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Species-dependent role of crossmodal connectivity among the primary sensory cortices

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Abstract

When a major sense is lost, crossmodal plasticity substitutes functional processing from the remaining, intact senses. Recent studies of deafness-induced crossmodal plasticity in different subregions of auditory cortex indicate that the phenomenon is largely based on the "unmasking" of existing inputs. However, there is not yet a consensus on the sources or effects of crossmodal inputs to primary sensory cortical areas. In the present review, a rigorous re-examination of the experimental literature indicates that connections between different primary sensory cortices consistently occur in rodents, while primary-to-primary projections are absent/inconsistent in non-rodents such as cats and monkeys. These observations suggest that crossmodal plasticity that involves primary sensory areas are likely to exhibit species-specific distinctions.
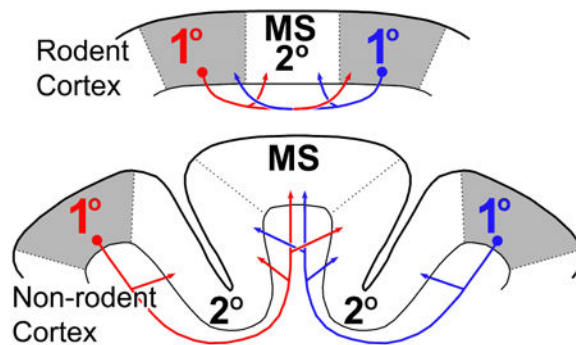
Graphical abstract

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1.0 Introduction: Crossmodal Plasticity

The adaptive effects of crossmodal plasticity are renowned throughout history as the extraordinary ability of blind poets and musicians. However, how the brain replaces a lost sense (e.g., blindness, deafness) with the remaining, intact sensory systems has only recently become the focus of experimental studies (see Bavelier and Neville, 2002; Merabet and Pascual-Leone, 2010; Lomber et al., 2010, 2011). As little as 20 years ago, it was postulated (Rauschecker, 1995) that crossmodal plasticity in a deprived sensory region resulted from either the ingrowth of novel inputs from neural sources representing the other sensory modalities, or that the plasticity resulted from the unmasking of existing connections. At that time, the reigning paradigm regarding cortical sensory organization and function (e.g., Jones and Powell, 1970; Felleman and van Essen, 1991; Paperna and Malach, 1991) regarded the primary, lower, or entry-level cortices as exclusive processors of responses to stimuli transduced by a single sensory modality. In that context, if a primary sensory area were to lose its source of activation, it was logical to *assume* that the ensuing crossmodal plasticity was the result of the ingrowth of novel inputs. However, over the last decade, a plethora of studies have revealed that primary sensory cortices actually encode, or are influenced by the presence of inputs from different sensory modalities (e.g., Ghazanfar and Schroeder, 2006; Kayser and Logothetis, 2007; Karns et al., 2012). In fact, functional studies within the defined borders of a given primary sensory cortex have now demonstrated that neuronal activity can be driven (or influenced) by more than one sensory modality. For example, electrophysiological examinations[1] of V1 (for full list of abbreviations, see Table 1) have identified non-visual responses and/or influences in a variety of species (Hunt et al., 2006; but see Wang et al., 2008). Similar studies of A1 have likewise revealed non-auditory responses and/or influences (Kayser et al., 2007; Lakatos et al., 2007 Bizley et al., 2007; Meredith and Allman, 2015) and a few investigations of S1 have observed non-somatosensory influences (Zhou and Furster, 2000; 2004). Although there may be species-specific bases for these crossmodal effects in primary sensory areas (to be discussed later),

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[1]Although several fMRI studies have addressed this same issue, these imaging studies are not included in the present review due to the well-known difficulty of accurately correlating single-unit electrophysiology with this more indirect measure of neural activation.

these observations alone should have re-opened the debate on the connectional mechanisms underlying crossmodal plasticity. However, only very recent studies have directly examined this issue, especially in the context of deafness.

1.1 Crossmodal Plasticity and Novel Crossmodal Projections?

To test the notion that hearing loss might induce novel connections to subserve crossmodal plasticity, combined functional and connectional studies of early-deaf (Meredith and Allman, 2012) and late-deaf (Allman et al., 2009) ferrets revealed that although the core auditory cortices were crossmodally reorganized following deafness, few if any new connection sources (e.g., not present in hearing animals) were identified. Subsequently, examinations of the effects of deafness in a region-by-region comparison of connectional changes in specific auditory cortices in cat auditory cortex have revealed that fundamental patterns of connectivity are preserved regardless of whether or not an acoustically deprived region of auditory cortex exhibits crossmodal plasticity. Areas that have been examined include to dorsal zone of the auditory cortex (DZ; Kok et al., 2013; Barone et al., 2013), primary auditory cortex (A1; Barone et al., 2013; Chabot et al., 2015), anterior auditory field (AAF; Wong et al., 2015), auditory field of the anterior ectosylvian sulcus (FAES; Meredith et al., 2016), and posterior auditory field (PAF; Butler et al., 2016a, b). This comprehensive effort conducted by three different investigative groups found small, if any, evidence for novel projections that were sufficient to underlie the robust crossmodal functional effects observed in each of the regions. None of these studies identified significant new sources of projections from cortical regions or thalamic nuclei that were sufficient to generate the broad levels of reorganized activity in the target cortices. In fact, in study after study of the effects of deafness, the overwhelming trend was for the cortical and thalamic projections seen in hearing animals to be preserved in the deaf. These collective observations can be explained by the possibility that the generation and maintenance of the projecting axons largely occurred before the developmental period that would have eliminated them by activity-dependent mechanisms, as proposed in Meredith et al. (2016). Thus, novel projections are insufficient to account for the broad and robust functional effects of crossmodal plasticity.

1.2 Crossmodal Plasticity and Unmasking of crossmodal inputs

The collective results of the comprehensive series of connectional studies of deafness appear to favor the alternative mechanism subserving crossmodal plasticity, which is that of unmasking existing projections. In fact, auditory cortical regions in hearing animals with normal developmental experiences have been shown to receive substantial connections from non-auditory sources. It needs to be pointed out that several categories of projections have been examined in relation to crossmodal plasticity based on their source: ipsilateral cortico-cortical connections, contralateral (commissural) corticocortical connections, and thalamo-cortical connections. By far the most consistently examined has been ipsilateral cortico-cortical inputs, which have recently been shown to be essential (when compared to thalamo-corticals) for crossmodal functions (Iurilli et al., 2012). Therefore, unless stipulated otherwise, projections described in this review refer to those derived from ipsilateral cortical regions. In cats, non-auditory inputs represent approximately 11.3% of the total ipsilateral corticocortical projection to A1 (Chabot et al., 2015), 13% to AAF (Wong et al., 2015), and 7% to PAF (Butler et al., 2016a) which are all tonotopically organized, while non-auditory

afferents to higher-level auditory areas represent approximately 52% of the inputs to area DZ (Kok et al., 2013) and 59% to the FAES (Meredith et al., 2016). Connectional studies of A1 in other species also report non-auditory cortical sources of inputs, including rats (Paperna and Malach, 1991), voles (Campi et al., 2010) and gerbils (Henschke et al., 2015). Ultimately, these connectional data are consistent with the modality distribution of neuronal responsiveness observed by electrophysiological recording, as illustrated in Figure 1. Note especially, for each of the regions tested, that neuronal responses tend to resemble the pattern of connectivity more in the deaf than in the hearing animals. These data are consistent with the possibility that some of the non-auditory inputs to auditory cortex of hearing animals are unmasked by deafness. For example, increases in non-auditory responses in AAF changed from 2% in hearing animals to >130% in the early-deaf cats (values >100% due to multisensory neurons; Meredith and Lomber, 2011), in DZ from 49% in the hearing to >104% in deaf cats (Kok et al., 2016a, b) and in FAES from 31% in hearing animals to >101% in early-deaf cases (Meredith et al., 2011). That neuron populations which were predominantly auditory in function in hearing animals changed in deafened animals to exclusively non-auditory function - rather than becoming unresponsive – supports the notion that non-auditory inputs to these regions were enhanced by deafness. It should be added that non-auditory projections to auditory cortices in normal hearing animals are quite robust. For example, sources of inputs to hearing FAES from visual cortical areas AEV, ALLS and PLLS represent >16% of the ipsilateral cortical inputs (Meredith et al., 2016) to a region that exhibits visual functions in 25% of its constituent neurons (Meredith et al., 2011). Likewise, visual sources of inputs from cortical areas ALLS and PLLS to hearing DZ represent >33% of total corticocortical inputs (Kok et al., 2013) and underlies visual functions in 49% of its neuronal population (Kok et al., 2016a). Ultimately, these observations indicate that non-auditory inputs to auditory cortex in hearing animals appear sufficient to drive non-auditory function (activation and/or modulation) following hearing loss, and these non-auditory connections seem to become unmasked and/or strengthened in early-deaf animals.

1.3 Functional Properties of Crossmodal Plasticity

It is quite clear that many apparently 'unisensory' cortical regions receive projections from regions that represent other sensory modalities and, as a likely consequence, exhibit crossmodal effects. Curiously, however, no studies (to our knowledge) have parametrically examined the sensory properties of such crossmodal inputs. Instead, the effects of non-auditory stimulation in auditory cortex has largely been probed with simple visual stimuli, such as a light flash or an LED. However, some insight may be derived from the few examinations of the sensory features of crossmodal inputs subsequent to deafness-induced reorganization, especially because the crossmodal projection sources are quite similar among the hearing and early-deaf cases. The visual receptive fields observed in the early-deaf FAES are quite large (average 63° diameter), lack global visuotopy, predominantly exhibit direction selectivity and high velocity movement preferences, as summarized in Figure 2A (Meredith et al., 2011). These visual receptive field properties are dissimilar to those which characterize primary visual areas but more closely reflect the processing features of their higher-order visual sources, such as the PLLS, ALLS and AEV (Palmer et al., 1978; Mucke et al., 1982; Benedek et al., 1988; Scannell et al., 1996). The

somatosensory receptive fields encountered in the early-deaf/reorganized AAF are quite large, often encompass an entire body region (e.g., hindlimb) or include the entire half of the contralateral body surface (Meredith and Lomber, 2011). Furthermore, a global somatotopy could not be detected in either the AAF of early-deaf cats (Meredith and Lomber, 2011) or the core auditory cortices of deafened ferrets (Allman et al., 2009; Meredith and Allman, 2012). These features are consistent with somatosensory receptive field properties of higher-level, not primary somatosensory cortices. Although a direct comparison of sensory processing properties of non-auditory responses in auditory cortex before and after deafening has not been conducted, these data suggest that non-auditory processing in core (A1, AAF) and higher-level (FAES) auditory cortex represents the synthesis of higher-order non-auditory projections to those regions.

1.4 Animal Models of Deafness-induced Crossmodal Plasticity

Many of the illustrative examples provided so far involve the study of the auditory system in the cat, which has been a reliable and robust model not only of auditory organization and function (Davis and Saul, 1931), but also of hearing loss/crossmodal plasticity (congenital, post-natal and adult; Rawdon-Smith and Hawkins, 1939) for more than three-quarters of a century. By contrast, investigations of deafness-induced cortical crossmodal plasticity in experimental animal models other than cats are quite rare: congenitally deaf mice exhibit visual-somatosensory reorganization of the auditory fields (A1 and AAF; Hunt et al., 2006); early-deaf (Meredith and Allman, 2012) and adult-deaf ferrets (Allman et al., 2009) demonstrate somatosensory reorganization of core auditory fields (A1 and AAF). Interestingly, like the connectivity-plasticity relationship seen in cats (above), the somatosensory crossmodal plasticity reported in ferrets core auditory regions strongly corresponds with the presence of somatosensory activity and connectivity in hearing ferrets (Meredith and Allman, 2015; note that the studies by Bizley et al., 2007 did not test for somatosensory effects). Similar to cats, cortical and thalamic connectivity of ferret core auditory regions were fundamentally the same for hearing and deaf conditions (Allman et al., 2009; Meredith and Allman, 2012). Collectively, these observations in ferrets provide further support for the notion that crossmodal plasticity is subserved by the unmasking of existing connections. However, a major difference is that the crossmodal plasticity observed in deaf ferret auditory cortex is largely somatosensory, while that of cats is region-dependent visual or somatosensory dominance (i.e., see Figure 1). Specifically, ferret core auditory regions (A1, AAF) receive substantial input (~40% of cortico-cortical connections) from a bimodal auditory-somatosensory region (designated the LRSS; Meredith and Allman, 2015) and, likewise cat AAF receives most of its non-auditory inputs from somatosensory cortical areas (Wong et al., 2015) and shows predominantly somatosensory crossmodal effects following deafness (83%; Meredith and Lomber, 2011). In contrast, cat area DZ receives sparse somatosensory inputs (<0.5% of total corticocortical projection; Kok et al., 2013), reveals few somatosensory functional effects and, following deafness, demonstrates not somatosensory, but visual crossmodal reorganization (Kok et al., 2016b). Ultimately, these collective results reassert that not only are cortical regions functionally dependent on their own particular array of effective inputs, but that these input patterns are likely to be species-specific.

Perhaps nowhere are the species-specific connectional differences more apparent than those of primary-to-primary sensory cortical connections of rodents versus non-rodents. To be explicit, the term "primary sensory cortex" is classically defined as the cerebral area receiving the first synapse from lemniscal/primary thalamic inputs (olfaction not included), such as V1 receiving afferents from dLGN, A1 from vMGN and S1 from VB thalamus. The well-examined visual (V1, or area 17), somatosensory (S1, or areas 1, 3 and 2) and auditory (A1, or areas 41/42; includes area AAF in some species) regions share numerous cytoarchitectonic, connectional and functional features despite the different sensory modalities they encode.

2.0 Species specificity of primary-to-primary connections: Rodents

As revealed in numerous studies involving different species of rodents, the primary sensory cortices of rodents often connect directly with one another. Table 2 provides a summary of published reports of primary-to-primary connections in several rodent species. Receiving by far the most investigative attention is V1 in the rodent. Most anatomical investigations of inputs to V1 from A1 in different rodent species consistently demonstrate a connection that is small-to-modest in size (Karlen et. al., 2006; Campi et al., 2009; Charbonneau et al., 2012; Laramee et al., 2013; Henschke et al., 2015; Ibrahim et al., 2016). Furthermore, optogenetic stimulation of A1 effected neuronal responses in V1 (Iurilli et al., 2012), although this phenomenon could be mediated through direct and indirect pathways. Similarly, a consistent and reciprocal projection is present between V1 and S1 (Campi et al., 2009; Charbonneau et al., 2012; Laramee et al., 2013; Henschke et al., 2015), and whisker deflections evoke V1 responses while visual flashes induce subthreshold effects in S1 (Iurilli et al., 2012). A sparse but topographically inconsistent projection is apparent between A1 and S1 (Henschke et al., 2015), although noise bursts can induce responses in S1 and whisker deflections activate responses in A1 (Iurilli et al., 2012) which is consistent with the attribution of the S1-A1 connection in gerbils as "strong" (Budinger et al., 2006; 2009). In contrast, the projection, from V1 to A1 is inconsistent and/or sparse, and visual flashes or gratings fail to elicit responses in A1 neurons in mice (Hunt et al., 2006; Iurilli et al., 2012) or opossum (Karlen et al. 2006). Collectively, these observations show that the anatomical and functional status of these connections are fairly consistent and that primary-to-primary projections in rodents are mostly sparse in proportion (only 3 of 26 observations were regarded as "strong" or were estimated to represent >10% of total projections).

2.1 Species specificity of primary-to-primary connections: Non- Rodents

In contrast, evidence for such a primary-to-primary connectional pattern is rare or non-existent in non-rodent (carnivores and monkeys) species, as detailed in Table 3. It should be pointed out that, historically, many connectional studies of primary sensory cortices did not specifically search for projections from non-related sensory areas (e.g., Lee and Winer, 2008). In their defense, adding the collection and assessment of all potential cortical sources to a given area would be unnecessarily burdensome if the goal of the study was to understand the circuitry underlying the sensory-specific function of a given primary area. Nevertheless, several exceptional studies have deliberately sought the identification of "non-related" inputs to a given primary area. It must also be pointed out, however, that this

particular literature is rife with inconsistency in terms of nomenclature, especially in relation to the definition of the areas examined, and a careful reading of the methods and results is required to correctly understand the information they provide. For example, one heavily-cited study explicitly states that the examined connections were between the "posterior auditory association cortex" and visual cortical regions (Rockland and Ojima, 2003), yet numerous subsequent publications repeatedly mis-cite this work as indicative of primary auditory cortical projections to primary visual cortex in macaque monkeys. In addition, whereas rodents demonstrate moderate/strong connections from S1 to other primary areas (as well as the reverse projections into S1), there is no published evidence (to our knowledge) for such connections in carnivores or in non-human primates.

Few studies of non-rodent species have examined primary-to-primary connections to A1, as depicted in Table 3. Specifically, V1 projections to A1 have been "occasionally" identified in some ferret studies (Bizley et al., 2007), but not in others (Meredith and Allman, 2015) and not in cat, macaque or marmoset. Furthermore, to our knowledge, no connections from S1 to A1 have been reported in these animals.

For studies of non-visual primary projections to V1 in non-rodents, the data seems to be interpreted differently from what was actually reported. Again, the heavily cited study in macaques by Rockland and Ojima (2003) explicitly involved posterior auditory association cortical (which is not A1) projections to V2, which exhibited only "sparse projections to V1." In another heavily cited study in macaque, A1 projections to V1 were reported to represent ~0.034% of non-visual cortical inputs that, on average, occur as 0.21 neurons/ section (calculated from Table 1, Falchier et al., 2002). However, it should be pointed out that this projection value is derived from neurons labeled not only within A1, but both auditory core and belt areas as well, as depicted in the published figures in this study. Although the authors stipulate that acetylcholinesterase (AChE) staining techniques were used to define and identify A1 "in the posterior bank of the lateral sulcus", Figure 4 clearly indicates that the area used for counting labeled neurons within "A1" in this study (between arrowheads, see Figure 4C; Falchier et al., 2002) also included the gyral surface and even the adjoining bank of the STS. As such, the area of inclusion corresponds best with a designation of "auditory cortex" (inclusive of core and belt regions) rather than exclusively A1, as claimed within the text and Figure 4B in this same work. Furthermore, the study on which this definition of A1 is based described macaque A1 using AChE labeling as entirely contained within the bank of the lateral sulcus (Figure 3A, Hackett et al., 2001). In addition, the proportional measure of the auditory projection to V1 was limited to only a subset of inputs from cortices that process visual and multisensory signals (STP and STS; Falchier et al., 2002). This does not provide a measure of auditory cortical inputs to V1 relative to all other cortical inputs, and therefore provides an overestimation of the size of the projection. Had only A1 been considered (as implied by the use of AChE staining), and had all corticocortical inputs been included in the comparison, the size of this inconsistent (present in 6 of 9 cases) projection, calculated as 0.034% of inputs would be vanishingly smaller. Last, in cats, "little to no labeling" was observed in A1 following area 17/18 injections (Hall and Lomber, 2008).

From these published studies, when data from only defined primary areas is compared, it is evident that primary-to-primary connections in non-rodent species are either non-existent or extremely weak and inconsistent. Thus, at least with the current set of published data, it is not logical to regard primary-to-primary cortical connectivity in non-rodent species as equivalent, or even similar, to that demonstrated in rodents, as summarized in the schematic flow diagram in Figure 3. It seems intuitive that, for larger-brained animals, there is simply more tissue and more regions from which projections to primary areas might arise. Furthermore, it is possible that the evolution of new cortical areas in non-rodents provides expanded representations of processing capabilities that are contained within the primary cortices in rodents. It is also possible that the behavioral dependence of carnivores and primates on the distance senses of vision and hearing, and rodents on somatosensation, may also contribute to the connectional distinctions among their primary cortices. Nevertheless, all species must deal with a complex sensory environment and there is a considerable literature that documents **higher-level** (non-primary) cortical projections to primary sensory cortices of another modality, of which many examples are quite robust (representing >30% of total corticocortical projections; e.g., Meredith & Allman, 2015). Ultimately, such higher-level connections are consistent with multisensory functions within primary sensory areas (e.g., Bizley et al., 2007; Karns et al., 2012; Meredith and Allman, 2015).

3.0 Discussion

The published reports summarized in Table 3 demonstrate that, if primary-to-primary connections occur in non-rodent species, those projections are proportionally very sparse. Few mechanistic explanations of how such sparse connections might generate a specific neural effect have been proposed. On the one hand, they may subserve a specific contextual role that is not discernable by anatomical or acute-recording techniques. Specifically, cat area DZ receives sparse somatosensory inputs (<0.5% of total corticocortical projection; Kok et al., 2013), reveals few somatosensory functional effects and, following deafness, demonstrates not somatosensory, but visual crossmodal reorganization (Kok et al., 2016b). Another possibility is that the few projecting neurons from a region exhibit axonal arbors that are extremely branched in order to access a sizeable extent of their targeted primary field. This notion is challenged by the basic relationship of neuronal soma size to the axonal tree supported by that cell body, a relationship that has been extensively studied and is defined as the "Size Principle" of motor function. According to this neurophysiological rule (e.g., Henneman et al., 1965; Clamann and Henneman, 1976; Llewellen et al., 2010), during movement, motoneurons are recruited from smallest to largest, such that those units with the smallest force are recruited first. Here, size corresponds not only to the dimensions of the parent motoneuron, but also to the extent of the motor unit (muscle fibers innervated by one neuron), and the axon diameter and its conduction velocity. This is functionally logical because it takes a larger parent cell body to support more extensive axonal branching and end-plates (with the attendant increase in mechanisms supporting axonal transport and synaptic transmitter and vesicle function). If this system is applied in the current analysis of how a small (corticocortical) projection can influence the overall function of a primary cortical target, there is the possibility for branching within proportionally small projections (e.g., <1-3% of corticocortical connectivity) but the axonal branches would need to be

extensive and the parent neurons would correspondingly enlarge to provide the metabolic support for such an extensive and highly branched axonal arbor. Such a soma-axonal branching relationship, to our knowledge, has not been directly examined in the primary-to-primary system, although the essential features of this relationship are readily evident in cortex. For example, in the neocortex, neurons with short, local axon distributions, such as inhibitory interneurons, exhibit the smallest soma sizes of neurons in the cortical mantle (e.g., from 7-10 μm). At the same time those cortical neurons with the longest axons, such as the layer 5 upper motoneurons (pyramidal cells of Betz) in motor cortex, display amongst the largest soma diameters in the entire cortex (up to 100μm). Following these principles, if primary-to-primary projections in non-rodents are carried by sparse but very highly-branched neurons, their soma sizes should be significantly larger than other corticocortical neurons. So far, none of the literature has commented on the extreme size (which should be obvious) of primary-to-primary corticocortical neurons, but this possibility empirically testable.

Another consideration is that the net effect of a projection results from the combined features of neuronal number and extent of axonal branching as well as the synaptic efficacy of their terminal boutons. Indeed, within the thalamo-cortico-thalamic system there is strong evidence for different synaptic effects characterized as "drivers" or as "modulators" (e.g., Sherman and Guillery, 2002) that are dependent on features related to synaptic size and location. Although experiments have not yet directly assessed these possible features of primary-to-primary projections, the documented inhibitory effects of acoustical cues on rodent V1 responses (Iurilli et al., 2012) would suggest that such projections are largely modulatory in arrangement and effect.

3.1 Implications for crossmodal plasticity

To this point, data for non-rodents indicate that crossmodal plasticity provides functional properties that are consistent with processing in higher-level cortices, such as large receptive fields and lack of topographic organization. To our knowledge, the response features of crossmodal responses in rodents have not been extensively examined (but see Iurilli et al., 2012; Ibrahim et al., 2016), but it would be predicted that the responses would be consistent with lower-level inputs, such as those derived from primary sensory areas.

4.0 Conclusions

Crossmodal plasticity exhibits region-dependent differences based on differences on their underlying connectivity. Among the potential connection sources for primary sensory cortex are other primary sensory areas. Although primary-to-primary connectivity has received a great deal of attention recently, the literature clearly shows that primary-to-primary cortical connectivity occurs in rodents, but there is little consistent evidence for this in non-rodents such as carnivores and non-human primates. One of the major sources of error in interpreting the original literature has been that the definitions of primary, secondary and higher-level cortices have been blurred; the term A1 is not interchangeable with "auditory cortex," etc. Ultimately, connectional distinctions among species that exhibit primary-to-

primary connections (or not) suggest that crossmodal plasticity in these different orders of animals may also be different.

Acknowledgments

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**Highlights**

- Crossmodal plasticity occurs following major sensory loss.

- Functional properties of crossmodal plasticity differ; dependent on input pattern.

- Primary-to-primary cortical inputs are consistent among rodent species.

- Primary-to-primary cortical inputs are absent/ inconsistent in non-rodents.

- Crossmodal plasticity in primary sensory areas is likely to be species-specific.
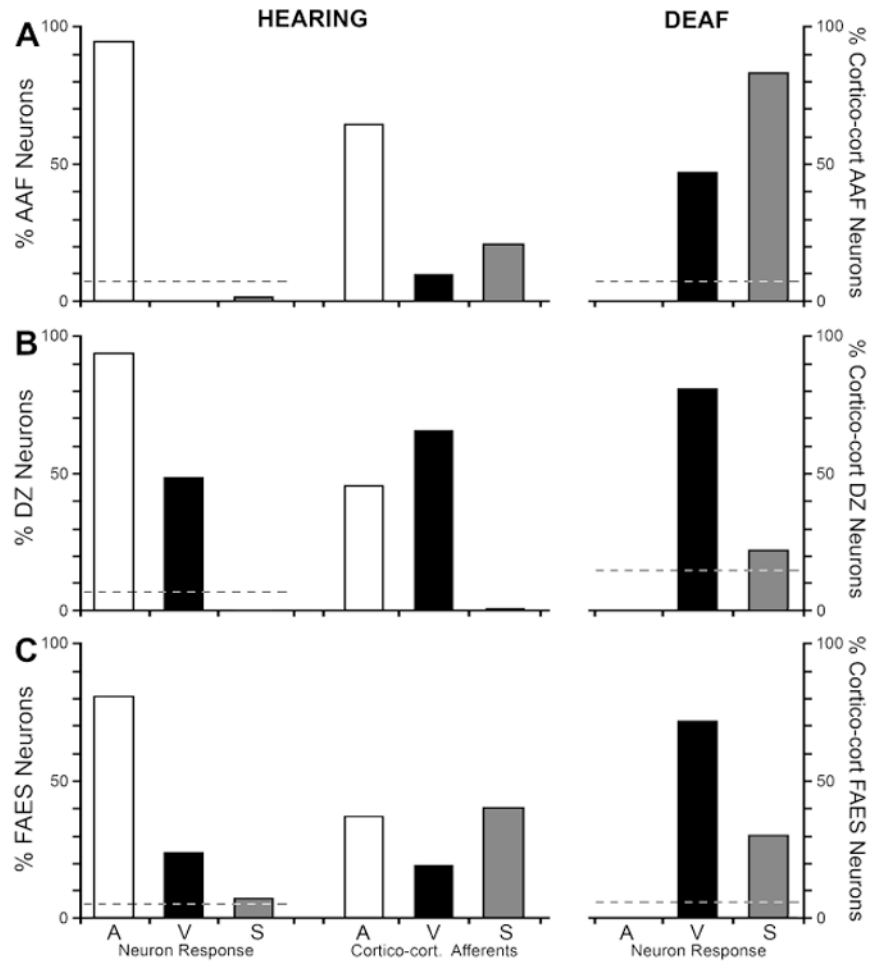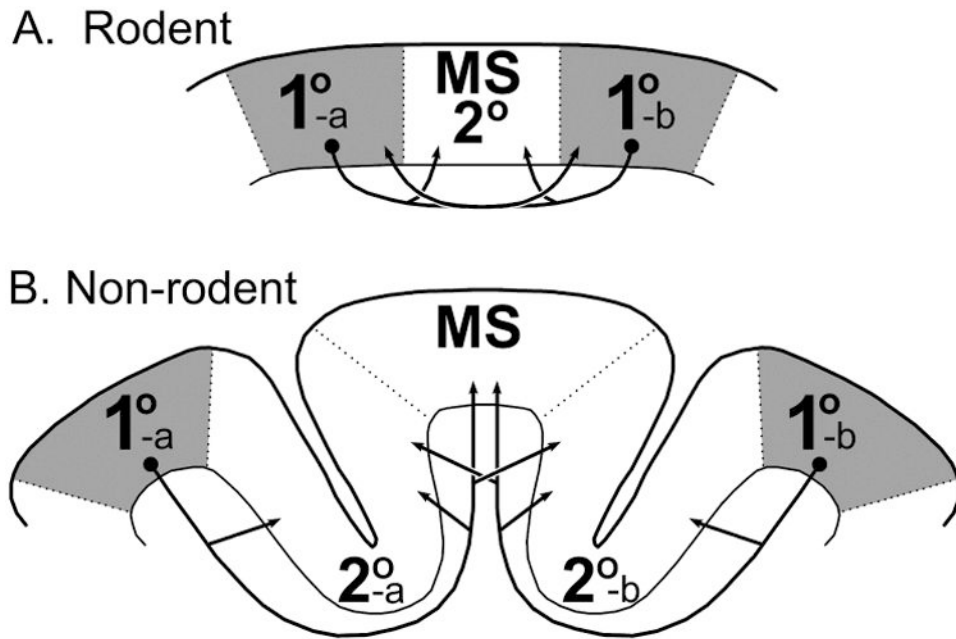
Figure 1.
Relationship of crossmodal plasticity to anatomical connectivity prior to hearing loss. Data from auditory regions AAF (panel A), DZ (panel B) and FAES (panel C) depict proportions of neurons that respond to auditory (A, white bar), visual (V, black bar) or somatosensory stimulation (S, grey bar) in hearing (left of dashed line) or early-deaf cats (right of dashed line) (values sum>100% due to multisensory neurons). Dashed horizontal lines represent the proportion of unresponsive neurons. All measures of neuron responsivity refer to the left, y-axis scale. The central column shows the anatomical proportion of total ipsilateral corticocortical neurons that project to the stipulated area (right, y-axis scale) by the modality (A, V, S) of their afferent source. Note that after deafening the crossmodal response distribution in all 3 areas correlates with the presence of the non-auditory anatomical connections observed in hearing animals. This trend suggests that deafness unmasks the effects of at least some afferent projections to auditory cortical areas. AAF data derived from Meredith and Lomber, 2011; Wong et al., 2015; DZ data derived from Kok et al., 2013; 2016b; FAES data from Meredith et al., 2011; 2016.
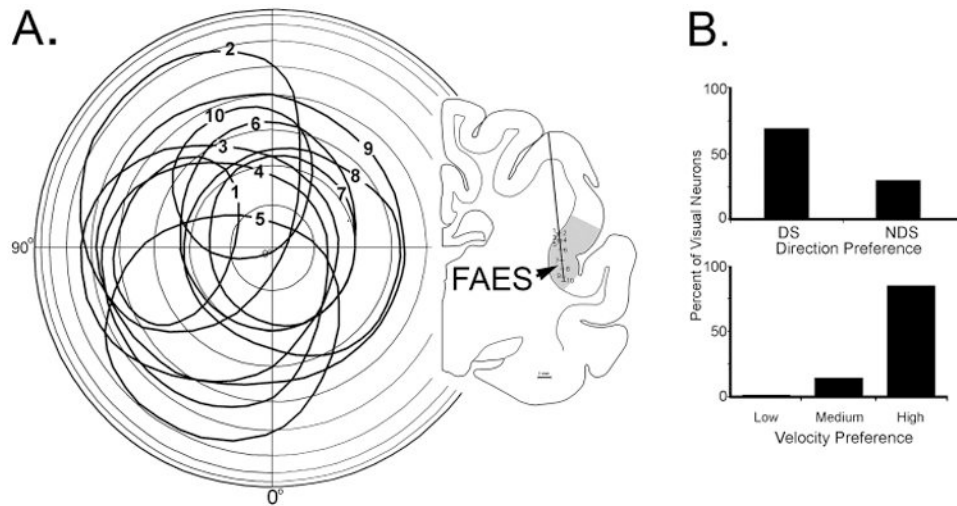
Figure 2.
Visual receptive field properties of reorganized, early-deaf FAES are consistent with higher-order visual processing. Panel (A) depicts visual space (plotted in polar coordinates) with the receptive field positions mapped for 10 different neurons isolated within the FAES of an early-deaf cat. The coronal section of cortex shows the electrode position with the FAES (grey area at arrow) with the location of neurons 1-10 indicated. Note that the visual receptive field of each neuron is quite large and shifts in elevation and azimuth in a non-sequential manner that is not consistent with a global visuotopy. Panel (B) illustrates that the majority of crossmodal visual responses in early-deaf FAEs show preferences for stimulus direction (DS=direction selective; NDS=non-direction selective) and high velocity movement (>100°/sec). Redrawn from Meredith et al., 2011.

A. Rodent

B. Non-rodent

Figure 3.
Summary comparison of primary-to-primary cortical connectivity in (A) rodent and (B) non-rodent species (carnivores and monkeys). Depicted are sections through the cortical mantle showing the pial surface (thick contour) and grey-white border (thin contour) with primary (1°) cortical areas for different sensory modalities (-a; -b) rendered as grey-filled regions. Cortical areas between primary representations are designated as secondary (2°) or multisensory (MS) which are oversimplified in this schematic. Neurons (black circles) in primary areas send their axons (black lines with arrows) to target other cortical areas. For the cortex of rodents (A), the literature indicates that primary sensory areas not only project to intervening secondary/multisensory areas, but also target primary representations of other sensory modalities. For the non-rodent species (B) that have been examined, the preponderance of observations indicates that primary sensory representations target expanded secondary and multisensory regions, there is little evidence for consistent connections between different primary sensory areas.

Table 1

List of Abbreviations

AChE	Acetylcholine esterase (stain)
A1	Primary auditory cortex
A2	Second auditory cortex
Area 1	Primary somatosensory cortex
Area 17	Primary visual cortex
Area 18	Secondary visual cortex
AAF	Anterior Auditory field
AEV	Anterior Ectosylvian Visual area
ALLS	Anterolateral Lateral Suprasylvian visual area
DZ	Dorsal zone of auditory cortex
FAES	Field of the anterior ectosylvian sulcus
fMRI	Functional Magnetic Resonance Imaging
PAF	Posterior auditory field
PLLS	Posterolateral Lateral Suprasylvian visual area
PMLS	Posteromedial Lateral Suprasylvian visual area
S1	Primary somatosensory cortex
S2	Second somatosensory cortex
V1	Primary visual cortex
V2	Second visual cortex

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Table 2

Published Anatomical Reports of Primary-to-Primary Cortical Connections in Rodents

Primary Cortex	with inputs from:	Species	Reference
S1 (septa pref.)	V1	Mouse	Wang & Burkhalter, 2007
S1	V1("few cells")	Rat	Paperna & Malach, 1991
S1	V1 ("strong") [*]	Gerbil	Henschke et al., 2015
S1	A1 ("sparse")	Gerbil	Henschke et al., 2015
V1	A1 ("few cells")	Rat	Paperna & Malach, 1991
V1	A1/T ("low density" 2 cases)	Opossum	Martinich et al., 2000
V1	A1 (1.2%)	Opossum	Karlen et al., 2006
V1	A1 (sparse)	Vole	Campi et al., 2010
V1	AC (includes A1; 1.2%)	Mouse	Larsen et al., 2009
V1	Au (includes A1; 28%)	Mouse	Charbonneau et al., 2012
V1	A1-Layer 5	Mouse	Laramee et al., 2013
V1	A1 ("moderate")	Gerbil	Henschke et al., 2015
V1	A1	Mouse	Ibrahim et al., 2016
V1	S1 (0.0%)	Opossum	Karlen et al., 2006
V1	S1 (2/3 cases; 3-10%)	Vole	Campi et al., 2010
V1	S1 (sparse, % not calculated)	Mouse	Larsen et al., 2009
V1	Som (barrel field; 6%)	Mouse	Charbonneau et al., 2012
V1	S1-Layer 5	Mouse	Laramee et al., 2013
V1 [*]	S1 ("moderate")	Gerbil	Henschke et al., 2015
A1	V1 ("few cells")	Rat	Paperna & Malach, 1991
A1+AAF	V1 (3/5 cases; 3-22%)	Vole	Campi et al., 2010
A1	V1 (0.0%)	Gerbil	Budinger et al., 2006
	[V2 (8%)	Gerbil	Budinger et al., 2006]
A1	V1 [*] (faint)	Gerbil	Henschke et al., 2015
A1+AAF	S1 (2/5 cases; Vibr; 0-<3%)	Vole	Campi et al., 2010
A1	S1 (9.7%; Hindlimb, Trunk)	Gerbil	Budinger et al., 2006
A1	S1 ("faint")	Gerbil	Henschke et al., 2015

[*] Defined as V1/V2 in Table1 Henschke et al., 2015.

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Table 3

Published Anatomical Reports of Primary-to-Primary Cortical Connections in <u>Non</u>-rodents (Carnivores and Monkeys)

Primary Cortex	with inputs from:	Species	Reference
S1	V1 (None observed)	Marmoset	Cappe & Barone, 2005
S1	V1 (Not mentioned; none from V2)	Macaque	Falchier et al., 2010
S1	A1 (None observed)	Marmoset	Cappe & Barone, 2005
V1 (Incl. 17/18)	A1 ("Little to no labeling" 14 cases)	Cat	Hall and Lomber, 2008
V1	Aud (Core <u>&</u> Belt; 0.03% [*]; 9 cases)	Macaque	Falchier et al., 2002
V1	A1 (Belt, not core examined)	Macaque	Rockland & Ojima, 2003
V1	A1 (No data presented)	Macaque	Clavagnier et al., 2004
V1	A1 (Review, No data presented)	Macaque	Cappe et al., 2009
V1	A1 (Not examined)	Marmoset	Cappe & Barone, 2005
V1	S1 (Not reported; 14 cases)	Cat	Hall & Lomber, 2008
A1	17 ("occasional" 11 cases)	Ferret	Bizley et al., 2007
A1/AAF	17 (None)	Ferret	Meredith & Allman, 2015
AAF	17 (0.9%; 5 cases)	Cat	Wong et al., 2015
A1	17 (0.0%; 5 cases)	Cat	Chabot et al., 2015
A1	17 (0.0%; 2 cases)	Cat	Barone et al., 2013
A1	V1 (None)	Marmoset	Cappe & Barone, 2005
A1	V1 (None)	Macaque	Falchier et al., 2010
A1	S1 (None)	Marmoset	Cappe & Barone, 2005
A1	S1 (None reported; 5 cases)	Cat	Chabot et al., 2015
AAF	S1 (None reported; 5 cases)	Cat	Wong et al., 2015
A1	S1 (None reported; 2 cases)	Cat	Barone et al., 2013

[*] Data from core and belt auditory cortex are blended; percentage determined from the reported subset of non-auditory corticocortical connections and is not a proportion of all corticocortical connections.

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