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NEUROSCIENCE FOREFRONT REVIEW

AUDITORY CRITICAL PERIODS: A REVIEW FROM SYSTEM'S PERSPECTIVE[☆]A. KRAL^{*}

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Abstract—The article reviews evidence for sensitive periods in the sensory systems and considers their neuronal mechanisms from the viewpoint of the system's neuroscience. It reviews the essential cortical developmental steps and shows its dependence on experience. It differentiates feature representation and object representation and their neuronal mechanisms. The most important developmental effect of experience is considered to be the transformation of a naive cortical neuronal network into a network capable of categorization, by that establishing auditory objects. The control mechanisms of juvenile and adult plasticity are further discussed. Total absence of hearing experience prevents the patterning of the naive auditory system with subsequent extensive consequences on the auditory function. Additional to developmental changes in synaptic plasticity, other brain functions like corticocortical interareal couplings are also influenced by deprivation. Experiments with deaf auditory systems reveal several integrative effects of deafness and their reversibility with experience. Additional to developmental molecular effects on synaptic plasticity, a combination of several integrative effects of deprivation on brain functions, including feature representation (affecting the starting point for learning), categorization function, top-down interactions and cross-modal reorganization close the sensitive periods and may contribute to their critical nature. Further, non-auditory effects of auditory deprivation are discussed. To reopen critical periods, removal of molecular breaks in synaptic plasticity and focused training therapy on the integrative effects are required. © 2013 The Author. Published by Elsevier Ltd. All rights reserved.

Key words: sensitive periods, deprivation, development, plasticity, top-down, hearing loss.

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INTRODUCTION

Brain development includes periods of higher susceptibility to alterations by experience called sensitive periods (Kennard, 1938). Periods of higher plasticity allow the juvenile brain to cope with environmental demands and adapt to the conditions into which it was born to. Interestingly, in terms of behavior, some of these sensitive periods are called critical: absence of certain juvenile experiences cannot be fully compensated later in life. The best known examples have been observed during visual development (Cynader and Chernenko, 1976; Cynader and Mitchell, 1977; Daw et al., 1992; Daw, 2009a,b; Hubel and Wiesel, 1970; LeVay et al., 1980) and in the developmental process of visuo-auditory alignments in birds (Knudsen, 1998, 2004). Several types of sensitive periods have been observed:

- periods when experience is required for the development of a particular skill (sensitive periods for development);
- periods where the system is vulnerable by manipulation of experience like monocular deprivation (sensitive periods for damage);

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Abbreviations: DZ, dorsal zone; PAF, posterior auditory field.

- periods when therapy (compensation of a deficit) is only partially possible after some age has been missed (sensitive periods for recovery);
- a distinct type of sensitive periods has to be additionally differentiated: periods for recovery from total deprivation. Complete sensory deprivation from birth leaves the sensory system functionally “naive”, which is distinct from abnormal juvenile experience (like monocular deprivation or strabism). It leaves the deprived sensory system functionally incompetent to perform its function in controlling behavior, which differs from consequences of abnormal experience. In abnormal experience, the manipulated sensory system is still used to control the behavior, but is subject to abnormal input. The naive state opens the possibility for cross-modal reorganization, degenerative processes (functional and morphological) and other processes that do not take place if the system remains functional (albeit with abnormal input).

When auditory sensitive periods have been investigated at the synaptic or single-cell level (see e.g. Morishita and Hensch, 2008; Barkat et al., 2011; Yu et al., 2012), their critical nature remained difficult to explain: although synaptic plasticity generally decreases with increasing age, it does not disappear completely. Whereas some synapses lose substantial amount of plasticity with age (Kotak et al., 2007; Barkat et al., 2011), other do less and should be, in principle, able to compensate the loss of plasticity in the former. Thus, other participating processes have to be considered.

The present review focuses on auditory sensitive periods for sensory deprivation from the system's perspective and uncovers the involvement of a combination of integrative effects that can make sensitive periods critical.

SENSORY SYSTEMS: FROM FEATURE TO OBJECT REPRESENTATION AND BACK

Neuroscientists often consider the sensory systems with respect to their representational feature maps, in other words they investigate how physical features of stimuli are represented in the brain. In the auditory system, such features are sound frequency and intensity, binaural time and intensity differences, frequency modulation, amplitude modulation, etc. In recent times considerable interest has shifted also to the way how the brain generalizes and abstracts from individual physical features to generate auditory objects (Griffiths and Warren, 2004; some authors call them events – Blauert, 1997): did I hear a horn of a car, breaking of a glass bottle fallen on the ground, ringing of a bell? The auditory object can be defined as a neuronal representation of a delimited acoustic pattern that is subject to figure-background separation.

Sensitive periods are important for the development of the brain that has to “bootstrap” its function from a general inborn pattern of connectivity. Correspondingly, discrimination performance improves during development. The longest developmental behavioral improvement can be traced for complex tasks like

discrimination of sounds (e.g. speech) in noise which continues to improve after discrimination of simple acoustic features has already matured (review in Warner et al., 2012). This demonstrates that representation of complex stimuli possibly requires more experience than the establishment of feature maps, although feature maps represent a precondition for the classification of acoustic input into objects.

Some auditory functions show optimal performance if learned early in life: e.g. musical experience has most pronounced effects on performance during early childhood (reviewed in Penhune, 2011). Also language learning is easiest early in life. In fact, the best known auditory examples of critical periods were observed in language development (review in Kuhl, 2010; Friederici, 2012). Young children are able to discriminate phonetic contrasts of all languages, however, they specialize in mother language with increasing age and lose the ability to discriminate phonetic contrasts that do not exist in their mother language at around 8th–10th month after birth. This has been observed for many languages (Werker and Tees, 1992). Consequently, the newborn brain is initially very sensitive to acoustic differences. With time, it specializes and remains sensitive only to so-called distinctive features of phonemes in their mother language. Non-distinctive acoustic differences are ignored (abstracted from)¹.

This is an excellent example how the brain establishes the world of auditory categories (objects). The brain aims to withstand the enormous variability of the physical world. It gains the ability to identify sounds that belong to the same class of events in the physical world, and learns to ignore their insignificant variability. This increases the robustness of perception. If the acoustic input is e.g. affected by several concurring sound sources, even though some features of the objects are masked, the object of interest remains discernible because some of its other distinctive features are less affected. A side-effect of the appearance of auditory objects is the loss in sensitivity to contrasts that do not contribute to the discrimination of the objects in the given world of experiences. It has to be kept in mind that several objects may in combination constitute another object: phonemes are objects themselves, but they combine into words that are objects on their own. Which object level is appropriate in the given condition may depend on the behavioral context.

One perceptual example of how auditory objects help to cope with distorted input is the so-called continuity illusion or filling-in phenomenon. Perceptual filling-in appears when a portion of input is physically occluded by a concurring stimulus, yet the input is perceived undisturbed. For example, masking individual phonemes in a sentence by brief noise does not preclude the perception of these phonemes (Warren, 1970). More complex filling-in phenomena have been described in the auditory system (Davis and Johnsrude,

¹ Nonetheless, during development also sensitivity to new contrast may appear (Lasky et al., 1975). This indicates that actually the auditory system can also “sharpen” some contrasts.

2007; Petkov et al., 2007; Riecke et al., 2012; Wild et al., 2012). The majority (if not all) of them may be related to auditory objects. Presently, most scientists assume that auditory objects are represented at the level of the cerebral cortex (Nelken et al., 2003). For proper functioning, the cortex requires interactions between several levels of information representation (Hochstein and Ahissar, 2002). Often, the higher-level representation is required to interpret the lower-level information, as suggested by the theory of inverse hierarchy (Hochstein and Ahissar, 2002). This theory assumes that feature representation and object representations are in constant interaction, and higher-order representations shape lower-level representations.

Consequently, an important part of the postnatal developmental sequence is related to the establishment of object representation. This involves complex functional interactions at different levels of representation.

CORTICOCORTICAL INTERACTIONS ARE THE FUNDAMENT OF BEHAVIOR

As a prerequisite of these perceptual functions, the cerebral cortex has to develop a complex architecture. The auditory cortex contains several auditory fields with distinct cytoarchitecture and distinct functions. Their functions have been elucidated using different experimental procedures. Behavioral functions can be associated with the activity of distinct auditory fields (Casseday and Diamond, 1977; Neff, 1977; Neff and Casseday, 1977; Heffner, 1997; Malhotra et al., 2004). Historically, cortical areas have been viewed as hierarchically organized (Felleman and Van Essen, 1991), with lower order fields supplying the cortical input to higher order fields. This hypothesis implicated that information flow demonstrates a distinct stepwise progression through these different fields. Indeed, latencies of unit responses are largely in accord with such a hypothesis. Recently, functional data revealing cortical propagating waves passing through auditory areal borders in a continuous fashion (among other evidence) contradict such a hierarchical concept (Reimer et al., 2011). Nonetheless, there is an asymmetry of the anatomic projections between auditory fields so that “lower-order” fields project in a different way to “higher-order” fields than higher-order fields project to the lower-order fields (Hackett, 2011). That allows to still consider a “hierarchical order” in the cortex, despite of the fact that some form of activity does not respect areal borders. In what follows, we understand the term “hierarchy” in this less strict sense; the auditory cortex with all auditory fields forms a functional unit.

Feedforward projections connect lower to higher-order areas and feedback projections connect higher-order to the lower-order areas (Rouiller et al., 1991). Feedforward connections originate predominantly from supragranular layers and target layer IV, feedback projections target both infra- and supragranular layers, avoiding layer IV (Felleman and Van Essen, 1991; Rouiller et al., 1991). (Lateral connections, connecting

areas at the same level, form an intermediate pattern of connections.) As mentioned above, based on layer-specific morphological connectivity a “hierarchical” order of cortical fields can be identified. To make the interactions between cortical areas possible and thus allow the appropriate integration of feedforward and feedback information, the intrinsic cortical connections forming the cortical column have to become functional.

Functional interactions and morphological connectivity are different things: morphological connectivity represents the prerequisite for functional interactions, but this prerequisite may not be always functionally exploited. To differentiate morphological connections from functional interactions, the latter are referred to as couplings or functional connectivity. In terms of couplings, bottom-up interactions couple lower-order to higher-order structures and top-down interactions vice versa (Gilbert and Sigman, 2007; Kral and Eggermont, 2007). The integration of bottom-up and top-down stream of information is a fast, in part instantaneous process: if an activity in the feature map of a primary auditory field does not correspond to the next higher level of representation (does not “fit” to the patterns stored in “secondary” areas), it will be difficult to stabilize such activity due to the heavy reciprocal interareal couplings. An instantaneous process of correction of patterns in the form of e.g. “an adaptive resonance”, suggested by computational neuroscientists (Grossberg, 1987), is likely to operate between different level of representation and is likely to adapt activity in lower-order fields to the representations stored in the higher-order fields (Mumford, 1992).

An interesting feature of these interareal connections is their asymmetry in another sense: feedforward connections bind lower order fields to the next higher level of hierarchy, whereas feedback connections often cross several levels of hierarchies (de la Mothe et al., 2006; Hackett, 2011). The top-down interactions from high order associative fields can consequently directly access the primary auditory cortex (de la Mothe et al., 2006). Attentional top-down modulation is an additional type of top-down interaction exploiting these long-range top-down interactions.

The example of filling-in phenomena is strongly related to top-down interactions, as has been shown in brain imaging studies (Giraud et al., 2004; Davis and Johnsrude, 2007; Riecke et al., 2009, 2012; Wild et al., 2012). Through such interactions, word-level of representation may affect phonemic level of representation and fill-out gaps in auditory input (Warren, 1970; Riecke et al., 2009, 2012; comp. Petkov et al., 2007). These phenomena are likely very important in speech understanding in noisy environments and other difficult listening conditions (Schofield et al., 2012; for visual system, see Kok et al., 2012). In hearing children, perceptual filling-in can be demonstrated only after the 2nd year of life has been reached (Newman, 2006). It is therefore tempting to assume that these phenomena are dependent on experience and consequently affected by hearing impairment (Kral and Eggermont, 2007; Riecke et al., 2012).

DEVELOPMENT OF THE NEOCORTEX IS IN PART REGULATED BY EXPERIENCE

These complex cortical interconnection patterns appear during development. The cerebral cortex develops in an inside-out pattern, with deep-layer neurons arriving in the cortex first, followed by the upper layers (Luskin and Shatz, 1985; review in Kral and Pallas, 2010). These migrations take place during early development, but cortical interneuronal connections become functional much later. First, neuronal branchings (dendritic and axonal) establish the background for a first connectivity matrix. Second, this matrix becomes functional after synapses have gained basic functionality, which is at relatively late stages of development. Although the thalamic afferents arrive in the layer IV of human cortex around postconceptual day 130 (Clancy et al., 2001), the dendritic morphology continues to mature over long periods (reviewed in Kral, 2007) and synaptic development is not complete around birth and the years after (Huttenlocher and Dabholkar, 1997).

In the visual system, extensive research on local connections has revealed that the vertical connectivity (between layers) develops precisely and specifically before the visual system receives sensory input (Rakic et al., 1986; Katz, 1991; Katz and Callaway, 1992). Vertical connectivity seems to develop in a timescale that is not related to the time of generation of neurons (the typical inside-out pattern, Luskin and Shatz, 1985). The data on the auditory system demonstrate that the details of columnar intrinsic coupling do change in deaf animals, although the general pattern is partially preserved (Kral et al., 2000). Horizontal (tangential) connections develop later than vertical connections, within the first months after birth in the cat (Katz and Callaway, 1992; Galuske and Singer, 1996; for indirect evidence in the auditory system, see Kral et al., 2006). Their first appearance is not dependent on sensory input, but the phase of refinement (change from crude to refined clusters of staining) depends on patterned activity (Katz and Callaway, 1992; Galuske and Singer, 1996). Thalamocortical connections appear to precede or develop in synchrony with the development of corticothalamic connections, whereas the latter depend on cortical activity (Shatz and Rakic, 1981; Arimatsu and Ishida, 2002; Jacobs et al., 2007; Yoshida et al., 2009). Further, feedforward cortical connections precede the development of feedback connections (Barone et al., 1996; Batardiere et al., 2002). The existing evidence indicates that local cortical connections develop before long-range cortical connections appear (Dalva and Katz, 1994; Katz and Shatz, 1996; Dye et al., 2011). Sensory deprivation in the visual system does not eliminate feedforward connectivity (Striem-Amit et al., 2012), and bottom-up information is preserved up to the level of secondary auditory cortex in congenital deafness, too (see below). Top-down interactions are more affected by auditory deprivation (Kral et al., 2005; Kral and Eggermont, 2007).

In the human cerebral cortex, the development of cortical axons is very protracted, lasting into teen ages

(Paus et al., 1999; Moore and Guan, 2001). Cortico-cortical interactions thus mature over very extended periods in humans. Potentially, correlated activity in different cortical areas, evoked by sensory input and cortical activation by already established thalamocortical afferents, through mechanisms of synaptic plasticity, will strengthen the connections between different areas of the same modality and by that functionally couple together areas within the same modality (function). Further, the immaturity of the corticocortical connections indicates that the potential for this plasticity is high in juvenile animals. The protracted development of cortical phosphorylated neurofilaments (Moore and Guan, 2001) does not implicate that cortico-cortical interactions are not functional at all, only that their structure is not fully mature and potentially highly plastic (Pundir et al., 2012). However, an axonal immaturity suggests that the different auditory areas, receiving afferent input from thalamic nuclei, can shape their interareal communication by experience more than the thalamic inputs to the cortex.

Development of neuronal (axonal and dendritic) branching patterns generates the precondition for forming functional circuits, yet the circuits can function only once contacts (synapses) have been formed. Therefore, mainly the most final phases of the development of dendritic and axonal branches (particularly in the cortex) and synaptic development are assumed to be influenced by evoked activity. Indeed, the adult auditory system of the cat is capable of relying cochlear input up to the level of the auditory cortex even in total absence of hearing (Hartmann et al., 1997; Tillein et al., 2012). Thus, the connections of the afferent auditory pathway up to the level of cortex develop independently of experience.

These considerations are supported by functional imaging of the human auditory cortex. Electroencephalographic data demonstrate a massive reorganization of the auditory system, from first large-amplitude long-lasting responses to the more mature responses of the adult individuals. First evoked responses can be recorded from preterm infants (for review, see Rotteveel, 1992), confirming that thalamic input can activate the auditory cortex already before birth (see above). However, the cortical P1/N1 response, generated by thalamic and cortical sources, systematically decreases in latency within the first 12–16 years of life (Ponton et al., 2000; Ponton and Eggermont, 2001; Ceponiene et al., 2002).

In conclusion, the brain continues to mature during many years of postnatal life, while it already interacts with the acoustic world.

COCHLEAR IMPLANTS REVEAL A CRITICAL PERIOD FOR THERAPY OF PRELINGUAL DEAFNESS

Restoration of profound hearing loss (deafness) has become possible using cochlear implants. Cochlear implants are artificial electronic devices that bypass the

non-functional inner ear and electrically stimulate the auditory nerve directly. They consist of a microphone, a processor worn behind the ear, a transmitter coil, and the intracorporal electrode carrier (Fig. 1). The electrode carrier consists of a receiver coil, a feedthrough with some electronics and the electrode contacts themselves. The electrodes are inserted into the cochlea (scala tympani) so that they come to lie underneath the organ of Corti. The electrical current can then stimulate the surviving neurons. Communication of information and energy between the behind the ear device and the intracorporal electrode is possible via magnetic fields through the intact skin between the transmitter and receiver coil.

As a rule, hearing loss is associated with very good preservation of auditory nerve in humans (Nadol and Eddington, 2006). Stimulation of these surviving fibers is possible through cochlear implants also many years after the onset of deafness (Dorman and Wilson, 2004). Nowadays cochlear implants represent the standard of therapy of congenital deafness in childhood (Kral and O'Donoghue, 2010). Remarkably, in contrast to adult-onset of deafness the final outcome of implantation in “prelingually” (congenitally) deaf children is optimal only in early implantations (within the first 1–3 years of life, Niparko et al., 2010). Clinical outcomes differentiate early and late implantations with regard to auditory performance. Very late implantation (in teen ages) in prelingually deaf does not lead to speech understanding and includes difficulties in more complex auditory tasks (counting of auditory stimuli, electrode position discrimination, and gap detection; Tong et al., 1988; Busby et al., 1992, 1993). Even after years of experience, performance is influenced by implantation age (Yoshinaga-Itano et al., 1998; Geers, 2006; Niparko

et al., 2010; Geers and Sedey, 2011). Early implanted children perform significantly better than later-implanted children (review in Kral and O'Donoghue, 2010). Consequently, a critical period for the therapy of human prelingual deafness exists (Fryauf-Bertschy et al., 1997; Niparko et al., 2010). Correspondingly, central neuronal correlates of hearing confirm such a period: N1 waves are dependent on hearing experience, as absence of hearing prevents the development of this wave (Ponton et al., 1996, 2000). The decrease in latency of the P1 component is dependent on hearing experience: absence of hearing arrests this component (Ponton et al., 1996), but early implantation normalizes it within few months (Sharma et al., 2005, 2007). Late implantation, on the other hand, is not longer able to promote this fast development and the reorganization arrests after a few months of hearing through a cochlear implant (Sharma et al., 2005, 2007). Although late-implanted subjects often profit from cochlear implant by the awareness of sound, their ability to differentiate complex acoustic patterns remains low even after many years of hearing through cochlear implants.

In conclusion, data on prelingually-deaf children convincingly demonstrate that loss of hearing cannot be fully compensated late in life, and thus that this sensitive period has a critical nature.

In close correspondence with these findings, the human cerebral cortex develops synapses peri- and postnatally (Conel, 1939; Huttenlocher and Dabholkar, 1997; for similar observation in cats, see Winfield, 1983). Therefore, information processing starts in the cortex during the time when the sensory systems already transduce information about the world. Synaptic development is consequently dependent on activity (Cragg, 1975a,b; O'Kusky and Colonnier, 1982;

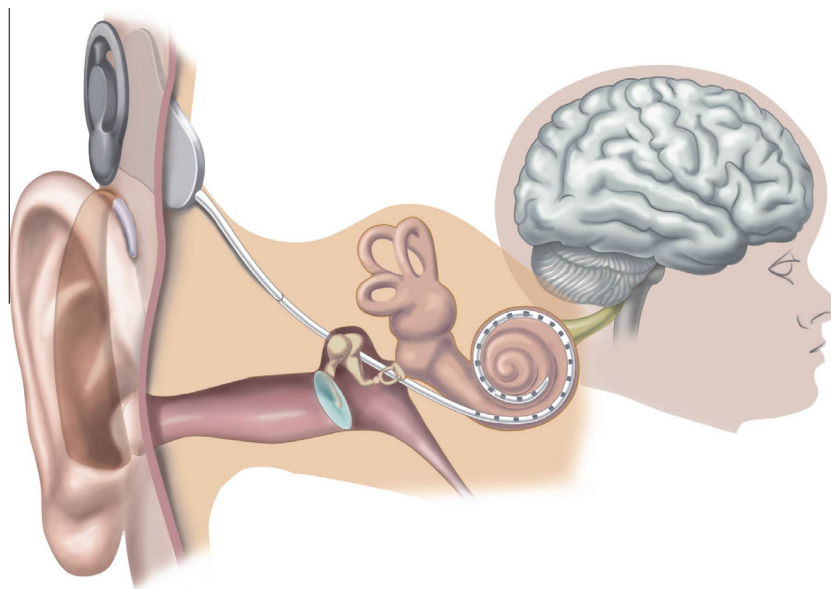


Fig. 1. Schematic illustration of the position of a cochlear implant. Proportions are distorted. The cochlear implant consists of an extracorporal signal processor with a microphone and a transmitter coil. The intracorporal part contains a receiver coil, a processor and the electrode array inserted into the cochlea (the scala tympani). Sounds are split into frequency bands, low-pass filtered and adjusted to the dynamic range of electric hearing. The resulting envelope is transformed to pulse trains that are delivered to the individual contacts of the electrode array with respect to the tonotopic cochlear organization.

Winfield, 1983), although the idea that synaptic elimination is the key element adapting the microcircuits to the environment (Changeux and Danchin, 1976), supported by decreased synaptic counts in blind animals (O'Kusky and Colonnier, 1982; Winfield, 1983), seems to be only a part of the story: data from current source density signals in the auditory cortex replicated the early morphological data by showing that the functional synaptic pruning is exaggerated in deafness, nonetheless, demonstrated an even more extensive effect on synaptogenesis (Fig. 2; Kral et al., 2005, 2006). Also at the level of individual synapses a similar observation has been made recently: the emergence of synapses is more dependent on activity than the elimination (Kerschensteiner et al., 2009). In total, this suggests that the period of synaptic development is regulated by neuronal activity. Studies on rodents demonstrate that plasticity needs to be considered from the view of a constant synapse turnover (Trachtenberg et al., 2002) that may lead to a net spine (synaptic) gain in early development (Hofer et al., 2009), but not in adults, where the overall synaptic counts are more constant and the formation of new spines (synapses) is connected with the loss of others (Trachtenberg et al., 2002). Although the literature is not consistent in all aspects of synapse formation by experience (review in Holtmaat and Svoboda, 2009), one can currently conclude:

- (1) Cortical synapses develop under the influence of neuronal activity.

- (2) When activity is absent, the synaptic development is delayed and takes place later (Kral et al., 2005; Kral and Sharma, 2012), regulated by other principles (not related to sensory input). This may lead to lack of development of synapses that may be crucial for adequate processing of sensory stimuli, to the development of synapses that would normally not develop – and also to pruning of synapses essential for adequate cortical processing. Further, balance changes in excitation and inhibition are likely in deafness, as an increasing inhibitory influence with increasing age was observed in hearing animals (data are, however, not entirely consistent in all aspects, compare Gao et al., 1999; Dorn et al., 2010; Sun et al., 2010; Sanes and Kotak, 2011).

Analysis of the functional microcircuitry of the cortical column identified several functional deficits in progression of synaptic activity through cortical layers in congenitally deaf adult animals (Kral et al., 2000). Not only was the onset of synaptic activity desynchronized (delayed in supragranular layers and infragranular layers), also deep layers V/VI showed reduction of synaptic activity following the first inputs at short latencies. These two effects could be related: a desynchronization of cortical inputs may lead to insufficient excitation of those neurons at which the inputs converge extensively, which include infragranular neurons. The reduced activity in deep layers has led to the hypothesis that in primary auditory field A1 these layers cannot perform their

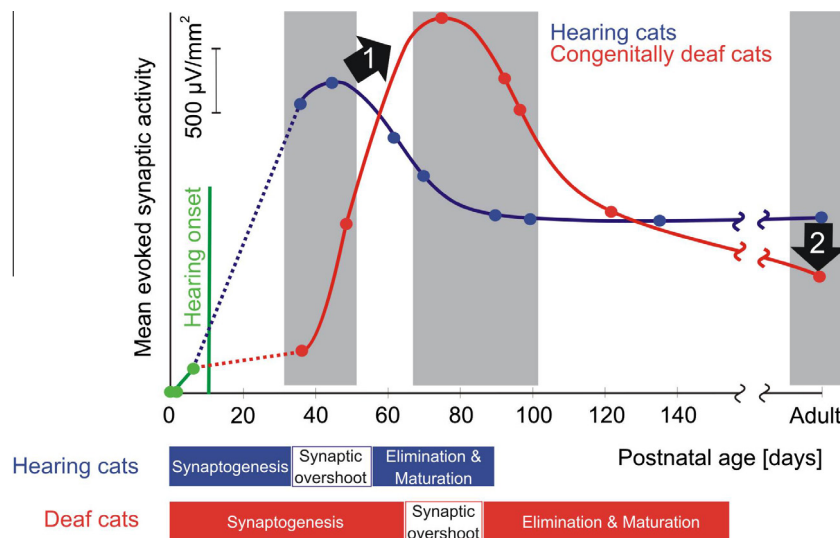


Fig. 2. Developmental changes in mean synaptic activity in the primary auditory cortex of cats evoked by stimulation through a cochlear implant in hearing controls (blue) and congenitally deaf (red) animals. The feline cochlea becomes functional around day 10, sexual maturity is reached around day 180 after birth. Values for adult animals are grand mean averages from four hearing and four deaf cats. Reproduced with permission from Kral and O'Donoghue (2010), data from Kral et al. (2005) extended by animals investigated before hearing onset. The synaptic activity was assessed using current source density analysis, i.e. the synaptic currents represent activity averaged from many synapses around the tip of the microelectrode. The assessment was performed in six penetrations within the most active area of the cortex ("hot-spot", size 1.5×1.0 mm) determined in a detailed mapping procedure. The data show an early increase in synaptic activity (functional synaptogenesis) observed within the first 40 days after birth, with subsequent functional synaptic pruning, resulting in adult-like activity between day 80 and 100 in hearing controls. In deaf animals, the functional synaptogenesis was delayed (1) and the pruning was exaggerated (2). Areas of statistical significance shown by the gray bar (two-tailed Wilcoxon–Mann–Whitney test, $\alpha = 5\%$). The data demonstrate extensive effects of sensory deprivation on the development of synapses (and neuronal networks) in the auditory cortex.

function in congenital deafness, leading to reduction in the corticofugal drive (e.g. corticothalamic interactions). Cortical efferents are, among other functions, involved in the control of subcortical plasticity (Ma and Suga, 2005; Tang and Suga, 2008). Deficits in corticofugal interactions will influence how information is processed in temporal succession as well as how memory adapts to individual needs of the subject. Deep layers further modulate the function of supragranular layers, conveying top-down effects to the intrinsic columnar circuits (reviews in Raizada and Grossberg, 2003; Callaway, 2004).

In conclusion, deafness has a disrupting effect on the development of several control functions of the cortical column.

AUDITORY PLASTICITY DECREASES WITH AGE

Ongoing (passive) presentation of a tone during development leads to expansion of the representation around this tone in the cortex, whereas the expansion is larger if the presentation starts earlier (Stanton and Harrison, 1996; Zhang et al., 2001). Indeed, auditory plasticity is higher at juvenile age, allowing to significantly reorganize the tonotopic organization of the cortex with passive acoustic stimulation (Zhang et al., 2002; Chang and Merzenich, 2003). The development of tonotopic gradients can be affected and even disrupted by ongoing presentation of tone sequences or clicks (Zhang et al., 2002; Nakahara et al., 2004; for complete deafness, compare Snyder et al., 1990; Raggio and Schreiner, 1999, 2003; Fallon et al., 2009a). 'Environmental noise' (i.e. ongoing white noise of moderate intensity), however, can delay the developmental steps and extend the sensitive period for plasticity of the tonotopic organization (Chang and Merzenich, 2003), and this may even happen in circumscribed cortical regions (de Villers-Sidani et al., 2008). These studies in combination demonstrate that an orchestrated sequence of sensitive developmental period for auditory plasticity exists (de Villers-Sidani and Merzenich, 2011).

But what is the consequence of profound hearing loss on the sensitive periods? The absence of auditory input may arrest of developmental processes and thus extend the sensitive periods, similarly as e.g. environmental noise. However, the fact that functional synaptogenesis, although delayed, finally takes place even in complete deafness (Fig. 2, Kral et al., 2005; Winfield, 1983), demonstrates that such an arrest is not forever.

Environmental noise and profound deafness have different consequences in the brain: in deafness, there is no evoked and no spontaneous activity in the auditory nerve. In contrast, masking noise reduces (but does not eliminate) patterned auditory input, it preserves spontaneous activity and increases the firing rate of auditory nerve fibers. It thus initially increases the level of peripheral input in the auditory system, whereas deafness removes it. The central effects of noise and deafness differ. Ongoing masking noise increases the

excitation thresholds in the central auditory system (Chang and Merzenich, 2003; Noreña et al., 2006). Deafness, on the other hand, decreases cortical thresholds (Kral et al., 2005; Fallon et al., 2009a,b). In congenital deafness, the dynamic range of unit rate-level functions decreases when tested with cochlear implants (Tillein et al., 2010), a phenomenon not observed with masking noise. Thus, congenital deafness and noise exposure are different phenomena triggering different pathophysiological processes in the brain.

A cortical correlate of a developmental sensitive period in auditory plasticity has been demonstrated in deaf cats chronically stimulated with cochlear implants (Kral et al., 2001, 2002). Using single-channel implants, the cortical area activated with an electric pulse applied to the auditory nerve expanded in course of the stimulation and the responses decreased in latency (Fig. 3; Klinke et al., 1999). Such plastic adaptation is adequate for the single-channel stimulation, as it attributes larger neuronal resources for processing of the stimulus. Extracellular recordings of action potentials in the hot spot demonstrated development of feature sensitivity and indicate functional maturation of the cortex (Klinke et al., 1999; Kral et al., 2006). This reorganization had, however, a decreasing trend with increasing implantation age (Fig. 3; Kral et al., 2002; review in Kral and Sharma, 2012). Further, in hearing animals cortical responses have shorter latency and larger amplitude for stimulation at the contralateral ear, a phenomenon that disappears in congenital deafness (Kral et al., 2009). Asymmetry in hearing, caused either by conductive hearing loss (Popescu and Polley, 2010) or by single-sided deafness (Kral et al., 2013) may further shift this relation in favor of the better hearing ear, leading to a change in the "aural preference" at the cortex ipsilateral to the "hearing" ear (Fig. 4; Kral et al., 2013). This effect is strongest in congenital single-sided deafness and ceases with increasing age of onset of single-sided deafness, demonstrating a developmental sensitive period (Figs. 4 and 5; Kral et al., 2013). In children with sequential implantations and long delays between implantation, the speech recognition at the second-implanted ear lags behind the first implanted ear even after years of bilateral hearing, and the improvements are very slow (Graham et al., 2009; Illg et al., 2013). Results consistent with this outcome were obtained in human single-sided deafness with imaging after stimulation of the hearing ear (Burton et al., 2012). Hearing asymmetry in children is a factor that is under investigation of clinicians, supporting the above experimental studies in humans (Graham et al., 2009; Gordon et al., 2010, 2011). Interestingly, although these results appear similar to monocular deprivation in the visual system, there is one important difference: in all investigated cases the deaf ear remained capable of substantial activation of the auditory cortex, which differs from the situation found in amblyopia.

These results show that neuronal plasticity decreases with age in congenital deafness, with decreasing adaptability to sensory input. There is some indication

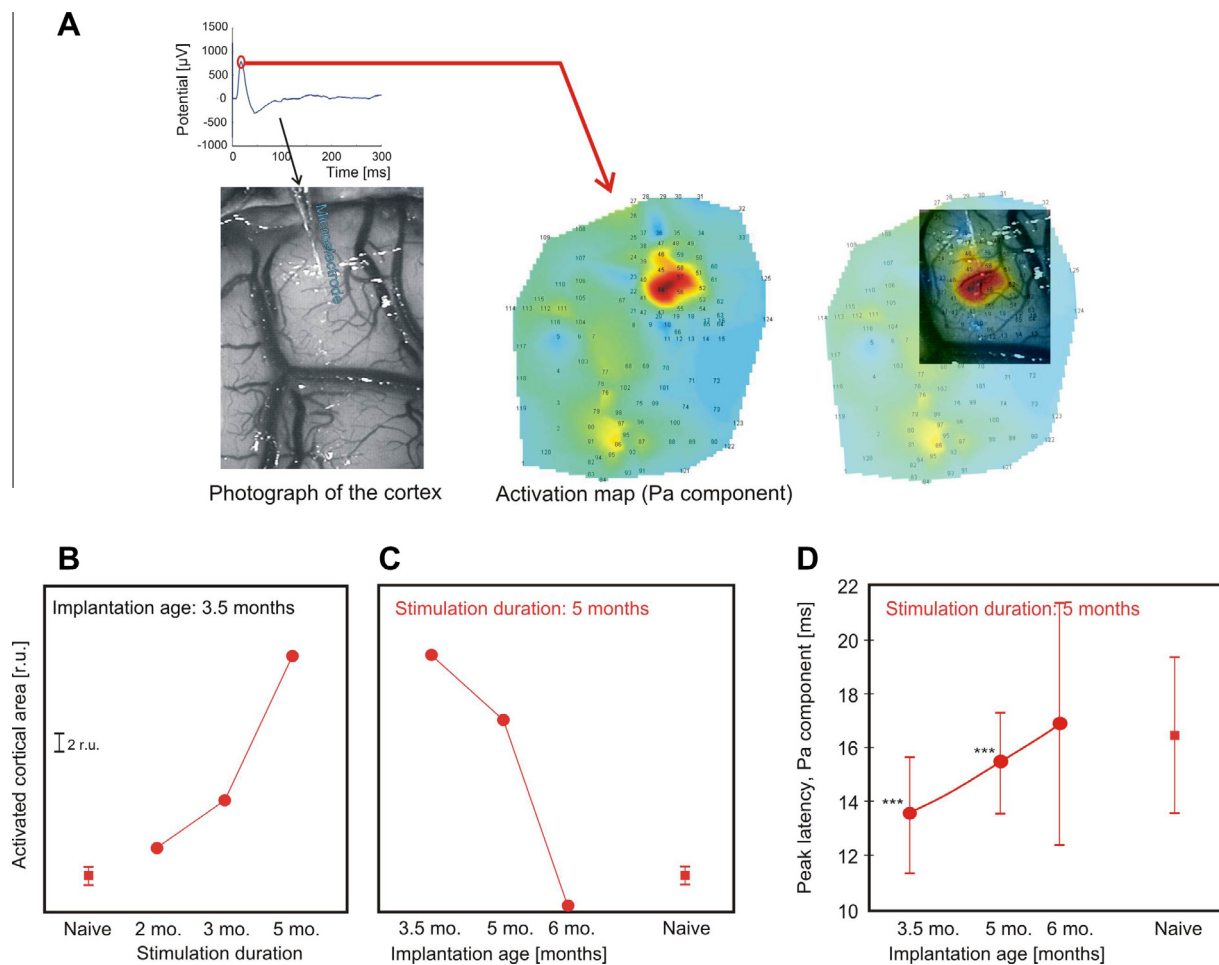


Fig. 3. Auditory plasticity studies in congenitally deaf cats. (A) The method: in anaesthetized animals, the surface of the primary auditory cortex was mapped using microelectrode-recorded local field potentials. Stimulation was a biphasic pulse applied through a cochlear implant at the contralateral ear. Based on the amplitude of the P_a components activation maps could be constructed and overlaid over the photographs. (B) Activated areas (areas with P_a responses $> 300 \mu\text{V}$) were determined in naive animals (not stimulated) and animals implanted between 3 and 4 months after birth (left panel). With increasing stimulation duration, the activated area expanded slowly (over months of experience) but extensively. (C) Active areas in animals stimulated for 5 months and implanted at three different ages. Increasing implantation age lead to smaller active area (smaller plastic changes), demonstrating a sensitive period for therapy. (D) Peak latencies of P_a components in animals stimulated for 5 months and implanted at three different ages. Earlier implantations shortened the latencies significantly. Implantation in adult age did not have the effect, again confirming a sensitive period. Data from Kral et al. (2002).

from brain slice experiments that some synapses may lose the ability for plastic changes after deprivation (Kotak et al., 2007). Hearing experience through a cochlear implant restores the activation pattern within the cortical column and reduces the deficits observed in adult deaf animals (Kral et al., 2006). Particularly, activity within the cortical column became more synchronous (Kral et al., 2006) and activity in deep layers V and VI was strengthened in chronically cochlear-implanted animals (Klinke et al., 1999), two findings probably tightly related. Consequently, hearing experience with cochlear implants recruited the deep layers. The precondition for their main function, i.e. integrating top-down information into the processing of the cortical column, therefore needs experience to develop. Long-latency activity, observed in hearing controls, appeared after chronic electrostimulation (Klinke et al., 1999; Kral et al., 2001, 2006). These data in combination provide evidence that corticocortical

interactions become functional after chronic hearing experience through cochlear implants, and consequently indicate that these require experience for attaining full functionality. Further, chronic electrostimulation through a portable signal processor increased the dynamic range of action potential responses (Kral et al., 2006; comp. Fallon et al., 2009a,b) and thus compensated the deafness-induced reduction of the dynamic range.

The data correspond to electroencephalographic studies on implanted children that demonstrate a sensitive period within the first 1–3 years after birth (Sharma et al., 2007; Kral and Sharma, 2012). Consequently, an early sensitive period for therapy of deafness has extensive impact on the development of the brain in the absence of hearing.

The view on the function of the auditory cortex would not be complete without considering activity in the higher-order auditory cortex. The only data available at the moment are from two higher-order fields: dorsal zone

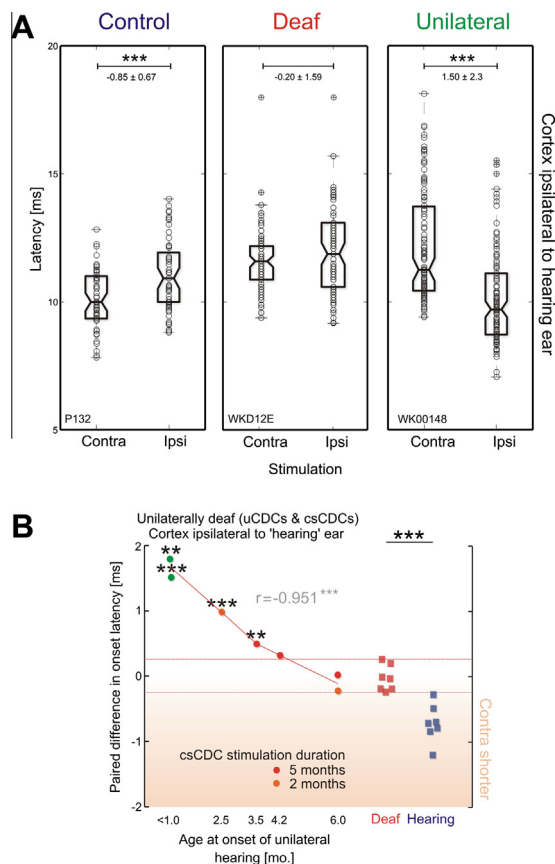


Fig. 4. Results of mapping are similar as shown in Fig. 3, but at the cortex ipsilateral to the chronically trained ear. Stimulation in all animals was with cochlear implants. (A) Onset latencies of three different animals: adult hearing control (left), adult congenitally deaf cat (middle) and adult single-sided congenitally deaf animal (right). Shown are onset latencies of P_a components with stimulation of contralateral and ipsilateral ear. The value on the top of the figure shows the median paired difference in latency and the absolute deviation of the median, together with its significance. Hearing controls showed significantly shorter onset latency if the contralateral ear was stimulated. Deaf cats did not show a significant difference. Single-sided animals showed (at the cortex ipsilateral to the hearing ear) a reversal of the latencies with shortest latencies with stimulation of the ipsilateral (hearing) ear. (B) Presentation of seven naive animals (red boxes), seven normal hearing controls (blue boxes) and seven unilateral animals (circles), congenitally unilaterally deaf animals shown in green (green circles), the other animals were implanted at chronically stimulated through cochlear implants (red circles). In unilateral animals, the paired difference of latencies (contralateral–ipsilateral) shifts away from the naive animals if implantations are early (up to 3.5 months), later implantations do not show a significant paired difference in latencies. The onset of unilateral experience significantly correlates with the paired difference in latency. Consequently, there was a sensitive period for this reorganization, and it was shorter than the sensitive period observed in Fig. 2. Data from Kral et al. (2013), figure modified.

(DZ) and posterior auditory field (PAF) in the cat. In our lab we could demonstrate that neurons in DZ (and also PAF) can be well driven by cochlear implants even in naive (completely deaf) adult animals (Fig. 6; Land et al., 2013). Although the responses in these areas were in part abnormal (in terms of latency and duration), the neurons did respond to electrical stimuli applied to the auditory nerve. This demonstrates that at least a

part of the bottom–up pathway remained functional up to this “secondary” level despite congenital deafness. This is important, since we could also show that both DZ and PAF are responsible for supranormal visual abilities in deaf animals (behavioral data: Lomber et al., 2010). These were related to “supramodal” functions (which different senses share, like localization or motion, Lomber et al., 2010) and possibly require a preexisting connectivity (Lomber et al., 2010; Voss and Zatorre, 2012). Further evidence indicates a cross-modal reorganization of field AAF by somatosensory modality (Meredith and Lomber, 2011). Thus, other sensory systems can make use of the deaf auditory system. Two possible mechanisms have been suggested to explain these findings: (a) growth of new connections from other brain regions into auditory regions that recruit these for other functions; or (b) different use of these

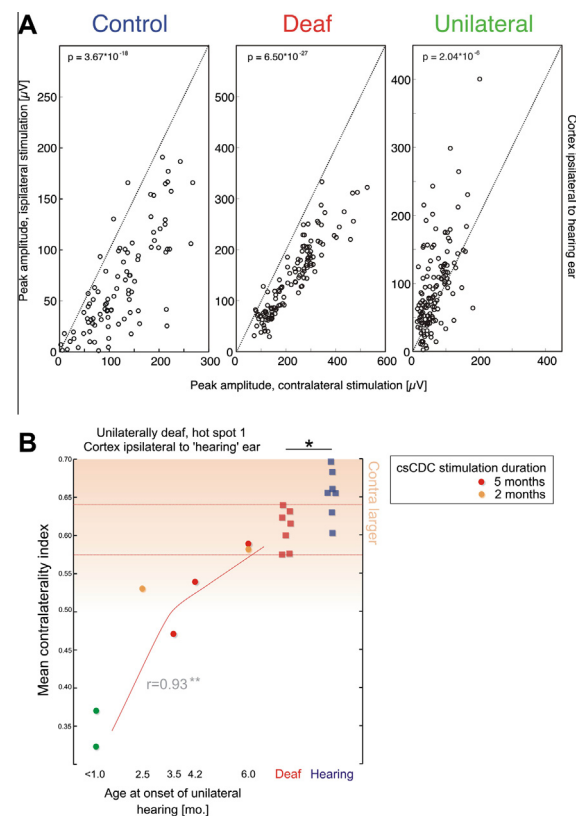


Fig. 5. Analysis of P_a peak amplitude in unilateral animals. (A) Results on three individual animals: a hearing control (left), congenitally deaf cat (middle) and a single-sided deaf animal (right). Both the controls and deaf animals have significantly larger contralateral responses (on the top of each panel is the p -value for paired amplitude differences). The unilateral animal shows a reversal of the amplitude relation. (B) Data from hot spots of the activation maps for all unilateral (single-sided congenitally deaf and binaurally congenitally deaf equipped with a unilateral cochlear implant and chronically stimulated) animals, naive deaf animals and normal hearing controls. Shown is the contralaterality index (contralateral amplitude/(contralateral + ipsilateral amplitude)). Although the effect of unilateral hearing was weaker than for onset latency, also here a significant correlation of age of onset of unilateral hearing and the contralaterality index was observed, demonstrating a sensitive developmental period. Data from Kral et al. (2013), figure modified and expended by part A.

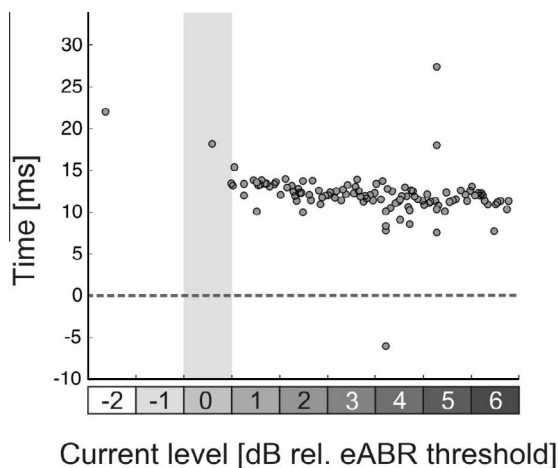


Fig. 6. Raster plot of multiunit response in area DZ (dorsal zone) to auditory stimulation at nine different current levels in an adult, congenitally deaf cat. Each dot represents the time of occurrence of an action potential. Stimulation was wide bipolar using a feline cochlear implant. Each stimulus level was repeated 30 times. Horizontal dotted line depicts the onset of three charge-balanced biphasic pulses (200 μ s/phase, 500 pps). Vertical bar designates electrical hearing threshold level determined with auditory brainstem evoked responses elicited with single electrical biphasic pulses (200 μ s/phase). The figure demonstrates that in congenitally deaf adult animals, auditory-evoked activity reaches secondary auditory areas. Data from Land et al. (2013). Corresponding data from our laboratory demonstrate similar results for field PAF (unpublished).

structures in recruiting attention and its interactions with auditory and non-auditory areas (Neville and Lawson, 1987; Lomber et al., 2010). In the present context, due to the presence of auditory responses in the same fields, the latter hypothesis appears better substantiated. Correspondingly, recent retrograde tracer study in field DZ of deaf cats demonstrated some visual reorganization of cortical inputs (Barone et al., 2013). On the other hand, the auditory inputs to auditory areas were in majority preserved in congenital deafness (Barone et al., 2013).

From this point of view, the work on brain development and restoration of hearing in animals and humans at least five mechanisms participate on the sensitive periods:

- (1) A developmental decrease in synaptic plasticity (Carmignoto and Vicini, 1992; van Zundert et al., 2004; Phillips et al., 2011).
- (2) A modification of synaptic development in the cortex, with extensive effects on synaptogenesis and synaptic pruning. In consequence, coupling between neurons within a neuronal network are not established by their function in congenital deafness but by other (not yet completely elucidated) principles (Kral et al., 2005; Kral and O'Donoghue, 2010).
- (3) Smearing of gradients in feature representation at the early sensory areas (Kral and Sharma, 2012). This complicates the starting point for learning: features not appropriately represented in the primary fields will be difficult to use for learning the discrimination of acoustic stimuli.

- (4) The breakdown of corticocortical interareal interactions due to the absence of activity during the time when these connections develop and mature. The present data indicate a particularly pronounced effect on the top-down interactions in deafness (review in Kral and Eggermont, 2007).
- (5) A change in intermodal interactions by a differential recruitment of the deprived areas by other systems of the brain (Lomber et al., 2010; Barone et al., 2013). However, preserved auditory responsiveness of these areas indicates that these areas are not completely functionally uncoupled from the auditory system.

The developmental processes that normally take place between sensory systems in a well-coordinated fashion are developmentally altered in congenital deafness. That explains why it is so difficult to reestablish full functionality if the sensory function is restored late in life. Sensitive periods for recovery from deprivation become critical because they are determined by several factors that are intermingled and difficult to therapeutically address in combination.

JUVENILE AND ADULT LEARNING DIFFER

Development results in a rearrangement of synaptic conductivities to allow adequate function; this corresponds to changing connection weights in a neuronal network model. The cortical neuronal networks receive input corresponding to the auditory features decoded by the cochlea. These inputs are classified into categories. A change in non-distinctive features does not influence the output of the neuronal network, whereas a change in distinctive features does, as the input crosses the categorial boundary. With respect to neuronal processing, “energy” (or “error”) functions have been suggested (Hopfield and Tank, 1986) that, in a simplified view, characterize the difference between the desired and the actual output of the network. In such a view the neuronal network performs an optimization task in minimizing the value of the energy function (Hopfield and Tank, 1986).

Such networks typically require a supervisor (e.g. for computing the energy function). The supervisor is the “director” in the network that makes decisions about whether to modify connection weights. It contains the information on the “desired” output of the network that is compared to the actual one. Such supervisor information could be conveyed by top-down interactions in the brain. These sometimes cross several hierarchical levels (see above) and can therefore convey the information from associative prefrontal and frontal areas (including goals and action planning) to the early sensory areas. They contain information on success of behavior in achieving these goals. They thus allow to include information on the behavioral goals and allow to match the goal, its successful approach and the contribution of auditory processing.

A naive neuronal network is likely characterized by flat energy functions (comp. Knudsen, 2004), with different inputs resulting in different outputs of the network. The

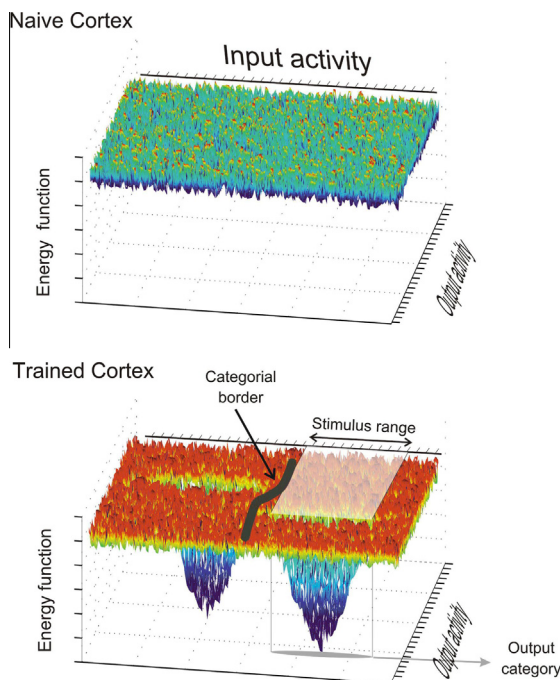


Fig. 7. A model of the hypothetical neuronal network changes during development. The plot depicts the output of the network as a function of the input and the energy of the state. In this model, the neuronal network performs an optimization task to achieve the state of minimal Hopfield “energy”. Therefore, the state of the network moves along the energy plane and approaches the local minima. In other words, energy is inversely proportional to the probability of the network achieving that state. Top: A naive neuronal network is characterized by flat and noisy energy functions. That implies that with the same input, from trial to trial different outputs can be observed, as these are equally probable. No attractors are discernible in the network. This condition facilitates the learning in the network by making all output equally probable. Bottom: After learning, the energy function shows in this example two local minima to which activity is attracted from several inputs. Thus, a number of inputs are “grouped” into one output, corresponding to a categorization (or generalization) behavior of the network. As a consequence, two output categories appear, with a distinct category border. Relearning (“erasing”) such established patterns is more difficult than patterning the naive network and requires well controlled neuronal processes, as found in adult learning.

influence of neuronal noise (spontaneous activity) may be high and result in highly varying outputs of the network with same inputs (Fig. 7). At an initial juvenile stage, learning is dominated by bottom-up mechanisms and high juvenile plasticity. Only with increasing age, more top-down control (“supervised learning”) takes part in the processing. After initial learning has taken place, the mapping of inputs to outputs is characterized by local minima in the energy function, corresponding to high probabilities of these outputs when the given inputs are presented to the network. In consequence, the network “clusters the outputs” as it tends to achieve minimal energy states. Because of the local minima attributed to several different input patterns, the neuronal network learns to generalize and abstract the features of the input it is confronted with – auditory objects appear.

Abnormal sensory experience during the time when synaptic plasticity is high and the network remain in

unpatterned state (naive configuration) leads to high probability of change, resulting in aberrant function of the neuronal networks. Examples of this type are e.g. the above-mentioned effects of single-sided deafness on the auditory cortex. Once a trained (experienced) state of the network has been achieved and the juvenile high synaptic plasticity expired, learning new patterns requires more control of the neuronal function. In this state the brain becomes more determined by stored patterns and the influence of sensory input becomes weaker. It further allows it to be less dependent on the statistics and physical properties of the sensory input and more dependent on the internal needs of the organism.

As two extremes in the developmental sequence, adult learning therefore differs from developmental (juvenile) learning in several respects: juvenile synaptic plasticity is higher due to a juvenile composition of perineural nets, ionic channels and their anchoring in postsynaptic densities (reviews in Berardi et al., 2004; van Zundert et al., 2004; Carulli et al., 2010). The neuronal machinery in the juvenile brain allows a faster change in the synaptic efficacy. This is further related to neurotrophic factors that boost plasticity (Sale et al., 2009; Yoshii and Constantine-Paton, 2010; Kaneko et al., 2012) in the juvenile age. Further, the naive neuronal networks have an architecture that allows easy and fast incorporation of information into the neuronal networks without the initial need of a supervisor. Unsupervised learning based on high synaptic plasticity shape the naïve juvenile neuronal networks. Once first patterns have been stored in synaptic contacts and the network attained the ability to generalize over the input space, auditory objects represent categories of sensory inputs.

Adult learning, on the other hand, is characterized by plasticity supervised through top-down interactions. The substrate for these is established both in form of feedback connections as well as in the form of local columnar connectivity. As perceptual filling-in has been first demonstrated at 2 years in hearing children (Newman, 2006), it is likely that some of the top-down interactions appear first around this age (juvenile age of 3 months in hearing cats, Kral et al., 2005). Modulatory systems that boost plasticity (Weinberger, 2004; Weinberger et al., 2006) are a substantial part of the complex, well-controlled circuitry for adult learning. However, not all forms of adult plastic changes involve such control: recent experiments with noise exposure demonstrated bottom-up driven cortical plasticity in both adult cats and juvenile rats (Norena et al., 2006; de Villiers-Sidani and Merzenich, 2011; Pienkowski et al., 2011; Zhou and Merzenich, 2012). These studies identified a neuronal mechanism of habituation-type of plasticity that involves inhibition and neurotrophic factors and critically depend on the temporal structure of the sound presented (Pienkowski et al., 2011; Zhou and Merzenich, 2012). Also injury-related plasticity (Robertson and Irvine, 1989) requires distinction, as injury-related plasticity most likely does not require top-down modulation but involves a distinct fast bottom-up

mechanism starting with loss of lateral inhibition from the injured regions (Snyder and Sinex, 2002).

In sensory deprivation, some developmental steps transforming juvenile to adult learning have taken place while others did not. Supervised learning is compromised by dysfunctional cortical columns that cannot integrate top-down modulations into the function of infragranular layers. However, the phase of high synaptic plasticity terminates, although in delayed timeline. Some synapses even lose the ability for plastic change. The naive network is then neither in the juvenile highly-plastic state, nor in the state designed for supervised learning. Adult plasticity cannot be properly controlled and directed during learning, and therefore adaptive learning is compromised. If we could find ways to restore juvenile plasticity in the naive network, more weight could be put on bottom-up mechanisms and therefore more beneficial effect of sensory input could be expected (Duffy and Mitchell, 2013). As the general interareal (morphological) connectivity within the auditory system is preserved in congenital deafness (e.g. in A1 and DZ of deaf cats, Barone et al., 2013) and the effects of deafness are more observed in couplings, this might be a promising new strategy.

In conclusion, learning differs in juvenile and adult brains. The developmental transition from juvenile to adult learning requires steps that crucially depend on experience. Complete deprivation from birth therefore leaves an auditory system that has not the same capacity for synaptic plasticity as the juvenile brain, but also lacks the control mechanisms that boost learning in adult age.

DEAFNESS AFFECTS NON-AUDITORY FUNCTIONS OF THE BRAIN

Finally, sensory systems are not completely equivalent: the visual system provides excellent spatial information (visual acuity reaching, depending on the type of task, the level of few dozens of second of the arc), whereas the temporal acuity is low (flicker fusion at ~ 60 Hz). In the auditory system, the spatial localization ability is low (minimal audible angles in the order of $1\text{--}3^\circ$), yet the temporal acuity is high (temporal code up to 3–4 kHz). Therefore, different types of information are optimally represented in different sensory systems, leading to dominance of perception in sensory conflicts (auditory or visual capture, Recanzone, 1998, 2003). The theory has been put forward that the primary sensory areas serve as a high-resolution buffer (“blackboard”) for cognition (Mumford, 1992), whereas each sensory system has a particular function with regard to certain physical characteristics. In this regard it is tempting to speculate that the auditory system has a particular function in representing the timeline (sequence) of events at high temporal resolution. Deafness, particularly congenital deafness, would consequently interfere with this ability and affect many cognitive functions.

Indeed, absence of hearing affects more than hearing itself (reviewed in Kral and O'Donoghue, 2010): deaf

subjects underperform hearing children in visual sequence learning (Conway et al., 2011). This could be related to reduced working memory, as observed in signing subjects compared to hearing subjects (Pisoni and Geers, 2000). Nonetheless, this type of reduced working memory is most likely related to the linguistic representation by visual signs (Boutla et al., 2004). An alternative representation may be a reduced ability for organizing sensory inputs along the temporal dimension. Deaf children show alterations in fine motor coordination (Horn et al., 2006, 2007). To what extent this finding relates to the absence of auditory input remains to be verified.

Finally, attention not only affects sensory systems, also sensory systems can attract attention (if the stimuli are salient). Hearing is particularly suitable for controlling attention in situations when changes in environment happen outside of the field of view. Most interestingly, deaf children distribute more attentional resources to the peripheral visual field (Bavelier et al., 2000; Bottari et al., 2010), as if they would constantly “scan” the periphery. This leads to deficits in sustained attention (Yucel and Derim, 2008; Barker et al., 2009). Such condition affects the interaction with caretakers and limits joint attention: the ability of children to orient attention to the object attended by the caretaker. Joint attention is an important process in the phase of learning from parents. In consequence, even though the deficit in sustained attention is alleviated with age, the early juvenile learning phase must be extensively affected by this deficit.

More focus needs to be put on these non-auditory effects of deafness in the future. They clearly demonstrate that the congenitally deaf brain differs from a “hearing” brain by much more than the absence of cochlear function. Training after restoration of the peripheral hearing deficit may be necessary to compensate the deficits that developed. The deficits could be highly dependent on the subject and its mode of exploitation of the cognitive resources of the brain. These cognitive factors likely further contribute to the closure of critical periods.

CRITICAL IS NOT ALWAYS CRITICAL: RELEASE OF MOLECULAR BREAKS

To demonstrate a critical nature of some sensitive periods is not straightforward in an animal model. However, experience with patients after sensory loss may serve as a guide, confirming that some forms of monocular deprivation, complete visual deprivation and complete absence of hearing from birth are difficult to reverse despite years-long sensory experience following therapy of the defect.

Nevertheless, recent work indicates that release of some molecular breaks of plasticity, particularly those related to inhibition, may reopen some critical periods in animal experiments (Pizzorusso et al., 2002; Morishita and Hensch, 2008). Also, periods of constant low-level noise or darkness appear to have the potential to delay or even ‘reset’ developmental stages and reinstall

juvenile plasticity in some types of sensitive periods (Zhou et al., 2011; Duffy and Mitchell, 2013). This is related to molecular changes in the cortex that, after dark rearing, increase plasticity (Duffy and Mitchell, 2013). In the auditory system, the critical period for plasticity of frequency tuning and tonotopic organization can similarly be extended by stimulation with continuous noise and terminated by tonal stimulation or just through spontaneous recovery (Chang and Merzenich, 2003; Zhou and Merzenich, 2012). In this regard the potential for plastic reorganization is developmentally limited by e.g. by neurofilament modification (Duffy and Mitchell, 2013), maturation of inhibitory transmission, neurotrophic factors release or chondroitin-sulfate (Pizzorusso et al., 2002; Carulli et al., 2010; Zhou and Merzenich, 2012). Removal of such molecular breaks at later age can restore juvenile synaptic plasticity (Pizzorusso et al., 2002; Zhou et al., 2011; Duffy and Mitchell, 2013) and potentially compensate many effects of juvenile pathologic experience. However, so far these studies concentrate on abnormal (pathological) experience during development (monocular deprivation or strabism, i.e. critical periods for damage, or disruption of tonotopic organization in the auditory system).

Whether restoration of juvenile plasticity may compensate also the here-described systemic effects of complete sensory deprivation remains to be investigated in the future. There is substantiated hope that neuroscience will learn to counterbalance the devastating effect of experience also in adult age. If the here-reviewed systemic contributions to critical periods should indeed be the key element, the critical periods would not be set in stone. Focused manipulations in sensory input, combined with training methods could alleviate deprivation-induced deficits. At present, early intervention remains the gold standard in therapy of early hearing loss, enabled by neonatal hearing screening (Kral and O'Donoghue, 2010).

CONCLUSIONS

The available evidence shows that many basic cerebral functions are inborn. Learned, on the other hand, are representations of sensory objects that are highly individual and depend on the subject's experiences. Related to it, corticocortical interactions and the function of the cortical column depend on experience and are shaped by sensory inputs. Periods of high susceptibility to environmental manipulations are given by higher synaptic plasticity and a naive state of neuronal networks that may easily be patterned by sensory input. Adult learning, on the other hand, is characterized by weaker synaptic plasticity but the ability to control and modulate plasticity by the need of the organism through top-down interactions and modulatory systems. Congenital deafness affects the development not only by delaying it, but also by desynchronizing different developmental steps. In its ultimate consequence, congenital deafness results in an auditory system that lacks the ability to supervise early sensory processing and plasticity, but also lacks the high synaptic plasticity

of the juvenile brain. Critical developmental periods result. It remains an open question whether restoring juvenile plasticity by eliminating molecular breaks of plasticity will reinstall functional connectivity in the auditory cortex and bring a new therapy for complete sensory deprivation in the future. Focus on integrative aspects of critical periods will be required to counteract the reorganization taken place in the deprived sensory system and the other affected cerebral functions by training procedures.

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