CROSS-MODAL PLASTICITY: WHERE AND HOW?

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Animal studies have shown that sensory deprivation in one modality can have striking effects on the development of the remaining modalities. Although recent studies of deaf and blind humans have also provided convincing behavioural, electrophysiological and neuroimaging evidence of increased capabilities and altered organization of spared modalities, there is still much debate about the identity of the brain systems that are changed and the mechanisms that mediate these changes. Plastic changes across brain systems and related behaviours vary as a function of the timing and the nature of changes in experience. This specificity must be understood in the context of differences in the maturation rates and timing of the associated critical periods, differences in patterns of transiently existing connections, and differences in molecular factors across brain systems.

NEUROPLASTICITY
The capacity of the nervous system to modify its organization. Such changes can occur as a consequence of many events, including the normal development and maturation of the organism, the acquisition of new skills ('learning') in immature and mature organisms, after damage to the nervous system and as a result of sensory deprivation.

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doi:10.1038/nrn848

The investigation of NEUROPLASTICITY has expanded rapidly over the past ten years and has uncovered a remarkable capacity of both the juvenile and the adult brain to be shaped by environmental input. In particular, a wealth of studies has documented striking effects of sensory deprivation in one modality on the development of the remaining modalities. These studies indicate not only behavioural changes in the remaining modality, but also a reorganization of cortical functions. It is generally agreed that multimodal brain areas show enhanced processing of input to the remaining modalities in unimodally deprived animals and in blind and deaf humans. There are also reports that the primary sensory cortices that are associated with the deprived modality can become colonized by the remaining modalities in deprived animals or humans. By characterizing the regions that are susceptible to cross-modal plasticity, we might discover the roles of intrinsic constraints and environmental input in determining cortical functional specificity. In addition, such information will be key to predicting and evaluating the success of sensory implants in humans[1,2]. For example, cross-modal reorganization of the deprived auditory cortex in deaf individuals might hinder its RECRUITMENT by new auditory input from an implant. Accordingly, in one study, deaf individuals in whom cross-modal plasticity was the most extensive were the least likely to benefit from cochlear implants[3]. The identification of brain systems that are susceptible to cross-modal reorganization has recently received much interest, and the first part of this review discusses the latest results.

Fewer studies have been directed towards determining what boundary conditions or constraints might limit within- or cross-modal experience-dependent plasticity. The burgeoning literature on this topic indicates that plastic changes vary widely across brain systems, giving rise to highly specific alterations as a function of the nature of the altered experience, its timing and the brain systems involved. The nature of altered experience can vary widely between modalities. Even within a modality, sensory deprivation can result from a natural event, such as the lack of differentiation of ganglion cells in the retina in the case of early blindness, a traumatic event, such as denervation or removal of a sensory organ (for example, ENUCLEATION), or pauperization of sensory stimulation, as in the case of DARK REARING. It is known that these different types of deprivation lead to different plastic changes. Although this specificity and diversity prevents broad generalization, plastic changes might rely on a limited number of mechanisms that could be discovered in animal studies, including differences in the timing of expression of receptors that are

important for synaptic plasticity, differences in the molecular factors that control the development of different neural pathways, and differences in the degree of exuberant or redundant early connectivity and activity-dependent shaping of this connectivity.

Loci of plastic changes

Early sensory areas of spared modalities. The sensory systems of animals are highly sensitive to experimental manipulations, as reflected by reports of plastic effects not only in the deprived sensory system, but also in the remaining intact sensory modalities. For example, increased spine density and neuron density have been reported in the auditory cortex of rats after early visual or somatic deafferentation[4]. A similar hypertrophy of the auditory cortex occurs in mice, whether young or adult, after dark rearing for three months or more[5]. Several explanations might account for the hypertrophy of the spared sensory cortices, but two are particularly relevant. The abnormal maturation or recruitment (or both) of the deprived sensory area might result in the abnormal stabilization of usually transient connectivity in the remaining sensory areas[6–9]. In addition, hypertrophy of the remaining sensory cortices might be mediated by the greater reliance of the individual on the remaining modalities after deprivation[10]. Although no studies have directly linked behavioural changes with morphological changes in primary cortices of the remaining modalities, a handful of studies has indicated that there is such a link. The best-documented example is perhaps that of the effects of visual loss on somatosensory functions. For example, enucleation in newborn rats results in better maze performance (mediated by somatosensory perception using the whiskers) and concomitant changes in the size and angular sensitivity of the receptive fields of the (primary) barrel cortex[11,12]. Interestingly, this compensatory effect is much greater if deprivation occurs early in life than if it occurs later, as rats that are enucleated during adulthood always perform more poorly than early-enucleated rats[13].

Evidence for such changes in humans is scarce, in part because very few studies have used neuroimaging techniques to characterize the primary cortical areas that are associated with intact modalities. Changes in the tactile perception of the fingers in blind Braille readers have been linked to changes in the somatosensory cortex[14], but these effects seem to be driven by experience with Braille reading, rather than by blindness *per se*[15–17]. Reports that visual areas V1 and V2 (the primary and secondary visual cortices, respectively) are recruited during auditory language processing in POST-LINGUALLY DEAF individuals after they receive cochlear implants also indicate a link between plastic changes in the spared modality and deprivation of the auditory system. However, this finding seems to reflect the greater reliance of cochlear-implant users on visual cues during the processing of oral language, rather than plasticity caused by deafness *per se*[18,19].

In general, a notable feature of the literature on functional changes after blindness and deafness is the lack of effects on absolute sensitivity thresholds in the remaining modalities. For example, psychophysical thresholds for visual contrast sensitivity, visual flicker, brightness discrimination, direction of motion and motion velocity are similar in deaf and hearing individuals[20–24]. Studies of auditory and somatosensory thresholds, as determined by standard audiometry or absolute tactile thresholds, have similarly failed to reveal differences between blind and sighted individuals[25–28]. This is not to say that deafness and blindness do not lead to compensatory changes, but rather that these changes seldom seem to lead to absolute sensitivity differences. Instead, they can clearly lead to differences in performance on more complex tasks (see below). This pattern of results indicates that compensatory changes are not widespread over the cortex, but instead are specific and might occur primarily at higher or more central levels of the central nervous system. Clearly, further careful anatomical and functional studies of the remaining primary and secondary sensory cortices in blind (somatosensory and auditory areas) and deaf (somatosensory and visual areas) individuals, with controls for perceptual experience (such as Braille reading), are called for.

Polymodal association areas. Converging evidence indicates that POLYMODAL ASSOCIATION AREAS become reorganized following sensory deprivation. For example, after visual deprivation in juvenile rats, cats and monkeys, there is an increase in the number of neurons that respond to somatosensory and auditory information in multimodal areas, including the superior colliculus, the anterior ectosylvian region in cats and the parietal cortex in primates[29–32]. Cats that are visually deprived from birth show improved auditory localization and greater auditory spatial tuning of cells in the anterior ectosylvian cortex. In addition, the part of this region that typically responds to visual stimuli in sighted animals becomes predominantly auditory or somatosensory in visually deprived animals[32,33]. Along the same lines, area 19, which is predominantly visual in sighted monkeys, becomes recruited by tactile input in monkeys that are deprived of visual information during the first year of life[30]. Although further sprouting of inputs cannot be excluded, it is generally agreed that the takeover by non-visual inputs of predominantly visual sections of multimodal areas is mediated by mechanisms similar to those that operate during normal development: that is, activity-based competition between different inputs. It is unfortunate that there are few data on the period during which such reorganization is possible, which reflects the fact that virtually all of these studies included only animals that had been deprived early in life. One rare study in which animals were also deprived during adulthood indicates an intermediate level of compensatory plasticity[34]. Studies in which the age of onset of the sensory deprivation is varied are an important direction for future research.

Recent studies of deaf and blind humans have provided convincing behavioural, electrophysiological and neuroimaging evidence of increased capabilities and compensatory expansion in their remaining modalities. Individuals who became blind early in life, but not

RECRUITMENT
Neurons in an area are observed to be responsive to a certain type of stimulation, and are said to be recruited by that stimulation. This can be measured directly by a change in a neuron's firing rate, or indirectly by a change in the BOLD signal from fMRI, or a change in the scalp potentials from ERP and MEG recordings.

ENUCLEATION
Removal of the eyeballs.

DARK REARING
An experimental condition in which an animal is reared in total darkness so that only endogenous activity is present in the developing visual system.

POST-LINGUALLY DEAF
Individuals who have become deaf after learning to speak and understand their native language.

POLYMODAL ASSOCIATION AREAS
'Higher' areas of cortex that receive and integrate inputs from multiple sensory modalities.

those who lost their sight later, can process sounds faster, localize sounds more accurately and have sharper auditory spatial tuning — as measured both behaviourally and using EVENT-RELATED POTENTIALS (ERPs) — than sighted individuals[35–37]. Blind subjects also have better two-point tactile discrimination skills and superior auditory recognition memory than do sighted subjects[27]. In addition, auditory and somatosensory ERPs over posterior cortical areas are larger and faster in blind than in sighted subjects, indicating that these areas are recruited by the remaining modalities[36,38–40]. Similarly, deaf individuals show enhanced tactile accuracy[41] and enhanced visual attention, specifically in the peripheral visual field. For example, a few studies have shown that deaf individuals process events in the peripheral visual field more accurately than do hearing individuals[42–47]. Such behavioural compensation might be mediated by enhanced recruitment of multimodal areas of cortex by the remaining modalities. In particular, functional magnetic resonance imaging (fMRI) has revealed that there is increased recruitment of the posterior superior temporal sulcus — one of the principal sites of multimodal integration — in deaf individuals when they attend to visual displays of moving stimuli[48]. Similarly, there is increased recruitment of the inferior parietal lobe (BRODMANN AREA 40) in the deaf and in the blind[48–50] when they process stimuli in the spared modalities.

Not surprisingly, the areas that show reorganization after sensory deprivation seem to be part of the cortical network that mediates cross-modal processing in normally sighted, hearing individuals[51–53]. A few studies indicate that training or spatial attention can bias the recruitment of these areas for one modality rather than another[54–56]. This observation indicates that cross-modal reorganization of multimodal areas might not always be limited to congenitally deaf or blind individuals, but might also occur in individuals with a late onset of sensory loss. Accordingly, Büchel *et al.*[50] found that the inferior parietal lobe was recruited during Braille reading not only in early-onset, but also in late-onset, blind individuals. The extent to which reorganization after late-onset deprivation might be similar to reorganization after early-onset deprivation still needs to be investigated, as animal studies have shown that, within a modality, the timing of sensory deprivation influences the type of reorganization that results.

Primary cortices associated with the deprived modality. There is some evidence that even primary sensory areas that would normally process information from the deprived modality might be able to process information from remaining modalities. For example, when retinal afferents are surgically forced to innervate primary somatosensory (S1) or auditory (A1) areas in hamsters and ferrets, neurons in S1 and A1 respond to light and show some degree of retinotopy as well as direction and orientation selectivity for visual stimuli[57–59]. There is also evidence that the 'rewired' cortex in these animals actually mediates visual behaviour[60,61]. Such results confirm that sensory inputs have a central role in specifying the functional architecture of the brain regions that they contact. Could a similar reorganization arise without surgical manipulation after deafness or blindness? Evidence that it might comes from studies of naturally blind mole rats and visually deprived cats or mice, in which the primary visual cortex can be driven by auditory input[12,62–66]. It has also been reported that the primary auditory cortex can be driven by visual stimuli in congenitally deaf cats[67]. The normally transient cross-modal connectivity between sensory transducers and thalamic relays that exists in the young of at least some species could mediate such effects[6,8,9].

In humans, MAGNETOENCEPHALOGRAPHY (MEG), ERP, positron emission tomography (PET), fMRI and TRANSCRANIAL MAGNETIC STIMULATION (TMS) studies have shown that posterior visual areas are active during somatosensory processing in the blind, and that auditory areas are active during visual and somatosensory processing in the deaf[50,68–74]. All of these studies report changes in secondary sensory areas, but some also report changes in primary cortices. A widespread view is that, as has been shown in animals, primary cortices might mediate, at least in part, the functional changes that are seen in blind or deaf individuals. For example, Cohen *et al.*[75] have reported that tactile discrimination in the blind is reduced when TMS is used to disrupt the function of the occipital cortex, whereas performance in sighted individuals is unchanged. This indicates that disabling the visual cortex, and in particular the primary visual cortex, hinders tactile performance in the blind.

However, it could be argued that the techniques that were used in these studies do not have the spatial resolution to distinguish between recruitment of primary cortices and that of neighbouring areas that are known to show multimodal recruitment. Indeed, the spatial resolution of TMS, PET and fMRI, as used in these studies, is poor, either inherently or owing to the use of normalization to a common brain space[76]. The variable size and location of primary cortices in human brains[77,78] means that the process of normalization can blur activation in primary cortices with that in secondary and possibly in higher cortices. To establish unequivocally the participation of primary cortices in cross-modal reorganization in humans would require the use of a high-resolution technique such as fMRI, coupled with single-subject analysis. A few recent, unpublished studies that have adopted this approach have found recruitment of the primary visual cortex in blind subjects who were processing oral language[79,80]. At present, it is unclear whether this reorganization is induced by blindness or mediated through extensive training with Braille reading, which could allow these regions to become part of the language system. This is likely to be an exciting avenue of research for future investigations.

Using a single-subject approach, we compared recruitment of the primary auditory cortex during visual processing in more than 15 congenitally deaf individuals with that in hearing individuals, but failed to observe population differences (D.B. and H.J.N., unpublished observations). Similar failures to observe activation of

EVENT-RELATED POTENTIALS
Electrical potentials that are generated in the brain as a consequence of the synchronized activation of neuronal networks by external stimuli. These evoked potentials are recorded at the scalp and consist of precisely timed sequences of waves or 'components'.

BRODMANN AREAS
(BA). Korbinian Brodmann (1868–1918) was an anatomist who divided the cerebral cortex into numbered subdivisions on the basis of cell arrangements, types and staining properties (for example, the dorsolateral prefrontal cortex contains subdivisions, including BA 44, BA 45, BA 47 and others). Modern derivatives of his maps are commonly used as the reference system for discussion of brain-imaging findings.

MAGNETOENCEPHALOGRAPHY
(MEG). A non-invasive technique that allows the detection of the changing magnetic fields that are associated with brain activity.

TRANSCRANIAL MAGNETIC STIMULATION
(TMS). A technique that is used to induce a transient interruption of normal activity in a relatively restricted area of the brain. It is based on the generation of a strong magnetic field near the area of interest, which, if changed rapidly enough, will induce an electric field that is sufficient to stimulate neurons.

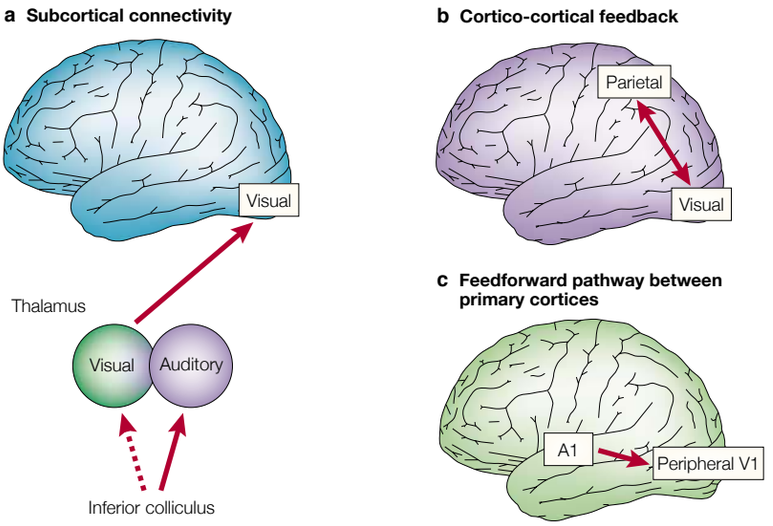


Figure 1 | **Possible mechanisms at the system level for cross-modal plasticity.** **a** | Changes in subcortical connectivity. In blind mole rats, there is evidence that the inferior colliculus, an auditory relay, projects not only to the part of the thalamus that is auditory (the medial lateral geniculate body), but also to the part of the thalamus that is usually visual (the dorsal lateral geniculate body), resulting in the recruitment of the non-degenerated visual cortex by auditory stimuli. Similar changes might occur in the case of hereditary blindness (or deafness), allowing visual areas (or auditory areas) to be recruited for auditory (or visual) processing. **b** | Changes in cortico-cortical feedback. In non-deprived animals, feedback connections are important for shaping the functional characteristics of the areas that they contact. Modulation of the strength of these connections would allow flexible recruitment of sensory areas as a function of experience. **c** | Changes in the strength of long-range connections between primary cortices. Recently, tracing studies in the primate have documented projections between the primary auditory cortex (A1) and the part of V1 (the primary visual cortex) that mediates peripheral vision. In the absence of vision, this connection might expand, and would provide a possible neural substrate for the recruitment of V1 by sound stimuli in the blind. In the absence of audition, this pathway is likely to be weaker, possibly allowing direct visual input to more efficiently recruit peripheral V1, and so might provide a possible neural substrate for the enhancement of peripheral visual attention in the deaf.

the primary auditory cortex in deaf individuals have been reported by others[73,81]. In our study, although most deaf subjects showed significant activation in area A1 during visual stimulation, some showed no activation. This inter-individual variability matches that reported by Rebillard *et al*. in the genetically deaf cat[67]. In that study, out of three genetically deaf cats, only one showed visually evoked potentials in A1. Interestingly, cats that were cochleoectomized before the age of three weeks all showed visually evoked potentials in A1, whereas none of the cats that was cochleoectomized at a later stage did, indicating that there is a SENSITIVE PERIOD for this effect. The inconsistent recruitment of A1 in genetically deaf individuals seems to be consistent with the report of large inter-individual differences in the timing of cochlear degeneration in such individuals[82].

Even more surprising in our study was the observation that a small number of hearing controls also showed some activation in the primary auditory cortex when viewing alternations of moving and static dots. This observation raises the possibility that unimodal cortex might not be truly unimodal, even in non-deprived individuals. This possibility will be discussed further below; in any case, knowledge of the time course of activation in primary cortices will be crucial in specifying whether the recruitment of these areas is due to afferent input or feedback.

SENSITIVE/CRITICAL PERIOD
The developmental time period during which experience can significantly alter the organism's behavioural performance, and related aspects of brain structure and/or function.

Mechanisms of cross-modal plasticity

Even if the remaining modalities can recruit the primary visual cortex in blind individuals and the primary auditory cortex in deaf individuals, an important question concerns the mechanisms that might mediate such reorganization. Understanding the mechanisms that are involved in cross-modal plasticity is central to a basic understanding of the differentiation of sensory systems, and also has important implications for the success of sensory implants, such as cochlear or retinal implants. The available animal literature points to a few possible mechanisms — some that might easily be modified as a result of implants, and others that are more likely to interfere with the success of implants. For example, reorganization might be due to alterations in local connectivity, as has been described in the case of changes in sensory maps. Such changes have been shown in the young as well as in adults, and should be easily modified by implants. On the other hand, reorganization could result from the stabilization of normally transient long-range connections during development; these would not be easily reversed by implants. We review below the few mechanisms at the system level that might mediate plastic changes. It should be noted that there are, at present, no *a priori* reasons to believe that the mechanisms at play during cross-modal plasticity differ from those involved in intra-modal plasticity; accordingly, we will draw on examples from both types of plastic change.

Changes in local connectivity. Probably the best-studied type of plasticity is that observed in sensory maps after sensory stimulation or deafferentation. This plasticity is not limited to developing organisms — it can also be observed in adults (although it might be more extensive in the young)[83,84]. Several local mechanisms have been proposed, including local sprouting, unmasking of silent synapses and/or changes in the modulatory effects of lateral connections. Although it is true that changes within sensory maps are constrained by the topographical organization of sensory cortices, large-scale reorganization can nevertheless be observed secondary to changes in long-range horizontal connectivity[85,86] or to the widespread repercussions of reorganization at the level of the thalamus or the brainstem. The latter has been shown to mediate re-mapping of the auditory field in barn owls that were raised with visual prisms[87], and re-mapping of the somatosensory cortex after deafferentation of the hand in adult macaques[88,89].

Changes in subcortical connectivity. Reorganization of long-range subcortical connectivity can also mediate plastic changes. However, this form of plasticity seems to be limited to developing organisms and to rely on the stabilization of normally transient and redundant pathways (FIG. 1a). In the case of cross-modal plasticity, the most striking example is that of the congenitally blind mole rat. In this subterranean animal, the retinal innervation is sparse, visual structures are partially degenerated and

the cortical map of visual space is imprecise[90]. However, it has been shown that the non-degenerated occipital cortex is occupied by either somatosensory or auditory representations, depending on the species. In the case of 'auditory colonization' in one species, *Spalax ehrenbergi*, tracing studies have found an alteration in the projection from the inferior colliculus — an auditory relay — to the thalamus. In addition to projecting to the auditory thalamus, the inferior colliculus also projects to the non-degenerated visual thalamus, leading to the recruitment of the non-degenerated occipital cortex by auditory stimuli[62,91,92]. This animal model shows that large changes in subcortical connectivity can occur under evolutionary pressure, raising the possibility that they could also occur in genetically blind or deaf humans. It is unclear whether the visual cortex of these animals could be recruited to mediate visual functions if it were actively stimulated — for example, by retinal implants or direct electrical stimulation of the optic nerve.

Although not directly related to cross-modal plasticity, there are other examples of plasticity that is mediated by changes in long-range subcortical connectivity. For example, removal of area TE in adult monkeys leads to a durable deficit in visual memory (area TE is a part of the inferotemporal cortex, at the final stage of the ventral visual pathway, which is thought to be essential for the visual discrimination and recognition of objects). However, a similar lesion in young monkeys has few behavioural consequences. The immature state of the cortex and its connectivity at the time of the lesion could allow such sparing in young monkeys. In particular, exuberant, normally transient connections between cortical area TEO — another area in the inferotemporal cortex — and the amygdala (which are normally pruned down during development) were maintained as the pathway that normally connects TE and the amygdala degenerated and failed to compete in the juvenile monkeys. This process involves the maintenance of normally transient TEO–amygdalar connections as well as the sprouting of further TEO–amygdalar connections. Such extensive reorganization was not seen if the lesion occurred in adulthood[93]. Removal of the target visual areas 17 and 18 in the cat has similar consequences. Ablation of these areas at birth has a very different effect from removal during adulthood, not only on visually mediated tasks, but also on the pattern of connectivity from the thalamic visual relay to the cortex. In particular, a specific pathway from the lateral geniculate nucleus to the middle suprasylvian cortex, which is normally small, becomes significantly expanded after early, but not late, ablation of areas 17 and 18 (REFS 94,95).

The few available data indicate that changes in long-range subcortical connections are rare in adults. If such reorganization is at the core of cross-modal reorganization, adaptation to implants is likely to be slow and difficult, especially in the adult. This view is supported by the finding that congenital deafness leads to deficits in cortico-thalamic and cortico-cortical connectivity, which can be corrected by cochlear implants only if the implantation is carried out during the sensitive period of the auditory system (that is, during the first five months of life in the cat)[96,97]. In fact, Klinke, Kral and collaborators have shown that synaptic activity and columnar organization in the auditory cortex of congenitally deaf adult cats are abnormal, indicating the presence of functional deficits that are likely to hinder the success of implants[98].

Changes in cortico-cortical feedback. Another possible mechanism for cross-modal reorganization of early sensory cortices in the deaf and the blind is the enhancement of cortico-cortical feedback (FIG. 1b). The efficacy of feedback pathways in shaping neuronal responses in early sensory areas has received much support recently[99,100]. For example, feedback connections from area MT to earlier visual areas are crucial in determining the centre–surround organization of neurons in these earlier visual areas[101]. Although it is not known whether feedback connectivity can recruit early sensory areas in the absence of feedforward activation, several studies support the view that the strength of the feedback connectivity can be modulated by sensory input. Such a modulation has been implicated, for example, in cross-modal facilitation in the sensory cortex of non-deprived adult individuals. Macaluso, Frith and Driver[102] have found that recruitment of infero-temporal regions that are important for visual object recognition can be enhanced by simultaneous tactile stimulation of the hand on the same side as the visual target. Analysis of the functional connectivity between brain areas in this condition has led them to propose that the enhancement is mediated through backprojections from multimodal areas, such as the parietal cortex, to visual cortical areas.

The proposal that cortico-cortical feedback, especially from parietal cortex, might be a source of cross-modal rearrangement has recently been advocated on the basis of a few imaging studies of the blind and the deaf[44,49]. For example, there is enhanced functional connectivity between the parietal cortex and earlier visual areas in deaf individuals when they are attending to the peripheral visual field[44]. The range of plastic changes that relies on modifications of feedback connectivity is still unknown, but it is clear that this connectivity is more likely to be modifiable, even in adulthood, after implants or any kind of altered experience, and should therefore be more widespread.

Changes in long-range cortico-cortical connectivity. An alternative mechanism, albeit more hypothetical, is the stabilization of long-range cortico-cortical connections between sensory modalities (FIG. 1c). Such cross-modal connections have been described in immature cats and hamsters[9,103], and more recently in mature primates[104,105]. One of these studies reports that there is a sizeable pathway from the primary auditory cortex to the zone that represents peripheral vision in the primary visual cortex in adult monkeys[104]. Degeneration of that connection in deaf individuals might reduce the interactions between auditory and visual projections in this convergence zone that mediates peripheral vision, allowing enhanced visual skills in the peripheral field, which have been noted in deaf individuals. Along the same lines, in blind

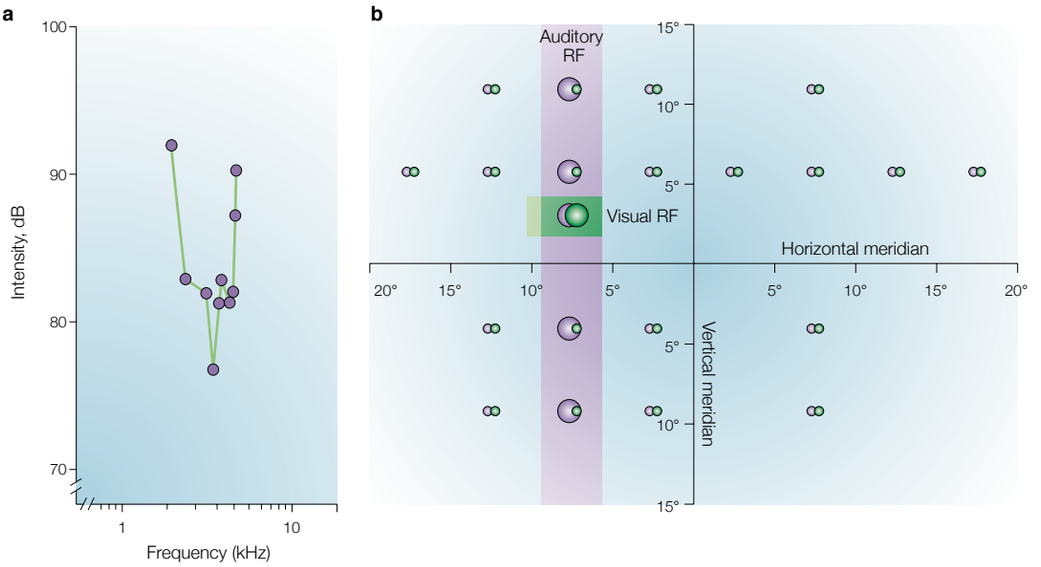


Figure 2 | **Auditory responses of primary visual cortical neurons. a** | Example of the tuning curve of a V1 (primary visual cortex) neuron to pure tones. Different cells were observed to have different optimal frequencies, all with similar narrow tuning, indicating that they are not just part of a general arousal system, but that they participate in the analysis of auditory and visual stimuli. Modified, with permission, from REF. 114 © 1973 Elsevier Science. **b** | Illustration of the spatial specificity of bimodal units in V1. Typically, the auditory field is aligned with the visual field along the horizontal meridian, whereas the acoustic receptive field (RF) is unbounded in the vertical dimension. This organization is consistent with the observation that the spatial localization of auditory cues is difficult in the vertical plane. The greater the size of the symbol, the greater the response. Green, visual RF; purple, auditory RF. Modified, with permission, from *Nature* (REF. 109) © 1972 Macmillan Magazines Ltd.

individuals, reinforcement of that A1–V1 connection, owing to the lack of input from the visual pathway, could account for the recruitment of V1 during the processing of oral language[79,80].

This direct connectivity between the primary auditory cortex and the primary visual cortex could also account for a number of cross-modal effects that have been interpreted so far as reflecting modulation through back projections from multimodal areas[102]. For example, silent lip reading has been associated with activation of the parabelt regions of the auditory cortex[106]. This result is often understood as a form of 'auditory' imagery associated with lip reading, which could occur through strengthening of the connectivity between auditory areas and the multimodal superior temporal cortex area as a result of everyday speech perception. But a direct connection from the visual cortex to the auditory cortex could provide an alternative mechanism. Along the same lines, Shams and Shimojo[55] have recently described a visual illusion in which the same visual stimulus is perceived as either one flash in the absence of auditory stimulation or two in the presence of two auditory beeps. Electroencephalographic (EEG) recordings made while subjects view these stimuli show an early visually evoked potential in the illusory flash condition, indicating an early site for this cross-modal effect (but see REF. 107 for a discussion of early components of the ERP and the possibility that they represent feedback from multimodal areas).

Probably the most direct evidence for the view that cross-modal plasticity could occur very early in the hierarchy of brain areas comes from a handful of pioneering studies that have reported auditory and/or somatosensory evoked activity in neurons of the primary visual cortex of non-deprived animals[108–115]. The two most detailed studies, using microelectrode recordings in unanaesthetized cats, found that ~35–40% of units in V1 were multimodal. Interestingly, auditory responses in these V1 neurons were tuned to a narrow frequency range, indicating functional specificity (FIG. 2a), and had receptive fields that were spatially aligned with their visual ones along the horizontal meridian[109,114] (FIG. 2b). Although these studies are tantalizing, their findings need to be confirmed. It will be particularly important to determine the latency of these cross-modal responses to clarify their origin. On the one hand, in mice, Bonaventure and Karli[66] have reported auditory evoked responses in visual areas with a latency as short as 10 ms, and have shown that these auditory responses are dependent on the integrity of the connections between the inferior colliculus and the visual areas. On the other hand, work in cats has shown responses with latencies longer than those of the primary visual afferents. These responses could therefore result from other processes, such as cortico-cortical feedback[110,115]. In humans, there is little evidence available on this topic. Anecdotal reports indicate that brief visual deprivation in adults can lead to improved performance on auditory or tactile tasks. More recently, studies that combine behavioural and imaging approaches have begun to look at this issue[116]. Clearly, investigating the degree of multimodality in primary cortices will be an important avenue for future research. Although assessing this issue in humans is one of our goals, it will prove difficult to

distinguish true cross-modal feedforward connectivity from effects that are due to imagery, cross-modal attentional modulations or other kinds of feedback process using blood-flow techniques alone[107]. These possible confounds highlight the value of concurrent electrophysiological studies and animal investigations of this issue.

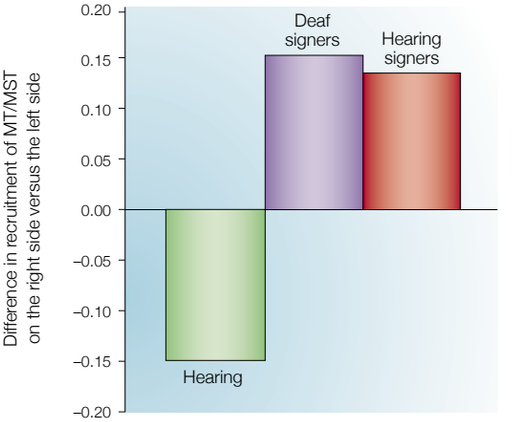
Specificity, constraints and outstanding issues

This review has focused primarily on the cortical and subcortical sites of reorganization after sensory deprivation, and has documented several behaviours that are modified following sensory deprivation. However, if we are fully to characterize and understand the functional consequences of sensory deprivation, we need to distinguish the specific aspects of processing that are modified by deprivation from those that stay unchanged. Furthermore, it will be necessary to separate out the effects of sensory deprivation from those of altered language experience that usually accompany sensory deprivation in humans (such as the use of Braille or sign language). Indeed, alterations in behaviour and cortical organization in deaf or blind individuals are attributed as frequently to altered language experience as they are to altered sensory experience. Our behavioural, ERP and fMRI studies of congenitally deaf subjects indicate that there are marked and specific changes in visual processing that are due to auditory deprivation, and that these are separate from the effects of acquiring sign language, as they are not observed in hearing native signers. Other effects are seen in both hearing and deaf native signers. For example, early exposure to sign language leads to a change in the lateralization of the motion-detection system (FIG. 3a). Whereas non-signing, hearing individuals can detect motion direction more accurately in the left than in the right visual field, and show greater recruitment of motion areas in the right than in the left hemisphere during motion processing, the opposite pattern is observed in signers, regardless of whether they are deaf or hearing[46,48,117–119]. By contrast, changes in peripheral visual attention are observed in deaf individuals but not in hearing signers, indicating that signing, even though it requires monitoring of ~15° of visual angle, is not sufficient to promote this change (FIG. 3b).

Our research highlights the specificity of plastic changes. For example, we have found that only certain aspects of visual attention are modified by early deafness. Deafness leads to a change in the spatial distribution of visual attention over the visual field, with an enhancement of visual attention towards the peripheral visual field. But other aspects of visual attention seem to remain unchanged by deafness, such as the ability to detect the presence of a target among distracters, or the number of items that can be attended at once[43,120]. These results raise the possibility that, within a domain of processing (such as vision), there is considerable variability and specificity in the nature and the timing of the effects of altered sensory experience.

This variability probably reflects different sensitivities within different brain systems to the timing of changes in experience. Indeed, over the past 30 years,

a **Signing alone can alter the lateralization of area MT/MST**



b **Deaf but not hearing signers display enhanced peripheral visual attention**

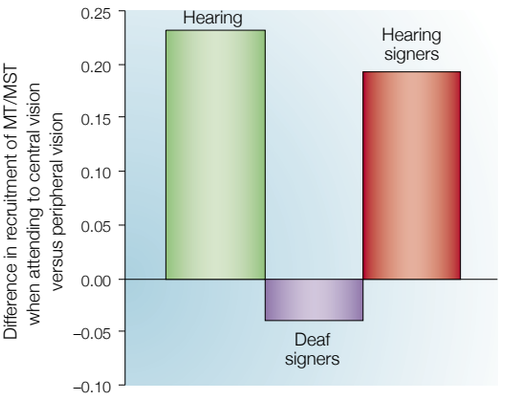


Figure 3 | **Studies of cross-modal plasticity in the deaf have indicated separate effects of altered language experience and of altered sensory experience. a** | Early exposure to sign language, for example, leads to a change in the lateralization of the motion-detection system (MT/MST). Whereas hearing individuals show greater recruitment of the motion areas in the right hemisphere than in the left hemisphere during motion processing, the opposite pattern is observed in signers, independently of whether they are deaf or hearing. **b** | Deafness, on the other hand, leads to changes in the spatial distribution of visual attention, with enhanced allocation over the peripheral visual field. These changes are observed only in deaf individuals. The fact that they are not found in hearing signers indicates that signing, even though it requires monitoring of ~15° of visual angle, is not sufficient to promote this change.

animal research has documented highly variable and specific effects of both sensory deprivation and training on the organization of cortical areas that represent that sensory system. These studies have shown that some neural systems and associated behavioural capabilities are affected by experience only during specific time periods (sensitive periods), and that different systems have different sensitive periods[121]. For example, within the visual system, the development of acuity, orientation preference, ocular dominance

columns, stereopsis, and photopic and scotopic vision have different sensitive periods[122–124]. More recently, Maurer and Lewis[125] have shown not only that different visual functions mature at different rates, but also that, for a given function, different timings are observed depending on the plastic events studied. In particular, these authors have shown that the period in which a function is impaired by altered experience, the period in which a function can still recover from injury, and the period in which the function reaches adult levels of proficiency overlap, but are different. For example, in humans, visual acuity reaches adult levels at ~6–8 years of age; however, visual acuity is affected permanently by cataracts with an onset of up to ~10 years of age, and recovery from early cataracts ceases at ~4 years of age[125]. This variability in the timing of experience-dependent modifiability probably arises in part from differences between subsystems in the rate of maturation, the extent and timing of redundant connectivity, and the presence of chemicals and receptors that are important for plasticity[126–128]. By contrast, some neural systems do not seem to be constrained by sensitive periods. For example, re-mapping of the representation of the visual fields after retinal lesions can occur throughout life[129], as can re-mapping of the primary cortical representation of the digits after amputation or training[83,130], and of auditory representations following auditory training[131,132].

The available data, therefore, raise the working hypothesis that it might be possible to distinguish between several broad classes of brain systems on the basis of the nature and extent of neuroplasticity that they show. Probably the best-studied case is that of sensory maps. Sensory maps develop early, but unlike most early-developing perceptual processes, they retain the capacity to be reshaped by temporal coincidences at all ages[83,129,131,133]. In addition to sensory maps, it might be helpful to contrast two other different types of brain system. On the one hand, some systems show a well-defined sensitive period during their development. The development of such systems will proceed normally only if the relevant experience is available during this sensitive period; modifications of experience after this period are less likely to induce change, but lack of experience during the sensitive period will undoubtedly result in durable abnormalities. For example, this is the case for the development of early visual functions, such as depth perception or ocular dominance columns[124,134], but also for more slowly maturing visual functions, such as the integration of long-range orientation or the ability to detect pinpoints of light at the far edges of the visual field[135,136]. On the other hand, there are brain systems that show a remarkable capacity for learning throughout life. Even if experience during development is abnormal, these systems might be less influenced by early aberrant experience, and can make use of enduring mechanisms of plasticity to become tuned to the processing requirements that are imposed by environmental inputs. One example is the case of word and object recognition. Our capacity for learning new shapes and associating them with semantic tags is extremely robust throughout altered sensory or language experience. In fact, one of the few functions to improve with age is the size of one's vocabulary. This is not to say that these functions always show the same level of plasticity in infancy and adulthood; in fact, many show greater plasticity in infancy. Whereas infants acquire about one new word per waking hour between the ages of 1 and 4 years, the acquisition of lexical items is arguably slower in the adult. However, the striking feature of these functional systems is their maintained ability to change with learning, albeit slowly, even in adulthood.

It is interesting to note that some of the brain functions that seem to be susceptible to early experience — such as visuo-spatial attention[36,44], global processing[137] and episodic memory[138] — are mediated by the dorsal pathway, whereas many functions that are more robust across early experience and throughout life — such as object recognition, local processing and factual knowledge — are mediated primarily by the ventral pathway. Although certainly underdefined, this trend might provide a common framework for the various developmental disorders that have been shown to alter dorsal-stream processing, such as dyslexia[139], autism[140] and WILLIAMS' SYNDROME[141].

Conclusions

There are important gaps in our knowledge of the consequences of unimodal sensory deprivation on the anatomy and function of primary sensory areas that are associated with both the remaining and the missing sensory modalities. We need to determine the uni- or multimodal nature of these areas, the impact of sensory deprivation on their efferent and afferent connectivity, and the extent to which the structural changes that are observed mediate behavioural changes. Future studies using methods and approaches that allow high spatial and high temporal resolution will clarify the roles of these areas in compensatory changes in behaviour following sensory deprivation.

There is converging evidence for both behavioural enhancements in processing within remaining modalities in deaf and blind people, and increased activation within multimodal brain areas in such individuals. Looking across studies of both within- and between-modality neural plasticity, we have proposed several mechanisms at the system level that might mediate such changes, and have shown how some of these mechanisms are available only at certain times in developing organisms, whereas others are accessible at all times, even in adults. These mechanisms are not mutually exclusive; rather, they are likely to combine to give rise to the complex palette of plastic changes described. However, one common feature that is highlighted by this work is that the character of the observed plastic changes is specific and depends on the nature of the altered experience, the timing of the altered experience and the particular brain systems that are modified.

WILLIAMS' SYNDROME
A hereditary developmental disorder that is characterized by cognitive impairment (usually mild mental retardation), distinctive facial features and cardiovascular disease.

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Acknowledgements
This work was supported by grants from the National Institutes of Health to D.B. and H.J.N., and from the James S. McDonnell-Pew Foundation to D.B. We thank B. Röder for insightful comments and advice.

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