal responses across much of visual cortex, with similar patterns of activation both across different tasks, and across different modalities. The extent of this plasticity is significantly larger than that found in previous studies (see Chapter 1). There are three reasons for this: (1) many previous experiments compared responses across two auditory or two tactile tasks; (2) we used a sparse pulse sequence; and (3) we collected a larger amount of data on a high-quality scanner. As shown by Figure 6 and 7, because the pattern of activation across tasks tends to be very similar, measuring task differences is likely to underestimate the scale of the cortical changes that occur as a result of blindness.

Across most of visual cortex, a large proportion of cross-modal responses tend be unspecific for either task or modality. It should be noted that this is unlikely to be a general arousal effect given that no such effect was noted in sighted subjects. However, cross-modal responses tended to be stronger for tactile than for auditory stimuli within visual cortex (whereas for tactile stimuli blind subjects tended to find the tasks somewhat easier than sighted subjects). Additionally, we found a general left hemisphere dominance across visual cortex of cross-modal response for *tactile trigrams*, and right hemisphere dominance across visual cortex of cross-modal response for auditory tasks.

We then examined responses within three areas of visual cortex (occipito-temporal, dorsal-occipital, and ventral cortex) in more detail. For all these areas, although a significant proportion of responses were unspecific for task, we also saw additional significant task-dependent modulation.

In the case of the occipito-temporal ROIs, modulation over and above the basic cross-modal response was entirely task-specific (i.e. no effect of modality). This occipito-temporal ROI was likely to have included a number of visual areas – it responded well to most visual stimuli. However this general region is close to the location of MT+, a region known to have well-defined task selectivity for visual motion processing in sighted subjects. In support of this we did find strong responses to auditory motion in the occipito-temporal ROIs. In *Study 2* we further examined responses in this general area by testing the specific hypothesis that we might see selective auditory motion responses in MT+ - i.e. that this area was not simply modulated by task, but that the task-specific modulation corresponded with the normal function of MT+.

In the case of the dorsal-occipital and ventral ROIs we saw an additional effect of modality in the modulation of cross-modal responses, with stronger responses for tactile than auditory tasks. These results are again consistent with previous findings. Dorsal-occipital areas have been shown to exhibit strong cross-modal plasticity to tactile tasks (Merabet et al., 2004; Sathian & Zangaladze, 2002; Zangaladze et al., 1999). Strong tactile cross-modal responses in ventral areas have also been shown previously (e.g Burton et al., 2006; Cohen et al., 1999; Sadato et al., 1998), although to some extent auditory cross-modal responses have also been reported in ventral areas (Burton et al., 2002b; Burton & McLaren, 2006). Our finding of additional task-specific modulation within ventral ROIs is also consistent with the previous literature; a left ventral occipital cross-modal response was found for the auditory letter task, suggesting that cross-response to letters in ventral occipital cortex is perhaps due to left hemisphere connectivity with language areas (Burton et al., 2002b).

Interestingly, we also found a similar trend in these same regions of visual cortex in normally sighted subjects, when those regions were responding to visual stimuli. In all cases the amount of task-specific modulation for non-visual tasks in blind subjects was similar to that seen within these ROIs for visual stimuli in sighted subjects, suggesting a similar degree of task-selectivity as is normally seen in visual cortex. Visual cortex in sighted subjects thus also exhibits a degree of *pluripotency* – exhibiting a large baseline response to most visual stimuli, with modulation above that baseline response depending on task. It therefore seems likely that *pluripotency* to some extent is an inherent property of visual cortex: for visual tasks in normally sighted subjects, and for cross-modal tasks in the case of early blindness. It is of course for this reason that fMRI studies normally compare modulations across pairs of tasks. However such analyses can sometimes lead researchers to overestimate the selectivity of visual cortex, and overlook the fact that strong signals can be evoked in most areas for most tasks.

CHAPTER 5: Study 2: Visual Motion Area MT+/V5 Responds to Auditory Motion in Human Sight-Recovery Subjects

(5.1) Introduction

In our first study, we found cross-modal plasticity (greater fMRI response in blind than sighted subjects) in visual cortex for all auditory and tactile tasks, with many areas showing cross-modal plasticity for all the tasks that we tested. This suggests that much of visual cortex may be relatively *pluripotent* – across much of cortex the degree of specialization underlying cross-modal plasticity seems to be relatively weak. However, in certain regions, we did find evidence for some modulation based on modality or specific task.

As described in *Study 1*, one set of our ROIs – those in occipito-temporal cortex – showed no modulation based on modality, but a strong effect for task. While this ROI probably included a number of visual areas, it probably overlapped significantly with area MT+/V5 - an area that shows highly selective responses to visual motion in sighted subjects, as can be seen from comparing the position of this ROI with responses to visual motion (see Figure B1 in Appendix B). Consistent with the idea that these ROIs included MT+, strong auditory motion responses were evident within this ROI.

However, although the results from *Study 1* suggest that modulations of cross-modal plasticity based on task played an important role within this anatomical area (the weak version of *functional specificity*), our first study was not designed to definitively test for the strong version of *functional specificity* (wherein cross-modal task responses are related to the normal function of the area).

In our second study we specifically examined the strong version of the *functional specificity* hypothesis - that cross-modal processing of non-visual tasks in visual cortex of blind subjects might systematically map onto sub-regions specialized for similar visual processing in normally sighted subjects, i.e. we tested for selective responses to auditory motion processing in visual motion area MT+/V5, an area strongly implicated in visual motion processing (Tootell, Reppas, Kwong, Malach, Born, Brady, Rosen & Belliveau, 1995; Watson, Myers, Frackowiak, Hajnal, Woods, Mazziotta, Shipp & Zeki, 1993).

Study 2 differed from *Study 1* in a number of factors. First we compared auditory motion responses to a wider variety of auditory stimuli. Second, we used closely matched control tasks rather than the *no stimulus/key-press* task. Third, it is likely in the first study that the responses within the occipito-temporal ROIs included responses from other nearby areas responsive to auditory motion in both blind and sighted subjects, as described below.

In our *Study 1*, comparison of the *auditory motion* task to the *auditory frequency* task (Figure 11A and B) localizes a sub-region of the occipito-temporal ROI that is likely to more closely localize to the group average location of MT+. Thus this sub-region is likely to contain only a small area of overlap - if any - between all individuals. Indeed, in *Study 1*, this group-averaged sub-region is small in the right hemisphere, and non-significant in the left hemisphere.

Furthermore, given the known variability in the location of MT+ it is likely that the group average location of MT+ includes, across subjects, significant overlap with other areas. Because MT+ (as well as other visual cortical sub-regions) cannot be reliably defined based on anatomy, it is typically identified in normally sighted subjects based on functional responses to visual motion – which is obviously not possible in blind subjects. Accordingly, it is possible that previous studies of cross-modal plasticity in blind subjects (i.e. auditory motion: Poirier et al., 2006; tactile motion: Ricciardi, Vanello, Sani, Gentili, Scilingo, Landini, Guazzelli, Bicchi, Haxby & Pietrini, 2007), as well as our first study, did not accurately localize MT+.

This is a particular concern, because, as demonstrated by our results below, there are auditorily-responsive polysensory temporal lobe regions (Beauchamp, Lee, Argall & Martin, 2004) directly adjacent to MT+. In a study by Poirier et al. (2006), responses to auditory motion near (the presumed location of) MT+ were found both in early blind and sighted subjects, and thus they did not find a differential response in blind subjects; however, because they averaged across subjects, it is likely that the area they localized in fact was minimized due to subject averaging, and contaminated by auditory responses from adjacent areas.

However, in *Study 2*, we had rare access to two early-blind subjects with partial sight recovery in adulthood (“sight-recovery subjects”). Sight-recovery subjects afforded a unique opportunity to localize MT+; we could define MT+ based on functional responses to visual motion (a moving versus stationary visual stimulus, as is the standard method with sighted subjects), and observe cross-modal auditory responses in that area (because these subjects had been blind since early in their lives), all within the same individual’s visual cortex. This direct comparison is neither possible in typical sighted nor in typical blind subjects. If MT+ in these subjects responded selectively to auditory motion, this would suggest that cross-modal reorganization can be guided by the normal functional specialization of a cortical region. Our goal was therefore to determine whether responses in MT+ would be functionally selective: would auditory responses within MT+ be motion-specific?

Sight-recovery subject MM, age 53, was blinded in a chemical accident at age 3 and had vision partially restored (postoperative acuity, 20:1000) after a corneal stem cell replacement in the right eye 7 years ago at age 46. Postoperatively, MM showed successful performance on many visual motion tasks and exhibited normal MT+ responses to visual motion as measured using fMRI (Fine et al., 2003). Subject MS, also age 53, whose blindness was congenital as a result of retinopathy of prematurity and cataracts, had vision partially restored (postoperative acuity, 20:400) after cataract removal in the right eye ten years ago at age 43.

Not only did these sight recovery subjects provide us with the ability to directly localize visually-defined areas in visual cortex to which we could compare cross-modal responses within the same individual, but they also provided us with insight into the relationship between cross-modal plasticity and restored sight in visual cortex. Understanding the implications of cross-modal plasticity for visual restoration, and vice versa, is of increasing importance given current developments in technologies for restoring vision to the blind such as corneal stem cell transplants, retinal prosthetics, and gene therapy (Aguirre, Komaromy, Cideciyan, Brainard, Aleman, Roman, Avants, Gee, Korczykowski, Hauswirth, Acland, Aguirre & Jacobson, 2007; Merabet, Rizzo, Amedi, Somers & Pascual-Leone, 2005).

(5.2) METHODS

Subjects

Twelve subjects (two partial sight-recovery: both age 53, one man; 10 normally sighted controls: ages 21–53, six men) without neurological or psychiatric problems participated having given written, informed consent. Data from one additional control subject were excluded from analysis because of significant head-motion artifacts. Experimental procedures were approved by the California Institute of Technology Committee for the Protection of Human Subjects.

MRI Scanning

Blood oxygenation-level dependent (BOLD) functional imaging was performed with a 3 Tesla Siemens (Erlangen, Germany) TRIO scanner at California Institute of Technology (3x3x3 mm voxels; TR, 12 s; echo time, 30 ms; flip angle, 90°; field of view, 192; 30 slices). Slices were obliquely oriented for optimal coverage of visual and auditory cortices. Three-dimensional (3D) anatomical images were acquired using a T1-weighted MPRAGE (magnetization-prepared rapid gradient echo) sequence.

A sparse echo planar imaging pulse sequence was used in all experiments so that the presentation of stimuli (both auditory and visual) was uninterrupted by MRI scanner noise (Hall et al., 1999). Two-second volume acquisitions were preceded by 8–10 s quiet delay periods (10 s in Experiment 1, 8 s in Experiments 2 and 3) during which visual or auditory stimuli were presented. Because of the hemodynamic delay [~5 s to peak response (Boynton et al., 1996)], each volume acquisition measured the BOLD response to stimulation during the middle of the stimulus presentation period, with relatively little contribution from the auditory noise of the previous acquisition. Note that the shorter delay period of Experiments 2 and 3 may have resulted in lower measured response amplitudes in those experiments.

Auditory Stimuli

Stimuli were generated using MATLAB and the Psychophysics Toolbox (www.psychtoolbox.org) (Brainard, 1997; Pelli, 1997). See www.klab.caltech.edu/~saenz/soundstimuli.html for samples of the auditory stimuli. Auditory stimuli were delivered via MRI-compatible stereo headphones (MRCONFON), and all subjects were instructed to keep their eyes closed during all auditory scans.

Interaural level difference (ILD) motion noise bursts (Experiments 1–3) were created by linearly ramping (between 0 and maximum intensity) the volume of a white noise stimulus in opposite directions between the left and right speakers, creating the vivid perception of a sound source moving horizontally from one side of the head to the other. Maximum auditory intensity was ~50 dB and was adjusted to a comfortable level for individual subjects. All subjects reported a strong motion perception. ILD motion responses were contrasted with responses to stationary auditory white noise bursts that had equal intensity (0.5 of maximum) in the two speakers, creating the perception of a centrally located stationary sound source. All noise bursts had a duration of 1 s ± 200 ms.

Interaural time difference (ITD) motion noise bursts (Experiment 2) consisted of low-pass-filtered (at 2 kHz) auditory white noise presented to the two ears. The time lag between the two ears was stepped from +1 to -1 ms in 16 evenly spaced increments. In Experiment 3, noise bursts were resampled so that interaural time lags could be smoothly and linearly ramped. The corresponding stationary stimulus had an interaural time lag of 0.

Volume changing stimuli (Experiment 2) were stationary auditory white noise bursts presented binaurally. These stimuli (identical in both speakers) alternated between half and maximum volume. Volume levels were chosen to match the maximum monaural sound difference present in the ILD moving versus stationary stimuli.

Frequency-modulated (FM) sweeps (Experiment 2) were generated by linearly ramping the auditory frequency from 75 to 800 Hz over time. FM sweeps were normalized using ISO226 equal-loudness curves to minimize perceived loudness changes that could be associated with spatial motion in depth. FM sweeps were contrasted with an unchanging, midrange monotone (438 Hz).

Speech stimuli (Experiment 2) consisted of nouns (recorded voice) spoken by a male native English speaker. Common concrete nouns (e.g., “chair,” “fork”) were chosen from the MRC psycholinguistic database (www.psy.uwa.edu.au/MRCDataBase/uwa_mrc.htm). Speech stimuli were contrasted with the same speech recordings played in reverse.

Stimulus Procedures

Sight-recovery subjects MM and MS participated in Experiments 1–3. Six control subjects (C1–C6) participated in Experiment 1 (ILD motion responses). An additional four control subjects (C7–C10) were tested for auditory ITD motion responses in Experiment 2. Two control subjects (C3, C7) participated in Experiment 3.

Experiment 1: ILD Auditory Motion Versus Stationary White Noise and Rest. Auditory scans (four per subject) consisted of thirty 12 s blocks of moving white noise (ILD motion), stationary white noise, and silent rest (10 alternated blocks of each condition, for a total of 372 s including an initial dropped acquisition). Block order was counterbalanced across subjects. Each 12 s block consisted of a 10 s stimulation period followed by a 2 s data acquisition period.

Each stimulation period contained four two-alternative forced choice (2-AFC) trials (2500 ms each). During each trial, two noise bursts were presented, separated by a 100 ms blank interval, followed by a 400 ms response interval. During motion blocks, the sound moved in opposite directions during the two intervals. Each trial contained one shorter noise burst (800 ms) and one longer noise burst (1200 ms), the order of which was randomized across trials. Subjects pressed one of two keys to indicate which interval contained the longer-duration noise burst. The same task was used on both moving and stationary trials, so task demands did not vary across the compared conditions. Task performance was not significantly different across moving versus stationary conditions (93.1 vs. 92.1% correct; *p*=0.56) nor across control versus sight-recovery subjects (91.7 vs. 93.7% correct; *p*=0.22).

Experiment 2: Measuring Responses to Auditory ITD Motion, ILD Motion, Volume Changes, Frequency Sweeps, and Speech. Auditory scans (two per subject per condition) consisted of forty 10 s blocks that alternately presented the given test stimulus and its respective contrast stimulus. We measured responses to (1) ITD motion versus stationary noise bursts, (2) ILD motion versus stationary noise bursts, (3) stationary volume changes (white noise bursts at maximum vs. half-maximum volume, (4) frequency sweeps versus mid-range monotone (438 Hz), and (5) forward spoken words versus unintelligible reverse spoken words. Two additional conditions were run with subject MS only (with whom we had more time): (6) peripheral versus central stationary white noise bursts and (7) ILD moving versus stationary noise bursts played monaurally (thus removing the motion information).

The same 2-AFC duration judgment task from Experiment 1 was used in all conditions of Experiment 2 (except the speech condition) to keep task demands as similar as possible across all experiments. Each 10 s block contained three 2-AFC trials (2500 ms) that fit within the 8 s silent delay period followed by a 2 s scanning period. During FM sweep trials, the two intervals swept in opposite directions (from low to high and high to low), to parallel the motion conditions. In the speech condition, a single noun was presented every 2 s during the 8 s stimulation periods (four words per stimulation period). Subjects were asked to make a covert word association with the heard noun during forward speech blocks and to listen passively during the reverse speech blocks. The stimulus presentation and task for speech blocks were modeled after those used in previous studies of cross-modal verbal responses in blind subjects (Burton et al., 2002b; Amedi et al., 2003).

Experiment 3: Measuring Responses as a Function of ITD and ILD Motion Strength. ITD and ILD motion strength were parametrically varied by changing the slopes of the interaural temporal and volume ramps, respectively, as shown in Figure 25. For the ITD data session, each scan (five per subject) consisted of forty 10 s blocks of ITD motion presented at five different motion strengths (eight blocks per motion strength). The same procedure was repeated for the ILD data session on a separate day. During both sessions, single 1 s noise bursts were presented every 2 s during each 8 s stimulation period (four noise bursts per stimulation period) followed by 2 s of scanning. Each single noise burst swept from left to right or right to left in randomized order, and subjects indicated the perceived direction by pressing one of two keys (2-AFC direction discrimination task). Trials were blocked by motion strength and were presented either in order of increasing or decreasing motion strength (counterbalanced across scans). Task performance for the sight-recovery subjects at the 0, 25, 50, 75, and 100% levels of motion strength was 51% (chance level since there was no motion), 88, 90, 92, and 93% correct for ITD stimuli and 56, 93, 95, 93, and 91% correct for ILD stimuli.

Data Analysis

Brain Voyager QX (Brain Innovation, Maastricht, The Netherlands) and MATLAB were used for data analysis. fMRI data preprocessing included linear trend removal, temporal high-pass filtering, and motion correction.

For general linear model (GLM) analyses (Experiment 1 only), individual 3D anatomical images were transformed into Talairach space and were segmented at the gray/white matter boundary allowing for cortical surface reconstruction of each individual subject's brain hemispheres. Cortex-based alignment was applied to further improve intersubject alignment beyond Talairach correspondence. The reconstructed cortical surfaces were each transformed into a spherical representation that was subjected to nonrigid alignment to a selected target brain sphere based on the gyral/sulcal folding pattern (Fischl et al., 1999). fMRI data were aligned to same-session anatomical volumes and transformed into the cortex-based aligned coordinate space. Fixed-effects GLM analyses were corrected for serial correlations and for multiple comparisons using the false discovery rate (FDR) method (Genovese et al., 2002).

Region-of-interest (ROI) analyses (as used in Experiments 1–3) have the benefit of being based on individual subject data and are more sensitive than whole-brain analyses. This allows us to localize regions with more precision and to quantify responses to multiple auditory stimulus conditions. ROIs were defined within each subject's 3D Talairached anatomical coordinate space (not on 2D surfaces).

Defining MT+ ROIs

MT+, the probable human homologue of visual motion-responsive macaque areas MT and MST, is typically located posterior to the intersection of the lateral occipital sulcus (LOS) and the inferior temporal sulcus (ITS). However, identifying human MT+ by anatomical landmarks and/or stereotaxic coordinates alone is problematic because of significant anatomical variability across individuals (Watson et al., 1993; Dumoulin, Bittar, Kabani, Baker, Le Goualher, Bruce Pike & Evans, 2000), and because of its proximity to polysensory temporal lobe regions (Beauchamp et al., 2004). As a result, the location of MT+ is normally defined functionally, by its response to moving visual stimuli (Watson et al., 1993; Tootell et al., 1995).

The visual MT+ localizer stimulus was projected onto a rear projection screen visible from within the MRI scanner via an angled mirror. There were two to four visual scans per subject, each consisting of 30 alternating blocks of moving (8°/s radially inward and outward) versus stationary white dots on a black background. Random dot arrays subtended ±10° from a central fixation point. Individual dots (50 per field) subtended 1°. This large dot size was used with all subjects to compensate for MM's and MS's limited acuity. Both MM and MS, despite very low spatial acuity, reliably reported when the visual stimulus was moving versus stationary. MT+ ROIs for sight-recovery subjects and controls were individually selected as contiguous 3D regions near the LOS/ITS that responded more to moving than to stationary conditions [q(FDR)<0.05]. To show that results did not depend on the particular threshold used for defining the ROI, MT+ ROI thresholds were also defined at q(FDR)<0.01 and q(FDR)<0.1 (supplemental Figure B3 and Figure B4, available in Appendix B).

ROI analyses (as used in Experiments 1–3) have the benefit of being based on each individual subject's data, thereby allowing us to localize (and measure responses to multiple auditory stimulus conditions within) regions sensitive to visual motion with precision for each individual subject. It was important to precisely define MT+ because of its proximity to multimodal areas. ROIs were defined within each subject's 3D Talairached anatomical coordinate space (not on 2D surfaces).

Defining Other ROIs

Auditory cortex ROIs were defined as contiguous regions on the lateral sulcus that responded more to stationary white noise than to silent conditions [q(FDR)<0.05]. This ROI likely included primary and secondary regions of auditory cortex. Ventral occipito-temporal voxels (inferior to MT+) that responded to ILD motion in Experiment 1 were chosen as a third ROI (from subject MM only, because no such activation was evident in subject MS).

ROI Statistics

In Figure 23-25, error bars represent standard error of the mean (SEM). In all cases, *t* tests are performed over repeated scan runs per hemisphere per subject. The following are examples: auditory ILD motion responses of each subject (see Figure 22A): four repeated runs x two hemispheres yields (n=8); ITD motion responses in MT+ of sight-recovery subjects (see Figure 24A): two repeated runs x two hemispheres x two subjects yields (*n*=8).

(5.3) RESULTS

We first present statistical activation maps that give an initial broad overview of cortical responses to auditory ILD motion in sight-recovery subjects and normally sighted control subjects. Then, we use specific ROI analyses and a range of auditory stimuli to specifically test for the motion specificity of auditory responses within MT+ on an individual-subject basis. Samples of auditory stimuli can be found at www.klab.caltech.edu/_saenz/soundstimuli.html. A sparse MRI pulse sequence was used in all experiments so that stimulus presentation was uninterrupted by scanner noise.

Experiment 1: Cross-modal Auditory Motion Responses Coexist with Regained Visual Responses in MT+

In Experiment 1, we measured responses to visual motion (standard MT+ localizer stimulus) and to auditory ILD motion in the two sight-recovery subjects (MM and MS) and six normally sighted control subjects.

GLM Analyses. In Figure 22, yellow regions show cortical brain areas that responded more to moving (ILD) than to stationary auditory white noise stimuli. Statistical activation maps are the result of fixed effects GLM analyses, corrected for multiple comparisons [q(FDR)<0.01]. In both the control group and in subjects MM and MS, auditory ILD motion activated the auditory cortex with a right-hemispheric dominance along the planum temporal (Figure 22A–C) [Talairach coordinates, control group: right hemisphere (RH): 50, -31, 19; left hemisphere (LH): -48, -33, 17], consistent with previous reports of auditory motion responses in sighted subjects (Baumgart et al., 1999; Warren, Zielinski, Green, Rauschecker & Griffiths, 2002).

In the control group (Figure 22A), auditory ILD motion also activated the bilateral temporal lobes, beginning on the ITS and extending across the middle temporal gyri (MTG) toward the superior temporal sulci (STS) (RH: 52, -57, 6.4; LH: -51, -62, 3.1). The auditory response partially overlapped with the anterior end of MT+ in the control group analysis (Figure 22A, green), although blurring attributable to intersubject averaging contributes to this overlap in the group-averaged analysis. (See supplemental Figure B2, in Appendix B, for individual control subject activation maps.) This auditory response is consistent with previously reported responses to complex auditory stimuli (not limited to motion) on the posterior MTG, which may partially overlap with the anterior end of MT+ (Lewis, Wightman, Brefczynski, Phinney, Binder & DeYoe, 2004). The existence of auditory responses adjacent to MT+ in control subjects further emphasizes the importance of functionally verifying MT+ location on an individual-subject basis.

Auditory ILD motion responses from subjects MM and MS are shown individually (Figure 22B and C). MM and MS had auditory ILD motion responses that extended posteriorly into the visual occipital lobe [q(FDR)<0.01]. Unlike control subjects, their auditory responses colocalized very well with their own visually defined MT+.

A subtraction analysis (Figure 22D) shows regions that were more strongly activated during auditory ILD motion (vs. auditory stationary motion) in sight-recovery subjects compared with control subjects [q(FDR)<0.01]. Auditory ILD motion more strongly activated a bilateral occipital region in the sight-recovery subjects (LH: -40, -78, -2.6; RH: 42, -70, -0.7), consistent with MT+ location in those subjects. Thus, these initial results are consistent with auditory ILD motion responses colocalizing with MT+ in sight-recovery subjects but not control subjects.

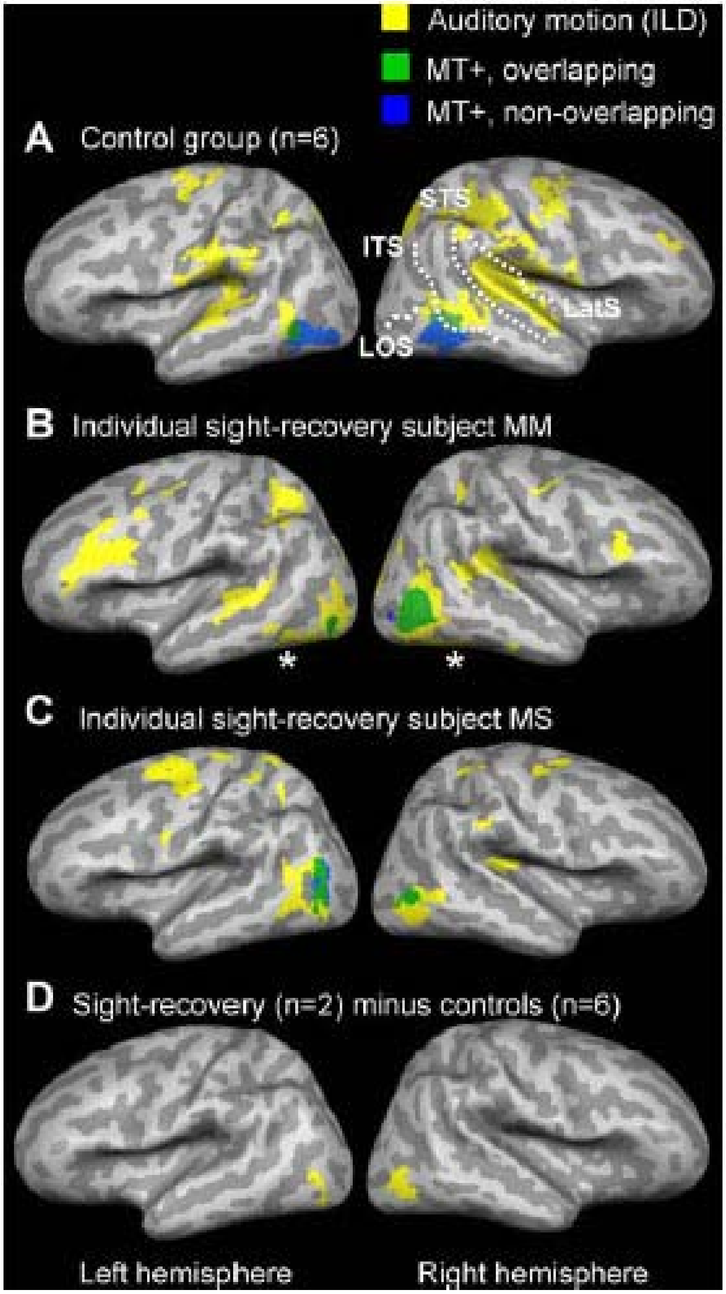
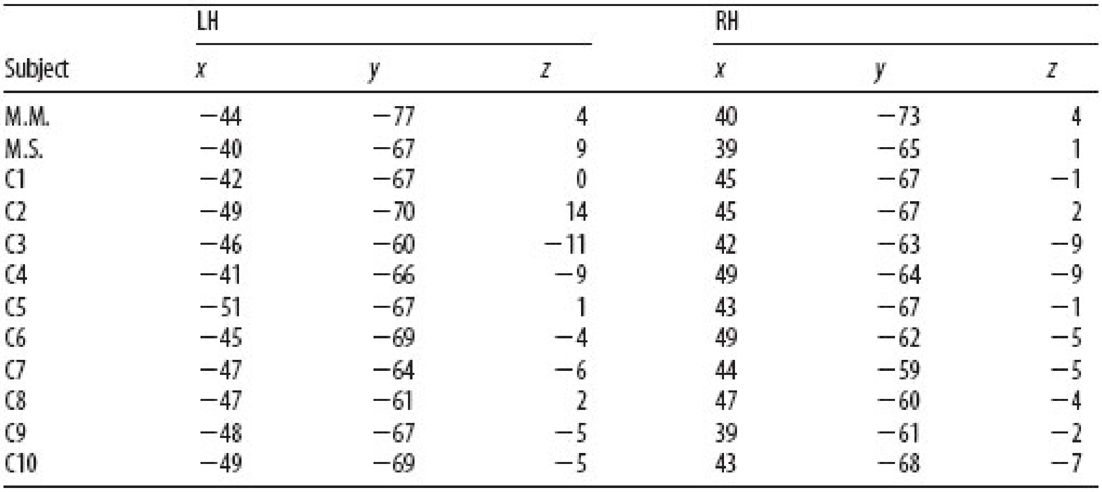


Figure 22: Study 2: Experiment 1: surface maps of auditory ILD motion responses and MT+. (**A)–(C)**, Yellow regions responded more to moving (ILD) versus stationary auditory white noise in the control group **(A)**, subject MM **(B)**, and subject MS **(C)**. Statistical activation maps are the result of a fixed-effects GLM analysis [q(FDR)<0.01]. Green and blue regions show MT+ location as determined by visual MT+ localizer scans run in the same subjects (green, MT+ overlapped by auditory ILD motion responses; blue, MT+ not overlapped by auditory ILD motion responses). Note the near-complete overlap (very little blue) in subjects MM and MS indicating colocalization of auditory ILD responses with their visually defined MT+. **(D)**, A subtraction analysis shows regions more activated by auditory ILD motion (vs. stationary) in sight recovery subjects compared with controls [q(FDR)<0.05]. Data from all subjects are projected onto a single anatomical image (inflated cortical surface) using cortex-based alignment.

ROI Analyses. Next, we sought to further verify this result by performing ROI analyses to measure the amplitude of the BOLD response to auditory ILD motion within the MT+ ROI of all subjects. These ROI analyses offer several important advantages. First, these ROI analyses are performed separately on each individual subject and are performed in 3D anatomical space (not surface projections). This avoids potential distortions resulting from group averaging and transformation onto surface representations. These concerns are of particular importance in a region of the cortex that shows high anatomical intersubject variability. Second, the ROI analyses report actual BOLD response amplitudes (not statistical values) and are therefore capable of revealing any auditory responses within MT+ that might be subthreshold in a given GLM analysis.

Bilateral MT+ ROIs were individually defined in each subject (in 3D coordinate space) based on that individual subject’s response to the visual MT+ localizer stimulus (visual moving vs. stationary). The stereotaxic locations (Table 5) and volumes (supplemental Table B1, available in Appendix B) of the MT+ ROIs in subjects MM and MS were consistent with previous studies (Watson et al., 1993; Tootell et al., 1995; Dumoulin et al., 2000) and were within the ranges found in our own control subjects.

Table 5: Study 2: Center-of-gravity Talairach coordinates for MT+ ROIs.



	LH			RH		
Subject	*x*	*y*	*z*	*x*	*y*	*z*
M.M.	−44	−77	4	40	−73	4
M.S.	−40	−67	9	39	−65	1
C1	−42	−67	0	45	−67	−1
C2	−49	−70	14	45	−67	2
C3	−46	−60	−11	42	−63	−9
C4	−41	−66	−9	49	−64	−9
C5	−51	−67	1	43	−67	−1
C6	−45	−69	−4	49	−62	−5
C7	−47	−64	−6	44	−59	−5
C8	−47	−61	2	47	−60	−4
C9	−48	−67	−5	39	−61	−2
C10	−49	−69	−5	43	−68	−7

In Figure 23, fMRI response magnitudes (percentage of BOLD signal change) to visual motion and to auditory ILD motion are plotted within each subject's MT+ ROI. In each control subject, MT+ responded positively to visual motion (*t* test, *p*<0.001 for each subject; as expected because the MT+ ROI was defined using this condition) but not to auditory ILD motion (*p*>0.07, minimum for each subject). For each control subject, there was a significant difference between their own visual and auditory motion responses (*p*<0.001, each subject). In MM and MS, MT+ responded to both visual motion (*p*<0.001, each subject) and auditory ILD motion (*p*<0.001, each subject; with no significant difference between visual and auditory responses: MM, *p*=0.6; MS, *p*=0.9).

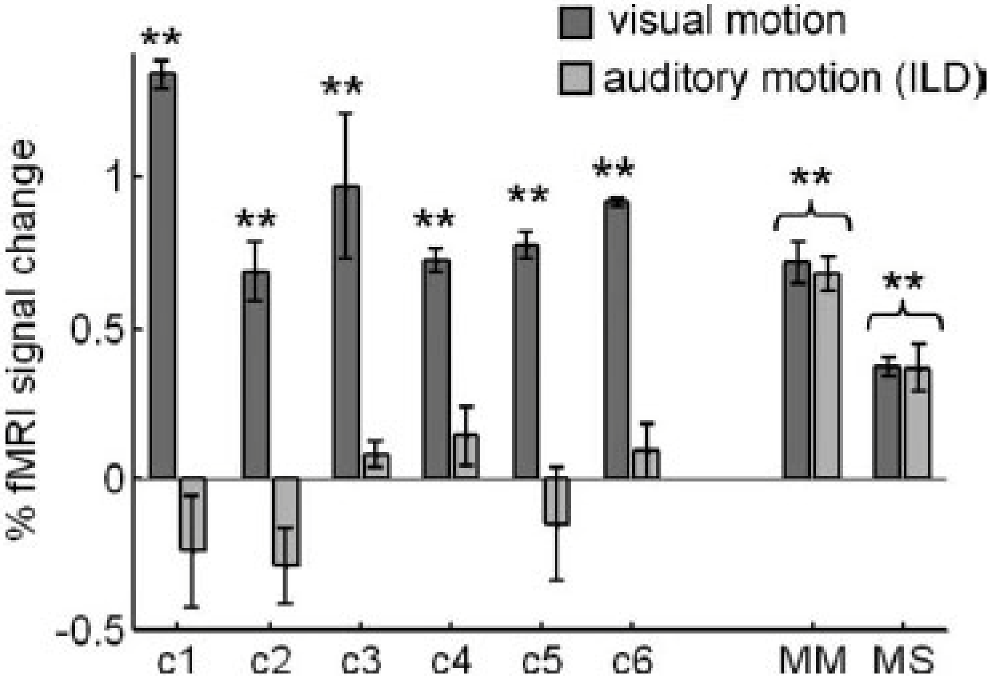


Figure 23: Study 2: Experiment 1: ROI analysis. MT+ responds to both visual and auditory motion stimuli in sight-recovery subjects. Responses (% fMRI signal change) to moving versus stationary visual stimuli and to moving (ILD) versus stationary auditory stimuli within visually defined MT+ ROIs are shown. MT+ responded to visual motion in all individual subjects. MT+ responded to auditory ILD motion in sight-recovery subjects MM and MS but not in normally sighted controls. Error bars denote SEM. Asterisks denote significant differences from zero (**$p<0.01$).

In additional control analyses, we verified that these results were highly consistent over a range of thresholds used to define the MT+ ROI, which included equating MT+ ROI size across subjects (supplemental Figure B3, available in Appendix B).

Experiment 2: MT+ Auditory Responses are Specific to Motion

In Experiment 2, we sought to verify whether the sight-recovery subjects' auditory responses within MT+ were specific to motion. If motion-specific, MT+

should also respond to auditory motion defined by ITDs but should not respond to other complex or temporally changing auditory stimuli that do not induce the perception of motion.

We measured responses within the MT+ ROIs of MM and MS to (1) moving versus stationary noise defined by ITDs; (2) moving versus stationary white noise defined by ILD (replication of Experiment 1); (3) stationary volume changes (white noise at maximum vs. half-maximum volume); (4) FM tonal sweeps versus monotone (FM sweeps are a rising and falling of pitch); and (5) human speech versus unintelligible reverse speech. Additionally, in subject MS only, we measured responses to two other control conditions: (6) peripheral versus central stationary white noise (to test for peripheral bias); and (7) the ILD moving versus stationary stimulus played monaurally (thus removing the motion information).

Consistent with the hypothesis of motion specificity in sight-recovery subjects, MT+ (Figure 24A) responded both to ITD motion ($p<0.001$) and to ILD motion ($p<0.003$), consistent with Experiment 1, with no difference between responses to the two types of motion ($p=0.5$). MT+ did not respond to stationary volume changes ($p=0.7$), frequency sweeps ($p=0.22$), or speech ($p=0.21$). Nor did MT+ (measured in MS only; data not shown) respond to peripheral stationary stimuli (mean, 0.06% signal change ± 0.1; $p=0.6$) or to ILD stimuli played monaurally (mean, 0.01% signal change ± 0.03; $p=0.9$). The same pattern of results was observed for MM and MS individually (ITD, $p<0.01$ each; ILD, $p<0.01$ each; volume change, $p>0.4$ each; frequency sweeps, $p>0.1$ each; speech, $p>0.2$ each). We also verified that these results were consistent over a range of thresholds used to define the MT+ ROI (supplemental Figure B4, available in Appendix B).

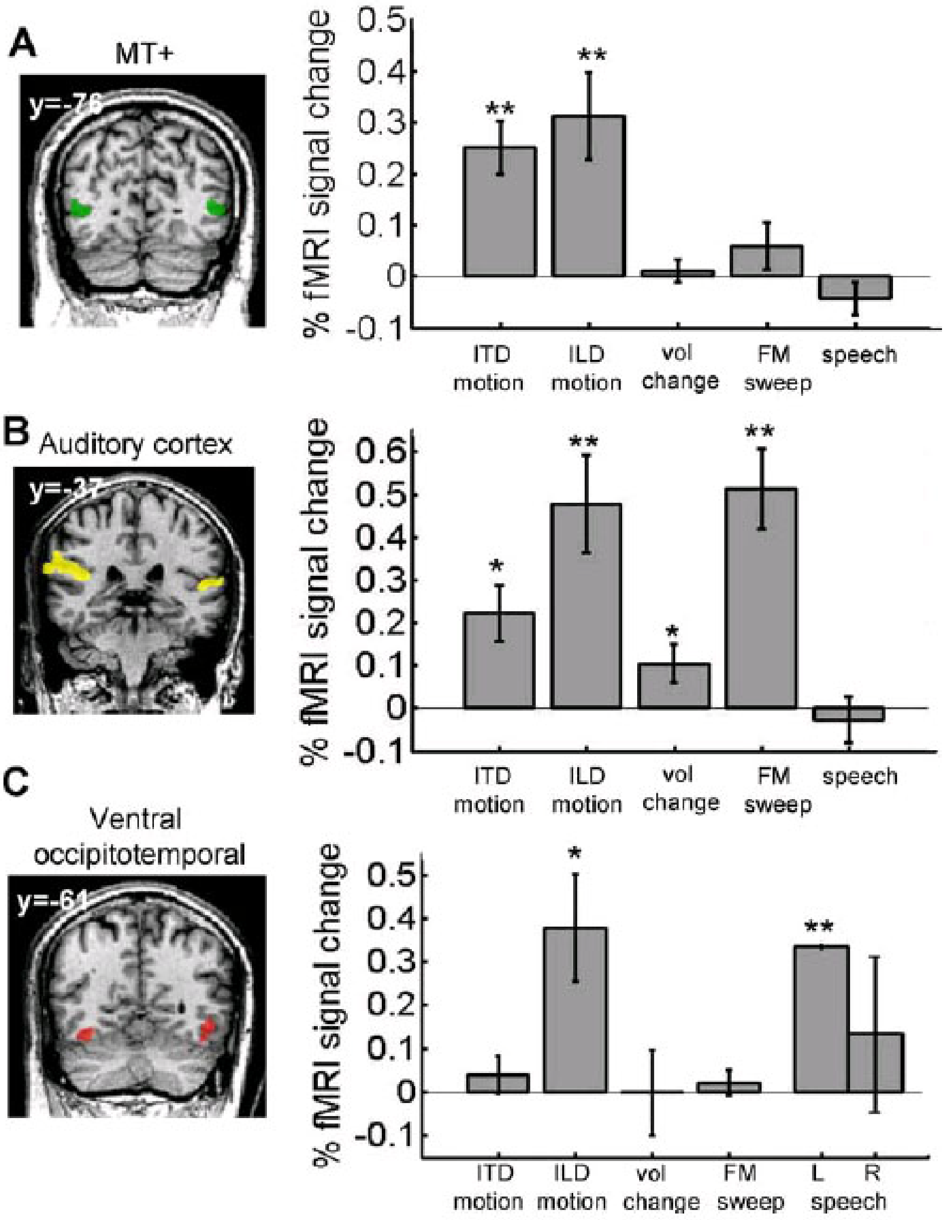


Figure 24: Study 2: Experiment 2: MT+ auditory responses are motion-specific. (**A**)–(**C**), Responses (% fMRI signal change) from MM and MS to ITD motion, ILD motion, stationary volume changes, FM sweeps, and human speech within MT+ (**A**), auditory cortex (**B**), and ventral occipito-temporal cortex ROIs (**C**) are shown. Responses to all stimuli are relative to their respective baseline control stimuli. Only area MT+ had motion-specific responses. In the left column, sample coronal slice views from subject MM illustrate ROI locations (Talairach *y*-coordinates are given). Note that ventral occipito-temporal ROIs were identified in MM only, and left/right-hemispheric responses within that ROI are shown separately for the speech condition because it evoked a highly lateralized response. All other responses are averaged across the LH and RH. Error bars denote SEM. Asterisks denote significant differences from zero (*$p<0.05$; **$p<0.01$). vol, Volume; L, left; R, right.

We also measured auditory ITD motion responses within the MT+ ROI of four normally sighted control subjects (data not shown). In contrast to the sight-recovery subjects, MT+ in controls was weakly inhibited by ITD motion (mean, -0.11% signal change ± 0.05; $p<0.05$). This is consistent with a previous study that reported slight deactivation of MT+ by auditory ITD motion stimuli (Lewis et al., 2000).

Next, we defined bilateral auditory cortex ROIs in MM and MS based on responses to stationary auditory white noise versus silence (Figure 24B). Responses within this ROI were significant for ITD motion ($p<0.05$), ILD motion ($p<0.01$), FM sweeps ($p<0.001$), and for volume changes ($p=0.05$). Unlike MT+, this region responded to auditory stimuli that were not limited to motion.

We also defined bilateral ventral occipito-temporal ROIs (Figure 24C) in subject MM because this region responded to ILD motion in Experiment 1 (see asterisked region inferior to MT+ in Figure 22; no such activation was evident for subject MS). We chose to investigate this region further, because it is more typically associated with object than with motion processing (Grill-Spector, Kourtzi & Kanwisher, 2001). In MM, responses were marginally significant to ILD motion ($p=0.05$) but not to ITD motion ($p=0.4$), volume changes ($p=0.9$), or to FM sweeps ($p=0.5$). The LH of this region responded strongly to speech (LH, $p<0.01$; RH, $p=0.6$), consistent with previous reports of left-hemispheric verbal responses within visual cortex of early blind subjects (Amedi et al., 2003). Thus, visual regions adjacent to MT+ that are not normally implicated in visual motion processing did not respond specifically to auditory motion.

The results of Experiment 2 demonstrated that, in sight-recovery subjects, volume changes were neither necessary nor sufficient to evoke an MT+ response, nor did MT+ respond more generally to complex, continuously changing, peripheral, and/or meaningful stimuli including frequency sweeps or speech. Other regions of the brain that were not expected to show motion specificity responded more generally to this battery of auditory stimuli.

Experiment 3: MT+ is Sensitive to Weak Auditory Motion Signals

In normally sighted subjects, MT+ is highly motion sensitive, responding even to weak motion signals (Britten, Shadlen, Newsome & Movshon, 1992). In Experiment 3, we tested whether MT+ in the sight-recovery subjects was sensitive to a range of auditory motion signal strengths. For the ITD stimulus (low-pass-filtered auditory white noise), motion was generated by linearly ramping interaural temporal differences. We parametrically varied ITD motion strength by varying the slope of that linear ramp (Figure 25A). For the ILD stimulus (auditory white noise), motion was generated by linearly ramping ITDs. We parametrically varied ILD motion strength by varying the slope of that volume ramp (Figure 25C). In both cases, increasing the slope of the ramp effectively increased both the apparent speed and path length of the motion stimuli.

Within sight-recovery subjects MM and MS, MT+ was highly sensitive to ITD motion, responding to motion stimuli with small ITD ramps (Figure 25B) ($p<0.005$ at all motion strengths) and rapidly saturating. In contrast, MT+ of controls ($n=2$) was not activated by ITD motion of any strength and was, in some cases, weakly inhibited (not different from zero at 50 and 75% levels, $p > 0.3$; below zero at 25 and 100% levels, $p < 0.05$). For ILD motion, MT+ responses within sight-recovery subjects increased monotonically with motion level and were well fit by a linear model (Figure 25*D*) ($R^2 = 0.97$; slope, 0.34/100; intercept, 0.01 of linear fit; difference from zero at 50, 75, and 100% levels; $p < 0.001$; individual-subject data also had a good linear dependence: MM, $R^2 = 0.97$; MS, $R^2 = 0.95$). In controls ($n = 2$), MT+ did not respond to ILD motion at any level ($p > 0.1$; $R^2 = 0.31$). These results were consistent over a range of thresholds used to define the MT+ ROI. Additionally, the response within the ventral occipito-temporal ROI of subject MM did not show a linear dependence on ILD motion strength ($R^2 = 0.01$).

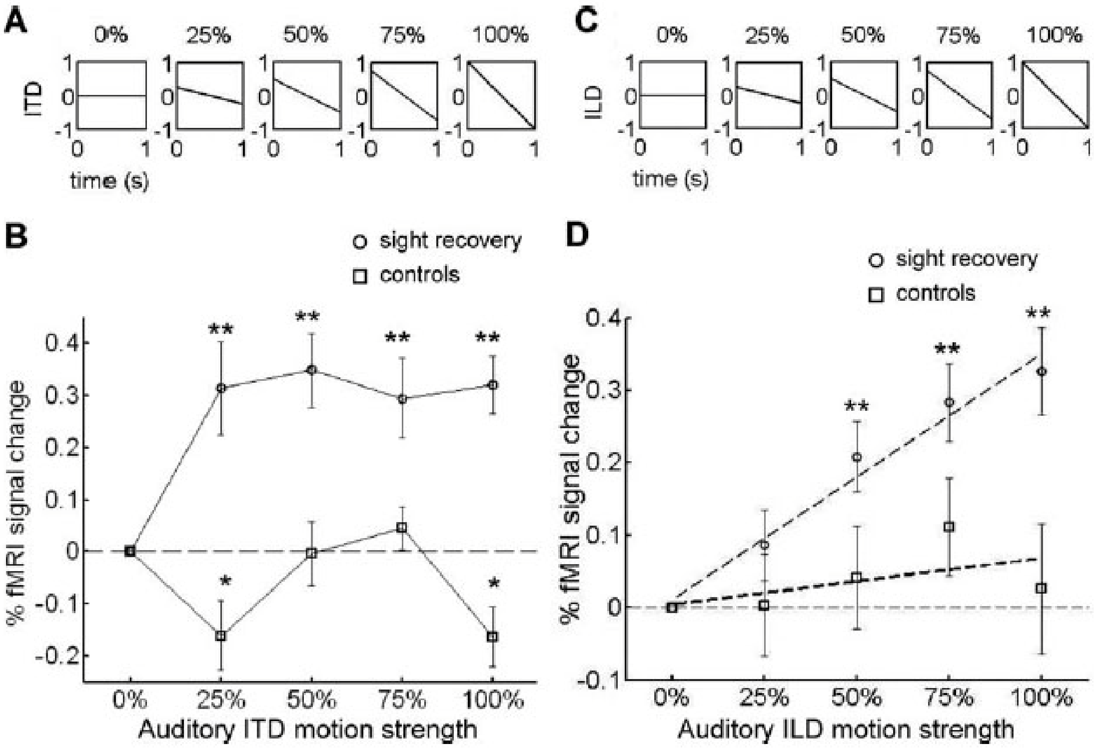


Figure 25: Study 2: Experiment 3: MT+ responds to a range of auditory motion strengths. (**A)**, For ITD motion, interaural temporal differences were linearly ramped from positive to negative (e.g., leading in left ear to leading in right ear, or vice versa). The slope of the ITD ramp was parametrically varied using even increments. The 0% condition (stationary perception, no temporal lags) and the 100% condition (temporal lag ramped from +1 to -1 ms during the stimulus duration of 1 s) were equivalent to the stationary and moving conditions of Experiment 2. (**B)**, MT+ responses (% fMRI signal change) to each motion condition are relative to the response to the 0% (stationary) condition for sight-recovery subjects ($n = 2$) and controls ($n = 2$). MT+ responded to all ITD motion strengths within sight-recovery subjects, but not controls. (**C)**, For ILD motion, interaural level (volume) differences were linearly ramped from positive to negative (e.g., louder in left ear to louder in right ear, or vice versa), with the slope again varying between 0% (stationary) and 100% (volume difference ramped from positive to negative maximum value). (**D)**, MT+ responses to each motion condition are plotted relative to the 0% (stationary) condition. MT+ responses increased linearly (R^2=0.97) with ILD motion strength within sight-recovery subjects, but not controls. Error bars denote SEM. Asterisks denote significant differences from zero (*p<0.05; **p<0.01).

(5.4) CONCLUSIONS

To summarize, we have shown that (1) MT+ responded to two types of auditory motion as a result of cross-modal plasticity in two sight-recovery subjects and did not respond to either type of auditory motion in visually normal controls; (2) this auditory response in MT+ was motion-specific and could not be attributed to volume changes, a peripheral bias, or a responsiveness to complex or changing auditory stimuli, in general; and (3) MT+ responded to a range of auditory motion strengths, consistent with high sensitivity to visual motion in MT+ of normally sighted subjects. Furthermore, these results demonstrate for the first time that robust and specific auditory responses coexist with regained visual responses after sight recovery after long-term blindness.

Experiment 3 demonstrated that MT+ in the sight-recovery subjects was sensitive to a range of auditory motion strengths. One possible explanation for the observed linear dependence with ILD motion stimuli (but not ITD) is that with the ILD stimulus the motion information, such as the noise, is carried by the volume. Previous results in normally sighted subjects have shown that MT+ population responses increase linearly when the visual motion signal is increased relative to noise (i.e., visual motion coherence) (Rees, Friston & Koch, 2000), whereas MT+ responses as a function of speed are relatively invariant.

Previous Studies of Cross-modal Responses in MT+

In subjects MM and MS, we do not know to what extent cross-modal plasticity occurred during their years of blindness or in the time after sight recovery (or both). MM's and MS's sight had been restored for over 7 and 10 years, respectively. Thus, cross-modal responses coexist with restored visual responses in MT+, even many years after sight recovery in adulthood.

A previous study of early-blind subjects reported auditory ILD motion responses in a region consistent with MT+ location, and we have replicated this result in five blind subjects (data not shown), suggesting that similar cross-modal responses may exist in individuals who are still blind (Poirier et al., 2005, Poirier et al., 2006). However, as described above, it is not possible to functionally verify MT+ location in subjects who are blind. Nor did Poirier et al. (2005, 2006) test whether the responses that they found near the presumed location of MT+ were selective for motion stimuli. Interestingly, another study in early-blind subjects reported acquired tactile motion responses in a region consistent with MT+ (Ricciardi et al., 2007). Independent of when plasticity occurred in our sight recovery subjects, what is remarkable is the specificity of the acquired MT+ response to auditory motion and the consistency of these findings across two rare individuals.

Some previous studies have measured both auditory and visual motion responses in normally sighted subjects. In these studies, auditory motion stimuli were found to have a suppressive effect (Lewis et al., 2000) or no effect (Baumann & Greenlee, 2007) on MT+ responses. More recently, Alink, Singer & Muckli, 2008) found that MT+ responses to combined audiovisual motion stimuli were modulated by whether or not the auditory and visual stimuli moved in congruent directions. Overall, these studies suggest a modulatory, but not driving, effect of auditory motion on MT+ responses in normally sighted subjects.

Functional Specificity of Cross-modal Plasticity

Some previous studies have suggested that during cross-modal reorganization, cortical regions may retain their normal functional specialization, regardless of the input modality. For example the LOtv, a subregion of the lateral occipital complex that is normally responsive to object-related tactile and visual information, became responsive to object-related auditory information in blind and sighted users trained on a visual-to-auditory sensory substitution device (Amedi, Stern, Camprodon, Bermpohl, Merabet, Rotman, Hemond, Meijer & Pascual-Leone, 2007). Our results provide further evidence that during cross-modal reorganization, the colonization of a cortical region by a novel modality can be influenced by the normal functional specialization of the region.

Retaining *functional specificity* may make efficient use of existing neural circuitry both within and between cortical areas that are already optimized for a particular function (in this case, motion processing). One possibility is that MT+ is susceptible to "colonization" by auditory motion processing because the computational principles underlying the representation of auditory motion may have similarities to those underlying the representation of visual motion. A second possibility, not mutually exclusive with the first, is that retaining *functional specificity* may help a colonized area to continue to play its functional role within a pathway of multiple cortical areas.

However, as suggested by the results from other ROIs in *Study 1*, it may not be the case that all instances of cross-modal plasticity retain *functional specificity*. Some studies report that in blind subjects, early visual areas are recruited to serve verbal and memory functions that do not clearly map onto to the known function of the visual cortex (Amedi et al., 2003; Burton et al., 2002b; Ofan & Zohary, 2007; Raz, Amedi & Zohary, 2005). In these cases, cross-modal plasticity could potentially lead to competition between the acquired function and any later restored visual function. In the case of MT+, we speculate that the preservation of motion responses by cross-modal plasticity may even contribute to the relatively good restoration of visual motion perception (compared with acuity and form perception) that has been consistently reported within the few documented accounts of sight recovery after long-term, early blindness (Fine et al., 2003; Gregory & Wallace, 1963; Sacks, 1995).

This work will have significant implications for clinical strategies guiding rehabilitation and sensory restoration in visually-impaired individuals, particularly in light of the increasing frequency of such efforts.

Sections of Chapter 5 are based on material from a paper in Journal of Neuroscience, 2008 [Saenz, M., Lewis, L.B., Huth, A.G., Fine, I., & Koch, C. (2008). Visual motion area MT+/V5 responds to auditory motion in human sight-recovery subjects. *Journal of Neuroscience*, 28(20), 5141-5148]. Dr. Saenz was the primary investigator and author of this paper; the dissertation author was the second author of this paper.

DISCUSSION

This work, by explicitly comparing a variety of tasks across both tactile and auditory modalities, provides a variety of insights into the mechanisms of cross-modal plasticity in visual cortex of early blind subjects.

First, *Study 1* demonstrates a larger extent of cross-modal plasticity than has previously been shown, partially due to our protocol, and partially due to our excellent signal-to-noise ratio. This study was novel in that it compared a variety of auditory and tactile tasks within the same group of subjects – previous studies have only examined tasks within a single modality. Additionally, although we had relatively few subjects (though comparable to most other studies of blindness) we carried out a large number of repetitions/task. Compared to many previous studies, our current study had very high signal-to-noise ratio. This allowed us to use extremely conservative thresholds in determining regions of activation.

In *Study 1,* cross-modal plasticity (greater fMRI response in blind than sighted subjects) was shown in visual cortex for all tasks, with many areas showing cross-modal response for all the tasks that we tested – across much of cortex the degree of specialization underlying cross-modal plasticity seems to be relatively weak (*pluripotency*). However, in particular regions, we did find evidence for modulation based on modality or task. In dorsal-occipital and ventral regions of visual cortex, we found that responses were driven more strongly by tactile than by auditory tasks. In occipito-temporal regions of cortex, although there was no effect of modality, there was strong modulation of cross-modal response by task. The results from *Study 1* lend support to the weak version of *functional specificity* - that modulations of cross-modal plasticity based on task played an important role within this anatomical area.

Interestingly, we found a generally similar trend in these same regions of visual cortex in normally sighted subjects, when those regions were responding to visual stimuli. Visual cortex in sighted subjects exhibited a large baseline response to most visual stimuli, with only some modulation of that response depending on task. While most fMRI studies are designed to exploit the selectivity of occipital cortex, it is very relevant to this study that visual cortex in fact shows a surprising amount of *pluripotency* – most regions of visual cortex respond to most stimuli. It seems likely that *pluripotency* is to some extent an inherent property of visual cortex: for visual tasks in normally sighted subjects, and for cross-modal tasks in the case of early blindness.

In *Study 2*, we conducted a direct investigation of task-dependent modulation of this response in occipital-temporal areas. We specifically examined the strong version of the *functional specificity* hypothesis - that cross-modal processing of non-visual tasks in visual cortex of blind subjects might systematically map onto sub-regions specialized for similar visual processing in normally sighted subjects, i.e. we tested for selective responses to auditory motion processing in visual motion area MT+/V5, an area strongly implicated in visual motion processing (Tootell et al., 1995; Watson et al., 1993). In *Study 1*, while this ROI probably included a number of visual areas, it probably overlapped significantly with area MT+ (consistent with the idea that these ROIs included MT+, strong auditory motion responses were evident within this ROI in *Study 1*).

In *Study 2* we found that (1) MT+ responded to two types of auditory motion as a result of cross-modal plasticity in two sight-recovery subjects and did not respond to either type of auditory motion in visually normal controls; (2) this auditory response in MT+ was motion-specific and could not be attributed to volume changes, a peripheral bias, or a responsiveness to complex or changing auditory stimuli, in general; (3) MT+ responded to a range of auditory motion strengths, consistent with high sensitivity to visual motion in MT+ of normally sighted subjects; and (4) MT+ was sensitive to a range of auditory motion strengths. These results confirm that, at least in the occipito-temporal region, task-specific modulation found in *Study 1* is related to the normal function of the area. These results further demonstrate for the first time that cross-modal responses can coexist with regained visual responses after sight recovery after long-term blindness.

Much remains to be learned about the nature of cross-modal responses in MT+. One question is where these cross-modal signals originate. As described above, multiple mechanisms for cross-modal plasticity have been proposed including the growth of new axons, altered synaptic pruning during development, and the unmasking of cross-modal connections that are weak, modulatory, or silent in the mature brain (Bavelier & Neville, 2002; Pascual-Leone et al., 2005). Projections from auditory cortex to primary visual cortex have been reported in the adult primate (Falchier et al., 2002; Clavagnier et al., 2004), but there have been no reports yet of direct projections between auditory cortex and MT+. Nearby multisensory regions of the temporal lobe are a potential source of cross-modal connections to MT+ during cross-modal reorganization (Beauchamp, 2005).

Our finding that sight recovery patients show “hybrid” responses, to both visual and auditory stimulation has important implications for sight recovery procedures. Improved knowledge of how visual and auditory responses interact in sight-recovery patients may be important in aiding patients to achieve optimal use of their restored vision. For example, in our sight-recovery subjects, it remains an open question to what extent single neurons in MT+ respond to both visual and auditory motion and whether these neurons show directional tuning. Neither subject MM nor MS reported obvious difficulty in distinguishing visual from auditory events or synesthetic motion perceptions. However, cross-modal interactions, in which auditory stimulation influences visual motion perception, are measurable even in visually normal subjects (Sekuler, Sekuler & Lau, 1997; Seitz, Kim & Shams, 2006; Brooks, van der Zwan, Billard, Petreska, Clarke & Blanke, 2007). Additional testing will be needed to determine whether audiovisual interactions are enhanced in sight-recovery patients.

Intuitively, cross-modal reorganization of visual cortex as a result of blindness might seem to be strictly beneficial; rather than the visual cortex going unused, it is instead used as a resource for improved processing of the remaining senses. However, in recent years there has been an increasing number of revolutionary clinical procedures designed to restore (with varying levels of success) vision in the visually-impaired, such as restorative surgeries, sensory prostheses, and rehabilitative training. The question then arises: how does cross-modal plasticity interact with restored vision?

Although cross-modal plasticity presumably plays a positive role during blindness, if the original cause of blindness is removed cross-modal processing of other senses could be detrimental to visual restoration. One possibility is that cross-modal plasticity may “usurp” connections normally devoted to the missing sense. If allocation of visual cortex to other senses is irreversible, cross-modal processing could decrease the ability of visual cortical neurons to process restored visual input. According to this model, those visual cortical regions that show the most cross-modal plasticity will show the greatest deterioration in their ability to respond appropriately to vision once sight has been restored.

There seems to be an overall assumption in the literature that this possibility is the case; cross-modal plasticity in blind subjects may usurp occipital neurons, such that those neurons are no longer able to process visual information (for a review see Merabet et al., 2005). This has obvious negative implications for visual restoration/prostheses. However, this assumption seems to very much rest on research from deaf subjects, in which subjects who show high metabolic activity in auditory cortex (presumably due to processing of other senses) show the least benefit from cochlear implants (i.e. Lee, Lee, Oh, Kim, Kim, Chung, Lee & Kim, 2001). Additionally, cochlear implant users who have been deaf from an early age show larger amounts of cross-modal plasticity, and less ability to make sense of auditory input (Harrison, Gordon & Mount, 2005; Sharma, Dorman & Kral, 2005).

It is not entirely clear, though, whether it is appropriate to generalize from auditory cortex to visual cortex. Furthermore, although it is presumed that metabolic activity in the deprived cortex is related to processing of other senses, the relationship of metabolic activity to cross-modal processing is not directly confirmed.

In the blind literature, several studies have used TMS to investigate in blind subjects the relationship between induced phosphenes and neuronal function in visual cortex (Cowey & Walsh, 2000; Gothe, Brandt, Irlbacher, Roricht, Sabel & Meyer, 2002; for a review see Theoret et al., 2004). The likelihood of phosphene elicitation has in fact been found to be correlated with extent of blindness; the less residual visual functioning a blind subject exhibits, the less likely he or she is to perceive phosphenes during stimulation (Gothe et al., 2002)[29]. Subjects with severe blindness (no light perception) only rarely perceive phosphenes; this finding suggests that the more severe blindness is, the more abnormal visual cortical functioning is. This might further be taken to imply that the more severe blindness is, the more cross-modal plasticity there is – the low likelihood of phosphene perception in severely blind subjects in response to TMS may be due to increased cross-modal processing of other senses in visual cortex, suggesting a detrimental effect of cross-modal plasticity on visual processing (Theoret et al., 2004). However, again, although it is presumed that reduced

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[29] However the majority of blind subjects who participated in this study were late blind, and had visual experience at some point in their lives. It would be interesting to see this experiment also implemented for early vs. late blind subjects.

phosphene elicitation in the deprived cortex is related to processing of other senses, the relationship of phosphene sensitivity to cross-modal processing is not directly confirmed.

Alternatively, it is possible that cross-modal plasticity may have beneficial effects, maintaining neuronal activity within cortical areas that would otherwise be silent and consequently susceptible to neural degeneration. If so, those regions that show most cross-modal plasticity will show a greater ability to recover once visual input is restored. According to this model, early-deafened subjects show more cross-modal plasticity and less recovery of auditory function simply because sensory systems are more plastic at a younger age, not because of direct competition between auditory and visual senses.

The present findings in *Study 2,* of course, show that regained visual responses can coexist with cross-modal responses in visual cortex. This suggests that cross-modal processing in visual cortex (at least in area MT+) in the case of blindness may not necessarily exhibit similar interference with regained senses as it exhibits in auditory cortex in the case of deafness.

Understanding the effects of cross-modal plasticity has important clinical implications. For example, it is important to understand whether these adaptations are maladaptive (or are perhaps maladaptive in particular regions or for particular functions) and may limit an individual’s ability to make use of the restored sense. On the other hand, if cross-modal plasticity serves a protective function, then this may encourage the development of cross-modal abilities in blind children. Currently, parents of children with impaired vision are often surprisingly reluctant to teach their children Braille or the use of a cane. This reluctance is partially due to encouragement of their children to make the best use of any remaining vision, with the hope that some way of curing the child’s vision loss will one day be found. If research demonstrates that the use of alternative sensory modalities has helpful rather than deleterious effects on restoration of visual function, it would encourage parents to feel that training their child to use Braille or a cane is complementary rather than competitive with their child’s potential future ability to use vision.

Sections of the Discussion are based on material from a paper in Journal of Neuroscience, 2008 [Saenz, M., Lewis, L.B., Huth, A.G., Fine, I., & Koch, C. (2008). Visual motion area MT+/V5 responds to auditory motion in human sight-recovery subjects. *Journal of Neuroscience*, 28(20), 5141-5148]. Dr. Saenz was the primary investigator and author of this paper; the dissertation author was the second author of this paper.

APPENDIX A

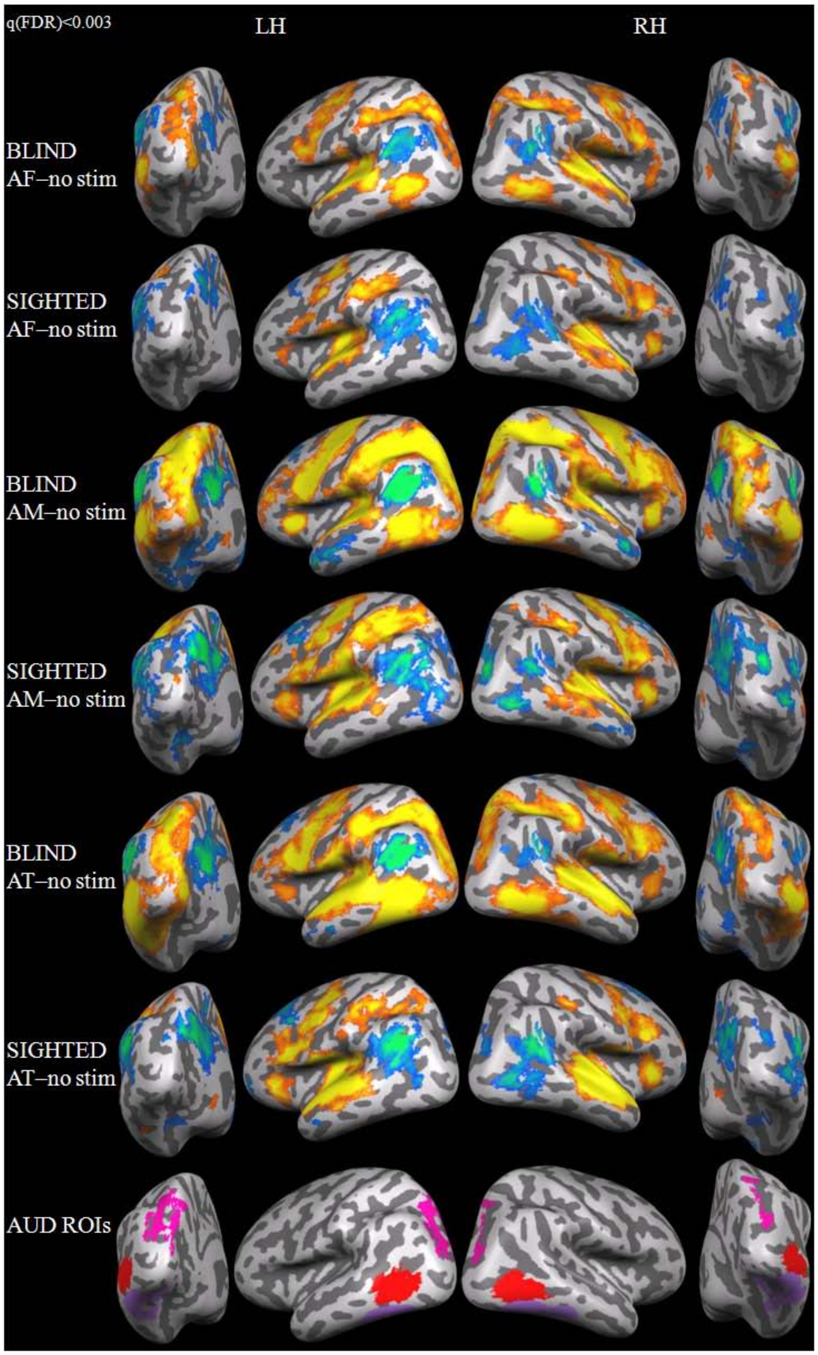


Figure A1: Study 1: BOLD response in blind and sighted subjects for all auditory tasks vs. the *no stimulus/key-press* task, and cross-modal auditory ROI ($\mathrm{AUD}_{\mathrm{OccTemp}}$, $\mathrm{AUD}_{\mathrm{DorsOcc,}}$ and $\mathrm{AUD}_{\mathrm{Vent}}$) overlays. Lateral views are presented in the center, whereas views from behind occipital pole are presented on the sides. Warm colors represent greater BOLD response to the task, cool colors represent greater BOLD response to the *no stimulus/key-press* (no stim) task. AF = *auditory frequency*; AM = *auditory motion*, AT = *auditory trigrams*; $\mathrm{AUD}_{\mathrm{OccTemp}}$ = light red, $\mathrm{AUD}_{\mathrm{DorsOcc}}$ light pink, $\mathrm{AUD}_{\mathrm{Vent}}$ = light purple; LH = left hemisphere, RH = right hemisphere. Data are conservatively thresholded at q(FDR)<0.003.

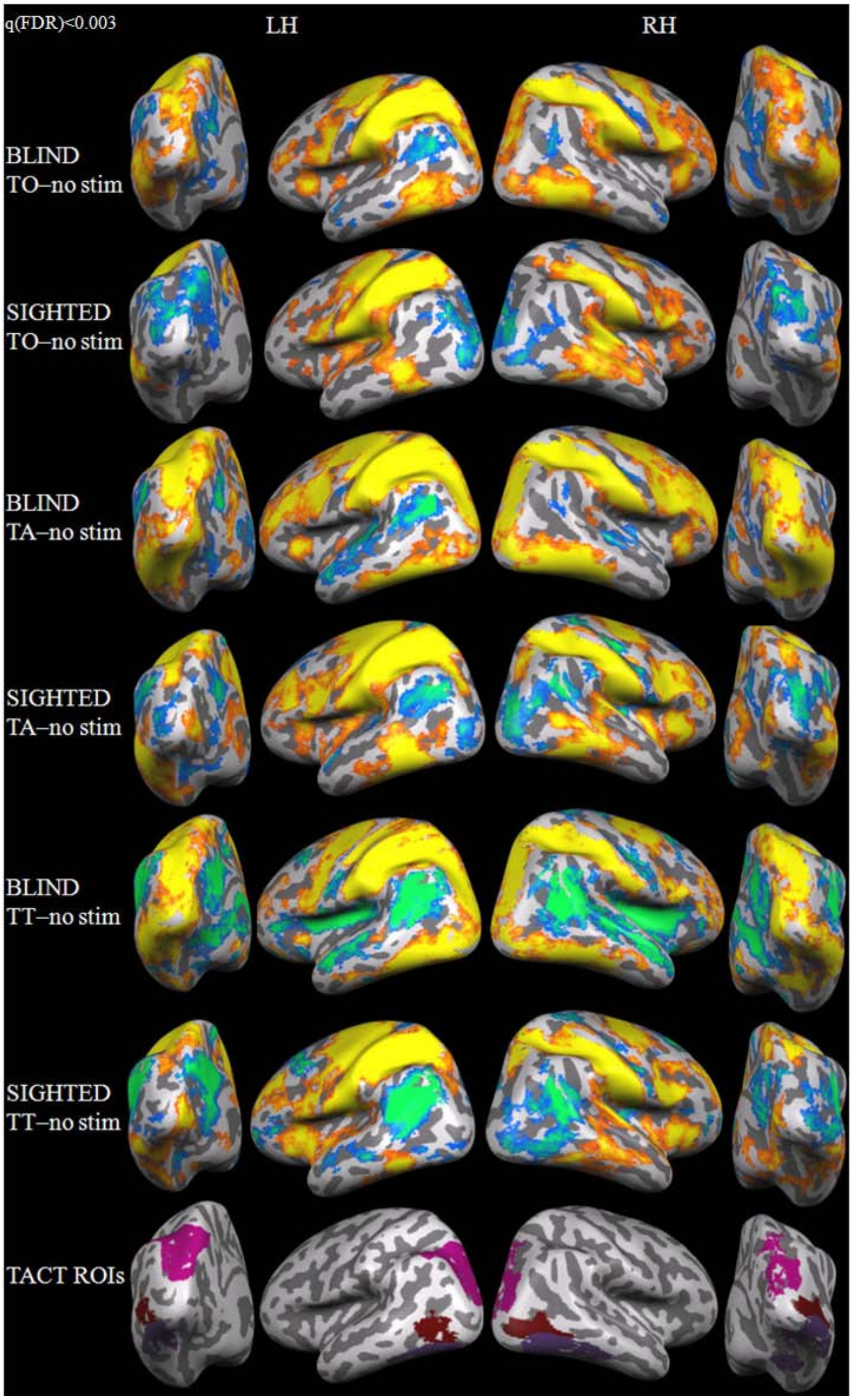


Figure A2: Study 1: BOLD response in blind and sighted subjects for all tactile tasks vs. the *no stimulus/key-press* task, and cross-modal tactile ROI ($TAC_{OccTemp}$, $TAC_{DorsOcc,}$ and TAC_{Vent}) overlays. Lateral views are presented in the center, whereas views from behind occipital pole are presented on the sides. Warm colors represent greater BOLD response to the task, cool colors represent greater BOLD response to the *no stimulus/key-press* (no stim) task. AF = *auditory frequency*; AM = *auditory motion*, AT = *auditory trigrams*; $TAC_{OccTemp}$ = dark red, $TAC_{DorsOcc}$ dark pink, TAC_{Vent} = dark purple; LH = left hemisphere, RH = right hemisphere. Data are conservatively thresholded at q(FDR)<0.003.

Regions Showing Larger Responses for Tactile Tasks in Sighted than Blind Subjects

In the case of auditory cortex we saw bilaterally larger BOLD responses in sighted than in blind subjects across all three tactile tasks, though these differences were relatively small for the *tactile orientation* task as compared to the other two tactile tasks (see Figure 7 in main text). As will be described below, auditory cortex is one of the two areas where we consistently found a difference in cross-modal responses between auditory and tactile stimuli.

There were large differences in cross-modal BOLD responses between sighted and blind subjects bilaterally within the supramarginal gyrus at the posterior end of the lateral fissure (Brodmann area 40) for the *tactile animals* and *tactile trigrams* tasks (much smaller differences between sighted and blind subjects were seen in this area for the *tactile orientation* task). These effects may have been due to the tactile tasks being easier for blind than sighted subjects. Despite carrying out a more difficult task, blind subjects performed significantly better than sighted subjects on the *tactile trigrams* task (see Figure 4). Although there was no difference in performance between sighted and blind subjects on the *tactile animals* and *tactile orientation* task, mean performance on these tasks was always above 90%. Ceiling effects may have masked differences in task difficulty that could, for example, have resulted in blind subjects requiring less time to make a decision about tactile stimuli, resulting in lower activation within these areas.

In the case of the *tactile trigrams* task these differences in activation seemed to extend bilaterally to the opercular and triangular sections of the inferior frontal gyrus that contain Broca's area (Brodmann area 44). One interesting possibility is that these weaker responses in blind, as compared to sighted, subjects were due to a greater need for articulatory suppression in blind subjects for the *tactile trigram* task. Blind subjects were asked to read Braille trigrams, whereas for sighted subjects we used an easier task (an embossed Roman letter “I” for every distractor and the Roman letter "O" as the target) that was less likely to require articulatory suppression. Closer inspection of the data (see Figure A2) reveals that while sighted subjects generally show a positive BOLD response to *tactile trigrams* vs. the *no stimulus/key-press* task within this area, blind subjects generally show a negative response – providing support for the possibility of articulatory suppression.

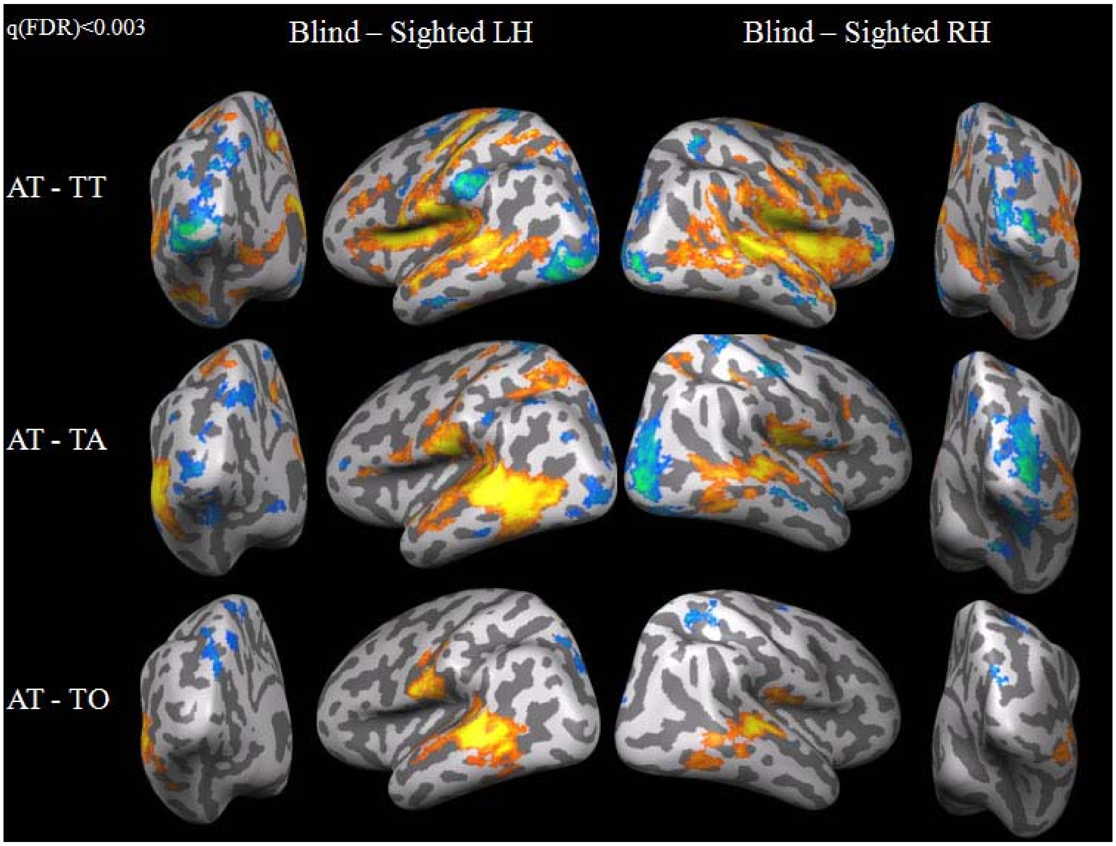


Figure A3: Study 1: *Auditory trigrams* (AT) versus each tactile task. Warm colors represent greater cross-modal plasticity in auditory tasks, cool colors represent the opposite. TT = *tactile trigrams*, TA = *tactile animals*, TO = *tactile orientation*; LH = left hemisphere, RH = right hemisphere. Data are thresholded conservatively at q(FDR)<0.003.

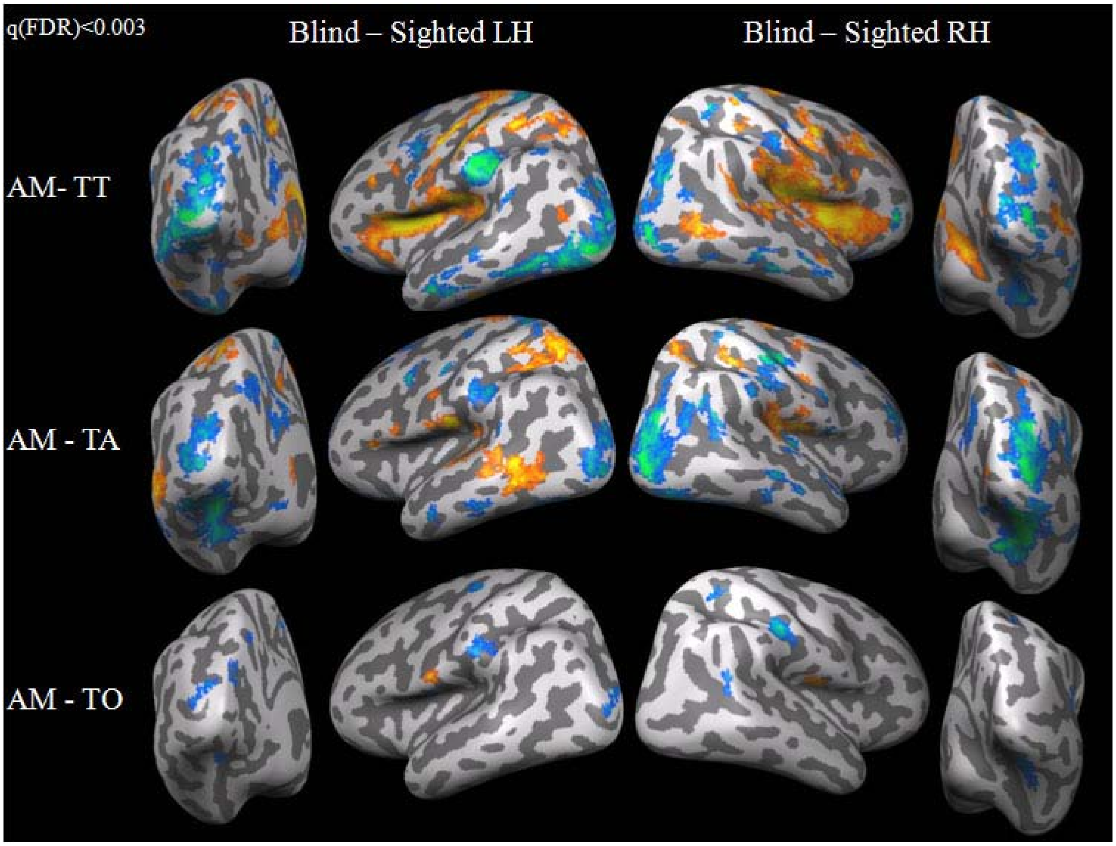


Figure A4: Study 1: *Auditory motion* (AM) versus each tactile task. Warm colors represent greater cross-modal plasticity in auditory tasks, cool colors represent the opposite. TT = *tactile trigrams,* TA = *tactile animals,* TO = *tactile orientation*; LH = left hemisphere, RH = right hemisphere. Data are thresholded conservatively at q(FDR)<0.003.

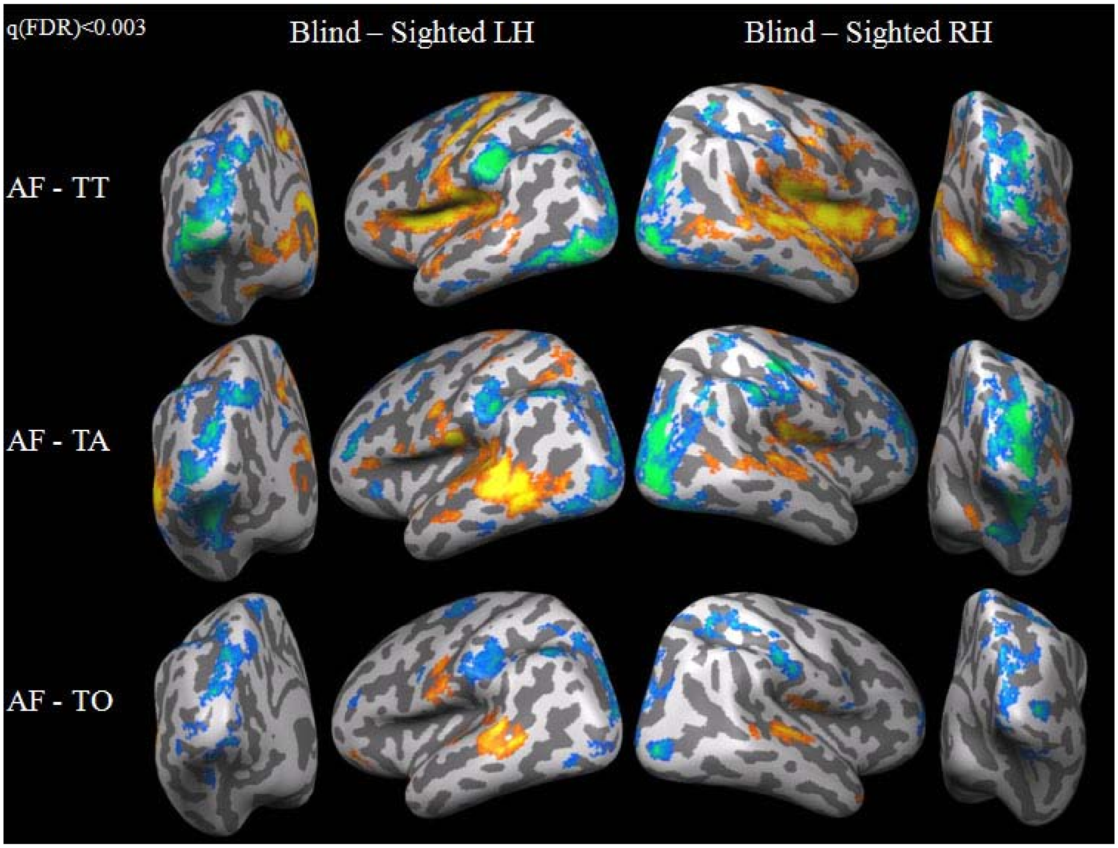


Figure A5: Study 1: *Auditory frequency* (AF) versus each tactile task. Warm colors represent greater cross-modal plasticity in auditory tasks, cool colors represent the opposite. TT = *tactile trigrams*, TA = *tactile animals*, TO = *tactile orientation*; LH = left hemisphere, RH = right hemisphere. Data are thresholded conservatively at q(FDR)<0.003.

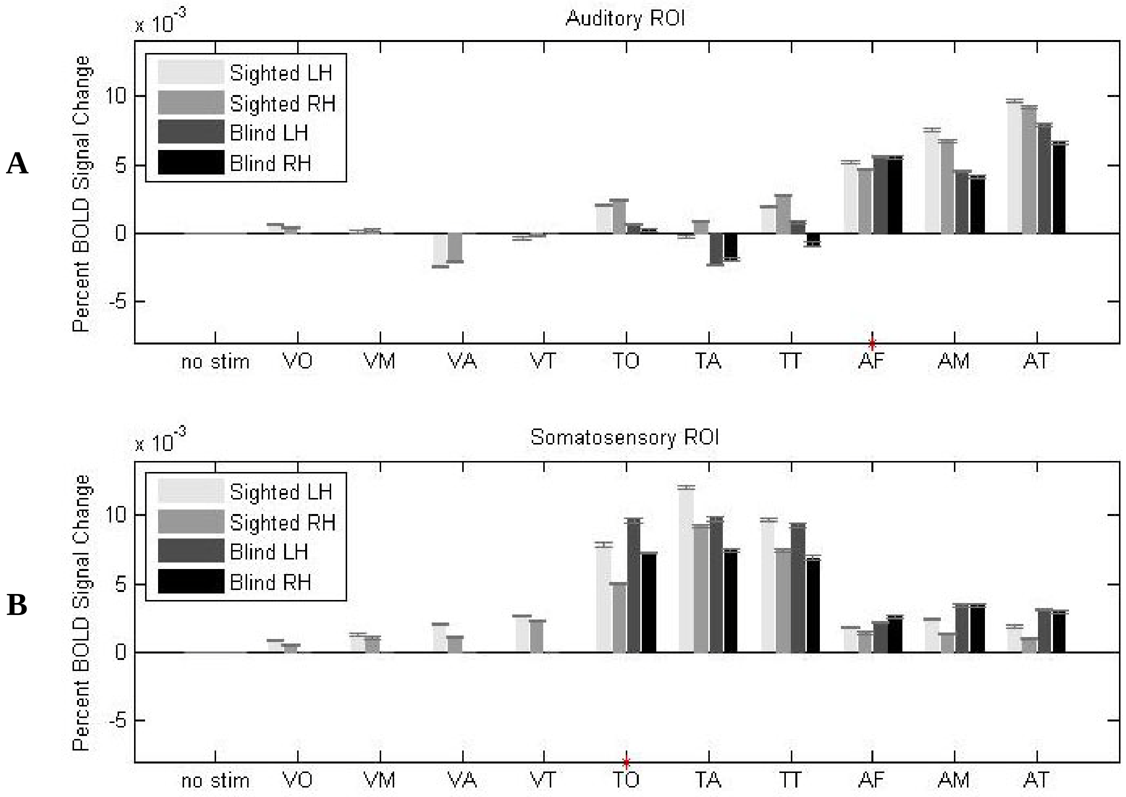


Figure A6: Study 1: Response amplitudes for sensory ROIs (auditory and somatosensory cortex), all subjects. **(A)** Auditory ROI: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. **(B)** Somatosensory ROI: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. Single standard errors are shown. No stim = *no stimulus/key-press*, VO = *visual orientation*, VM = *visual motion*, VA = *visual animals*, VT = *visual* trigrams, TO = *tactile orientation*, TA = *tactile animals*, TT = *tactile trigrams*, AF = *auditory frequency*, AM = *auditory motion*, AT = *auditory trigrams*; LH = left hemisphere, RH = right hemisphere. The task used to define each ROI is shown with a red asterisk.

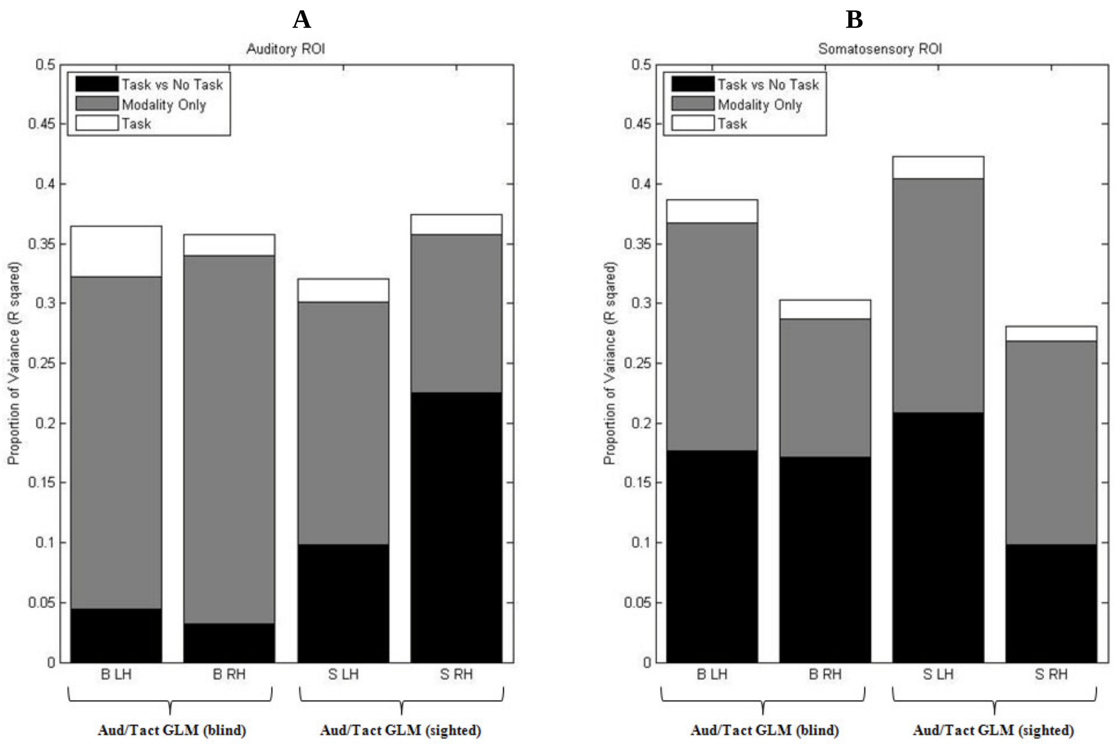


Figure A7: Study 1: ANOVA analyses [proportion of variance (R^2)] for sensory ROIs [**(A)** auditory and **(B)** somatosensory cortex ROIs)], for all subjects, explained across three different models, as described in the main text. B LH = blind subjects, left hemisphere; B RH = blind subjects, right hemisphere; S LH = sighted subjects, left hemisphere; S RH = sighted subjects, right hemisphere. “Task vs No Task” = “task vs. no task” model, “Modality Only” = “modality” model, “Task” = “Task-Specified” model.

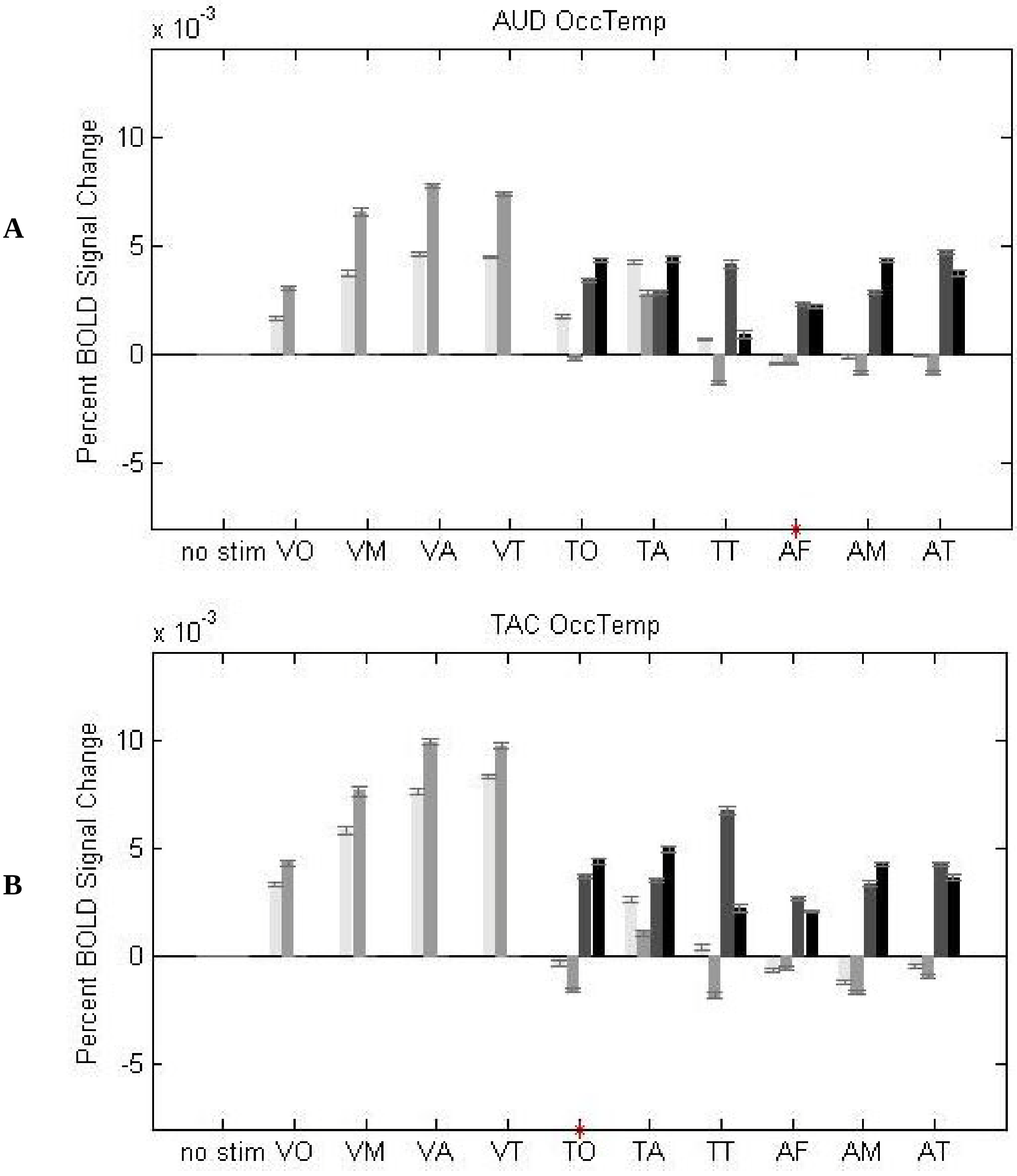


Figure A8: Study 1: Response amplitudes for cross-modal occipito-temporal ROIs ($\mathrm{AUD}_{\mathrm{OccTemp}}$ and $\mathrm{TAC}_{\mathrm{OccTemp}}$), for all subjects. **(A)** $\mathrm{AUD}_{\mathrm{OccTemp}}$: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. **(B)** $\mathrm{TAC}_{\mathrm{OccTemp}}$: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. Single standard errors are shown. No stim = *no stimulus/key-press*, VO = *visual orientation*, VM = *visual motion*, VA = *visual animals*, VT = *visual* trigrams, TO = *tactile orientation*, TA = *tactile animals*, TT = *tactile trigrams*, AF = *auditory frequency*, AM = *auditory motion*, AT = *auditory trigrams*; LH = left hemisphere, RH = right hemisphere. The task used to define each ROI is shown with a red asterisk.

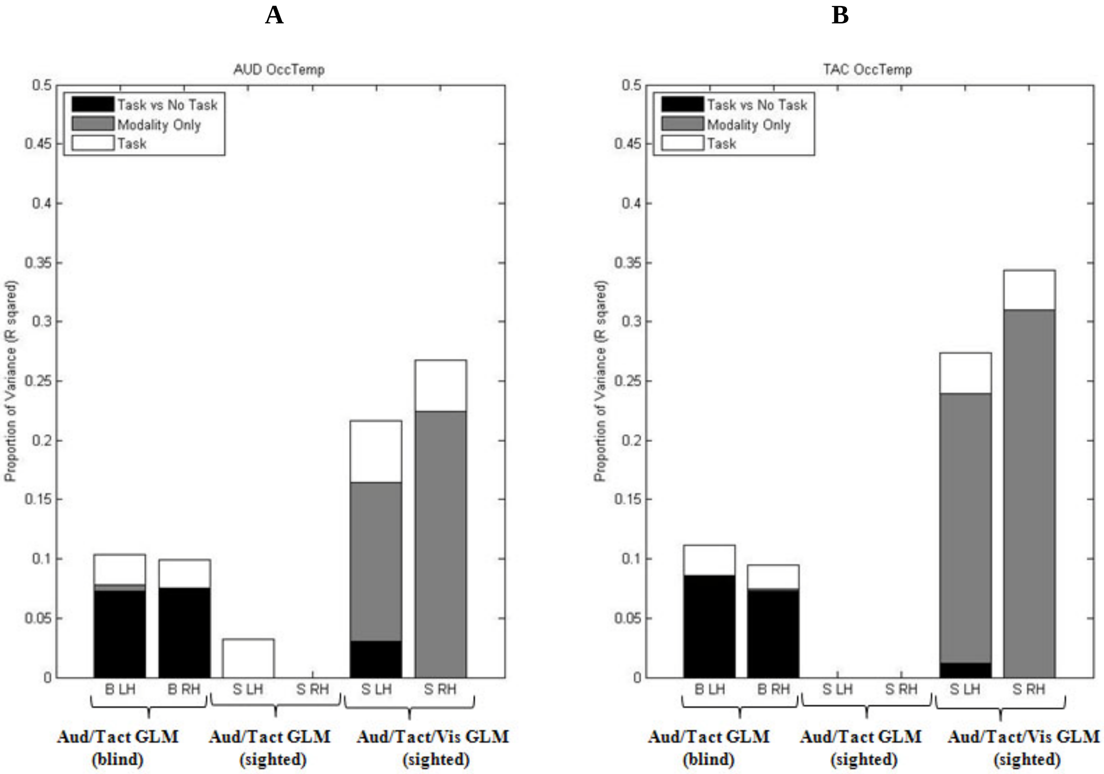


Figure A9: Study 1: ANOVA analyses [proportion of variance (R^2)] for occipito-temporal ROIs [**(A)** AUD$_{OccTemp}$ and **(B)** TAC$_{OccTemp}$], for all subjects, explained across three different models, as described in the main text. B LH = blind subjects, left hemisphere; B RH = blind subjects, right hemisphere; S LH = sighted subjects, left hemisphere; S RH = sighted subjects, right hemisphere. "Task vs No Task" = "task vs. no task" model, "Modality Only" = "modality" model, "Task" = "Task-Specified" model.

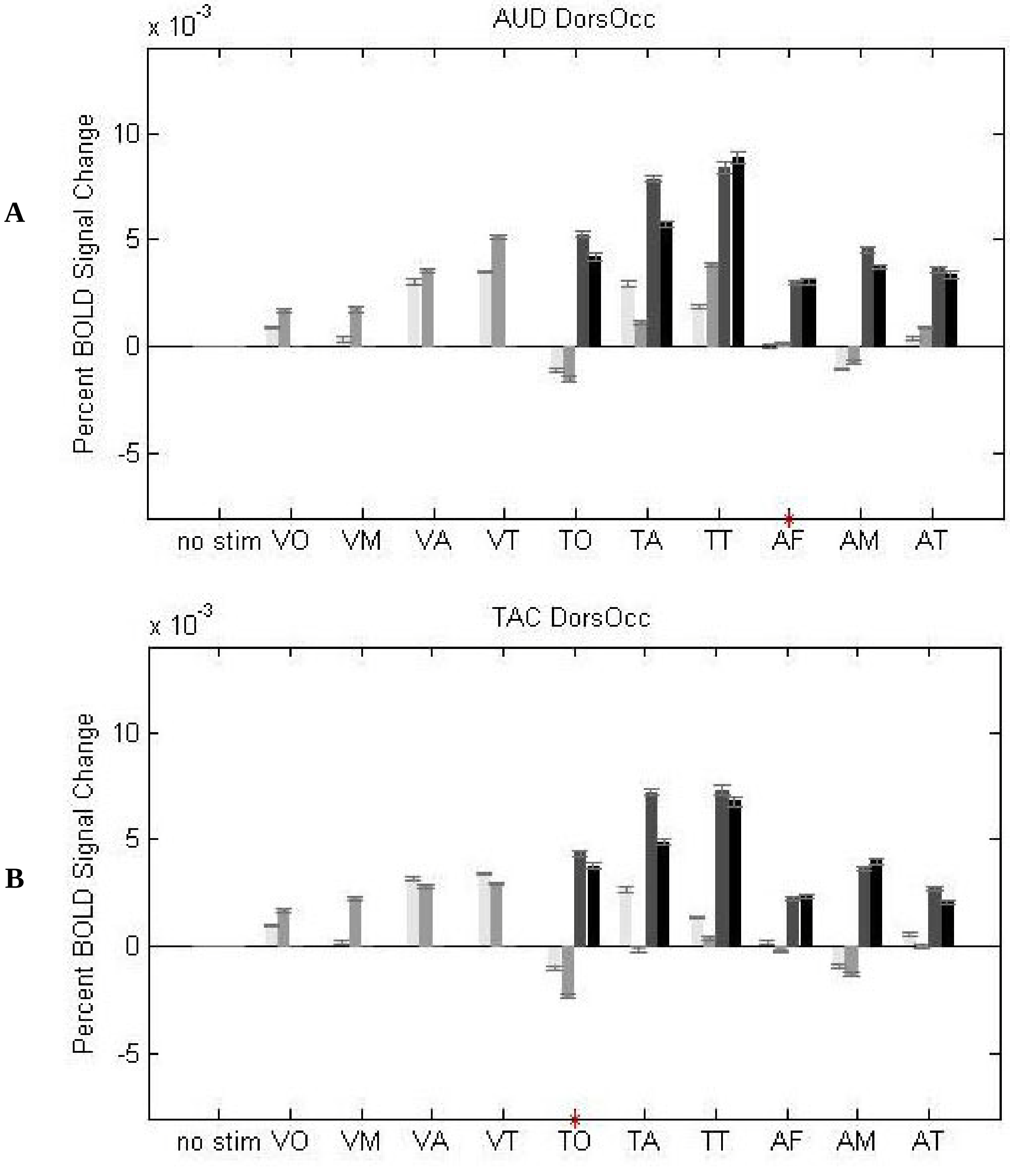


Figure A10: Study 1: Response amplitudes for cross-modal dorsal-occipital ROIs (AUD$_{\text{DorsOcc}}$ and TAC$_{\text{DorsOcc}}$), for all subjects. **(A)** AUD$_{\text{DorsOcc}}$: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. **(B)** TAC$_{\text{DorsOcc}}$: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. Single standard errors are shown. No stim = *no stimulus/key-press*, VO = *visual orientation*, VM = *visual motion*, VA = *visual animals*, VT = *visual* trigrams, TO = *tactile orientation*, TA = *tactile animals*, TT = *tactile trigrams*, AF = *auditory frequency*, AM = *auditory motion*, AT = *auditory trigrams*; LH = left hemisphere, RH = right hemisphere. The task used to define each ROI is shown with a red asterisk.

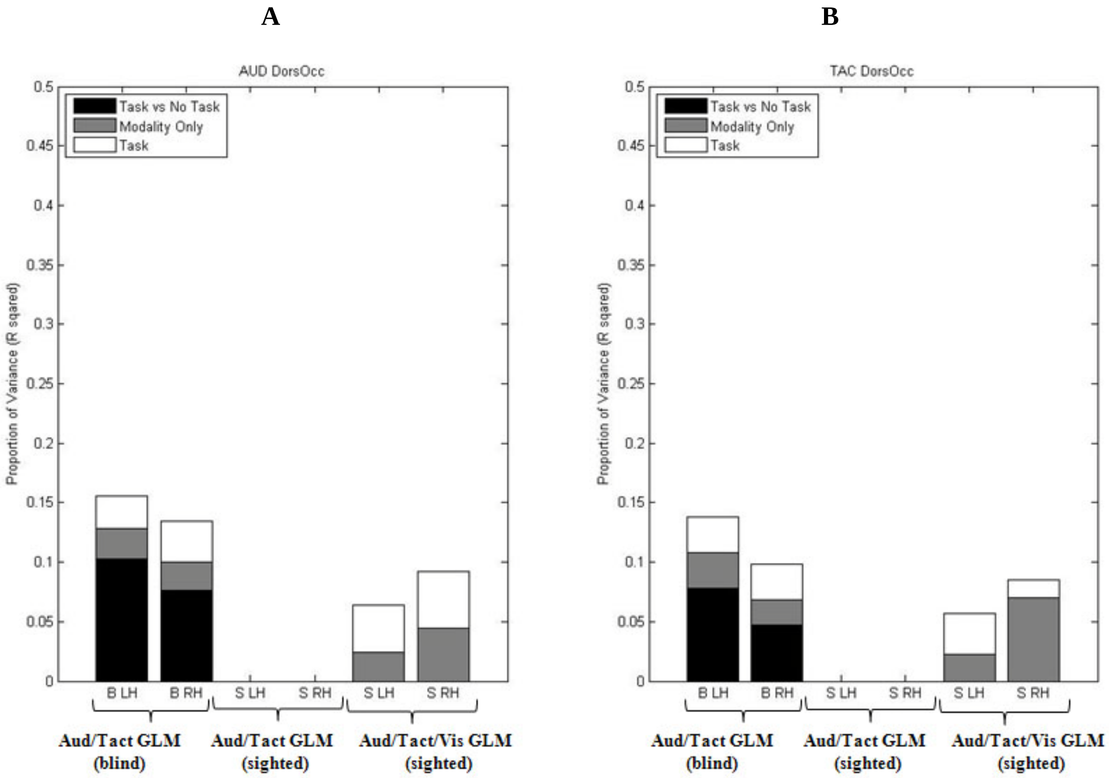


Figure A11: Study 1: ANOVA analyses [proportion of variance (R^2)] for dorsal-occipital ROIs [**(A)** $\text{AUD}_{\text{DorsOcc}}$ and **(B)** $\text{TAC}_{\text{DorsOcc}}$], for all subjects, explained across three different models, as described in the main text. B LH = blind subjects, left hemisphere; B RH = blind subjects, right hemisphere; S LH = sighted subjects, left hemisphere; S RH = sighted subjects, right hemisphere. “Task vs No Task” = “task vs. no task” model, “Modality Only” = “modality” model, “Task” = “Task-Specified” model.

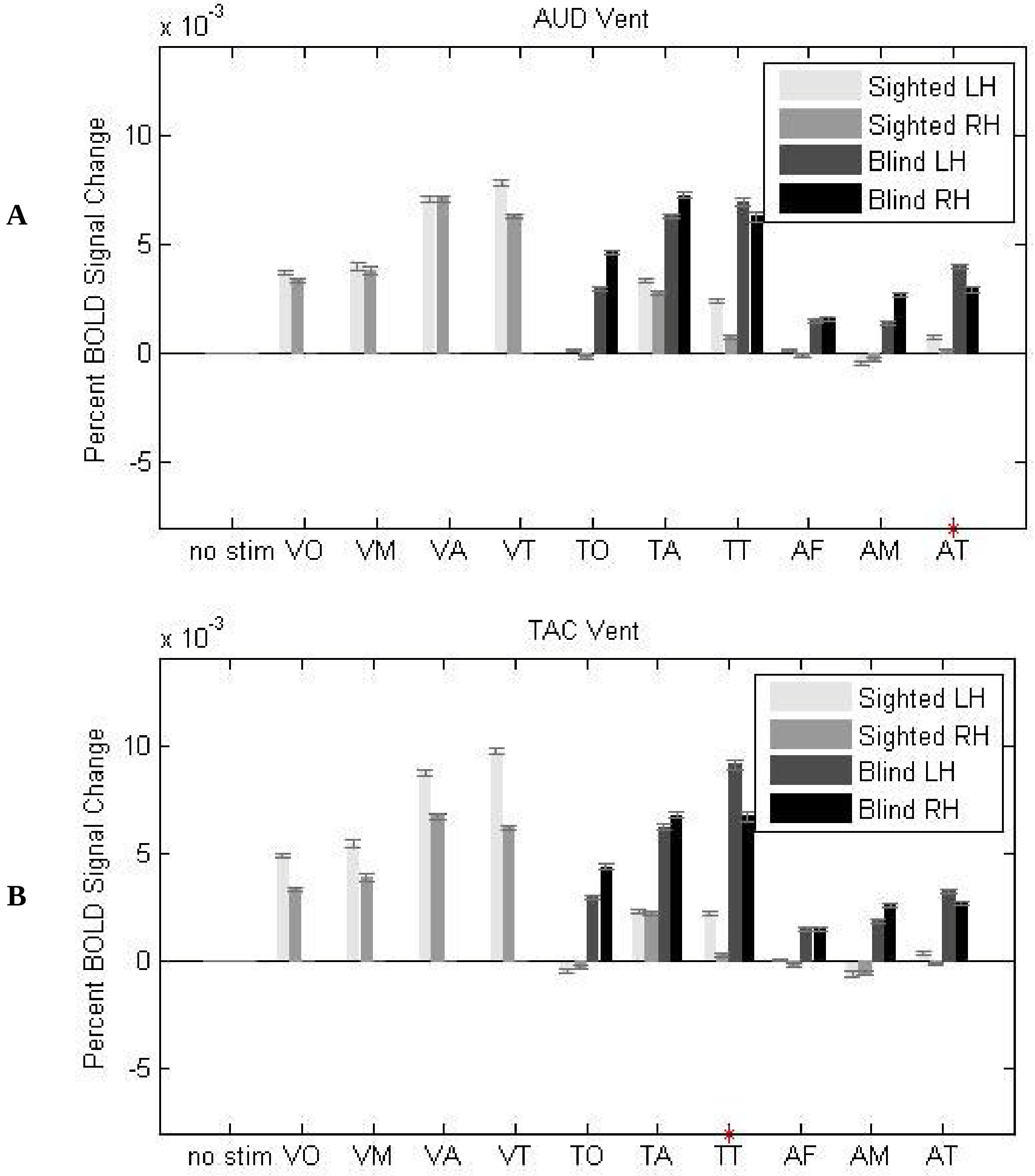


Figure A12: Study 1: Response amplitudes for cross-modal ventral ROIs (AUD_{Vent} and TAC_{Vent}), for all subjects. **(A)** AUD_{Vent}: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. **(B)** TAC_{Vent}: Percent signal change in the BOLD response for left and right hemispheres for right-handed blind and sighted subjects, across all tasks. Single standard errors are shown. No stim = *no stimulus/key-press*, VO = *visual orientation*, VM = *visual motion*, VA = *visual animals*, VT = *visual* trigrams, TO = *tactile orientation*, TA = *tactile animals*, TT = *tactile trigrams*, AF = *auditory frequency*, AM = *auditory motion*, AT = *auditory trigrams*; LH = left hemisphere, RH = right hemisphere. The task used to define each ROI is shown with a red asterisk.

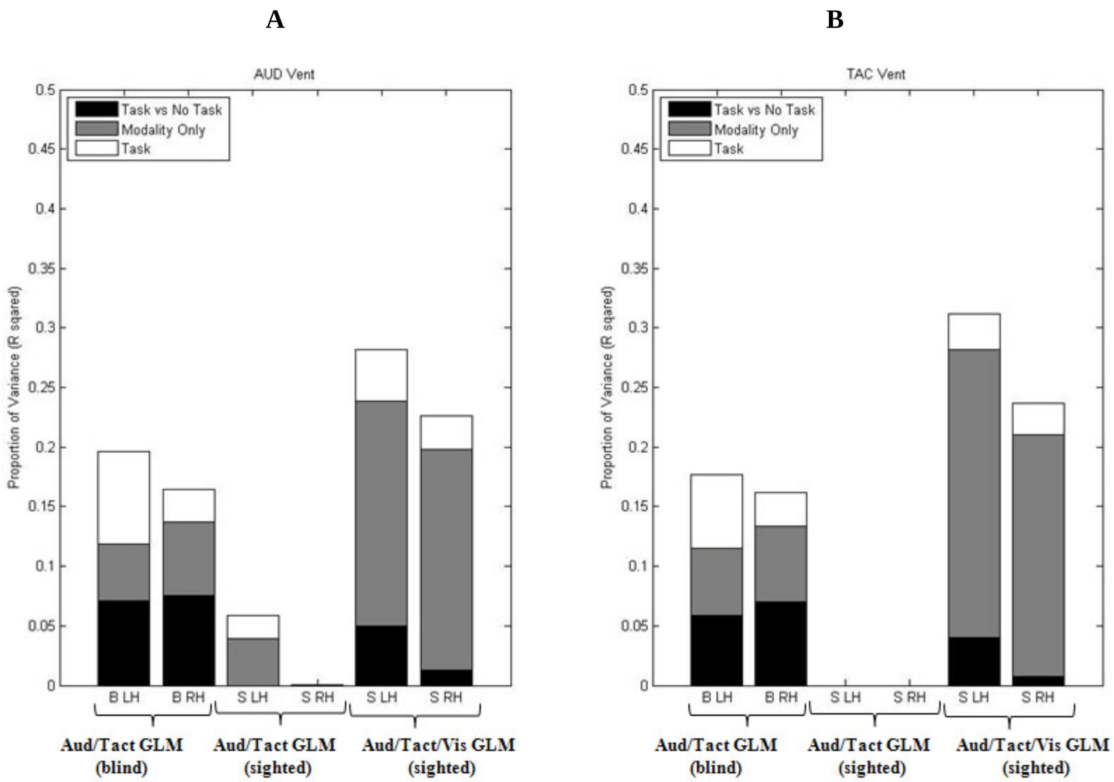


Figure A13: Study 1: ANOVA analyses [proportion of variance (R^2)] for ventral ROIs [**(A)** AUD$_{\text{Vent}}$ and **(B)** TAC$_{\text{Vent}}$], for all subjects, explained across three different models, as described in the main text. B LH = blind subjects, left hemisphere; B RH = blind subjects, right hemisphere; S LH = sighted subjects, left hemisphere; S RH = sighted subjects, right hemisphere. "Task vs No Task" = "task vs. no task" model, "Modality Only" = "modality" model, "Task" = "Task-Specified" model.

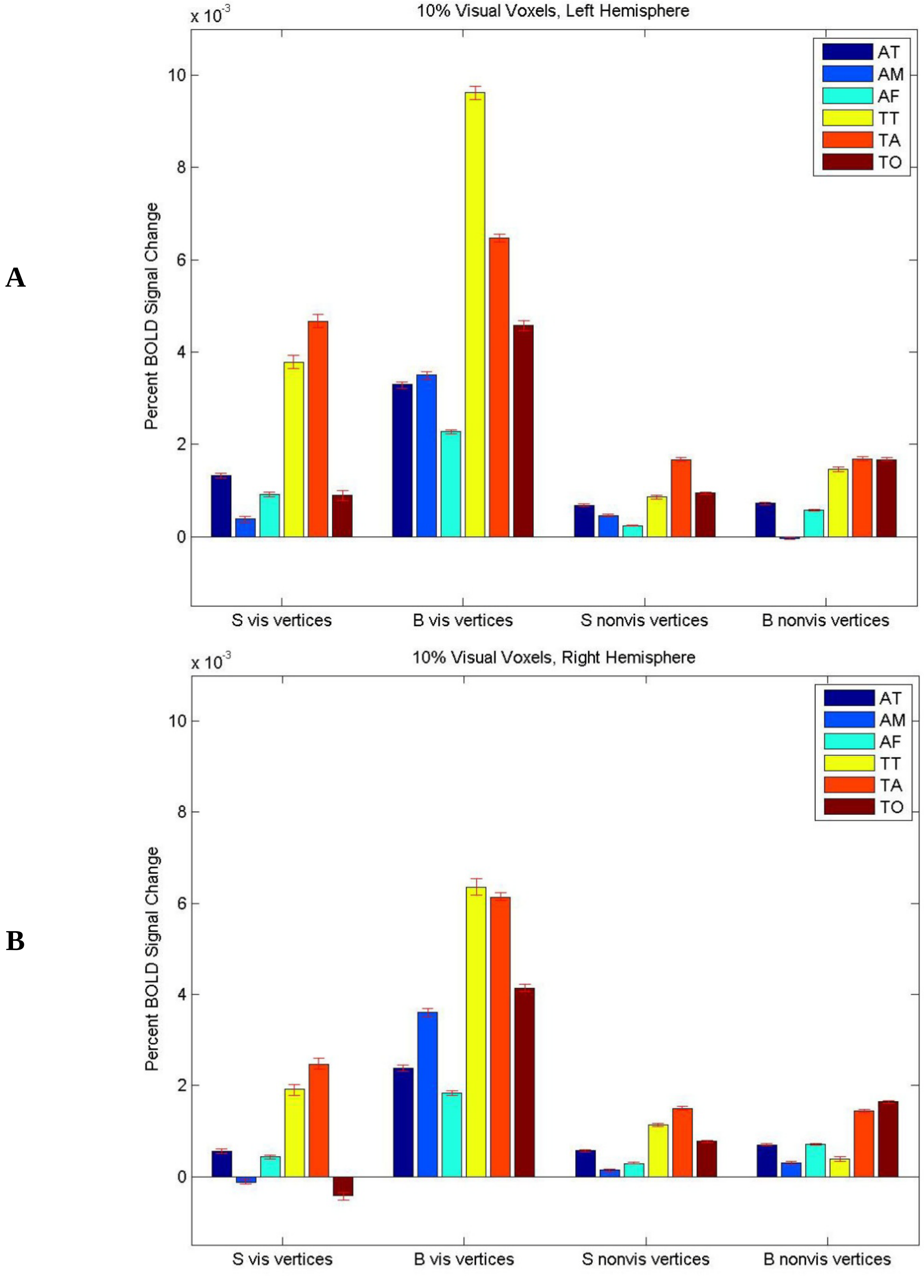


Figure A14: Study 1: Response amplitudes for all subjects across the entire cortex for 10% visual vertices in **(A)** the left hemisphere and **(B)** the right hemisphere (RH). “S” = sighted, “B” = Blind, “vis vertices” = visual vertices; “nonvis vertices” = non-visual vertices; AT = auditory trigrams, AM = auditory motion, AF = auditory frequency, TT = tactile trigrams, TA = tactile animals, TO = tactile orientation. Single standard errors are shown.

APPENDIX B

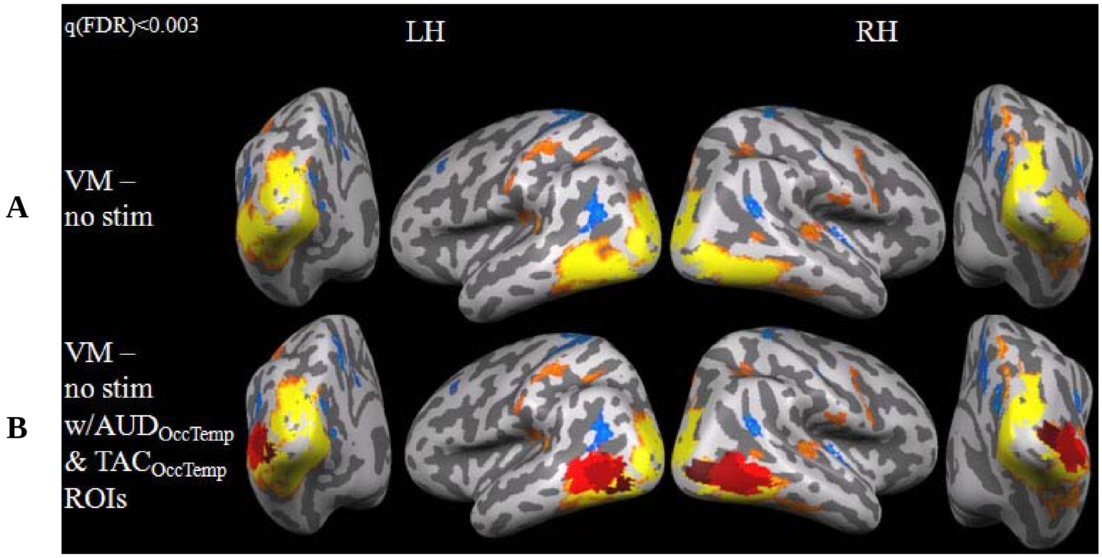
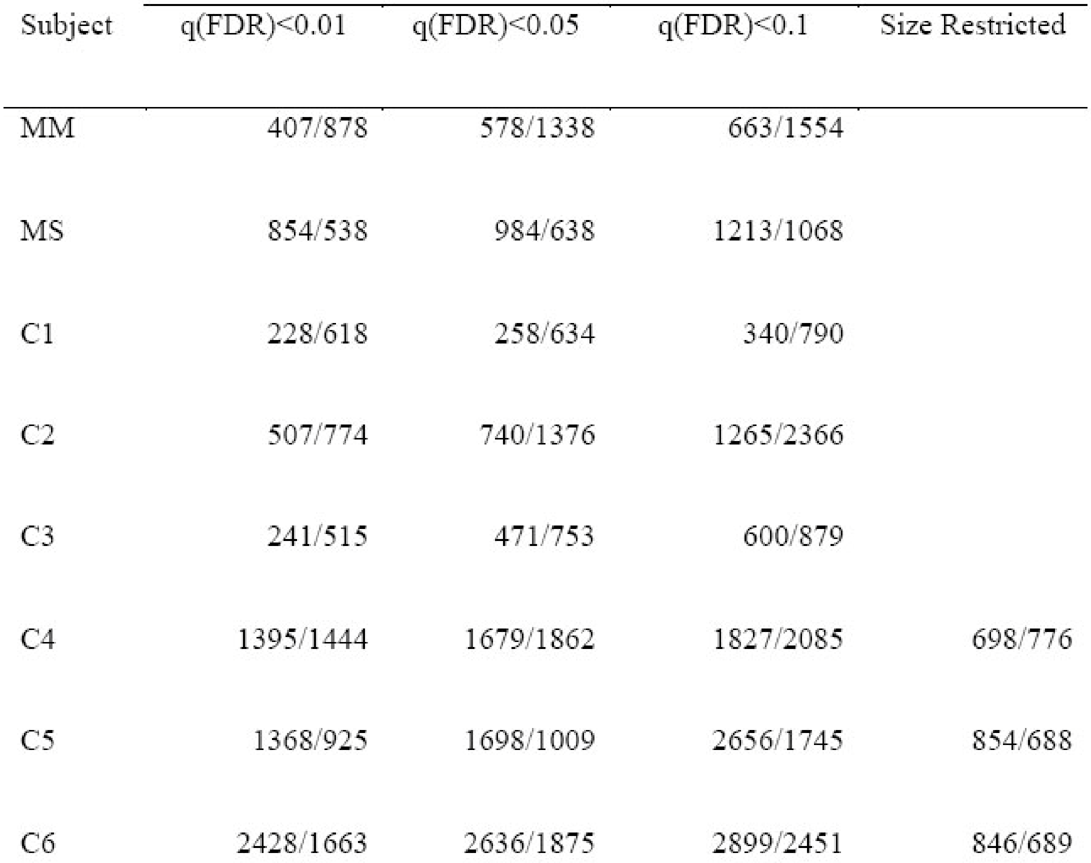


Figure B1: Study 1: Cross-modal BOLD response for the *visual motion* task (VT) vs. the *no stimulus/key-press* task (no stim) (using Vis GLM", see Table 2.) **(A)**, with cross-modal occipito-temporal ROIs (AUD$_{OccTemp}$ TAC$_{OccTemp}$) overlaid **(B)**. Lateral views are presented in the center, whereas views from behind occipital pole are presented on the sides. AUD$_{OccTemp}$ = light red, TAC$_{OccTemp}$ = dark red, overlap between AUD$_{OccTemp}$ and TAC$_{OccTemp}$ = medium red; LH = left hemisphere, RH = right hemisphere. Data are conservatively thresholded at q(FDR)<0.003.

Table B1: Study 2: Experiment 1: MT+ ROI volumes (in mm^3) over a range of thresholds used to define the MT+ ROI in the left and right hemispheres (L/R) in sight-recovery subjects MM and MS and in control subjects. ROI volumes of MM and MS were within the range found in our control subjects. Three of the control subjects (C4, C5, C6) had substantially larger ROIs. In a control analysis (last column), thresholds were further restricted in those three subjects to limit the ROI size to be no larger than the average MT+ ROI size in sight-recovery subjects at q(FDR)<0.05 (877 mm^3).



Subject	q(FDR)<0.01	q(FDR)<0.05	q(FDR)<0.1	Size Restricted
MM	407/878	578/1338	663/1554	
MS	854/538	984/638	1213/1068	
C1	228/618	258/634	340/790	
C2	507/774	740/1376	1265/2366	
C3	241/515	471/753	600/879	
C4	1395/1444	1679/1862	1827/2085	698/776
C5	1368/925	1698/1009	2656/1745	854/688
C6	2428/1663	2636/1875	2899/2451	846/689

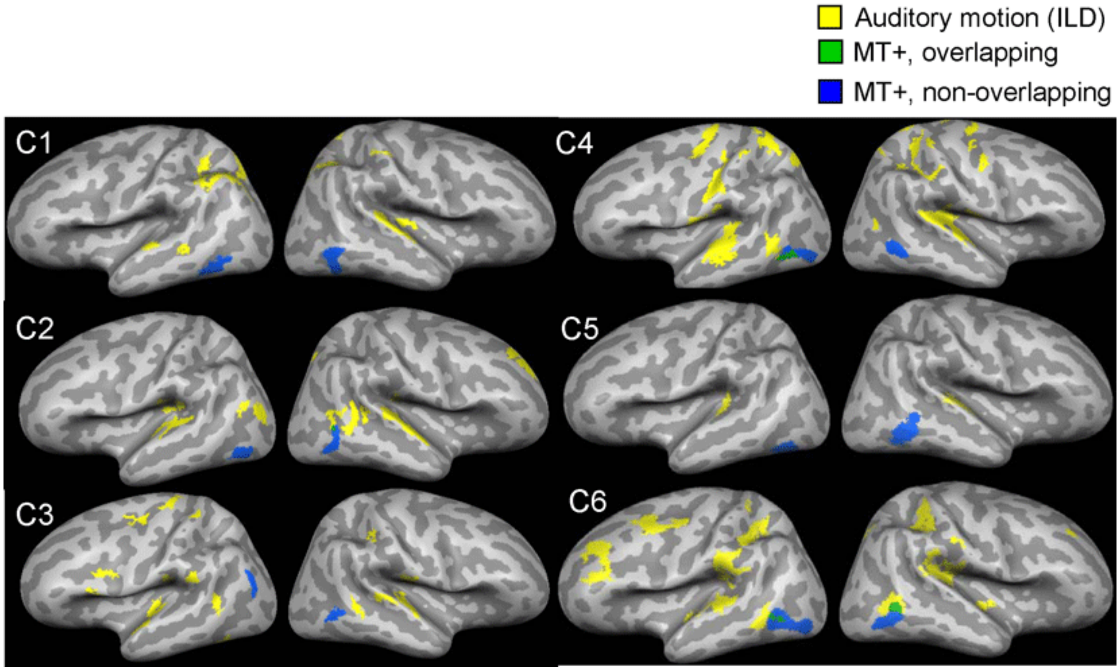


Figure B2: Study 2: Experiment 1: Individual Control Subject Responses. As in Main Figure 22, yellow regions responded more to moving (ILD) vs. stationary auditory white noise. Statistical activation maps are the result of a fixed-effects general linear model analysis (GLM) [q(FDR)<0.01]. Green and blue regions show MT+ location as determined by *visual* MT+ localizer scans run in the same subjects (green = the part of MT+ overlapped by auditory ILD motion responses, blue = the part of MT+ not overlapped by auditory ILD motion responses). Note that individual control subjects consistently showed little or no overlap (very little green). In contrast sight recovery subjects MM and MS (See Figure 22) showed near-complete overlap (very little blue).

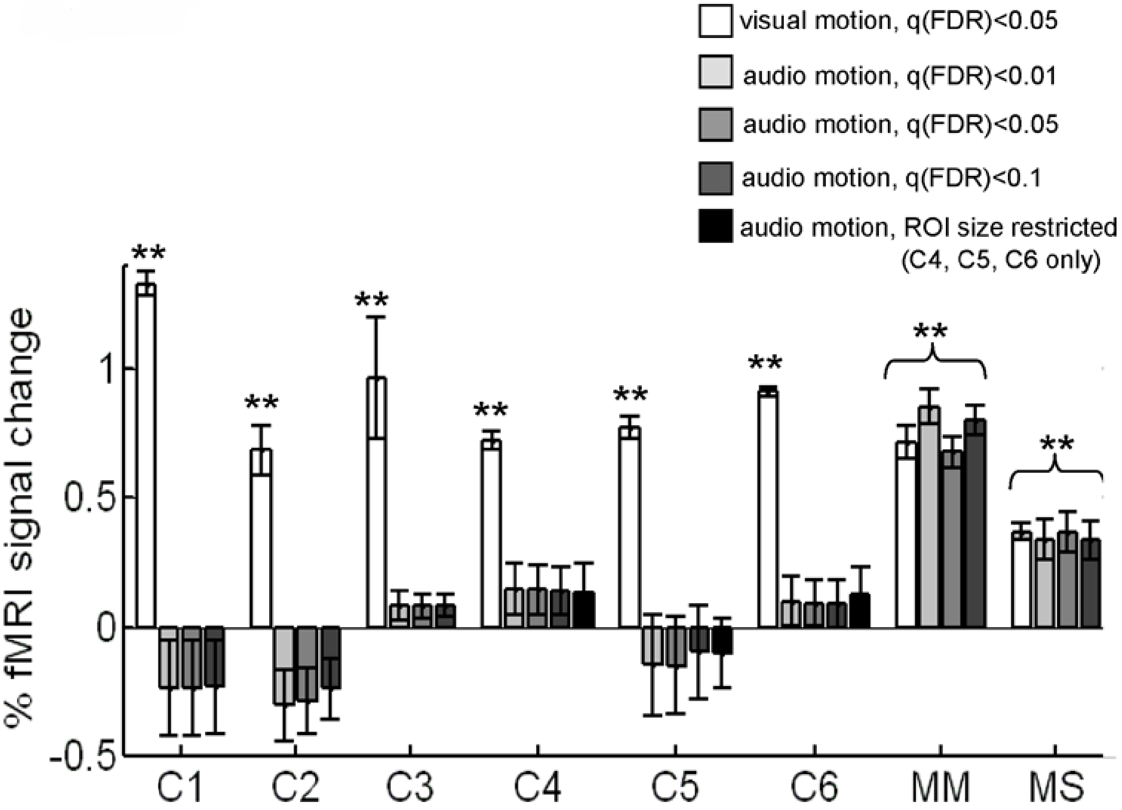


Figure B3: Study 2: Experiment 1: MT+ ROI responses are consistent over a range of thresholds used to select the MT+ ROI. As in Main Figure 23, responses (% fMRI signal change) to visual motion and to auditory ILD motion within visually-defined MT+ ROIs. Here, auditory motion responses are plotted over a range of thresholds used to define the MT+ ROIs (q(FDR)<0.01, q(FDR)<0.05, q(FDR)<0.1). Results are plotted for each subject individually. Visual motion responses were highly significant for all subjects (*p*<0.001 each bar). Auditory (ILD) motion responses were highly significant for both MM and MS at all thresholds (*p*<0.001 each bar). In contrast, MT+ did not respond have a positive response to auditory (ILD) motion in any of the individual control subject at any threshold (*p*>0.07 minimum). Only MM and MS had no significant difference between their own response to visual motion and auditory ILD motion. Error bars denote SEM. Three of the control subjects (C4,C5,C6) had substantially larger MT+ ROIs than the sight-recovery subjects at any given threshold (See Table B1 for ROI volumes). To better equate for size, thresholds were further restricted in those 3 control subjects to limit the MT+ ROI size to be no larger than the average MT+ ROI size in sight-recovery subjects (877 mm^3). The results were robust to this restriction (black bars) – there was still no significant response to ILD motion in these subjects. (*p*>0.15 minimum).

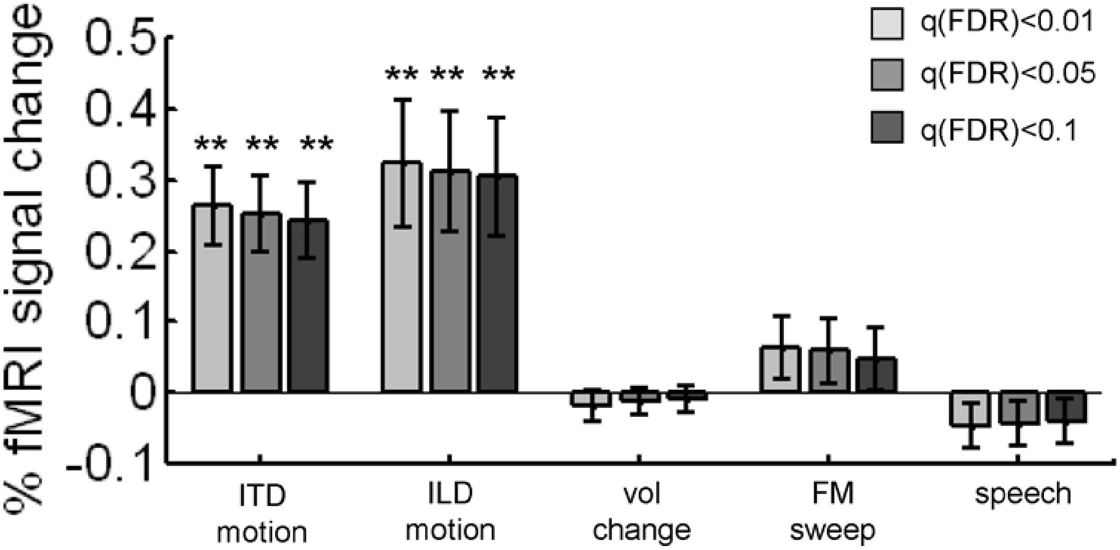


Figure B4: Study 2: Experiment 2: MT+ ROI responses are consistent over a range of thresholds used to select the MT+ ROI. As in Main Figure 24, response amplitudes (% fMRI signal change) from MM and MS to auditory ITD motion, auditory ILD motion, stationary volume changes, frequency sweeps, and human speech within the MT+ ROI. MT+ ROIs were selected at the following thresholds: q(FDR)<0.01, q(FDR)<0.05, q(FDR)<0.1. MT+ responded to both types of auditory motion at all thresholds (*p*<0.01 each bar). MT+ did not respond to the other auditory stimuli which did not induce the percept of motion (*p*>0.2 each bar). Error bars denote SEM.

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