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Functional-structural reorganisation of the neuronal network for auditory perception in subjects with unilateral hearing loss: Review of neuroimaging studies.

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ABSTRACT

Objective: This paper aims to provide a review of studies using neuroimaging to measure functional-structural reorganisation of the neuronal network for auditory perception after unilateral hearing loss. **Design:** A literature search was performed in PubMed. Search criterions were peer reviewed original research papers in English completed by the 11th of March 2015. **Study sample:** Twelve studies were found to use neuroimaging in subjects with unilateral hearing loss. An additional five papers not identified by the literature search were provided by a reviewer. Thus, a total of 17 studies were included in the review. **Results:** Four different neuroimaging methods were used in these studies: Functional magnetic resonance imaging (fMRI) (n = 11), diffusion tensor imaging (DTI) (n = 4), T1/T2 volumetric images (n = 2), magnetic resonance spectroscopy (MRS) (n = 1). One study utilized two imaging methods (fMRI and T1 volumetric images). **Conclusion:** Neuroimaging techniques could provide valuable information regarding the effects of unilateral hearing loss on both auditory and non-auditory performance. fMRI-studies showing a bilateral BOLD-response in patients with unilateral hearing loss have not yet been followed by DTI studies confirming their microstructural correlates. In addition, the review shows that an auditory modality-specific deficit could affect multi-modal brain regions and their connections.

Key Words: Unilateral hearing loss, single-sided deafness, plasticity, neuroimaging, fMRI, DTI

Abbreviations: SSD: Single-sided deafness, UHL: Unilateral hearing loss, PTA: Pure tone average, VS: Vestibular Schwannoma, MRI: Magnetic resonance imaging, DTI: Diffusion tensor imaging

INTRODUCTION

This paper aims to provide a review of studies using neuroimaging to measure functional-structural reorganisation of the neuronal network for auditory perception after unilateral hearing loss (UHL). Differences in structure and function between neuronal networks receiving bilateral auditory input and those receiving unilateral input may provide important knowledge on the plasticity of the adult human brain in general.

Plasticity is often used as an umbrella term, describing both functional as well as structural plasticity in the brain as response to learning. On the synaptic level, plasticity is a well-known phenomenon, seen as long-term potentiation (LTP) and depression (LTD), and describes the long-term enhancement, or reduction, respectively, of signal transmission after repeated stimulation of neurons, in particular those of the hippocampus (Bliss & Lomo 1973; Bliss & Collingridge 1993; Lynch 2004). However, plasticity has not only been shown on the neuronal level and is not restricted to the hippocampus.

Reorganization of the human auditory system after UHL has been shown using a range of different techniques both shortly after such a hearing loss occurs and several years later (Hanss et al 2009) in both developing and mature auditory systems (Khosla et al 2003). In adults with UHL, Vasama & Mäkelä (1995) found auditory evoked magnetic fields (AEFs) in auditory association areas not seen in normal hearing subjects following unilateral stimulation, suggesting that the effects of a UHL is not restricted only to the auditory cortex. Hanss et al (2009) investigated long latency auditory evoked potentials (AEPs) following monaural stimulation in normal hearing subjects and in subjects with UHL. In subjects with left side hearing loss they observed a symmetrical activation pattern elicited by non-speech sound, similar to that of a binaural stimulation of normal hearing subjects. These

neurophysiological changes, seen both for amplitudes and time course of the AEPs were not present in subjects with right side hearing loss. Thus, Hanss and colleagues (2009) showed that the side of the hearing loss may influence the central auditory plasticity.

Current neuroimaging methods allow measuring neuronal plasticity on cortical levels with a variety of different methods. One important method rests on various applications of magnetic resonance imaging (MRI). Using structural MRI with high-resolution T1/T2-weighted images, structural plasticity can be measured as changes in grey- and white matter volume (GMV / WMV) as well as cortical thickness (Driemeyer et al 2008). This is typically supplemented by measures of white matter integrity in terms of fiber-connections or degree of myelinations, using diffusion tensor imaging (DTI). Functional plasticity, by contrast, comprises changes within given functional networks, representing a certain function, either as increase or decrease of activity, or as changes in the connectivity between remote areas of the brain. This information is revealed by functional magnetic resonance imaging (fMRI). fMRI does not only reveal information on neuronal activity, as indirectly reflected through the blood oxygenation level dependent (BOLD) effect, it also allows to explore neuronal networks in terms of functional and effective connectivity and their changes through learning (Basset et al 2011). A further method, yet less used in this research field, is magnetic resonance spectroscopy (MRS). This method allows quantified measures of important metabolites and neurotransmitters (Shen & Rothman 2002, Martin 2007).

DESIGN AND STUDY SAMPLE

A literature search was performed in PubMed at the 11th of March, 2015. Search criterions were peer reviewed original research papers in English completed by the 11th of March 2015. Separate searches were made looking for search terms in the title and / or the abstract: "Unilateral hearing loss" (*n* = 486), "Single sided deafness" (*n* = 113), "Acoustic neuroma" (*n* = 2153), "Vestibular Schwannoma" (*n* = 1602), "Unilateral deafness" (*n* = 291). The abstracts of the papers were read and only studies utilizing neuroimaging methods were included: "Unilateral hearing loss" (*n* = 8), "Single sided deafness" (*n* = 1), "Acoustic neuroma" (*n* = 1), "Vestibular Schwannoma" (*n* = 0) "Unilateral deafness" (*n* = 2). An additional five papers not identified by the literature search were provided by a reviewer. Thus, a total of 17 studies were included in the review, and these are presented in table 1. Four different neuroimaging methods were found to be used in these studies: fMRI (*n* = 11), DTI (*n* = 4), T1/T2 volumetric images (*n* = 2), MR-spectroscopy (*n* = 1). One study utilized two different imaging methods (fMRI and T1 volumetric images).

RESULTS

Functional magnetic resonance imaging (fMRI)

fMRI rests on the blood oxygenation level dependent (BOLD) contrast that gives an indirect measure of neuronal activity (Buxton 2012, Ogawa et al 1992, Kwong 1991, Turner 2012, Friston et al 1996). The spatial distribution of the hyperoxygenation is therefore not necessarily directly comparable to the location of activated neurons (Scheffler et al 1998). fMRI is not a quantitative method, as it depends on changes of the BOLD signal, reflected in spatially restricted changes in signal intensities within MRI images acquired through MR sequences sensitive to susceptibility artefacts, such as an gradient-echo echo-planar imaging (EPI) sequence. An a-priori defined experimental design including at least two conditions that differ in at least one cognitive component is thus needed. This approach is typically known as "cognitive subtraction" (Friston et al 1996, Raichle 1998).

Scheffler et al (1998) investigated the BOLD-response to binaural and monaural acoustic stimulation for five patients with complete UHL and 10 healthy subjects. Pulsed 1 kHz sine tones were used as stimuli. In normal hearing subjects a strong contralateral lateralization of cortical response to monaural stimulation was seen. In monaurally deaf subjects, a much smaller lateralization was observed, indicating a more balanced response to a monaural stimulation, comparable to a binaural stimulation of normal hearing subjects. A similar finding was made by Schmitorst et al (2005), which investigated differences in reorganization of the auditory and language pathways in subjects with right and left UHL using fMRI. Eight children (7 – 12 years) with idiopathic hearing loss (4 left ear, 4 right ear) were included. The worse ear had a pure tone average (PTA) of at least 65 dB HL. Stimuli were pure tones with randomized durations and frequencies. The subjects showed bilateral activation of the

auditory cortex. In addition, bilateral activation was seen in the inferior frontal gyrus and the cuneus.

In a single case study, Bilecen et al (2000) followed a subject with sudden UHL after resection of an acoustic neuroma. fMRI-images were acquired 1 month before surgery and 1, 5, and 55 weeks after surgery. The BOLD-response was measured, and in the pre-operative condition with bilateral normal hearing a strong contralateral BOLD-response to acoustic stimulation to either ear was obtained. One week post-surgery stimulation of the unaffected left ear still elicited a strong contralateral response. Five weeks post-surgery the same stimulation now also produced an ipsilateral BOLD-response, and an almost bilaterally balanced response was found 55 weeks after surgery. The balance of activity was mostly due to an increase of the ipsilateral activity. In an additional single case study, cortical organization following hearing recovery in a 41 year old female with congenital severe to profound mixed hearing loss was investigated by Firszt et al (2013). fMRI was performed prior to middle ear surgery and 3 and 9 months after surgery. BOLD responses to auditory stimulation of the unaffected ear were analyzed. They used an interrupted single event design and determined activation magnitudes in core, belt and parabelt auditory cortex regions. The auditory cortex was reorganized after hearing recovery, showing an increase in contralateral auditory cortex responses. The auditory cortex was activated bilaterally including a greater portion of the posterior superior temporal plane. Thus, Firszt et al (2013) showed auditory system changes after restored binaural hearing in a patient with congenital UHL.

Results of these fMRI studies indicate that the neuronal network for auditory perception is reorganized after UHL in both children and adults. This reorganization seems to cause a

bilateral response to monaural stimuli, and there is sign of a secondary plasticity where such reorganization is, at least to some extent, reversed after hearing restoration.

The effect of side of deafness on lateralization and magnitude of evoked blood oxygen level-dependent responses in different auditory cortical fields was investigated by Burton et al in 2012. Normal hearing subjects had one ear blocked, with the open ear receiving monaural stimulation. The normal hearing subjects showed asymmetric responses in several auditory cortical fields, due to a larger contralateral response, with both left and right monaural stimulation. Subjects with left side hearing loss, receiving monaural stimulation of the right ear, showed larger ipsilateral responses in core and belt auditory cortical fields when compared to the normal hearing subjects, possibly due to a neuroplastic process in the right hemisphere. The subjects with a hearing loss in the right ear only showed larger ipsilateral responses in posterior core auditory cortical fields when compared to normal hearing subjects, indicating that the other auditory cortical fields in the left hemisphere were less affected by the reduced amount of signals received from the right ear. In parabelt regions the subjects with both left and right side hearing loss showed reduced activity compared to normal hearing subjects. Burton and colleagues (2012) therefore suggest that the effect of UHL on activation magnitudes in auditory cortical fields compared to normal hearing subjects differs in cortical fields and depends on the side of the hearing loss. A similar suggestion was made by Hanss et al (2009) when they observed a symmetrical activation pattern elicited by non-speech sound, similar to that of a binaural stimulation of normal hearing subjects in subjects with left side hearing loss, but not in those with a hearing loss in the right ear.

In 2013, Burton et al aimed to investigate if there was a correlation between pre- and post-operative hearing thresholds and activation of the ipsilateral auditory cortex when stimulating

the unaffected ear in subjects with UHL. In subjects with acoustic neuromas (8 subjects) and Ménières disease (1 subject), Burton et al (2013) did pre- and post-operative (3 and 6 months) fMRI while subjects listened to random spectrogram noise-like sounds presented to the unaffected ear. In addition, hearing thresholds were measured over the same time period. Six of the nine subjects showed ipsilateral activation of the auditory cortex in the pre-operative measurement. The ipsilateral activation was spatially larger than the contralateral activation in 3 out of 9 subjects. This did not change significantly after surgery, and it is suggested that this was caused by the presence of hearing loss pre-operatively. This may be sign of cortical reorganization caused by developing hearing loss less than profound. Results of these two latter studies (Burton et al 2012, Burton et al 2013), show that both side of hearing loss, and duration and magnitude of hearing loss may affect the plastic process, and thus the results of fMRI-studies.

Measurements of resting-state fMRI in subjects with UHL have shown altered functional connectivity not only in regions associated with auditory processing, but also in higher-order structures involved in executive functions and memory formation, both in children and in adults. Using resting state functional connectivity MRI (rs-fcMRI), Tibbetts et al (2011) tested 16 children (age 7 – 17) with severe to profound UHL and 10 normal hearing siblings (age 7 – 17). The study consisted of three groups (Right UHL, left UHL and normal hearing controls). For these groups, correlation maps were compared using group wise t-tests. This was done to identify voxels where correlations with seed region time course differed significantly between groups. Compared to normal hearing controls the children with UHL, both left and right, showed more correlated resting state activity in a left posterior opercular region when the inferior parietal lobule was used as a seed. The left medial globus pallidus, left middle temporal gyris, right parahippocampal gyrus and the mid-cingulate cortex showed

differences in resting-state functional interactions between children with UHL and controls. In a study including 34 adult patients with UHL due to acoustic neuroma and 22 matched normal controls, Wang et al (2014) investigated intrinsic activity with resting-state fMRI. All patients had untreated acoustic neuroma and were right-handed. 17 had acoustic neuroma in the right ear. Significant group differences in regional homogeneity (ReHo) were seen in cortical regions including left parahippocampal cortex, right anterior insular cortex and bilateral calcarine cortices. Patients showed higher ReHo values in the right anterior insular cortex than compared to controls. Patients with right UHL had higher ReHo values in the left parahippocampal cortex than both controls and patients with left UHL. ReHo was lower in patients than in controls in bilateral calcarine cortices. Left parahippocampal cortex, right anterior insular cortex and bilateral calcarine cortices were used as seeds for resting-state functional connectivity. Significant group differences were seen in the medial prefrontal cortex, right pregenual anterior cingulate cortex and right postcentral gyrus when investigating the functional connectivity of the right anterior insular cortex seed region. Using the left parahippocampal cortex as a seed, patients showed stronger connectivity in the right angular gyrus, right precuneus and the left cuneus than controls, regardless of side of hearing loss. Most of the regions showing altered resting-state functional connectivity were associated with higher-order structures. No correlation was seen between ReHo or resting-state functional connectivity and hearing loss duration or grade of hearing loss. Related findings were made when twelve children with UHL and 23 normal hearing subjects underwent fMRI while listening to narrow band noise and speech-in-noise in a study conducted by Propst et al (2010). In normal hearing children, the narrow band noise activated auditory association areas and attention networks in addition to the auditory areas. Children with UHL only showed activation of the auditory areas, and this was smaller than that seen in normal hearing children. Though measured with a different method, it might be of interest to note that this

result stands in contrast to that of Vasama & Mäkelä (1995). They found auditory evoked magnetic fields (AEFs) in auditory association areas in adults with unilateral hearing loss not seen in normal hearing subjects following unilateral stimulation. An important difference between these studies is also the age of subjects. When listening to speech in noise, the normal hearing children in Propst et al`s study activated secondary auditory processing areas, while the children with UHL only showed activation of these areas in the left hemisphere. Propst et al also showed differences related to side of hearing loss. A right side hearing loss seemed to prevent activation of attention areas activated in normal hearing children and those with left-sided hearing loss. Also, only those with hearing loss in the left ear showed activation of bilateral visual association areas.

Results of these three studies (Tibbetts et al 2011, Wang et al 2014, Propst et al 2010), suggests that a UHL may affect brain functions and structures beyond areas known to be directly associated with auditory perception and processing. This was addressed directly when the effect of UHL on functional brain networks for cross-modal processing was investigated by Schmitorst et al (2014). Their study included 21 children (age 7 – 12) with UHL and 23 normal hearing controls. fMRI was measured while the children performed a classic receptive language test. The test consists of an arrow moving from one object to another on a video screen, while the child hears a sentence. The child then is instructed to push a button if events on the screen match events described in the sentence heard. The children with UHL showed less activation of the right inferior temporal, middle temporal and the middle occitipal gyrus. This is seen as sign of differences in cross-modal modulation of the visual processing pathway in children with UHL when compared to normal hearing controls. Increased activations of the left posterior superior temporal gyrus were seen in children with UHL. Schmitorst et al (2014) suggests that monaural hearing affects development of networks

related to cross-modal sensory processing and regulation of the default network when processing spoken language.

Results of these studies indicate that monaural hearing in children may prevent development of normal cognitive function, and further builds on the argument that a UHL may affect behavioral and educational performance. Also, results of these studies argue against the existence of strictly unimodal cortical regions and demonstrate multimodal interactions between cortical regions. The development of these connections seems to be affected by UHL, at least in children with severe hearing loss (Schmithorst et al 2014). Further signs of that a UHL may affect the default mode network were seen in a study by Yang et al (2014) that aimed to investigate the aberrant regional brain activity at baseline in patients with UHL by measuring the amplitude of low-frequency fluctuation (ALFF) of the fMRI signal. The study included 14 patients with right-sided hearing loss and 19 controls with normal hearing. The control group was matched to the patient group in terms of sex, age and education. Patients had right sided hearing loss (PTA $\geq$ 40 dB HL) with a duration of six months or more, and normal hearing in the left ear (PTA $\leq$ 25 dB HL). Compared to controls, patients with UHL showed decreased ALFF in the right inferior frontal gyrus and insula, bilateral precuneus and the left inferior parietal lobule. Increased ALFF was seen in the right inferior and middle temporal gyrus, and the right inferior temporal gyrus. For several regions disease duration showed a positive correlation with ALFF values. No areas showed negative correlation between ALFF values and disease duration. No correlation was seen between PTA and ALFF values. Thus, Yang et al (2014) showed that a UHL affects ALFF values in regions associated to execution and attention.

Diffusion tensor imaging (DTI)

DTI allows measuring the diffusion of water molecules in brain tissue (Shimony et al 2006). In brain tissue, water molecules will diffuse faster parallel than perpendicular to white matter tracts. This is known as anisotropy, and may be used to study the properties of white matter tracts in the human brain. Usually reported is the fractional anisotropy (FA) with values ranging from 0 to 1 meaning from maximum isotropy with no perpendicular restriction to maximum anisotropy with total perpendicular restriction (Colombo et al 2009). Also reported is the mean diffusivity (MD) that ranges from 0 to 1 and measures how easily water diffuses averaged over all directions (Rachakonda et al 2014).

In a pilot study, Rachakonda et al (2014) aimed to investigate differences in FA and MD in various brain structures between children (age 7 – 17) with UHL (n = 29) and normal hearing siblings (n = 20) serving as controls. Children with UHL showed significantly lower FA of the left lateral lemniscus (LL) when compared with normal hearing siblings. Also, Rachakonda et al found that DTI parameters in a range of brain regions were correlated to educational outcome in children with UHL. Thus, it seems that a UHL may affect the microstructural integrity of brain regions, such as the middle cerebellar panducle and the superior temporal gyrus, believed to hold other functions than auditory perception and processing. Asymmetries between right and left hemisphere in white matter microstructural patterns seen in normal hearing controls were found to be retained in the children with UHL. A similar result was obtained when Vos et al (2015) conducted a study utilizing DTI in five patients with long term single-sided deafness and five normal hearing controls. Patients included had hearing loss $\geq$ 70 dB HL for frequencies 0.5, 1, 2 and 4 kHz. No laterality differences were seen in FA or MD for normal hearing controls, or between the affected and unaffected side in patients. When comparing patients and controls, a significantly lower FA

was seen in both affected and unaffected sides in patients. No such difference was seen in MD. Statistical tests used the averaged values for left and right segments for controls, due to no observed difference between left and right tracts.

Unlike the results of these two recent studies, two earlier studies measuring DTI in UHL showed altered microstructural integrities of the inferior colliculus (IC) and the LL. Lin et al (2008) compared DTI measures (axial diffusivity, radial diffusivity, MD and FA) between patients with sensorineural hearing loss and normal hearing controls. Amongst the patients included in the study, 12 had UHL. DTI measures were compared between the side with hearing loss and the contralateral normal hearing side. FA was lower on the contralateral side for the LL and the IC than on the side with the hearing loss. The contralateral side showed increased radial diffusivity for LL and the IC compared to the ipsilateral, affected ear. No difference in axial diffusivity or mean diffusivity was found between the affected and unaffected ears. Mean values of DTI measures at the LL and the IC were compared between the affected ear and the normal hearing control group. FA was found to be significantly reduced at the IC and the axial diffusivity was found to be increased. No significant difference was seen in the LL.

Wu et al (2008) enrolled 19 patients with UHL in a study measuring DTI. They selected two regions of interest, LL and IC. Axial diffusivity, radial diffusivity, MD and FA were extracted from the images. Patients had PTA $\geq$ 70 dB HL in the affected ear for $\geq$ 5 years. The study also included 10 normal hearing controls. All patients and controls were right handed. In both regions of interest, mean FA values were significantly lower at the side contralateral to the hearing loss. Radial diffusivity was significantly elevated in the contralateral LL. No change was seen in axial diffusivity for either of the regions of interest. MD did not differ

significantly between the ipsilateral and contralateral side of the hearing loss. Compared to the control group, FA was reduced at both the LL and IC for the normal hearing side in the patients. No such difference was seen in MD. Radial diffusivity in the contralateral side of the patients increased. Axial diffusivity remained unchanged.

In contrast to the more recent findings of Rachakonda et al (2014) and Vos et al (2015), Lin and colleagues (2008) found lower FA values on the contralateral side to the hearing loss in adults, while Wu et al (2008) showed a decrease in FA and an increase in MD in a group of subjects with UHL aged 8 – 29 years. Thus, these two studies reveal microstructural alternations that could correlate to reorganization revealed by the change in the BOLD-response in fMRI studies. On the other hand, the more recent DTI studies are not consistent with the fMRI findings of Bilecen et al (2000) and Firszt et al (2013) that showed how the sudden occurrence or reversal of monaural hearing resulted in an increase or decrease, respectively, of the contralateral BOLD-response. In light of these fMRI-findings one could expect differences in white matter microstructures between the monaural and binaural hearing subjects. Rachakonda et al (2014) suggests that the lack of such differences in white matter microstructures may be due to a compensatory plasticity, causing these structures to handle signals from the hearing ear, or that they have been recruited for other brain functions. This plasticity, regardless of what task the structures have taken, could explain the retained asymmetries in white matter structures reported by Rachakonda et al (2014) and Vos et al (2015).

Differences in results of these DTI studies could be due to between-study differences in age, hearing loss configuration and statistical methods. Also, studies differ in regions of interest.

Yet, no uniform body of evidence on the microstructural mechanics of the bilateral fMRI BOLD-response in patients with UHL has been brought forward by DTI studies.

High resolution and volumetric T1 / T2 images

In an attempt to determine prevalence of cochlear nerve deficiency in children with UHL, Clemmens et al (2013) investigated high-resolution T-2 MRIs in 128 children (age 3 weeks to 16 years). Signal intensity, area and diameter of the cochlear nerve was measured and compared to normative data. Results showed that 26 % had cochlear nerve deficiency. In the children with severe or profound hearing loss the prevalence was 48 %. The prevalence of cochlear nerve deficiency was higher the younger the child was at diagnosis, with 100 % prevalence in 10 infants with UHL. A modest correlation between hearing loss severity and nerve size was observed. A narrow bony cochlear nerve canal strongly predicted a cochlear nerve deficiency.

In the study conducted by Yang et al (2014) previously described, they also measured T1-weighted volumetric images. Here they found that the patients with right sided hearing loss showed a decrease in GMV in bilateral posterior cingulate gyrus and precuneus, left superior/middle/inferior temporal gyrus and the right parahippocampal gyrus and lingual gyrus. No increase in GMV was found in any region. Compared to normal hearing controls no differences were seen in WMV. These regions that show sign of decreased gray matter volume includes both the auditory cortex and non-auditory regions supporting functions such as language, visual processing, semantic memory, spatial processing and episodic memory. Thus, this finding could be a structural correlate to the functional differences seen between subjects with UHL and those with normal hearing in the previously described fMRI studies (Tibbetts et al 2011, Wang et al 2014, Propst et al 2010, Schmithorst et al 2014).

MR-spectroscopy

Kilicarslan et al (2014) used MRS to evaluate neurochemical alterations in Heschl`s gyri in fifteen patients with acoustic neuroma. Also, they aimed to determine the most affected side in these cases of UHL. MRS metabolite values were compared between both Heschl`s gyri and showed that N-acetylaspartate (NAA) and creatine (CR) in the Hechl`s gyrus contralateral to the tumor were significantly lower than ipsilateral to the tumor. This suggests neuronal damage to the contralateral side of the tumor with a decreased energy metabolism. Such a difference in energy metabolism between the unaffected and affected side in patients with acoustic neuroma could affect results obtained measuring both fMRI and DTI. In light of the diversity in results from fMRI and DTI studies, MR-spectroscopy could provide valuable information of the biochemical processes induced by UHL.

DISCUSSION

The studies discussed above differ in regards to age of subjects and the grade, cause and duration of hearing loss. This must be taken into account when comparing results between studies. Studies on hearing loss and plasticity should carefully describe the characteristics of hearing loss in subjects, including duration of hearing loss, as the present findings on the influence of these parameters on the reorganization of the neuronal network differ between studies. Also, the potentially crucial difference between a UHL and a single-sided total deafness must be considered when reviewing results from such studies. It could be hypothesized that a single-sided total deafness to a greater extent, and at an earlier stage, will impose a functional and structural reorganization of neuronal networks, than what would be the case with a UHL with residual hearing in the affected ear.

Results of our literature search, with an increase in studies published the past two years, may be sign of a growing interest in investigating the functional and structural organization of different brain regions in patients with ULH.

fMRI-studies showing a bilateral BOLD-response in patients with UHL have not yet been followed by DTI studies confirming their microstructural correlates. It is essential to keep in mind that the studies included in this review differ in a number of aspects. One key point is that the severity of hearing loss in subjects in the different studies varies significantly. Burton et al (2013) reports hearing as good as 39.8 dB HL PTA in some subjects, while Scheffler et al (1998) states that all subjects had total loss of hearing in the affected ear. As suggested by Burton et al (2013), cortical reorganization could occur even with a hearing loss less than profound. It is thus important to consider that an eventual plastic process could be taking place long before an ear is defined as deaf or with a profound hearing loss. This latter point is

maybe of particular importance when dealing with duration of hearing loss as a parameter. Also, when comparing results of studies utilizing different neuroimaging methods, especially when introducing methods such as EEG in the comparison, it is important to remember that these methods by nature differ from each other and that they are based on different physical and physiological principles (Scheffler et al 1998).

CONCLUSION

Several studies discussed in this review show that a UHL not only affects regions of the brain known to be involved with auditory perception and processing, but also non-auditory cortical regions. This information seems highly relevant when considering the educational and behavioral difficulties faced by children with UHL. Neuroimaging techniques could provide valuable information regarding the effects of UHL on both auditory and non-auditory performance in patients with UHL. In addition, results from the studies discussed in this paper show that a modality-specific deficit could affect multi-modal brain regions and their connections.

DECLARATION OF INTEREST

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1: Studies included in review. Data presented as means (M) and standard deviations (±). Abbreviations: RE: Right ear, LE: Left ear, UHL: Unilateral hearing loss, SSD: Single sided deafness

(Table submitted as separate TIFF file).

Table 1) Studies included in review

Study	Method	Subjects (*n*)	Controls (*n*)	Hearing loss (PTA dB HL)
Schmithorst et al 2005	fMRI	8 Age 9 ± 1.8	0	4 LE, 4 RE. > 65
Scheffler et al 1998	fMRI	5 Age not reported	10 21 - 32	"Total hearing loss in affected ear"
Burton et al 2012	fMRI	26 Age 47 ± 2.8	24 47 ± 2.8	13 RE, 13 LE. ≥ 84
Burton et al 2013	fMRI	9 Age 45 ± 2.9	0	5 RE, 4 LE. M= 39.6 ± 5.7 at first fMRI
Propst et al 2010	fMRI	12 Age 9 ± 1.4	23 10 ± 1.4	6 RE, 6 LE. ≥ 65
Yang et al 2014	fMRI, T1	14 Age 53.9 ± 7.6	19 53.6 ± 5.4	Sudden hearing loss RE. M= 80.9 ± 17.4
Firszt et al 2013	fMRI	1 Age 41	0	Mixed. Pre-surgery 90 dB HL. Post-surgery 51.7
Tibbetts et al 2011	fMRI	16 Age 11 ± 3.5	10 11.8 ± 2.6	UHL. 9 RE, 7 LE ≥ 70
Bilecen et al 2000	fMRI	1 Age 53	0	Pre-surgery normal bilateral. Post-surgery SSD RE.
Schmithorst et al 2014	fMRI	21 Age 9.2 ± 1.7	23 9.7 ± 1.5	UHL. 10 RE M= 105.6 ± 9.35, 11 LE M= 80.36 ± 30.2
Wang et al, 2014	fMRI	34 Age LE 45.7, RE 43	22 46	UHL. 17 LE 67.2 ± 19.2. 17 RE 66.8 ± 15.6
Rachakonda et al 2014	DTI	29 Age 12.2 ± 2.4	20 12.7 ± 2.9	UHL ≥ 70 . 13 RE. 16 LE.
Lin et al 2008	DTI	12 Age 30.1 ± 10.1	10 31.1 ± 11.6	UHL ≥ 90.
Wu et al 2008	DTI	19 Age 24.1 ± 13	10 31	UHL ≥ 70. 9 LE 10 RE. 16 participants PTA ≥110
Vos et al 2015	DTI	5 Age 50.6 ± 13.7	5 40.6 ± 11.3	UHL ≥ 70. 2 RE 3 LE
Clemmens et al 2013	T2	128 Age 5.6	0	UHL. Ranging fra 32 db HL to anacusis
Kilicarslan et al 2014	MRS	15 Age 54.6 ± 12	0	UHL. 5 LE 10 RE. PTA not described