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Higher-order auditory areas in congenital deafness: Top-down interactions and corticocortical decoupling

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ABSTRACT

The theory of predictive coding assumes that higher-order representations influence lower-order representations by generating predictions about sensory input. In congenital deafness, one identified dysfunction is a reduced activation of deep layers in the auditory cortex. Since these layers play a central role for processing top-down influences, congenital deafness might interfere with the integration of top-down and bottom-up information flow. Studies in humans suggest more deficits in higher-order than in primary cortical areas in congenital deafness. That opens up the question how well neurons in higher-order areas can be activated by the input through the deprived auditory pathway after restoration of hearing with cochlear implants. Further it is unclear whether their interconnections to lower order areas are impaired by absence of hearing. Corticocortical anatomical fiber tracts and general auditory responsiveness in both primary and higher-order areas are generally preserved in absence of auditory experience. However, the existing data suggest a dichotomy between preservation of anatomical cortical connectivity in congenital deafness and functional deficits in corticocortical coupling. Further, cross-modal reorganization observed in congenital deafness in specific cortical areas appears to be established by functional synaptic changes and rests on anatomically preserved, genetically-predetermined and molecularly patterned circuitry connecting the sensory systems. Current data indicate a reduced corticocortical functional coupling between cortical auditory areas in congenital deafness, both in bottom-up and top-down information stream. Consequently, congenital deafness is likely to result in a deficit in predictive coding that affects learning ability after late cochlear implantation.

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1. Introduction

The brain continuously generates predictions about the environment that shape perception. While a city dweller visiting the rain forest perceives an irritating complex mixture of unfamiliar sounds coming from the nature, the native person can easily disentangle the mixture of acoustic features and instead perceives the presence of the animals generating these sounds. In familiar soundscapes the individual sensory features of sounds step into background and the sensory objects step forward (Ahissar et al., 2009; Hochstein and Ahissar, 2002).

The brain, based on experience and active interaction with the environment, groups individual sensory features into meaningful sensory objects. A sensory object is here understood as a neuronal representation of a delimited pattern of features that is subject to a figure-background distinction. In this sense, sensory objects are the result of grouping features into stable perceptual units (Bizley and Cohen, 2013). They are the result of abstraction of the sensory input into the essential, distinctive features defining the object. The object, once created, is consequently invariant to non-distinctive features. Many features are required to be able to safely discriminate between individual objects, but once the objects have been defined by experience as a perceptual category, already few, and even downgraded features in the sensory stimulus can be used to perceive the corresponding object. This greatly facilitates the identification of sensory objects even in noisy backgrounds.

Adult, experienced subject's cognition is not a passive blank slate that is bottom-up written by the sensory systems. Cognitive structures formed by experience are constantly active, forming a "framework" for perception. The cognitive framework is defined at any given moment by the active objects and the sensory input is fed into this active framework. This framework, given by the behavioral context, can significantly affect perception. Consequently, we have expectations on the type of sensory input we are likely to receive in the given situation, shaping the perception.

Indeed, cortical responses to sensory stimuli measured by imaging methods were suggested to reflect the difference between the expectation and the actual stimulus (Arnal et al., 2011; den Ouden et al., 2010; Friston, 2010; Sedley et al., 2016). Learning itself, e.g. learning of a sensory skill, is possibly initiated by a difference between prediction and actual input, and the goal of learning is to minimize this difference, the "prediction error" (Rescorla and Solomon, 1967; Sevenster et al., 2013; Sohoglu and Davis, 2016). The error signal resulting from the comparison between expectation and actual sensory input is the driving signal for learning (Rescorla and Solomon, 1967).

The computation of the prediction error requires a circuitry that compares what has been learned previously and what enters the brain through the sensory systems (Bastos et al., 2012; Friston, 2010). This postulates a cortical circuitry capable of performing a comparison between bottom-up information, reflecting the sensory stimulus, and top-down information, reflecting the information on sensory objects. Cortical columns represent a candidate for such function (Kral and Eggermont, 2007; Raizada and Grossberg, 2003; Bastos et al., 2012).

Here we review evidence that congenitally deaf show deficits in this circuitry indicating that top-down information cannot be integrated in the processing of sensory input when sensory restoration is performed late. We suggest that such functional deficits in

the columnar microcircuitry contribute to deficits in auditory perception and closure of sensitive periods in congenitally deaf subjects after late cochlear implantation.

2. Congenital deafness and the representation of sensory features and objects

The effects of sensory loss can be differentiated into deficits in the ability to discriminate stimuli (i.e. perceive their difference) and deficits in the ability to identify auditory objects (i.e. to abstract from the features and to identify the same stimulus as the same one). The restoration of hearing with cochlear implants allows investigating the deficits that were caused by development in absence of hearing with regard to feature sensitivity and the ability to form auditory objects. There is a remarkable difference in auditory performance between subjects that lost hearing in adult age and those that lost hearing in early childhood, if both groups receive cochlear implants in adulthood (reviewed in Kral and O'Donoghue, 2010; Kral, 2013). It is important to note that when stimulated with a cochlear implant, both groups of subjects "hear" a sound. However, after receiving the cochlear implant, the adult deafened subjects tune-in to the new auditory input and can learn to discriminate and categorize the electrical stimuli even after decades of complete deafness. Within three months after implantation such late-deafened subjects as a rule reach a reasonable hearing performance and start to understand spoken sentences in a natural environment. In contrast, early-deafened subjects who are implanted late in life show persisting deficits in discrimination and identification of sounds and in speech understanding (Busby et al., 1992). Despite some improvement in auditory performance with time (Busby et al., 1992; Schorr et al., 2005), they do not reach performance comparable to late-deafened subjects. Implantation has to take place during first years of life to allow development of auditory performance and speech understanding (Fryauf-Bertschy et al., 1997; Kral and O'Donoghue, 2010; McConkey Robbins et al., 2004; Niparko et al., 2010; Schorr et al., 2005; Waltzman et al., 1992). It is one major task of auditory neuroscience to understand the reasons behind these differences between early- and late-implanted congenitally deaf individuals.

Historically, auditory neuroscience has mostly concentrated on easily observable feature sensitivity like tonotopic/cochleotopic organization in primary auditory areas. In contrast, higher-order areas have been so far less in the focus of research. Because of this, more knowledge is required about interareal interactions and the function of categorization in auditory processing. As suggested previously (Kral, 2013), however, feature sensitivity and categorization are interdependent: feature representation is a prerequisite for categorization, and the framework of active objects can influence feature representation. In natural conditions, lower order and higher-order representations continuously interact. As we will show below, the precondition for this interaction, the cortical microcircuitry, requires hearing experience to develop and become functional.

3. Models of auditory deprivation

The role of experience on interactions between higher and lower order cortical areas can be ideally investigated in an animal model that is congenitally deprived of sensory experience. This

review will focus on animal models with a total absence of hearing during development. Total absence of experience is important, since even brief periods of vision are sufficient to initiate developmental processes in the visual cortex (Maffei and Turrigiano, 2008; Mower et al., 1983; Olson and Freeman, 1980; Rosen et al., 1992). Also in the auditory system limited hearing over brief developmental periods affects the outcome of auditory therapy with cochlear implants (Schramm et al., 2002; Waltzman et al., 1992). Thus, even a short period of limited hearing experience may already initiate some maturation of the auditory pathway.

This review will therefore focus on congenitally deaf animal models that provided information on the reversibility of the deficits in deafness by auditory experience (thus demonstrated that the effects are truly due to hearing loss). These animal models include:

Congenitally deaf white cats (Bosher and Hallpike, 1965; Kral and Lomber, 2015), where an inborn dysplasia of the organ of Corti initiated in stria vascularis eliminates hair cells and prevents hearing experience (Heid et al., 1998; Mair and Elverland, 1977; Mair, 1973). In these animals early chronic electrostimulation with cochlear implants reversed most of the deficits observed in deaf animals (reviewed in Kral et al., 2006), demonstrating that the absence of hearing experience was the cause of the deficits in this animal model.

Pharmacologically deafened cats before onset of hearing (**neonatally deafened animals**, Matsushima et al., 1991; Snyder et al., 1990). Also in these animals early chronic electrostimulation has provided evidence of reversibility of the deafness-induced deficits (Fallon et al., 2009b; Fallon et al., 2014; Leake et al., 1992; Snyder et al., 1990, 1991).

Although some effects of deafness are more pronounced in the congenitally deaf cats compared to neonatally deafened cats (Baker et al., 2010; Ryugo et al., 2010), in general they show similar consequences of deafness and we will consider these models together as congenital deafness models.

Furthermore, additional models will be used where complementary information is available which has not been provided for the completely deaf animal models. These models include **early deafened animals**, with some limited early hearing experience (Isaiah et al., 2014; Meredith and Lomber, 2011; Wong et al., 2013), animals that were deafened using surgical intervention like **cochlear ablation** where function on the deaf ear and reversibility is no longer possible to investigate (Moore and Kitzes, 1985), or models with only **moderate conductive hearing loss** induced by mechanical intervention in the ear canal or the middle ear (Keating et al., 2014; Mowery et al., 2016; Popescu and Polley, 2010; Vale and Sanes, 2002). However, we will neither extensively review all of the data concerning these latter models nor will we focus on adult-onset of deafness.

4. Bottom-up information flow: feature representation in deafness

To identify an auditory object, one has to discriminate that object from similar, yet different objects. The discrimination requires the ability to extract and represent those features in the brain that are distinctive for the objects. The ability to discriminate between different auditory stimuli thus requires feature representation. Also learning to discriminate two stimuli eliciting the exact same patterns of neuronal excitation in the brain will be difficult, since potentiating an aspect of one pattern will automatically potentiate also the other pattern. Initial feature discrimination is required for learning new discriminations.

Indeed, significant feature discrimination ability is inborn and rests on the functional architecture of the brain stored in the genes (Aslin and Pisoni, 1980; Maurer and Werker, 2014; Kral et al., 2016).

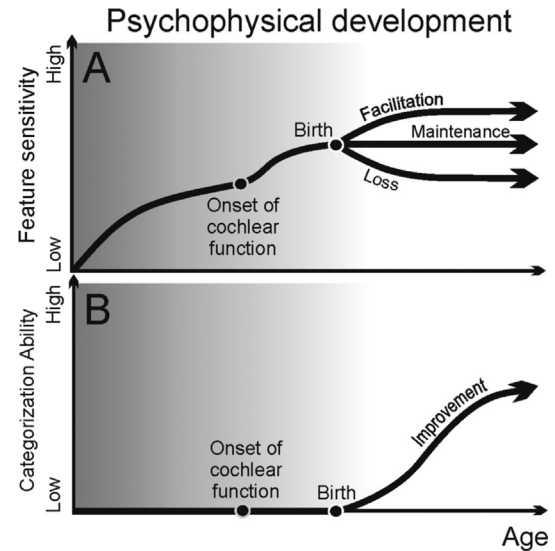


Fig. 1. Schematic description of psychophysical development in the auditory system (Kral et al., 2016). A: Feature discrimination is based on inborn architecture of the auditory system that increases throughout development (Aslin and Pisoni, 1980; Maurer and Werker, 2014). After birth some feature sensitivity, based on experience, is maintained, some is improved and some is lost. B: Categorization is established after birth, when the subject can interact with the environment. At present there is no indication of any inborn categories.

Some feature sensitivity can further improve with experience, some is lost with experience, depending on biological importance of the feature in the given environment (Fig. 1A). For example, the ability to discriminate sounds of a foreign language may be lost if they are not discriminated in the native language (Werker, 2012; Maurer and Werker, 2014). The ability to categorize sensory stimuli and by that to establish auditory objects is coupled to active experience and behavioral goals. The ability to categorize therefore can appear only after birth, when active experience is possible (Fig. 1B, see Kral et al., 2016). Interestingly, differential maturation timelines for different features were observed in hearing subjects (Maurer et al., 2007; Sanes and Woolley, 2011), as if all features could not be refined at one time by the brain. Maturation of feature representation is thus a well-timed, partly sequential developmental process that is dependent on hearing experience.

The general pattern of internuclear connections in the auditory system develops before function can shape it. The function of general connections along the auditory pathway seems to developmentally precede the cochlear function (Tillein et al., 2012). In congenital deafness, the general connectivity of the afferent auditory system is preserved and even partly functional (Barone et al., 2013; Hartmann et al., 1997; Heid et al., 1997; Saada et al., 1996; Snyder et al., 1995; Tillein et al., 2012). This conserves a basic functionality of the auditory system even in absence of hearing experience and allows the late-implanted early deaf subjects to have auditory sensations with the cochlear implant.

Despite such preserved afferent auditory pathway, the auditory system shows morphological and functional deficits related to reduced feature sensitivity in the deaf auditory system (Table 1). Dystrophic changes in the somata of the neurons throughout the auditory pathway demonstrate a reduction of activity in deaf auditory system (Heid, 1998; Hultcrantz et al., 1991; Moore, 1992). Also smeared cochleotopic gradients in the patterns of projections have been observed (Barone et al., 2013; Leake et al., 2008). More extensive functional alterations in the synapses, for example in the detailed arrangement of the endbulb of Held in the cochlear nucleus (Baker et al., 2010; Chen et al., 2010; Ryugo et al., 2010) and

Table 1

Studies concentrating on feature sensitivity in deaf animal models.

Feature sensitivity changes	Reference
Dystrophic changes in auditory pathway, anatomy	Hultcrantz et al., 1991 Moore, 1992 Heid, 1998
Reduced cochleotopic organization, anatomy	Heid et al., 1997 Leake et al., 2008 Barone et al., 2013
Reduced dynamic range	Raggio and Schreiner, 1999 Kral et al., 2006 Fallon et al., 2009a Tillein et al., 2016
Reduced cortical temporal dynamics	Kral et al., 2009
Reduced evoked firing rate	Tillein et al., 2010
Reduced temporal sensitivity	Snyder et al., 1995 Shepherd et al., 1999 Beitel et al., 2011 Sanes and Kotak 2011
Reduced contralaterality	Kral et al., 2009 Kral et al., 2013
Absent binaural facilitation	Shepherd et al., 1999 Tillein et al., 2016
Reduced ITD sensitivity	Hancock et al., 2010 Tillein et al., 2010
Reduced cortical threshold compared to brainstem threshold (cortical hypersensitivity)	Unit: Raggio and Schreiner, 1999 LFP: Kral et al., 2005 Unit response: Tillein et al., 2016
Desynchronization of activity in cortical layers	Kral et al., 2000 Kral et al., 2006
Reduced activity in infragranular layers	Klinke et al., 1999 Kral et al., 2000
Reduced cortical long-latency activity	Kral et al., 2005 Klinke et al., 1999 Kral et al., 2006

inferior colliculus (Hardie and Shepherd, 1999; Hardie et al., 1998) were further demonstrated. Correspondingly, a decrease in temporal sensitivity of midbrain neurons was found (Sanes and Kotak, 2011; Shepherd et al., 1999; Snyder et al., 1995; Vollmer et al., 1999), along with reduced dynamic range (Fallon et al., 2009a; Fallon et al., 2014; Raggio and Schreiner, 1999; Tillein et al., 2016), reduced maximum firing rate (Tillein et al., 2010) and reduced cortical cochleotopic organization (Barone et al., 2013; Fallon et al., 2009a, 2014). The region activated by cochlear implants in monopolar stimulation is not only spatially shifted laterally and caudally in the auditory cortex of congenitally deaf animals (Fig. 2), but also simplified in the dynamics with respect to temporal sequence of activation (Kral et al., 2009). Thus a response is present even in congenitally deaf animals, but the changed sequence of neuronal activation indicates changed synchrony within neuronal networks and thus consequences for more complex analysis of the evoked activity. Although some preserved extraction of for example binaural cues was observed in congenital deafness, extensive loss of interaural time difference sensitivity was demonstrated (Hancock et al., 2010, 2013; Tillein et al., 2010, 2016) along with reduced bimodal structure of the post-stimulus time histograms likely involved in the precedence effect (Tillein et al., 2010). Taken together, although the congenitally deaf auditory system retains a basic functionality, more deficits in feature representation were observed for more complex stimuli.

Feature sensitivity can be conceptualized as inborn with ongoing refinement through experience, thus sharing inborn and learned aspects. Therefore absence of hearing experience from

birth significantly degrades feature sensitivity when sensory input is restored late in life.

5. Top-down influences: auditory objects and deafness

The final goal of sensory processing is to identify the sensory

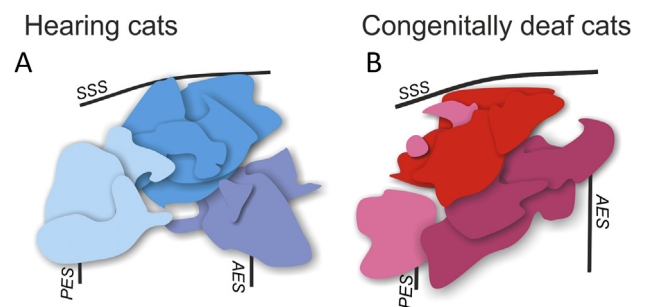


Fig. 2. Contours of 100 μ V amplitudes of local field potentials measured at the cortical surface in response to single-pulse electrical stimulation in the auditory nerve with a cochlear implants, data from (Kral et al., 2009). The size is normalized to the distance between anterior and posterior ectosylvian sulcus (AES, PES). Three hot spot were identified based on the cortical location and the morphology of the recorded local field potentials. Colors represent hearing status (red = CDCs, blue = hearing controls), spots with the same hue have same characteristics of responses (hot spot 1, hot spot 2 and hot spot 3 defined in Kral et al., 2009). A: In hearing-experienced cats, the activated spots cover the extent of both the primary field A1 as well as neighboring higher-order fields. B: In congenitally deaf cats, the activated spots are shifted ventrally and caudally, and appear more localized in the field A1. SSS - superior sylvian sulcus.

category (object) that best corresponds to the stimulus. Sensory categories start developing after birth when the subject can influence the environment and can interact with the environment (Fig. 1B). While they develop, the subject is likely to lose or decrease sensitivity for those features that are not biologically relevant for the subject, particularly if they fall in the range that is within one sensory object. This is meaningful, as it allows abstracting from insignificant feature variability. It explains the loss of feature discrimination observed in the first months after birth in children, as with regard to speech sounds that are not discriminated in the mother tongue (Fig. 1A, Maurer and Werker, 2014). In this perspective, the loss of some feature sensitivity with experience would represent an active byproduct of the increase in sensitivity for other, distinctive features of new sensory objects. As such the loss of some feature sensitivity in normal development would be very different from the generally reduced feature sensitivity observed in completely deaf subjects, as reviewed above.

Auditory objects, once established, will influence the representation of features, since not all features are relevant for all objects. Consequently, in a given context very different features may become crucial and others will be more obsolete or even distracting. It is therefore likely that those objects that are active at the given moment will influence the sensitivity to features. A constant interaction between feature representations and object representations, and between the different levels of representational hierarchy, contributes significantly to perception. A top-down effect in perception is reflected in perceptual filling-in phenomenon (Riecke et al., 2009, 2012; Wild et al., 2012).

The neural representation of sensory objects itself is difficult to observe experimentally and it remains unclear at which neural level their representation is established. Consistent with other authors (Bizley and Cohen, 2013; Giordano et al., 2013; Nelken et al., 2014), we assume that auditory objects are constructed in a distributed fashion at the cortical level.

While auditory cortical fields are in constant interaction and form a functional unit in processing auditory inputs, different functions can be assigned to different cortical fields (Lomber and Malhotra, 2008; Lomber et al., 2007). Furthermore, the cortico-cortical interactions follow schemes proposed for the visual system (Felleman and Van Essen, 1991) and allow differentiating lower-order and higher order fields in the auditory cortex, too (Rouiller et al., 1991). It is tempting to speculate that primary areas represent biologically-relevant auditory features that are used in defining the auditory objects, whereas higher-order areas synthesize these features into objects and influence the feature maps by feedback signals.

Three types of information have to be integrated during sensory processing:

1. **Bottom-up** sensory stimulus, which is the main driving influence in a sensory area. This input provides information on sensory features of the stimulus.
2. **Specific top-down** modulating influences that either come from higher order areas of the same sensory system or from multi-sensory, motor and associate areas of the cortex. These convey the information on currently “active” sensory objects and define the distinctive features that are processed preferentially based on “expectation”. There are likely both instantaneous (pre-attentive) and active (attentive) top-down interactions, as discussed previously (Kral, 2013).
3. **Non-specific wide-spread modulatory influences** from neuromodulatory systems (e.g. cholinergic, dopaminergic, noradrenergic, serotonergic systems, Edeline, 2012). These inputs are essential for control of synaptic plasticity, learning and

modulation of vigilance and can likely be activated also by sensory stimuli (and their level of “surprise”)

6. Neuronal substrates of bottom-up and top-down integration

We suggest that in order to establish the circuitry for the formation of auditory objects and the bottom-up and top-down interactions, experience is required. The substrate for such interactions is likely represented by the minicolumn of the cortex. The cortical minicolumn is a cylindrical vertical structure of ca. 200–300 μm diameter comprising all neocortical layers and consisting of cortical neurons sharing similar (yet not identical) functional properties (Douglas and Martin, 2004; Markram et al., 2015). Cortical columns are observed in carnivores and primates, but less clearly in rodents, which, however, share the laminar structure of the neocortex (Markram et al., 2015). The neurons within the column show a canonical circuit of connections described morphologically and functionally (reviews in Raizada and Grossberg, 2003; Harris and Mrsic-Flogel, 2013; Jiang et al., 2015). The layer receiving strongest thalamic input is layer IV (granular layer, “lamina granularis interna”); layers I–III are called supragranular (superficial) layers, layers V and VI infragranular (deep) layers.

It is generally assumed that the structure and function of the canonical columnar microcircuit is similar in all neocortical regions (Raizada and Grossberg, 2003; Douglas and Martin, 2004; Bastos et al., 2012; Jiang et al., 2015). In the cortical column, deep layers have a pivotal role in receiving bottom-up thalamic input, feed-forward input from supragranular layers, and top-down input from higher-order areas (Fig. 3A), allowing to compare the top-down information with the cortical input and the processing in the given column (Harris and Mrsic-Flogel, 2013). Deep layers have a modulating influence on supragranular layers (Raizada and Grossberg, 2003; Barbour and Callaway, 2008; Olsen et al., 2012).

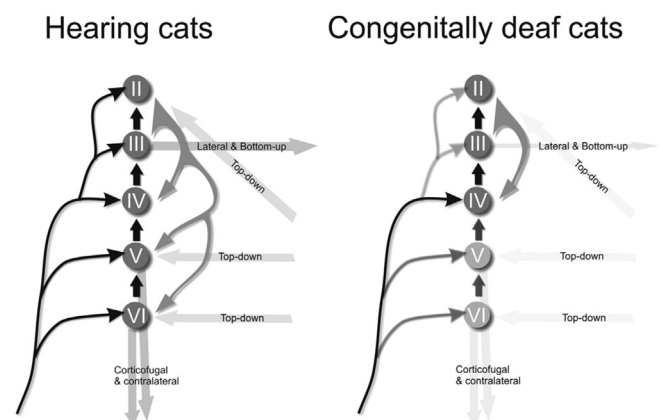


Fig. 3. Cortical column microcircuitry in hearing competent and congenitally deaf cats, based on the analysis of current source density signals from primary field A1 in hearing and deaf cats (Kral et al., 2000), combined anatomical and functional studies on auditory cortical columns in field A1 of hearing cats (Mitani et al., 1985), data from other species (Harris and Mrsic-Flogel, 2013), figure extended and modified from (Kral and Eggermont, 2007). While in hearing animals activity is initiated simultaneously in all layers and activity involves the deep (infragranular) layers V and VI, in congenitally deaf animals the deep layers show reduced activity and the pattern deviates from the normal pattern. In consequence, the data indicate that the suggested function of the cortical column, integrating bottom-up and top-down information streams, is compromised in congenital deafness. Chronic electrostimulation with a cochlear implant in early age after 2 months of stimulation (24/7 schedule) normalizes the pattern (Kral et al., 2006), demonstrating reversibility of the deficit with hearing experience.

This stereotyped microcircuit of a cortical column is a likely candidate for the function of integrating bottom-up and top-down information flow (Raizada and Grossberg, 2003; Callaway, 2004; Kral and Eggermont, 2007; Bastos et al., 2012). Things are, of course, more complex: there is an additional direct top-down input targeting layer I (review in Harris and Mrsic-Flogel, 2013, Fig. 3), potentially related to increasing the coding reliability and conveying effects of attention (Zagha et al., 2013). This projection to supragranular layers, however, does not seem to occur in all cortical areas (see e.g. Noudoost et al., 2010). The top-down projection to deep layers in early sensory areas, on the other hand, has been suggested to be the substrate of object-feature interaction (review in Kral and Eggermont, 2007; Kral, 2013).

While most of information on columnar microcircuitry rests on data from the visual and somatosensory systems, this canonical circuitry is consistent with the dissections of the cat cortical column in the primary auditory cortex at both morphological and single neuron functional data (Mitani and Shimokouchi, 1985; Mitani et al., 1985; Ojima et al., 1992, 1991; Ojima, 1994; Atencio and Schreiner, 2010a,b; for rodents comp. e.g. Barbour and Callaway, 2008). This is despite some specificity of the auditory cortex e.g. with regard to the specific cell subclasses in layer IV (Smith and Populin, 2001). Specific differences in cortical areas cause cytoarchitectonic differences between areas and document, despite similarity of the canonical circuit, also differences in detail.

Functional studies demonstrated changes in the function of cortical column of primary auditory cortex in congenital deafness (Kral et al., 2000, 2001). Congenital deafness reduced evoked activity in deep cortical layers. Chronic electrostimulation via a cochlear implant initiated early in life allowed to recruit the deep layers back into cortical processing and reestablish the normal columnar activity in the same animal model (Klinke et al., 1999; Kral et al., 2006), demonstrating that these deficits were caused by absence of hearing. Infragranular layers are a major target for feedback projections from higher-order areas (Barone et al., 2000; review in Bastos et al., 2012; Harris and Mrsic-Flogel, 2013) and are the substrate for conveying top-down interactions. Feedback projections appear late in the cortical development of the visual system (Batardiere et al., 2002; Markov et al., 2014). Due to their long developmental timelines, they are also more likely affected by sensory experience.

Absence of hearing during development interferes with the functional microcircuit required for incorporation of top-down and bottom-up stream of information in the primary auditory cortex (Kral et al., 2000, 2005, Fig. 3). The loss of activity in deep layers in deaf cats implicates their reduced influence on supragranular layers and thus deficits in integration of activity from higher-order areas with thalamic and supragranular activity. The observation further indicates additional deficits in the cortical column, including the loss of the effective connection from supragranular to infragranular layers (Kral et al., 2000). A reduced synchrony of the activity within the cortical column likely aggravates these functional deficits (Kral et al., 2001). While all deficits of the column are beyond the possible scope of this text (discussion in Kral et al., 2000, 2006), the reduced activity in deep layers of congenitally deaf cats will interfere with their role in linking the bottom-up and top-down information stream.

According to the decoupling hypothesis (Kral and Eggermont, 2007; Kral and Sharma, 2012), the effects of congenital deafness on the cortical column indicates deficits in the incorporation of information on auditory objects into auditory feature processing and thus a functional decoupling of primary fields from the influence of higher-order fields. This would preclude active shaping of auditory activity by past experience and auditory categories (Kral, 2013). The data obtained from cochlear implanted prelingually

deaf children suggests reduced or desynchronized activity in higher-order areas following late implantation (Gilley et al., 2008; Ponton and Eggermont, 2001; Ponton et al., 1996), supporting this concept.

7. The role of top-down influence in learning and plasticity

So far we have analyzed the function of interactions between different representational levels for perception and discussed the role of experience for their development. However, these interactions have also a central function in sensory learning, and have therefore important implications for learning to hear with cochlear implants.

Learning in adults is likely determined by the discrepancy between sensory input and expectation, and thus has the goal to reduce the prediction error signal (Rescorla and Solomon, 1967; Sohoglu and Davis, 2016). Because expectation is based on higher-order representations, integration of bottom-up and top-down influences, as occurring within the cortical column, are of central importance for the control of learning.

In the brain of a newborn, higher-order representations (auditory objects) are not yet established. The corresponding neural circuitry for integration of bottom-up and top-down information flow is yet immature. In the immature brain, plasticity is mainly determined by the statistics of sensory input. During development, neuronal plasticity changes from such a statistics-driven bottom-up stimulus-determined plasticity to a controlled process under the supervision of the cortical networks and the behavioral needs of the subject (reviewed in Kral, 2013). This is best documented for thalamocortical synapses (Barkat et al., 2011; Blundon et al., 2011). Supervised, adult-type plasticity, but not the juvenile plasticity, requires disinhibition (Letzkus et al., 2011; Rozas et al., 2001) and activation of modulatory systems (Chun et al., 2013; Edeline, 2012). It is likely controlled not only by the vigilance of the organism and its motivation, but also by more subtle and specific processes that include expectation of a sensory input that in case of a mismatch between expectation and stimulation can drive plastic changes.

Layer-specific profile of activity evoked by a cochlear implant in developing hearing cats in primary auditory cortex revealed that strong responses in infragranular layers appeared many weeks after responses in supragranular layers occurred for the first time (Kral et al., 2005). Consequently, the function of deep layers develops later than the function of upper layers in hearing animals. As deep layers form ontogenetically before upper layers, this finding may be related to the fact that feedback projections are established late, after feedforward projections are already set in place (visual system: Barone et al., 1996; Batardiere et al., 2002; Markov et al., 2014). Also the integration of top-down information is only meaningful after higher-order representations have been set up, and therefore the circuitry is not required during early development. The recipients of top-down inputs therefore may remain less excitable during the juvenile developmental phase. Only after some experience and the formation of auditory categories, meaningful top-down can be integrated into bottom-up processing. Only then the infragranular layers can be effectively involved into sensory processing.

But given these facts how does the deaf system develop? In the functional domain, developmental alterations and degenerative processes were demonstrated in the auditory cortex of both deaf cats (Kral and Sharma, 2012; Kral et al., 2005) and humans (Ponton and Eggermont, 2001; Sharma et al., 2002, 2005). While long-latency responses (indicative of corticocortical interactions) appeared later than early components and showed degenerative changes during development in deaf cats (Kral et al., 2005), extensive modification of the normal developmental sequence

itself was shown in functional synaptogenesis in congenitally deaf cats (Kral, 2013; Kral et al., 2005). Not only was the functional synaptogenesis delayed (and consequently controlled by mechanisms different from sensory input), also the subsequent synaptic pruning was pronounced in congenitally deaf animals. The resulting pattern of columnar activation differed from hearing controls (Fig. 3). The developmental process in congenitally deaf animals thus generated a different neuronal network than in hearing animals.

In the congenitally deaf cats the functional synaptic pruning has led to disappearance of infragranular activity after the age of three months (Kral and Sharma, 2012; Kral et al., 2005). This supports an early existence of an anatomical substrate for such columnar microcircuitry that undergoes a functional degeneration in deafness (for similar findings in the visual system, see Galuske and Singer, 1996; Katz and Callaway, 1992). It, however, does not mean that supragranular layers are mature early in life. Their structural components continue maturing and some characteristics may even mature longer than infragranular layers, e.g. in their neurofilament structure (Moore and Guan, 2001).

Learning and plasticity following congenital and neonatal deafness has been extensively studied. For this, cochlear implantation and chronic electric stimulation has been used to provide hearing experience to deaf animals (Table 2). Using this approach, animals were trained to respond either to changes in the temporal structure (Beitel et al., 2011; Snyder et al., 1995) or to specific acoustic stimuli (Benovitski et al., 2014; Fallon et al., 2009a; Klinke et al., 1999; Kral et al., 2002). The data correspond well to data from cochlear-implanted children obtained with electroencephalography (Ponton and Eggermont, 2001; Ponton et al., 2001; Sharma et al., 2005, 2007; review in Kral and Sharma, 2012). In experiments on deaf cats, several parameters of cortical function were demonstrated as developmentally plastic. Cortical responsiveness matured and substantially adapted to auditory stimulation in cases where chronic electro-stimulation with cochlear implants has been initiated early in life (Table 2; Klinke et al., 1999; Kral et al., 2002). Cortical neurons developed differential sensitivity to different sensory stimuli (Kral et al., 2006),

demonstrating emerging feature representation. Long-latency responses emerged, indicative of more complex corticocortical interactions (Klinke et al., 1999). Also temporal sensitivity could be improved by cochlear implant stimulation in neonatally deafened animals, particularly in active training procedures (Beitel et al., 2011). Dynamic ranges increased with hearing experience through cochlear implants (Fallon et al., 2009a; Kral et al., 2006). The age of onset of hearing was critical in some of these changes, and later implantations showed decreasing maturational effects, demonstrating multiple sensitive periods in the cortex (Kral et al., 2002, 2006; 2013a, 2013b).

Plastic changes involve mechanisms of changed synaptic efficiencies (Hebbian learning and spike-timing dependent plasticity, Markram et al., 2011), changes in excitatory-inhibitory balance due to differential changes in synaptic condition at these synapses (Froemke, 2015), but also include processes of homeostatic plasticity and synaptic scaling mechanisms assuring long-term stability of firing rate (Ranson et al., 2012; Shin et al., 2012; Turrigiano, 2012). There is evidence that all these processes participate on both the deficits and the adaptation to cochlear implants: expansions of the representations of the stimulated cochlear regions fit to Hebbian plasticity (Klinke et al., 1999). Late implantations did not show the same effect (Kral et al., 2002), consistent with a reduction of long-term potentiation but preserved long-term depression observed in animals following moderate hearing loss (Kotak et al., 2007). Changes in dynamic ranges and thresholds (Tillein et al., 2016; Kral et al., 2006; review in Kral and Sharma, 2012) are consistent with an involvement of homeostatic synaptic mechanisms. Change in inhibition has been implicated both from reduced amplitudes of current sources in the “deaf” auditory cortex (Kral et al., 2005) and suppressive interactions (Tillein et al., 2016), but also has been directly demonstrated in the midbrain and cortex following moderate hearing loss and cochlear ablation (Sanes and Kotak, 2011; Vale and Sanes, 2002; Vale et al., 2004). Also a habituation of the inhibitory synapse following repetitive stimulation was observed in hearing-impaired animals but not in normal hearing animals (Sanes and Kotak, 2011), likely related to temporal sensitivity of the auditory system discussed above. Furthermore, a

Table 2

Studies investigating maturation of the auditory system following compensation of congenital or neonatal deafness.

Maturation with experience	Reference
Restoration of cochleotopic organization with multichannel stimulation	Fallon et al., 2009a Leake et al., 2000
Increased variability in unit responses interpreted as differential feature sensitivity in the cortex	Klinke et al., 1999
Increased dynamic range	Kral et al., 2006 Fallon et al., 2009a
Increased evoked firing rate	Klinke et al., 1999 Kral et al., 2006
Improved temporal sensitivity	Snyder et al., 1995 Shepherd et al., 1999 Beitel et al., 2011 Sanes and Kotak, 2011
Changes in contralaterality based on experience	Kral et al., 2013 Kral et al., 2013b
Increase in infragranular layer activity & increase in synchrony across layers	Klinke et al., 1999 Kral et al., 2006
Expansion of activated area with single-channel stimulation	Snyder et al., 1990 Kral et al., 2002
Reduced response latency	Shepherd et al., 1999 Kral et al., 2013
Increase in long-latency activity	Kral et al., 2006 Fallon et al., 2009a

loss of long-term potentiation at the inhibitory cortical synapses was demonstrated in hearing-impaired animals (Sanes and Kotak, 2011). Finally, also changes in neuronal membrane properties were described in hearing loss (Mowery et al., 2015). Taken together, many cellular adaptations due to developmental absence of sensory input contributes to the learning problems observed in late-implanted congenitally deaf auditory system. Whether these differentially contribute to the bottom-up and top-down interactions is not yet clear.

Sensitive periods for the therapy of congenital deafness are likely to results from several neuronal processes (review in Kral and Sharma, 2012), involving the above cellular mechanisms. On one hand there are molecular changes in synaptic transmission during development that allow more extensive plastic changes in juvenile synapses that decrease during development (Aramakis et al., 2000; Barkat et al., 2011; Blundon et al., 2011; Takesian et al., 2012). This leads to a reduced amount of plasticity with increasing age. On the other hand there are systems changes that limit therapy of hearing loss in late developmental stages. The smeared feature representation in congenital deafness limits the potential of learning both discrimination and categorization. If distinctive features for two essential categories of input (like the voice onset time in discrimination of “ba” and “pa”) are no longer represented in the brain, their discrimination will become difficult and learning may become unsuccessful.

Normally, feature sensitivity improves in a developmental sequence with differential maturation rates for different features (Maurer et al., 2007; Sanes and Woolley, 2011). This indicates that feature sensitivity has to be learned by statistic learning of individual features “one at a time”. When hearing is restored late, this natural sequence cannot take place, increasing the demands for statistical learning.

Due to the immaturity of cortical columns, the auditory categories cannot influence feature representation effectively. A change in control of synaptic plasticity from statistical bottom-up learning to controlled top-down-modulated, supervised learning cannot happen. While the period of high (juvenile) synaptic plasticity has expired, the supervised learning was not established. The cortex is neither in the juvenile nor the adult supervised state, therefore learning is not adaptive.

It is likely that it is the combination of all these factors that closes the sensitive periods (Kral, 2013). In other words, not one single developmental factor makes sensitive periods critical; it is the combination of many factors that yields learning difficult and unsuccessful.

8. Function of higher-order auditory areas in deafness

To better understand the role of top-down interactions in the discussed issues, the function of higher order areas needs to get into focus of research. Higher-order cortical areas remained largely unexplored in deafness. Previous studies, with few exceptions, focused on primary auditory areas (review in Kral and Sharma, 2012). Are higher-order auditory fields auditory responsive in deafness? Are they dedicated to other functions and loose auditory responsiveness? Is the postulated reduced top-down influence on primary areas due to the loss of auditory responsiveness in these areas?

Electro-encephalographic studies indicated reduced long-latency responses in deaf individuals (Ponton and Eggermont, 2001; Ponton et al., 1996, 2000; Sharma et al., 2005). Since these signals are generated in higher-order areas, this provides indirect evidence of their insufficient activation in congenital deafness. Studies that attempted to separate primary and higher-order areas indicated a more extensive reduction of responses in language association areas in humans (Gilley et al., 2008; Naito et al., 2000a,

2000b). Studies investigating the behavioral function of primary and higher-order areas in animal models of deafness demonstrated differential cross-modal plasticity, mainly located in higher-order auditory areas (Lomber et al., 2010; Meredith et al., 2011; but see Meredith and Lomber, 2011), corresponding to imaging studies in humans (Nishimura et al., 1999; Finney et al., 2001, 2003; Lee et al., 2001; Leonard et al., 2012). Thus higher-order areas may swap modality in congenital deafness.

It was suspected that cross-modal reorganization eliminates the auditory nature of higher-order areas, changing them from auditory to visual areas (Kral, 2007). This different function in primary versus higher-order areas would explain why primary areas are functionally decoupled from higher-order areas in congenital deafness. However, recent findings changed this view. The secondary auditory area DZ, but not area A1, has been implicated in a behavioral visual function in congenitally deaf cats (Lomber et al., 2010). The subsequent study directly comparing projection patterns of a primary (A1) and a higher-order area (DZ) demonstrated more abnormal ectopic projections in a higher-order area than in primary auditory cortex (Barone et al., 2013) (Fig. 4). However, the extent of these anatomical changes, particularly those of new, ectopic projections to other sensory systems, was surprisingly moderate. In general, the majority of projections within the auditory system were weakened, and the majority of the distant projections with targets outside of the auditory system were slightly strengthened in congenitally deaf animals. The total number of projections within the auditory system still by far outnumbered the non-auditory projections. Anatomically, DZ thus did not become a visual area in congenitally deaf, despite its involvement in visual function demonstrated behaviorally. The “dormant” auditory structures remained the most abundant source of inputs to the “deaf” field DZ (Barone et al., 2013). This demonstrates that anatomically, visual takeover is far from complete even in congenital deafness. These outcomes have been replicated in early deaf cats in field A1 (Chabot et al., 2015), and extended to anterior auditory field (Wong et al., 2015), posterior auditory field (Butler et al., 2016) and the anterior ectosylvian area (Meredith et al., 2015). Overall, the data using different models of deafness (congenitally deaf and early deaf animals) show that the main thalamic and interareal anatomical connections (the fiber tracts) are not cardinal affected by congenital and early absence of hearing experience. The anatomical development of fiber tracts is consequently mainly dependent on the genetic makeup and molecular guiding factors.

The function of these reorganized areas, however, is cardinal dependent also on synaptic distribution on the neuron and on synaptic efficacies and is dependent on early hearing experience. Therefore, functional and synaptic studies are required to elucidate the functional consequences of deafness on these areas.

To elucidate the functionality of these dormant auditory inputs in the “deaf” dorsal auditory cortex (field DZ), we have analyzed visual and auditory responsiveness in congenitally deaf cats (Land et al., 2016). The auditory field DZ and its neighboring visual areas sending ectopic projection to this field (areas of the anteromedial and posteromedial suprasylvian sulcus, Barone et al., 2013), were mapped in electrophysiological experiments in hearing and congenitally deaf cats (Land et al., 2016). Stimulation was visual, auditory (with cochlear implants) and bimodal (visual and auditory). Visual responsiveness was moderately increased in field DZ of deaf animals (Fig. 5), representing a substrate of cross-modal reorganization observed in behavioral experiments (Lomber et al., 2010). However, the auditory responsiveness in DZ tested with acutely implanted cochlear implants was strong in deaf animals (Land et al., 2016). In fact it was three times more frequent

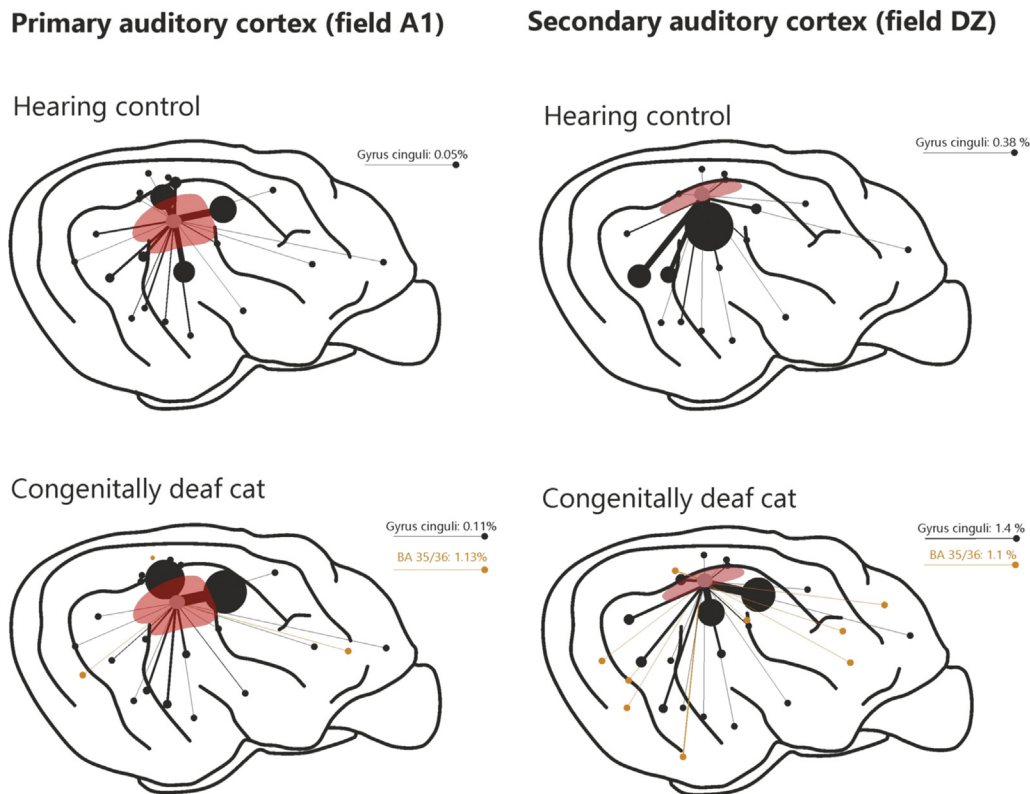


Fig. 4. Anatomical connectivity revealed by a retrograde traced in the primary field A1 and a higher-order field DZ in hearing and congenitally deaf cats, data from (Barone et al., 2013). The reddish region identifies the area with dye injection, the thickness of lines are proportional to the means proportions in hearing cats and congenitally deaf cats. For calibration, see the inset with areas not visible from lateral view (gyrus cinguli and BA 35/36). Ectopic projections to the primary auditory cortex in congenitally deaf cats are rare, to the secondary auditory cortex are slightly more abundant (orange color). BA: Brodmann area.

than visual responsiveness (Fig. 6). This is likely due to the strong thalamic inputs to DZ that are preserved (Barone et al., 2013) and thus retain the ability to drive the neurons, similarly as it is the case for field primary auditory cortex (Hartmann et al., 1997). Visual responsiveness was spatially scattered and distributed between the auditory-responsive units. These data are consistent with the theory that these visually-responsive units are the consequence of developmental exuberant projections from the visual system (Innocenti and Price, 2005) that were not pruned but strengthened (Land et al., 2016). In other words, cross-modal reorganization does not make the dorsal auditory cortex a visual cortex, it only allows it to participate on some visual function. In this regard the nurture (cross-modal takeover) is a weaker factor than nature (genetic developmental programs shaping fiber tracts and responsiveness).

The two inputs, one from the visual and one from the auditory system, were in most cases exclusive: only very few bimodally-responsive units were found, and those few that responded bimodally did show weak subadditive interactions (Land et al., 2016). Thus, the two streams of input, the dormant auditory and the reorganized visual, remained segregated. This implicates that later restoration of hearing is not likely to profit from cross-modal reorganization, as inputs from both modalities project to disjunct population of neurons. The idea is consistent with experience being necessary for developing multimodal integration (Wallace et al., 2006; for review, see Stein et al., 2014). Finally, the presence of strong auditory responsiveness is not a peculiarity of field DZ; strong auditory responsiveness was also found in the higher-order field PAF (Hubka et al., 2014), also involved in visual behavior in congenital deafness (Lomber et al., 2010).

These data on auditory responsiveness of higher-order auditory

fields indicate that congenital deafness does not functionally eliminate the thalamic drive of these fields, in other words these fields remain more auditory than visual despite cross-modal reorganization. Due to persistence of auditory responsiveness in higher-order areas we suggest that congenital deafness affects the mutual functional interactions between cortical areas as opposed to anatomical connections (Fig. 7), i.e. that deafness reduces cortico-cortical coupling (Kral and Eggermont, 2007; Kral and Sharma, 2012). Early hearing experience, by evoking synchronized activation in all auditory areas due to their auditory thalamic input,¹ initiates strengthening of their mutual corticocortical couplings and allows the development of top-down interactions. In absence of such experience the corticocortical interareal projections (fiber tracts) are largely conserved, but their synaptic efficacy and therefore their functional coupling remains low.

9. Future perspective: coupling analysis between auditory areas in deafness

The view that corticocortical coupling is impaired in congenital deafness has theoretical implications. Besides the potential of investigating the effects of deafness on predictive coding in cochlear-implemented subjects, it also requires quantifying connectivity within the auditory system of hearing and congenitally deaf

¹ Both A1 and DZ receive common input from ventral, medial and rostral pole of the medial geniculate body. However, their thalamic input also differs: e.g. DZ receives an anatomically strong input from dorsal medial geniculate body, but in A1 this input is anatomically weak (for details, see Lee and Winer, 2008; Barone et al., 2013).

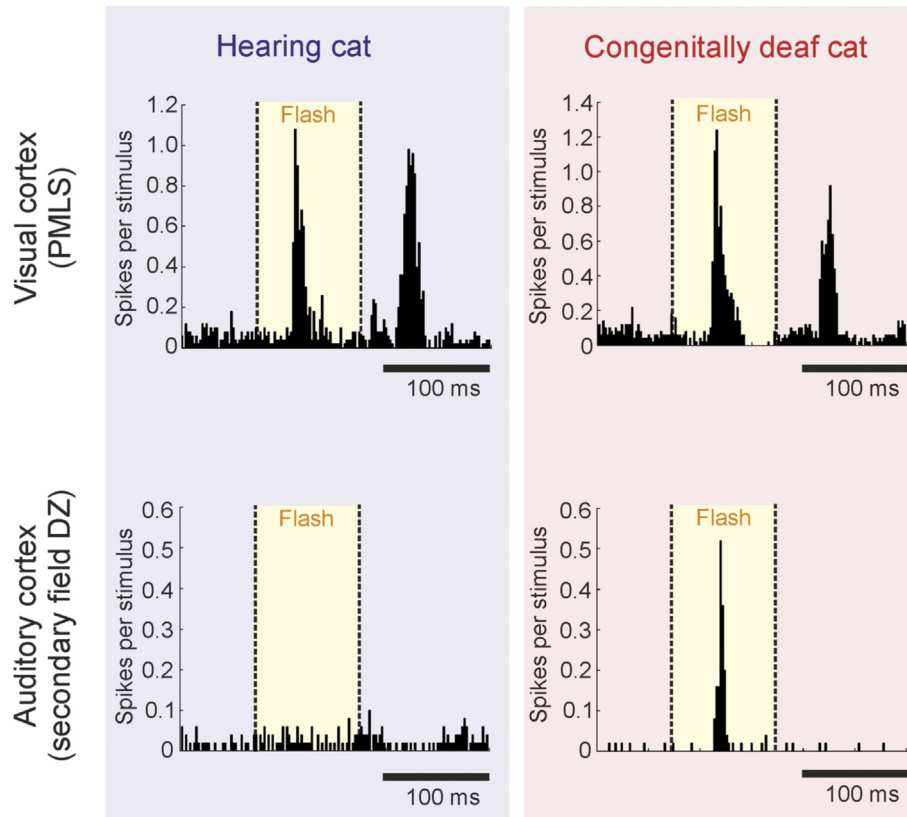


Fig. 5. Peri-stimulus time histogram of example units in visual cortex and the secondary dorsal zone (DZ) in hearing and congenitally deaf cats stimulated with a visual full screen flash. In the visual cortex similar onset and offset responses can be observed in both animal groups. In field DZ, no clear responsiveness was observed in hearing controls. In congenitally deaf cats, some units showed prominent responses to the visual flash, demonstrating a cross-modal reorganization. Bin size: 2 ms. Data from Land et al., 2016.

animals. These must go beyond anatomical analysis, given that the influence of one brain area on another is not only defined by the presence of anatomical pathways, but also on their effectiveness given by the synaptic counts and strengths. Two general types of

connectivity have been differentiated (Friston, 2011):

Anatomical connectivity. This connectivity is given by the number of projecting neurons between one and the other structure. This connectivity, however, does not involve synaptic strengths and counts and does not reveal more subtle effects of experience. As shown above, anatomical connectivity is only modestly changed by congenital or early deafness.

Connectivity measured by function, which can be further subdivided depending on the methods used to analyze it:

Functional connectivity characterized by statistical dependencies of two structures (e.g. cross-correlation). These quantify the interaction between two structures, but do not provide directional information.

Effective connectivity, characterizing the directed influence of one structure on another.

Loss of anatomical connectivity prevents functional interactions, but strong anatomical connectivity does not directly imply high coupling strength. We particularly need to analyze connectivity by functional means, as anatomical pathways appear to be more determined by genetic makeup than experience itself. It is the effect of one system exerted on the other, i.e. the function mediated by synapses that is extensively affected by experience, particularly in the cortex.

The data discussed above allow formulating further hypotheses about the deaf brain:

1. Congenital deafness should lead to reduced corticocortical effective connectivity between primary and higher-order areas. Preliminary results of experiments on simultaneous recordings from the secondary field PAF and primary field A1 in deaf cats

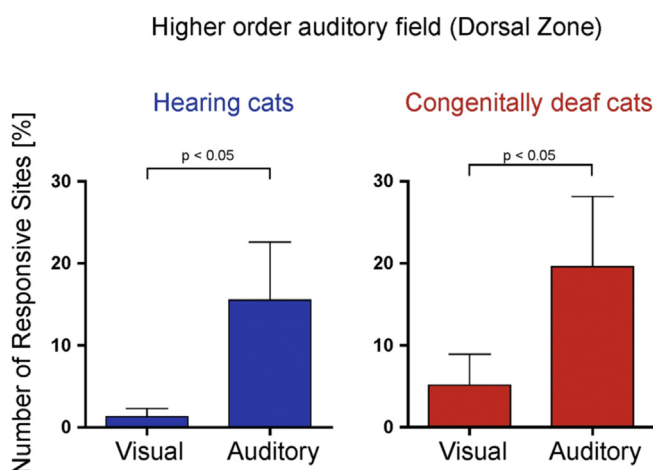
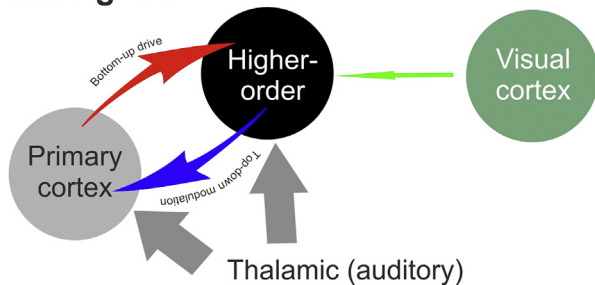


Fig. 6. Comparison of auditory and visual responsiveness of large units (>50 μ V) in field DZ of hearing controls (blue) and congenitally deaf cats (red). Shown are results for very large units that are encountered only in minority of recording positions (for smaller units and substantially stronger responsiveness, see Land et al., 2016). While visual responsiveness is significantly increased in congenitally deaf cats, auditory responsiveness remained more abundant also in congenitally deaf cats. This demonstrates that the cross-modal reorganization does not eliminate auditory responsiveness. Data from small units ("hash") yields much higher responsiveness but the same relation between modalities (not shown). Data from Land et al., 2016.

Hearing cats



Congenitally deaf cats

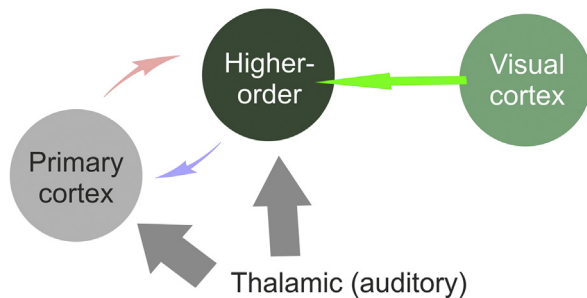


Fig. 7. Schematic illustration of functional drive in congenital deafness. While thalamic input retains functionality and can drive both primary and higher-order areas in deafness, corticocortical couplings between the auditory areas are reduced. Coupling to the visual areas is moderately increased in those areas that take over a behavioral visual function in congenital deafness.

and the analysis of their effective connectivity support this concept (Hubka et al., 2014).

2. The sparse nature of the cross-modal reorganization at single neuron level suggests that changes probably result from non-pruned exuberant connections observed transiently during development in hearing animals (Land et al., 2016) and are suggested lateral or bottom-up projections from neighboring visual fields (Fig. 7).

These hypotheses are experimentally testable. The methodological problem is the absence of a generally accepted method of coupling analysis that is artifact-free and provides strong results in all possible conditions (Bastos and Schoffelen, 2015). The most well-known issues are volume conduction in the case of local field potential analysis and the distinction of common input from mutual interconnections.

Corticocortical interactions might be reflected in the so-called induced activity, which is related to the sensory stimulus, but contrary to evoked responses its timing is not determined solely by the stimulus, therefore showing significant trial-to-trial variations in latency (Donner and Siegel, 2011; Herrmann et al., 2014; Siegel et al., 2012). Corticocortical interaction can therefore shape these induced responses. First results suggest reduced induced activity in deaf animals, with smaller effects on evoked activity (Yusuf et al., 2015). Moreover, the induced response was shown to be mediated by top-down interactions (Chen et al., 2012).

Coupling quantification can then be performed using simultaneously-recorded signals from two different areas (Bastos and Schoffelen, 2015; Uhlhaas et al., 2009), e.g. using either a phase-based analysis (like coherence and the derived measures) or using energy-based analysis, like Granger causality or mutual

information analysis. Using these tools, it is possible to demonstrate changes in strengths of corticocortical connections in dependence on hearing experience. The preliminary data on both the analysis of induced and evoked signals (Yusuf et al., 2015) and effective connectivity measured with transfer entropy (Hubka et al., 2014) support a corticocortical decoupling in deafness.

10. Conclusions

We discussed central deficits that may limit the outcome of hearing restoration with cochlear implants. We suggest that additional to compromised feature representation and reduced synaptic plasticity, changes in columnar microcircuits and interareal couplings limit the outcome of sensory restoration if performed late in life.

The experienced adult brain relies on higher-order representations for generating expectations about the environment based on the context and behavioral goals. These expectations are possible since the brain has developed a meaningful representation of the world (sensory objects) that is constantly updated and compared with external events. With the mature microcircuitry the auditory cortex can integrate bottom-up and top-down information flow. In cases of conflict between the input and these expectations, error signals drives plastic changes and learning. These processes require experience and a functional interareal and intrinsic cortical circuitry.

While primary and higher-order cortical areas are present at birth in many mammals including humans, their mutual interconnections mature during postnatal experience. In congenital deafness, such circuitry cannot develop. In addition, the bottom-up driven learning is not sufficiently effective if the periods of juvenile plasticity have already expired. In congenital deafness, the genetic program develops a naive auditory circuitry that is somewhere in between the adult experienced, less plastic but top-down supervised, and the juvenile, highly plastic but solely bottom-up driven. In this naive condition, plastic reorganization cannot be controlled by top-down modulation and, at the same time, the plasticity is not sufficient to allow adaptive changes based solely on bottom-up mechanisms. Sensitive periods close.

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