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Strengthening of Hearing Ear Representation Reduces Binaural Sensitivity in Early Single-Sided Deafness

Andrej Kral[a, b], *Peter Hubka*[a], *Jochen Tillein*[a, c]

[a]Institute of AudioNeuroTechnology and Department of Experimental Otology, ENT Clinics, School of Medicine, Hannover Medical University, Hannover, Germany; [b]School of Behavioral and Brain Sciences, The University of Texas at Dallas, Dallas, Tex., USA; [c]MED-El Comp., Innsbruck, Austria

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Asymmetric hearing · Cochlear implants · Hearing loss · Unilateral deafness

Abstract
Single-sided deafness initiates extensive adaptations in the central auditory system, with the consequence that a stronger and a weaker ear representation develops in the auditory brain. Animal studies demonstrated that the effects are substantially stronger if the condition starts early in development. Sequential binaural cochlear implantations with longer interimplant delays demonstrate that the speech comprehension at the weaker ear is substantially compromised. A pronounced loss of the ability to extract and represent binaural localisation cues accompanies this condition, as shown in animal models.

Introduction

Single-sided deafness has attracted scientists' attention due to its scientific and clinical importance. At first sight, the condition appears to correspond to monocular deprivation, which illustrated the extent and limits of developmental plasticity in the visual system [Daw, 2009]. However, due to the technical difficulties with reversible deafness, stimulation at the deaf ear remained an issue until recently. Therefore, research concentrated on a less dramatic condition such as moderate asymmetric hearing loss induced by manipulation of sound conductions [Popescu and Polley, 2010; Keating et al., 2013; Keating and King, 2013; Polley et al., 2013] or investigated the representation of the hearing ear alone [Nordeen et al., 1983; Kitzes and Semple, 1985; Moore and Kitzes, 1985]. In particular, the latter approach has made it possible to investigate even reorganisations following single-sided deafness in humans [Bilecen et al., 2000; Propst et al., 2010; Burton et al., 2012]. The studies have consistently shown that the hearing ear is more extensively represented in the brain. The 'functional fate' of the deaf ear in single-sided deafness remained unclear.

Cochlear implants have reopened this discussion in recent years, particularly due to the need to investigate the function of the deaf ear since therapy of deafness on that ear has become a realistic option. In postlingual onset of single-sided deafness, tinnitus in the deaf ear has driven the need for cochlear implantation on that ear, with success in alleviating the tinnitus while the implant is functionally active [Vermeire and Van de Heyning, 2008; Buechner et al., 2010; Arndt et al., 2011; Arts et al., 2012]. Furthermore, restoration of binaural hearing improves speech understanding in adverse conditions and, therefore, remains important for the main goal of full hearing restoration in humans.

Monaural therapy of binaural deafness using one cochlear implant only [Kral and O'Donoghue, 2010], in fact, also results in single-sided (although electrical) hearing and opens the question of the effectiveness of a later therapy on the deaf ear. In acquired deafness in adulthood, periods of asymmetric hearing and sequential implantation, even with long delays, do not compromise the benefit for the second implanted ear [Lazard et al., 2012; Távora-Vieira et al., 2013]. Consequently, in adult onset of deafness, hearing in both ears seems to be resistant to periods of asymmetric hearing. Evidence for the ability of the brain to extract residual spatial information with binaural cochlear implants and to activate the 'where' pathway in such a condition has been provided [Senkowski et al., 2014]. This demonstrates that both the individual ears as well as the spatial localisation preserve their function even after year-long asymmetric hearing if deafness occurs in adult age; however, localisation is more difficult and less accurate than syllable discrimination [Senkowski et al., 2014].

The situation is different in children following monaural cochlear implants. Here, the outcome in speech performance for the second-implanted ear in sequential implantation is significantly dependent on interimplant delay [Zeitler et al., 2008; Graham et al., 2009; Illg et al., 2013]. Waiting for more than 3–5 years with the second cochlear implantation does significantly decrease the benefit of the therapy on the second ear [Zeitler et al., 2008; Graham et al., 2009; Gordon et al., 2013; Illg et al., 2013]. Both auditory brainstem response and EEG studies on sequentially implanted children confirmed such an effect with objective measures [Sharma et al., 2005; Gordon et al., 2011, 2013]. Similarly with respect to localisation performance, early single-sided deafness after cochlear implantation shows a smaller benefit compared to postlingual onset [Firszt et al., 2012b].

A common technical difficulty of human electrophysiology is that the observed effects essentially combine the contribution of several structures and auditory fields, so that, for example, conclusions on the representation of each ear are significantly influenced by hemispheric specialisation on language and complex sound analysis. Furthermore, brain sensitivity to binaural cues, observed

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at the level of individual neurons but not at the level of whole auditory structures or individual cortical fields, cannot be observed by brain imaging at the moment.

Therefore, animal studies are required to investigate plastic consequences of single-sided deafness on ear representation to binaural hearing and complement human imaging studies. The present review focuses on these studies to provide the background for scientific and clinical considerations.

Aural Reorganisations

Absence of hearing in one ear is likely to affect the balance of representation of the ears in the brain, particularly if its onset is during development, when the brain is highly plastic, with modifiable corticocortical connections [Barone et al., 2013] and when sensitive periods for plasticity are still open [Kral, 2013]. Hearing deprivation from birth prevents maturation of the auditory cortical networks [Kral et al., 2005]. Sensitive periods for plasticity induced by hearing loss could recently be traced down to molecular changes in the neuronal membranes of cortical neurons [Mowery et al., 2014], demonstrating that hearing loss affects both integrative aspects of auditory processing [Kral, 2013] as well as molecular properties of individual neurons [Mowery et al., 2014].

The human cerebral cortex continues to mature even many years after birth [for reviews, see Kral, 2007; Fallon et al., 2009; Kral, 2013]. The brainstem, in contrast, matures earlier and more quickly. Consequently, effects of auditory deprivation are more pronounced in the cortex [Kral et al., 2005] than in the brainstem [Tillein et al., 2012]. Nonetheless, morphological and functional effects of early deafness are also observed subcortically [Snyder et al., 1990; Hultcrantz et al., 1991; Snyder et al., 1995; Hardie et al., 1998; Shepherd et al., 1999; Ryugo et al., 2005; O'Neil et al., 2010; Hancock et al., 2010].

Clearly, the consequences of developmental unilateral hearing are extensive. The hearing ear becomes overrepresented in the auditory system if unilateral deafness happens early [Moore and Kitzes, 1985; Reale et al., 1987; Kitzes et al., 1995; Moore et al., 1995]. Novel brainstem projections are formed when the cochlea is removed in animals near birth, but not if manipulation is performed in adult animals [Nordeen et al., 1983; Kitzes et al., 1995; Russell and Moore, 1995; McAlpine et al., 1997]. Asymmetric moderate hearing loss (e.g. by simply plugging one ear) similarly, but less extensively, reorganises the central representation of auditory space and binaural interactions [King et al., 2001; Vale and Sanes, 2002; Vale et al., 2004; Popescu and Polley, 2010; King et al., 2011; Keating and King, 2013; Polley et al., 2013], although some differences between moderate and profound hearing loss mechanisms exist [Hutson et al., 2008]. Residual spatial localisation abilities in asymmetric hearing are secured by increasing reliance on monaural (spectral) cues [Slattery and Middlebrooks, 1994; Keating and King, 2013]. Changes in inhibitory-excitatory balance are involved in these processes [Mossop et al., 2000; Vale and Sanes, 2002; Vale et al., 2004; Hutson et al., 2008].

But what is the potential of therapy for the deaf ear? In moderate hearing loss by ear plugging, the ear is functional after removal of the plug [for a review, see Keating and King, 2013]. The consequences of unilateral deafness are more extensive. In the physiological binaural condition, as a consequence of contralateral representation in the brain, cortical neurons respond better (faster and stronger) to the stimulation of the contralateral ear (contralateral dominance) [Imig and Adrián, 1977]. In ablation models, the function of the deaf ear is difficult to assess, but the use of congenitally deaf animals makes it possible to investigate functions of deaf ears with electrical stimulation using cochlear implants. Congenital binaural deafness reduces the normal aural dominance [Kral et al., 2009]. In congenital single-sided deafness, the contralateral dominance is changed to a preference for the hearing ear in both cortical hemispheres [Kral et al., 2013a, b]. Single-sided deafness, thus, leads to the development of a stronger ear (more extensively represented in the auditory system) and a weaker ear (less well represented in the auditory system). In none of the investigated animals were, however, the responses for the deaf ear completely eliminated in the cortex [Kral et al., 2013a, b]. This is relevant, as it supports the concept that appropriate training might restore hearing in the previously deaf ear.

Most importantly, the reorganisation following unilateral electrical stimulation to a congenitally deaf born cat (thus creating the setting for single-sided deafness) shows an early sensitive period with progressively increasing age [Kral et al., 2013a, b]. The early onset of unilateral hearing puts the deaf ear into significant disadvantage in the competition of cortical resources. This negative effect was observed much less in later-onset, single-sided hearing [Kral et al., 2013a, b].

Furthermore, in the case of early-onset, single-sided deafness, the brain became asymmetric, as there was one hemisphere that lacked the ipsilateral and frequently inhibitory input, and the other hemisphere lacked the contralateral, mainly excitatory input [McAlpine et al., 1997; Vale et al., 2004; Kral et al., 2013a, b]. Differences in developmental time courses of inhibitory and excitatory synapses in the hearing brain [Gao et al., 1999, 2000] facilitate distinct reorganisations taking place in these two hemispheres in sequential implantations. Consequently, the mechanisms of the reorganisation and the final functional state following early single-sided deafness differ in the two hemispheres – the reorganisations show a strong hemispheric specificity [Kral et al., 2013a]. Such a re-sculptured, asymmetric brain is specialised for the unilateral hearing condition, which may be detrimental for the later use of the initially deaf ear. The earlier the asymmetry sets in, the larger the effects [Kral et al., 2013a, b]. Interestingly, additionally to a sensitive period for plasticity in the cortex contralateral to the trained ear [for a review, see Kral and Sharma, 2012], the ipsilateral cortex showed even a shorter sensitive period and, within it, more extensive reorganisations [Kral et al., 2013a].

Auditory Space and Localisation

The effect of single-sided deafness is particularly detrimental for binaural hearing. Binaural hearing requires strong and symmetric representation of both ears. Accordingly, an extensive change in the aural preference, as observed in juvenile single-sided deafness, must be detrimental for binaural hearing.

Source localisation depends on monaural (pinna cues) but more importantly on binaural cues (interaural level and time differences, with time being the more important localisation cue). Auditory neurons become sensitive to binaural cues early in development, soon after hearing onset [Brugge et al., 1988], although some maturation takes place later [Mossop et al., 2000]. Consequently, the basic circuitry for binaural processing in the brainstem is inborn and a residual functionality is observed even in total congenital hearing deprivation [Tillein et al., 2010]. However,

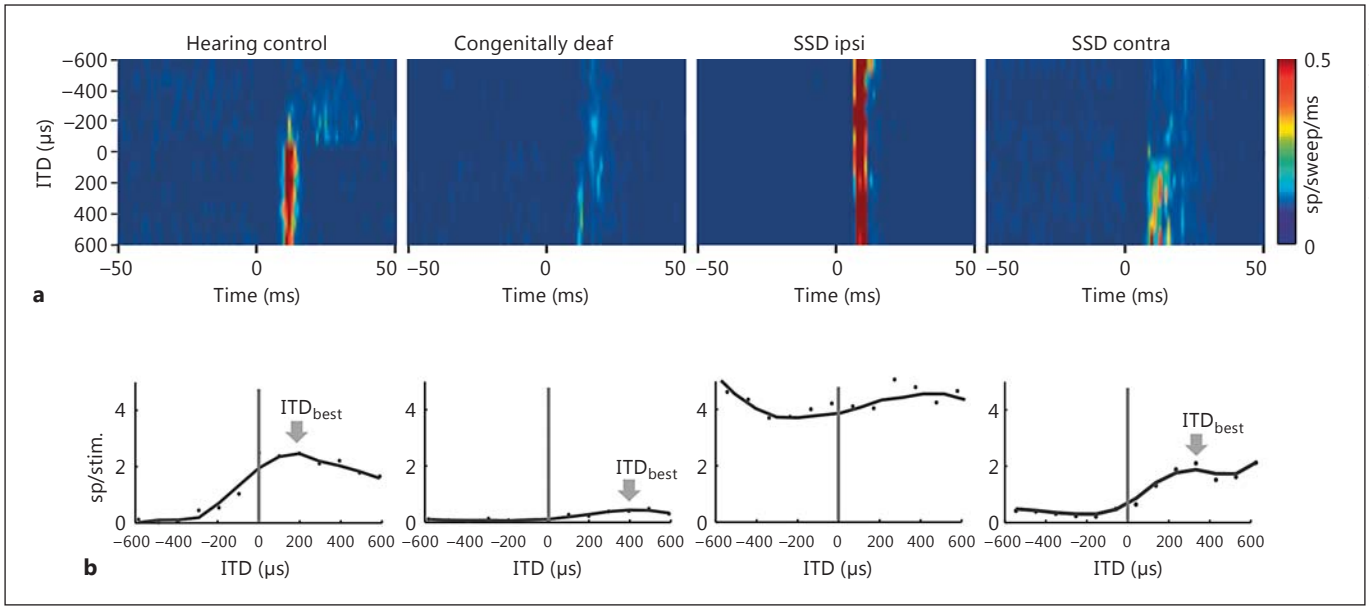

Fig. 1. a Examples of binaural sensitivity in individual unit recordings obtained from a hearing control, congenitally deaf cat and a congenitally single-sided deaf cat on both hemispheres. The firing rate is colour coded (see online version for colours). Single-sided deaf cats show flat ITD functions, particularly at the cortex ipsilateral to the hearing ear. **b** Same data presented for overall firing rate as a function of ITD; ITD_{best} is marked by an arrow. Recordings were performed in field A1 within the most excited region of the cortex determined by a mapping procedure [Kral et al., 2009]. Note: for colour figures, see the online PDF version, for details see the text.

postnatal development is affected by alterations in sensory input [for a review, see Grothe et al., 2010].

The representation of interaural level differences that are critically dependent on overall excitation from each ear, therefore, obviously change under asymmetric hearing condition. Indeed, even moderate hearing asymmetry reduces the sensitivity to interaural level differences in the mouse, corresponding to the above findings on stronger representation of the hearing ear [Popescu and Polley, 2010; Polley et al., 2013]. However, less obvious is the consequence for representation of interaural time differences (ITD). These must be investigated on species that have large enough heads (to provide ITD) and with enough low-frequency hearing to encode ITD. Congenital deafness in cats has been shown to affect the sensitivity to ITD cues significantly: despite rudimentary-preserved ITD-sensitive units in the cortex, the overall number of these units was reduced to ~50% of the hearing controls, and the individual sensitivity of the units was significantly decreased in a similar extend [Tillein et al., 2010, 2011]. In total, the overall reduction in the sensitivity to ITD was extensive in congenitally deaf cats [Tillein et al., 2010]. A study published few months later showed a similar deficit in the midbrain of congenitally deaf cats [Hancock et al., 2010], further demonstrating that the effect in the cortex is passed along from subcortical structures (most likely from the olivary complex).

However, when congenitally single-sided deaf cats were compared to the binaurally deaf cats, they revealed a further reduction in ITD sensitivity (fig. 1). The number of ITD-sensitive units was reduced in comparison to the binaurally deaf cats, and the distribution of the best ITD was also dramatically affected. To determine where in space the highest localisation precision is found, the interaural time of each ITD function showing the highest firing rate (ITD_{best}) was determined. The more that neurons show the highest firing rate at the given ITD, the easier and more reliable will this ITD become differentiated from other ITD within the population of all neurons. Between these 'best' ITDs and ITDs close to 0 µs (near midline) are the positions where the neurons most precisely code ITD, as there the firing rate changes most extensively with changing ITD [Tillein et al., 2010, 2011]. In normal-hearing cats, most units preferred ITD of +100 to 200 µs (i.e. favouring the contralateral hemifield). When units from both hemispheres in field A1 are considered, under the assumption of symmetry in hemispheric representation of hearing controls, this results in distributions compiled in figure 2 (blue colour; see online version for colours). It reveals that the best localisation ability is when sound emanates from the front in hearing controls, particularly between –200 and 200 µs (corresponding to approx. ±45° from midline), and the number of cells sensitive to more peripheral locations is smaller (blue area; fig. 2). The midline position usually represents the focus of attention and the gaze direction. The minimal audible angle is smallest for midline and paramidline positions.

In binaural congenital deafness, the coding of acoustic space retains some localisation ability mainly close to the midline (red line; fig. 2). In other words, there is a collapse of the space representation to the midline in binaural congenital deafness [Kral et al., 2009; Tillein et al., 2010].

In single-sided deaf animals, there was no strong preferred spot along the ITD dimension at all (fig. 2). The ITD_{best} was nearly evenly distributed throughout the whole ITD dimension, extensively

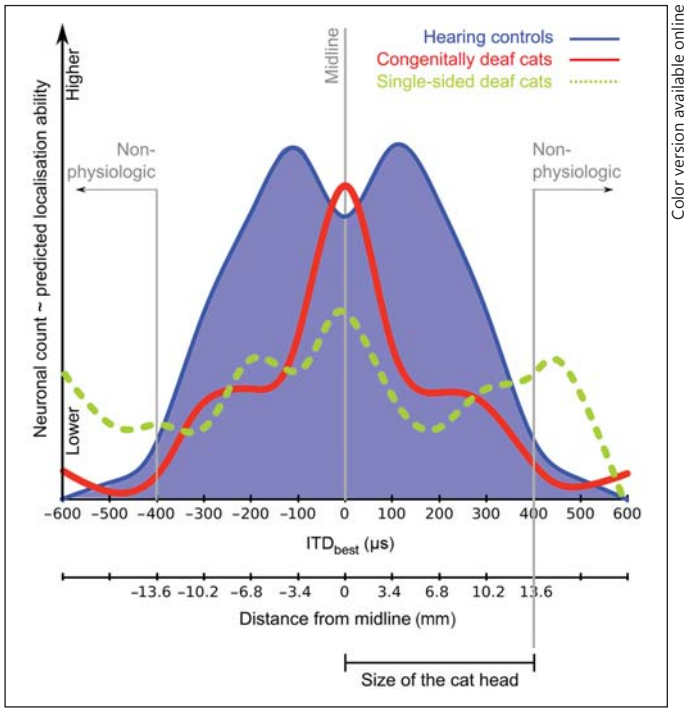

Fig. 2. Distribution of ITD with highest firing rates (ITD_{best}) in hearing controls (n = 4; blue: filled area), binaurally congenitally deaf cats (n = 4; red: thicker solid line) and congenitally single-sided deaf cats (n = 2; green: dashed line) obtained from ~300 unit recordings in the primary auditory cortex (field A1) in the most excited region at 6 dB above the threshold from each animal group (procedure after Tillein et al. [2010]). ITD of 0 µs correspond to midline location, 400 µs to 90° from midline, i.e. lateral to the pinna locations. In hearing controls and congenitally deaf cats, the functions were mirrored and summed to represent both hemispheres; in single-sided deaf cat recordings this was performed on both hemispheres and summed. Due to asymmetry of the hemispheric reorganisations in single-sided deaf cats (described in Kral et al., [2013a, b]), the corresponding function is not midline symmetric. The number of units is assumed to correspond to the localisation ability for sources with the given ITD; the data, therefore, predict a collapse of auditory space to midline locations in binaurally deaf cats. In single-sided deaf cats (green: dashed line), the units were nearly uniformly distributed through all ITD, demonstrating a pronounced reduction in the localisation ability for midline locations. Note: for colour figures, see the online PDF version, for details see the text.

reducing the information on spatial location around the midline positions. Even more, non-physiologic ITD were more extensively represented in single-sided animals. These deficits most likely are the consequence of the strengthening of the representation of the hearing ear and weakening of the representation of the deaf ear. No compensation for the single-sided hearing was observed (i.e. there was no increase in ITD sensitivity for the deaf side). As single-sided deafness does not lead to a compensatory increase in sensitivity at the deaf ear (where no input is provided at all), the data are in agreement with results on conductive hearing loss and are consistent with the theory of a reweighting of mon-/binaural cues in asymmetric hearing loss, with the consequence of more reliance on monaural cues [Keating and King, 2013]. The deficits in ITD sensitivity in congenital single-sided hearing shows that this condition is detrimental for binaural hearing. Given that sensitive periods of plasticity limit relearning in adulthood [Kral, 2013], congenital single-sided hearing may degrade localisation ability if hearing on the deaf ear has been restored after the sensitive periods have expired [Kral et al., 2013a, b]. Data obtained in children support this suggestion [Arndt et al., 2011; Firszt et al., 2012a, b; Hassepass et al., 2013; Illg et al., 2013].

Color version available online

Clinical Implications

The current data imply that there is a change in aural preference in maturational single-sided deafness with development of a 'stronger' and a 'weaker' ear during an early sensitive period [Kral et al., 2013b], which results in a reduced ability for sound source localisation. Although animal experiments cannot provide information on the duration of the sensitive period in humans, the observed sensitive period was shorter than the previously described period of general adaptability to the implant in the contralateral cortex [Kral and Sharma, 2012]. Extrapolating from the known duration of this period in humans (3.5 years), the data suggest that single-sided deafness should be treated well before the child reaches 3.5 years. Furthermore, a weakness of one ear can possibly be compensated by providing input through the weaker ear only, as this ear retains rudimentary connections to the cortex. Even brief periods of such monaural weaker ear training, e.g. during listening to bedtime stories, might further help this ear to overcome an already existing preference for the other ear. Furthermore, binaural sound localisation requires more consideration in these kids.

Conclusion

These data suggest that in congenital single-sided deafness, binaural hearing is traded for a stronger representation of the hearing ear. In doing so, the brain sacrifices binaural sound localisation (that it cannot access) for better access of the input through the remaining ear. This effect includes higher-order auditory processing, access to language circuits and monaural localisation. Sacrificing the binaural localisation for strengthening monaural hearing is an optimal adaptation for the condition of single-sided hearing, but it compromises possibilities to restore hearing on the deaf ear and binaural localisation later in life. Combining the available evidence from animal and human studies on both conductive and sensory hearing loss, support is given to the need for early identification of hearing asymmetry and an early therapy for hearing on the 'weaker' ear.

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J.T. is employed by MedEl Comp. The other authors have nothing to disclose.

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Corresponding author:
Prof. A. Kral
Institute of AudioNeuroTechnology
Feodor-Lynen-Strasse 35
DE–30625 Hannover (Germany)
E-Mail kral.andrej@mh-hannover.de