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Neuronal Development of Hearing and Language: Cochlear Implants and Critical Periods

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Abstract

The modern cochlear implant (CI) is the most successful neural prosthesis developed to date. CIs provide hearing to the profoundly hearing impaired and allow the acquisition of spoken language in children born deaf. Results from studies enabled by the CI have provided new insights into (*a*) minimal representations at the periphery for speech reception, (*b*) brain mechanisms for decoding speech presented in quiet and in acoustically adverse conditions, (*c*) the developmental neuroscience of language and hearing, and (*d*) the mechanisms and time courses of intramodal and cross-modal plasticity. Additionally, the results have underscored the interconnectedness of brain functions and the importance of top-down processes in perception and learning. The findings are described in this review with emphasis on the developing brain and the acquisition of hearing and spoken language.

Contents

INTRODUCTION

The auditory system has become a leading model of sensory deprivation in recent decades, primarily because a treatment has been developed to produce or restore highly useful hearing for previously deaf or severely hearing-impaired persons. As a side benefit, it has enabled investigations of effects of the onset and duration of sensory deprivation in studies with human subjects.

The treatment is the modern cochlear implant (CI) (**Figure 1**). Similarly effective treatments do not yet exist for any of the other senses, including vision, and thus studies with the CI and a combination of laboratory (animal) studies and studies on human subjects offer unique opportunities. Such studies have allowed insights into the development of a sensory system; the sensitive or critical developmental periods; plastic changes in brain function resulting from the absence of a sensory input and the subsequent provision of the input; and, for the human auditory system, the acquisition of spoken language and the minimal representations at the auditory periphery that are consistent with speech understanding.

In this review, we describe the CI and its performance, provide background information on how neuroprosthetic input is processed in the brain, and then review the neural mechanisms responsible for the outcomes of cochlear implantation.

THE BRAIN ALLOWS SPEECH UNDERSTANDING WITH MINIMAL CUES

Speech is an acoustically highly complex and dynamic signal. The brain dedicates extensive neuronal resources for speech processing (Hickok & Poeppel 2007, Hickok 2012). They include the temporal lobe, the parietotemporal boundary, the inferior frontal cortex, and the premotor cortex and can be divided into a ventral and a dorsal route of language processing [dual-stream model (Hickok & Poeppel 2007)]. This complex circuitry is developmentally tuned to extract language cues in a very efficient and rapid way.

Consonants and vowels, the basic building blocks of spoken language, are characterized by acoustic features such as the short-term spectra of the sounds and variations in the spectra over time (so-called distinctive features). The sounds may be periodic (voiced speech), aperiodic (unvoiced speech), or a mixture of the two. Additionally, some of the consonants are defined by the

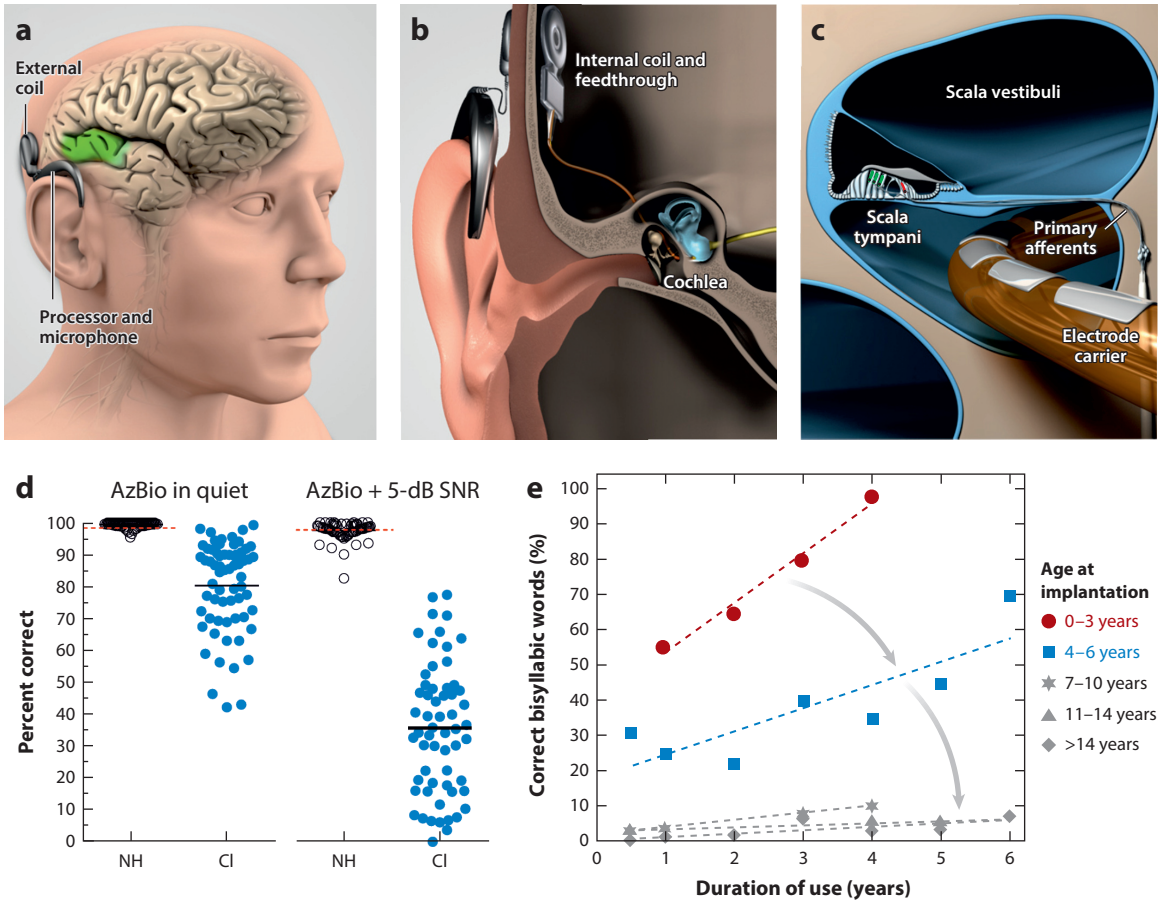


Figure 1

Components and performance of the modern CI. (*a*) External components and auditory cortex (*green*). (*b*) Internal components and a different view of the external components. (*c*) Electrode array inserted into the scala tympani. (*d*) Recognition of the multitalker and low-context AzBio sentences by subjects with NH and by CI users, with the sentences presented in an otherwise quiet environment or in competition with noise at the indicated SNR. The circles represent scores for individual subjects, and the horizontal lines represent the averages of the scores. Panel *d* adapted with permission from Wilson & Dorman (2018); data provided by Dr. R. Gifford, Vanderbilt University Medical Center. (*e*) Comparison of cochlear-implanted prelingually deaf children in a sample of 98 children. Mean bisyllabic word recognition in quiet over time of implant use in five groups of children is shown, grouped based on the age at implantation. Children implanted after the third year, and particularly those after the sixth year, show substantially reduced outcomes that improve with time but are not counterbalanced by 6 years of CI use. More recent data demonstrate that implantations within the first 12–18 months provide the best outcomes. Data used in panel *e* taken with permission from Manrique et al. (1999). Abbreviations: AzBio, Arizona Biomedical; CI, cochlear implant; NH, normal hearing; SNR, speech-to-noise ratio.

delay in the onset of periodicity following a burst of aperiodic energy (the voice onset time). For speech understanding, some of these features must be represented with at least minimal fidelity in the discharge patterns of the auditory nerve, and the brain must preserve and analyze the features for accurate decoding of the sensory input. The representation at the periphery can be degraded by (*a*) the presence of concurrent sounds such as noise or competing talkers, (*b*) hearing impairments of cochlear origin, or (*c*) distortions introduced by hearing prostheses such as the coarse representation of spectral information produced by the current CIs. The representation in the

brain can be degraded by multiple causes, including the prolonged absence or substantial attenuation of input from the periphery. Degradations in the representations—either at the nerve or in the brain—can impair and even preclude the reception of spoken speech.

CIs bypass damaged or missing sensory hair cells in the cochlea by directly stimulating neurons in the auditory nerve using electrical pulses (**Figure 1*a–c***). The components include a microphone; a processor to transform the microphone into stimuli for the implanted array of electrodes; a transcutaneous link for the transmission of power and stimulus information across the skin; an implanted receiver and stimulator unit to decode the information received from the radio-frequency signal produced by the external transmitting coil and to generate stimuli using the instructions obtained from the decoded information; a cable to connect the outputs of the receiver/stimulator to the electrodes; the array of electrodes; and, of course, the user's brain. Ideally, stimuli delivered to the different electrodes excite different (albeit overlapping) subpopulations of neurons and thereby produce an approximation to the tonotopic mapping of frequencies along the length of the cochlear helix in normal hearing (**Figure 1*c***).

The continuous interleaved sampling (CIS) strategy (Wilson et al. 1991) transforms the microphone input into specifications for the patterns of electrical stimuli that are delivered through the implanted array of electrodes in the cochlea. Other strategies in current use are based on CIS or are close variations of CIS (Fayad et al. 2008, Zeng et al. 2008, Zeng & Canlon 2015). CIS filters the input signal into bands of frequencies and then detects the variations of energy in each band. The variations are limited to a maximum frequency of 200–400 Hz (the so-called pitch saturation limit; see Zeng 2002) and enable a representation of the fundamental frequencies of speech for most or all speakers, including children. The energy variations are then compressed into the narrow dynamic range of electrically evoked hearing. The outputs of each of these bandpass channels of processing are used to modulate trains of balanced biphasic pulses that are interlaced in time across the channels. The pulses generated for each channel are directed to the corresponding electrode in the cochlea, with the outputs for channels with high center frequencies for the bandpass filters directed to electrodes at basal positions along the cochlea and the outputs for channels with low center frequencies for the filters directed to electrodes at more apical positions. The interlacing of the stimuli across electrodes eliminates a principal component of interactions among the electrodes that otherwise would be produced by direct summation of the electric fields from the different electrodes. The frequencies and amplitudes of sound inputs are represented with both the place of stimulation and the frequency and amplitude variations in the modulation waveforms for each place. To date, up to 24 electrodes have been used for the CIS and other processing strategies for CIs; however, only 4–8 appear to provide independent information (Friesen et al. 2001, Garnham et al. 2002). Although that number is sufficient for understanding everyday sentences in otherwise quiet conditions (Shannon et al. 2004a), it is not sufficient for more difficult speech items or for sentences presented in competition with noise or other talkers (**Figure 1*d***).

CI subjects improve in speech understanding within 12 months after implantation (Krueger et al. 2008). Scores for the everyday (high context) sentences presented in quiet increase from 40% correct at 2 weeks after the initial fitting of the CI to 90% correct at 12 months and beyond for one of the populations of subjects (Helms et al. 1997) and to ~70% correct for less predictable sentences presented in quiet (Wilson & Dorman 2008, Wilson et al. 2016). This means that most implanted subjects can understand speech even if it is presented through a telephone and without reading from lips. Scores for the CI subjects are highly variable, especially for challenging tests (see, e.g., the scores for +5-dB speech-to-noise ratio in **Figure 1*d***); performance in noise falls significantly, down to mean scores of ~30% at +5-dB speech-to-noise ratio, where normal hearing subjects still score at above 90% correct (Wilson et al. 2016). This large drop in performance shows that while CIs provide an excellent solution in quiet, their performance

levels off in noisy conditions (where more speech features may be required) (Shannon et al. 2004b).

The modern CI became the standard therapy for severe or worse losses in hearing and is now applied even for persons with a severe or worse loss on one side and normal or nearly normal hearing on the other side. The CI is the most successful neural prosthesis developed to date, in terms of both the restoration of function and the number of people helped, which at present exceeds half a million (including ~100,000 deaf-born children) and is growing exponentially (Wilson & Dorman 2008).

The first systematic attempts to understand electrical stimulation of the auditory nerve (Simmons et al. 1965) were met with skepticism and rejection by neuroscientists who could not believe that the intricate inner ear structure with ~3,500 inner hair cells and ~36,000 auditory nerve fibers could be replaced by a crude technical device that stimulates neurons via one or a few electrodes, providing only a minimal representation of sound for the listening brain.

The success of the CI, providing only minimal acoustic cues, is based on how complex sensory input is processed by the brain. The brain perceives physical features as belonging to perceptually coherent and meaningful wholes (Lewkowicz 2014). After the brain has analyzed and partitioned the acoustic stimulus into features, the features need to be categorized into perceptual groups or auditory objects. Auditory objects are sensory representations resulting from a process of feature grouping that are subject to foreground-background distinction (Kral 2013), such as the horn of a car, the meow of a cat, and a fallen keychain on the ground, or a speech sound. This feature grouping helps to overcome the enormous variability of the acoustic world. Categorical borders of auditory objects can change by context and top-down influences (Savin & Bever 1970, Studdert-Kennedy 1980, Goldinger & Azuma 2003), and objects and features are in tight functional interaction and dependence (Kral 2013). With object representations, the brain can easily fill in gaps in some features by top-down interactions (Riecke et al. 2012, Wild et al. 2012). Making use of object representation, perception becomes more robust to interfering influences (such as degraded input). In fact, many perceptual effects are initiated at the object level before we consciously perceive features (Hochstein & Ahissar 2002). Learning involves facilitating access to the level of representation containing the cue that is relevant for performance (Ahissar et al. 2009).

Consequently, even a severely degraded speech input can be understood by an experienced native speaker (Remez et al. 1981, Shannon et al. 1995). For example, the acoustic speech signal can be degraded to three sinusoids that track formant frequencies (Remez et al. 1981) or four bands of noise (Shannon et al. 1995), and still be understandable in quiet. In difficult listening conditions (thus masking additional distinctive features), however, these manipulations lead to a breakdown of speech understanding (for a similar effect with CI, see **Figure 1*d***). Speech thus contains many redundant discrimination cues for differentiating phonemes (distinctive features) that are partially disposable in easy listening conditions but essential in more complex conditions. The disposability of some cues facilitates the CI perception, particularly in quiet.

CRITICAL PERIODS FOR HEARING AND LANGUAGE

Are CIs similarly effective if the subject could not learn language acoustically due to inborn deafness? Learning language is a demanding task for the immature brain. Likely due to intrauterine hearing, newborns prefer the voice of their mother and the mother language (Partanen et al. 2013) and 3 months postpartum activate similar brain structures as adults when exposed to their mother language (Dehaene-Lambertz et al. 2006) or naturalistic sounds (Wild et al. 2017). The development of the auditory system is thus affected by sensory input before birth in humans (reviewed in Kral et al. 2017). However, the developmental steps of language acquisition extend until the teenage years (Kuhl 2004).

Deaf children do not enter the very early developmental steps of language acquisition (canonical babbling) and fail to develop spoken language (Oller & Eilers 1988, Eilers & Oller 1994). CIs eventually demonstrated a critical period for language development: Subjects born deaf and cochlear-implanted in adult age could hear with the CI (perceived sound), but they demonstrated persistent auditory deficits and did not gain effective speech understanding with the CI (Busby et al. 1992, 1993; Busby & Clark 1999; Manrique et al. 1999). Thus, early deafness, if treated in adult age, prevents sufficient speech understanding, even after long experience with CIs.

When surgeons implanted deaf-born children with CIs early in life, outcomes were substantially better (House et al. 1981). Systematic studies investigating speech comprehension as a function of implantation age confirmed a critical period for therapy that expires within the first 3 years (**Figure 1*e***) (Fryauf-Bertschy et al. 1997, Manrique et al. 1999), with the best performance occurring with implantations in the first 12–18 months (McConkey Robbins et al. 2004, Svirsky et al. 2004, Kral & O'Donoghue 2010, Niparko et al. 2010, Nicholas & Geers 2013). Newborn hearing screening has been introduced in many countries to promote early therapy (Kral & O'Donoghue 2010, Yoshinaga-Itano 2014).

COCHLEAR IMPLANT STIMULATION SHAPES THE AUDITORY SYSTEM

The neuronal mechanisms of auditory critical periods have been investigated in higher mammals, including neonatally deafened cats (NDCs) and congenitally deaf cats (CDCs). Similar to human implantees, chronic CI stimulation in NDCs induced adequate behavior in training sessions (Snyder et al. 1990, Leake et al. 1992, Vollmer et al. 2005). Deaf animals could learn to react to and differentiate CI stimuli (Klinke et al. 1999, Beitel et al. 2011, Benovitski et al. 2014). Using a portable signal processor and 24/7 stimulation using ambient natural sounds paired with auditory training, CDCs demonstrated a remarkable cortical reorganization following early implantation (Klinke et al. 1999): The active area responding to stimulation in primary auditory cortex extensively expanded during the first 3 months of stimulation (**Figure 2**), with a corresponding decrease in response latency and the maturation of neuronal responses. The dynamic range of cortical unit responses increased, and the neurons developed differential responses to different electrical stimuli and developed long-latency activity not seen in deaf animals but observed in hearing cats (Kral et al. 2006).

Implantations at later stages of development, and particularly implantation at the adult age, were increasingly less successful (Kral et al. 2006, 2013b,c), demonstrating a neural correlate of a critical period for deafness therapy in the primary auditory cortex. Similarly, in early deaf children, critical periods were observed with CI-evoked cortical electroencephalographic responses (Ponton & Eggermont 2001, Sharma et al. 2002). Based on these observations, the latency of the auditory component P_1, generated in primary and secondary auditory cortical areas, has been suggested as an objective measure of developmental hearing experience (Sharma et al. 2005a,b). The correspondence suggests that similar processes take place in the auditory cortex of CDCs and prelingually deaf children (Ponton & Eggermont 2001, Kral & Sharma 2012).

MECHANISMS OF DEVELOPMENTAL PLASTICITY AND CRITICAL PERIODS

The juvenile brain with its high synaptic plasticity can spontaneously adapt to environmental input governed by stimulus statistics alone (Stanton & Harrison 1996, Zhang et al. 2001, Barkat et al. 2011) and can passively organize acoustic features into increasingly refined representational

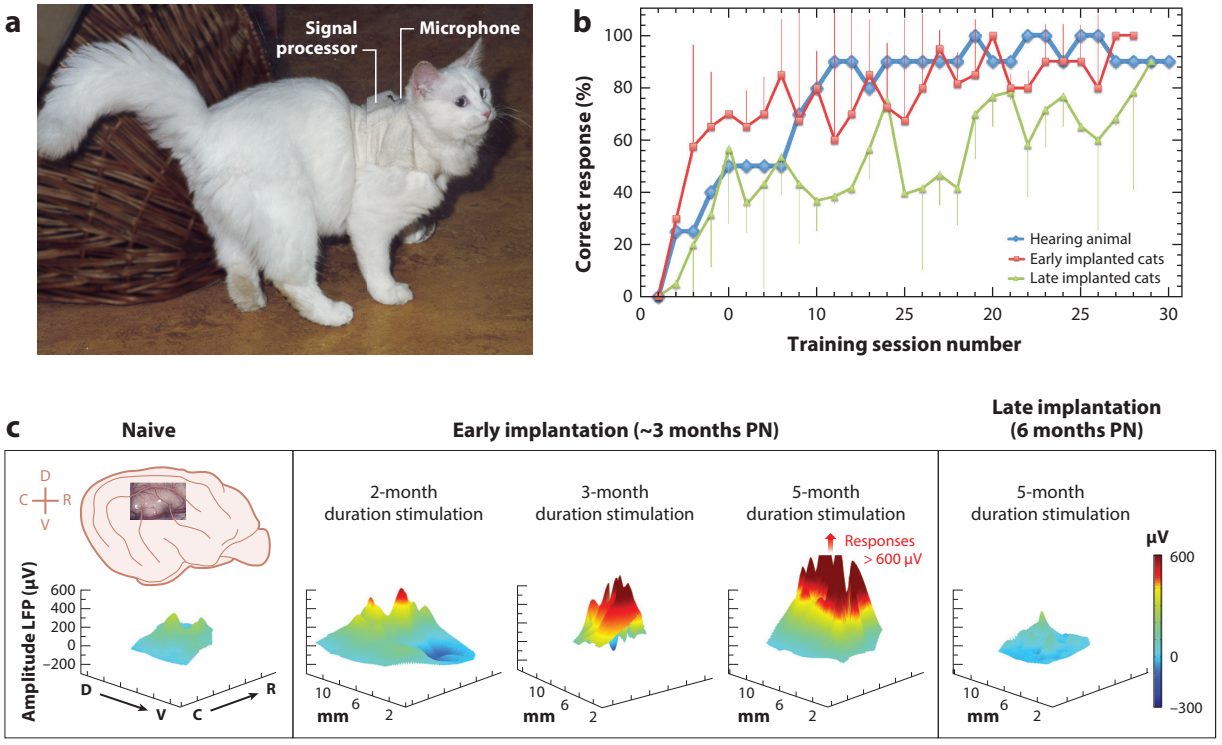


Figure 2

Chronic electric stimulation with biologically meaningful stimuli in early age causes maturation in the auditory cortex. (*a*) CDC with a portable signal processor in a jacket can freely move and be stimulated on a 24/7 schedule. (*b*) Cats with CIs learn within a few sessions to pair a CI stimulus to a reward. Animals implanted late (6 months PN) show a more variable performance. Data used in panel *b* from Kral et al. (2013a), shown as means plus or minus standard deviation. (*c*) Maps of activity at the primary auditory cortex in deaf naive animals (*left*), CDCs implanted early and stimulated chronically (*middle*), and CDCs implanted late (*right*). The expansions of activated areas are slow (take months) but extensive. Late implantations do not lead to such adaptation. Panel *c* adapted with permission from Kral & Sharma (2012). Abbreviations: C, caudal; CDC, congenitally deaf cat; CI, cochlear implant; D, dorsal; LFP, local field potential; PN, postnatal; R, rostral; V, ventral.

maps. With increasing age, synaptic plasticity becomes progressively reduced (Crair & Malenka 1995, Barkat et al. 2011, Chun et al. 2013), and the organization of the sensory systems becomes more stable. In the visual system, this change in synaptic plasticity is caused by decreased synaptic conductivity related to developmental, genetically determined changes in synaptic channels and related proteins (van Zundert et al. 2004). A corresponding developmental reduction in synaptic conductivity was also observed in the auditory system (Aramakis et al. 2000), but the molecular processes may involve other additional components (Chun et al. 2013).

Consequently, in adults and in contrast to juveniles, cortical representations are not influenced by stimulus statistics alone. Passive presentation of meaningless stroboscopic flashes (Cynader & Chernenko 1976) or click trains (Zhang et al. 2002) can destroy topographic representation in the primary sensory areas in juveniles but not in adults. Similarly, in adult onset of deafness, even decades without hearing did not interfere with good speech understanding following implantation in humans (Lazard et al. 2012).

Adult plasticity is thus less dependent on statistical characteristics of the input but is instead actively controlled (or gated) by context (Seitz & Watanabe 2005, Chun et al. 2013). During

postnatal development, such gated plasticity gradually replaces the juvenile passive plasticity. In addition to changes in glutamatergic transmission (Sun et al. 2018), inhibitory interneurons play a crucial role in gating since they can decrease excitability and prevent plasticity in other neurons and be modulated in their level of activity, e.g., by cholinergic inputs (Chun et al. 2013, Froemke 2015). Inhibition fully matures late during development (Gao et al. 2000). Activity initiates the development of inhibition by promoting the release of brain-derived neurotrophic factor (Rutherford et al. 1997). In the absence of hearing, inhibitory function does not mature normally (Pallas et al. 2006, Mowery et al. 2015), interfering also with its role in adult gated plasticity. In addition to inhibition, molecular brakes of plasticity delineating the critical period have been identified, including substances in the extracellular matrix, perineuronal networks, and the NoGo system (reviewed in Weinberger 2004, Edeline 2012, Takesian & Hensch 2013). Biological intervention into such modulatory systems can rejuvenate the auditory cortex and reopen the possibility for the influence of passive stimulus exposure (Blundon et al. 2017).

Such developmental molecular changes participate in the sensitive period for deafness therapy. Reduced synaptic plasticity in some synapses was reported following neonatal cochlear destruction (Kotak et al. 2007), and many neuronal membrane properties were also abnormal (Mowery et al. 2015). Interestingly, however, synaptic plasticity is not completely eliminated in congenital deafness (CD): The late-implanted animals and late-implanted prelingually deaf humans retained residual plasticity after implantation, with changes in cortical responses traceable many months after the implantation (Schorr et al. 2005, Sharma et al. 2005a). Similarly, late-implanted children learned to recognize some auditory events and even some speech patterns (Waltzman et al. 2002, Schorr et al. 2005), and in the blind visual system, there is residual plasticity observed in adulthood as well (Mitchell 1988, Scheiman et al. 2005). Then why is this residual, albeit reduced, plasticity not capable of providing speech comprehension comparable to early implantations, even when learning is allowed over long time scales in an active, engaged attentive subject? In other words, why do sensitive periods become critical? As it is the brain that learns (as opposed to an individual synapse), it is likely that additional systems' mechanisms are involved in closing sensitive periods.

Two popular candidates for system-level limitations in learning are (*a*) cross-modal plasticity, the abnormal recruitment of the deprived sensory modality by another sense, potentially interfering with the neurosensory restoration at later ages, and (*b*) intramodal deficits caused by the absence of hearing during development, which renders the auditory circuits incompetent in adequately processing the sensory input and in learning. In what follows, we explore these alternatives in detail.

Role of Cross-Modal Plasticity in Critical Periods

Unused cortical sensory regions can take on new, cross-modal functions (Bavelier et al. 2006, Merabet & Pascual-Leone 2010, Barone et al. 2016). The closure of sensitive periods has often been attributed to a visual takeover of auditory areas in deaf children (Nishimura et al. 1999, Lee et al. 2001, Glick & Sharma 2017), where the reorganized cortices were assumed to lose responsiveness to the original modality.

Recent findings, although confirming cross-modal reorganization, contradict such extensive trade-offs between modalities: Supranormal visual performance, caused by visual recruitment of two secondary auditory areas, has been documented in CDCs (Lomber et al. 2010), yet this functional reorganization was astonishingly specific to the cortical area and was even related to the area's auditory function in hearing animals. Retrograde tracer injections revealed that the anatomical substrate for this cross-modal reorganization was small (Barone et al. 2013, Meredith et al.

2015, Butler et al. 2017), where only about 5–10% of the fibers were ectopic, and most connections preserved auditory targets in both reorganized areas. This finding suggests that fiber tracts develop largely independent of experience. Indeed, even late-implanted prelingually deaf humans can hear with the implant. The main problem for the late-implanted is to discriminate and recognize complex sounds.

Recently, electrophysiological responsiveness to CIs and to visual stimulation was compared directly in the functionally reorganized dorsal auditory cortex of CDCs (Land et al. 2016). The cross-modally reorganized (visual) neurons were scattered along the involved area and cortical layers (Land et al. 2016). Responsive units were rarely bimodal, suggesting a deficit in intersensory integration following deafness (see Mayers et al. 1971, Schorr et al. 2005, Wallace et al. 2006). Not only was auditory responsiveness found in the reorganized area, it was three times more frequent than the cross-modal responsiveness to the visual stimulus. Cross-modal reorganization did not degrade auditory responsiveness significantly (Land et al. 2016; for humans, see Corina et al. 2017), and it also did not prevent dystrophic cortical changes in the cortical areas involved (Berger et al. 2017), further documenting the modest influence of cross-modal inputs. These observations suggest that the increased visual responsiveness may result from a few exuberant connections between the visual and auditory cortex that appear during early development and that were not pruned due to the absence of hearing (Land et al. 2016). The extent to which the few ectopic inputs may functionally reorganize the networks and the exact developmental timing of cross-modal plasticity remain unclear.

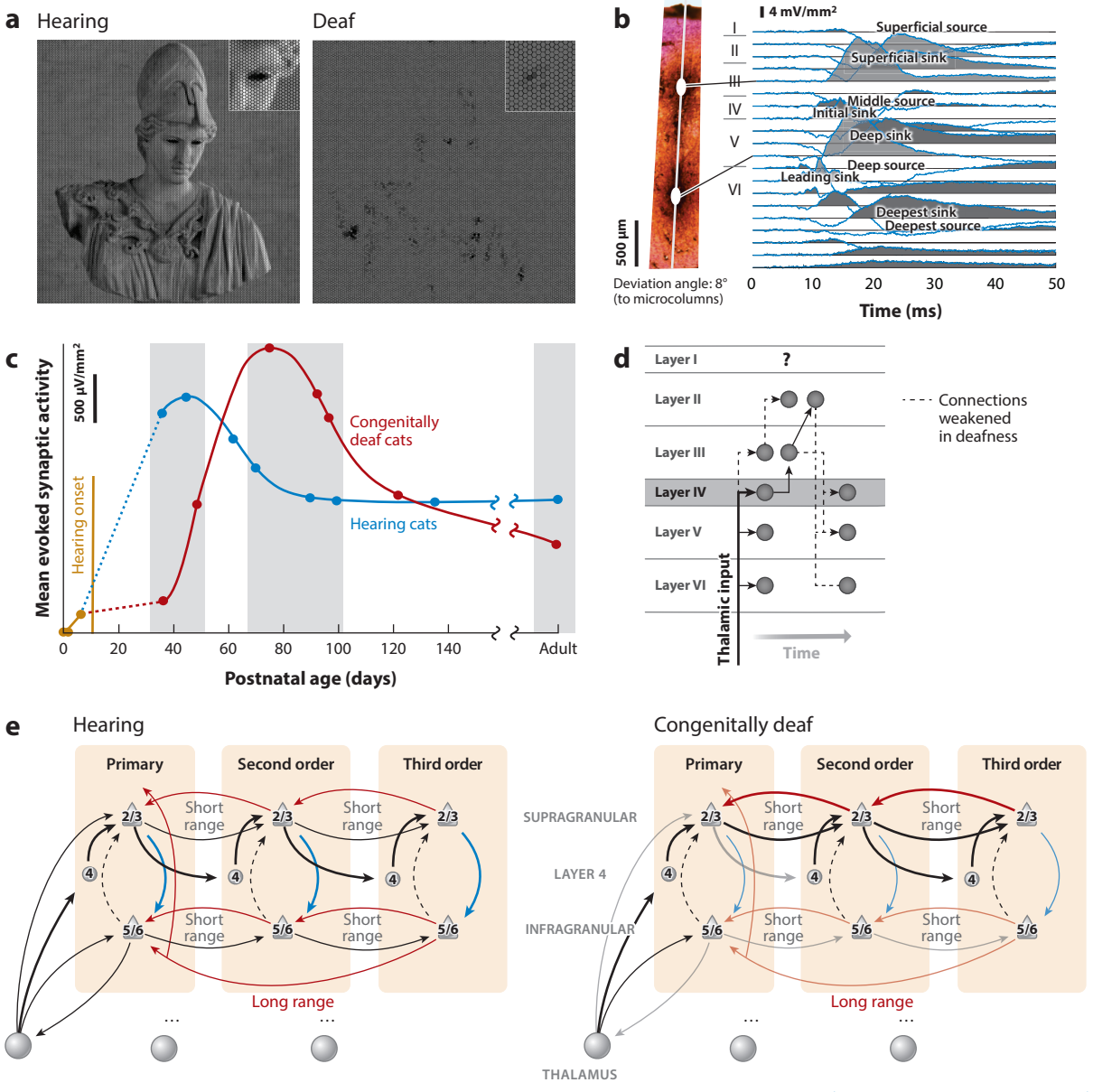
In the extrastriate visual cortex of CDCs, auditory modulatory influence was reduced but not eliminated (Land et al. 2018). This is surprising given that the neurons in the visual cortex are driven by visual stimuli, and despite this, the nonactive auditory synapses were not all lost. Genetic makeup is thus an important factor in the development of anatomical connectivity and responsiveness. These data also support the concept that the cross-modal takeover, instead of resting on an extensive bottom-up reorganization, is mainly driven by high-order multimodal areas that make use of the auditory areas in a top-down fashion (Benetti et al. 2017). Although bottom-up cross-modal reorganization itself may not be the main reason for the closure of auditory sensitive periods, a stronger reliance on the spared sensory systems following sensory restoration, driven by associative areas, leads to a visual dominance in audiovisual stimuli (Schorr et al. 2005, Benetti et al. 2017).

Deafness Results in Extensive Auditory Processing Deficits

Following CD, or after neonatal pharmacological deafening in animals, deficits in the brain's feature sensitivity have been demonstrated using CIs, including reduced tonotopy (Raggio & Schreiner 1999, Fallon et al. 2009, Barone et al. 2013), reduced dynamic range (Fallon et al. 2009, Tillein et al. 2010), reduced temporal resolution (Shepherd et al. 1999, Ryugo et al. 2005, Baker et al. 2010), and reduced sensitivity for binaural cues (Hancock et al. 2010, Tillein et al. 2010) (other deficits reviewed in Kral et al. 2017). Thus, the acuity of the congenitally deaf brain's representation of auditory features is severely degraded (**Figure 3*a***). Developmentally, that is well in line with auditory feature sensitivity improving with experience (reviewed in Litovsky 2015).

The deficits in feature representation involve synaptic effects. First, the adaptation of the neuronal network to extract the statistical regularities (features) of the sensory input (Krizhevsky et al. 2012, Marcus 2018), facilitated by high juvenile synaptic plasticity in early childhood, has not taken place in CD. Instead, the deaf auditory system has adapted to detect any, even the weakest, inputs, e.g., by reducing inhibition (Pallas et al. 2006, Mowery et al. 2015), decreasing cortical response

thresholds (Kral et al. 2005), and increasing neuronal gain and thus reducing the neurons' dynamic range (Tillein et al. 2010). Consequently, feature extraction in the deaf auditory system is abnormal and the system is functionally more suitable for stimulus detection than for stimulus discrimination. Second, synaptic microstructural deficits were observed throughout the auditory pathway of deaf cats (Hardie et al. 1998; Ryugo et al. 2005, 2010) despite the preservation of anatomical fiber tracts in the brainstem (Heid et al. 1997), preserved cortical cytoarchitectonics (Berger et al. 2017), and general auditory responsiveness (Hartmann et al. 1997). In contrast to



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

Mechanisms responsible for the critical period for cochlear implantation in deafness. (*a*) Feature sensitivity of cortical neurons is degraded, and this analogy captures the changes in the auditory cortex of deaf animals. The whiteness of each pixel is assumed to correspond to a firing rate of a neuron in response to a complex stimulus, resulting in the complex cortical firing pattern shown in the image (*left*) and the pattern degraded the same way as evoked responses are degraded in deaf animals (*right*). Panel *a* adapted from Kral et al. (2013a). The extent of the degradation precludes the identification of the stimulus. (*b*) CSD profile obtained from a columnar penetration with a microelectrode shown on the left inset (horseradish peroxidase marks in Nissl staining) in a hearing animal in response to a biphasic pulse applied through the CI. CSDs reveal detailed patterns of synaptic activity in time and across layers. (*c*) Synaptic activity quantified by mean sink temporal integrals in the cortex of hearing and deaf cats from birth to adulthood with CI stimulation. Deaf cats demonstrate an extensive modification of synaptic development, with a delay in synaptogenesis, but also enhanced pruning. Panel *c* adapted from Kral & O'Donoghue (2010). (*d*) Columnar microcircuits reveal a functional deficit in the deep layers of CDCs. Panel *d* adapted from Kral et al. (2006). (*e*) Bottom-up and top-down effective connectivity of hearing and deaf cats. Changes in effective connectivity of CDCs implied from morphological and functional analyses; weakened connections are shown by pale colors and strengthened connections by thicker lines. Thalamic connections, as for the primary auditory cortex, exist also for the other cortical areas but were replaced by three dots in second-order and third-order cortex for clarity. Panel *e* adapted from Berger et al. (2017). Abbreviations: CDC, congenitally deaf cat; CI, cochlear implant; CSD, current source density.

the afferent auditory pathway, the majority of functional corticocortical synapses are formed after birth (Huttenlocher & Dabholkar 1997, Kral et al. 2005). This process is profoundly modified in CD (Kral et al. 2005), with a delay in functional synaptogenesis and a subsequently augmented synaptic pruning (**Figure 3*b*,*c***). Synaptic cortical development in the absence of sensory input thus generates impoverished neuronal networks that differ extensively from those in hearing animals.

Consequently, although the general anatomical features are less affected by the absence of hearing, synaptic and functional development—and some microanatomical features—depends strongly on sensory input.

When the circuitry of cortical columns was investigated (**Figure 3*b*,*d***), a desynchronization of cortical layers and a reduced responsiveness in the infragranular layers V and VI were noted in CDCs (Kral et al. 2000). CD thus results in profound deficits in columnar processing. The functional deficits in deep layers were reversible by 3 months of chronic CI experience (Kral et al. 2006). Reduced cortical thickness, which is also a morphological correlate of effects on columnar microcircuitry in deafness, was observed in layers IV, V, and VI, but not in supragranular layers of the auditory cortex in CDCs (Berger et al. 2017). Deep layers are both a major source of feedback (top-down) projections (Rouiller et al. 1991, Galaburda & Pandya 1983) and a target of feedback projections (**Figure 3*e***; compare to Rouiller et al. 1991, Callaway 1998, Hackett 2011, Markov et al. 2014). Thus, the observed deficits indicate a significant compromise of top-down interactions in CD.

Auditory objects perceived in a given auditory scene affect the features that are important in the given condition and vice versa. Although feature analysis is dependent on the physical properties of the stimuli, auditory objects are subjective and depend on the individual's experience. If features and objects are represented at different levels of the auditory cortex and objects involve higher-order auditory areas (Nelken et al. 2014, Teki et al. 2016), their interaction will depend on the ability to integrate bottom-up and top-down streams of information. Such integration allows computing a prediction error (the difference between expectation and actual input)—a signal that initiates and drives adult learning (reviewed in Friston 2010, Bastos et al. 2012, Harris & Mrsic-Flogel 2013, Kral et al. 2017). Reduced activity in the deep layers of CDCs and the dystrophic changes in these layers suggest that CD impairs the circuits that generate top-down information and allow integrating the information into bottom-up processing (Kral 2013, Kral et al. 2017). A fingerprint of such integration of sensory input and top-down (corticocortical) input is induced oscillatory activity. Induced activity is caused by a sensory stimulus, but, in contrast to evoked responses, appears about 150–500 ms after stimulus onset and varies in timing and phase between

trials (Yusuf et al. 2017). Induced activity is the substrate for corticocortical interactions. The auditory cortex of CDCs showed substantially reduced induced responses in both the primary and secondary auditory cortex (Yusuf et al. 2017). These findings suggest that hearing experience is required for the development of the microcircuits integrating sensory input with active cortical representations and ongoing brain processing, which is essential for perception, top-down interactions, and adult auditory learning.

All these deficits in congenitally deaf animals lead to a condition that is somewhere in between the juvenile and adult stage. Neither the cellular mechanisms of juvenile plasticity nor the network mechanisms required for adult (gated) plasticity are functional in CD. Together, all these factors in combination close the critical period, ultimately limiting performance after late implantation.

NEW VISTAS: ACTIVE LISTENING FACILITATES LANGUAGE ACQUISITION

Early in development, the visual and auditory inputs become linked to each other and to motor and proprioceptive feedback, i.e., to the internal representation of the body. If successful, one can, for example, identify their own hand in the visual field and relate the sound of feet walking on gravel to the movement of their own legs. It is the motor system that allows linking the sensory input with the developing internal model of the self and the world.

Adaptation to visual stimulation during development is substantially facilitated by active interaction with the environment (Levi & Li 2009). Visuomotor contingencies are important for visual plasticity (Buisseret et al. 1978). There is motor influence on sensory cortices, both in the visual cortex (Kaneko et al. 2017) and in the auditory cortex of behaving rodents (Nelson et al. 2013, Schneider et al. 2014), primates (Eliades & Wang 2008, Morillon et al. 2015), and humans (Reznik et al. 2015).

In humans, phonetic information is represented in the temporal cortex and is organized based on distinctive acoustic features (Mesgarani et al. 2014). If attention and effort are involved, listening to speech recruits additional neuronal resources beyond the classical language circuit (Wild et al. 2012, Du et al. 2014). Passive exposure to language, although effective for some statistical learning in early development, is not effective enough to acquire language competence in infants (Bishop & Mogford 1993, Kuhl et al. 2003, Goldstein & Schwade 2008). Active use thus facilitates auditory and language processing (Lametti et al. 2014, Wu et al. 2014, Schneider & Mooney 2015, Schomers & Pulvermüller 2016). This suggests that nonauditory regions of the brain, including the motor cortex (Murakami et al. 2015), have a modulatory influence that can increase the effectiveness of auditory processing. Invasive recordings in the human premotor cortex document a sensorimotor representation of syllables that is activated during listening, even though the activation is substantially weaker than during syllable production (Cheung et al. 2016).

Indeed, functional imaging allows predicting good and poor performers with CIs. If reading involves the dorsal route, i.e., the route between audiovisual representations and frontal and motor language representations, the chance that the subjects will perform well after implantation is higher than if they recruit the ventral (lexical) route (Lazard et al. 2010, 2014), suggesting that there may be a successful and a less successful strategy for processing electrical stimuli, the former involving access to motor circuits.

The "connectome model of deafness" (Kral et al. 2016) suggests that in a CI user, we need to consider the function of the neuronal networks, the many interwoven levels of representation, and strong top-down effects—we need to consider the whole brain, including other sensory, motor, and cognitive systems.

CONCLUSION

CIs are an excellent example of successful biomedical engineering, and of bench-to-bedside research. The first studies with CIs investigated sensory processing with electrical stimulation in animals and humans and paved the way for future neuroprostheses in other sensory systems. The studies with electrical stimulation of the ear led to today's highly effective, multichannel CIs that enable previously deaf persons to understand speech with their restored hearing and enable the majority of deaf-born children to learn their mother language. The clinical data collected from adults, and especially infants and children, have prompted new questions to be answered in bench research. Moreover, the combination of clinical data from children implanted after different periods of auditory deprivation and data from animal models of CD has (*a*) allowed unprecedented insights into fundamental questions of speech comprehension, auditory development, and neuroplasticity, involving system's aspects on brain plasticity; (*b*) highlighted the importance of other brain functions for auditory and linguistic functioning; and (*c*) emphasized the role of hearing for nonauditory functions and vice versa. CIs have provided critical data relative to long-standing questions about brain development and have provided a better, more complete view of our brains and ourselves.

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