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Review Article

Cortical reorganization in postlingually deaf cochlear implant users: Intra-modal and cross-modal considerations

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ABSTRACT

With the advances of cochlear implant (CI) technology, many deaf individuals can partially regain their hearing ability. However, there is a large variation in the level of recovery. Cortical changes induced by hearing deprivation and restoration with CIs have been thought to contribute to this variation. The current review aims to identify these cortical changes in postlingually deaf CI users and discusses their maladaptive or adaptive relationship to the CI outcome. Overall, intra-modal and cross-modal reorganization patterns have been identified in postlingually deaf CI users in visual and in auditory cortex. Even though cross-modal activation in auditory cortex is considered as maladaptive for speech recovery in CI users, a similar activation relates positively to lip reading skills. Furthermore, cross-modal activation of the visual cortex seems to be adaptive for speech recognition. Currently available evidence points to an involvement of further brain areas and suggests that a focus on the reversal of visual take-over of the auditory cortex may be too limited. Future investigations should consider expanded cortical as well as multi-sensory processing and capture different hierarchical processing steps. Furthermore, prospective longitudinal designs are needed to track the dynamics of cortical plasticity that takes place before and after implantation.

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1. Introduction

In 2008, one of us (S.D.) reported on a 71-year-old male cochlear implant (CI) user, who had been using a CI for 4 years before he entered our laboratory (Debener et al., 2008). This gentleman could easily communicate without the help of visual cues. He had suffered from a gradually deteriorating sensori-neural hearing loss since the age of four and reported being severely hearing impaired for half of his life, with no satisfactory benefits from hearing aid use. By the age of 67, after decades of silence, he received a CI, and speech perception returned within a few months. Remarkably, in the electroencephalogram (EEG) laboratory, we found near normal, age-appropriate late cortical auditory evoked potentials (AEPs). This case is of course anecdotal and should be treated with care, but it is a reminder that humans retain clear capacity for brain plasticity, even during later years and even after decades of sensory deprivation.

In sensory and motor systems, lack of experience (or lack of use) results in shrinkage of the cortical representations of non-used systems or limbs (Polley et al., 2006; Steven and Blakemore, 2004). This shrinkage process is typically paralleled by a redistribution or invasion of abandoned regions by remaining sensory modalities, representation zones or effectors (e.g., Milliken et al., 2013). Here the more relevant findings than reports of usedependent plastic changes are studies on the potential interaction between deprivation-induced and restoration-induced changes. A seminal study exploring this interaction in the motor system showed that individuals cannot be expected to easily regain their original pre-deprivation movement and corresponding cortical representations after experiencing a shrinkage of cortical representation induced by movement restriction (Milliken et al., 2013). A similar variability of recovery is observed in adult CI users. Despite CIs being by far the most successful neuro-prosthesis available (Wilson and Dorman, 2008), some CI users recover poorly, and changes in cortical representation have been found to contribute to this variation.

Several previous reviews on deprivation-induced cortical reorganization highlighted for instance the mechanisms of underlying maturation during early development and prelingual deafness (Kral and Eggermont, 2007; Kral, 2007; Kral et al., 2016; Merabet and Pascual-Leone, 2010; Sharma and Glick, 2016). Others have explored similarities between the cortical changes of early deaf and blind individuals (Heimler et al., 2014; Merabet and Pascual-Leone, 2010). However, given our aging society and the prevalence of agerelated hearing loss that often develops during adulthood, postlingually deaf individuals are nowadays the principal population for CI therapy. Mechanisms and patterns of cortical reorganization may differ between pre- and postlingually deaf CI users, because the auditory system is assumed to be normally developed before the onset of deafness in postlingually deaf, but not in prelingually deaf individuals (Heimler et al., 2014; Kral, 2007; Petersen et al., 2013). Thus in the present review, we focus on cortical differences in adult, postlingually deaf CI users.

Fig. 1 is a schematic illustration of possible patterns of reorganization due to auditory deprivation (B-D) and hearing restoration with a CI (E-G). The figure will be used throughout the review to illustrate configurations of changes and possible pathways of reorganization. All illustrated differences in cortical configurations are shown in comparison to the normally matured auditory system (A). Different stages of sensory deprivation such as moderate hearing loss or profound deafness might induce various patterns of cortical changes. The take-over of the auditory cortex by other modalities, as presented here the visual system, can be weaker or more pronounced (B, C). Cross-and intra-modal changes could as well emerge within and between both the visual and the auditory modality (D). It is not well understood how these changes contribute to changes following sensory restoration with a CI. So far, the common view mainly interprets the particular configuration of reorganization known as visual take-over, as reflecting residual, deafness-induced changes that have not been fully reversed by CI use (Fig. 1 A versus E). However, extended CI use may not necessarily result in either a restored pre-deprivation organization

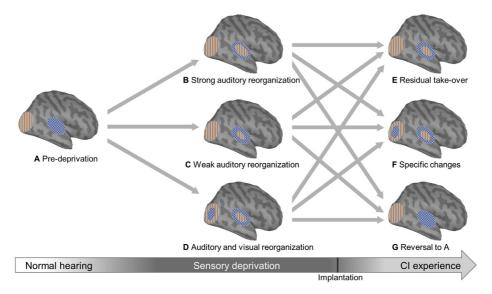


Fig. 1. Schematic sketch illustrating cortical reorganization patterns resulting from sensory deprivation and hearing restoration with a CI. All illustrated cortical changes are shown in comparison to the normally-matured auditory system (A). Different stages of sensory deprivation such as moderate hearing loss or deafness might induce various patterns of cortical changes (B, C, D). It is not well understood how these contribute to changes following sensory restoration with a CI (E, F, G). The (orange) vertical line patterns represent visual input, which is primarily processed in visual regions and the (blue) chequer patterns represent auditory processing which is primarily processed in auditory regions. The small amount of cross-modal processing which is generally found in NH individuals is not considered in this schematic illustration. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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(Fig. 1 G) or a pre-implantation organization (Fig. 1 B-D). Other patterns of cortical changes after implantation of the CI are possible, such as intra- and cross-modal changes within or between the visual and the auditory system (F). Note that we focus in this review on cortical changes of the visual and the auditory system only, even though differences within the somatosensory modality have been identified as well (Landry et al., 2014, 2013; Nava et al., 2014). The small amount of cross-modal processing which may be evident in NH individuals is not considered in this schematic illustration. It is likely that patterns of cortical reorganization induced by sensory deprivation and subsequent CI experience are much more complex than these illustrated in Fig. 1. So far, little is known about which of these final configurations is most desirable in terms of CI outcome, even though, from a clinical point of view, it is of utmost importance how these patterns of reorganization relate to the individual CI benefit.

The aim of this review is to summarize cortical changes in postlingually deaf CI users induced by sensory loss and/or sensory restoration, and their relationships to CI outcome. The most optimal approach to track cortical changes over time is a longitudinal design (e.g. Fig. 1 from A to B-D to E-G). However, since longitudinal studies are extremely time-consuming and rather difficult to conduct, current investigations are typically limited to crosssectional, or incomplete longitudinal investigations. In a crosssectional design. CI users are compared to normal hearing (NH) controls with the underlying assumption that observed group differences reflect cortical changes induced only by divergent sensory experience. To justify this assumption, it is crucial to control for other potentially influencing factors such as age, gender, and handedness. Here we review evidence using both cross-sectional and longitudinal approaches and discuss design and techniques suitable for advancing the clinically-motivated goal of outcome prediction while keeping track of the general goal, which is to provide new insights into the potential (and limits) of adult brain plasticity in postlingually deaf CI users.

2. Factors influencing speech recognition abilities with a CI

Why do some individuals obtain excellent hearing with a CI and regain the ability to communicate on the phone, for instance, while others do not benefit much even in relatively simple listening situations? This question has been intensively investigated in large multi-center studies (Blamey et al., 2012; Lazard et al., 2012). A multi-center approach provides the advantage of a huge sample size but may suffer at the same time from difficulties in comparing individual parameters across centers. For example, currently the most widely used indicator of CI benefit is speech perception ability, which may be highly dependent on the speech test used. Furthermore, definitions of subjective variables such as onset and duration of deafness are difficult to standardize and might be differentially used between the centers (Holden et al., 2013). So far, only a few single-center studies with longitudinal designs and decent sample sizes exist (Holden et al., 2013; Moon et al., 2014).

Despite these difficulties, several pre- and post-implantation factors have been identified across studies. The duration of severe to profound hearing loss (i.e., deafness) seems to have the most substantial negative influence on speech recognition abilities in postlingually deaf CI users (Blamey et al., 2012, 1996; Green et al., 2007; Holden et al., 2013; Lazard et al., 2012). Furthermore, the age at implantation and the age at onset of severe to profound hearing loss account for variability in CI outcome, with the earlier the implant and the later in life the onset of hearing loss, the better the CI outcome. Post implantation CI experience also contributes to outcome, with more experience being typically associated with better speech recognition abilities. At present, it is known that

these factors influence speech perception, but what the underlying mechanisms are is less well understood. A common view is that all these factors are related to cortical changes, which in turn determine CI outcome (other factors may be relevant and are not discussed in this review). Supporting evidence comes from studies showing that longer deprivation and CI experience both correlate with a higher level of cortical reorganization (Giraud et al., 2001b: Green et al., 2005; Oh et al., 2003; Sandmann et al., 2014; Viola et al., 2011). In a seminal animal study, Lomber and colleagues demonstrated a causal relationship between cortical reorganization of auditory cortex and behavior (Lomber et al., 2010). However, evidence in humans is largely correlational, and correlations between cortical reorganization and CI speech recognition outcome do not directly imply causality. Nevertheless, cortical changes seem to be at least closely related to - if not the driving force for - CI outcome. Neural measures may allow an objective characterization of the individual. Moreover, they help to predict outcome and could contribute to the selection of optimal rehabilitation strategies.

3. Methodological constraints measuring cortical changes in CI users

Due to technical challenges and safety concerns, measuring brain activation in CI users is far from trivial. Current CI technology precludes the use of functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). By far the most commonly used approaches are therefore positron-emission-tomography (PET) and multi-channel EEG. However, PET studies are invasive and not suitable for repeated assessments within subject. EEG on the other hand suffers from the inverse problem, thus a purely sensor-level based spatial analysis of EEG data does not reveal cortical generator sites unambiguously and should be interpreted with caution. Although EEG source localization approaches can be used to capitalize on the spatial information provided by highdensity EEG recordings, EEG source localization results are only estimations of cortical activation patterns, not direct observations. Moreover, EEG suffers from electrical artifacts caused by CI stimulation, although methods have been developed to deal with this problem (e.g. Viola et al., 2012). A relatively recent and quickly evolving neuroimaging technology is functional near-infrared spectroscopy (fNIRS). fNIRS is an optical imaging technique that detects changes in cerebral blood flow by measuring oxygenated and deoxygenated hemoglobin concentrations. It is non-invasive, compatible with the CI technology, relatively inexpensive, and portable, unlike MEG and fMRI, which makes fNIRS a promising candidate for the investigation of cortical functions in CI users (cf. Saliba et al., 2016). Recent fNIRS studies have shown evidence of cortical reorganization in both deaf individuals and postlingually deaf CI users (Chen et al., 2016a; Dewey and Hartley, 2015). Although the spatial resolution of fNIRS is not as good as fMRI, it provides good spatial accuracy and perfect compatibility with EEG. This makes simultaneous EEG-fNIRS feasible and provides the added value of multi-modal imaging (Chen et al., 2015; Debener et al., 2006; Huster and Debener, 2012). With the complementary information provided separately from EEG and fNIRS, the simultaneous approach could provide a better view on functional cortical configurations and changes in CI users.

4. Evidence of cortical reorganization

4.1. Cortical reorganization in postlingually deaf and individuals with moderate hearing loss

First evidence of altered cortical organization induced by auditory deprivation came from studies of congenitally deaf individuals.

It has been repeatedly found that the auditory cortex of these individuals is more activated for visual stimuli compared to NH controls, suggesting that deafness induces a visual take-over or cross-modal reorganization in auditory cortex (Bottari et al., 2014; Fine et al., 2005; Finney et al., 2003, 2001; Karns et al., 2012; Shiell et al., 2014; Vachon et al., 2013). In addition to a recruitment of auditory cortex, visual responses in the visual cortex in early-deaf individuals have also been found to differ from NH controls suggesting that the absence of auditory input may additionally induce intra-modal reorganization in the visual cortex of early deaf individuals (Bavelier et al., 2000; Bottari et al., 2014; Hauthal et al., 2013).

Note however, these group differences in cortical responses were mostly found in early, prelingually deaf individuals and may not apply to postlingual deafness. At present, there is only little evidence of visual take-over in the auditory cortex of postlingually deaf individuals not using CI technology. For instance, Lee and colleagues showed that speech reading and counting of dynamic faces activated areas in post-lingually deaf individuals that are classically activated by auditory processing in the normal hearing population (Lee et al., 2007), indicating evidence for visual takeover of auditory cortex (condition B and C in Fig. 1). Additionally, other indirect evidence of cortical changes indicated that resting state and glucose metabolism in auditory cortex differed between postlingually deaf and normal hearing individuals (Lee et al., 2003). Studies investigating auditory imagery and memory observed that a subgroup of postlingually deaf individuals showed a deprivationinduced decline of non-speech sound representation compared to NH controls, suggesting that the non-speech network is reorganized to improve speech processing (Lazard et al., 2013, 2011). Evidence for intra-modal reorganization of the visual cortex in postlingually deaf individuals without a CI is even more sparse. More work is needed to determine whether cortical changes observed in postlingually deaf CI users are initiated during the period of deafness (Fig. 1 B-D) or later acquired during the adaptation process to the CI (Fig. 1 E-G).

Interestingly, individuals with moderate hearing loss were recently considered alongside deaf individuals. Individuals with a moderate hearing loss showed higher activation in auditory cortex for visual stimuli compared to NH controls (Campbell and Sharma, 2014), a pattern similar to that seen in postlingually deaf individuals. Even though evidence comes from only one study, this result might indicate an early onset of cross-modal reorganization of auditory cortex that is initiated even before the onset of profound deafness, pointing to first evidence for conditions B and C as illustrated in Fig. 1. Additionally, the same research group investigated differences in auditory processing between individuals with moderate hearing loss and NH controls. The group of individuals with moderate hearing loss showed decreased activation in temporal regions suggesting intra-modal reorganization in, but not limited to, auditory cortex, which supports condition D in Fig. 1. Furthermore, group differences in the frontal cortex were observed, which might indicate large scale cortical changes from adaptation to hearing loss (Campbell and Sharma, 2013). These findings support the assumption that cortical changes start to develop with progressing hearing loss, even though evidence relating the time course of hearing loss to cortical changes is lacking.

4.2. Habilitation and auditory processing

Due to the rather coarse representation of sound with current CI technology, CIs only allow partial hearing recovery, and this may not result in complete rehabilitation. Here we refer to the recovery of hearing abilities with CIs as a habilitation process, pointing out that the brain learns new strategies to adapt to the electrical input

and thereby improves hearing (cf. Fig. 1 F). Table 1 provides an overview of studies that investigated cortical changes in response to the new auditory input in terms of magnitude and the spectral and temporal features of the neural response following CI implantation. A recent longitudinal study showed that within days after the initial switch-on of the implant, postlingually deaf CI users improved significantly in their speech perception ability, which was even more pronounced after several weeks of CI use. The improvement in speech perception was accompanied by an increase in their neural responses in auditory cortex to complex tones (Sandmann et al., 2014). Additionally, auditory cortex activation seems to become more focal and stimulus specific with CI use (Giraud et al., 2001c). These findings of recovered auditory processing after implantation manifest that the auditory system remains capable to process acoustic events even though auditory input was previously deprived and even though the auditory cortex was potentially invaded by other sensory modalities such as the visual and the somatosensory modality (Pantev et al., 2002). This relatively quick adaptation (within one year) seems to take place even in individuals who experienced a long period of hearing deprivation (see Table 1). This is furthermore reflected in a positive relation between the increase in activation in auditory cortex and the increase in speech perception, resulting in a pattern of nearlynormal cortical activation in better-performing CI users (cf. Table 1 and Fujiki et al., 1999; Green et al., 2005; Naito et al., 2000; Olds et al., 2015; Roland et al., 2001).

Different cortical responses between good and bad performers have been identified and related to CI outcome. Well-performing CI users showed similar activations compared to NH controls (Fig. 1 G), indicating a recovery of auditory functions (see Table 1 for more studies finding similar results). Good performers also showed a stronger adaptation of late AEPs to repeated stimulation and a larger mismatch-negativity, indicating a good habilitation of the auditory system to CI input (Zhang and Anderson, 2010; Zhang et al., 2013, 2011). Bad performers in contrast showed an altered activity pattern compared to NH controls, which seems to be not advantageous for speech perception (e.g. Lazard et al., 2010). The average speech perception score as well as the increasing activation of auditory cortex usually saturated roughly around one to two years after implantation, but, on average, despite an intense improvement, stabilized at a lower level in CI users compared to NH controls (Ito et al., 1990; Viola et al., 2012, 2011, Sandmann et al., 2014). Overall, existing evidence suggests that the more similar the activation pattern between CI users and NH controls, the better the CI users experience recovery with the device. This might further support the idea that the variation in CI benefit might be partially due to differences in cortical changes.

In addition to the recovery of auditory cortex with respect to the processing of auditory stimuli, some evidence has indicated a potential recruitment of the visual cortex for auditory processing in post-lingually deaf CI users. Specifically, Giraud and colleagues showed first evidence of a higher activation of early visual areas in CI users compared to NH controls for various types of auditory stimuli, suggesting cross-modal reorganization of visual cortex (see lower part of Table 1 for an overview of studies). The cross-modal activation in visual cortex of postlingually deaf CI users was stimulus-specific towards meaningful sounds but not to white noise (Giraud et al., 2001b, 2001c). Furthermore, cross-modal activation in visual areas was more prominent in betterperforming CI users, and additionally correlated with speech perception and lip-reading abilities. The finding of a higher crossmodal activation of the visual cortex in postlingually deaf CI users compared to NH controls has recently been replicated independently by our group using simultaneous EEG-fNIRS recordings (Chen et al., 2016a). Interestingly, cross-modal reorganization in the M. Stropahl et al. / Hearing Research xxx (2016) 1-10

 Table 1

 Studies investigating cortical processing of auditory stimuli in adult, postlingually deaf CI users.

Author	Sample	Design (sessions)	Stimuli	Dependent variable	Main finding
Suarez et al., 1999	CI n = 5	Longitudinal 1 pre-CI	Click stimuli Sequential	SPECT Left + right AC	Significant increase post-implantation for both stimulus conditions
		1 post-CI	sentences	SPECT	increased activity during sentence condition
Giraud et al., 2001c	CI n = 4	Longitudinal	Speech	Frontal lobes PET	Increasing and more focused activity in primary AC with CI
Giraud et al., 2001C	Ci ii = 4	2 post-Cl	Noise	AC	use for speech
Pantev et al., 2002	CI n = 1	Longitudinal	Tone bursts	EEG	Similar latency, amplitudes and distributions of early N1
		1 pre-CI		AEP N1 and P2 at	peak for pre- vs. post-implantation stimulation; N1
		3 post-CI		M1 and Cz	components seem to develop differently over time
Oh et al., 2003	CI n = 17	Longitudinal	Speech perception	Speech perception	Plateau after 2 years; CI users with shorter duration of
Dantau et al. 2006	CI n 2	6 post-Cl Longitudinal	test	score MEG sensor	deafness showed faster recovery
Pantev et al., 2006	CI n = 2 NH n = 10	10 post-CI	Tone (frequency shift)	N1m	After 2 years almost normal contralateral AEF N1m component configuration
	1411 II = 10	To post-Ci	Silit)	MEG source	Activity localized in AC
				AC	Theriting focusing a minimum of the focusing and the focu
Lazard et al., 2010	$CI \ n = 8$	Longitudinal	Rhyming words	fMRI	Higher activation for CI users versus NH controls, negative
	NH n = 8	1 pre-CI	Speech perception	RSMG	correlation with pre-operative phonological scores and
		1 post-CI	test	O (D)	post-CI word recognition
				fMRI phonological	Good performers maintain dorsal phonological circuits and activate occipito-temporal regions; Bad performers switch
				circuits	to alternative lexico-semantic ventral route
Petersen et al., 2013	CI n = 11	Longitudinal	Multitalker babble	PET	A contrast of speech and babble noise revealed in
	(NH n = 6)	1 pre-CI	Speech	BA 21/22	postlingually deaf CI user higher activity to speech than
		3 post-CI			babble noise
				PET	Postlingually deaf CI users showed increased activation over
				Broca's area PET	time
				Right parietal lobe	Increased activity during babble for CI users versus NH controls
Sandmann et al.,	CI n = 11	Longitudinal	Noise	EEG AEP (global	Enhanced N1 amplitude and reduced latency with
2014	NH n = 11	4 post-CI	Complex tones	field power)	increasing CI use. Ipsilateral N1 latency reduction positively
				N1	correlated with duration of deafness;
				EEG	after 1 year, normalization of AC activity in CI group
Donder and Waller	CI - 10	Iit di1	Т	Source AC	MID and detectable in all providences considered and
Purdy and Kelly, 2016	CI n = 10	Longitudinal 5 post-CI	Tones	EEG (sensor) MLR	MLR not detectable in all participants, varied and no consistent change over time
2010		J post-ci		CAEP (N1, P2)	Significant changes over time for P2 high variability in CI
				C. D. (, 12)	group; high variability in N1
				MMN	MMN results showed trends for reduced latencies, larger
					amplitudes and better detectability over time
Giraud et al., 2001a	CI n = 6	Cross-sectional	Speech stimuli	PET	Activation to speech sounds by CI users only
	NH $n = 6$			Left BA 18	Dogwited in both groups but with different appointment
Giraud et al., 2001b	CI n = 6	Cross-sectional	Speech stimuli	(left) BA 22 PET	Recruited in both groups but with different specialization Activation to stimulus specific sounds with eyes closed in CI
difaud et al., 2001b	NH n = 6	1-year follow-up	Specen stiniun	BA 17/18/19	users; increase of activation with Cl use
		(n=3)		211 17/10/10	does, mercase of activation with er asc
Giraud and Truy,	$CI \ n = 6$	Cross-sectional	Speech stimuli	PET	Activation to meaning full speech sounds in CI users but not
2002	NH n = 6			BA 20/36, 37, 39, 47	in controls
Strelnikov et al.,	CI n = 10	Longitudinal:	Speech stimuli	PET	Positive correlation between cortical activation
2013	NH $n = 6$	2 post-CI	Perception score	right occipital (left inferior frontal,	immediately after activation of implant and speech
				left posterior	perception score 6 months later
				temporal,	
				right middle STG/	
				STS)	
				Speech perception	Increase of performance with CI use
Chen et al., 2016a	CI n = 19 NH n = 19	Cross-sectional	Words Reversed words	fNIRS visual areas	Higher cross-modal activation for CI users compared to NH controls

Abbreviations: (C)AEP/F, (cortical) auditory evoked potential/field; AC, auditory cortex; BA, Brodmann area; CI, cochlear implant; EEG, electroencephalography; (f)MRI, (functional) magnetic resonance imaging; fNIRS, functional near-infrared spectroscopy; MEG, magnetoencephalography; MLR, middle latency response; MMN, mismatchnegativity; NH, normal hearing; PET, positron emission tomography; rCBF, regional cerebral blood low; SPECT, single photon emission tomography.

visual cortex was found using a passive task, in which participants were instructed to ignore the presented sound and to focus on a simultaneously presented video. This potentially minimizes the possibility that such observation is driven by different strategies applied by postlingually deaf CI users, for example visual imagery, when processing sound. Our findings strengthen the observation that the visual cortex may be reorganized for auditory processing in CI users, which is illustrated as condition F in Fig. 1.

4.3. Habilitation and visual processing

In addition to the changes of auditory processing discussed above, changes of visual processing have also been identified in postlingually deaf CI users (see Table 2 for a summary). Several EEG studies observed differences on the sensor level in visual evoked potential (VEP) amplitudes between CI users and NH controls over occipital and (occipito-) temporal sensors. The CI

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Table 2Evidence for the cortical changes in processing visual stimuli in adult, postlingually deaf CI users.

Author	Sample	Design	Stimuli	Depending variable	Main finding
Doucet et al., 2006	CI n = 13 NH n = 16	Cross-sectional	Sinusoidal concentric grating,	VEP P2 at Oz, O1 and O2	Good CI performers showed larger amplitudes than poor CI performers and NH
			followed by star- shaped grating	VEP P2 at anterior regions	The activation was larger and more widespread within the group of poor CI performers than NH
Buckley and Tobey, 2011	$\begin{aligned} &\text{CI } n = 10 \\ &\text{NH } n = 12 \end{aligned}$	Cross-sectional	Peripheral visual motion stimuli	VEP N1 at FT8, T8 and TP8	The amplitude in prelingually deaf CI users correlated negatively with speech performance, but not in postlingually deaf CI users
Landry et al., 2012	CI n = 7 $NH n = 17$	Cross-sectional	Speech reading video	Speech-reading	No difference between proficient and non-proficient CI users
Sandmann et al., 2012	CI n = 12 NH n = 12	Cross-sectional	Reversing checkerboard	EEG Source VC	CI users show lower activation than NH controls
Strelnikov et al., 2013	$\begin{array}{l} \text{CI } n=6 \\ \text{NH } n=10 \end{array}$	Semi- longitudinal 2 post-CI	Speech reading video	PET Right BA18 Left BA45/46	Activation from both areas correlated positively with speech performance (6 months later)
				PET Right middle STG/STS	Activation correlated negatively with speech performance (6 months later) and activation in right BA18
Kim et al., 2016	$\begin{aligned} &\text{CI } n = 12 \\ &\text{NH } n = 14 \end{aligned}$	Cross-sectional	Reversing checkerboards	VEP P1 at FT8, T8, TP8	Amplitude was larger in poor CI performers than good CI performers/NH, and it correlated negatively with speech performance
				VEP P1 at O1, O2, Oz	Amplitude was smaller in poor performers than good performers/NH, and it correlated positively with speech performance
				Visual field (VF)	Poor CI users showed decreased central VF than good CI users/NH, but no group difference in far peripheral VF. Central VF correlated positively with speech performance. Difference between far VF and central VF correlated negatively with speech performance
Rouger et al., 2012	CI n = 10 NH n = 6	Longitudinal 2 post-Cl	Speech reading video	Speech reading PET Right BA38 PET Broca's area	At both TO and T1 Cl users perform better than NH controls At T0 Cl users showed higher activation than NH controls, but the group difference disappeared at T1 At T0 Cl users showed lower activation than NH controls, but the group difference disappeared at T1
Sandmann et al., 2012	CI n = 12 $NH n = 12$	Cross-sectional	Checkerboard	EEG Source AC	CI users showed higher activation than NH controls, and the activation correlated negatively with speech performance
Stropahl et al., 2015a	$\begin{array}{l} \text{CI } n = 21 \\ \text{NH } n = 21 \end{array}$	Cross-sectional	Face-house	EEG Source AC	CI users showed higher activation than NH for faces but for not houses. The auditory activation for faces correlated positively with face recognition and lip reading ability
Chen et al., 2016a	$\begin{array}{l} \text{CI } n = 19 \\ \text{NH } n = 19 \end{array}$	Cross-sectional	Checkerboard	fNIRS	CI users showed higher activation in auditory cortex than NH controls

Abbreviations: AC, auditory cortex; BA, Brodmann area; CI, cochlear implant; EEG, electroencephalography; fNIRS, functional near-infrared spectroscopy; NH, normal hearing; PET, positron emission tomography; VEP, visual evoked potential; STS/G, superior temporal sulcus/gyrus.

users with larger VEP amplitudes over occipital areas compared to NH controls showed a positive correlation to speech performance, whereas the poor performers of the CI groups showed a more widespread activation to visual stimuli reaching more anterior occipito-temporal areas, which seems to be negatively correlated to speech performance (e.g. Doucet et al., 2006; Kim et al., 2016). However, as previously mentioned, observations in sensor space cannot be directly linked to cortical generator sites, and thus the evidence only suggests cortical changes in CI users without clear information on where changes took place.

On the source level, lower visual cortical activation in CI users compared to NH controls for visual stimuli has been reported, suggesting intra-modal reorganization of the visual cortex (see Table 2, e.g. Sandmann et al., 2012). Responses to repeated visual stimuli seem to adapt more strongly in the visual cortex of CI users than of NH controls, which may reflect a better or more efficient encoding of visual stimuli in CI users (Chen et al., 2016b). Additionally, evidence suggests a contribution of intra-modal visual response magnitude to speech recognition. CI users with stronger visual cortex activation for visual stimuli immediately after surgery had better speech performance after 6 months of CI use compared to CI users with a less responsive visual system (Strelnikov et al., 2013).

In a similar manner to that seen in early deaf individuals, a difference in the recruitment of the auditory cortex for visual processing (Fig. 1 E/F) has been observed between postlingually deaf CI users and NH controls (see lower part of Table 2 for a summary). Specifically, studies have found higher activation for various visual stimuli, such as visual patterns or more complex stimuli, in the auditory cortex of CI users compared to that of NH controls, which is observed even after some experience with a CI (Chen et al., 2016a; Rouger et al., 2012; Sandmann et al., 2012; Stropahl et al., 2015a). This suggests a cross-modal reorganization of the auditory cortex for visual processing, which seems to be not completely reversed after CI implantation. Cross-modal reorganization may alter processing of auditory stimuli. Although only few studies investigated the relationship between cross-modal activation in the auditory cortex and speech recognition abilities, different patterns of influence of cross-modal activation in auditory cortex on speech performance have been reported. On the one hand, a negative correlation between cross-modal activation in the auditory cortex and speech performance has been observed (e.g. Sandmann et al., 2012; see Fig. 2 A; blue line). On the other hand, cross-modal activation in the auditory cortex correlated positively with lip reading and face recognition skills (Stropahl et al., 2015a; see Fig. 2 B; blue line).

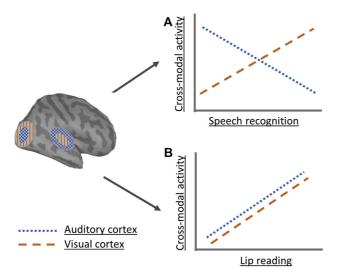


Fig. 2. Schematic illustration of possible relationships between reorganized cross-modal activation in visual (occipital) and auditory (temporal) cortices and CI outcome. (A) Relationship between cross-modal reorganization and speech recognition. Evidence suggests a negative correlation between speech recognition and auditory cross-modal activation and a positive correlation between speech recognition and cross-modal activation in the visual cortex (orange). (B) Relationship between cross-modal reorganization and lip reading. Evidence suggests a positive correlation between visual as well as auditory cross-modal activation with lip reading skills. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

5. Temporal evolution of cortical changes in postlingually deaf Clusers

We have reviewed evidence focusing on cortical responses to visual and auditory stimuli in moderately hearing impaired individuals, postlingually deaf individuals and postlingually deaf CI users (cf. Fig. 1). Behavioral as well as electrophysiological and neuroimaging evidence suggests that qualitatively new patterns of cortical activation can emerge in both the auditory as well as the visual sensory system (Fig. 1 F and see Tables 1 and 2 for detailed references). Although clear temporal evolvement of cortical changes from hearing impairment to CI use has not been investigated systematically, a few preliminary indication may be observed when combining most evidence so far, which will be discussed in the following.

Intra-modal changes in the auditory cortex after implantation could be shown by longitudinal CI studies in which auditory cortex evoked potentials (or the electromagnetic counterpart) successfully recovered to processing auditory stimuli. However, the recovery does not happen instantly and the dynamic habilitation process typically takes at least several months. This suggests that a deprivation of auditory input during the period of deafness does not limit responsiveness of the auditory cortex to a CI, despite that the level of recovery may not reach a normal hearing level. Additionally, intra-modal differences in the visual system were observed in postlingually deaf CI users, even though evidence is rather sparse compared to other observations. As intra-modal differences in the visual cortex have similarly been observed in congenitally deaf individuals, this suggests that deafness may induce intra-modal changes in visual cortex, and accordingly that the observation in postlingually deaf CI users may reflect left-over cortical changes. However, more detailed investigations are needed to understand visual processing in postlingually deaf individuals and the consequences on hearing rehabilitation.

Cross-modal reorganization in auditory cortex for visual processing could be observed in moderately hearing-impaired individuals, postlingually deaf individuals, and postlingually deaf CI users. Although evidence for the first two groups is sparse, it seems possible that the higher cross-modal activation in the auditory cortex of CI users may have been initiated during moderate hearing impairment (Fig. 1 A to B-D), further develops until profound deafness (Fig. 1 B-D to E-G), and remains incompletely reversed even after partial hearing recovery with CIs. Cross-modal reorganization in the visual cortex for auditory processing in postlingually deaf CI users was observed as well. Based on a small sample size (N = 3), one study found that cross-modal activation in visual cortex increased with increasing experience of CI use (Giraud et al., 2001b), which potentially suggests such cortical changes to be associated with the habilitation to new input. Since it is not possible to measure cross-modal activation in visual cortex during profound deafness, the question remains as to whether such changes may have already started during an initial period of hearing impairment (Fig. 1 A to B-D). First preliminary evidence of cortical differences resulting from mild to moderate hearing impairment exists, but no differences in activation of the visual cortex for auditory stimuli have been reported (Campbell and Sharma, 2014, 2013). In future studies it would be interesting to determine whether cross-modal activation in visual cortex is induced only after implantation or whether there may have been an early onset of such cortical changes during moderately hearing loss.

The observation of cross-modal reorganization in visual and auditory cortex in postlingually deaf CI users raises the question of the functional purpose of such changes, which may be puzzling at first. However, since communication in daily life often involves multi-sensory integration, it may be that speech recognition is facilitated in CI users for example by recruiting visual areas or by using the auditory cortex for aspects of non-oral communication. In addition, the mechanism behind cross-modal reorganization in deaf and CI users is still unknown. One theory to address crossmodal take-over is that the mechanism is based on the preexisting connections between visual and auditory areas, which is robustly observed in several animal experiments (Bavelier and Neville, 2002; Bizley et al., 2007; Merabet and Pascual-Leone, 2010), suggesting that audio-visual connections may be bidirectional. In other words, it is possible that CI users show higher cross-modal functional connectivity compared to NH controls, which may indicate that CI users are more efficient at using both visual and auditory modalities to facilitate communication. Preliminary results from our group support the idea of increased cross-modal functional connectivity in CI users (Chen, unpublished data).

6. Cortical changes and their relationship with CI outcome

It is of utmost relevance to reveal the influence of cortical changes to CI outcome. However, is there any evidence of a relationship between cortical changes and CI benefit, and furthermore, how is CI outcome defined? So far, CI outcome research appears to have a near exclusive focus on aural speech recognition abilities. However, this may not be the best approach to estimate CI benefit. Communication in daily life usually is not purely auditory, but rather multi-sensory. It is not yet clear how aural speech recognition abilities interact with other communication channels such as lip reading, which contributes significantly to speech perception. Therefore, we discuss influences on CI outcome separately for aural speech recognition and lip reading ability.

Several studies indicated a positive correlation of changes in the neural responses in auditory cortex to auditory stimuli with aural speech recognition abilities (see Table 1). In other words, it seems

as if the improvement of hearing abilities depends on how much the auditory cortex recovers its responsiveness to auditory stimuli after the period of deprivation. Studies investigating visual takeover of the auditory cortex in CI users showed evidence indicating a negative correlation between cross-modal activation in the auditory cortex in response to simple visual stimuli and oral speech recognition abilities (amongst others Sandmann et al. (2012), Fig. 2 A; blue line). Putting together, it is reasonable to assume that intramodal auditory recovery may negatively correlate with left-over cross-modal activation in auditory cortex. Unfortunately, this relationship remains unclear, but the investigation holds some promise in order to identify whether intra-modal auditory recovery is related to cross-modal reorganization.

On the other hand, cross-modal activation in visual cortex was found to correlate positively with aural speech recognition (Fig. 2A; orange line). This further strengthens the hypothesis that auditory processing benefits from recruiting visual cortex. Moreover, intramodal changes in visual cortex for visual stimuli also contribute to improved aural speech recognition abilities. Specifically, activation in visual cortex for visual speechreading seems to predict positively the aural speech recognition six months after surgery (Strelnikov et al., 2013). Altogether, the relationship between cortical changes and aural speech recognition is not simple. Our group recently showed that speech outcome with CIs is likely related to multiple factors that cannot be associated exclusively with either of the cortical changes alone. Specifically, we found that CI users with more cross-modal activation in auditory cortex compared to visual cortex performed worse in a speech recognition task than CI users exhibiting the opposite pattern (Chen et al., 2016a). In other words, assuming that cross-modal reorganization in the visual cortex is mostly induced after CI implantation, it may be that post-implantation habilitation might potentially compensate for pre-implantation changes. This strengthens the view of a habilitation process after CI implantation, meaning that evolving qualitatively new patterns might be more efficient than a complete reversal to the pre-deprivation state to improve aural speech recognition abilities.

In contrast, cross-modal activation in auditory cortex for complex visual stimuli such as faces was found to be positively related to lip reading skills (Stropahl et al., 2015a, Fig. 2 B; blue line). This potentially provides alternative explanations for the functional purpose of the left-over reorganization in the auditory cortex. In other words, cross-modal activation of auditory cortex may contribute to the observed facilitation in daily life communication, simply by enhancing the visual component of natural speech (Desai et al., 2008; Kawase et al., 2015). Additionally, cross-modal activation in visual cortex was also found to correlate positively with lip reading abilities (Fig. 2 B, orange line), which supports again the view that new patterns of cortical changes are induced on a general purpose to facilitate communication including both lip reading and aural speech recognition abilities.

7. Current issues and future perspectives

Despite intensive research on cortical changes in response to auditory deprivation and hearing restoration with a CI, many open questions remain. Our literature review revealed that direct comparisons between plastic changes occurring before and after implantation are missing. As a result, very little direct evidence exists on how cortical reorganization evolves from early stages of auditory deprivation to auditory recovery with CIs, even though understanding the temporal evolvement of cortical changes may provide valuable clinical information on predicting CI outcome. Several possible views might explain difference in CI outcome based on the degree of cortical reorganization. On the one hand,

individuals adapting more strongly to sensory deprivation may be better off with a CI, simply because their brain systems demonstrate a stronger or larger capacity for plastic changes during deafness. We define this idea as the "flexibility view". These individuals may also adapt easily later on to the artificial sensory input as delivered through a CI, reflected in adaptive plasticity (e.g. Fig. 1 A to B to F/G). On the other hand, taking a "limited capacity view", adult cortical systems do not have unlimited capacity for change, and therefore, individuals that adapt strongly to sensory deprivation (e.g. Fig. 1 B) may have insufficient capacity for adapting well to restored sensory input as delivered by a CI (e.g. Fig. 1 E). This latter view would predict maladaptive influences of deprivation on CI outcome. To summarize, prospective longitudinal designs, which should include the period before implantation, as schematically illustrated in Fig. 1 from A to E/F/G, are needed to unambiguously identify and dissociate adaptive and maladaptive patterns of cortical reorganization. fNIRS and EEG-fNIRS recordings allow for a direct comparison of pre- and post-implantation conditions, which is considered as a promising approach for future studies (Saliba et al., 2016).

Another crucial factor that remains underexplored is differences. between congenitally deaf and postlingually deaf individuals. It is not yet clear whether postlingually deaf individuals indeed show cortical changes that are similar to those reported for prelingually deaf individuals. From studies with blind individuals, it is known that cortical changes can be significantly different between individuals with congenital versus acquired sensory loss mostly due to the critical period of development (for a review cf. Heimler et al., 2014). Moreover, congenital versus postlingual deafness is often confounded by experience in sign language, since most postlingually deaf individuals remain dependent on oral language and lip reading instead of sign language. A negative correlation between cross-modal activation in auditory cortex and aural speech recognition in postlingually deaf CI users does not necessarily imply that it may be maladaptive for congenitally deaf individuals to learn sign language. A few studies have investigated postlingually deaf CI users with extensive sign language experience (Nishimura et al., 2000), but this population has not been investigated in detail. Overall, it remains unknown to what extend sign language influences CI outcome and one should be careful not to overgeneralize the findings in postlingually deaf CI users to congenitally deaf individuals or vice versa.

The group of mild to moderately hearing-impaired individuals should receive more attention for several reasons. Firstly, it seems important to understand how much sensory loss is necessary to induce cortical changes as such knowledge could guide clinical intervention strategies. Secondly, learning form this group could also promote our understanding of plastic changes induced by hearing deprivation and restoration. Specifically, since CI technology can provide only a degraded form of auditory input, it is likely that CI users will perform more similarly to hearing-impaired rather than NH individuals. Thus, in terms of cortical reorganization, CI users may be more likely to return to a pre-deafness hearing-impaired condition rather than to a normal hearing state. Lastly, since it appears to be almost impossible to track plastic changes in individuals from the onset of gradual hearing loss to deafness, longitudinal designs may not be able to fill in this gap and thus it would be crucial to investigate similarities and differences between CI users and hearing impaired individuals in crosssectional studies.

Habilitation to CI input may require brain-wide changes and may not be limited to visual and auditory sensory systems and speech processing areas. For example, some studies with hearing impaired individuals reported changes in frontal and other temporal areas (Campbell and Sharma, 2013; Giraud et al., 2001a).

Additionally, multi-sensory integration networks show plastic changes in response to hearing deprivation and restoration with Cls (Barone and Deguine, 2012; Landry et al., 2012; Song et al., 2014; Strelnikov et al., 2015) and evidence for a behaviorally different multi-sensory integration exists as well (Champoux et al., 2009; Desai et al., 2008; Rouger et al., 2008, 2007; Stropahl et al., 2015b). In any case, a more complete, detailed picture of adaptive and maladaptive reorganization patterns in CI users could be achieved by running prospective, longitudinal designs, using multimodal recording techniques, including brain-wide investigation, and considering a wide array of unisensory as well as multisensory processing conditions.

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