Trends in Neurosciences

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Review

Crossmodal plasticity in hearing loss

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Crossmodal plasticity is a textbook example of the ability of the brain to reorganize based on use. We review evidence from the auditory system showing that such reorganization has significant limits, is dependent on pre-existing circuitry and top-down interactions, and that extensive reorganization is often absent. We argue that the evidence does not support the hypothesis that crossmodal reorganization is responsible for closing critical periods in deafness, and crossmodal plasticity instead represents a neuronal process that is dynamically adaptable. We evaluate the evidence for crossmodal changes in both developmental and adult-onset deafness, which start as early as mild–moderate hearing loss and show reversibility when hearing is restored. Finally, crossmodal plasticity does not appear to affect the neuronal preconditions for successful hearing restoration. Given its dynamic and versatile nature, we describe how this plasticity can be exploited for improving clinical outcomes after neurosensory restoration.

Highlights

Crossmodal plasticity is a textbook example of the ability of the brain to reorganize based on use. In the auditory system, crossmodal plasticity is evident in all degrees of auditory deprivation and may be reversed in some cases of adult-onset hearing loss.

Neither developmental nor adult crossmodal plasticity appear to involve extensive reorganization of structural connectivity. Instead, they typically involve strengthening and weakening of existing connections, often top-down heteromodal projections.

The auditory system is a model system for neurosensory restoration with neuroprostheses, and the dynamic and versatile nature of crossmodal plasticity can be exploited clinically for improving the outcomes of neurosensory restoration.

Crossmodal plasticity in the auditory system

Crossmodal plasticity (see Glossary) is an adaptive change in the drive of neurons from one (deprived) sensory input towards another (non-deprived) sensory input; in other words, it is a form of between sensory systems (intermodal) plasticity [1]. Crossmodal plasticity represents a textbook example of the capacity of the brain for plastic changes.

In early studies in animal models, massive crossmodal visual takeover of the auditory cortex has been found when early deafness was combined with aspiration of the auditory midbrain: such combined intervention led to reorganization of anatomical inputs to the thalamus and large-scale remapping of the auditory cortex by visual inputs [2,3]. These studies probably demonstrated the maximal possible functional adaptation of the auditory cortex to novel input. What was subsequently often overlooked is that this extensive reorganization was made possible by aspiration of the auditory midbrain that allowed the visual afferents to target auditory thalamus (in addition to visual thalamus) during development. That is, anatomical rerouting of visual information to the auditory thalamus (that does not normally accompany sensory deprivation) was a precondition for this massive reorganization. In the case of auditory deprivation, many textbooks subsequently suggested that the entire auditory cortex becomes a battlefield between sensory systems, and each of its areas can be recruited for a new sensory function (Figure 1). This is often considered to be a key reason for the developmental critical periods for sensory restoration: such 'colonization' of the auditory system would preclude processing of auditory inputs after neurosensory restoration, for example via cochlear implants. Therefore, such crossmodal reorganization would be a key reason why critical developmental periods close. This has important clinical consequences: to prevent fostering this effect it was traditionally recommended not to use visual communication (sign language) before cochlear implantation. However, as our review will show, the aforementioned concept of massive crossmodal reorganization and its negative influence is not consistent with recent findings and requires modification.

We propose that crossmodal reorganization is a dynamically modified process initiated already in mild or unilateral hearing loss continuing into complete deafness, and occurs both in congenital

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and adult-onset hearing loss (albeit with significant differences). It is a primarily a top-down driven process that exploits pre-existing neuronal connections. In essence, we argue, crossmodal reorganization is not detrimental for neurosensory restoration; instead, it is compensatory and can be used to enhance communication before therapy or aid in enhancing real-world speech perception.

Crossmodal effects in deafness

Crossmodal 'supranormal' enhancements of visual and somatosensory modalities have been extensively documented in subjects that were deaf from childhood [10–18]. The extensively studied visual effects have been related to enhanced visual motion detection and localization abilities [12,19–23], better visual change detection [24], or faster reactions to visual stimuli in deaf subjects [25,26]. However, not all visual functions show such supranormal performance [27]: for example, there was no change in visual acuity, brightness discrimination, contrast sensitivity, or visual motion direction sensitivity. Predominantly those functions that the visual and auditory systems have in common (e.g., localization, movement detection, and change detection, namely 'supramodal' functions [28]) have the capacity to become compensated by crossmodal plasticity. This specificity of crossmodal reorganization raises the question of the extent and limits of reorganization of the brain with respect to crossmodal plasticity.

In developmental deafness, in both humans and animal models, enhanced visual spatial localization and visual movement detection are associated with cortical auditory areas underlying localization and movement (congenitally deaf cats, CDCs [28]; early deafened cats [29]; and humans [23]). In humans, face processing was observed in the temporal voice area of prelingually deaf humans [30]. Auditory cortex contribution to face processing was also noted in postlingually deaf adults [31]. Given these findings, it appears that crossmodal reorganization switches the sensory (but not behavioral) roles of the auditory cortex [23,28,29]. Supporting this, a recent human study emphasized the overlap of the crossmodally reorganized region with the previously observed region of auditory motion detection in hearing subjects [32]. This is compatible with a change in the driving sensory input during crossmodal reorganization – from auditory to visual – but the change principally preserves the subsequent corticocortical processing.

The normal auditory system, characterized by exceptional timing precision, provides key 'calibration' timing information to other sensory systems (similarly to the way the visual system is key for spatial information owing to its high spatial acuity) [33,34]. Indeed, in cases of conflict in timing, hearing can 'override' visual information (e.g., auditory capture effect [35,36]), whereas vision similarly overrides hearing in spatial location discrepancy (e.g., the ventriloquist effect [37]). Therefore, visual and somatosensory temporal processing are negatively affected by deafness [33,38]. It is interesting to note that deaf individuals, when tested under well-controlled conditions, may also infer timing properties from spatial cues, but they only perform well in these situations if both are correlated [39]. Auditory feedback of motor actions through secondary auditory cortex has also been demonstrated to be key for action timing [40]. Consequently, hearing loss may have adverse effects on the spared sensorimotor functions.

Causality and specificity in crossmodal reorganization

Causal evidence of crossmodal reorganization is difficult to obtain. Studies that directly test the causality of crossmodal reorganization have been conducted primarily in animal models where invasive studies are feasible, for instance in the CDC, an important model of pediatric congenital deafness [41–43]. CDCs show supranormal performance in visual localization and visual motion detection compared to normal hearing cats [28]. Using cooling deactivation of specific auditory areas, activity in these areas can be reversibly silenced and behavior can be assessed to test for potential causal links between deactivated areas and their behavioral functions. Regions

Glossary

Crossmodal plasticity: a change in properties of neurons leading to stronger responsiveness to stimuli of the non-deprived modality. In the present text, the term 'crossmodal' is reserved for conditions with hearing loss. This could refer to structural reorganization which involves formation of new fiber tracts, or functional reorganization referring primarily to changes from latent unmasking of existing pathways.
Heteromodal inputs: inputs to a given sensory area originating from another modality; namely visual or somatosensory inputs into the primary or secondary auditory cortex.
Multimodal areas: cortical areas that are responsive to stimulation via more than one modality; the neurons in these areas can even be non-responsive to stimulation from a single modality. Multimodal responses are classified into subadditive, additive, and superadditive depending on the amount of change caused by adding another modality.
Multimodal reorganization/ plasticity: a change in the properties of neurons owing to multimodal stimulation in subjects without sensory deprivation.

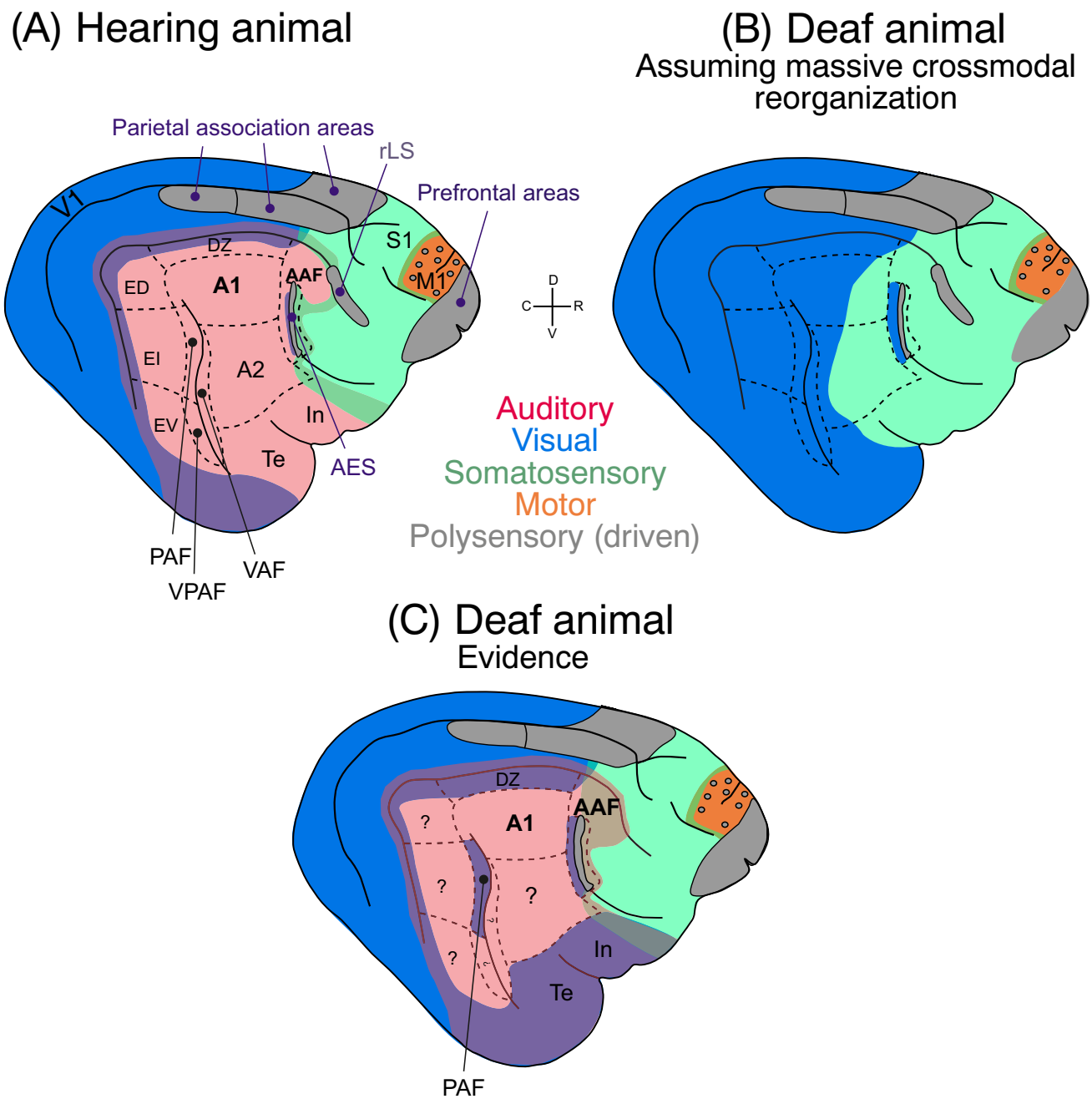

Figure 1. Schematic illustration of the approximate locations of sensory brain areas in the cat and their reorganization in deafness. Color key: blue, visual; red, auditory; green, somatosensory; orange, motor; grey, association areas. A mixture of colors at sensory borders (that appear as violet, light brown/golden, and deeper green) depicts bimodal responsiveness (~two colors). (A) The area of the anterior ectosylvian sulcus (AES), together with areas corresponding to human insular cortex [4]. The ectosylvian sulcus (divided into the dorsal area, ED; intermediate area, EI; and ventral area, EV) corresponds to human superior temporal gyrus [5]. Feline prefrontal cortex is likely multisensory based on tracer studies [6]. Rostral lateral sulcus (rLS) and/or AES allow multisensory integration in the superior colliculus [7]. The 'parietal association cortex' comprises two separate areas within Brodmann area 7 [8,9]. Visual responsiveness was observed in the posterior belt not only in ED [5] but also in DZ. Auditory and visual responses have been described around the cruciate sulcus in M1. Visual responses and auditory responses were reported in the pericruciate association cortex, shown here as grey circles within the motor cortex (orange). Cingulate cortex on the medial hemisphere and ventral limbic areas (entorhinal cortex

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found to be subserving supranormal visual performance were the posterior auditory field and dorsal auditory cortex (dorsal zone), whereas the primary auditory field A1 and the anterior auditory field (AAF) were not involved [28]. The CDC replicates crossmodal effects observed in humans and allows exact identification of the cortical regions responsible for the behavioral effects. Taken together, the CDC data and the aforementioned human studies indicate that crossmodal plasticity shows a strict areal specificity and that crossmodal plasticity switches the sensory but not behavioral roles; in other words, supranormal visual behavior in deafness is subserved by auditory cortical regions that underlie the same auditory behavior.

Areas involved in this crossmodal plasticity, when studied using retrograde tracers to reveal their anatomical connections (fiber tracts), generally showed only a small percentage of new (ectopic) connections to non-auditory areas. That means that the connectivity patterns to other sensory systems were similar for CDCs and hearing cats, and only individual connection strengths were changed in CDCs (dorsal cortex [44] and posterior auditory field [45]; later deafening in cats is addressed in [46,47]). The overall effect size of ectopic connections (which were a small percentage of all connections) did not explain the behavioral outcomes of supranormal visual motion detection and visual localization ability in CDCs. The few ectopic projections observed are unlikely to be a consequence of new axonal sprouting targeting new cortical areas, but instead may represent developmental exuberant projections [48] that are normally pruned by experience but were preserved in congenital deafness [44,49]. These exuberant connections are often formed between anatomically bordering areas and may provide these with a higher susceptibility to crossmodal change than distant areas. The data are not completely consistent with this concept only in the anterior auditory field AAF of early deafened cats, where more anatomical reorganization was observed [47]. However, area AAF is special because of the large number of somatosensory areas and fibers closely neighboring it, which are potential candidates for tracer pickup and require further study.

However, this does not mean that there is no effect of congenital auditory deprivation on the auditory cortex (reviewed in [43]). Two consequences of deafness in CDCs are relevant in the present context: (i) a specific reduction of corticocortical interactions [50], and (ii) reduction in functional intrinsic cortical connectivity between supragranular and infragranular layers [51]. These deficits could be related to a specific reduction of top-down interactions between secondary and primary auditory cortices [52]. Infragranular layers are the source of top-down interactions. Indeed, dystrophic effects (reduced thickness) were observed in infragranular and granular layers but not in supragranular layers in A1, dorsal zone (DZ), and secondary auditory cortex (A2) [53]. Reduced activity in infragranular layers of area A1 has also been observed [54]. This all suggests that top-down interactions (that are known to develop after bottom-up interactions [55]) are more sensitive to developmental alteration of hearing than are bottom-up interactions. A change in balance between bottom-up and top-down interactions may play an important role in crossmodal plasticity [53,56]. Reduced functional connectivity (measured by spike-field coherence) between superficial and deep cortical layers appears to be a key element responsible for integration of cortical column and contributes to the reduced top-down interactions between primary and secondary cortical areas in deafness [51]. Taken together, the cortical column becomes reorganized in congenital deafness, potentially to change the balance between thalamocortical and corticocortical inputs towards corticocortical inputs. It is important to

and parahippocampal gyri) are not shown. (B) A putative cortical map under the assumption of massive crossmodal reorganization in congenital deafness. (C) An approximate representation of actual cortical organization in congenitally deaf cats according to the evidence reviewed in the text. Abbreviations: A1, primary auditory field; A2, secondary auditory field; AAF, anterior auditory field; In, insular cortex; M1, primary motor cortex; PAF, posterior auditory field; S1, primary somatosensory cortex; Te, temporal cortex; VAF, ventral auditory field; VPAF, ventro-posterior auditory field.

emphasize that both the thalamic input and bottom-up interactions were not eliminated in CDCs [52] or posterior auditory field [50], explaining why auditory responsiveness is preserved when stimulated with a cochlear implant (*ibid.*).

The timeline of feline auditory cortical synaptogenesis covers the first 1–2 months of life, followed by synaptic pruning [57]. In CDCs this process was delayed by 1 month and the pruning was significantly increased [57]. It is likely that such pruning predominantly eliminates existing inactive cortical synapses, which may involve the majority of auditory corticocortical synapses in deafness. The more active 'visual' synapses, on the other hand, may survive and become stabilized in deafness. These visual synapses are likely those that come from other cortical areas and from multimodal thalamic regions such as lateral posterior nucleus. These may convey multimodal interactions in the auditory cortex of hearing animals.

Taken together, these lines of evidence indicate that it is not the reorganized fiber tracts but predominantly the synapses, their number, and synaptic efficacy that convey crossmodal effects. Compared to adult-onset deafness, congenital deafness has additional effects in preventing multimodal integration and potentially preserving exuberant heteromodal connections (see below). Future studies of functional connectivity would provide clearer insights into the changes related to sensory deprivation and crossmodal reorganization (see Outstanding questions).

Multimodal integration and its relation to crossmodal effects

The high specificity of the crossmodal effects described above suggests a tight relationship between crossmodal plasticity and regions that receive **heteromodal inputs** (and even multimodal inputs) in hearing (Figure 2) [58–61]. Heteromodal influences in sensory cortices are modulating rather than driving [62,63], often involving phase effects on oscillations [61,64,65] and reflecting behavioral low-dimensional effects [66]. Multimodal integration requires higher associative areas with large functional interareal connectivity [67] that provide the top-down heteromodal inputs to sensory areas [68].

Heteromodal influences are more pronounced in higher-order auditory areas [64,69,70]. This has been in part related to attention and motor activity, including the corollary influence of movement [66,71]. Their effect is often inhibitory in nature, possibly with the aim to suppress responses to self-produced or otherwise predicted sounds [71,72]. This all makes clear why a sensory system cannot be completely encapsulated or isolated in the brain: there is a need for the ability to modulate it depending on behavioral context. Overall, heteromodal influences in auditory cortex are not driving but modulatory in a 'normal' brain, and they increase with increasing level of 'cortical hierarchy'.

Visual influences in auditory cortex have been observed in subjects with normal hearing when visual and auditory inputs were coherent, for example during lipreading [73–75]. Similar effects were further documented in hearing subjects using sign language [14]. Pre-existing visual influences have been found in areas of hearing animals that are known to undergo crossmodal plasticity (visual responses in cats [76], visual responses in mice [70], somatosensory responses in ferrets [77], and visual responses in ferrets [78]). The role of these visual inputs was to modulate an auditory response [62], including inhibitory effects [79].

These effects were sometimes reminiscent of the influence of attention on oscillatory responses [64]. The effect has been stronger in higher-order auditory areas than in primary areas [80]. Similar subthreshold influences have also been described in higher-order somatosensory and multisensory regions [81]. Heteromodal top-down influences may be interpreted in the sense of the

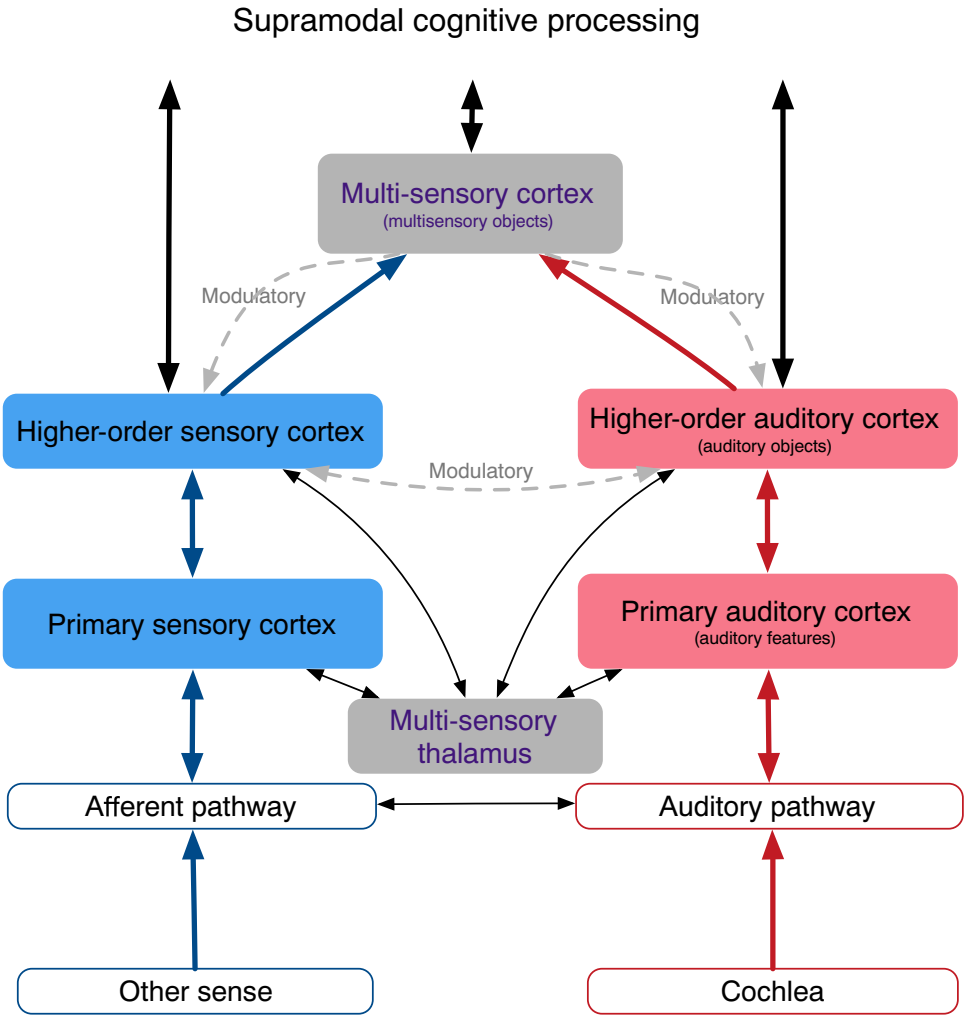


Figure 2. Simplified schematic of connections between sensory systems in hearing subjects. The auditory system is shown in red, non-auditory in blue, and multisensory in grey. Connections are differentiated into driving (shown as straight lines), defined as connections able to elicit action potentials in the absence of other active connections, and modulatory (shown as curved dashed lines), which affect the activity of neurons but fail to cause postsynaptic action potentials in the absence of other inputs (text for details). Connections between primary areas not shown because these differ between different sensory cortices. Multisensory information is observable in all cortical areas (filled background), but mainly as a modulatory influence. The main driving input comes from within the sensory system (the adequate input).

prediction error hypothesis, where predictions penetrate through the network hierarchically from top to bottom [82,83] and modulate the information flow in the reverse direction.

Cortical **multimodal areas** are extensively connected to sensory areas by top-down modulations [67,84], and thus provide multimodal and hetermodal inputs to the auditory cortex (Figure 2). Interestingly, in early deafness, higher-order auditory cortex additionally takes over functions related to cognitive processes [85–87]. In age-related hearing loss, cognitive processes compensate for degraded auditory input [88]. Reduced auditory acuity may reorganize the interaction between sensory and higher-order cortices, such that cognitive and crossmodal processes are upregulated to compensate for effortful listening, thus depleting cognitive reserve

[89] and possibly underlying the association between hearing loss and cognitive decline in adults [90].

The existing evidence thus suggests that the source of heteromodal activity in deafness depends on pre-existing modulatory influences on neurons, partly caused by top-down inputs from associative (multisensory) areas (Figure 3). Thus, the specificity of crossmodal plasticity with respect to cortical areas is likely due to fiber tracts that normally connect these areas to heteromodal and multimodal areas and provide heteromodal information also in hearing animals. Their role is stronger, accentuated, and becomes driving only when these cortical areas are deprived of their dominant driving input.

Studies on hearing restoration following congenital deafness additionally document issues with multimodal binding, particularly fusion of visual with auditory inputs; processing of multimodal

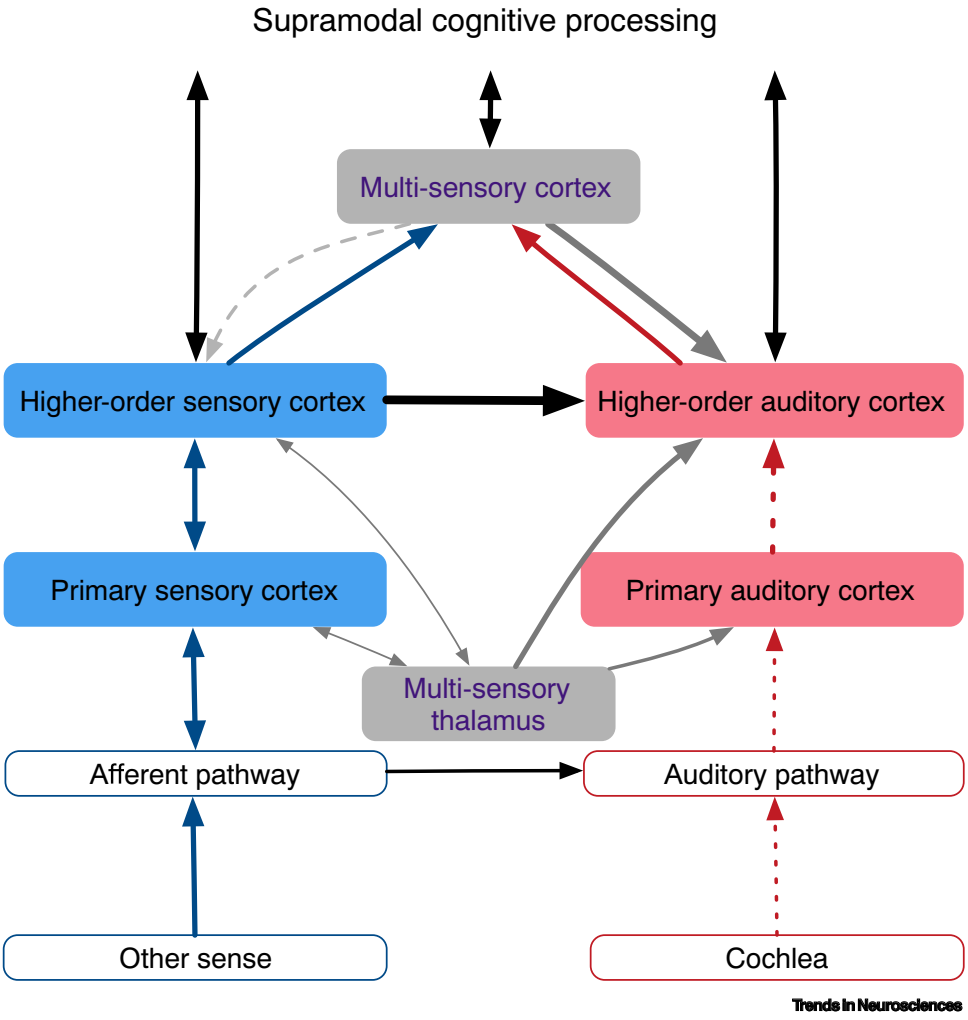


Figure 3. Schematics of the crossmodally reorganized hearing-impaired auditory system. The main reorganization is the change of the modulatory heteromodal inputs into driving inputs, both from the secondary heteromodal areas as well as from multimodal areas. The effect is assumed to rely on resetting the working point of neurons in the auditory cortex. The absent auditory (adequate) input is shown by dashed lines.

stimuli is instead dominated by the visual inputs if hearing restoration is later in life [91]. Correspondingly, in CDCs the neurons in the crossmodally reorganized area dorsal cortex did not show evidence of audiovisual fusion [49]. Corresponding outcomes have been recently reported in congenital blindness [92]. This confirms studies showing that early multimodal experience is essential for the development of multimodal processing capabilities [93–95]. The full potential of multisensory rehabilitation cannot be harvested if sensory restoration occurs too late in congenital deafness. In humans, the timeline for full effectiveness in restoration interventions is probably the first 2 years of life [91]. These considerations also explain why developmental deprivation has more severe consequences compared to late (adult-onset) deprivation.

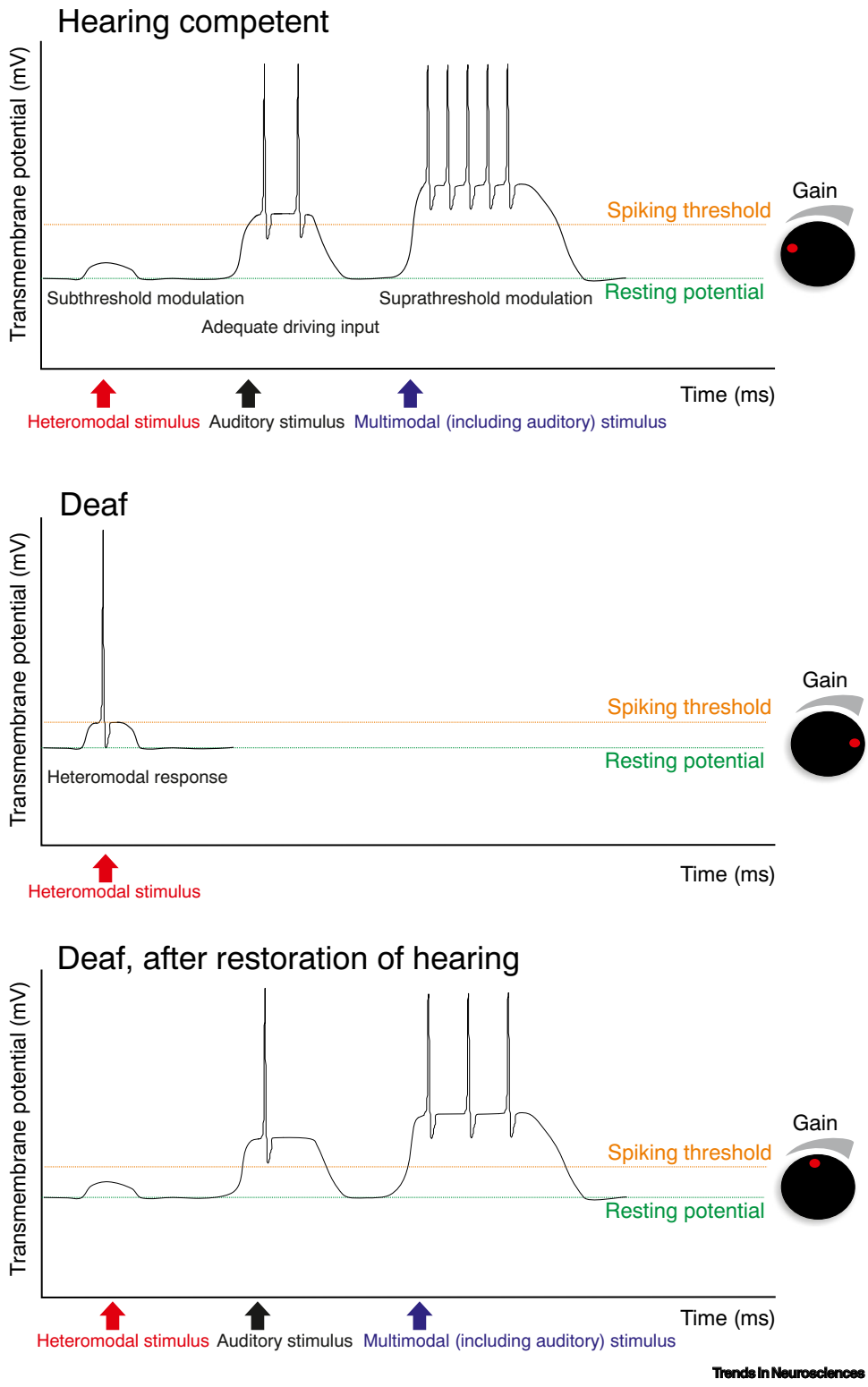
Crossmodal plasticity: a dynamic, flexible and reversible process?

There is growing evidence of crossmodal effects in mild and aging-related hearing loss. This is underscored by the high incidence of hearing loss in aging and the key importance of hearing loss in the pathophysiology of age-related cognitive decline [90]. In rats, crossmodal visual plasticity has been observed in secondary auditory areas following partial hearing loss in adulthood [96]. This suggests that even partial adult hearing loss can induce crossmodal plasticity. Indeed, in a series of studies in people with mild–moderate aging-related hearing loss, crossmodal effects have been described [89,97–102]. Recent evidence shows that crossmodal reorganization appears early, within 3 months of adult-onset hearing loss [89], and can be reversed with as little as 6 months of treatment with hearing aids [102]. Adding to its versatility, crossmodal plasticity reported in unilateral hearing loss can be reversed after cochlear implant use, although somatosensory cross modal effects appear to reverse more completely than visual effects [103], which is consistent with a continued reliance on the visual modality for disambiguating the auditory signal through a hearing aid or cochlear implant [91]. However, reversibility is more limited with congenital deafness compared to adult-onset hearing loss [104], and there is an abnormal dominance of visual inputs and absence of multisensory fusion if congenital deafness is restored after the second year of life [91].

These studies demonstrate that crossmodal reorganization is a dynamic and relatively fast process. It does not require structural changes and waxes and wanes with mild sensory deprivation. The same neuronal circuitry can thus be used for crossmodal effects as well as for physiological processing of multimodal inputs.

We propose that the first neuronal step in fast crossmodal changes is a change in overall neuronal responsiveness (Figure 4). This is finely regulated in cortical neurons, and, in experimental models, changes in excitability of neurons can be induced through various paradigms, such as by using acetylcholine which can enhance intrinsic excitability [105] or by manipulations that cause changes in the excitatory–inhibitory balance [106,107]. In deafness, the main driving input to auditory neurons is eliminated, and heteromodal inputs in auditory regions are typically too weak to drive neurons. This means that, as a first step, the neurons are silenced, leading to an inevitable sequence of adaptation that counteracts this effect. Homeostatic plasticity [107–110] adapts the working point of synapses and the spiking threshold of neurons, and synaptic changes affect the excitatory–inhibitory balance to allow neurons to generate action potentials. In our view, reduced neuronal input will cause adaptation of neuronal responsiveness by these cellular and network mechanisms. In the absence of the adequate sensory input, it causes increased sensitivity to the remaining inputs. This cannot fully compensate for the non-existing auditory inputs, but heteromodal inputs may transition from an originally modulatory to a driving role, and activate deprived cortical areas.

Upregulation of excitability is well documented in the cortex of deaf cats ([57,111], reviewed in [42]) and of hearing-impaired rodents [96,112,113]. Provided that inputs to neurons include



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heteromodal sensory information, a previously modulatory effect may change to driving input. Such responses will be consistent with the auditory responses observed normally in these regions and can be well processed by the same auditory circuitry. In milder hearing impairment, these changes will provide *a priori* information (in the Bayesian sense) and will thus be naturally adaptive. In complete deafness, crossmodal effects will only affect functions that the auditory system has in common with other sensory systems and that are normally used to form multimodal representations.

In this concept of dynamic adaptive crossmodal plasticity, homeostatic excitability adaptations will serve as a volume knob on a HiFi music audio system: when input is reduced, excitability will be increased to guarantee that all information that is available, including non-auditory information, will be optimally exploited for behavioral advantage by strengthening functional connectivity via synaptic plasticity. When input to the auditory cortex is appropriately restored via hearing aids and/or cochlear implants, then excitability is dynamically downregulated, thus reversing the crossmodal changes to some extent.

A direct consequence of such adaptation in neuronal responsiveness is a change in functional connectivity. The appearance of heteromodal responses provides the window of opportunity for strengthening functional interactions to other regions [114,115] that are structurally connected but are normally functionally coupled only under specific conditions (multimodal stimulation). Neuronal oscillations ubiquitously present due to properties of neuronal membranes and environmental or self-produced rhythms [116] allow an effective mechanism of long-distance coupling by synchronized activity. Increased responsiveness also facilitates coupling under unimodal stimulation in the spared modality (i.e., the sensory system that is preserved). Phase synchronization of such oscillations has been demonstrated for between-modality coupling in hearing subjects [61,116]. Phase synchrony between primary and secondary auditory areas have been observed during top-down interactions in CDCs [51,52]. This mechanism is thus a plausible candidate for crossmodal reorganization in hearing loss: oscillatory synchronization, particularly in the form of phase reset, is under top-down control (reviewed in [116]). Dynamic crossmodal plasticity based on increased gain in the impaired sensory input allows exploitation of top-down influences from multisensory and cognitive centers to synchronize increased heteromodal responses with activity from the spared modalities. This leads to the picture of a crossmodally reorganized functional connectome. Increased functional coupling can lead to new axon collaterals, increase the synaptic counts and efficacies for heteromodal inputs in the sensory-deprived areas, and explain the easier retrograde tracer pickup in anatomical tracer studies, thus explaining more abundant ('stronger') existing connections but no ectopic connections, as observed in cats.

Functional connectivity can be studied using many methods (Box 1), including some that are applicable in humans. Functional connectivity analyses thus allow crossmodal effects to be studied in humans both in resting state as well as in response to a stimulus (reviewed in [114,117,118]).

Figure 4. Suggested mechanism of dynamic crossmodal plasticity. In a hearing auditory cortex (A), the heteromodal inputs are only modulatory and are therefore dependent on the driving auditory input. Provided that this is present, the responses can be significantly modified by heteromodal inputs. In hearing loss (B) there is reduced or no driving input, and thus homeostatic plasticity may increase excitability to such an extent that the previously weak modulating input becomes driving. Both the heteromodal response and neuronal sensitivity thereby increase; in other words, the spiking thresholds to an input decrease. After hearing restoration (C), the gain is reduced due to the restoration of a strong driving input. The heteromodal input becomes modulating again. Because hearing restoration is rarely complete, the gain of cortical neurons is between that of deaf and hearing subjects. In the schematics illustrated, the changes are modeled only by an effect on spiking threshold and response increase. This is a simplification of the multiplicity of homeostatic processes that are present physiologically.

Box 1. Connectivity quantification

The connectome, defined here as the totality of all synaptic connections between neurons in the brain, can be studied using many different methods [150]:

Structural connectivity

This defines the totality of fiber tracts connecting the brain. It can be analyzed using diffusor tensor imaging in humans or anatomical tracers in animals. Fiber tracts are established early in development, driven mainly by genetic makeup. Fiber tracts are a precondition for functional interactions, but structural and functional connectivities correlate only weakly [151]. Functional connectivity additionally depends on synaptic counts, synaptic efficacies, and excitatory–inhibitory balance.

Functional connectivity (FC)

FC defines statistical dependencies of neural activity. It can be subdivided into stimulus-related and stimulus-independent functional connectivity. Effective connectivity refers to the influence that one system exerts over the other (is directed).

Stimulus-independent FC can be assessed by (i) direct stimulation of one neural structure (electric or optogenetic) and recording in the other. In addition to fiber tracts (structural connectivity), it also depends on synaptic organization, synaptic efficacy, and the receptiveness of the target structure [52,152]; (ii) ongoing activity reveals different brain networks activated at rest or in the attentive condition such as the default mode network [118]. This method provides general information on brain networks and their hubs.

Stimulus-dependent connectivity includes the effects of stimuli on the networks. The overall brain networks can reconfigure depending on stimulation (reviewed in [118,153]). Stimulus-dependent connectivity must disentangle common inputs from direct interactions. It allows conclusions on how stimuli propagate in the brain.

Measures allowing quantification of connectivity

Several measures allow functional connectivity to be quantified

(i) Correlations [154] have the disadvantage of being dependent on the temporal function of the response, but have historically allowed pioneering insights into brain networks.
(ii) Granger causality [155,156] quantifies effective ongoing and stimulus-dependent connectivity. It provides the directionality of the connection, but is influenced by signal power and requires longer time-windows for calculation.
(iii) Mutual information and transfer entropy [157,158] directly quantify information transfer. They are influenced by signal power and require longer time-windows for calculation.
(iv) Phase-based measures such as phase coherence, pairwise phase consistency, and spike-field coherence [159,160] are power-independent and when computed on induced activity are also independent of common input. Their predominant advantage is the short time-window required for quantification; however, they do not provide directionality.
(v) A combination of several methods. For example, separating the time-frequency bands in which phase-based methods detect connectivity at high temporal resolution allows subsequent extraction of directional information (in the corresponding bands) using effective connectivity measures (e.g., Granger causality) [52].

Several publications have reported increased functional connectivity between visual, multisensory, and auditory cortex following hearing loss [119–121], with a contribution from multisensory parietal areas [122]. A decrease in intramodal connectivity and an increase in crossmodal connectivity have been reported [120]. Crossmodal reorganizations were susceptible to compensation of hearing loss by hearing aids [123] and were predictive or related to outcomes after hearing compensation [121,124,125]. These findings support the concept of dynamic flexible crossmodal plasticity that appears with hearing loss and partially subsides after hearing therapy.

In CDCs, reduced activity in the ongoing alpha band has been found in the crossmodally reorganized posterior auditory area, but not in area A1 [50] (similar visual effects in congenitally blind humans are discussed in [126]). Alpha oscillations have been additionally related to excitability changes of neurons [115]. At the same time, a loss of top-down interactions between secondary and primary auditory cortex in CDCs was prominent in the alpha band [52]. This could indicate that loss of alpha power reflects loss of top-down influence on early areas rather than crossmodal

reorganization *per se*. Similarly, alpha oscillations convey top-down interactions in humans [127], and their power has been related to speech intelligibility in hearing subjects [128,129]. Adult onset of hearing loss may also provide a different oscillatory signature than congenital hearing loss (e.g., theta oscillations [130] or delta oscillations [131]). Methodologically, oscillatory activity has the advantage of allowing a focus on different oscillatory bands, thus separating parallel neural processes [117], and further allowing separation of common input from corticocortical interaction by calculating induced oscillations (Figure 5) [114,116,132]. This is essential for studying corticocortical interactions in the absence of common thalamic input, to a large extent reflected in the traditional evoked response components. Current neuroscience techniques provide the tools required for more detailed analysis of these effects in the future (Box 1).

Crossmodal plasticity resulting from gain change and subsequent effects on functional connectivity, although adaptive, has limitations: in congenital deafness it cannot provide the substrate for multisensory integration and cannot guarantee normal development of the auditory system. Critical auditory periods are not due to colonization by the visual or somatosensory systems from crossmodal processes; they are instead a consequence of an absence of adequate sensory input, consequent abnormal development, and pronounced loss of cortical auditory synapses (reviewed in [42,43]). Therefore, corticocortical interactions are predominantly affected by early deprivation [50]. Only some auditory areas can take over specific visual and somatosensory functions. Reduced thickness in deep cortical layers (a predominant source of top-down interactions) throughout all studied auditory cortical areas [53] suggests that, despite crossmodal reorganization in congenital hearing loss, massive alterations in the cortical microcircuitry are observable [50,52]. Furthermore, dystrophic changes in deep layers were observed in all studied auditory areas, including those not involved in crossmodal reorganization. This means that the effect is due to auditory deprivation *per se*, and is not compensated by crossmodal reorganization. In vision loss, processing within auditory cortex is strengthened in the bottom-up direction, consistent with a shift in the sensory balance in favor of hearing [56,79]. This supports the present concept and represents another interesting aspect of future crossmodal research in hearing loss.

There are also limitations regarding the compensatory nature of this plasticity: visual stimuli may help (in the Bayesian sense) to disambiguate the auditory inputs. Visual stimulation alone, however, obviously cannot compensate for loss of auditory experience nor can it negatively interfere after early restoration of hearing. Finally, the early developmental auditory effects of deafness are subject to critical periods, and this may compromise the ability to form multimodal representation by use of the deprived modality.

Clinical implications

Dynamic flexible crossmodal plasticity has several clinical implications. In adult-onset hearing loss, crossmodal plasticity can be adaptive and compensatory in many ways. When it is not possible to restore a deprived input, a 'sensory substitution' approach is used to transform information from the spared modality (within certain limits using its specific properties) to compensate for deficits in the deprived modality [133]. Such an approach has been reported in blind subjects using acoustic sonification of the visual information stream [134,135]. Similarly, eyeglasses which convert speech to subtitles for persons with hearing loss have recently become technically possible and represent a future commercial crossmodal application. In hearing loss, lipreading which activates auditory cortex is used routinely for rehabilitation [104,136–141]. Somatosensory enhancement of speech perception via cochlear implants was reported to aid speech understanding in deaf patients [142,143]. Thus, crossmodal stimulation can be harvested for clinical applications using the spared modalities [144].

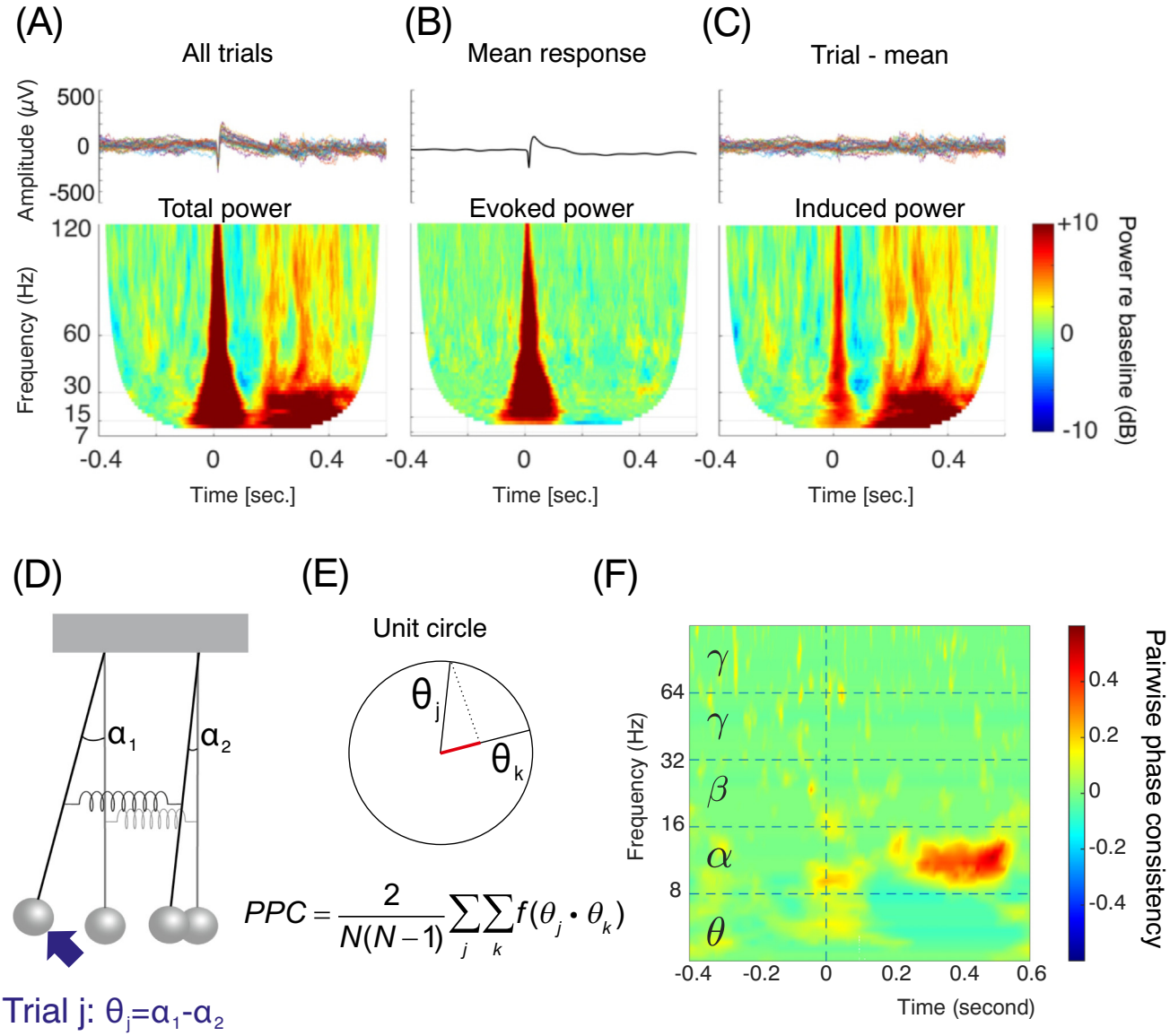

Figure 5. Functional connectivity related to an auditory stimulus determined from oscillatory activity. (A) Primary auditory cortex response to an auditory stimulus (click train, three clicks, train duration 0.006 s) as observed in local field potentials recorded with a microelectrode. (Top) 30 trials of the stimulus presented at 0 s result in a response that is reproducible (phase-locked) in each trial (within 0–0.1 s post-stimulus) and a response that jitters in time from trial to trial (0.2–0.6 s). (Bottom) Time–frequency representation (TFR) allows computation of the mean total power, revealing both responses that cover all relevant frequency ranges. (B) Computing an average LFP in the time domain mainly preserves the phase-locked response (0–0.1 s). TFR reveals the evoked power. (C) Subtracting the average from each trial better isolates the non-phase-locked induced activity that is well preserved in the TFR where the response does not disappear during averaging because power is averaged but not the amplitude. (D) To compute connectivity between two oscillators, the trial-to-trial stability in phase differences of oscillations quantifies the coupling strength (spring stiffness). θ_j defines the phase difference in oscillations for trial j. (E) When the phase differences in two different trials (denoted j, k) are plotted on the unit circle, the projection of one onto another reveals their stability. This is achieved by calculating the sum all mutual dot products of the unitary vectors for each trial combination, normalized to the number of trial combinations. Abbreviation: PPC, pairwise phase consistency. (F) Example of two sites recorded in primary and secondary auditory cortex of a hearing cat, demonstrating a PPC increase in the time between 0.2 and 0.5 s after presentation of the brief click train. Using this approach, the synchrony of the activity between cortical sites can be determined with specificity to frequency and with millisecond precision. Using induced activity for PPC computation additionally eliminates common inputs. Data from [52].

In prelingual (congenital) deafness, including visual cues in communication is adaptive and may be leveraged clinically, particularly in the time before intervention. The disputed maladaptive consequences of visual crossmodal plasticity are in our view unlikely to be an issue if restoration of hearing is provided as soon as is feasible (within the critical period) to assure a functional auditory system and multisensory interactions that include the auditory modality.

Consistent observations in other sensory systems

The notions discussed here are further supported by observations on other sensory systems. In blindness, rewiring does not appear to be necessary for the crossmodal effects being reported [145]; however, response properties and implicitly functional interactions in occipitotemporal network are affected by blindness [146–148]. Similarly, somatomotor reorganization following amputations is somewhat limited and corresponds to the present considerations [149]. Taken together, it appears as if the textbook examples of brain plasticity in function loss need revision: the crossmodal adaptations do not rely on the ability of the brain to take over (any) functions, but rather uses pre-existing circuitry that is modified depending on the overall input to the given areas, governed by excitatory–inhibitory balance and homeostatic plasticity. In such a perspective, crossmodal plasticity is exploitable for therapeutic approaches and allows objective monitoring of the efficacy of neurosensory restoration and subsequent rehabilitation.

Concluding remarks

The brain can make use of the same neuronal circuitry for qualitatively different functions by dynamically adapting synaptic gain (synaptic rescaling) and inhibition, causing stimulus- and condition-dependent functional connectivity reorganization in the absence of structural changes. This is particularly advantageous in the case of reduced sensory input. The evidence discussed in this article is consistent with the notion that the substrate of crossmodal reorganization is essentially synaptic and functional, that it operates at the microscopic scale, and leads to functional connectivity changes in the absence of large-scale rewiring of the brain. Auditory responsiveness is generally preserved in the absence of hearing experience, both in primary and higher-order auditory cortical areas. Crossmodal reorganization is likely supported by (i) few exuberant connections are formed during development and abnormally persist into adulthood in congenital hearing loss, and (ii) local increases in axonal collaterals and in the synaptic efficacy of heteromodal inputs, facilitated by (iii) increased sensitivity of target neurons deprived of their natural (adequate) auditory input, attentional modulation, and (iv) their influences on neuronal oscillations and their interareal coupling. Heteromodal inputs originate predominantly from top-down interactions that can similarly affect neuronal oscillations. This explains why even adult-onset mild-to-moderate hearing loss can facilitate crossmodal reorganization that is reduced or reversed after hearing restoration. Understanding the neuronal mechanisms of how functional connectivity and thus information flow can be reversed from bottom-up to top-down will provide further insight into the constraints of crossmodal plasticity.

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Declaration of interests

A.K. has received consultation fees from Cochlear Ltd and Advanced Bionics GmbH. A.S. declares no completing interests.

Outstanding questions

What are the exact molecular mechanisms of gain change in crossmodal plasticity, and are they the same for the different cortical areas involved? Can they be leveraged clinically? Identifying such molecular mechanisms would open a wide field for pharmacological modulation of cortical plasticity.

Given its top-down nature, is crossmodal reorganization associated with up- or downregulation of cognitive reserve in age-related hearing loss, and does it play any role in the link between hearing loss and cognitive decline?

How can multimodal representations be established at a later age in congenital deprivation? Are there ways to extend critical periods by behavioral or new molecular approaches?

What is the therapeutic potential of sensory substitution in hearing-impaired individuals (e.g., glasses that translate speech into written text in real time) for auditory cortical representations? How effective are these approaches for clinical applications – do they support or prevent adaptations to the newly provided auditory input?

How different is crossmodal plasticity between sensory systems? A different developmental sequence and different roles of the sensory systems in cognition suggest that differences in crossmodal plasticity across sensory systems may exist. Addressing this question is challenging, partly because the reversibility of total deprivation is most clinically feasible in the auditory system; it is often an elusive goal in the other systems. New methodological approaches would be required for progress in this area.

Should oral language learning for deaf children with cochlear implants be multimodal, exploiting all crossmodal adaptations, or should it be primarily auditory-focused to prevent excessive crossmodal reliance?

Is crossmodal reorganization reversible even after very long periods of age-related hearing, given that typically older adults receive hearing aids after 10+ years of hearing loss onset?

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