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## Hearing Research

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## Review Article

## Animal and human studies on developmental monaural hearing loss

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## ARTICLE INFO

## Article history:

Received 14 November 2018

Received in revised form 29 May 2019

Accepted 30 May 2019

Available online xxx

## Keywords:

Cochlear implant

Plasticity

Single-sided deafness

Deprivation

Unilateral hearing loss

## ABSTRACT

Asymmetric hearing has been the focus of many studies on brain plasticity in the past. Recently, the topic has gained clinical importance in cases with sequential cochlear implantation or in cases with deafness in one ear and preserved hearing in the other ear. Convergent evidence from animal experiments and from hearing impaired children suggest that asymmetric hearing during early development can reorganize the central auditory representation of the two ears with the consequence of a “stronger” representation of the better hearing ear with a “weaker” representation of the other, more poorly hearing, ear. These changes lead to a persistent aural preference for one ear, demonstrated by asymmetric speech comprehension when each ear is tested separately. Further, binaural integration is compromised as shown by reduced binaural fusion and reduced sensitivity for binaural cues. Finally, the data demonstrate a significant difference in cortical plasticity in response to juvenile monocular deprivation in the visual system and juvenile monaural deafness in the auditory system. The topic represents a unique example of translational research whereby mechanisms explored in animal models are combined with data from children to understand the clinical consequences of asymmetric hearing in early development.

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## 1. Introduction

Single-sided sensory loss has been the focus of both clinical and experimental studies for decades. The Nobel-prize winning research of David Hubel and Torsten Wiesel uncovered the potential for plastic reorganization of the developing visual system by manipulating vision of one eye. In the auditory system, the condition of single-sided hearing loss received interest for its potential to similarly investigate auditory plasticity. The research has been more complex than research on visual plasticity because, in contrast to the primary visual cortex, essentially all neurons in the primary auditory cortex receive inputs from both sides (ears). This means that even complete deafness of one ear does not deprive cortical neurons of their input completely. Studies of auditory system plasticity are also challenging because a reversible intervention in the ear canal or middle ear (e.g. suture of the outer ear canal or disarticulation of the ossicular chain) causes only mild hearing loss and sensory (cochlear) hearing loss cannot be reversed at present. Rather, sensory hearing loss must be treated by introducing a hearing prosthesis and the ability of the auditory system to adapt to this novel input has to be investigated.

There is a substantial clinical interest in the potential benefits of fitting an auditory prosthesis to treat single sided hearing loss (i.e. clinically relevant hearing loss on one ear only). Although the clinical consequences of single sided hearing in both adults and children are becoming clear (Borg et al., 2002; Dillon et al., 2017; Fischer and Lieu, 2014; Firszt et al., 2017; Kishon-Rabin et al., 2015; Purcell et al., 2016; Sangen et al., 2017) there is no clinical consensus on treatment. Hearing aids do not provide sufficient access to sound in the case of profound degrees of sensorineural impairments and, even in the presence of more moderate hearing loss they may be disregarded because of potential “interference” with the better hearing ear (e.g. by bone conduction to the better ear, Fitzpatrick and Leblanc, 2010). The same reservations accompanied the idea of cochlear implantation to treat single sided deafness (i.e. one normal hearing ear and one deaf ear). This treatment was first introduced in subjects with adult onset of deafness who had disturbing tinnitus in their deaf ear. Cochlear implantation in these cases has provided some tinnitus relief (Vermeire and Van de Heyning, 2008; Punte et al., 2011; Fitzgerald et al., 2015). However, tinnitus does not occur in congenital single-sided deafness (Eggermont and Kral, 2016; Lee et al., 2017). Instead, cochlear implants are being provided to children to prevent the potential of developmental hearing loss to permanently reorganize the hearing brain. The following review focuses on the developmental effects of single sided hearing by exploring the physiological background through studies in animal models of deafness and related findings in clinical populations. The animal and clinical studies of cochlear im-

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plantation, often done in parallel, provide a unique view of the importance of combining “bench” and “bedside” research.

## 2. Developmental plasticity promoted by cochlear implants

Hearing loss can be of different severity (mild, moderate, severe and profound, e.g. Kral and O'Donoghue, 2010) and is classified as “deafness” (profound hearing loss) if hearing thresholds drop below 90 dB HL. Such residual hearing does not provide sufficient input to understand speech even in aided condition (with hearing aids) and, as a rule, is treated using cochlear implants.

Cochlear implants are arguably one of the most successful medical devices in history (O'Donoghue, 2013). Interestingly, initial data came from clinical explorations of electrical stimulation of the auditory nerve in deaf adults (Chouard, 2015; House et al., 1981). Animal models followed, providing essential information on the safety of cochlear implantation and on the effects of electrical stimulation on the neuronal substrate. These studies were mainly performed on higher mammals (cats and monkeys), but also on rodents, particularly on guinea pigs (due to their exceptional low-frequency hearing among rodents). Important insights from animal models regarding cochlear implant use have included physical characteristics of the stimulation and relation to audibility (Barretto and Pflugst, 1992; Hartmann et al., 1984; Miller et al., 2006; Parkins and Colombo, 1987; Pflugst et al., 1991); effects of implant position in the scala tympani (Hatsushika et al., 1990; Shepherd et al., 1993); possible methods to focus currents to specific areas of the auditory nerve (Kral et al., 1998; Ifukube and White, 1987; Bierer and Middlebrooks, 2002; George et al., 2014); interactions between different channels (Hartmann and Klinke, 1990); neuronal adaptation of the auditory nerve (Litvak et al., 2001); long-term stability of the implants (Pflugst, 1990; Shepherd et al., 1983, 1984); relations of neuronal activity and perception of electrical stimulation (Pflugst, 1988); and electroacoustic interactions (Stypulkowski and van den Honert, 1984; van den Honert and Stypulkowski, 1984; Sato et al., 2017). As clinical experience with cochlear implants grows, so do the questions regarding the most effective use of this technology and how it might be used in new populations of individuals with hearing loss. Use of cochlear implants in children with prelingual hearing impairment has been particularly informed by work in animals with congenital hearing loss.

Outcomes of cochlear implantation in children with bilateral deafness are often remarkable, with many children acquiring oral spoken communication (Geers et al., 2009; Niparko et al., 2010; Papsin and Gordon, 2007). On the other hand, not all children achieve the same results and one of the most prevalent factors to explain this variability in outcomes is the age at implantation (Manrique et al., 1999; Niparko et al., 2010; review in Kral et al., 2016). Evidence from higher mammal models has been particularly important to explain these clinical findings. Significant effects of hearing deprivation in early development were found involving extensive deficits in central auditory processing (review in Kral and Sharma, 2012). Importantly, however, cochlear implant stimulation promoted experience-dependent developmental processes (Kral et al., 2006; 2013a,b; Raggio and Schreiner, 1999; Fallon et al., 2009a,b; Beitel et al., 2011; Vollmer and Beitel, 2011; Ryugo, 2015). Auditory plasticity with cochlear implant stimulation allowed near normal cortical maturation, but only when provided within an early sensitive period (Kral et al., 2002, 2006; 2013b; Fallon et al., 2009a,b). Electroencephalography in children using cochlear implants was consistent with these data: development in children with early onset deafness was altered and the normal maturation of latencies of evoked potentials was substantially delayed

compared to normal hearing children. Following cochlear implantations after the 5th year of age, cortical maturation was initiated and latencies decreased but remained delayed compared to age-matched hearing peers (Ponton and Eggermont, 2001). The response latencies thus reflected the developmental “time in sound” in these children (Ponton and Eggermont, 2001). However, such remaining developmental delays were quickly compensated (within a year of cochlear implant use) in children who were implanted earlier, within the first 3.5 years of life (Sharma et al., 2002, 2005). Such sensitive periods are likely defined by juvenile composition of ionic channels of the synapses, combined with formation of new synapses; sensitive periods end (become critical) as too many synapses that depend on sensory input are eventually eliminated, compromising the computational power of the corresponding neuronal networks (Kral, 2013). These insights provided an explanation for (i) why changes in cortical responses were more limited in children who had received their cochlear implants late, and (ii) why hearing outcomes declined with age at implantation (reviewed in Kral and Sharma, 2012).

## 3. Balance between ears: an ongoing dynamic developmental process

Given the importance of ensuring hearing ability within sensitive periods in development, it is important to consider development of spatial hearing, which provides our only sensory input from all directions around us. Spatial hearing is important for distinguishing between multiple concurrent sound sources (Grothe et al., 2010) and it is particularly important for children who are learning language while constantly on the move (Gordon et al., 2015).

The brain exploits three major sound localization cues: (i) interaural time differences (ITDs), (ii) interaural level differences (ILDs), and (iii) monaural spectral cues caused by pinna, head and torso (Grothe et al., 2010). These cues together define the so-called head-related transfer functions. The head and the body grow during childhood, slowly changing the head related transfer function (including the interaural time and level cues). Experiments in developing and adult ferrets show that spatial response fields in auditory cortical neurons are defined by the changing filtering abilities of the pinna and body (Mrsic-Flogel et al., 2003). This means that, as children grow, their developing auditory system must remap the relation between these cues and spatial locations in the external world, dynamically “recalibrating” sound in space to be consistent with the central representation of binaural and monaural cues. The use of other modalities, particularly vision, contributes to this recalibration. The visual system has higher acuity for spatial position than hearing and guides the formation of auditory spatial maps (Isaiah et al., 2014; King et al., 1988; Knudsen and Knudsen, 1989). In addition, the motor system may also play a role, providing the active feedback and the possibility to test the internal model of the “outer” space (Kral et al., 2019).

## 4. Mild unilateral hearing loss affects binaural processing

Unilateral mild hearing loss, as occurring in otitis media, is very common in childhood (review in Ruben, 1997) and introduces an additional (very potent) driver for realigning the representations of auditory and visual space. Binaural hearing was found to be compromised in a group of children who had histories of early conductive hearing loss (Graydon et al., 2017) but, as is typical in clinical cohorts, the specific time course of the hearing loss or bilateral versus unilateral involvements were not available for analyses. By contrast, developmental effects of chronic mild unilateral hearing loss (~30 dB) have been systematically studied by ligation or obstruction

of the ear canal in animal models. This manipulation reduces spatial localization accuracy (Keating et al., 2014; Kumpik et al., 2010; Moore et al., 1999; Polley et al., 2013) and initiates a reorganization of central representation of the strongly threshold-dependent cues like ILDs. In mice and rats (lacking ITD sensitivity due to predominantly high-frequency hearing), a weakening of cortical ILD sensitivity was demonstrated when this form of hearing loss was introduced within an early sensitive period (Polley et al., 2013; Popescu and Polley, 2010). In the cat, a species that uses all three major spatial localization cues, deleterious consequences on ITD sensitivity were also observed, but they were smaller than the effects on ILD sensitivity (Brugge et al., 1985). Adaptation to ear plugging (both in juvenile and adult age) can occur over time, improving sound localization (Hofman et al., 1998; King et al., 2001, 2000). The plasticity of spatial hearing in the presence of unilateral ear plugging relies primarily on the reweighting of localization cues whereby cues that are unchanged, such as monaural spectral cues in the normal ear, are weighed more heavily than binaural cues (review in Keating and King, 2013). However, binaural cues continue to be used (Kumpik and King, 2019). This reweighting strategy is primarily effective at high frequencies (where spectral cues are available) and thus compensates mainly for ILD cues (that also operate at high frequencies). Additionally, monaural localization has lower acuity than localization using binaural cues, and thus the compensation for unilateral ear plugging is far from perfect and recovers only some specific spatial localization abilities. Importantly, these changes to support spatial hearing can be reversed once the earplug is removed. Normal localization returns after more than a year of normal binaural hearing in ferrets (Moore et al., 1999). Thus, animal models of a specific and consistent mild unilateral hearing loss indicate that spatial hearing is plastic and can be recalibrated over the lifespan. Experimental ear plugging in humans affecting spectral and binaural cues demonstrate and confirm similar plasticity in localization ability in adults (Hofman et al., 1998; Hofman and Van Opstal, 2003; Van Wanrooij and Van Opstal, 2005).

Binaural plasticity after unilateral hearing loss has also been explored in barn owls. Owls have developed specialized sound localization and low- and mid-frequency hearing to hunt prey in the night. They show exceptionally high phase locking capacity in the auditory nerve (Köppl, 1997), which provides an excellent input for ITD-detecting circuits and allows extraction of ITDs (the dominant binaural cue in humans) with high acuity. In young owls, binaural cues are rapidly remapped after unilateral hearing loss by increased central nervous sensitivity to the reduced input (from the ear affected by hearing loss). Unilateral hearing loss correspondingly promotes compensatory remapping of binaural tuning in neurons within spatial brain maps (Knudsen, 2002). Yet, the owl provides a unique view into binaural hearing plasticity given its particular ecological niche. It has an ordered topological map of interaural time differences in the brainstem. Mammals, instead, likely extract spatial information by a population code from all binaurally-sensitive neurons in absence of ordered topological maps (Grothe et al., 2010). This coding may be the reason why such compensatory remapping in binaural sensitivity following unilateral hearing loss in owls is not found in mammals (Brugge et al., 1985; Clopton and Silverman, 1977; Moore and Irvine, 1981a, 1981b; Silverman and Clopton, 1977; Tillein et al., 2016). Mammals rather reweight the behavioral importance of individual cues (e.g. by putting more emphasis on unchanged monaural cues, see above). The mechanistic explanation of this species difference has yet to be provided. It is possible that compensatory remapping of binaural cues with unilateral hearing loss has its drawbacks and is not the optimal strategy for mammals. These adjustments

could interfere with the representation of other auditory features required for e.g. communication. As an example: deprivation down-regulates inhibition (Kotak et al., 2005; Vale et al., 2004) and up-scales synaptic sensitivity (Desai et al., 2002) that together affect spike timing precision and thus information about a vital auditory cue for temporal analysis of complex sounds. Consequently, there is a trade-off between hearing sensitivity and neural processing acuity (required for e.g. speech understanding and perception of complex sounds).

In development, the onset and duration of unilateral hearing loss requires consideration. Even very brief early hearing experience can have extensive developmental effects and prevent deprivation-induced developmental deficits in the visual system (Collignon et al., 2015; Iwai et al., 2003; Maffei and Turrigiano, 2008; Mower et al., 1983; Olson and Freeman, 1980; Rosen et al., 1992). Similarly, consequences of congenital deafness in the cochlear nucleus are more severe compared to neonatal pharmacological deafening, where hearing loss sets in after the age of normal developmental onset of hearing (Baker et al., 2010; Ryugo, 2015). Therefore, the exact onset and duration of hearing loss together play a critical role.

This issue opens an important clinical question: how much does transient unilateral hearing loss affect speech processing and thus the development of language? While some studies have indicated lasting effects of transient mild-to-moderate hearing loss on language development in children (review in Ruben, 1997), later studies failed to find a consistent effect (Roberts et al., 2004a, 2004b). As discussed above, clinical populations are typically heterogeneous, making it difficult to assess the true consequences of transient unilateral hearing loss. Often critical factors such as the onset, the duration, and the degree of the loss are not known. Moreover, effects may be clearer in other types of psychophysical testing which target expected effects on binaural hearing such as those involving speech perception in noise. By contrast, both untreated congenital single sided deafness and unilateral cochlear implantation following congenital bilateral hearing loss provide a more clearly characterized, more extreme and more clinically relevant condition than mild unilateral hearing loss.

## 5. Single-sided deafness leads to a “stronger” and a “weaker” ear

An important question is whether unilateral auditory deprivation should be treated and, if so, how exactly. In this research area, clinical data from children receiving bilateral cochlear implants and from children with bimodal hearing (cochlear implant in one ear with acoustic hearing with or without a hearing aid in the other) have been combined with essential information from animal models to define the major barriers and provide potential solutions.

Cochlear ablation in animal models provided important initial insights into the representation of the only hearing ear in this extreme hearing asymmetry (e.g. McAlpine et al., 1997; Moore and Kitzes, 1985; Moore et al., 1993), but the central representation of the ablated ear or binaural sensitivity could not be tested. Effects of this extreme condition have been investigated for both ears by providing cochlear implants to a natural higher mammal model of deafness, the congenitally deaf cat (Kral et al., 2006). Single-sided cochlear implantations in these cats were compared to rare cases of unilateral congenital deafness in this animal strain (Kral et al., 2013a,b). The exceptional condition in unilaterally congenitally deaf cats is the severity of the effect. In contrast to mild hearing loss of 25–30 dB induced by manipulation of the middle ear, the unilaterally congenitally deaf animals have a total absence of hearing on one ear, combined with normal hearing on the other ear, but have a well-surviving spiral ganglion cells which can be stimulated with cochlear implants in both

ears (Heid et al., 1998). Thus, this model provided a well-defined onset, duration and degree of unilateral deprivation, which could additionally be directly compared with data from early experiments of monocular deprivation in the visual system.

Effects of congenital single-sided deafness in the cats included weakened cortical representation of the deaf ear with increased response latency and smaller response amplitude (Kral et al., 2013b). Interestingly, hemispheric specificity of the changes was observed (Kral et al., 2013a; Tillein et al., 2016). The strongest reorganization was measured at the hemisphere ipsilateral to the hearing ear (contralateral to the deaf ear); this cortex underwent an extensive reorganization both with respect to response amplitudes and response latencies. Local field potential amplitudes were larger for stimulation at the ipsilateral ear, and the latencies were shorter for stimulation of the ipsilateral ear. Such results were never observed in hearing animals nor in animals with congenital binaural deafness (Kral et al., 2013a, 2013b). The observations implicated a change in the aural preference of the cortical area ipsilateral to the hearing ear, and an extensive change in representation of auditory space.

Because these measures were also investigated in deaf animals that received a single-sided cochlear implant at different ages and had hearing experience over several months through the cochlear implant, it became clear that the reorganization of aural preference presented only in animals with early onset of asymmetric hearing. After the age of ~4 months, long-term (up to five months, corresponding to several years in humans) use of single-sided CIs did not induce a significant change in aural preference, thereby demonstrating a critical developmental period for reorganization of aural preference in primary auditory cortex (Kral et al., 2013a, 2013b). This means that the abnormal aural preference develops only if monaural hearing occurs early in life. Clinically, it remains important to determine how long this critical period would last in children. Given differences in developmental sequences between species (review in Kral and Pallas, 2010), it is a difficult and risky undertaking to infer from developmental times in one species to another species (e.g. humans). Despite this serious limitation, several publications provide an approximate translation of developmental timelines between species (Clancy et al., 2001; Finlay et al., 2001; Workman et al., 2013). Using such relations, the predicted duration of the corresponding critical period would be ~36 months after birth in children.

While the above neuronal changes in latency and amplitude in the cat model were found at the earliest cortical response component ( $P_a$ ), they were even more pronounced in the later components  $P_b$  and  $N_b$  (Kral et al., 2013a). This indicates that, while some of the reorganizations take place subcortically and are present in cortical input, the effects of aural preference are even more extensively expressed in subsequent cortical processing.

A follow-up study investigated the representation of both ears on individual neurons (Tillein et al., 2016) rather than at a group level using local field potentials. Stimulation with bilateral cochlear implants revealed that cortical neurons frequently responded to stimulation of both ears, the ear contralateral to the recorded cortex (crossed, Fig. 1A) as well as the ear ipsilateral to the recorded cortex (uncrossed, Fig. 1A). In animals with single sided deafness, either the crossed or the uncrossed ear was deaf, depending on the investigated hemisphere. In unit responses at the hemisphere ipsilateral to the hearing ear (Tillein et al., 2016) a prominent absence of E0 units (responding excitatory to the crossed, i.e. deaf ear, and not showing such response to the uncrossed, i.e. hearing ear) was found (Fig. 1B). In this hemisphere, more EE units (responding excitatory to each ear) have been observed. This result indicates that those neurons that in animals with normal hearing show an excitatory response only to the

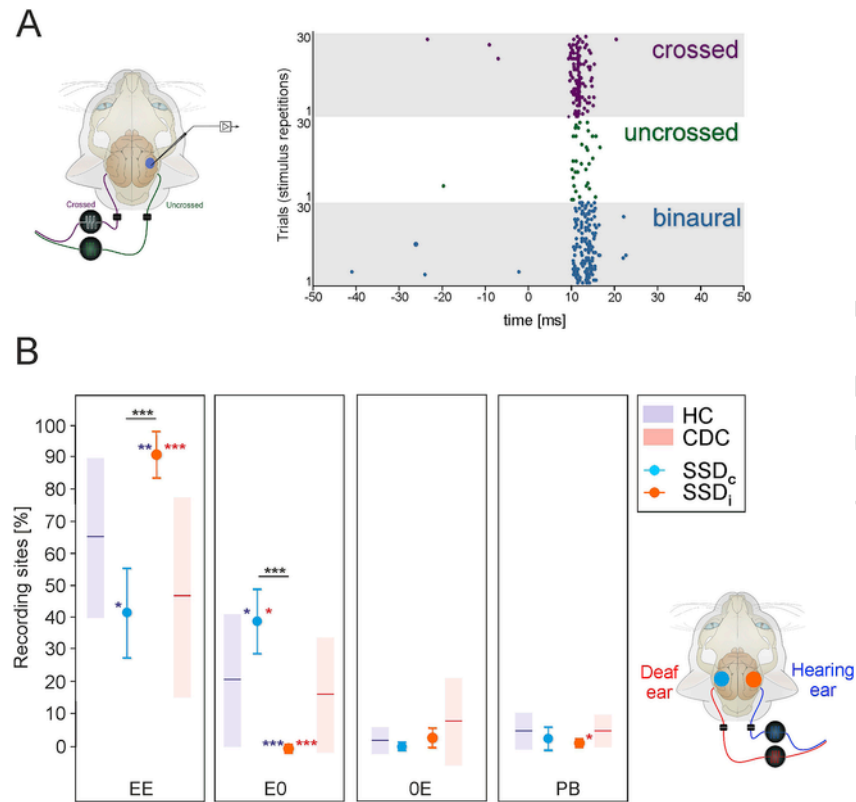
crossed ear, in congenital single-sided deafness may respond also to the uncrossed ear (i.e. to both ears). This effect was specific to the hemisphere ipsilateral to the hearing ear and was not observed in the other hemisphere of the same animals (see color code in the inset of Fig. 1B).

In summary, the data from animal models described above at both local field and unit level of analysis document that unilateral deprivation in early development promotes processes in the hemisphere ipsilateral to the hearing ear, which are different from those at the contralateral hemisphere. Consistently however, the representation of the only hearing ear was strengthened and the deaf ear was weakened on both hemispheres. Thus, the condition of single-sided deafness leads to the development of a “stronger ear” and a “weaker ear” (Kral et al., 2013a,b).

## 6. Bedside evidence of aural preference reorganization

Neuronal activity at this fine-grained level of representation cannot be obtained in humans, but electroencephalographic signals from large populations of neurons can be used to compute similar population measures. A difference in morphology of evoked potentials was noted for ears implanted sequentially in children born with bilateral deafness (Sharma et al., 2005; Jiwani et al., 2016), indicating differential maturational trajectories for the two inputs if activated at different ages. Cortical electroencephalography measured in children who received bilateral cochlear implants also provided evidence of unilaterally driven reorganization in the developing human auditory pathways and a sensitive developmental period for bilateral auditory input (Gordon et al., 2015), consistent with the animal studies reviewed above. Responses from the auditory brainstem had shown developmental effects of unilateral cochlear implant use measured by decreasing peak and interpeak latencies (Gordon et al., 2003, 2006). Longer latency responses from the newly implanted ear reflected the relative immaturity of these deprived pathways (Gordon et al., 2008). More concerning, however, was that the interaural asymmetry in brainstem response latencies persisted despite several years of bilateral cochlear implant use when the inter-implant period exceeded 2 years (Gordon et al., 2012). These mismatches in brainstem timing were not present in children receiving bilateral devices with more limited or no delay (simultaneous implantation), providing the first evidence of abnormal strengthening of pathways from one ear during human development.

Based on the data from unilaterally congenitally deaf cats, a measure of aural preference was also determined in each cortex of bilaterally implanted children (Gordon et al., 2013). Increased strengthening from the first implanted ear was found in children with inter-implant delays of >2 years both to the contralateral cortex, measured by more pronounced cortical lateralization, and to the ipsilateral cortex measured by an abnormal reversal of aural preference to the ipsilateral ear (Gordon et al., 2013). These effects increased with increasing delays to implant. Moreover, after bilateral implantation, these measures of cortical reorganization to prefer the first hearing ear did not resolve despite several years of bilateral implant use. Responses maintained the expected contributions from each ear in children with more limited delays and children receiving bilateral cochlear implants simultaneously, suggesting that bilateral pathways could be protected by providing bilateral access to sound within a developmental sensitive period. Together with the animal data described above, it was clear that an aural preference was established by asymmetric hearing in both cats and humans, with matching neural correlates. These findings have informed clinical recommendations to provide input to



**Fig. 1.** In congenital single-sided deafness (SSD), the representation of the hearing ear is strengthened and the deaf ear is weakened. A) Methodological approach. With recordings in one hemisphere (in the inset: right hemisphere), stimulation can be either at the ear in the other hemisphere (crossed ear) or in the same hemisphere (uncrossed ear), or on both ears (binaural). B) Ear representation changes differently in the two hemispheres following congenital single-sided deafness. Shown is responsiveness of neurons in the primary auditory cortex in response to stimulation of each ear. Units responsive to both ears by increased firing rate (irrespective of response strength) are classified as EE (excitatory-excitatory), units such as responsive to crossed ear only as E0, those to the uncrossed ear OE, and those that respond only during binaural stimulation are PB (preferentially binaural). In single-sided deaf and in the hemisphere ipsilateral to the hearing ear (orange color) the responsiveness to the deaf ear only (E0) disappeared, instead units gained responsiveness to the hearing ear, too, and thus became responsive to both ears (EE). The effect on the hemisphere contralateral to the hearing ear are similarly oriented towards the hearing ear, but in lesser extent. Means and standard deviations shown, for hearing controls (HCs) and congenitally (binaurally) deaf cats (CDC) means and standard deviations are shown as rectangles and horizontal lines. HC: hearing controls; CDC: congenitally deaf cats; SSD: congenitally single-sided deaf animal, hemisphere ipsilateral to the hearing ear; SSD<sub>c</sub>: congenitally single-sided deaf animal, hemisphere contralateral to the hearing ear; \*\*\* ~  $p < 0.001$ ; \*\* ~  $p < 0.01$ ; \* ~  $p < 0.05$ . Red asterisk indicates comparison to CDCs, blue to HCs, black between hemispheres. Data from Tillein et al. (2016), for corresponding results in local field potentials see Kral et al. (2013a,b). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

each ear as early as possible (Gordon et al., 2015; Ramsden et al., 2012).

With the clinical recommendations for bilateral auditory input in mind, attention shifted to children who had a severe to profoundly deaf ear but who were not being considered for cochlear implantation because their other ear had sufficient residual hearing to benefit from hearing aid use. Once these children were provided with a cochlear implant in their deaf ear, the bimodal stimulation was used to assess effects of asymmetric hearing. Encephalographic measures of activity in the left and right auditory areas of the brain confirmed that an aural preference was established by depriving pathways from the deaf ear and allowing strengthening of input from the better hearing ear (Polonenko et al., 2018). Again, these effects were more pronounced as the delay to bilateral input increased. More symmetric cortical representation from each ear was found in children who received the cochlear implant with limited delay, indicating that treatment of asymmetric hearing loss could make use of very different inputs in each ear (electric through a cochlear implant and amplified acoustic hearing in the other) so long as the bilateral input was provided early in development. Given the successful use of bimodal hearing when provided in a sensitive period, cochlear implantation has been extended to children with single sided deafness. Other treatment options

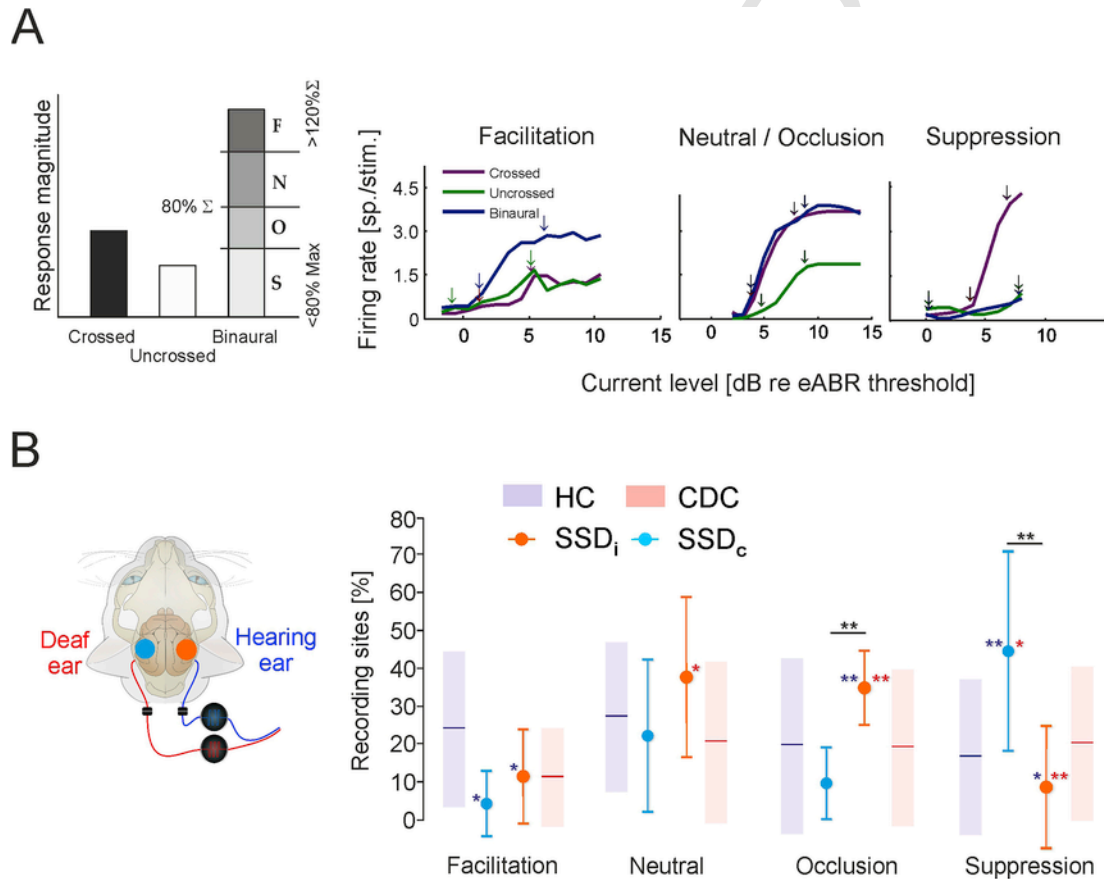
have included hearing aids with Contralateral Routing of Signal (CROS) and bone conducting devices which attempt to provide the hearing ear with better access to sounds coming from the opposite side of the head (Hol et al., 2005; Vincent et al., 2015). These methods do not provide access to binaural cues and, indeed, rely on strengthened pathways from the hearing ear (Gordon et al., 2015). Outcomes reveal questionable benefits in this population (Agterberg et al., 2018; Kitterick et al., 2016). Sensitive periods in auditory development decline significantly over the first 3–4 years of life, corresponding to 36 months after birth as predicted from the cat studies detailed above. This has led to the recommendation that cochlear implantation is performed within this time period to limit the duration of asymmetric hearing in early life (Gordon et al., 2015; Illg et al., 2017b; van Wieringen et al., 2019). This approach of limiting unilateral deprivation during sensitive periods in development has successfully reestablished input from the deaf ear to the auditory cortex in young children with pre-lingual single sided deafness; indeed, aural preference for the hearing ear was reversed within 6 months of cochlear implant use in toddlers with single sided deafness (Polonenko et al., 2017b). It is also prudent to limit the period of deafness in children who acquire bilateral or unilateral deafness.

### 7. Single sided deafness disrupts integration of binaural input

An additional question is whether binaural inputs can be integrated for the extraction of binaural information. Binaural computations can be directly studied with unit recordings that are currently systematically possible only in animal models. Unit recordings allow to investigate to what extent the two inputs from the two ears are fused in the brain. For this, binaural firing rates are usually compared to the sum of monaural responses (Fig. 2A) and classified into binaural facilitation, suppression and in-between interaction (neutral and occlusion, Fig. 2A). Such approach in cats with congenital single sided deafness revealed severely weakened binaural computations in the primary auditory cortex (Fig. 2B, Tillein et al., 2016): Binaural facilitation (an increase in the response with stimulation on both ears compared to the sum of responses with stimulation of each ear alone) was nearly absent in single sided deaf animals. Thus, neurons in the auditory cortex of congenital single sided deafness lost the ability to boost responsiveness in binaural condition and by that to take advantage of the binaural input. This is a sign of reduced binaural computations, or in other words, a reduced integration of binaural inputs.

Binaural suppression was also affected by congenital single sided deafness (Fig. 2), which showed a reduced binaural suppression in the cortex ipsilateral to the hearing ear (Fig. 2B). Binaural suppression was replaced by binaural excitation (Tillein et al., 2016; comp. other conditions with similar outcome in McAlpine et al., 1997; Mossop et al., 2000; Vale et al., 2004; Illing et al., 2005). In the hemisphere contralateral to the hearing ear stronger suppression was noted (Fig. 2B, Tillein et al., 2016). This latter observation implicates a common inhibition pathway fed by both ears with mutual suppression between these inputs. Absence of one input thus boosts the use of the pathway and facilitates inhibition. These data demonstrate that asymmetric auditory input impairs binaural integration by reducing inhibition on the side of the hearing ear (from the hearing ear) and increasing inhibition on the deaf side (from the deaf ear). The developmental changes are likely aimed at improving the processing of the only hearing ear but, in so doing, degrade the binaural representation of the auditory input that becomes apparent when bilateral input is restored.

Indeed, binaural integration is impaired in children who show a preference for one ear. Children with bilateral cochlear implants report that bilateral input sounds like two separate sounds rather than one “fused” image (Salloum et al., 2010; Steel et al., 2015). Children



**Fig. 2.** Binaural interactions documenting loss of binaural fusion following single-sided deafness. A) Based on responsiveness to stimulation at crossed, uncrossed and both ears, facilitatory, suppressive and neutral/occlusive interactions are defined. Borders of the categories are defined based on either the sum of responses to crossed and uncrossed ear ( $\Sigma$ ) or the larger monaural response (Max). B) The results document a significant decrease of binaural facilitation on both hemispheres of single sided deaf when compared to the hearing controls. At the hemisphere contralateral to the hearing ear, binaural stimulation suppresses the response in nearly 50% of the units, documenting the detrimental effect of binaural stimulation on neuronal responsiveness. HC: hearing controls; CDC: congenitally deaf cats; SSD<sub>i</sub>: congenitally single-sided deaf animal, hemisphere ipsilateral to the hearing ear; SSD<sub>c</sub>: congenitally single-sided deaf animal, hemisphere contralateral to the hearing ear; \*\*\* ~ p < 0.001; \*\* ~ p < 0.01; \* ~ p < 0.05. Red asterisk indicates comparison to CDCs, blue to HCs, black between hemispheres. Data from Tillein et al. (2016). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

implanted sequentially initially report sounds in the second implanted ear to be louder than the first ear (Gordon et al., 2016) and, in some cases, input from the weaker ear appears to “inhibit” the stronger ear (Burdo et al., 2016), potentially leading to non-use of the second cochlear implant. Poor binaural fusion increases response time and causes pupil dilation, suggesting an increase in listening effort (Steel et al., 2015). Nonetheless, children typically benefit from hearing devices which provide bilateral input (bilateral cochlear implants or bimodal hearing; Cullington et al., 2017; Polonenko et al., 2018). This suggests that imperfect binaural hearing remains preferable over unilateral deprivation (as discussed further below).

When taken together, these data confirm that the brain of a single sided deaf subject becomes highly asymmetric, with reduced inhibition on the side of the hearing ear (from the hearing ear) and increased inhibition on the deaf side (from the deaf ear). The developmental changes are likely aimed at improving the processing of the only hearing ear, but at the same time degrade the representation of the auditory input if binaural condition is restored.

## 8. Impaired processing of binaural cues

The major role of the binaural auditory system is to detect interaural level and timing differences (ILDs and ITDs, respectively), which form the basis of our spatial hearing. Effects of unilateral deafness on sensitivity to these binaural cues were further explored in bilaterally implanted congenitally single sided deaf cats. Since the consequence of single sided deafness on interaural level sensitivity follows from the differential effect of single sided deafness on inhibition in the two hemispheres (see above), investigations focused on interaural time sensitivity, the major binaural cue where the consequence of single sided deafness was far less obvious.

Response sensitivity to changes in ITDs were investigated in detail at the level of cortical neurons (Fig. 3). In the first step, responses were automatically classified into four typical ITD function templates, resulting in four classes of responses (Fig. 3A). Those units that could not be classified because the response did not systematically vary with ITD formed the “non-classified” group, and those that did not show a significant modulation of firing rate by stimulation were considered non-responsive (Tillein et al., 2010). Using this classification the overall sensitivity of cortical units for binaural inputs (classified vs. non-classified units) and for auditory input in general (responsive vs. non-responsive units) was quantified. Significantly more units were auditory responsive in single sided deaf animals than in binaurally deaf animals (Fig. 3B), showing that single-sided hearing protects cortical neurons from deprivation-induced loss of responsiveness (Tillein et al., 2016). However, effects on binaural sensitivity were partly more severe in single sided deafness than in binaural deafness. Whereas sensitivity to interaural time differences at the hemisphere ipsilateral to the hearing ear was similarly reduced as in binaurally congenitally deaf animals (Tillein et al., 2010), it was even weaker at the hemisphere contralateral to the hearing ear in single sided deafness (Fig. 3B). This result was interpreted as a consequence of a trading of the ability to localize sound in space (which is highly impaired in single sided deafness due to lack of binaural sensitivity) for a stronger representation of the only hearing ear. Such constellation is beneficial for the condition of single sided deafness, but is less helpful for spatial orientation following restoration of hearing in the deaf ear.

Consistent with the deficits in extraction and representation of interaural timing cues in congenitally deaf cats (Tillein et al., 2010), children with bilateral devices struggle to perceive changes in interaural timing cues relative to normal hearing peers (Ehlers et al., 2017;

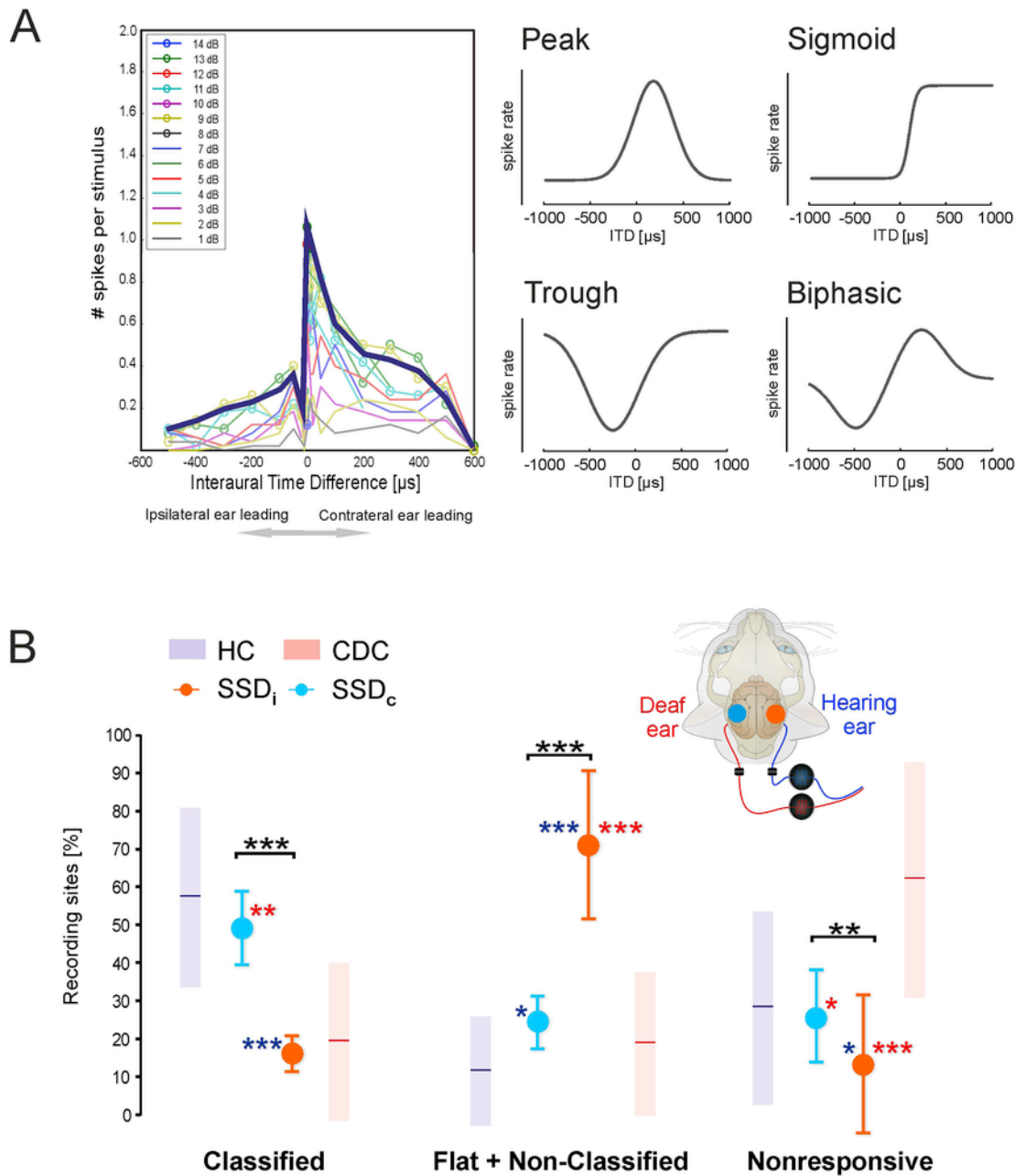
Gordon et al., 2014; Litovsky and Gordon, 2016, Fig. 4). This could be mediated by a lack of binaural integration and/or sensitivity to binaural cues as shown in the congenitally deaf cats. Even when symmetric bilateral development is promoted in children through bilateral cochlear implants provided simultaneously, cortical responses to bilateral stimulation do not show normal facilitation relative to unilateral input or changes in hemispheric lateralization with increasing interaural level of timing differences (Easwar et al., 2017a,b; Fig. 4C and D). Thus, binaural integration can be disrupted by congenital deafness in both or one ear and is not easily restored in children using present hearing device fittings.

## 9. Spoken language and single-sided deafness

The most important goal of identifying and treating pediatric hearing loss is to provide children with access to spoken language. Language is a human phenomenon that has no direct correlate in animals. Therefore the outcomes of monaural hearing on speech perception can only be tested in humans. The human brain's extensive neuronal resources for language serve specific linguistic functions in each hemisphere (Hickok, 2012; Hickok and Poeppel, 2007). This “linguistic network” receives auditory input from the auditory cortex. Binaural convergence takes place in the brainstem and neurons in the primary auditory cortex are essentially binaural (Zhang et al., 2004). The linguistic circuits therefore receive binaural input and in consequence, hearing with one ear is sufficient for developing the capacity of language. However, the access to language circuits for the previously deaf ear is determined by the extent of binaural integration – that, as shown above, is compromised in single sided deafness. Due to the constant advantage of the stronger ear (faster and larger responses) it is an inevitable consequence that higher-order areas including the linguistic network preferentially process the input from the stronger ear (Kral et al., 2013b; Gordon et al., 2015). Therefore, speech performance may differ for the inputs on the left and right ear depending on previous hearing experience in each ear.

The challenges of listening with one ear during early auditory development, even with normal access to sounds, is shown by slower speech and language development (Borg et al., 2002; Fischer, Lieu, 2014; Kishon-Rabin et al., 2015; Purcell et al., 2016), risks of educational deficits (Lieu, 2004; Sangen et al., 2017), social and behavioral challenges (Lieu et al., 2012), and reduced quality of life (Borton et al., 2010). Children with single sided deafness also experience problems with their balance (Wolter et al., 2016), which could reflect increased vestibular problems associated with the etiology of deafness (Sokolov et al., 2018) as well as the loss of spatial hearing. Bilateral cochlear implants and bimodal hearing improve speech perception relative to unilateral listening in children (Ching et al., 2009; Illg et al., 2014; Mok et al., 2010). In addition, bilateral listening appears to reduce listening effort in tasks which are difficult for cochlear implant users such as music perception (Crew et al., 2015; Giannantonio et al., 2015; Polonenko et al., 2017a).

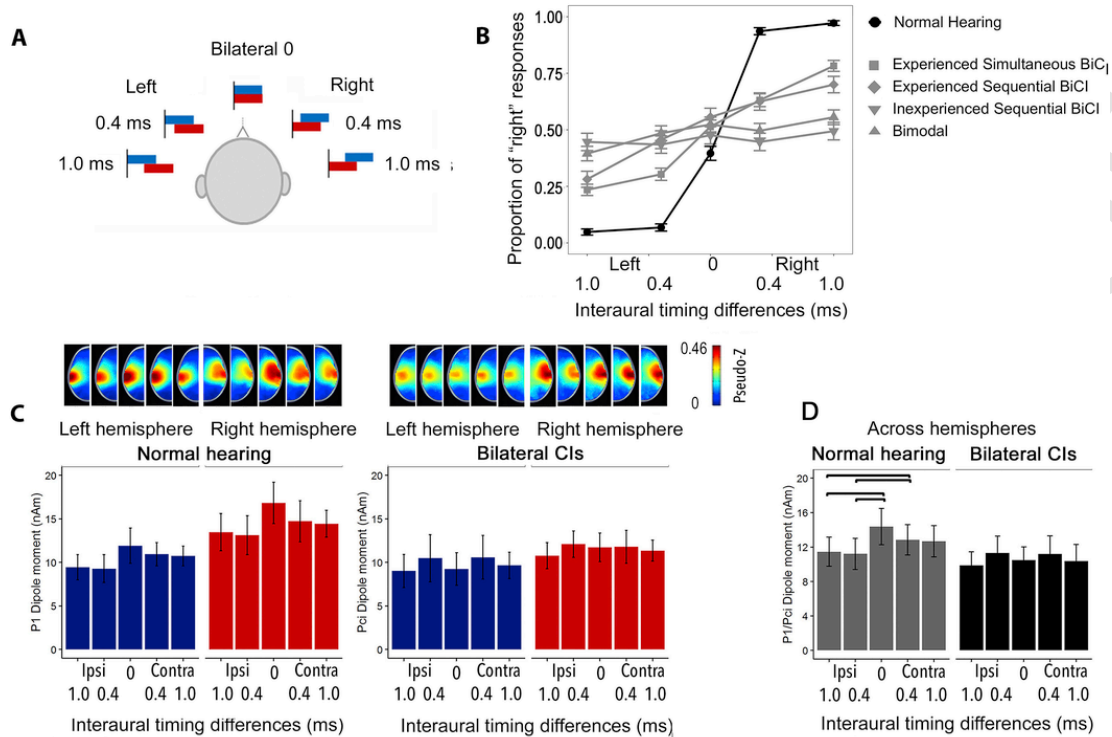
Many studies have shown asymmetric speech perception in children using bilateral cochlear implants. Sequentially implanted children show poorer speech performance when using the second implanted ear alone (Fig. 5A; Arndt et al., 2015; Boisvert et al., 2015; Firszt et al., 2012; Graham et al., 2009; Illg et al., 2013, 2017b; Peters et al., 2007; Távora-Vieira and Rajan, 2016; Távora-Vieira et al., 2013) and show very slow improvements of speech perception with years of use when tested with their second implant alone (Fig. 5B; Illg et al., 2013). These observations are consistent with the neuronal data on change in aural preference in animals and children reviewed above. There may be other effects of deafness which are not compen-



**Fig. 3.** Reduced sensitivity to binaural cues following single-sided deafness in deaf cats. A) Left panel: Example of a ITD sensitivity function in one unit from the primary auditory cortex. With increasing current (relative to unit's threshold in dB, inset) the activity increases, particularly for positive ITDs, resulting in a peak-type of function. Right panels: templates used for automatic classification of unit responses to peak, sigmoid, through and biphasic. ITD functions with modulation depth (relative difference of strongest vs. weakest response in the function) of less than 50% were considered flat. B) Results of an automatic classification of the variation of firing rate as a function of interaural time difference (ITD). If templates and responses yielded significant correlations ( $p=1\%$ ), ITD functions were considered classified. In hearing controls, nearly 60% of the units showed a regular change of firing rate with ITD, allowing classifying such ITD sensitivity function. In CDCs, this proportion dropped to 20%, showing a detrimental effect of absent hearing experience on binaural sensitivity. In SSD, one hemisphere (SSD<sub>i</sub>) was similar to hearing controls, whereas the other hemisphere (SSD<sub>c</sub>) was similar to CDCs. In general responsiveness, SSDs and HCs were similar, very different from the CDCs that showed more non-responsive units. From all classified units, the SSD animals showed highest variability of the descriptive parameters of the ITD sensitivity functions, and at the SSD, also the smallest modulation depth (i.e. smallest ITD sensitivity). HC: hearing controls; CDC: congenitally deaf cats; SSD<sub>i</sub>: congenitally single-sided deaf animal, hemisphere ipsilateral to the hearing ear; SSD<sub>c</sub>: congenitally single-sided deaf animal, hemisphere contralateral to the hearing ear; \*\*\*  $p < 0.001$ ; \*\*  $p < 0.01$ ; \*  $p < 0.05$ . Red asterisk indicates comparison to CDCs, blue to HCs, black between hemispheres. Data from Tillein et al. (2010, 2016). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

sated for with present fittings of bilateral devices: mismatches in place-frequency, level, and timing can occur between the implants, which can be exacerbated by differences in make and design of the two devices (both internal and external components; Kan et al., 2013, 2015b). These factors could explain why even simultaneous cochlear

implantation in children fails to establish normal binaural integration (as shown in Fig. 5). Yet, an independent component analyses of the demographic factors indicated that the delay to bilateral input was the factor which most strongly influenced speech perception outcomes in a group of >400 children using bilateral hearing devices (Polonenko



**Fig. 4.** Binaural integration and processing is impaired in children with cochlear implants. A) Bilateral stimuli were presented at balanced levels with no interaural timing differences (Balance 0) or leading in the left or right ear by 0.4 or 1.0 ms. Stimuli were trains of broadband clicks in children with normal hearing and trains of electrical pulses delivered at an apical electrode in children with bilateral cochlear implants (BCI). B) Children were asked to indicate whether bilateral stimuli were heard on the left or right side of their head. Children with normal hearing indicated highly accurate responses. By comparison, children with BCI and children using bimodal devices had more difficulty with this task, reflecting decreased sensitivity to ITDs. C) EEG activity evoked by stimuli shown in A at  $\sim 100$  ms (P1 or P1cI) was localized to left and right auditory cortices (top panel). Magnitude (dipole moment) of responses tended to be reduced in each cortex (left and right) when bilateral input was leading from the ipsilateral ear in children with normal hearing. D) Data pooled across both hemispheres confirmed that cortical processing of interaural timing cues includes suppression of bilateral input in the hemisphere ipsilateral to the leading ear in children with normal hearing. No significant changes in cortical responses to different interaural timing cues were found in children using bilateral CIs, consistent with the impairments found in behavioral testing. (Data from Easwar et al., 2017s; and Polonenko et al., ARO Poster, 2016).

et al., 2018). In children using bilateral cochlear implants, specifically, asymmetries in speech perception between the two ears decrease with reduced inter-implant delay (Fig. 5B and C). Good speech comprehension with the second implanted ear alone was, however, possible even in cases when second implantation was performed after the closure of the sensitive period for unilateral implants (Illg et al., 2017b). This demonstrates that there is a transfer of speech perception capabilities learned with the first implanted ear to speech processing with the second implanted ear. This was, however, only observed provided that single sided input did not last long enough to compromise the representation of the deaf ear and binaural fusion. Inter-implant delay combined with age at first implantation are the key factors determining the profit from second implantations.

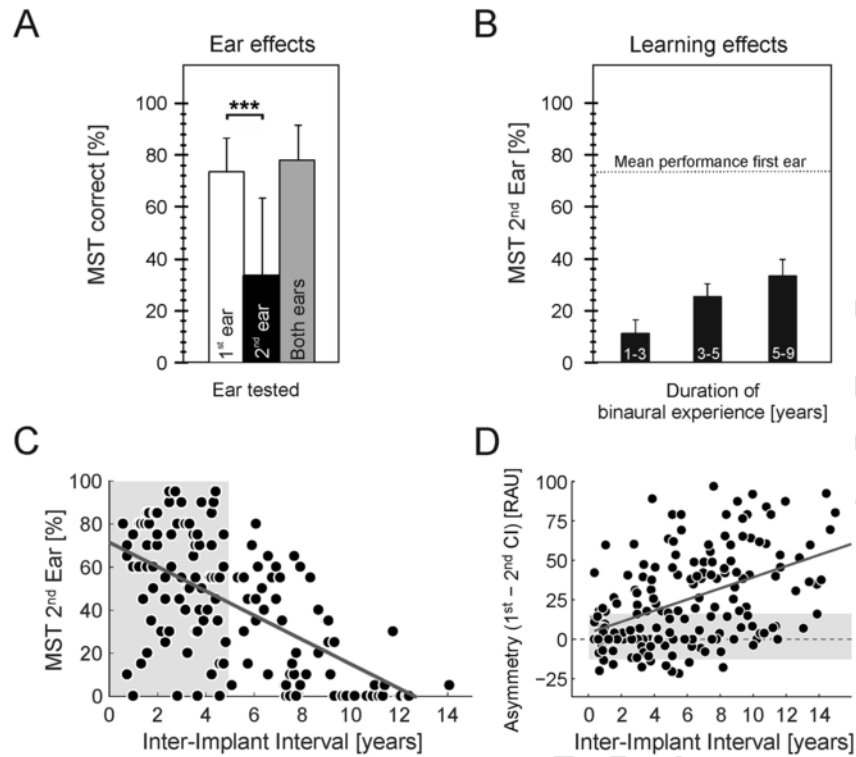
## 10. Effects of single-sided sensory input differ between visual and auditory systems

The historic visual studies on brain plasticity are often considered a textbook example of universal brain plasticity. This is, however, not completely accurate as shown by comparison of auditory and visual consequences of single sided sensory loss performed in the same animal species. Such comparisons reveal a striking difference between the visual and auditory systems in the overall extent of cortical response to single-sided sensory loss (Fig. 6).

In the cat visual system, five months of deprivation starting before eye opening, despite a subsequent period of binocular vision of  $>6$

months (Mower et al., 1983), eliminated the representation of the blinded eye in the feline binocular cortex (Fig. 6B; Mower et al., 1983). A moderate number of remaining inputs from the deprived eye was revealed by pharmacological disinhibition (Sillito et al., 1981). In the auditory system, however, more than a year of monaural hearing resulted in a shift of responsiveness in the same direction (towards the hearing ear), but did not eliminate the representation of the deaf ear in the auditory cortex to the same extent (Fig. 6D,F, Kral et al., 2013a, 2013b; Tillein et al., 2016). Monaural deprivation was consequently much less detrimental than monocular deprivation, despite the longer and more complete deprivation in the auditory than visual system.

This is likely due to three differences in the organization of the compared sensory systems: (I) while in the auditory system the binaural inputs converge at the level of the brainstem (Grothe et al., 2010), in the visual system, the point of binocular convergence is the visual cortex (Payne and Peters, 2002; Hubel and Wiesel, 1977); (II) while large monocular zones exist in the visual cortex (Gilbert and Li, 2012; Hooks and Chen, 2007; substantially larger in rodents, Dräger, 1975; Hooks and Chen, 2007; Tagawa et al., 2005), in the primary auditory cortex true monaural neurons are rare and do not segregate into enclosed zones (Zhang et al., 2004); (III) while in the visual cortex inhibition between ocular inputs plays an essential role (Hensch, Stryker, 2004; Katagiri et al., 2007), aural inhibition is less pronounced in the auditory cortex that inherits binaural properties



**Fig. 5.** As predicted by the neuronal data on strong and weak ear representation, speech perception through the ear that was implanted second, with a long delay to the first, is compromised in children with congenital profound hearing loss. A) In prelingually deaf children, sequential implantation with more than 5 years delay between first and second implantation results in poorer speech performance on the second implanted ear (middle bar) and no difference in binaural condition compared to the first implanted ear if measured with the Freiburg monosyllabic word test (MST). Thus there is no binaural benefit in these children, indicating deficient binaural fusion. Plot from Illg et al. (2013). B) Slower learning rates are observed in second implanted ear. Despite of many years of binaural hearing (5–9 years in the rightmost bar), the second implanted ear continues to underperform compared to the first implanted ear (dashed line). Data from Illg et al. (2013). C) Data from the German cohort (Illg et al., 2017a,b). Sequential pediatric cochlear implantation with inter implant intervals >4 years leads to reduced speech comprehension on the second implanted ear persisting despite bilateral cochlear implant use. Shown are results of the Freiburg monosyllabic word test (MST), testing on the isolated second implanted ear. Note the large variation of speech performance outcomes at all ages. D) Data from a Canadian cohort (Polonenko et al., 2018) quantified as side difference in “rationalized arcsine units” (RAU) is consistent, demonstrating increasing asymmetry between the ears with longer inter-implant intervals. These data reflect a persistent preference for the first hearing ear despite chronic bilateral cochlear implant use. MST ~ Monosyllabic test; RAU ~ rationalized arcsine units.

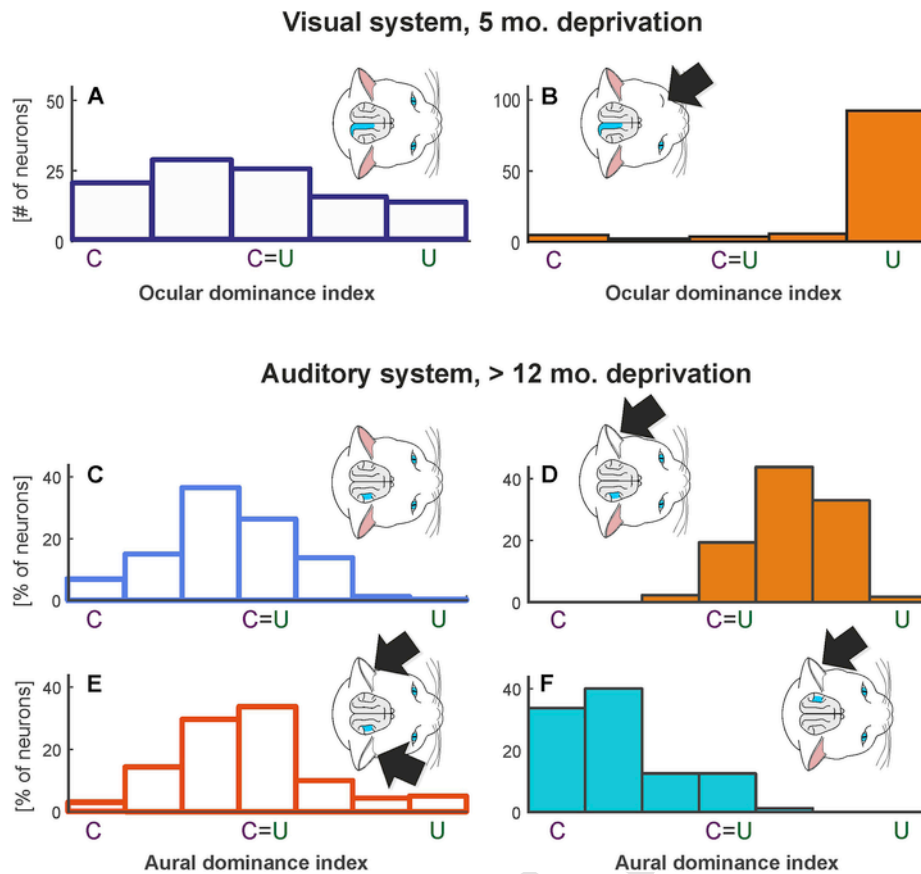
from the subcortical pathway and, rather, plays a role in the subcortical pathways (Grothe et al., 2010, discussion in Tillein et al., 2016).

Consequences of single sided deafness thus differ from monocular deprivation. In the visual system, the activity from the deprived eye is nearly absent in the cortex, explaining the central blindness of this eye (amblyopia). By contrast, in the auditory system sound awareness is present after hearing restoration in the previously deaf ear and there is potential for improvement of sound analysis with this ear.

Despite the less severe consequences of single-sided deafness when compared to visual monocular deprivation, we want to emphasize that fundamental reorganizations in the auditory system were observed in response to unilateral deafness in both cats (with recordings from neurons) and humans (with EEG and psychophysics), with deficits in aural preference, binaural fusion and binaural computation, including the sensitivity for binaural cues. Such changes strengthen the representation of the only hearing ear, and lead to reorganized aural preference (a “strong” ear), which is beneficial for the single sided hearing condition. This developmental adaptation to single sided hearing is, at the same time, detrimental for the deaf ear, which becomes underrepresented and thus “weak”. The asymmetry between the ears interferes with the normal development of binaural hearing and precludes physiological binaural computations.

## 11. Remaining challenges

As discussed above, children receiving bilateral implants and bimodal devices show poor binaural integration and processing, exacerbated by development of an aural preference, which deters their spatial hearing. Early efforts to tackle these remaining hearing challenges have suggested reversing the aural preference syndrome by patching the stronger ear (Burdo et al., 2016); however, we have found that this approach is challenging for children who rely on their better ear to communicate. It may be more effective to support consistent use of both devices, which plays an important role in helping to reduce asymmetries in speech perception between the two sides (Easwar et al., 2018). In addition, therapy which presently concentrates on spoken language acquisition, could evolve to support readjustment of binaural cues in context with visual support and using bilateral hearing in environments with multiple speakers and sound sources. These efforts, however, would require accurate and consistent binaural cues to be provided. Binaural cues are presently distorted by mismatches in place, level, and timing of bilateral input through two independent devices (Fitzgerald et al., 2015; Hu and Dietz, 2015; Kan et al., 2015a,b; 2013; Stelmach et al., 2017). Further complications occur in bimodal hearing due to differences between electric and acoustic hearing (Sato et al., 2016, 2017) which include an acoustic delay on one side (Polonenko et al., 2015; Zirn et al.,



**Fig. 6.** Comparison of the effects of single-sided sensory loss between visual and auditory systems. For subsequent panels, ocular or aural dominance index are computed by determining the number of neurons responding to either the crossed ear exclusively (C) or the uncrossed ear exclusively (U), or to both ears with different strength (for comparison see Fig. 1A). This relation is plotted on the abscissa in subsequent panels. A) Recording in the primary visual cortex (cyan color in the inset) of a normal sighted cat. Some preference for the crossed eye can be observed. B) In an animal with eyelid suture from birth and 5 months of deprivation, the histogram of ocular dominance indices is shifted to the uncrossed (open) eye, with nearly absent responsiveness to the previously closed eye. C) Corresponding data from a normal hearing adult animal, showing similarly a broad distribution of response sensitivity, with a preference for the crossed ear. D) In an animal with congenital single-sided deafness on the crossed ear (black arrow in the inset), the distribution is shifted to the uncrossed ear, but the effect is smaller than in the visual cortex (C) despite substantially longer period of deprivation. E) Congenital deprivation on both ears affects only slightly the contralateral aural preference. F) In an animal with congenital single-sided deafness on the uncrossed ear (black arrow in the inset), the distribution is shifted to the crossed ear, but again the effect is much smaller than in the visual system. Visual data from Mower et al. (1983); auditory data from Tillein et al. (2016). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2015), in itself reducing sensitivity to interaural time differences (Mossop and Culling, 1998; Zirn et al., 2015), and large mismatches in dynamic range and place of stimulation (Bernstein et al., 2018). Although these challenges will also exist in adults and older children with post-lingual hearing loss, advances in these areas are particularly important for young children who will only have the chance of developing binaural hearing once solutions to these concerns are in place.

## 12. Knowledge transfer from animals to humans

Advancements in our understanding of single sided hearing in development have been furthered by the parallel work done in animals and humans. However, there are caveats in the transfer of knowledge between animal and human data. Animals are specialized to their ecological niche, and consequently not every species represents the optimal model for humans in all aspects. A typical example is the hearing range (Fay, 1988). Here we compared mainly higher mammal models to humans. The currently most popular animal model in research, the mouse, shows poor low frequency hearing and therefore also lacks e.g. sensitivity to interaural timing cues at high precision (a characteristic shared with many rodents including rats). Furthermore, rodents typically live in burrows and in the grass, and therefore have

poor visual acuity and a very limited ability to accommodate the refraction; also as prey species they have limited binocular vision. Thus, when considering multisensory interactions or binaural hearing, mice (along with many rodents) are not the optimal model of humans. The higher mammal models, mainly discussed in the present review, may show better correspondence to human hearing.

The inclusion of cats, specifically, continues from previous work examining effects of bilateral deafness on development, including intramodal and cross-modal plasticity (Ponton et al., 2001; Kral and Sharma, 2012). The advantages of “comparing kittens to kids” (Ponton et al., 2001) include the level of corticalization, i.e. the phylogenetic shift of behavioral control from subcortical to cortical structures, which differs extensively between different species. This is anatomically discernible in the relative size of the cortex (Finlay and Darlington, 1995; Herculano-Houzel, 2009; Kaas, 2013; Krubitzer, 2007). By comparison, lysencephalic species (including rodents) show no neocortical folding and thus a much smaller neocortical area relative to the rest of the brain than gyrencephalic species (carnivores - ferrets, cats - and primates), where folding is observed.

One consequence of the increase in corticalization is also an overall increase in inhibition acting in the thalamus and the cortex, which is nearly 10 times more in cats than in rodents (Villa et al., 1999).

Furthermore, the neocortex of higher mammals is organized not only into six layers, but also into vertical columns. In rodents, a six-layer structure is present but with a more disordered “salt and pepper” functional architecture, without the typical columns (Espinosa and Stryker, 2012). This indicates fundamental differences between animal species that require careful consideration when addressing a given scientific question or medical condition focused on the thalamocortical circuits. There is no “one-fits-all” animal model and it requires consideration – sometimes extending beyond the standard laboratory practice – to identify the right animal model for the given question.

### 13. Recommendations

In conclusion, the existing studies investigating speech performance in sequential pediatric implantations are consistent with neuronal data obtained in animals and children. Based on these results, the existence of the aural preference syndrome has been suggested (Gordon et al., 2015), characterized by:

1. Asymmetric hearing during development.
2. Presence of bilateral auditory nerves.
3. Pronounced asymmetry in speech comprehension between ears which leave the later-restored ear disadvantaged.
4. Deficits in binaural fusion and extraction of binaural cues.

Pediatric audiology should consequently identify asymmetric hearing and aim at restoring a bilateral input with the most appropriate devices for each ear as soon as possible. Periods with asymmetric hearing should be avoided and, at least, limited to less than 2–4 years before more data are available on this matter.

### 14. Conclusion

The subject of single-sided deafness and pediatric sequential cochlear implantation has become an excellent example of combining “bench”-and-“bedside” knowledge, where information from in vivo experiments from many laboratories around the world over many decades has revealed neuronal mechanisms that result in underperformance for one ear. This work has also highlighted the existence of a syndrome of findings, shaping clinical recommendations for treatment of hearing loss in children. The animal data documenting only weakened, but not completely lost representations of one ear, combined with consistent data from children, suggest that we should prevent asymmetric hearing. In contrast to the visual system the representation of the weaker ear is not lost in the auditory cortex which means there is hope of restoring function in the weaker ear using focused stimulation and/or training procedures.

### Acknowledgements

Supported by Deutsche Forschungsgemeinschaft (Exc 1077) and MedEl Comp. (AK). AK would like to thank Drs. P. Hubka and J. Tillein for collecting and analyzing data shown in Figs. 1–4, for the many discussions on the topic. Dr. P. Baumhoff has designed the insets in Figs. 1–4. The authors thank the reviewers for the comments and edits of the previous version of this manuscript.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heares.2019.05.011>.

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