Review

Developmental neuroplasticity after cochlear implantation

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Cortical development is dependent on stimulus-driven learning. The absence of sensory input from birth, as occurs in congenital deafness, affects normal growth and connectivity needed to form a functional sensory system, resulting in deficits in oral language learning. Cochlear implants bypass cochlear damage by directly stimulating the auditory nerve and brain, making it possible to avoid many of the deleterious effects of sensory deprivation. Congenitally deaf animals and children who receive implants provide a platform to examine the characteristics of cortical plasticity in the auditory system. In this review, we discuss the existence of time limits for, and mechanistic constraints on, sensitive periods for cochlear implantation and describe the effects of multimodal and cognitive reorganization that result from long-term auditory deprivation.

Introduction

When listening, the brain has to accomplish two functions: First, it has to analyze sound into acoustic features and represent those features that are essential for the differentiation of biologically important sounds. Second, it has to categorize these essential acoustic features into a representation (i.e. an auditory object) resistant to the inherent variability present in the sensory world. The representation of auditory objects is individual (subjective) and is critically dependent upon learning.

During learning, a sensory stimulus gains new behavioral significance, resulting in a dynamic reorganization of the representation of the features and objects associated with that sensory stimulus [1]. Receptive fields in the auditory cortex change after sufficient training [2–4], reflecting improvements in the performance of the learned task [5]. Both subcortical and cortical mechanisms contribute to this process. In the juvenile brain, the capacity for such plastic reorganization is greater [6–8], partly because of developmental changes in the molecular machinery of synaptic plasticity [9,10]. Such developmental periods of higher neuronal plasticity are called 'sensitive periods' [11]. Different sensitive periods exist for different behavioral functions [12], probably because of differences in underlying neuronal structures and functions and maturational rates [13,14]. Although most sensitive periods have an end-point after which learning is compromised, recent evidence suggests that some sensitive periods can be extended by certain sensory manipulations, such as long-term exposure to continuous non-patterned acoustic stimulation [15,16]. Thus, given high levels of juvenile plasticity, the existence of sensitive periods, and the dependence of postnatal development and learning on sensory experience [17,18], an interesting question that arises is what are the effects of sensory deprivation on development? In this review, we explore the consequences of congenital deafness on auditory development and functioning.

Congenital deafness is frequent in humans (0.2–0.5 cases per 1000 live births) [19]. In profound sensorineural deafness, the human auditory nerve often survives the loss of inner ear hair cells [20–22] and is available to serve as a target for artificial (electrical) stimulation. Cochlear implants are devices that bypass a non-functional inner ear (organ of Corti) and provide direct stimulation to the auditory nerve. Electrical stimulation induces a pattern of activity that differs from acoustic stimulation, but which nonetheless, mimics the essential coding principles of the cochlea [23,24]. This allows most implant recipients to differentiate speech sounds and interpret auditory input [19]. There are approximately 200 000 cochlear implant users worldwide, including approximately 80 000 infants and children [19].

Children that become deaf before the development of language (i.e. prelingually deaf), if fitted with a cochlear implant early in childhood, demonstrate remarkable success in acquiring spoken language, especially if exposed to enriched language environments and supported by committed parents and caregivers [25,26]. However, implantation in later childhood results in successively less benefit [25,26], and implantation in the elementary school age or later, as a rule, does not lead to good speech understanding [27–30]. Late-implanted subjects can detect the auditory stimulus (i.e. they hear), but the majority of them are not able to discriminate complex sounds appropriately in everyday situations, even after many years of implant use. The consequence is substantially compromised speech understanding and oral language learning.

Taken together, the differences in performance of early and late-implanted children demonstrate a sensitive period for cochlear implantation in early childhood. As we discuss in this review, neuronal mechanisms underlying sensitive periods can be explored in animal models (from

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cellular, synaptic to systems level), but, owing to the frequent clinical use of cochlear implants, such theories can also be directly investigated in the human brain. Therefore, the auditory system has developed into a model system for exploring the effects of sensory deprivation (and its subsequent restoration) with remarkably complementary results being observed across animal and human cochlear implant users. In this article, we review the evidence for the existence of a sensitive period for successful cochlear implantation, explore its underlying neural mechanisms, and describe the developmental and functional consequences when implantation occurs beyond this sensitive period.

Sensitive periods for cortical development after cochlear implantation

Although many properties of the auditory system are innate [17], it is susceptible to extensive reorganization when extrinsic input is abnormal during development [7,31,32]. Complete absence of auditory input in animals,

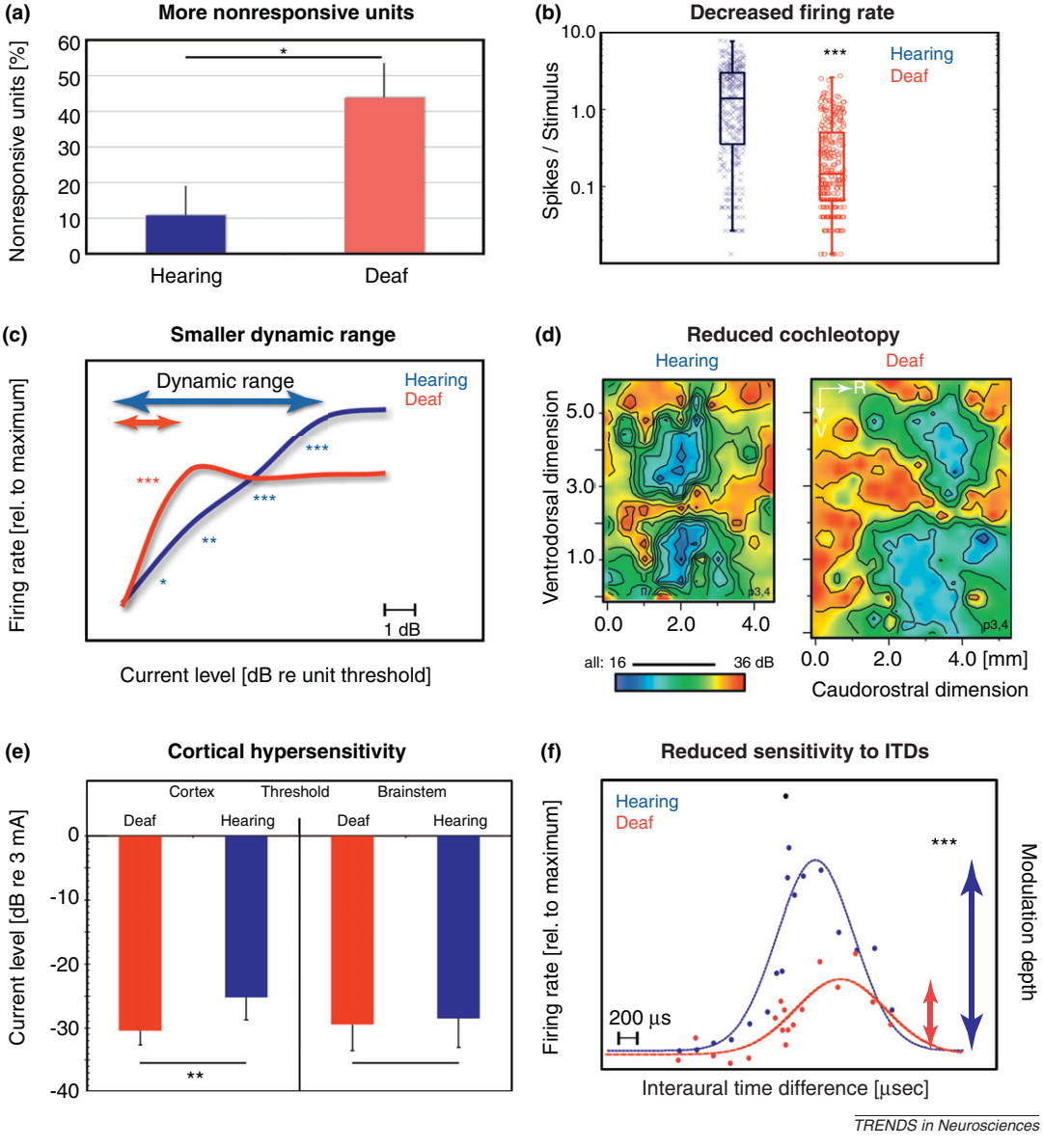

Figure 1. Summary of findings on cortical representation of electrical stimuli in congenitally deaf adult **(a–c,e,f)** or neonatally deafened cats **(d)** compared with hearing controls. **(a)** In deaf animals, a prominent increase in non-responding sites in the primary auditory field A1 has been documented, probably resulting in a reduction of represented information. **(b)** The maximum evoked firing rate is lower in deaf animals. **(c)** Population rate-intensity functions in deaf and hearing animals. Asterisks designate current levels where the increase in firing rate has been significant compared with the next lower current level [2 decibel (dB) steps]. In deaf animals, this was only the case within the first 2 dB above unit threshold, whereas in hearing animals the dynamic range was >8 dB [40,42] (compare the effects of electric stimulation versus acoustic stimulation [41]). **(d)** Distribution of thresholds for pulsatile stimulation along the cortical dimension in a hearing control (compare with [36,47]) and a long-term neonatally deafened animal, both with bipolar (spatially restricted) electrical stimulation. Although the hearing animal shows steeper gradients along the cortex, there is a rudimentary cochleotopy in the deaf animal, particularly in the dorsal part of A1 (upper half of the plots). **(e)** Cortical thresholds of local field potentials and brainstem evoked responses in the same animals as in **(d)**. Although there was no difference in the lowest thresholds of evoked responses in the brainstem, deaf animals showed significantly lower thresholds in the cortex, demonstrating a cortical hypersensitivity (compare with [53,55]). **(f)** Cortical feature sensitivity is rudimentarily preserved for interaural time differences (ITDs) that, in contrast to cochleotopy, are not the consequence of anatomical projection patterns but are extracted from auditory nerve activity in the olivary complex [40]. Thus, some feature sensitivity develops in the absence of hearing experience. However, the sensitivity to ITD was extensively reduced in deaf animals. Data from [40] **(a,c,f)** and [52] **(e)**. Reproduced, with permission, from [40] **(b)** and [37] **(d)**.

through either pharmacological deafening [33] or genetic deafness (e.g. congenitally deaf strains of animals [34]), may serve to differentiate innate versus extrinsically driven (or learned) properties of the auditory system. For example, the general wiring pattern in the subcortical afferent auditory system develops, in part, before hearing onset and is consequently preserved in deafness [35]. Therefore, cochlear implant stimulation results in activation of the auditory system from the auditory nerve up to the auditory cortex in implant recipients [36–38]. Some auditory feature sensitivity can be observed in deaf animals [39–42], although it is rudimentary [40,42]. Additionally, synaptic immaturity [43,44], dystrophic changes in neurons [45,46] and numerous other functional deficits have been observed in deaf animals. A prominent decrease in the number of responding cortical units has been found [40] (Figure 1a) along with reduced maximum evoked firing rate [40] (Figure 1b) and reduced dynamic range [40] (Figure 1c), possibly resulting from changes in homeostatic synaptic scaling in the absence of input. These deficits substantially compromise representation of dynamically changing sound intensity (e.g. speech) in deaf individuals. In addition, prominent changes in cochleotopic organization of the cortex have been described (Figure 1d) [37], although the extent of the effect differs in different experimental conditions, varying from rudimentary cochleotopy ([36,37,47] (see also [15] to compare effects of rearing under noisy conditions) to complete absence of cochleotopy [48]. Smeared, but rudimentary cochleotopy has been additionally observed in the inferior colliculus [49,50] and the cochlear nucleus [51]. Patchy patterns of cortical activity were observed in some neonatally deafened animals [37,47,48], possibly as a consequence of patchy degeneration of the spiral ganglion cells resulting from the deafening procedure using ototoxic agents. Reduced cochleotopy leads to smearing of the cochlear place information, thus further compromising discrimination of excited regions in the cochlea (spectral information). Additionally, cortical hypersensitivity has been described at the systems level (Figure 1e) [52] as well as at the cellular level [53,54]. Cortical hypersensitivity further aggravates effects of the reduced dynamic range. However, some preserved feature sensitivity has been reported in the auditory system [55–58]. For example, although cortical sensitivity to binaural localization cues is preserved at a rudimentary level [40], the sensitivity to this cue is significantly reduced in deafness, along with contralaterality and other features of cortical responses [59].

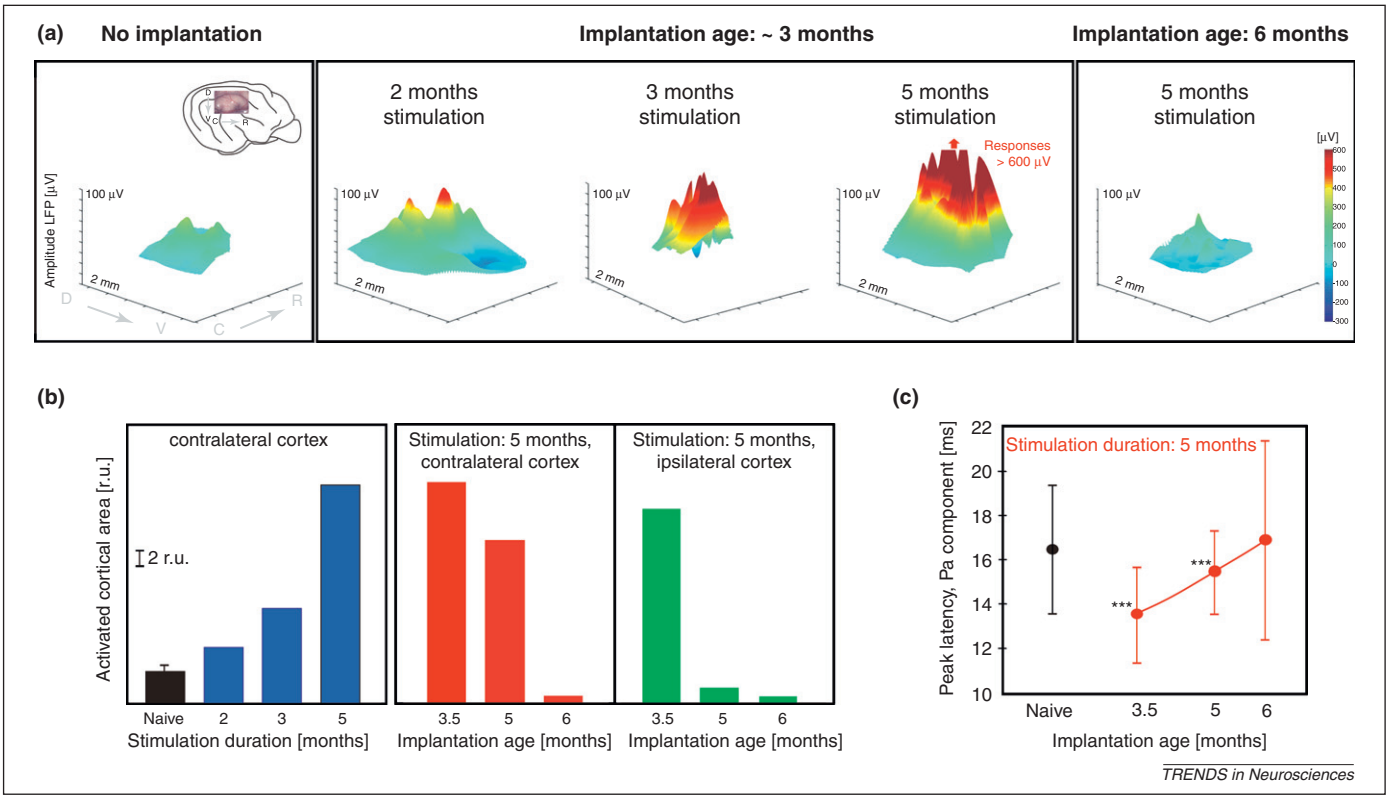

Figure 2. Cortical reorganization in congenitally deaf cats following chronic stimulation through a cochlear implant, investigated in primary area A1 [inset in the leftmost panel of **(a)**], demonstrates a sensitive period for cortical plasticity. **(a)** Reorganization of the cortical activation map after chronic electrical stimulation using a single-channel signal processor. The graph depicts the amplitudes of the local field potential (LFP) at the first positive peak (P_a component) as a function of the recording position at the cortical surface (C, caudal; D, dorsal; R, rostral; V, ventral). Compared are naive animals (without any stimulation, left panel) with chronically stimulated animals. The inset in the left panel shows the investigated region of the cortex. In early-implanted animals (approximately 3 months after birth), increasing stimulation duration expands the activated cortical area and amplifies the amplitudes of the LFPs [60,61,63] (corresponding data exist on the inferior colliculus [49]). Additionally, functional maturation of unit responses after chronic electrical stimulation has been demonstrated, along with a maturation of cortical intrinsic microcircuitry [60,63]. Increasing the implantation age, as shown in the extreme case of implantation at 6 months of age (i.e. after sexual maturity in the cat) substantially decreases the effect of stimulation compared with implantation at an earlier age [61,63]. **(b)** Increasing the stimulation duration slowly but extensively expands the activated cortical area (blue bars), yet increasing the implantation age decreases the area (red bars). It should also be noted that the effect is specific for the region investigated; at the cortex ipsilateral to the stimulated ear, the decrease in activated area with increasing implantation age was more pronounced (green bars) [61]. **(c)** Effect of implantation age on the latency of the responses in the cortex. Early implantation leads to a significant decrease in the latency of the P_a component after chronic electrical stimulation, yet delaying implantation decreases this effect. Data from [61] **(b)**. Reproduced, with permission, from [63].

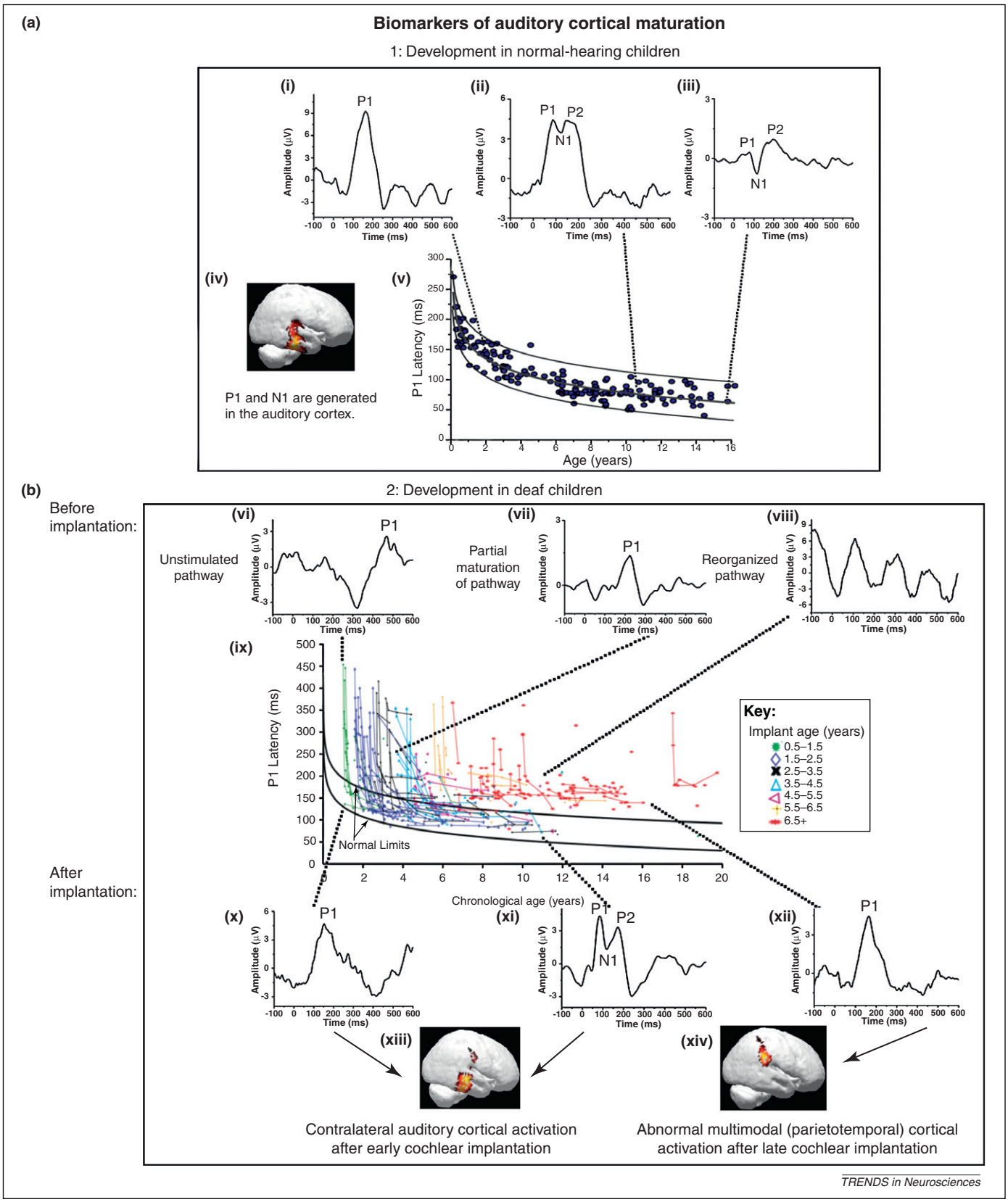

Figure 3. Auditory cortical maturation in children with normal hearing **(a)** or cochlear implants **(b)**. **(a)** Development in children with normal hearing: Latency and morphology of the P1 and N1 cortical auditory evoked potential (CAEP) components of the EEG are considered biomarkers of auditory cortical maturation. Schematic CAEP waveforms are shown in **(i–iii)** to illustrate morphological changes in development. The P1 is the predominant morphological component in infancy and early childhood **(i)**. Rapid decreases in P1 latency occur during the first 3 years of life **(v)**. Around pre-adolescence, the CAEP waveform invaginates, such that the N1 and P2 components appear in addition to the P1 component **(ii)**. Smaller latency decreases for the P1 component continue into adulthood **(v)** and the adult CAEP reflects a smaller P1 component along with larger N1 and P2 components **(iii)**. A normal range (and 95% confidence intervals) for the latency of the P1 waveform peak at different ages has been established using data from 190 normal hearing children **(v)**. High-density EEG (among other measurements) reveals that underlying generators of the P1 component include the primary auditory cortex, whereas the N1 component receives input from higher order auditory cortex **(iv)**. **(b)** Development in deaf children: CAEP responses have been measured in congenitally deaf children who received cochlear implants at different ages in childhood. Schematic CAEP waveforms are shown in **(vi–viii and x–xii)** to illustrate

Chronic electrical stimulation using a single channel portable signal processor (commonly used in animal studies) results in an expansion in cortical representation of the stimulated region of the cochlea [55,60] (Figure 1) and improves entrainment to the stimulus in the midbrain [55,57,58]. This process is extensive (expansions of activated cortical areas up to a factor of five were demonstrated [61]) and slow (it takes place over a period of several months [61]). By contrast, multichannel stimulation (similar to human cochlear implants), which activates many regions of the cochlea in an asynchronous manner, does not result in such extensive expansions, probably because of competition of individual channels for neuronal space [48,62]. In addition to the simple expansion of the activated areas, maturational changes in cortical response properties have also been documented [60,63]. In deaf animals that are acutely stimulated with an implant (i.e. naive deaf animals that have no hearing experience before the experiment), cortical units respond in a uniform manner to different electrical stimuli. However, in animals that are chronically stimulated, differential responses to different auditory stimuli are observed, indicating development of feature sensitivity [63]. Chronically stimulated animals also demonstrate an expanded dynamic range in unit activity [63]. These aspects of cortical maturation tend to diminish as the age at which cochlear implantation occurs increases, demonstrating a sensitive period for cortical plasticity [61,63] (Figure 2a). Age dependence is most prominent in long-term chronically stimulated animals and shows hemispheric specificity (Figure 2b,c): in congenitally deaf cats, a shorter sensitive period (of approximately 3.5 months) has been demonstrated for the cortex ipsilateral to the stimulated ear, and a longer sensitive period (of approximately 5 months) for the hemisphere contralateral to the stimulated ear [61]. This implies that several sensitive periods exist, depending on which hemisphere is investigated. Thus, both hemispheres profit from unilateral implantation only at a very young age.

Large population studies in congenitally deaf children have shown that these children benefit most when cochlear implantation takes place within the first 3.5 years of life, when the central auditory pathways show maximal plasticity [64–68]. The latency of the P1 component of the cortical auditory evoked potential (considered a biomarker of cortical maturation) decreases rapidly, and reaches the normal age range in children who receive an implant before 3.5 years of age [64–67]. By contrast, children who receive implants after the age of 7 show abnormal cortical responses, even after many years of cochlear implant use (Figure 3bix) [64–67]. These age cut-offs, determined by electrophysiological studies, correspond closely to studies of positron emission tomography (PET) measurements of resting cortical metabolic rate and regional density cerebral blood flow, which show decreased spontaneous glucose metabolism (owing to years of auditory deprivation) in the auditory cortices of children implanted before 4 years of age [69–71]. By contrast, children implanted after 6.5–7.5 years of deafness show normal metabolism in higher-order auditory cortices, suggesting that these areas were unavailable for auditory processing, probably because of functional re-specialization of these areas as a result of long-term sensory deprivation [69–72]. There is also a close correspondence between the age cut-offs described in the electrophysiological and PET studies and the speech and language performance of congenitally deaf, implanted children. Children who receive implants before 3–4 years of age show significantly higher speech perception scores and better language skills compared with children implanted after 6–7 years of age [25,26,73–77]. Recent studies investigated whether children implanted before 1 year of age demonstrate even greater benefit in behavioral auditory performance, with outcomes depending on the experimental paradigm [77,78].

Taken together, data from deaf children are largely consistent with animal studies and provide evidence of the existence of sensitive periods in early childhood. Thus, cochlear implantation during the sensitive period of the first 3–4 years takes place in a maximally plastic auditory system, allowing cortical maturation to progress.

Neuronal mechanisms underlying sensitive periods for cochlear implantation

Delays in synaptogenesis

Synapses are in constant turnover as they appear and disappear at all ages [79]. During development, there is a phase of pronounced turnover, with a predominance for establishing new contacts and, thus, a net synaptogenesis [80,81]; this is subsequently followed by a net loss of synapses [82]. The functional effects of synaptic development (i.e. synaptogenesis and maturation of synaptic properties) can be traced using functional measures at the mesoscale (Figure 4a,b). Functional synaptogenesis in auditory cortex accelerates around hearing onset in cats and culminates between the first and second month after birth in the hearing cat, to decrease to adult values at around 3–4 months [52] (a similar time course of synaptic counts, as evaluated anatomically, has been described in the primary visual cortex [83–85]). The timeframe for the appearance of activity in infragranular cortical layers is slightly delayed

morphological differences. In young children, prior to implantation, abnormal cortical response morphology is seen reflecting either an unstimulated auditory system **(vi)**, or a system that has received partial stimulation via hearing aids **(vii)**. Older deaf children show abnormal polyphasic waveforms suggestive of a reorganized auditory cortex **(viii)**. Developmental trajectories for P1 latencies examined in 231 congenitally deaf children fitted with an implant suggest a sensitive period for auditory cortical maturation. Children who received an implant early in childhood (<3.5 years of age) showed normal P1 latencies within 6–8 months of implant use, whereas children who were fitted with an implant late in childhood (>6.5–7 years of age) had delayed and/or abnormal cortical response latencies even after years of implant use. Children who received an implant between the ages of 3.5 and 7 years showed variable results, with P1 latencies reaching normal limits for some children and not for others **(ix)**. In early-implanted children, an age-appropriate P1 component is seen shortly after implantation and a P1, N1, P2 complex (similar to age-matched children with normal hearing) is seen after long-term experience with the implant **(x, xi)**. High-density EEG reveals activation of auditory cortical areas contralateral to the implanted ear for children implanted under the age of 3.5 years **(xiii)**. By contrast, children who have remained congenitally deaf for approximately 7 years or longer in childhood show polyphasic responses prior to implantation **(viii)** and delayed and/or abnormal P1 responses even after many years of implant usage **(xii)**. An N1 component is not apparent typically in late-implanted children, and high-density EEG recordings revealed that auditory stimuli abnormally activated multimodal cortical areas (as opposed to auditory cortical areas) [38]. Such findings suggest that cortical reorganization after the end of the sensitive period is largely final at 6.5–7 years of age **(ivx)**. Reproduced, with permission from [65] **(av)**; [38] **(aiv, bxiii, bxiv)**; [66] **(bix)**.

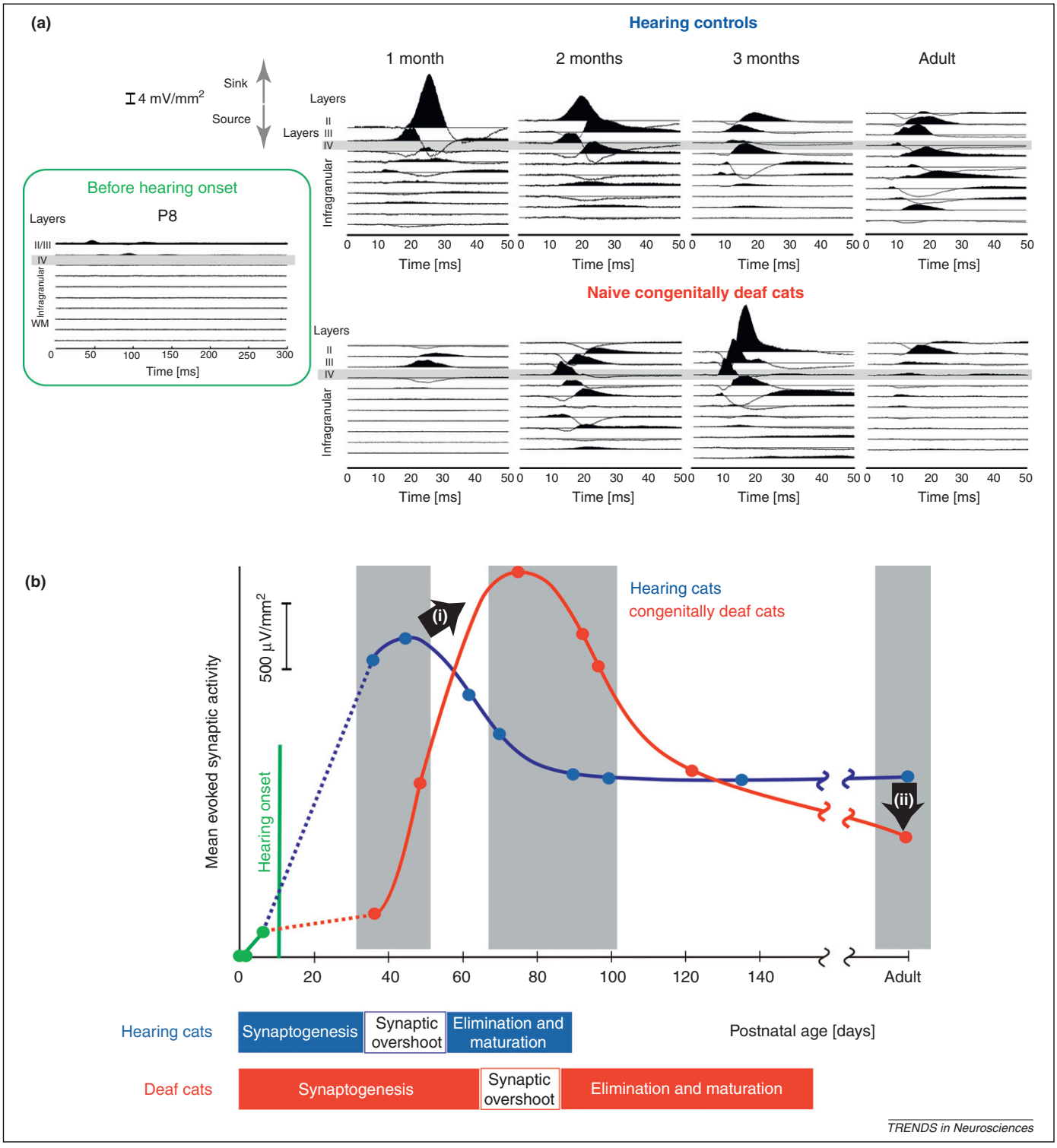

Figure 4. Developmental alterations in deafness. **(a)** Development of current source density (CSD) profiles (representing the summed extracellular components of synaptic currents) in field A1 with age in hearing controls versus congenitally deaf cats. Stimulus: biphasic pulse applied through a cochlear implant. At postnatal day (P) 0 and 3, no responses in the cortex could be elicited (not shown). At P8 (before hearing onset, hearing thresholds >>100 dB sound pressure level), small long-latency responses were recorded in supragranular layers. Large responses, mainly in layers 2, 3 and 4, were recorded from hearing controls at 1 month of age. Starting at the second month, amplitudes of the CSDs decreased. From the third month onwards, structured activity in deep cortical layers appeared. This timeline corresponds to synaptogenesis (first weeks of life) and subsequent synaptic pruning in the feline visual cortex [83–85]. In congenitally deaf cats, the development of CSD was delayed, with large responses only being observed at 3 months of age. Additionally, a pronounced reduction of synaptic activity in infragranular layers has been demonstrated at earlier ages in deaf animals [100,102]. **(b)** Quantification of the results from **(a)**. Depicted is the mean amplitude of current sinks over six penetrations within the most responsive part of the cortex in each animal. Grey bars designate the region of statistically significant differences between hearing and deaf animals (two-tailed Wilcoxon-Mann-Whitney test, $\alpha = 5\%$), and bullets show the data of individual animals. Bullets in the adult age range represent a grand mean average of four animals in each group. A delay in the period of functional synaptogenesis **(i)** is observed in deaf cats. Furthermore, a decrease in the mean evoked synaptic activity **(ii)**, as a result of an exaggerated functional synapse elimination and maturation period, is discernible in deaf adult cats. Reproduced, with permission, from [52] **(a)**; modified, with permission, from [19] **(b)**.

compared with the peak of synaptogenesis in hearing cats (Figure 4a,b).

In deaf animals, functional synaptogenesis has been found to be significantly modified; it is delayed by approximately 2 months (peaking at approximately 4 months) and the subsequent reduction in synaptic activity is more pronounced than in hearing controls [52] (Figure 4a,b). Although activity in the deep cortical layers is transiently observed in deaf animals, it disappears at 4 months of age [52], demonstrating incompetence to activate these layers sufficiently from this age onwards. These results demonstrate that the peak time and extent of postnatal synaptogenesis is dependent on experience. The visual system shows similar experience dependency in development [81,84,85]. When synapses are generated without reference to the needs of the organism, although overall synaptogenesis is increased (albeit delayed), essential synapses may not get established, and some of them are additionally lost in the subsequent phase of synaptic pruning in the absence of hearing. In congenital deafness, synaptic development in the absence of hearing thus leads to functionally incompetent neuronal networks [52,60,63]. Both persistent immaturity (developmental delays and alterations) and degenerative changes have been observed in the cortex of deaf cats [52].

In humans with normal hearing, synaptic density peaks at approximately 2–4 years of age in the temporal cortex, after which a decline in synaptic numbers follows [82]. It is of interest to note that the age of peak synaptogenesis coincides with the 3.5 year timeframe for optimal cochlear implantation in children. Latencies of cortical auditory evoked responses reflect age-related changes, including synaptogenesis [13] and delayed P1 latencies in deaf children (prior to cochlear implantation) (Figure 3bvi–viii) suggest that, in humans (as in cats), deafness results in a delayed synaptogenesis in the auditory cortex. Taken together, the animal and human data suggest that delays in experience-dependent synaptogenesis at least partly underlie the sensitive period during which auditory experience must be provided to a child to accelerate the establishment of essential synapses and subsequent refinement of synaptic networks.

Deficits in corticocortical interactions

As we have described, there is a pronounced reduction in synaptic plasticity in the auditory cortex during early deafness [86]. This change is also accompanied by changes in the excitatory–inhibitory balance [52–54]. Nevertheless, even in adults, there is some residual plasticity in both animals [61] and humans [27,28,66,87]. The presence of residual plasticity in late-implanted, prelingually, deaf subjects should in principle allow levels of speech performance comparable to early-implanted children after longer periods of experience with the implant. However, late-implanted subjects continue to show poor speech recognition and auditory performance even after long durations of implant use (albeit often with minor improvements [27]). This indicates that, in addition to decreasing synaptic plasticity, other, more complex factors are responsible for the closing of sensitive periods. As we describe below, these factors are related to the integrative functions of the auditory system. The naive auditory cortex shows a reduced sensitivity to features of auditory inputs (Figure 2), leading to a smeared central representation of auditory stimuli (e.g. deficient coding of stimulus intensity, incorrect representation of the position of the activated site in the cochlea as well as temporal properties of the input). To be able to categorize acoustic features into auditory objects, the distinctive features must be accurately represented in the brain. A deficient representation of acoustic (or electric) features complicates discrimination of auditory stimuli and subsequently affects the starting point for learning.

The auditory cortex represents a functional unit composed of areas with different functions; historically, these are viewed in a so-called 'hierarchical order', from lower order to higher order areas [88], although they together represent one highly interconnected functional unit. Proper functioning of the auditory system is dependent on tight mutual links between these areas. Only those patterns of neuronal activity can get stabilized in a given area that also fit into the circuitry of other tightly interconnected areas. These interactions between cortical areas and within modulatory systems of the brain are essential for normal auditory behavior. Both perceptually and anatomically, bottom-up (from lower order to higher order) and top-down (reverse) interactions have been demonstrated in the auditory system [88–91]. Cortical plasticity depends on this interplay. It is affected by permissive factors (e.g. acetylcholinergic modulation from the basal forebrain [2]) and by the behavioral context, acting via top-down interactions [1,92]. Attention further affects cortical processing [93], possibly via non-specific modulatory inputs, but also via top-down influences [94,95]. In the brain, a dynamic ongoing interaction of bottom-up and top-down information flow takes place [1]. The complex interactions within the cortical column are designed to compare bottom-up input, intrinsic processing and cortical top-down feedback [1,96]. Through this interaction, cortical processing can be reorganized depending on the context, biological importance and behavioral success of the function performed. In primary auditory cortex (field A1), such top-down modulation provides information on cognitive factors that affect acoustic feature representation. Top-down interactions may also contribute to filling-in phenomena [89–91], where higher-level representations affect perception at a lower level (e.g. acoustic feature perception is influenced by auditory object representation, or word representation, etc.). That is, primary areas (including A1) could act as a high-resolution buffer or holding area for information processing at higher levels [97]. Although it is currently not clear where and how auditory objects are represented in the brain, it is likely that this representation is generated in the cortex [98] and requires corticocortical interaction of many different fields.

Infragranular layers are a candidate for the locus of bottom-up and top-down interactions [96,97,99]. They receive input from the thalamus, from supragranular layers of the same column and also from higher order areas via top-down projections. The top-down projection targets infragranular neurons either within infragranular layers or via their apical dendrites located in supragranular layers. Infragranular layers exert a modulatory influence

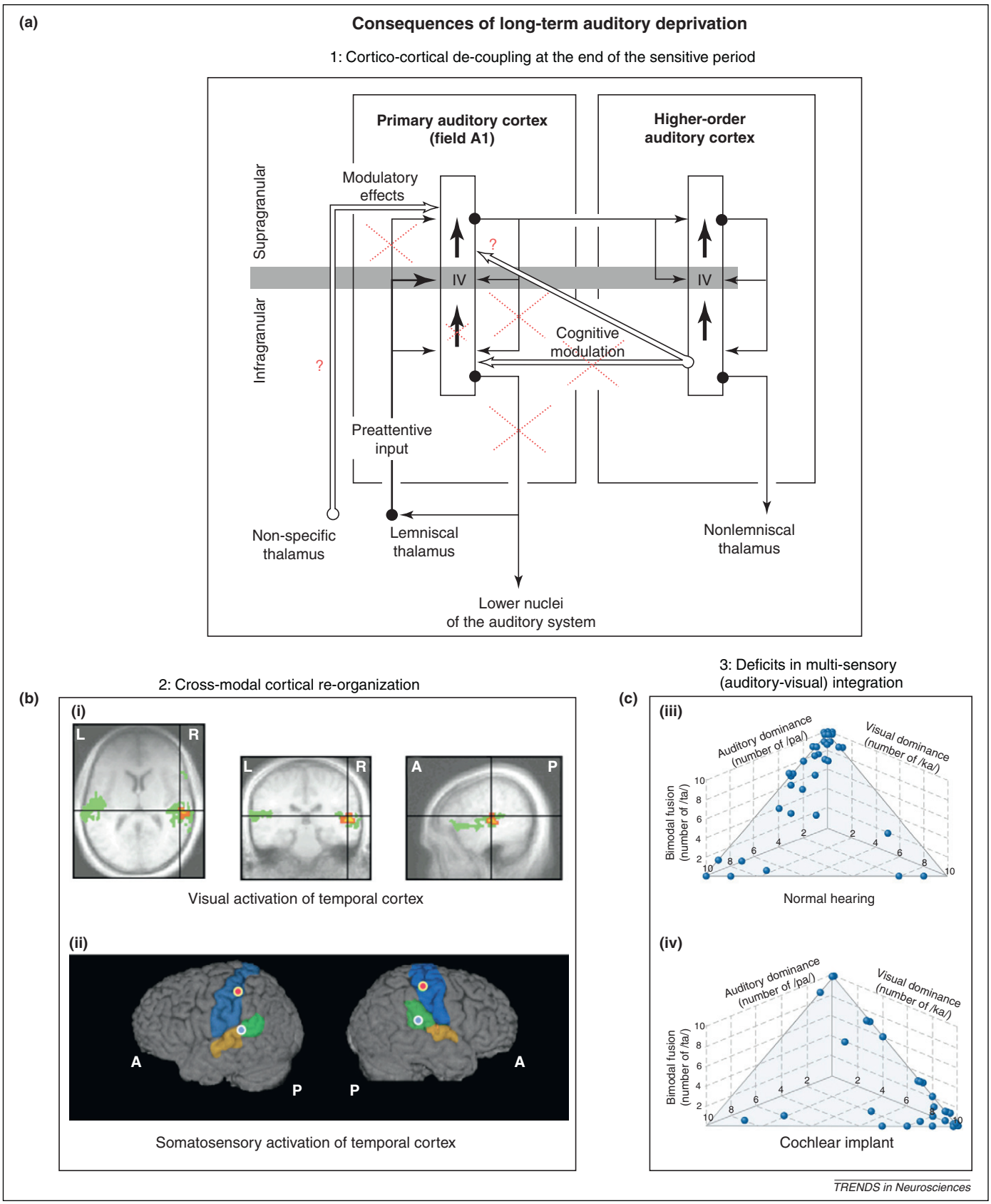

Figure 5. Cortical reorganization and its functional consequences as a result of long-term auditory deprivation in deaf children. **(a)** Corticocortical decoupling at the end of the sensitive period. Deaf children who receive a cochlear implant after the end of the sensitive period (at 7 years of age) typically show abnormal cortical auditory evoked potentials, including an aberrant P1 response and an absent N1 response (see Figure 3bxii). The lack of N1 (which reflects input from higher order auditory cortex) is consistent with animal data suggestive of corticocortical deficits. A model of functional decoupling in the auditory cortex in deafness is shown in **(a)**. Lemniscal input targets A1 mainly in layer IV (shaded bar), but also supragranular and infragranular layers. Neurons in infragranular layers project to layer IV and layer IV projects to supragranular layers. Supragranular layers project back to layer IV and infragranular layers (feedback). Infragranular layers send descending fibers to subcortical nuclei (corticofugal). Feedforward coupling to the higher-order auditory areas is accomplished via supragranular layers, descending projections from higher-order cortex target the infragranular and possibly supragranular layers in A1 (top-down or cognitive modulation). Dashed crosses show which connections are supposedly not functional in congenitally deaf

on layers 2, 3 and 4, and they send feedback (top-down) projections to lower order areas; in the case of field A1, this projection mainly targets the auditory thalamus (reviewed in [63]) (Figure 4a). This circuitry may be involved in the short-term store of information for comparisons of incoming stimuli [60,100].

In congenitally deaf animals, activity between cortical layers is significantly desynchronized in adults [100] and long-latency activity is substantially reduced [60]. Long-latency activity is known to be dependent on corticocortical interactions [101], indicating that deafness impairs corticocortical interactions. This deficit is reversible by chronic electrostimulation with cochlear implants [63]. Additionally, infragranular layers are less active in congenitally deaf animals [100] and this effect is reversed by early cochlear implant stimulation [63]. Such a deficit in activation of deep cortical layers in deaf animals indicates that the neuronal substrate for top-down modulation, control of plasticity and hypothetically filling-in phenomena is deficient in congenital deafness [102].

Consequently, the naive adult auditory cortex not only no longer shows the high juvenile plasticity required for bottom-up structuring of the neuronal networks, but it also lacks the substrate for perceptual modulation and control of reduced adult plasticity. A partial decoupling of the primary auditory field A1 from modulation from higher-order auditory fields probably contributes to the closure of the sensitive period in animals [63,102] (Figure 5a). Correspondingly, in late-implanted early-deaf children, cortical auditory evoked potentials elicited by cochlear implant stimulation are abnormal in morphology [e.g. they typically lack the N1 component with preserved (yet aberrant) P1 component [66,68,103] (Figure 3bix)]. N1 is generated in higher-order auditory areas and reflects corticocortical interactions, whereas P1 has generators both in primary and higher-order areas [104]. Consequently, the absence of the N1 component in late-implanted children demonstrates deficits in higher-order areas, supporting the notion that top-down influences in late-implanted deaf children are reduced, probably because of partial decoupling of higher order areas from primary auditory cortex at the end of the sensitive period [66,68,103] (Figure 5a). Some late-implanted children may be able to overcome these deficits with intensive auditory training and these children are likely to both have an N1 response and good oral language.

Cross-modal reorganization and deficits in multimodal processing

Functional decoupling of field A1 from higher-order areas is an example of disrupted functional unity of the auditory cortex in deafness. In support of this, different auditory areas are differentially recruited for new, non-auditory functions (Figure 5bi,ii), such as visual [72,105–108] and somatosensory [66,109] processing. Such cross-modal reorganization does not diffusely involve all auditory areas, but is rather differential and specific in the cortical areas it affects [110,111]: field A1 is not involved in visual [110,111] and somatosensory tasks [110], but higher-order areas, such as the posterior auditory field (PAF) and dorsal zone (DZ), aid visual localization and motion detection, respectively, in congenitally deaf cats [111]. This specific and localized cross-modal reorganization in deafness may result in a functional disintegration of the mutual interconnections between auditory areas and serve as one reason for the decreased top-down influence in A1 [63,102].

Consistent with functional disintegration of auditory cortical areas, psychophysical studies demonstrate that global high-level processing are substantially affected by congenital (or perinatal) deafness. Deficits in non-auditory functions have been observed; for example, early deaf subjects are deficient in fine motor coordination [112,113] and also demonstrate deficits in working memory and sustained attention in the visual system [114–118]. The working memory deficit is related to the type of language (signed vs spoken) used for communication [118]. Consequently, the demands of sign language on memory may be higher than those of spoken language. Finally, phonological awareness for spoken language is affected in signing deaf persons [119,120]. Although it is difficult to exclude comorbid disorders completely, these results indicate that higher-level functions (even non-auditory) possibly require an auditory reference (via top-down interactions) for proper function [19].

Compensatory (or cross-modal) plasticity in deafness probably occurs as a means to improve interaction with the environment in sensory deprivation [121]. Functional consequences of cross-modal plasticity in deafness include improved visual performance during visual localization, visual attention (both in the peripheral visual space) and in motion detection [122]. By contrast, it appears that understanding of speech and auditory–visual integration via the cochlear implant is negatively influenced by cross-modal reorganization [123–129] (Figure 5civ). Furthermore, certain neural networks have been associated with good and poor performance with the cochlear implant. Children who perform well with the cochlear implant appear to activate dorsolateral prefrontal networks, which participate in higher cognitive functions, such as reasoning, attentional control and working memory, whereas children who perform poorly with the implant repeatedly show functional specialization of auditory cortical areas for visual processing [125].

cats [52,63,100]. A similar lack of top-down modulation of incoming auditory stimuli in humans would explain difficulties in oral language learning that are experienced by late-implanted children. **(b)** Crossmodal cortical reorganization. Long-term deafness beyond the sensitive period results in crossmodal cortical reorganization, probably as a consequence of functional corticocortical decoupling between primary and higher-order auditory cortex. **(i)** Functional magnetic resonance imaging (fMRI) reveals activation (green and red patches) in response to visual stimulation in the temporal cortex (including higher-order auditory cortical areas) of deaf adults. **(ii)** Magnetoencephalograph (MEG) dipole reconstructions reflect activation of both somatosensory cortex (blue regions) and higher-order auditory cortex (green regions) (including Wernicke's area, in the left hemisphere) in response to tactile stimulation in deaf adults. A, anterior; L, left; P, posterior; R, right. **(c)** Deficits in multisensory (auditory–visual) integration. Auditory deprivation can result in deficits in processing of multimodal stimulation necessary for language learning. For example, bimodal fusion of the speech sound /ta/ occurs when a visual cue (lip-reading) for /ka/ is combined with an auditory cue (listening) for /pa/ (also known as the McGurk Effect [133]). In **(iii and iv)**, /ta/ responses indicate auditory visual fusion, whereas /pa/ responses indicate auditory dominance and /ka/ responses indicate visual dominance. Responses of children with normal hearing suggest auditory dominance **(iii)**. By contrast, responses of children with cochlear implants suggest a greater visual dominance **(iv)**. Modified, with, permission, from [102] **(a)**; reproduced, with permission, from [107] **(bi)**; [66] **(bii)** and [123] **(c)**.

More research needs to be done to understand the tremendous individual variability seen in children with cochlear implants. A more comprehensive understanding of the neural correlates of individual variability will be critical to developing better habilitation options that are aimed at, and customized for, individual patients. Future directions in patient rehabilitation may include the use of electrophysiological and brain imaging measurements as cortical biomarkers of the functional developmental state of the individual patient, and hence, allow customization of the habilitation options after cochlear implantation [67,103,125,130–132]. An individualized approach to the patient, which takes into account the individually different central compensation processes, would optimize rehabilitation success.

Concluding remarks

Studies of children fitted with cochlear implants have established the existence of, and the time limits for, a sensitive period for cochlear implantation. The optimal time for cochlear implantation is within the first 3.5–4.0 years of life (and best before the second year of life) when central auditory pathways show the maximum plasticity to sound stimulation. The eventual end of the sensitive period (at approximately 6.5–7.0 years of age in humans) has consequences for the reorganization of cortical areas and pathways. Animal models have identified mechanisms underlying the sensitive period, which include a kaleidoscope of different neuronal mechanisms. These mechanisms include developmental abnormalities in synaptic plasticity resulting in abnormal connectivity, functional disintegration and immaturity of auditory cortical areas, the smearing of feature representations in the auditory system, cross-modal recruitment of some auditory areas for non-auditory functions, and the reorganization of cognitive functions owing to absence of auditory input. The striking similarities between the animal and human studies suggest that deficits in synaptic plasticity, deficiencies in higher order cortical development and cross-modal recruitment are responsible for the well-documented difficulties in oral speech and language skills seen in late-implanted, congenitally deaf children.

By contrast, early implantation within a brief sensitive period allows more adequate cortical maturation, resulting in the development of speech perception and the acquisition of oral language. Early implantation enables hearing to be put within a behavioral framework by allowing the hearing modality to interact with the environment, which provides constant feedback. This is a prerequisite for appropriate learning. The brain is hard-wired for hearing and learning to listen.

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